Top 128 Articles for Query:

Title: TREM1, the first anti-TNF specific biomarker guiding therapeutic decision

Publication Date: nan

Authors: Verstockt B.; Verstockt S.; Dehairs J.; Ballet V.; Blevi H.; Wollants W.-J.; Breynaert C.; Van Assche G.; Vermeire S.; Ferrante M.

Journal: nan

Abstract: Background: With the expanding therapeutic armamentarium for inflammatory bowel diseases (IBD), biomarkers predicting efficacy are urgently needed. To predict outcome to anti-TNF therapy, we studied whole blood and mucosal expression of genes previously reported to predict outcome to anti-TNF therapy, and investigated whether the signature was specific for these agents. Method(s): We prospectively included 35 (discovery) and 19 (validation) consecutive IBD patients with active disease (both Crohn's disease and ulcerative colitis) initiating anti-TNF therapy, as well as 22 patients initiating ustekinumab and 51 patients initiating vedolizumab. Whole blood expression levels of OSM, TNF, TNFR2 and TREM1 (total and all individual transcripts separately) were measured prior to start of therapy using qPCR, and mucosal gene expression in inflamed biopsies using RNA-sequencing. Endoscopic remission was defined as an SES-CD <=2 at Week 24 for Crohn's disease and a Mayo endoscopic sub-score <=1 at Week 8-14 for ulcerative colitis. Result(s): Baseline whole blood TREM1 expression was significantly down-regulated in future anti-TNF healers ($p < 0.001$, both discovery and validation cohort) (Figure). Conclusion(s): We identified and validated low TREM-1 as a specific biomarker for anti-TNF-induced endoscopic remission. These results can aid in the selection of therapy in biological-naive patients, but should be confirmed in a randomised trial prior to translation into daily clinical practice.

DOI: /10.1093/ecco-jcc/jjy222.509

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjy222.509

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: An integrated multi-omics biomarker predicting endoscopic response in ustekinumab treated patients with Crohn's disease

Publication Date: nan

Authors: Verstockt B.; Sudahakar P.; Creyns B.; Verstockt S.; Cremer J.; Wollants W.-J.; Organe S.; Korcsmaros T.; Madgwick M.; Van Assche G.; Breynaert C.; Vermeire S.; Ferrante M.

Journal: nan

Abstract: Background: Ustekinumab (UST), an anti-IL12/23p40 monoclonal antibody, has been approved for Crohn's disease (CD). The aim of this study was to identify baseline predictors of response using several omics layers, which ultimately may result in a multi-omics panel allowing individualised UST therapy. Method(s): Inflamed colonic (n = 25) and ileal (n = 22) biopsies were retrieved prior to first UST administration in patients with active CD, in addition to sorted circulating CD14+ monocytes and CD4+ T cells (n = 39). RNA was extracted from both lysed biopsies and sorted cells, and RNA sequencing performed. Proteomic analysis was performed on baseline serum samples (n = 86) using OLINK Proseek inflammation. Genotyping data were generated using Immunochip (n = 38). The genetic risk burden was determined for every patient using the SNPs which overlap with genes encoding functional proteins or RNAs. The six above-described layers of omics data were integrated and analysed using Multi-Omics Factor Analysis (MOFA). The strongest omic layers in terms of variance contribution to the latent factors explaining endoscopic response (>=50% in SES-CD by w24) were identified. Dimensionality reduction and feature extraction from the strongest -omic layers were performed followed by predictive modelling on the top-ranked features. Cross-validation using distinct test and training sets was performed for the ensemble and individual classifiers, as an internal validation to avoid over-fitting. Result(s): MOFA identified 19 latent factors (LF, minimum explained variance 2%), with 3 LFs correlating with endoscopic response at w24 (r = -0.24, r = 0.27, r = -0.25; p = 0.03, p = 0.01, p = 0.02). The genomic and CD14 transcriptomic layers contributed significantly to the prediction of endoscopic response. Predictive modelling based on the results of the most dominant omic layers revealed a 10-feature panel predicting endoscopic response at w24 with an accuracy of 98%. In contrast, classification performance based on 10 randomly selected features resulted in a drastic drop in accuracy (66%). Only 2 of the 10 features exhibited significant correlation with baseline faecal calprotectin, and 1 with CRP, suggesting that this panel is not a simple surrogate of baseline inflammation. From the genetic risk burden, we identified a 15-gene panel which could classify (accuracy 96.6%) the patients based on endoscopic response. Conclusion(s): Through multi-omic data integration, we discovered pathways contributing to UST response, and identified a 10-feature transcriptomic and 15-feature genomic panel predicting endoscopic response to UST standard dosage. Further validation in larger and independent cohorts is warranted, as well as its UST specificity.

DOI: /10.1093/ecco-jcc/jjy222.104

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjy222.104

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Oncostatin M Is a Biomarker of Diagnosis, Worse Disease Prognosis, and Therapeutic Nonresponse in Inflammatory Bowel Disease.

Publication Date: Oct 2021

Authors: Verstockt, Sare; Verstockt, Bram; Machiels, Kathleen; Vancamelbeke, Maaike; Ferrante, Marc; Cleynen, Isabelle; De Hertogh, Gert; Vermeire, Séverine

Journal: Inflammatory bowel diseases

Abstract: Oncostatin M (OSM) has been implicated in the pathogenesis of inflammatory bowel disease (IBD) and as a marker for nonresponsiveness to anti-tumor necrosis factor (TNF) therapy. We further unraveled the potential of OSM and related receptors as markers of diagnosis, prognosis, and therapy response in IBD.

DOI: 10.1093/ibd/izab032

PMID: 33624092.0

Full Article: https://doi.org/10.1093/ibd/izab032

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Post-hoc analysis of tofacitinib Crohn's disease phase 2 induction efficacy in subgroups with baseline endoscopic or biomarker evidence of inflammation

Publication Date: nan

Authors: Sands B.E.; Panes J.; Higgins P.D.R.; Moscariello M.; Chan G.; Su C.; Wang W.; Maller E.

Journal: nan

Abstract: BACKGROUND: Tofacitinib is an oral, small molecule Janus kinase (JAK) inhibitor that is being investigated for IBD. In a recent trial of Crohn's disease (CD) patients (pts), small treatment effects for tofacitinib vs placebo (PBO) were noted using CD Activity Index (CDAI)-based enrollment criteria without endoscopic scoring (1). We report posthoc analyses of efficacy endpoints (CDAI-based and composite outcomes) in subgroups based on objective baseline (BL) criteria of disease activity. METHOD(S): In a randomized, double-blind, PBO-controlled multicenter Phase 2b trial (NCT01393626), pts with moderate to severe CD (CDAI 220-450) received PBO, tofacitinib 5 or 10mg twice daily (BID) for 8 weeks. Clinical remission (CDAI <150), clinical response 100 (100 CDAI reduction from BL), composite remission (remission and 50% C-reactive protein [CRP] or fecal calprotectin [FCP] reduction from BL) and composite response (CDAI-100 response and 50% CRP or FCP reduction from BL) were analyzed at Week 8, by subgroups defined by BL simple endoscopic score (SES) <11 (median 11; local read), SES 11 or biomarkers (CRP 5mg/L or FCP 250mg/kg). RESULT(S): In pts with BL SES 11, significantly higher proportions achieved remission, composite remission and composite response with tofacitinib vs PBO (all p<0.05 except clinical remission with tofacitinib 5mg BID; Table). Observations were similar in pts with BL CRP 5 or FCP 250. Pts with BL SES <11 had significantly higher rates of composite remission and composite response with tofacitinib vs PBO (all p<0.05 except composite remission with tofacitinib 5mg BID). CONCLUSION(S): Increased proportions of pts were in remission and achieved composite remission and composite response with tofacitinib vs PBO, when analyses were done using more objective BL criteria of active disease than simple measure of CDAI. Results from these post-hoc analyses support further investigation of JAK inhibition in CD. (Table Presented).

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: The JAK1-selective inhibitor filgotinib displays an anti-inflammatory biomarker signature in rheumatoid arthritis patients

Publication Date: nan

Authors: Taylor P.C.; Westhovens R.; Meuleners L.; Meuleman B.; Pan Y.; Vyncke V.; Van Der Aa A.; Harrison P.; Tasset C.; Galien R.

Journal: nan

Abstract: Background/Purpose : The potent and selective JAK1 inhibitor filgotinib (GLPG0634, GS-6034) has been evaluated in a 24-week phase 2B study in combination with methotrexate (MTX) in active rheumatoid arthritis (RA) patients with inadequate response to MTX (DARWIN 1 study). Significant improvement in signs and symptoms was observed after 12 weeks and efficacy was sustained or improved up to Week 24 with a safety profile overall acceptable. In order to gain insight in filgotinib mode of action in RA patients, we analysed the impact of this treatment on serum cytokines. Methods : Patients with active RA on stable dose of MTX were randomized 1:1:1:1:1:1:1 in a double blind manner to receive either placebo (PBO) or one of three doses of filgotinib (50mg, 100mg or 200mg) as once (qd) or twice daily (bid) regimen for 24 weeks (DARWIN 1 study). At baseline, Week 4 and Week 12, sera were collected from all patients and analysed using the 18-plex panel kit from Merck-Millipore (HSTCMAG-28SK) on BioPLEX-200 apparatus to measure concentration of GM-CSF, IFNgamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, IL-21, IL-23, MIP-1alpha, MIP-1beta and TNF-alpha. Data are presented as means of changes from the baseline. Results : Following treatment with filgotinib, IL-6 was the cytokine showing greatest decreases in concentration at all time points and doses analysed. The pro-inflammatory cytokine IL-1beta was also decreased at Week 12 at higher doses confirming the potent antiinflammatory activity of filgotinib. Of interest, serum concentrations of IL-2 and IFN-gamma, two TH1 cell markers, reduced significantly at Week 12 at the higher doses used, suggesting that filgotinib may impact the promotion of this cell subset. Notably, this is consistent with the Week 4 decrease in IL-12 concentration, a cytokine that, together with IFN-gamma, promotes TH1 cell expansion. The TH2-related cytokine IL-13 was decreased at Week 12 at all doses analysed, in contrast to IL-4 and IL-5 that were not impacted by filgotinib treatment. Of interest, concentration of IL-21 (a cytokine produced by TH17 cells) was decreased after 12 weeks of treatment with the higher dose of filgotinib. Higher doses of filgotinib also reduced levels of the B and T cell development cytokine, IL-7. Finally, MIP-1beta concentration was decreased by high doses of filgotinib after 4 weeks of treatment, in line with the effect observed on GM-CSF at all time points. Conclusion(s): Treatment of RA patients with filgotinib led to the decrease of multiple cytokines involved in various aspects of the inflammatory process. Reductions in IL-6 and IL-1beta establish the anti-inflammatory activity of filgotinib. Treatment effects on IL-2, IL-6, IL-7, IL-12 and IFN-gamma that play a key role in CD4+ T-cell differentiation and expansion further highlight the anti-inflammatory effects of filgotinib, likely by limiting the promotion of TH1, TH2 and TH17 cells. Finally, effects on innate immunity, through MIP-1beta and GMCSF decrease, were also mediated by filgotinib. Taken together, these data further demonstrate the anti-inflammatory activity of filgotinib in line with its efficacy observed in RA patients.

DOI: /10.1002/art.39977

PMID: nan

Full Article: https://doi.org//10.1002/art.39977

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serum amyloid A is a better predictive biomarker of mucosal healing than C-reactive protein in ulcerative colitis in clinical remission.

Publication Date: Apr 2020

Authors: Wakai, Masaki; Hayashi, Ryohei; Tanaka, Shinji; Naito, Toshikatsu; Kumada, Junko; Nomura, Motonobu; Takigawa, Hidehiko; Oka, Shiro; Ueno, Yoshitaka; Ito, Masanori; Chayama, Kazuaki

Journal: BMC gastroenterology

Abstract: Many studies have revealed that mucosal healing improves the long-term prognosis of ulcerative colitis. Frequent colonoscopy is difficult because of its invasiveness and cost. Therefore, in diagnosing and treating ulcerative colitis, noninvasive, low-cost methods for predicting mucosal healing using useful biomarkers are required in the clinical setting. This study aimed to evaluate whether serum amyloid A is a better serum biomarker than C-reactive protein in predicting mucosal healing in ulcerative colitis patients in clinical remission.

DOI: 10.1186/s12876-020-01229-8

PMID: 32245401.0

Full Article: https://doi.org/10.1186/s12876-020-01229-8

Methods:

MethodsPatientsThis study included consecutive outpatients or inpatients who underwent endoscopic examinations at Hiroshima University from April 2010 to March 2017. UC diagnosis was made based on the clinical, endoscopic, and pathological findings. Demographic, clinical, endoscopic, and laboratory data were obtained from patients' medical records. SAA and CRP values were measured via an automatic analyzer using a latex agglutination reaction.

Results:

A total of 199 colonoscopies were performed in 108 UC patients who underwent blood tests for CRP and SAA (63 men, 45 women). AUC, area under the receiver's operating characteristic curve; CI, confidence interval; CRP, C-reactive protein; MES, Mayo Endoscopic Score; SAA, serum amyloid AFull size imageTable 3 Ability to predict mucosal inflammation (MES 1 or 2 or 3) with optimal cutoff value by ROC curveFull size tableIn addition, we examined by disease duration about patients in clinical remission. AUC, area under the receiver's operating characteristic curve; CRP, C-reactive protein; MES, Mayo Endoscopic Score; SAA, serum amyloid AFull size imageWe also examined disease type. There was no difference between the two groups regarding age, disease duration, and CAI (data not shown).

Discussion:

Measuring fecal calprotectin levels has been proposed as a noninvasive test for evaluation of intestinal inflammation in IBD patients [16, 17]. Although the therapeutic goal of UC is mucosal healing, clinical and endoscopic findings do not necessarily match. Therefore, among the clinical remission patients without symptoms, it is clinically important to evaluate intestinal inflammation using biomarkers than through frequent endoscopies. Thus, SAA can be a better monitoring tool to predict mucosal inflammation than CRP in patients with clinical remission with low disease activity.SAA is produced by the liver; it has recently been reported that it is also produced extrahepatically (Intestinal epithelium) [21].

Conclusion:

ConclusionsIn conclusion, SAA has a strong correlation with endoscopic findings and is an excellent marker than CRP for predicting endoscopic activity in UC patients in clinical remission.

Title: TREM1, THE FIRST ANTI-TNF SPECIFIC BIOMARKER GUIDING THERAPEUTIC DECISION IN INFLAMMATORY BOWEL DISEASE

Publication Date: nan

Authors: Verstockt B.; Verstockt S.; Dehairs J.; Ballet V.; Blevi H.; Wollants W.-J.; Breynaert C.M.; Van Assche G.A.; Vermeire S.; Ferrante M.

Journal: nan

Abstract: Background: With the expanding therapeutic armamentarium for inflammatory bowel diseases (IBD), biomarkers predicting efficacy are urgently needed. To predict outcome to anti- TNF therapy, we studied whole blood and mucosal expression of genes previously reported to predict outcome to anti-TNF therapy, and investigated if the signature was specific for these agents. Method(s): We prospectively included 35 (discovery) and 19 (validation) consecutive IBD patients with active disease (both Crohn's disease and ulcerative colitis) initiating anti-TNF therapy, as well as 22 patients initiating ustekinumab and 51 patients initiating vedolizumab. Whole blood expression levels of OSM, TNF, TNFR2 and TREM1 (total and all individual transcripts separately)were measured prior to start of therapy using qPCR, and mucosal gene expression in inflamed biopsies using RNA-sequencing. Endoscopic remission was defined as an SES-CD<=2 at week 24 for Crohn's disease and a Mayo endoscopic sub-score<=1 at week 8-14 for ulcerative colitis. Result(s): Baseline whole blood TREM1expression was significantly downregulated in future anti-TNF healers (p<0.001, both discovery and validation cohort) (Figure). Receiver operator characteristic statistics showed an area under the curve (AUC) of 0.78 (p=0.001), resulting in post-test probabilities of 77.1% and 90.0% for endoscopic remission and non-remission, respectively. A similar accuracy could be observed in mucosal TREM1expression (AUC 0.77, p=0.003), which outperformed the accuracy of serum TREM1 at the protein level (AUC 0.58, p=0.31). Whole blood TREM1expression did not significantly correlate with CRP (spearmanr= -0.08, p=0.38), faecal calprotectin (spearman r= -0.06, p=0.64) or serum TNFa (spearmanr= - 0.15, p=0.63). OSM, TNFand TNFR2were not differentially expressed in whole blood (p=0.09, p=0.13, p=0.24 respectively), whereas they were at the mucosal level (p=0.007, p=0.02, p=0.008 respectively). The whole blood TREM1predictive signal was anti-TNF specific, as no changes in expression were seen in ustekinumab and vedolizumab treated patients, neither in whole blood (p=0.82, p=0.53 respectively), nor in tissue (p=0.24, p=0.10, respectively). Conclusion(s): We identified and validated low TREM-1 as a specific biomarker for anti-TNF induced endoscopic remission. These results can aid in the selection of therapy in biological-naive patients, but should be confirmed in a randomized trial prior to translation into daily clinical practice. [Figure presented]

DOI: /10.1016/S0016-5085%2819%2936953-7

PMID: nan

Full Article: https://doi.org//10.1016/S0016-5085%2819%2936953-7

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Insights into Therapeutic Response Prediction for Ustekinumab in Ulcerative Colitis Using an Ensemble Bioinformatics Approach.

Publication Date: May 2024

Authors: Koustenis, Kanellos; Dovrolis, Nikolas; Viazis, Nikos; Ioannou, Alexandros; Bamias, Giorgos; Karamanolis, George; Gazouli, Maria

Journal: International journal of molecular sciences

Abstract: Optimizing treatment with biological agents is an ideal goal for patients with ulcerative colitis (UC). Recent data suggest that mucosal inflammation patterns and serum cytokine profiles differ between patients who respond and those who do not. Ustekinumab, a monoclonal antibody targeting the p40 subunit of interleukin (IL)-12 and IL-23, has shown promise, but predicting treatment response remains a challenge. We aimed to identify prognostic markers of response to ustekinumab in patients with active UC, utilizing information from their mucosal transcriptome.

DOI: 10.3390/ijms25105532

PMID: 38791570.0

Full Article: https://doi.org/10.3390/ijms25105532

Methods:

None available

Results:

Tumor necrosis factor ligand superfamily member 14 (TNFSF14), while achieving statistical significance, displays a modest upregulation of just 1.38-fold. FASLG, CXCL5, and, to a lesser extent, CCR2 appear to be equally implicated in the activity of both sample groups, while TNFSF14 did not exhibit a strong correlation with any other gene in either group.To help us explore all the correlations further and quantify the gene significance within each group, we constructed co-expression networks (Figure 5) and applied graph analysis metrics to them. Once more, we see CCL11 and CCL22 in these results, which highlights their crucial significance within the network. It is worth noting here that DRF also included LTA and TLR5 in its top features, two genes which were not found to be dysregulated by DGEA, while XRT only uses LTA in addition to other dysregulated genes.

Discussion:

Additionally, He et al. [23] suggested that CXCL5 is among the significant DEGs that may be better predictors of ustekinumab non-response in patients with Crohn’s disease.Regarding the association between FASLG mRNA expression and ustekinumab treatment failure, there are not yet any studies to clarify this. It is possible that the dysregulation of apoptotic pathways, including those involving FASLG, may contribute to ustekinumab treatment resistance. Additionally, CRP is a known inflammatory marker [31] whose levels have been contradictorily associated with response to biological therapies. A negative correlation between CRP levels and response to anti-TNF therapies has been reported in UC [32]; however, these observations were not consistent with ustekinumab therapy [33].

Conclusion:

None available

Gene	Fold Upregulation	Gene	Fold Downregulation
CXCL2	6.95	IL23A	−24.3
CXCL3	6.66	CCR2	−16.86
BCL6	5.68	IL23R	−13.59
CXCL5	5.67	CCL24	−12.61
FASLG	3.93	CCL22	−9.44
CRP	3.04	ITGB2	−2.73
CCL21	3.03	CXCL9	−2.68
CXCR1	2.86	CCR1	−2.63
CD40	2.68	C3AR1	−2.25
IL22	2.61	CXCL10	−2.17
CCL11	2.55	NOS2	−2.13
CXCL1	2.34	CD40LG	−2.08
CCL2	2.2	LY96	−2.07
CCL16	2.19		
IL17A	2.19		
IL1B	2.14		

	Responders(n = 22)	Non-Responders(n = 14)	p*
Male (%)	16 (72.73)	10 (71.43)	0.932
Age, years, mean (SD)	48.43 ± 15.37	55.86 ± 19.37	0.205
Montreal classification, n (%)			0.721
E1	1 (4.55)	0 (0)	
E2	9 (40.91)	6 (42.86)	
E3	12 (54.55)	8 (57.14)	
Mayo score, median	7.5	7	0.517
Smoking status, n (%)			0.377
Never	8 (36.36)	3 (21.43)	
Former	4 (18.18)	1 (7.14)	
Active	10 (45.46)	10 (71.43)	
Anti-TNF exposed, n (%)			0.755
Yes	9 (40.91)	5 (35.71)	
No	13 (59.09)	9 (64.29)	
WBC, mean (SD)	8389.58 ± 3082.1	7951.67 ± 1917.6	0.656

CRP (mg/dL), mean (SD)	0.97 ± 1.11	1.95 ± 2.94	0.166
Platelets, mean (SD)	352,680 ± 118,288	274,727.3 ± 103,577	0.07
Hemoglobulin, mean (SD)	12.31 ± 1.71	13.45 ± 2.10	0.09

Title: Low TREM1 expression in whole blood predicts anti-TNF response in inflammatory bowel disease.

Publication Date: Feb 2019

Authors: Verstockt, Bram; Verstockt, Sare; Dehairs, Jonas; Ballet, Vera; Blevi, Helene; Wollants, Willem-Jan; Breynaert, Christine; Van Assche, Gert; Vermeire, Séverine; Ferrante, Marc

Journal: EBioMedicine

Abstract: With the changed therapeutic armamentarium for Crohn's disease (CD) and ulcerative colitis (UC), biomarkers predicting treatment response are urgently needed. We studied whole blood and mucosal expression of genes previously reported to predict outcome to anti-TNF therapy, and investigated if the signature was specific for anti-TNF agents.

DOI: 10.1016/j.ebiom.2019.01.027

PMID: 30685385.0

Full Article: https://doi.org/10.1016/j.ebiom.2019.01.027

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease.

Publication Date: May 2017

Authors: West, Nathaniel R; Hegazy, Ahmed N; Owens, Benjamin M J; Bullers, Samuel J; Linggi, Bryan; Buonocore, Sofia; Coccia, Margherita; Görtz, Dieter; This, Sébastien; Stockenhuber, Krista; Pott, Johanna; Friedrich, Matthias; Ryzhakov, Grigory; Baribaud, Frédéric; Brodmerkel, Carrie; Cieluch, Constanze; Rahman, Nahid; Müller-Newen, Gerhard; Owens, Raymond J; Kühl, Anja A; Maloy, Kevin J; Plevy, Scott E; ,; Keshav, Satish; Travis, Simon P L; Powrie, Fiona

Journal: Nature medicine

Abstract: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are complex chronic inflammatory conditions of the gastrointestinal tract that are driven by perturbed cytokine pathways. Anti-tumor necrosis factor-α (TNF) antibodies are mainstay therapies for IBD. However, up to 40% of patients are nonresponsive to anti-TNF agents, which makes the identification of alternative therapeutic targets a priority. Here we show that, relative to healthy controls, inflamed intestinal tissues from patients with IBD express high amounts of the cytokine oncostatin M (OSM) and its receptor (OSMR), which correlate closely with histopathological disease severity. The OSMR is expressed in nonhematopoietic, nonepithelial intestinal stromal cells, which respond to OSM by producing various proinflammatory molecules, including interleukin (IL)-6, the leukocyte adhesion factor ICAM1, and chemokines that attract neutrophils, monocytes, and T cells. In an animal model of anti-TNF-resistant intestinal inflammation, genetic deletion or pharmacological blockade of OSM significantly attenuates colitis. Furthermore, according to an analysis of more than 200 patients with IBD, including two cohorts from phase 3 clinical trials of infliximab and golimumab, high pretreatment expression of OSM is strongly associated with failure of anti-TNF therapy. OSM is thus a potential biomarker and therapeutic target for IBD, and has particular relevance for anti-TNF-resistant patients.

DOI: 10.1038/nm.4307

PMID: 28368383.0

Full Article: https://doi.org/10.1038/nm.4307

Methods:

Colon biopsies were also obtained from normal subjects who did not participate in the PURSUIT study to serve as controls. All biopsies were stored at –80 °C until RNA isolation was performed, which might have been up to 2 years following collection. The microarray data were pre-processed and normalized by Robust Multi-array Average using Array Studio software version 4.2 (OmicSoft Corp., St. Morrisville, NC). Endogenous peroxidase activity was blocked with 3% (v/v) hydrogen peroxide before masked antigens were retrieved by microwaving the tissue sections in target-retrieval solution (Dako).

Results:

Notably, OSMR was expressed more abundantly than the related IL-6 receptor by intestinal stromal cells from both healthy controls and patients with IBD (Supplementary Fig. The colon stroma from mice with inflammation also expressed high amounts of Il1b and Il6, which suggests that these cells adopt a proinflammatory state during colitis (Fig. 11a).OSM neutralization suppresses anti-TNF-resistant colitis in miceTo test the therapeutic utility of OSM, we treated wild-type C57BL/6 mice with an Fc-tagged soluble OSMR–gp130 fusion protein (OR-Fc; Fig. As compared to commercially available polyclonal anti-OSM antibodies, the OR-Fc construct was more efficient at neutralizing OSM in an ex vivo mouse

intestinal stromal cell assay (Supplementary Fig.

Discussion:

Nevertheless, data from other inflammatory diseases, such as rheumatoid arthritis, support the hypothesis that stromal cells are active contributors to immune pathology41. The high frequency of fibrotic complications in CD is consistent with a pathological role for intestinal stromal cells. Our data thus highlight the potential for developing a robust assay—one based on measuring the expression of OSM or similar inflammatory factors—that could help clinicians determine whether to prescribe anti-TNF antibodies or to explore alternative therapeutic options.Although OSM can influence tissue remodeling in organs such as the heart and liver44,45,46,47,48, Osm–/– mice are viable and healthy, which suggests that therapeutic blockade of OSM might cause minimal side effects. Indeed, OSM has been targeted for rheumatoid arthritis in phase 1 and 2 clinical trials using a humanized anti-OSM monoclonal antibody (GSK315234)49.

Conclusion:

None available

Title: Serum oncostatin M predicts mucosal healing in patients with inflammatory bowel diseases treated with anti-TNF, but not vedolizumab.

Publication Date: Oct 2022

Authors: Bertani, Lorenzo; Barberio, Brigida; Fornili, Marco; Antonioli, Luca; Zanzi, Federico; Casadei, Cesare; Benvenuti, Laura; Facchin, Sonia; D'Antongiovanni, Vanessa; Lorenzon, Greta; Ceccarelli, Linda; Baglietto, Laura; de Bortoli, Nicola; Bellini, Massimo; Costa, Francesco; Savarino, Edoardo Vincenzo; Fornai, Matteo

Journal: Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver

Abstract: Oncostatin M was recently highlighted as a promising biomarker for therapeutic effectiveness in inflammatory bowel diseases (IBD), with particular regard for infliximab. The primary aim was to evaluate the ability of serum oncostatin M to predict endoscopic response to different drugs in IBD.

DOI: 10.1016/j.dld.2022.03.008

PMID: 35393259.0

Full Article: https://doi.org/10.1016/j.dld.2022.03.008

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serum oncostatin M is a potential biomarker of disease activity and infliximab response in inflammatory bowel disease measured by chemiluminescence immunoassay.

Publication Date: Feb 2022

Authors: Cao, Ying; Dai, Yibei; Zhang, Lingyu; Wang, Danhua; Yu, Qiao; Hu, Wen; Wang, Xuchu; Yu, Pan; Ping, Ying; Sun, Tao; Sang, Yiwen; Liu, Zhenping; Chen, Yan; Tao, Zhihua

Journal: Clinical biochemistry

Abstract: Although endoscopy is the gold standard to assess disease activity and infliximab efficacy in inflammatory bowel disease (IBD), the invasive, costly, and time-consuming procedure limits its routine applications. We aimed to investigate the clinical value of serum oncostatin M (OSM) as a surrogate biomarker.

DOI: 10.1016/j.clinbiochem.2021.11.011

PMID: 34843732.0

Full Article: https://doi.org/10.1016/j.clinbiochem.2021.11.011

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serum oncostatin M at baseline predicts mucosal healing in Crohn's disease patients treated with infliximab.

Publication Date: Jul 2020

Authors: Bertani, Lorenzo; Fornai, Matteo; Fornili, Marco; Antonioli, Luca; Benvenuti, Laura; Tapete, Gherardo; Baiano Svizzero, Giovanni; Ceccarelli, Linda; Mumolo, Maria Gloria; Baglietto, Laura; de Bortoli, Nicola; Bellini, Massimo; Marchi, Santino; Costa, Francesco; Blandizzi, Corrado

Journal: Alimentary pharmacology & therapeutics

Abstract: Oncostatin M is upregulated in Crohn's disease inflamed intestinal mucosa, and has been suggested as a promising biomarker to predict responsiveness to anti-TNF therapy in patients with inflammatory bowel diseases.

DOI: 10.1111/apt.15870

PMID: 32506635.0

Full Article: https://doi.org/10.1111/apt.15870

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Combined Use of Fecal Biomarkers in Inflammatory Bowel Diseases: Oncostatin M and Calprotectin.

Publication Date: 2021

Authors: Cao, Ying; Dai, Yibei; Zhang, Lingyu; Wang, Danhua; Hu, Wen; Yu, Qiao; Wang, Xuchu; Yu, Pan; Liu, Weiwei; Ping, Ying; Sun, Tao; Sang, Yiwen; Liu, Zhenping; Chen, Yan; Tao, Zhihua

Journal: Journal of inflammation research

Abstract: Fecal biomarkers have emerged as one of the most useful tools for clinical management of inflammatory bowel disease (IBD). Oncostatin M (OSM), like fecal calprotectin (FC), is highly expressed in the inflamed intestinal mucosa which may have potential usefulness. We aimed to evaluate the additional utility of these two fecal biomarkers for IBD diagnosis, activity, and prediction of infliximab response over FC alone.

DOI: 10.2147/JIR.S342846

PMID: 34880643.0

Full Article: https://doi.org/10.2147/JIR.S342846

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Table 1Demographic and Clinical Characteristics of the Study Population in Group 1

Table 2Demographic and Clinical Characteristics of IBD Patients in Group 2

, and IBD. (C) ROC curves of fecal OSM and FC in discriminating IBD from controls. Fecal OSM (D) and FC levels (E) in CD and UC. (F) The ROC curve of fecal OS

HBI or pMS. The expression of FC in CD (D), UC (E), and combined CD and UC patients (F) classified by HBI or pMS. The expression of fecal OSM (G) and FC (H)

C expression (B) with SES-CD. Spearman correlation of fecal OSM (C) and FC expression (D) with MES. Fecal OSM (E) and FC levels (F) in IBD patients with and w

week 28. (CandD) ROC curves of fecal and blood biomarkers to predict therapeutic response at week 28. Baseline fecal OSM (E) and FC levels (F) in predicting the

Title: Colonic oncostatin M expression evaluated by immunohistochemistry and infliximab therapy outcome in corticosteroid-refractory acute severe ulcerative colitis.

Publication Date: Jul 2022

Authors: O'Connell, Jim; Doherty, Jayne; Buckley, Amy; Cormican, David; Dunne, Cara; Hartery, Karen; Larkin, John; MacCarthy, Finbar; McCormick, Paul; McKiernan, Susan; Mehigan, Brian; Muldoon, Cian; Ryan, Ciara; O'Sullivan, Jacintha; Kevans, David

Journal: Intestinal research

Abstract: nan

DOI: 10.5217/ir.2021.00073

PMID: 35263959.0

Full Article: https://doi.org/10.5217/ir.2021.00073

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Elevated Pretreatment Plasma Oncostatin M Is Associated With Poor Biochemical Response to Infliximab.

Publication Date: Oct 2019

Authors: Minar, Phillip; Lehn, Christina; Tsai, Yi-Ting; Jackson, Kimberly; Rosen, Michael J; Denson, Lee A

Journal: Crohn's & colitis 360

Abstract: We hypothesized that elevations of plasma Oncostatin M (OSM) would be associated with infliximab nonresponse.

DOI: 10.1093/crocol/otz026

PMID: 31667468.0

Full Article: https://doi.org/10.1093/crocol/otz026

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Mucosal IL23A expression predicts the response to Ustekinumab in inflammatory bowel disease.

Publication Date: Nov 2021

Authors: Nishioka, Kei; Ogino, Haruei; Chinen, Takatoshi; Ihara, Eikichi; Tanaka, Yoshimasa; Nakamura, Kazuhiko; Ogawa, Yoshihiro

Journal: Journal of gastroenterology

Abstract: Biologics against tumor necrosis factor-α (TNF) and the p40 subunit of interleukin (IL)-12 and IL-23 are increasingly used in inflammatory bowel disease (IBD) treatment. However, information on response prediction to these agents is limited. Thus, we aimed to identify factors for IBD treatment response prediction.

DOI: 10.1007/s00535-021-01819-7

PMID: 34448069.0

Full Article: https://doi.org/10.1007/s00535-021-01819-7

Methods:

One specimen per subject was obtained from the most inflamed areas that exhibited edematous, friable granular mucosae, marked erythema, no vascular patterns, erosions, spontaneous bleeding, or ulcer formation. Briefly, the total RNA was extracted from whole biopsy specimens using TRIzol reagent (Thermo Fisher Scientific). One microgram of RNA was reverse-transcribed using the QuantiTect Reverse Transcription kit (QIAGEN, Düsseldorf, Germany) to obtain cDNA. Spearman's correlation analysis was performed to evaluate correlations between the expression levels of two genes.

Results:

Thirty-three subjects were analyzed (22 UC, 11 CD); all of them suffered from moderate to severe disease with active mucosal inflammation. OSM oncostatin M, OSMR oncostatin M receptor, TNF tumor necrosis factor, IFN interferon, IL interleukin, GATA3 GATA binding protein 3, RORC RAR-related orphan receptor C, TGFB1 transforming growth factor β1, GAPDH glyceraldehyde-3-phosphate dehydrogenase, UC ulcerative colitisFull size imageAs subjects who had been previously treated with anti-TNF tended to be more resistant to another anti-TNF agent, we performed the same analysis including only biologic-naive subjects (Supplementary Fig. 2). Among the 18 genes analyzed, a higher expression of IL23A was most strongly associated with an improved response to UST. Performing statistical analysis separately for CD and especially UC was difficult due to the small number of subjects.

Discussion:

DiscussionAs biologics were relatively recently introduced for IBD, knowledge on drug response prediction is insufficient [11]. This suggests that Th17/Th1 immune responses in these subjects might be driven by factors independent of IL-23 and IL-12. 10 and 11).Our results suggest that the responses to biologics in IBD subjects can be predicted by performing mucosal qPCR analyses. However, the analysis requires endoscopy, biopsy, RNA extraction, and reverse transcription, which might hamper routine clinical use.

Conclusion:

None available

Title: High oncostatin M predicts lack of clinical remission for patients with inflammatory bowel disease on tumor necrosis factor α antagonists.

Publication Date: Jan 2022

Authors: Guo, Angela; Ross, Cameron; Chande, Nilesh; Gregor, Jamie; Ponich, Terry; Khanna, Reena; Sey, Michael; Beaton, Melanie; Yan, Brian; Kim, Richard B; Wilson, Aze

Journal: Scientific reports

Abstract: The interleukin-6 family cytokine, oncostatin-M (OSM) has been associated with response to tumor necrosis factor-α antagonists (anti-TNFs) in small cohorts of patients with inflammatory bowel disease (IBD). We aimed to evaluate the association between plasma OSM concentrations and response to anti-TNFs (infliximab and adalimumab) in both ulcerative colitis (UC) and Crohn's disease (CD). A retrospective cohort study was conducted in patients with IBD with a history of anti-TNF exposure. Blood samples, collected prior to anti-TNF exposure, were analyzed by enzyme-linked immunosorbent assay for the presence and quantity of OSM. Clinical remission was assessed at 1-year post anti-TNF exposure in addition to the occurrence of surgery, hospitalization, corticosteroid use, and adverse drug events. Lastly the threshold OSM plasma concentration associated with anti-TNF non-response was assessed by receiver operator characteristic (ROC) curve analysis. Patients with IBD (CD, n = 82; UC, n = 40) were assessed. In both UC and CD, mean pre-treatment OSM concentrations were significantly lower in those who achieved clinical remission at 1-year ($p < 0.0001$). A threshold plasma OSM concentration of 168.7 pg/ml and 233.6 pg/ml respectively separated those who achieved clinical remission at 1-year on an anti-TNF from those who did not in CD and UC respectively (CD: area under the receiver operator characteristic curve, AUROC = 0.880, 95% CI 0.79-0.96; UC: AUROC = 0.938, 95% CI 0.87-1.00). High OSM concentrations were associated with anti-TNF discontinuation and use of rescue steroids in CD and UC. High pre-treatment OSM concentrations identify IBD patients at-risk of anti-TNF non-response at 1-year as well as other deleterious clinical outcomes.

DOI: 10.1038/s41598-022-05208-9

PMID: 35075155.0

Full Article: https://doi.org/10.1038/s41598-022-05208-9

Methods:

MethodsParticipants and proceduresA retrospective cohort study was carried out in participants with either CD or UC. Participants were excluded if they were younger than 18 years of age, had prior exposure to an anti-TNF prior to the defined study period, had a sub-therapeutic infliximab or adalimumab concentration in the presence or absence of anti-drug antibodies during the follow-up period, or if there were missing data pertaining to their clinical response to the anti-TNF agent.The baseline data collected on all participants included age, sex, weight, disease type (CD or UC), smoking history, disease duration (years since initial diagnosis to time of blood sample collection), disease location, anti-TNF received (infliximab or adalimumab) and all other IBD drug exposures.Following inclusion, participants were monitored for up to one year following the commencement of the anti-TNF or until discontinuation of anti-TNF therapy. The lower limit of detection was 1.37 pg/mL with concentrations below this threshold reported as a 0 value. A p value < 0.05 was considered significant.Descriptive statistics were used to summarize data for all participants divided by the presence or absence of clinical remission at 1-year.

Results:

Of these individuals, 122 participants were included in the final analyses (CD, n = 82; UC, n = 40).Figure 1Study flowchart.Full size imageTable 1 Demographic characteristics by disease type.Full size tableTable 2 Demographic characteristics by disease activity.Full size tableThe baseline characteristics were similar for those achieving clinical remission on an anti-TNF versus those who did not with only a few exceptions (Table 2). Overall, mean plasma OSM concentrations were significantly higher in patients with CD or UC who did not achieve remission 1-year after receiving an anti-TNF (Fig. 2). Median values (thick horizontal line), 25th and 75th percentile values (box outline), 5–95% confidence intervals (whiskers); *p < 0.0001.Full size imageFor participants with CD, a plasma OSM concentration of 168.7 pg/ml (area under the receiver operator characteristic curve, AUROC = 0.880, 95% CI 0.79–0.96) separated those who achieved clinical remission at 1-year on an anti-TNF from those who did not with a sensitivity (95% CI) of 76% (58–88%) and specificity of 91% (80–96%) (Fig. 3A). Oncostatin-M, OSM; Crohn's disease, CD; ulcerative colitis, UC; area under the curve (AUC); confidence interval (CI).Full size imageFurthermore, in UC, participants with a plasma OSM concentration above the threshold concentration of 233.6 pg/ml were more likely to discontinue their anti-TNF prior to 1-year (OR 10.71, 95% CI 1.81–56.7, p = 0.0085) and require rescue corticosteroids (OR 6.71, 95% CI 1.58–24.9, p = 0.02).

Discussion:

DiscussionOur study demonstrates that high plasma concentrations of the IL-6 family cytokine, OSM are associated with poor therapeutic outcomes to anti-TNF therapy in both CD and UC. (2020) found that pre-treatment serum OSM concentrations were significantly higher in CD patients who did not achieve clinical or endoscopic remission at 1-year following treatment with infliximab16,17. Conversely, rather than acting synergistically, OSM and TNF-α cytokines may represent the activation of independent pro-inflammatory pathways. Interestingly, a higher proportion of participants went on to surgery in the high OSM groups; however, this did not achieve statistical significance.

Conclusion:

ConclusionUltimately, plasma OSM concentrations were significantly higher in patients who did not achieve remission 1-year after initiating anti-TNF therapy. High OSM concentrations were associated with anti-TNF discontinuation and increased use of corticosteroids in both UC and CD. These findings provide further support that OSM may represent an important biomarker of anti-TNF response. Further study is needed in larger, prospective cohorts and the mechanistic underpinnings linking OSM and anti-TNF response need to be defined.

Title: Prediction of early clinical response in patients receiving tofacitinib in the OCTAVE Induction 1 and 2 studies

Publication Date: nan

Authors: Lees C.W.; Deuring J.J.; Chiorean M.; Daperno M.; Bonfanti G.; Germino R.; Brown P.B.; Modesto I.; Edwards R.A.

Journal: nan

Abstract: Introduction: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). Outcome prediction based on early treatment response, along with clinical and laboratory variables, would be very useful for clinical practice. The aim of this study was to determine early variables predictive of responder status in patients with UC treated with tofacitinib. Method(s): Data were collected from patients treated with tofacitinib 10 mg twice daily in the OCTAVE Induction 1 and 2 studies (NCT01465763 and NCT01458951). Logistic regression and random forest analyses were performed to determine the power of clinical and/or laboratory variables to predict 2- and 3-point partial Mayo score responder status of patients at Weeks 4 or 8 after baseline. Result(s): From a complete list of variables measured in OCTAVE Induction 1 and 2, analyses identified partial Mayo score, partial Mayo subscore (stool frequency, rectal bleeding, and Physician Global Assessment), cholesterol level, and C-reactive protein level as sufficient variables to predict responder status. Using these variables at baseline and Week 2 predicted responder status at Week 4 with 84-87% accuracy and Week 8 with 74-79% accuracy. Variables at baseline, Weeks 2 and 4 could predict responder status at Week 8 with 85-87% accuracy. Conclusion(s): Using a limited set of time-dependent variables, statistical and machine learning models enabled early and clinically meaningful predictions of tofacitinib treatment outcomes in patients with moderately to severely active UC.Copyright © The Author(s), 2021.

DOI: /10.1177/17562848211054710

PMID: nan

Full Article: https://doi.org//10.1177/17562848211054710

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Evaluation of the relationship between fecal calprotectin concentrations and clinical and endoscopic outcome measures in a phase 2 study of tofacitinib, an oral janus kinase inhibitor, in active ulcerative colitis

Publication Date: nan

Authors: Sandborn W.; Panes J.; Zhang H.; Yu D.; Niezychowski W.; Su C.

Journal: nan

Abstract: Background Accurate biomarkers of disease activity and therapeutic response can be valuable in clinical practice and clinical trials. In this study the relationship between fecal calprotectin (FCP) and clinical/endoscopic outcomes based on Mayo score (MS) were assessed after 8 weeks of treatment with tofacitinib in moderate-to-severe ulcerative colitis. Methods In a multicenter, double-blind Phase 2 trial, 194 patients were randomized to tofacitinib 0.5, 3, 10, or 15 mg BID or placebo. Primary endpoint was clinical response (CR; Mayo score decrease >=3 points and >=30%; rectal bleeding subscore decrease >=1 point or absolute subscore <=1) at Week 8. Secondary endpoints included clinical remission (CRem; Mayo score <=2 and no subscore .1), endoscopic remission (ERem; endoscopic subscore of 0), and mucosal healing (MH; endoscopic subscore 0 or 1; post-hoc). Post-hoc analyses including receiver operating characteristic (ROC) analysis evaluated the relationship of FCP concentrations (conc; mg/kg) vs clinical/endoscopic outcomes at Week 8. Results Median Week 8 FCP concentrations were significantly lower (p<0.001) in patients achieving clinical responses vs patients with no response: 156 vs 725 (CR), 64 vs 617 (CRem), 44 vs 489 (ER), and 127 vs 753 (MH) mg/kg. Pts with lower Week 8 FCP concentrations were more likely to achieve Week 8 efficacy endpoints (Table 1). Area under the curve for ROC models with FCP were: CRem 0.80; ERem 0.81; MH 0.78. An FCP cut off of approx. 150 mg/kg achieved the highest summation of specificity (spec) and sensitivity (sens) for CRem (spec 0.79, sens 0.68, kappa 0.44) and ERem (spec 0.75, sens 0.79, kappa 0.38). Table 2 shows the proportion of patients achieving CRem and/or FCP,150 mg/kg at Week 8 based on treatment assignment. Safety outcomes were consistent with the known profile of tofacitinib. Conclusion Although a similar treatment effect was seen with an FCP cut off of 150 mg/kg, FCP levels had only fair to good accuracy in classifying patients' clinical or endoscopic outcomes. These data show limitations to the use of FCP in lieu of MS-based outcome measures in clinical trials. (Table Presented).

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Predicting Outcome in Acute Severe Colitis-Controversies in Clinical Practice in 2021.

Publication Date: Jul 2021

Authors: Gupta, Vipin; Mohsen, Waled; Chapman, Thomas P; Satsangi, Jack

Journal: Journal of Crohn's & colitis

Abstract: Acute severe ulcerative colitis [ASUC] remains a common medical emergency, with 25% of patients with ulcerative colitis experiencing at least one event in their disease course. Despite advances in medical therapy, ASUC continues to be associated with considerable morbidity and mortality, with up to 30% of patients requiring colectomy during initial admission. Our aim was to review the current controversies and recent progress in risk stratification, prediction of outcome, and personalisation of care in ASUC. We re-assess the use of Truelove and Witts' criteria, serum biomarkers, and the use of composite clinical indices in current clinical practice. We explore the potential for endoscopic prediction using defined validated indices for accurate and early prognostication, and the need to define outcome. We also consider the impact of the current COVID-19 pandemic. Finally, we discuss the current research agenda, including the application of new and emerging biomarkers coupled with multi-omics and the implications in management and optimisation of outcome. Research priorities for the prediction of outcome in acute severe colitis include the following. 1. Development of an accurate admission score to guide early medical rescue therapy or colectomy. 2. Utility of point-of-care faecal calprotectin, with determination of optimal cut-off values. 3. Role of serum and faecal infliximab levels to both predict outcome and guide accelerated infliximab dosing. 4. Role of novel biomarkers, including serum calprotectin, in predicting response to corticosteroids or rescue therapy. 5. Specific predictors of response to ciclosporin and infliximab to allow rationalisation of drug use. 6. Utility of validated endoscopic scores. 7. Utility of radiological assessment beyond use of plain abdominal X-ray. 8. The use of multiomics and machine learning to predict risk of Acute Severe Colitis in patients with Ulcerative Colitis.

DOI: 10.1093/ecco-jcc/jjaa265

PMID: 33388777.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjaa265

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Non-invasive predictors of maintaining remission in patients with moderately to severely active ulcerative colitis treated with tofacitinib who dose-reduced from tofacitinib 10 mg twice daily to 5 mg twice daily: 6-month data from the double-blind, randomised riveting study

Publication Date: nan

Authors: D'Haens G.R.; Dubinsky M.C.; Regueiro M.; Santana G.O.; Torres J.; Kulisek N.; Gardiner S.; Mundayat R.; Paulissen J.; Lawendy N.; Su C.; Modesto I.; Sandborn W.J.

Journal: nan

Abstract: Introduction: Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of ulcerative colitis (UC). RIVETING (NCT03281304) is an ongoing, double-blind, randomised, parallel-group study designed to evaluate the efficacy and safety of dose reduction to tofacitinib 5 mg twice daily (BID) vs remaining on 10 mg BID in patients with UC in stable remission on tofacitinib 10 mg BID maintenance therapy. Eligible patients had received tofacitinib 10 mg BID for >=2 consecutive years in an open-label, long-term tension study (NCT01470612), and had been in stable remission for >=6 months and corticosteroid-free for >=4 weeks prior to enrolment.1 Aims & Methods: We aimed to determine if faecal calprotectin (FCP), C-reactive protein (CRP) or partial Mayo score (PMS) can be used as predictors of maintaining remission after dose reduction. Median FCP levels, median CRP levels and mean PMS at baseline, Month 1 and Month 3 were analysed by efficacy endpoint status at Month 6 in patients who dose-reduced to tofacitinib 5 mg BID. The proportions of patients who achieved efficacy endpoints (modified Mayo score remission, remission, modified PMS remission, PMS remission, endoscopic improvement and clinical response) at Month 6 were analysed by their stool frequency (SF) subscore, rectal bleeding (RB) subscore and modified PMS at Months 1 and Results: Seventy patients were randomised to receive tofacitinib 5 mg BID in RIVETING. For patients in modified Mayo score remission at Month 6, PMS was relatively stable over time (mean [standard deviation]: baseline 0.3 [0.5]; Month 1 0.4 [0.7]; Month 3 0.4 [0.8]), whereas PMS increased from baseline to Month 1 and Month 3 in patients not in modified Mayo score remission at Month 6 (0.6 [0.6]; 1.1 [1.3]; 1.3 [1.3]). This trend was also observed for other efficacy endpoints. Median FCP levels did not change from baseline to Month 3 in patients in modified Mayo score remission at Month 6 (median change from baseline [interquartile range] 0.0 [-48.5- 40.5]), whereas median FCP levels increased in patients not in modified Mayo score remission at Month 6 (30.0 [-53.5-429.0]). Except for remission, this trend was also observed for other efficacy endpoints. No trend was observed in median CRP levels over time. A numerically higher proportion of patients with a SF subscore, RB subscore or modified PMS of 0 at Month 1 or Month 3 achieved most efficacy endpoints at Month 6, compared with patients with respective subscores >0 at Months 1 or 3 (Table). Conclusion(s): These analyses suggest that in patients previously in stable remission, an increase in FCP levels at Month 3, or PMS as early as Month 1, may help predict loss of efficacy after dose-reduction from tofacitinib 10 to 5 mg BID. A SF subscore, RB subscore or modified PMS of 0 at either Month 1 or Month 3 could indicate the likelihood of maintaining efficacy with tofacitinib 5 mg BID at Month 6. These analyses are post hoc, exploratory and limited by the small sample size.

DOI: /10.1002/ueg2.12144

PMID: nan

Full Article: https://doi.org//10.1002/ueg2.12144

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Prediction of early clinical response in patients receiving tofacitinib in the OCTAVE Induction 1 and 2 studies.

Publication Date: 2021

Authors: Lees, Charlie W; Deuring, J Jasper; Chiorean, Michael; Daperno, Marco; Bonfanti, Gianluca; Germino, Rebecca; Brown, Pritha Bhadra; Modesto, Irene; Edwards, Roger A

Journal: Therapeutic advances in gastroenterology

Abstract: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). Outcome prediction based on early treatment response, along with clinical and laboratory variables, would be very useful for clinical practice. The aim of this study was to determine early variables predictive of responder status in patients with UC treated with tofacitinib.

DOI: 10.1177/17562848211054710

PMID: 35154388.0

Full Article: https://doi.org/10.1177/17562848211054710

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Multiple Cytokine Profiling: A New Model to Predict Response to Tumor Necrosis Factor Antagonists in Ulcerative Colitis Patients.

Publication Date: Feb 2019

Authors: Obraztsov, Igor Vladimirovich; Shirokikh, Katerina Evgenievna; Obraztsova, Olga Isaakovna; Shapina, Marina Vladimirovna; Wang, Ming-Hsi; Khalif, Igor Lvovich

Journal: Inflammatory bowel diseases

Abstract: Ulcerative colitis (UC) is a form of inflammatory bowel disease, and antibodies against tumor necrosis factor (anti-TNF) are used for treatment. Many patients are refractory or lose response to anti-TNF, and predicting response would be an extremely valuable clinical tool. Unlike most biomarkers, cytokines directly mediate inflammation, and their measurement may predict the likelihood of response or no response.

DOI: 10.1093/ibd/izy358

PMID: 30544140.0

Full Article: https://doi.org/10.1093/ibd/izy358

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Association between Ustekinumab Trough Levels, Serum IL-22, and Oncostatin M Levels and Clinical and Biochemical Outcomes in Patients with Crohn's Disease.

Publication Date: Mar 2024

Authors: Bertin, Luisa; Barberio, Brigida; Gubbiotti, Alessandro; Bertani, Lorenzo; Costa, Francesco; Ceccarelli, Linda; Visaggi, Pierfrancesco; Bodini, Giorgia; Pasta, Andrea; Sablich, Renato; Urbano, Maria Teresa; Ferronato, Antonio; Buda, Andrea; De Bona, Manuela; Del Corso, Giulio; Massano, Alessandro; Angriman, Imerio; Scarpa, Marco; Zingone, Fabiana; Savarino, Edoardo Vincenzo

Journal: Journal of clinical medicine

Abstract: nan

DOI: 10.3390/jcm13061539

PMID: 38541765.0

Full Article: https://doi.org/10.3390/jcm13061539

Methods:

None available

Results:

This trend persisted through week 52, with 47 participants (69.1%) maintaining biochemical remission according to PCR levels (p = 0.017). At the fourth SC dose, patients in steroid-free clinical remission had higher mean TLs (4.08 μg/mL ± 3.46) than those who were not (2.71 μg/mL ± 2.51, p = 0.367). No notable differences in TLs were observed between patients experiencing AEs and those who did not by the fourth SC dose. TLs at the fourth SC dose were not influenced by interval dosing, and there were no significant differences in TLs among patients who underwent resection surgery during the study period.

Discussion:

IL-22 is a member of the IL-10 cytokine family, primarily from several immune cell types, with Th1 and Th22 cells being its main contributors [46]. Analysis of drug concentrations derived from pivotal induction UNITI clinical trials revealed that a steady state had been achieved by the second SC maintenance dose [68]. Real-world studies have indicated a correlation between UST levels and clinical outcome measures [69,70,71,72,73,74,75], endoscopic outcomes [70,76,77,78,79], or biochemical ones [72,73,74,76,80,81,82]. It is worth mentioning that subsequent observational studies have individuated higher optimal TL concentrations than those identified in RCTs.

Conclusion:

None available

		n= 84
Age at diagnosis (years)	Median (IQR)	27 (19–40)
Age at inclusion (years)	Mean (SD)	43 (14)

Female	n(%)	32 (38.1%)
Disease duration (years)	Median (IQR)	12 (7–21)
Follow-up (months)	Median (IQR)	15 (13–16)
Active smoking	n(%)	10 (11.9%)
Disease activity		
SES-CD score	Median (IQR)	7 (3.00–13.00)
HBI score	Median (IQR)	5 (2–9)
CRP above the upper normal limit	n(%)	38 (45.2%)
Faecal calprotectin (mg/kg)	Median (IQR)	1000 (452–1900)
Age at onset		
Below 16 years	n(%)	15 (17.8%)
Between 16 and 40 years	n(%)	47 (55.9%)
Above 40 years	n(%)	22 (26.2%)
Disease location		
Ileum	n(%)	17 (20.2%)
Colon	n(%)	18 (21.4%)
Ileocolonic	n(%)	40 (47.6%)
Additional upper GI	n(%)	9 (10.7%)
Disease behaviour		
Inflammatory	n(%)	22 (26.2%)
Stricturing	n(%)	31 (36.9%)
Penetrating	n(%)	33 (39.3%)
Perianal disease	n(%)	23 (27.4%)
Extraintestinal manifestations	n(%)	42 (50%)
Prior intestinal resection	n(%)	46 (54.8%)
Prior perianal fistula surgical intervention	n(%)	23 (27.4%)
Prior treatment		
1 anti-TNF	n(%)	81 (96.4%)
≥2 anti-TNF	n(%)	58 (69.0%)
Vedolizumab	n(%)	42 (50.0%)
Both vedolizumab and anti-TNF	n(%)	39 (46.4%)
Concomitant treatment		
Oral prednisone	n(%)	19 (22.6%)
Thiopurine	n(%)	8 (9.5%)
Methotrexate	n(%)	2 (2.3%)

Title: Correlation of a multi-biomarker disease activity (vectraTM DA) score with clinical disease activity and its components with radiographic progression in rheumatoid arthritis patients treated with tofacitinib

Publication Date: nan

Authors: Yamaoka K.; Kubo S.; Sonomoto K.; Hirata S.; Cavet G.; Bolce R.; Rowe M.W.; Chernoff D.; Defranoux N.; Saito K.; Tanaka Y.

Journal: nan

Abstract: Background/Purpose: A multi-biomarker disease activity (MBDA) score has been developed for evaluation of disease activity of rheumatoid arthritis (RA) to complement clinical assessment and to provide information about underlying disease processes. We have reported the usefulness of MBDA as clinical measures of disease activity. However, relation of MBDA score with clinical features in RA patients treated with a JAK-inhibitor tofacitinib is unknown. Method(s): DAS28(ESR), SDAI, MBDA and modified total sharp score (mTSS) were evaluated at baseline and 1 year in 37 patients (31 women, mean age: 54.6 years, mean disease duration: 78.9 months) enrolled in phase II and III clinical trials of tofacitinib. Patients were randomized to different doses of tofacitinib or placebo for the first 3 to 6 months (8 patients with dosed tofacitinib as monotherapy and 29 patients with concomitant MTX). All patients were treated with tofacitinib 5 mg or 10 mg BID after 6 months. MBDA combines 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) in a pre-specified algorithm resulting in a score between 1 and 100. Result(s): (1) Disease activity significantly improved: MBDA, 60.8 to 28.5 as well as SDAI 37.7 to 6.2, DAS28-ESR 6.4 to 3.0, HAQ-DI 1.4 to 0.8,. HAQ-DI >=0.5 was achieved in 19 patients (51%). Yearly progression of mTSS (DELTAmTSS) significantly decreased from 14.7 to 0.9 and 21 patients (56%) achieved structural remission. (2) Significant correlation was observed between yearly <=MBDA score and DELTADAS28(ESR), DELTASDAI or =CDAI (p<0.01). (3) When clinical remission was determined as MBDA <=25, remission rate was similar among measurements. (SDAI 37.8%, DAS28-ESR 35.1%, MBDA 40.5%) (4) No correlation was observed between DELTAmTSS and DELTAMBDA, DELTADAS28(ESR), DELTASDAI or =CDAI. (5) The proportion of radiographic progressors in remission was similar among different measurements. (38.5% (5/13) of DAS28-ESR remission, 35.7% (5/14) of SDAI remission and 33.3% (5/15) of MBDA remission) (6) IL-6 decreased from 163.0pg/ml to 25.1pg/ml and MMP-3 decreased from 159.1ng/ml to 39.5ng/ml. The measures of IL-6 and MMP-3 at 52 weeks significantly correlated with change of mTSS (69.1 to 70.0). (7) When patients were separated into 2 groups with median value of serum IL-6 (9.0ng/ml) at 52 weeks, 78% achieved structural remission in low concentration group, whereas 38% was achievable in high concentration group. Conclusion(s): MBDA significantly correlated with cpnventional composite measures of disease activity and equally contributed to remission rate in patients with RA. Although DELTAMBDA did not correlate with DELTAmTSS in this study size, concentration of IL-6 and MMP-3 at 52 weeks correlated with change of mTSS. These results indicate that tofacitinib acts through the inhibition of IL-6 and is able to prevent bone destruction. Our results further support the usefulness of MBDA as an additional composite measure for RA disease activity.

DOI: /10.1002/art.37735

PMID: nan

Full Article: https://doi.org//10.1002/art.37735

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Fecal calprotectin is a reliable marker of endoscopic response to vedolizumab therapy: A simple algorithm for clinical practice.

Publication Date: Nov 2020

Authors: Pauwels, Renske Wilhelmina Maria; de Vries, Annemarie Charlotte; van der Woude, Christien Janneke

Journal: Journal of gastroenterology and hepatology

Abstract: The association of fecal calprotectin (FC) and endoscopic response in inflammatory bowel disease patients during vedolizumab (VDZ) treatment is largely unknown. The aim of this study is to assess the diagnostic value of FC to predict endoscopic response.

DOI: 10.1111/jgh.15063

PMID: 32291796.0

Full Article: https://doi.org/10.1111/jgh.15063

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Interrogating host immunity to predict treatment response in inflammatory bowel disease.

Publication Date: Jan 2020

Authors: Digby-Bell, Jonathan L; Atreya, Raja; Monteleone, Giovanni; Powell, Nick

Journal: Nature reviews. Gastroenterology & hepatology

Abstract: IBD treatment is undergoing a transformation with an expanding repertoire of drugs targeting different aspects of the immune response. Three novel classes of drugs have emerged in the past decade that target leukocyte trafficking to the gut (vedolizumab), neutralize key cytokines with antibodies (ustekinumab) and inhibit cytokine signalling pathways (tofacitinib). In advanced development are other drugs for IBD, including therapies targeting other cytokines such as IL-23 and IL-6. However, all agents tested so far are hampered by primary and secondary loss of response, so it is desirable to develop personalized strategies to identify which patients should be treated with which drugs. Stratification of patients with IBD by clinical parameters alone lacks sensitivity, and alternative modalities are now needed to deliver precision medicine in IBD. High-resolution profiling of immune response networks in individual patients is a promising approach and different technical platforms, including in vivo real-time molecular endoscopy, tissue transcriptomics and germline genetics, are promising tools to help predict responses to specific therapies. However, important challenges remain regarding the clinical utility of these technologies, including their scalability and accessibility. This Review focuses on unravelling some of the complexity of mucosal immune responses in IBD pathogenesis and how current and emerging analytical platforms might be harnessed to effectively stratify and individualise IBD therapy.

DOI: 10.1038/s41575-019-0228-5

PMID: 31767987.0

Full Article: https://doi.org/10.1038/s41575-019-0228-5

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

ConclusionsIBD therapies are undergoing an exciting revolution with new biological agents and small-molecule therapies targeting cytokines, cytokine signalling and trafficking of leukocytes emerging into clinical practice. Promising studies have demonstrated differential expression of key genes that can be harnessed as predictive biomarkers to discriminate likely responders and non-responders to IBD therapies. It is foreseeable that a dedicated colonic biopsy sample for RNA analysis will be taken at the time of colonoscopy in patients with newly diagnosed IBD as well as those with active disease who require a change in therapy, as it could provide in-depth insights into immune biology and inform clinical decisions. Time will tell if other immune profiling approaches such as measurement of serum cytokines or mucosal immune cell phenotype or microbiota analysis will prove to be useful biomarker strategies.

Title: Robust clinical outcome prediction based on Bayesian analysis of transcriptional profiles and prior causal networks.

Publication Date: Jun 2014

Authors: Zarringhalam, Kourosh; Enayetallah, Ahmed; Reddy, Padmalatha; Ziemek, Daniel

Journal: Bioinformatics (Oxford, England)

Abstract: Understanding and predicting an individual's response in a clinical trial is the key to better treatments and cost-: effective medicine. Over the coming years, more and more large-scale omics datasets will become available to characterize patients with complex and heterogeneous diseases at a molecular level. Unfortunately, genetic, phenotypical and environmental variation is much higher in a human trial population than currently modeled or measured in most animal studies. In our experience, this high variability can lead to failure of trained predictors in independent studies and undermines the credibility and utility of promising high-dimensional datasets.

DOI: 10.1093/bioinformatics/btu272

PMID: 24932007.0

Full Article: https://doi.org/10.1093/bioinformatics/btu272

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: The predictive role of gut microbiota in treatment response to vedolizumab and ustekinumab in inflammatory bowel disease

Publication Date: nan

Authors: Caenepeel C.; Vieira-Silva S.; Verstockt B.; Ferrante M.; Raes J.; Vermeire S.

Journal: nan

Abstract: Background: The faecal microbiota is evolving as a useful predictive and diagnostic biomarker for IBD in the development of personalised medicine. We here investigated whether the faecal microbiota aids in predicting therapeutic response to vedolizumab (VDZ) or ustekinumab (UST) in Crohn's disease (CD) and ulcerative colitis (UC). Method(s): Faecal samples of 116 patients with IBD, treated with UST (n = 68 CD) or VDZ (n = 30 for CD, 18 for UC) with endoscopic active disease were collected prior to biological therapy. Quantitative microbiota phylogenetic profiling was conducted by combining 16S rRNA gene sequencing and microbial loads determination by flow cytometry. Endoscopic response in the UST cohort was defined as a 50% decrease in SES-CD score at Week 24. Remission in the VDZ cohort was defined as an endoscopic Mayo-subscore of <=1 at Week 14 in UC and absence of endoscopic ulcera at Week 24 in CD. Multi-variate hyperbolic tangent neural network models (JMP) were trained to predict treatment response based on features describing the baseline faecal microbiota, clinical data (age, sex, BMI, diagnosis, disease duration and smoking) and biomarkers (CRP, albumin, haemoglobin and faecal calprotectin) or the combination. Microbiota features comprised enterotypes and quantitative abundances of taxa significantly ($p < 0.1$) correlated with outcome. The cohorts were split into training (2/3) and validation sets (1/3). Result(s): Ten (14.7%) UST and 27 (56.2%) VDZ patients showed endoscopic response (UST) or remission (VDZ). 13 genera correlated with treatment outcome in the VDZ cohort and 14 in the UST cohort, with 3 overlapping. Neural networks were trained to predict treatment response in VDZ and UST (Figure 1) , based on clinical features and biomarkers, microbiota features, or both. Figure 1: Receiver-operating characteristic curves of the different neural network trained for treatment response prediction for VDZ and UST For VDZ treatment response prediction, all models had reliable training (AUC=[0.71-0.87]; sensitivity=[0.62-0.88], specificity=[0.55-0.85]), but the combined model had the best validation performance (misclassification rate=31%, N = 17). Similarly, UST response prediction was best with the combined model(training AUC=0.86, sensitivity=0.88, specificity=0.33, with a validation misclassification rate of 4% (N = 23). Conclusion(s): Our analyses do show that quantitative faecal microbiota profiling is helpful in predicting therapeutic outcome and provides valuable additional information beyond clinical features and biomarkers. Nevertheless, these predictive models were trained on still relatively small cohorts, and therefore further validation in preferably large prospective randomised cohorts is needed.

DOI: /10.1093/ecco-jcc/jjy222.960

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjy222.960

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: TREATMENT RESPONSE TO USTEKINUMAB AND VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE: THE PREDICTIVE ROLE OF GUT MICROBIOTA

Publication Date: nan

Authors: Caenepeel C.; Vieira-Silva S.; Vazquez-Castellanos J.F.; Verstockt B.; Ferrante M.; Raes J.; Vermeire S.

Journal: nan

Abstract: INTRODUCTION: The past decade has highlighted the central role of the gut microbiota in inflammatory bowel disease (IBD). The fecal microbiota is evolving as a useful predictive and diagnostic biomarker in the development of personalized medicine. We here investigated if the faecal microbiota aids in predicting therapeutic response to vedolizumab (VDZ) or ustekinumab (UST) in Crohn's disease (CD) and ulcerative colitis (UC). METHOD(S): Fecal samples of 116 patients with IBD, treated with UST (n=68 CD) or VDZ (n=30 for CD and 18 for UC) with endoscopic active disease were collected prior to biological therapy. Quantitative microbiota phylogenetic profiling was conducted by combining 16S rRNA gene sequencing and microbial loads determination using flow cytometry. Endoscopic response in the UST cohort was defined as a 50% decrease in SES-CD score at week 24. Remission in the VDZ cohort was defined as an endoscopic Mayo-subscore of 0-1 at week 14 in UC and absence of endoscopic ulcerations endoscopy at week 24 in CD. Multivariate hyperbolic tangent neural network models (JMP) were trained to predict treatment response based on features describing the baseline fecal microbiota, clinical data (age, sex, BMI, diagnosis, disease duration and smoking) and biomarkers (C-reactive protein, albumin, hemoglobin and faecal calprotectin) or the combination. The cohorts were split in a training (2/3) and validation set (1/3). Fecal microbiota features comprised the enterotypes and quantitative abundance of taxa significantly (P<0.1) correlated with outcome. Result(s): Ten (14.7%) UST and 27 (56.2%) VDZ patients showed endoscopic response (UST) or remission (VDZ). 13 genera correlated with treatment outcome in the VDZ cohort and 14 in the UST cohort, with 3 genera overlapping. Neural networks were trained to predict treatment response in VDZ and UST on 2/3 of the cohorts, based on baseline clinical features and biomarkers, baseline microbiota features, or both. For VDZ treatment response prediction, all models had reliable training (training: AUC=[0.71-0.87]; sensitivity=[0.62-0.88], specificity=[0.55- 0.85), but the combined model had the best validation performance (N=17; misclassification rate=31%). UST response prediction was not very reliably trained on microbiota features alone (AUC<0.70) and was best predicted by the combined features (training AUC=0.86, sensitivity=0.88, specificity=0.33, with a validation misclassification rate of 4% (compared to 13% for the clinical + biomarkers model). Conclusion(s): Our analyses do show that quantitative faecal microbiota profiling is helpful in predicting therapeutic outcome and provides valuable additional information beyond clinical features and biomarkers. Nevertheless, these predictive models were trained on still relatively small cohorts, and therefore further validation in preferably large prospective randomized cohorts is needed. [Figure presented]

DOI: /10.1016/S0016-5085%2819%2939775-6

PMID: nan

Full Article: https://doi.org//10.1016/S0016-5085%2819%2939775-6

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Gut Microbiota Offers Universal Biomarkers across Ethnicity in Inflammatory Bowel Disease Diagnosis and Infliximab Response Prediction

Publication Date: 2018

Authors: Zhou, Youlian; Xu, Zhenjiang Zech; He, Yan; Yang, Yunsheng; Liu, Le; Lin, Qianyun; Nie, Yuqiang; Li, Mingsong; Zhi, Fachao; Liu, Side; Amir, Amnon; González, Antonio; Tripathi, Anupriya; Chen, Minhu; Wu, Gary D; Knight, Rob; Zhou, Hongwei; Chen, Ye

Journal: mSystems

Abstract: Gut microbiota dysbiosis contributes to the onset and perpetuation of inflammatory bowel disease (IBD). Given that gut microbiotas vary across geography and ethnicity, it remains obscure whether any universal microbial signatures for IBD diagnosis and prognosis evaluation exist irrespective of populations. Here we profiled the fecal microbiota of a series of Chinese IBD patients and combined them with two Western IBD cohorts, PRISM and RISK, for meta-analyses. We found that the gut microbial alteration patterns in IBD are similar among Chinese and Westerners. Our prediction model based on gut microbiome for IBD diagnosis is robust across the cohorts, which showed 87.5% and 79.1% prediction accuracy in Crohn's disease (CD) and ulcerative colitis (UC) patients, respectively. A relative increase in the levels of

DOI: 10.1128/mSystems.00188-17

PMID: 29404425.0

Full Article: https://doi.org/10.1128/mSystems.00188-17

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Differential cytokine profiles and drop of faecal calprotectin for prediction of primary response to infliximab induction therapy in Crohn's disease

Publication Date: nan

Authors: Mateos B.; Saez E.; Moret I.; Hervas D.; Tortosa L.; Cerrillo E.; Iborra M.; Garcia M.; Nos P.; Beltran B.

Journal: nan

Abstract: Background: One third of Crohn's disease (CD) patients do not achieve a clinical response after the induction therapy with infliximab (IFX). Cytokines emerge as possible biomarkers of response, as they are directly implicated in the pathogenesis of CD. Furthermore, novel cytokines have been described recently (ie, Oncostatin M (OSM)1). Their utility as biomarkers remains to be explored. Response to IFX seems to be well reflected by a drop in faecal calprotectin (FC).2 We aimed to determine plasmatic cytokine profiles of active CD patients that started IFX treatment, their changes after the induction therapy, and their capacity to predict response to IFX. Method(s): Twenty-two active CD patients (68% males) receiving an induction therapy of IFX (5 mg/kg weeks 0, 2, 6) were included in the study (45% L1). Peripheral blood samples (for cytokine analysis) and faecal samples (for FC analysis) were collected on weeks 0 and 14. Fifteen cytokines (IL-1beta, -2, -6, -7, -8, -10, -12p70, -13, -17, -21, -22, -23, IFNgamma, TNFalpha and OSM) concentrations were measured by Luminex technology. FC concentration was determined by ELISA. Response to IFX was evaluated by the drop of FC based on its logarithm values (Ln FC week 0 - Ln FC Week 14). Other clinical parameters (HBI, CRP) were also considered. R statistical software, random forest predictive model, heatmap graphs and Rho Spearman (R2) were used for data analysis. Result(s): FC and HBI median values were 498 mug/g (IQR: 247, 918.5) and 7 (IQR: 5.25, 8) pre-induction; and 104 mug/g (IQR: 29, 767) and 3 (IQR: 1.25, 5) post-induction, respectively. Random forest model showed 10 pre-treatment cytokines on the top plot which were related to response: TNFalpha, IL-13, OSM, IL-7, IL-10, IL-8, IL-23, IL-17, IL-6 and IL-22. Among these cytokines, TNFalpha, IL-13 and OSM were statistically significant. Heatmap graphs showed that higher levels of IL-13 pre-treatment, low TNFalpha levels and the presence of OSM were significantly associated with a better IFX therapy response. The analysis of the cytokines' networks showed that most important correlations were established between IL-17, IL-1b, IL-2, and IFNgamma (R2 = 0.92; 0.82; 0.79; 0.77) where IL-13 was also present (R2 = 0.51). TNFalpha and OSM belonged to different networks: TNF was associated to IL-8 (R2 = 0.68), and OSM to IL-22 (R2 = 0.67). This is the first study exploring the plasma concentration of OSM and its utility as biomarker in CD. Conclusion(s): Determination of IL-13, TNFalpha, and OSM plasma concentrations could help to predict response to the IFX therapy. Networking analysis supports the idea that cytokines may be analysed in groups instead of individually. IL-13, TNFalpha and OSM seem to have differential and specific interconnections.

DOI: /10.1093/ecco-jcc/jjy222.725

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjy222.725

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Anti-TNF Therapy Response in Patients with Ulcerative Colitis Is Associated with Colonic Antimicrobial Peptide Expression and Microbiota Composition.

Publication Date: Aug 2016

Authors: Magnusson, Maria K; Strid, Hans; Sapnara, Maria; Lasson, Anders; Bajor, Antal; Ung, Kjell-Arne; Öhman, Lena

Journal: Journal of Crohn's & colitis

Abstract: Anti-tumour necrosis factor [TNF] therapy is used in patients with ulcerative colitis [UC], but not all patients respond to treatment. Antimicrobial peptides [AMPs] and the gut microbiota are essential for gut homeostasis and may be important for treatment outcome. The aim of this study was to determine AMP and microbiota profiles in patients with UC before anti-TNF therapy start and correlate these data to treatment outcome.

DOI: 10.1093/ecco-jcc/jjw051

PMID: 26896085.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjw051

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: The Effect of Guselkumab Induction Therapy on Inflammatory Biomarkers in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Results Through Week 12

Publication Date: nan

Authors: Lichtenstein G.; Dignass A.; Sandborn W.J.; Huang K.-H.; Germinaro M.; Wilson R.; Zhang H.; Chen B.; Chen M.; Hisamatsu T.; Feagan B.G.; Panes J.; Peyrin-Biroulet L.

Journal: nan

Abstract: Introduction: C-reactive protein (CRP) and fecal calprotectin (FeCal) are non-invasive inflammatory biomarkers used to assess disease activity in patients with inflammatory bowel disease (IBD). Here we report inflammatory biomarker results through Week 12 for QUASAR (NCT04033445) Phase 2b Induction. QUASAR is a randomized, double-blind, placebo-controlled study of guselkumab (GUS), an interleukin-23 p19 subunit antagonist, in patients with moderately to severely active UC who had an inadequate response or intolerance to conventional (ie, thiopurines or corticosteroids) or advanced therapy (ie, tumor necrosis factor alpha antagonists, vedolizumab, or tofacitinib). Method(s): Patients with moderately to severely active UC (defined as a modified Mayo score of 5 to 9, inclusive with a Mayo rectal bleeding subscore >= 1 and a Mayo endoscopy subscore >= 2 obtained at baseline [BL]) were randomized 1:1:1 to receive IV GUS 200 mg, 400 mg, or placebo at Weeks 0, 4, and 8. CRP and FeCal were assessed at BL and through Week 12. Result(s): Three hundred thirteen patients were included in the analysis; approximately 50% had a history of inadequate response/intolerance to advanced therapies. Median BL CRP and FeCal concentrations were similar across treatment groups. Greater median reductions in CRP and FeCal were observed at the earliest timepoint assessed (Week 4) with GUS and continued to Week 12 compared with placebo (Table). Median changes from BL to Week 12 in CRP were -1.86 mg/L for the combined GUS group compared with 0.06 mg/L for placebo (nominal p< 0.001). Median changes from BL to Week 12 in FeCal were -684.00 mg/kg and 0.00 mg/kg for the combined GUS group and placebo, respectively (nominal p< 0.001). At Week 12, higher proportions of patients treated with GUS compared with placebo had normalized CRP <=3 mg/L (44.2% vs 18.8%, nominal p< 0.001), and normalized FeCal <=250 mg/kg (33.0% vs 9.9%, nominal p< 0.001), respectively, among patients with abnormal CRP or FeCal at BL. Conclusion(s): Patients with moderately to severely active UC who received GUS IV induction treatment had greater reductions in CRP and FeCal concentrations throughWeek 12 compared with placebo with no dose dependent effect for GUS 200 mg and 400 mg. Reductions in CRP and FeCal were observed as early as Week 4 with GUS and continued toWeek 12. Higher proportions of patients had normalized CRP and normalized FeCal levels at Week 12 with GUS compared with placebo. (Table Presented).

DOI: /10.14309/01.ajg.0000859908.57086.61

PMID: nan

Full Article: https://doi.org//10.14309/01.ajg.0000859908.57086.61

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

End Note
Procite
Reference Manager

	Placebo IV(N=105)	Guselkumab200 mg IV (N=101)	Guselkumab400 mg IV(N=107)	GuselkumabCombined
CRP (mg/L)				
Baseline, NMedian (IQR)	1054.89 (1.35; 10.80)	994.31 (1.61; 17.80)	1044.38 (1.88; 8.81)	2034.37 (1.74; 11.
from baseline at Week 4, NMedian (IQR)	1040.00 (-1.32, 1.37)	98-2.18 (-8.60;-0.28)**	101-1.15 (-5.45; -0.06)**	199-1.45 (-6.69; -0.
from baseline at Week 8, NMedian (IQR)	1030.00 (-2.49; 1.74)	94-2.60 (-9.30; -0.39)**	102-1.55 (-4.80; -0.18)**	196-2.10 (-7.49; -0.
rom baseline at Week 12, NMedian (IQR)	1020.06 (-2.23; 2.94)	97-2.31 (-8.20; -0.33)**	100-1.06 (-4.76; 0.07)**	197-1.86 (-6.28; -0.
FeCal (mg/kg)				
Baseline, NMedian (IQR)	911457.00(749.00; 3054.00)	951667.00(771.00; 2859.00)	1011578.00(811.00; 2860.00)	1961619.50(791.00; 2
from baseline at Week 4, NMedian (IQR)	89-116.00(-830.00; 812.00)	89-358.00 (-1641.00; 226.00)	95-391.00 (-1301.00; 167.00)*	184-378.00 (-1503.00;
rom baseline at Week 12, NMedian (IQR)	770.00(-855.00; 1089.00)	82-745.00(-1946.00; 0.00)**	88-558.50(-1426.00; -12.50)**	170-684.00 (-1682.00,

Title: Plasma Oncostatin M, TNF-α, IL-7, and IL-13 Network Predicts Crohn's Disease Response to Infliximab, as Assessed by Calprotectin Log Drop.

Publication Date: 2021

Authors: Mateos, Beatriz; Sáez-González, Esteban; Moret, Inés; Hervás, David; Iborra, Marisa; Cerrillo, Elena; Tortosa, Luis; Nos, Pilar; Beltrán, Belén

Journal: Digestive diseases (Basel, Switzerland)

Abstract: Cytokines emerge as possible biomarkers of response in Crohn's disease (CD). We aimed to determine the plasmatic cytokine profiles of active CD patients who started infliximab (IFX) treatment and their capacity to predict the response to IFX.

DOI: 10.1159/000508069

PMID: 32325460.0

Full Article: https://doi.org/10.1159/000508069

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Evaluation of serum cytokines and acute phase proteins as possible pharmacodynamic biomarkers to monitor endoscopic remission during ustekinumab therapy in patients with Crohn's disease.

Publication Date: 2023

Authors: Van den Berghe, Nathalie; Alsoud, Dahham; Verstockt, Bram; Vermeire, Séverine; Declerck, Paul; Thomas, Debby

Journal: Therapeutic advances in gastroenterology

Abstract: Since not all Crohn's disease (CD) patients respond adequately to ustekinumab therapy, biomarkers could aid to monitor treatment response and optimize therapeutic outcomes.

DOI: 10.1177/17562848231189110

PMID: 37655059.0

Full Article: https://doi.org/10.1177/17562848231189110

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Fecal Calprotectin Responses Following Induction Therapy With Vedolizumab in Moderate to Severe Ulcerative Colitis: A Post Hoc Analysis of GEMINI 1.

Publication Date: 2019 03 14

Authors: Reinisch W; Bressler B; Curtis R; Parikh A; Yang H; Rosario M; Roseth A; Danese S; Feagan B; Sands BE; Ginsburg P; Dassopoulos T; Lewis J; Xu J; Wyant T

Journal: nan

Abstract: BACKGROUND: In patients with ulcerative colitis (UC), fecal calprotectin (FC) concentrations correlate with endoscopic inflammation evidence. This study investigated the effect of vedolizumab induction on FC concentrations and whether FC concentrations could be a reliable surrogate measure of disease status.

DOI: /10.1093/ibd/izy304

PMID: nan

Full Article: https://doi.org//10.1093/ibd/izy304

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Longitudinal multi-omics analysis identifies early blood-based predictors of anti-TNF therapy response in inflammatory bowel disease.

Publication Date: Sep 2022

Authors: Mishra, Neha; Aden, Konrad; Blase, Johanna I; Baran, Nathan; Bordoni, Dora; Tran, Florian; Conrad, Claudio; Avalos, Diana; Jaeckel, Charlot; Scherer, Michael; Sørensen, Signe B; Overgaard, Silja H; Schulte, Berenice; Nikolaus, Susanna; Rey, Guillaume; Gasparoni, Gilles; Lyons, Paul A; Schultze, Joachim L; Walter, Jörn; Andersen, Vibeke; ,; Dermitzakis, Emmanouil T; Schreiber, Stefan; Rosenstiel, Philip

Journal: Genome medicine

Abstract: Treatment with tumor necrosis factor α (TNFα) antagonists in IBD patients suffers from primary non-response rates of up to 40%. Biomarkers for early prediction of therapy success are missing. We investigated the dynamics of gene expression and DNA methylation in blood samples of IBD patients treated with the TNF antagonist infliximab and analyzed the predictive potential regarding therapy outcome.

DOI: 10.1186/s13073-022-01112-z

PMID: 36153599.0

Full Article: https://doi.org/10.1186/s13073-022-01112-z

Methods:

Values represent median ± standard deviationFull size tableReplication cohortA second independent replication cohort comprising 23 subsequent IBD patients (9 UC/14 CD; Fig. 1C, Table 2) treated with a TNF antagonist (22 infliximab, 1 adalimumab) for their first time was used to replicate results from the discovery cohort. First, pairwise gene correlations were calculated based on the log-transformed normalized expression counts across all samples. Transcription factor binding sites (TFBS) enriched in DMPs and DMRs were identified by conducting enrichment analysis using the Bioconductor package LOLA (version 1.14.0) [36].Feature selection and machine learningFeature selection was performed using a random forest approach implemented in the ranger package (version 0.12.1) of R [37].

Results:

Through principal component analysis (PCA), we observed a suggestive ex ante separation between patients achieving remission and non-remission at week 14 along the PC2 axis (Spearman's rho = 0.58, p-value = 0.04; Additional file 2: Fig. Differential expression analysis, after taking diagnosis as a covariate, further identified 387 genes that were nominally differentially expressed between remitters and non-remitters at baseline (Additional file 2: Fig. D Heatmap of DMPs, which are correlated with DEGs, showing scaled mean methylation intensities at each time point in remission and non-remission samples. E Heatmap showing significant enrichment, quantified by odds ratio, of transcription factor binding sites (TFBS) in DMPs that are correlated with DEGs.

Discussion:

This signature is consistent with the hypothesis of an underlying type II immunity in non-responders which could be aggravated by blocking TNF. The result corroborates earlier findings on an aggressive disease behavior and lower anti-TNF persistence in patients with high peripheral blood eosinophil levels [53, 54]. Higher-order gene regulation analysis using transcriptional network construction [30] was able to identify modules of co-expressed transcripts which were disrupted through effective

therapy in remitting patients from both cohorts. Future studies are warranted combining molecular assessments with more objective parameters such as endoscopy and histology, which could further improve outcome prediction aiming at optimal disease control.

Conclusion:

ConclusionsIn summary, our study focused on the dynamics of molecular changes occurring shortly after the induction of a targeted anti-cytokine therapy and their association to clinical outcome at week 14. The (ex-post) molecular signature identified includes features and biological processes such as type I interferon signaling, erythropoiesis, and platelet aggregation that are elicited by the impact of the targeted intervention and could be involved in inducing disease control as the ultimate success of such treatment in IBD. We propose that early shifts of immunological network states of circulating blood cells after a first probatory administration of the drug, i.e., ex-post signatures, could carry important information that might guide clinical decision-making such as intensifying or early switch of treatment. Our results in IBD could serve as a blueprint for immune-mediated inflammatory disorders in general to create personalized therapeutic strategies with the aim of making tailored therapeutic choices to achieve disease control.

Title: Gut Microbiome and Metabonomic Profile Predict Early Remission to Anti-Integrin Therapy in Patients with Moderate to Severe Ulcerative Colitis.

Publication Date: Jun 2023

Authors: Liu, Jie; Fang, Huaying; Hong, Na; Lv, Chaolan; Zhu, Qihua; Feng, Yinping; Wang, Bo; Tian, Jiashuang; Yu, Yue

Journal: Microbiology spectrum

Abstract: Patients with ulcerative colitis (UC) have low response rates to anti-integrin medications, necessitating the identification of noninvasive biomarkers for predicting remission to anti-integrin therapy. In this study, patients with moderate to severe UC commencing anti-integrin therapy (

DOI: 10.1128/spectrum.01457-23

PMID: 37199618.0

Full Article: https://doi.org/10.1128/spectrum.01457-23

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Fecal Microbiota Signatures Are Associated with Response to Ustekinumab Therapy among Crohn's Disease Patients.

Publication Date: 2018 03 13

Authors: Doherty MK; Ding T; Koumpouras C; Telesco SE; Monast C; Das A; Brodmerkel C; Schloss PD

Journal: nan

Abstract: The fecal microbiota is a rich source of biomarkers that have previously been shown to be predictive of numerous disease states. Less well studied is the effect of immunomodulatory therapy on the microbiota and its role in response to therapy. This study explored associations between the fecal microbiota and therapeutic response of Crohn's disease (CD) patients treated with ustekinumab (UST; Stelara) in the phase 2 CERTIFI study. Using stool samples collected over the course of 22 weeks, the composition of these subjects' fecal bacterial communities was characterized by sequencing the 16S rRNA gene. Subjects in remission could be distinguished from those with active disease 6 weeks after treatment using random forest models trained on subjects' baseline microbiota and clinical data (area under the curve [AUC] of 0.844, specificity of 0.831, sensitivity of 0.774). The most predictive operational taxonomic units (OTUs) that were ubiquitous among subjects were affiliated with Faecalibacterium and Escherichia or Shigella The median baseline community diversity in subjects in remission 6 weeks after treatment was 1.7 times higher than that in treated subjects with active disease (P = 0.020). Their baseline community structures were also significantly different (P = 0.017). Two OTUs affiliated with Faecalibacterium (P = 0.003) and Bacteroides (P = 0.022) were significantly more abundant at baseline in subjects who were in remission 6 weeks after treatment than those with active CD. The microbiota diversity of UST-treated clinical responders increased over the 22 weeks of the study, in contrast to nonresponsive subjects (P = 0.012). The observed baseline differences in fecal microbiota and changes due to therapeutic response support the potential for the microbiota as a response biomarker. IMPORTANCE CD is a global health concern, with increasing incidence and prevalence, causing large economic and health care impacts. Finding prognostic biomarkers that give clinicians the ability to identify patients more likely to respond to CD treatment at diagnosis will reduce the time subjects receive drugs that are unlikely to be beneficial. OTUs associated with remission after treatment induction, especially Faecalibacterium, could be biomarkers for successful UST treatment of anti-tumor necrosis factor alpha (anti-TNF-alpha) refractory CD patients. More broadly, these results suggest that the fecal microbiota could be a useful noninvasive biomarker for directing or monitoring the treatment of gastrointestinal diseases.

DOI: /10.1128/mBio.02120-17

PMID: nan

Full Article: https://doi.org//10.1128/mBio.02120-17

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Functional Molecular Network Analysis Enables Prediction of Response to Vedolizumab Therapy in Anti-TNF Refractory IBD Patients.

Publication Date: Apr 2020

Authors: Breidert, Matthias; Eftekhari, Pierre; Louis, François; Rotoiu, Claudia; Rath, Timo; Neurath, Markus F; Atreya, Raja

Journal: Crohn's & colitis 360

Abstract: We applied for the first time 2 label-free technologies, physiological intermolecular modulation spectroscopy (PIMS) and nematic protein organization technic (NPOT) in anti-tumor necrosis factor (TNF) refractory inflammatory bowel disease (IBD) patients to identify clinical responders to vedolizumab therapy and elucidate their underlying functional molecular network.

DOI: 10.1093/crocol/otaa037

PMID: 32776006.0

Full Article: https://doi.org/10.1093/crocol/otaa037

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Exploration of Predictive Biomarkers of Early Infliximab Response in Acute Severe Colitis: A Prospective Pilot Study.

Publication Date: 2018 Feb 28

Authors: Beswick L; Rosella O; Rosella G; Headon B; Sparrow MP; Gibson PR; van Langenberg DR

Journal: nan

Abstract: BACKGROUND: The outcomes of acute severe ulcerative colitis [ASUC] appear to be dependent on early intervention with the first and/or further infliximab [IFX] doses, although parameters to guide decision-making remain uncertain.

DOI: /10.1093/ecco-jcc/jjx146

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjx146

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Early fecal calprotectin levels at week 8 may guide therapeutic decisions on Ustekinumab therapy in patients with Crohn's disease.

Publication Date: 2023

Authors: Pauwels, Renske W M; Ten Bokkel Huinink, Sebastiaan; van der Woude, Christien J; Doukas, M; Oudijk, L; de Vries, Annemarie C

Journal: Scandinavian journal of gastroenterology

Abstract: Response evaluation after induction therapy with ustekinumab (UST) in Crohn's disease (CD) is important for decisions on maintenance therapy. We aimed to assess the potential of fecal calprotectin (FC) levels to predict endoscopic response at week 16.

DOI: 10.1080/00365521.2023.2194009

PMID: 36970968.0

Full Article: https://doi.org/10.1080/00365521.2023.2194009

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: The gut microbiome differentiates clinical phenotypes in moderate to severe crohn's disease: Results from the CERTIFI study

Publication Date: nan

Authors: Ding T.; Telesco S.; Monast C.S.; Brodmerkel C.; Yatsunenko T.; Das A.; Schloss P.

Journal: nan

Abstract: Introduction: The aim of this study was to investigate the relationship between the fecal microbiome and clinical phenotypes in subjects with moderately to severely active Crohn's disease (CD). Specifically, the potential of the microbiome to differentiate among Crohn's patient sub-groups as defined by specific clinical traits was examined. Aims & Methods: CERTIFI was a Phase 2b multicenter, randomized, doubleblind, placebo controlled clinical trial to evaluate the efficacy and safety of ustekinumab therapy in subjects with moderately to severely active CD who had previously not responded to anti-TNFalpha therapy. Fecal samples from 100 subjects, collected at screening, week 4, week 6, and week 22 study visits, and stored at -80degreeC, were selected for microbiome analysis. Bacterial DNA was extracted from the fecal samples using the MoBio PowerSoil DNA Isolation kit and subjected to 16S rRNA sequencing and shotgun metagenomic sequencing. 16S rRNA sequencing was performed on the GS-FLX 454 Titanium platform and the sequences were assigned genus-level annotations. Metagenomic sequencing was performed on the Illumina HiSeq 2000 using 100 base pair paired-end processing. Filtered sequences were mapped against the MetaCyc database of metabolic pathways and enzymes. Spearman correlation, LEfSe, logistic regression, and Adonis were applied to identify bacterial taxa or metabolic pathways that were associated with clinical variables of interest. Result(s): The gut microbiome of individuals with CD was characterized by pronounced inter-personal variation in the presence and relative abundance of specific bacterial taxa. Despite this heterogeneity, bacterial abundances and metabolic pathways correlated with patient sub-groups defined by specific baseline clinical traits. The baseline CDAI score significantly associated with the relative abundance of several bacteria, including Parabacteroides (rho= - 0.42, P<1e-4). The metagenomic data supported this result, demonstrating correlation between specific metabolic pathways and CDAI score. Baseline CRP, fecal calprotectin (FCALP), and lactoferrin (FLACT) concentrations also correlated with baseline bacterial abundances of specific taxa, including Dialister (rho=0.36, P=3e-4, Spearman correlation with FCALP), and with metagenomic data. Previous response to anti- TNFalpha therapy did not significantly correlate with the abundance of any specific bacteria or with metagenomic data. Conclusion(s): The fecal microbiome demonstrated the ability to discriminate clinical phenotypes in moderately to severely active CD patients who had previously not responded to anti-TNFalpha therapy. The strongest associations between metadata and the microbiome, supported by 16S and metagenomic data, were observed for CDAI score, FCALP, and FLACT. The results suggest the potential application of the fecal microbiome as a molecular marker of disease severity in CD.

DOI: /10.1177/2050640615601611

PMID: nan

Full Article: https://doi.org//10.1177/2050640615601611

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Identification of Candidate Biomarkers Associated with Response to Vedolizumab in Inflammatory Bowel Disease.

Publication Date: Sep 2018

Authors: Boden, Elisa K; Shows, Donna M; Chiorean, Michael V; Lord, James D

Journal: Digestive diseases and sciences

Abstract: Vedolizumab is an anti-α4β7 monoclonal antibody approved for the treatment of inflammatory bowel disease (IBD). This exploratory study aimed to identify biomarkers associated with vedolizumab response.

DOI: 10.1007/s10620-018-4924-8

PMID: 29372476.0

Full Article: https://doi.org/10.1007/s10620-018-4924-8

Methods:

None available

Results:

Responders and nonresponders had very similar demographic and clinical characteristics with no significant differences in reported variables including age, gender, race, IBD subtype, disease distribution, disease duration, prior anti-TNF use, baseline disease activity, CRP, albumin, concurrent smoking, or concomitant medication use (Table 1).Table 1 Clinical characteristics of patients according to responseFull size table Pretreatment α4β7 Expression on Multiple Cellular Subsets Correlates with Response to VedolizumabThe peripheral blood of responders collected prior to treatment with vedolizumab demonstrated a significantly higher per-cell expression of integrin α4β7 on naïve (CD45RA+CCR7+) CD4 and CD8 T cells as well as naïve (CD19+CD20+CD27−CD38−IgD+) B cells (Fig. 1a). p values reflect unpaired two-way t testsFull size image Other than α4β7 expression, few significant immunophenotypic differences were found between responders and nonresponders prior to treatment among a diverse array of cellular subsets evaluated in PBMC by flow cytometry. However, expression of the ectonucleoside triphosphate diphospohydrolase, CD39, was seen among significantly more thymically derived (Helios+FOXP3+) regulatory T cells (tTregs) in PBMC from responders than nonresponders prior to vedolizumab therapy (Supplemental Figure 4). Thus, it is possible that α4β7 receptor saturation on particular cell subsets might provide a more specific biomarker for vedolizumab response than serum levels.

Discussion:

DiscussionIn this exploratory study of inflammatory bowel disease patients undergoing therapy with vedolizumab, we identified several candidate biomarkers for treatment response. Future studies will focus on characterizing integrin expression in the intestinal tissues of patients before and during therapy with vedolizumab. While it will be important to address this in future studies, it should be noted that pretreatment α4β7 in this study was a superior biomarker for vedolizumab response than any reported outcomes associated with disease severity (CRP, albumin, and clinical scores).Vedolizumab treatment did appear to have an effect on α4β7 expression during therapy, with the percentage of α4β7-expressing TEM CD4 cells increasing during the maintenance phase of therapy. Because lymphocyte turnover is slow, α4β7 has been reported to remain almost completely saturated on memory T cells for over 100 days, while serum levels slowly decrease after infusion [20, 26].

Conclusion:

None available

Title: The gut microbiome differentiates clinical phenotypes in moderate to severe crohn's disease: Results from the certifi study

Publication Date: nan

Authors: Ding T.; Telesco S.; Monast C.; Brodmerkel C.; Yatsunenko T.; Das A.; Schloss P.

Journal: nan

Abstract: Background. The pathogenic role of the gut microbiome in inflammatory bowel disease (IBD) has been highly studied but remains unknown. Aims. The aim of this study was to investigate the relationship between the fecal microbiome and clinical phenotypes in pts with moderately-severely active CD. Methods. CERTIFI was a Phase 2b multicenter, randomized, double-blind, placebo controlled clinical trial to evaluate the efficacy and safety of ustekinumab therapy in pts with moderately- severely active CD who had previously not responded to anti-TNFalpha therapy. Fecal samples from 100 pts, collected at screening and stored at -80degreeC, were selected for microbiome analysis. Bacterial DNA was extracted from fecal samples and subjected to 16S rRNA sequencing and shotgunmetagenomic sequencing. 16S rRNA sequencing was performed on the GS-FLX 454 Titanium platform and the sequences were assigned genus-level annotations. Metagenomic sequencing was performed on the Illumina HiSeq 2000 using 100 base pair paired-end processing. Filtered sequences were mapped against the MetaCyc database of metabolic pathways and enzymes. Spearman correlation and Adonis were applied to identify bacterial taxa or pathways associated with clinical variables. Results. The gut microbiome of individuals with CD was characterized by pronounced inter-personal variation in the presence and relative abundance of specific bacterial taxa. Despite this heterogeneity, bacterial taxa and pathways correlated with patient sub-groups defined by specific baseline clinical traits. The baseline CDAI score significantly associated with the relative abundance of several bacteria, including Parabacteroides (rho = -0.42, P < 1e - 4). The metagenomic data supported this result, demonstrating correlation between specific metabolic pathways and CDAI score. Baseline CRP, fecal calprotectin (FCALP), and lactoferrin (FLACT) concentrations also correlated with baseline bacterial abundances of specific taxa, including Dialister (rho = 0.36, P = 3e - 4, Spearman correlation with FCALP), and with metagenomic data. Previous response to anti-TNFalpha therapy did not significantly correlate with the abundance of any specific bacteria or with metagenomic data. Conclusions. The fecal microbiome demonstrated the ability to discriminate clinical phenotypes in moderately-severely active CD pts who had previously not responded to anti- TNFalpha therapy. The strongest associations between metadata and the microbiome, supported by 16S and metagenomic data, were observed for CDAI score, FCALP, and FLACT. The results suggest the potential application of the fecal microbiome as a molecular marker of disease severity in CD.

DOI: /10.1155/2016/4792898

PMID: nan

Full Article: https://doi.org//10.1155/2016/4792898

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: HIGHLY STABLE EPIGENOME-WIDE PERIPHERAL BLOOD DNA METHYLATION SIGNATURES ACCURATELY PREDICT RESPONSE TO ADALIMUMAB, VEDOLIZUMAB AND USTEKINUMAB IN CROHN'S DISEASE PATIENTS

Publication Date: nan

Authors: Joustra V.; Yim A.L.; Hageman I.; Levin E.; Noble A.; Chapman T.; McGregor C.; Adams A.; Satsangi J.; Henneman P.; De Jonge W.; D'Haens G.

Journal: nan

Abstract: Background Despite the proven efficacy of biological treatments in Crohn's disease (CD), many patients fail to respond or lose response over time. Therefore, predictive biomarkers for treatment efficacy would be of extreme value. Previous epigenome-wide association studies associated differential DNA methylation with CD-specific phenotypes, suggesting a potential use in classification and prediction of response to treatment. Methods We prospectively collected and measured longitudinal peripheral blood DNA methylation profiles of 184 adult CD patients prior to (T1) and after a median of 28 weeks (T2) following biological treatment with Adalimumab (ADA), Vedolizumab (VEDO) or Ustekinumab (USTE) in a discovery (n=88) and independently collected internal validation cohort (n=96) using the Illumina EPIC BeadChip array. Response (R) was defined as the combination of endoscopic response (>=50% reduction in SES-CD score) and steroid-free clinical response (>=3 point drop in HBI or HBI <=4 AND no systemic steroids) and/or biochemical response (>=50% reduction in Creactive protein (CRP) and fecal calprotectin or a CRP <=5 g/ mL and fecal calprotectin <=250 mug/g). Biomarker identification and classification analyses were performed using stability selection gradient boosting on samples taken at T1 whereas samples taken at T2 and intraclass correlation (ICC) data were used to assess long-term stability of our identified CpG loci. Results A total of 58 ADA-patients (NR=29, NNR=29), 64 VEDO-patients (NR=36, NNR=28) and 62 USTE-patients (NR=30, NNR=32) were included. Prior to treatment, at T1, we identified distinct panels of 18 ADA-, 25 VEDO- and 68 USTE-associated CpG loci that, in combination, predict clinical- and endoscopic response with high accuracy (AUC ADA=0.81, VEDO=0.88 and USTE=0.94) upon validation. Notably, for these CpG loci, methylation levels did not significantly differ between T1 and T2, implicating stability during both induction and maintenance treatment, irrespective of inflammatory status and therapeutic intervention. In addition, the majority of these CpG loci (>60%) demonstrated long- term hyper stability (ICC-values >=0.90). Furthermore, genes annotated to the CpGs of interest suggest drug specific involvement in TNF-signaling, endothelial cell-cell adhesion, integrin dependent T-cell homing, the innate immune system and Th17/Treg differentiation, corroborating to the mode of action of each drug. Conclusion Here, we report on 3 validated panels of highly stable, epigenetic biomarkers that predict clinical and endoscopic response in CD patients treated with ADA, VEDO or USTE. Additional external- and clinical validation as part of EPIC-CD and the OMICROHN clinical trial are currently ongoing. (Table Presented).

DOI: /10.1136/gutjnl-2023-BSG.60

PMID: nan

Full Article: https://doi.org//10.1136/gutjnl-2023-BSG.60

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Baseline Peripheral Blood Mononuclear Cell Transcriptomics Before Ustekinumab Treatment Is Linked With Crohn's Disease Clinical Response at 1 Year.

Publication Date: Dec 2023

Authors: Granot, Maya; Braun, Tzipi; Efroni, Gilat; Picard, Orit; Fudim, Ella; Yavzori, Miri; Haj, Ola; Weiss, Batia; Ben-Horin, Shomron; Kopylov, Uri; Haberman, Yael

Journal: Clinical and translational gastroenterology

Abstract: Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin (IL)-12 and IL-23, is used for Crohn's disease (CD), and the documented clinical remission rate after 1 year was observed in approximately 50% of patients. We aimed to identify predictors for a clinical response using peripheral blood obtained from patients with CD just before ustekinumab treatment initiation.

DOI: 10.14309/ctg.0000000000000635

PMID: 37655708.0

Full Article: https://doi.org/10.14309/ctg.0000000000000635

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

End Note
Procite
Reference Manager

	All patients with CD (n = 36)	Responders (n = 22)	Nonresponders (n = 12)	Pvalue
Gender, female, n (%)	23 (64)	13 (59)	10 (71)	NS
Age at diagnosis, yr, median (IQR)	22 (19–34)	23 (20–37)	20 (18–23)	NS
Age at inclusion, yr, median (IQR)	35 (29–41)	37 (30–42)	31 (28–39)	NS
BMI, median (IQR)	22 (20–25.5)	24 (20–27)	22 (19.5–22.5)	NS
Smoking, n (%)	5 (14)	3 (14)	2 (14)	NS

Disease location, n (%)				
Small bowel (L1)	23 (64)	18 (82)	5 (36)	0.004
Small bowel + colon (L3)	11 (30)	3 (14)	8 (57)	0.005
Colon (L2)	2 (6)	1 (4)	1 (7)	NS
Disease duration, yr, median (IQR)	8.1 (4.7–16.1)	6.6 (4.2–15.8)	9.0 (5.7–16.5)	NS
Perianal disease, n (%)	12 (33)	10 (45)	2 (20)	0.053
Disease phenotype, n (%)				NS
Inflammatory (B1)	16 (44)	10 (45)	6 (43)	
Structuring (B2)	7 (19)	6 (27)	1 (7)	
Penetrating (B3)	13 (36)	6 (27)	7 (50)	
Lines of biologics, n (%)a				NS
2	17 (47)	13 (59)	4 (29)	
3	12 (33)	6 (27)	6 (43)	
4	6 (17)	3 (8)	3 (21)	
5	1 (3)	0 (0)	1 (7)	
Concomitant therapies, n (%)				NS
None	27 (75.0)	18 (81.8)	9 (64.3)	
Steroids	5 (13.8)	1 (4.5)	4 (28.5)	
Methotrexate	2 (5.5)	1 (4.5)	1 (7.1)	
Azathioprine	1 (2.8)	1 (4.5)	0 (0)	
CDED	1 (2.8)	1 (4.5)	0 (0)	
Prior surgery	16 (44)	10 (45)	6 (43)	NS
N availableb	N = 25	N = 14	N = 11	0.062
Baseline CRP >5 mg/L (%)	18/26 (73)	8/14 (57)	10/11 (91)	
N availableb	N = 12	N = 8	N = 4	NS
Baseline fecal calprotectin mic/g, median (IQR)	532 (285–1085)	405 (117–866)	953 (499–1380)	

	Gene	log2FoldChange	Direction of change (nonresponders vs responders)	Pvalue
1	F3	1.84	Increased	<0.01
2	CXCL1	1.75	Increased	0.01
3	FAM20A	1.74	Increased	<0.01
4	RAPH1	1.72	Increased	0.01
5	CCL2	1.63	Increased	0.03
6	CXCL3	1.54	Increased	<0.01
7	CXCL2	1.54	Increased	0.01

8	PF4V1	1.49	Increased	<0.01
9	ID1	1.31	Increased	0.02
10	HP	1.25	Increased	0.04

Title: The fecal microbiome as a tool for monitoring and predicting response outcomes in ustekinumab-treated, antiTNF refractory Crohn's disease patients: Results from the CERTIFI study

Publication Date: nan

Authors: Doherty M.K.; Koumpouras C.; Telesco S.; Monast C.S.; Brodmerkel C.; Schloss P.D.

Journal: nan

Abstract: Background: We investigated the relationship between the fecal microbiome and clinical phenotypes in subjects with moderate to severe CD treated with ustekinumab (UST) to determine whether the fecal microbiome at baseline is predictive of disease severity and therapeutic response and to assess changes in the fecal microbiota due to therapy. Method(s): CERTIFI was a phase 2b multicenter, double-blind, placebo-controlled trial to evaluate the efficacy of UST in subjects with moderate to severe CD who had not responded to anti-TNFa therapy. The 16S rRNA gene from stool samples collected from roughly 350 patients at baseline and following treatment with UST or placebo (PBO) was sequenced using the Illumina MiSeq platform. Sequences were assigned to taxonomic groups using the mothur software package to determine the relative abundance of bacterial taxa. The relative abundances in addition to clinical metadata were used as input to a random forest (RF) machinelearning algorithm to predict disease severity and clinical response to treatment with UST. Result(s): Fecal microbiome richness at baseline significantly correlated with clinical parameters, including CDAI, stool frequency, and disease duration (Table 1). Changes in the community structure of the microbiome (beta diversity) were significantly associated with stool frequency, CRP, fecal lactoferrin, fecal calprotectin, corticosteroid use, disease duration, and tissue involvement (Table 1). Community structure and species diversity were significantly different between Week 6 clinical responders and non-responders to UST and between clinical remitters and non-remitters. The microbiome of responders and remitters also changed over time but did not change in non-responders. Faecalibacterium, among other taxa, was significantly more abundant in responders and remitters. Using RF, the differences in the baseline microbiome and clinical metadata were able to predict response to UST with AUC values of roughly 0.85. Conclusion(s): The ability to predict response to treatment using the microbiome has the potential to provide a quantitative clinical tool for guiding the treatment of CD patients. In addition our results point to specific microbes that might contribute to CD pathogenesis and maintaining CD remission. Microbes related to achieving remission could be investigated as co-therapies designed to increase the likelihood of response to anti-inflammatory therapeutics. (Table Presented).

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: The fecal microbiome as a tool for monitoring and predicting response outcomes in ustekinumab-treated, anti-TNFalpha refractory Crohn's disease patients: Results from the CERTIFI study

Publication Date: nan

Authors: Doherty M.K.; Koumpouras C.; Telesco S.E.; Monast C.; Brodmerkel C.; Schloss P.D.

Journal: nan

Abstract: Background: We investigated the relationship between the fecal mi-crobiome and clinical phenotypes in subjects with moderate to severe CD treated with ustekinumab (UST) to determine whether the fecal microbiome at baselineis predictive ofdisease severity and therapeutic response and to assess changes in the fecal microbiota due to therapy. Method(s): CERTIFI was a phase 2b multicenter, double-blind, placebo-controlled trial to evaluate the efficacy of UST in patients with moderate to severe CD who had not responded to anti-TNFalpha therapy. The 16S rRNA gene from stool samples collected from roughly 350 patients at baseline and following treatment with UST or placebo (PBO) was sequenced using the Illumina MiSeq platform. Sequences were assigned to taxonomic groups using the mothur software package to determine the relative abundance of bacterial taxa. The relative abundances in addition to clinical metadata were used as input to a random forest (RF) machine-learning algorithm to predict disease severity and clinical response to treatment with UST. Result(s): Fecal microbiome richness at baseline significantly correlated with clinical parameters, including CDAI, stool frequency, and disease duration (Table 1). Changes in the community structure of the microbiome (beta diversity) were significantly associated with stool frequency, CRP, fecal lactoferrin, fecal calprotectin, corticos-teroid use, disease duration, and tissue involvement (Table 1). Community structure and species diversity were significantly different between Week 6 clinical responders and non-responders to UST and between clinical remitters and non-remitters. The microbiome of re-sponders and remitters also changed over time but did not change in non-responders. Faecalibacterium, among other taxa, was significantly more abundant in responders and remitters. Using RF, the differences in the baseline microbiome and clinical metadata were able to predict response to UST with AUC values of roughly 0.85. Conclusion(s): The ability to predict response to treatment using the microbiome has the potential to provide a quantitative clinical tool for guiding the treatment of CD patients. In addition our results point to specific microbes that might contribute to CD pathogen-esis and maintaining CD remission. Microbes related to achieving remission could be investigated as co-therapies designed to increase the likelihood of response to anti-inflammatory therapeutics.

DOI: /10.1093/ecco-jcc/jjx002.090

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjx002.090

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: The gut microbiome differentiates clinical phenotypes in moderate to severe Crohn's disease: Results from the certifi study

Publication Date: nan

Authors: Ding T.; Telesco S.; Monast C.S.; Brodmerkel C.; Yatsunenko T.; Das A.; Schloss P.

Journal: nan

Abstract: Background: The aim of this study was to investigate the relationship between the fecal microbiome and clinical phenotypes in subjects with moderately to severely active Crohn's disease (CD). Specifically, the potential of the microbiome to differentiate among Crohn's patient sub-groups as defined by specific clinical traits was examined. Method(s): CERTIFI was a Phase 2b multicenter, randomized, double-blind, placebo controlled clinical trial to evaluate the efficacy and safety of ustekinumab therapy in subjects with moderately to severely active CD who had previously not responded to anti-TNFalpha therapy. Fecal samples from 100 subjects, collected at screening, week 4, week 6, and week 22 study visits, and stored at-80degree C, were selected for microbiome analysis. Bacterial DNA was extracted from the fecal samples using the MoBio PowerSoil DNA Isolation kit and subjected to 16S rRNA sequencing and shotgun metagenomic sequencing. 16S rRNA sequencing was performed on the GS-FLX 454 Titanium platform and the sequences were assigned genus-level annotations. Metagenomic sequencing was performed on the Illumina HiSeq 2000 using 100 base pair paired-end processing. Filtered sequences were mapped against the MetaCyc database of metabolic pathways and enzymes. Spearman correlation, LEfSe, logistic regression, and Adonis were applied to identify bacterial taxa or metabolic pathways that were associated with clinical variables of interest. Result(s): The gut microbiome of individuals with CD was characterized by pronounced inter-personal variation in the presence and relative abundance of specific bacterial taxa. Despite this heterogeneity, bacterial abundances and metabolic pathways correlated with patient sub-groups defined by specific baseline clinical traits. The baseline CDAI score significantly associated with the relative abundance of several bacteria, including Parabacteroides (rho=-0.42, P<1e-4). The metagenomic data supported this result, demonstrating correlation between specific metabolic pathways and CDAI score. Baseline CRP, fecal calprotectin (FCALP), and lactoferrin (FLACT) concentrations also correlated with baseline bacterial abundances of specific taxa, including Dialister (rho=0.36, P=3e-4, Spearman correlation with FCALP), and with metagenomic data. Previous response to anti- TNFalpha therapy did not significantly correlate with the abundance of any specific bacteria or with metagenomic data. Conclusion(s): The fecal microbiome demonstrated the ability to discriminate clinical phenotypes in moderately to severely active CD patients who had previously not responded to anti-TNFalpha therapy. The strongest associations between metadata and the microbiome, supported by 16S and metagenomic data, were observed for CDAI score, FCALP, and FLACT. The results suggest the potential application of the fecal microbiome as a molecular marker of disease severity in CD.

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: The role of the microbiome in clinical response to golimumab in ulcerative colitis

Publication Date: nan

Authors: Monast C.S.; Telesco S.; Li K.; Hayden K.; Brodmerkel C.

Journal: nan

Abstract: Background: Extensive study has established associations between the gut microbiome and inflammatory bowel diseases but these associations have not yet led to meaningful clinical impact. In particular, the role of the microbiome in achieving clinical response with targeted therapeutics remains largely unknown despite possible relevance to clinical practice and trial design. Method(s): PURSUIT-SC was a phase 3 multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of golimumab induction therapy (anti-TNFalpha) in subjects with moderately to severely active ulcerative colitis (UC). Fecal samples were collected at screening (n = 997), and wk 2 (n = 801) and wk 6 (n = 801) post-treatment. Samples were submitted to 16S rRNA sequencing using the Illumina MiSeq, and bacterial taxa were quantified using established methods. PERMANOVA testing was used to evaluate associations with clinical metadata and DESeq2 was used to identify taxa that were differentially abundant between groups. Clinical response was assessed using the Mayo score. Result(s): The baseline UC microbiome was associated with multiple factors related to disease severity, country, smoking status, and 5-ASA use. Also at baseline, panels of specific taxa differentiated week 6 responders from nonresponders. Overlapping panels of taxa changed in responders between week 0 and week 6 but only in the 400/200 mg golimumab group, and not in the 200/100 mg group (despite similar clinical response and remission rates) or the placebo group. Generally, taxa in these related panels were increased in the most severe subjects at baseline, increased in nonresponders compared to responders (at both baseline and week 6) and decreased by week 6 in remitters who received 400/ 200 mg golimumab. Panels included B. Fragilis, B. Ovatus, and multiple members of the Enterobacteriaceae family. Lastly, remitter microbiomes were significantly more diverse compared to nonremitter microbiomes post-treatment. Conclusion(s): Our results extend previous reports by identifying specific taxa that may predict response to anti-TNF alpha treatment and specific taxa that shift in a dose and response dependent manner with anti-TNF alpha treatment. We find that clinical remission in this cohort was achievable following 200/100 mg golimumab treatment without concerted changes in specific taxa but that a higher golimumab dose of 400/200 mg appears to change levels of specific bacteria associated with clinical response. This suggests that partial resolution of microbial dysbiosis with a sufficient dose of anti- TNFalpha is possible and could conceivably provide added clinical benefit; further work is needed to clearly identify this benefit.

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Fecal calprotectin concentration and clinical remission in patients with active Crohn's disease treated with certolizumab pegol: Results from PRECiSE 1

Publication Date: nan

Authors: Sandborn W.; Ullman T.; Pierre-Louis B.; Binion D.

Journal: nan

Abstract: Purpose: Greater treatment effects with anti-TNF agents1 have been reported in patients with higher baseline inflammatory marker concentrations. In the pivotal phase III trial PRECiSE 1 (P1),2 maintenance therapy with the anti-TNF certolizumab pegol (CZP) was similarly effective in patients (pts) with active Crohn's disease (CD) who had high (>=10 mg/L) baseline plasma C-reactive protein (CRP) concentrations and in the overall patient population enrolled in the study. Calprotectin, a protein mainly contained in neutrophils, is a marker of intestinal inflammation; fecal calprotectin (FC) concentration quantitatively relates to neutrophil migration toward the gastrointestinal tract.3,4 The aim of this post hoc analysis of P1 data was to determine the relationship between concentrations of FC and clinical outcome in pts with active CD. Method(s): In P1 (NCT00152490), adult pts (N=662) with active CD (CD Activity Index [CDAI] 220-450) were randomized to CZP 400 mg or placebo induction at Wks 0, 2, and 4 and then every 4 wks during Wks 6-26. Remission rates (absolute CDAI score <=150) were determined in subgroups of pts stratified by FC concentrations at baseline and Wk 26. Result(s): The overall mean baseline FC concentrations were high (>200 mug/g) or very high (>250 mug/g). Baseline FC concentrations were numerically higher among remitters vs nonremitters for both placebo and CZP groups (Table). The largest decrease in FC concentration at Wk 26 from the baseline level was observed among remitters in the CZP group. No difference in the baseline vs Wk 26 FC concentration was observed among nonremitters in the placebo group. The difference between baseline vs Wk 26 FC concentration for the CZP nonremitter and placebo remitter groups was generally similar and intermediate between the placebo nonremitter and CZP remitter groups. Conclusion(s): High baseline FC concentrations suggest that patients in P1 carried a high inflammatory burden. Correlating inflammatory biomarkers and response to treatment may enhance the understanding of how biomarkers can guide therapy. (Table Presented).

DOI: /10.1038/ajg.2011.336_9

PMID: nan

Full Article: https://doi.org//10.1038/ajg.2011.336_9

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Single-Cell Transcriptomic and Targeted Genomic Profiling Adjusted for Inflammation and Therapy Bias Reveal

Publication Date: Jun 2024

Authors: Gorenjak, Mario; Gole, Boris; Gori■an, Larisa; Jezernik, Gregor; Prosenc Zmrzljak, Uršula; Pernat, Cvetka; Skok, Pavel; Poto■nik, Uroš

Journal: Pharmaceutics

Abstract: The lack of reliable biomarkers in response to anti-TNFα biologicals hinders personalized therapy for Crohn's disease (CD) patients. The motivation behind our study is to shift the paradigm of anti-TNFα biomarker discovery toward specific immune cell sub-populations using single-cell RNA sequencing and an innovative approach designed to uncover PBMCs gene expression signals, which may be masked due to the treatment or ongoing inflammation; Methods: The single-cell RNA sequencing was performed on PBMC samples from CD patients either naïve to biological therapy, in remission while on adalimumab, or while on ustekinumab but previously non-responsive to adalimumab. Sieves for stringent downstream gene selection consisted of gene ontology and independent cohort genomic profiling. Replication and meta-analyses were performed using publicly available raw RNA sequencing files of sorted immune cells and an association analysis summary. Machine learning, Mendelian randomization, and oligogenic risk score methods were deployed to validate DEGs highly relevant to anti-TNFα therapy response; Results: This study found

DOI: 10.3390/pharmaceutics16060835

PMID: 38931955.0

Full Article: https://doi.org/10.3390/pharmaceutics16060835

Methods:

None available

Results:

Single-Cell RNA Sequencing AnalysisTo uncover gene expression signals potentially masked due to the treatment and ongoing inflammation, we performed a three-stage scRNA-seq analysis. Thus, the involvement of targeted regions with ADA non-response is further additionally confirmed.Additionally, information about eQTLs was retrieved from publicly available data sources (Table 3). Out of 24, 18 variants exhibited significant eQTLs with gene expression in selected genomic regions and immune system-related tissues. However, four variants related to the TLR3 gene exhibited significant eQTLs, and one was listed without statistical significance.

Discussion:

This, in turn, yielded 33 genes, which were further analyzed using a modified integration approach with genomic profiling, as previously described [30,82,83]. Furthermore, it was brought to our attention that the PLCB1 gene plays a pivotal role in histone deacetylase HDAC8-mediated protein kinase B (AKT) activation [94]. An additional limitation may also be metadata scarcity from Belgian CD patients (Bioproject: PRJEB32332), which prevented further adjustments of the fitted model. We also state that using GO analysis as a sieve for stringent gene selection may have caused the loss of genes not yet functionally characterized and, thus, should be omitted in studies examining functional connections.

Conclusion:

None available

r to Induction of Biologicals	Sampling Timepoints and Therapy Response Assessments					
Age at Inclusion	Sex	5-Amino-Salicylate	Cortico-Steroids	Azathioprine	T0	A3
59	Male	Yes	Yes	No	S	RE/NA
27	Male	Yes	Yes	Yes	S	RE/RE
63	Female	Yes	Yes	Yes	NA	RE/RE
39	Male	Yes	Yes	No	NA	NR/NR
43	Male	Yes	Yes	Yes	NA	RE/RE

Chr	Base Pair	dbSNP ID	A1	Gene	Rank	Subset	OR	L95	U95	pValue	AdjP Value
17	50,042,849	rs12150443	G	PPP1R9B	5	1	0.3	0.1	0.7	0.009	0.017
11	122,774,340	rs60999716	T	CRTAM	5.3	1	0.2	0.1	0.6	0.004	0.004
4	186,049,848	rs13123257	T	TLR3	6.3	1	4.8	1.7	13.6	0.003	0.021
4	186,100,161	rs9312342	C	TLR3	7.1	1	3.7	1.5	9.1	0.005	0.028
1	27,877,578	rs12140013	C	THEMIS2	8	1	3.9	1.4	10.8	0.008	0.008
9	104,789,257	rs2297406	T	ABCA1	8.1	1	0.1	0.0	0.3	0.001	0.001
2	86,942,294	rs201118660	T	CD8B	8.4	2	16.0	2.1	123.0	0.008	0.008
9	104,982,380	rs4743784	A	ABCA1	9.2	2	0.2	0.1	0.6	0.002	0.004
17	50,222,983	rs67288212	A	PPP1R9B	10	2	16.9	2.2	131.9	0.007	0.014
17	40,458,620	rs10305315	C	CCR7	10.7	2	12.2	2.1	72.7	0.006	0.006
20	8,147,472	rs2327025	T	PLCB1	10.9	2	5.2	1.5	17.6	0.008	0.008
7	18,770,935	rs62446605	A	HDAC9	11.6	2	4.1	1.5	11.8	0.008	0.023
17	74,541,040	rs1532800	C	CD300A	12.4	3	3.8	1.4	10.2	0.010	0.010
4	15,679,295	rs11722854	G	CD38	13.8	3	0.3	0.1	0.7	0.006	0.019
1	221,839,608	rs4579763	A	DUSP10	14.5	3	5.8	1.5	21.9	0.009	0.009
10	96,773,725	rs2861627	A	PIK3AP1	15.1	3	13.2	2.1	83.0	0.006	0.006
4	186,098,752	rs12645085	T	TLR3	15.8	3	0.3	0.1	0.7	0.006	0.037
4	186,028,258	rs62335289	G	TLR3	16.6	3	11.5	2.0	67.8	0.007	0.040
4	15,857,239	rs10001128	A	CD38	17.2	6	3.8	1.5	10.1	0.007	0.020
4	186,077,934	rs6811484	G	TLR3	17.2	6	4.6	1.8	12.0	0.002	0.010
4	15,722,169	rs10018756	T	CD38	17.7	6	0.2	0.1	0.6	0.005	0.015
4	186,063,851	rs35114430	G	TLR3	19.3	6	0.2	0.1	0.6	0.006	0.034
7	18,580,458	rs1012658	C	HDAC9	19.5	6	3.3	1.4	7.8	0.007	0.020
7	18,729,677	rs35242513	G	HDAC9	20.3	6	5.1	1.6	15.7	0.005	0.014

dbSNP ID	Gene	Tissue	NES	SE	pValue
rs12150443	PPP1R9B	Th2 memory	–0.13	0.04	0.0020
rs60999716	CRTAM	CD8+T naïve	–0.058	0.034	0.0912 *
rs13123257	TLR3	T cells	0.18	0.09	0.0427
rs9312342	TLR3	T cells	0.28	0.069	0.0001
rs12140013	THEMIS2	Th1-17 memory	–0.5	0.17	0.0044
rs2297406	ABCA1	T cells	–0.17	0.077	0.0275
rs201118660	CD8B	Tfh memory	1.33	0.65	0.0457
rs4743784	ABCA1	CD4+T cell	–0.26	0.096	0.0072
rs67288212	PPP1R9B	Monocytes	0.075	0.031	0.0155
rs10305315	CCR7	Blood	–0.46	0.18	0.0115
rs2327025	PLCB1	Th1 memory	–0.26	0.094	0.0076
rs62446605	HDAC9	NA	NA	NA	NA
rs1532800	CD300A	Th1-17_memory	0.17	0.071	0.0219
rs11722854	CD38	T cells	–0.074	0.039	0.0562 *
rs4579763	DUSP10	B cell naïve	0.19	0.068	0.0056
rs2861627	PIK3AP1	Th2 memory	–0.37	0.18	0.0490
rs12645085	TLR3	T cells	–0.13	0.071	0.0646 *
rs62335289	TLR3	T cells	0.51	0.21	0.0145
rs10001128	CD38	Blood	0.1	0.045	0.0251
rs6811484	TLR3	Blood	0.11	0.037	0.0040
rs10018756	CD38	Monocytes	0.2	0.077	0.0105
rs35114430	TLR3	Macrophage naïve	–0.21	0.13	0.1072
rs1012658	HDAC9	NA	NA	NA	NA
rs35242513	HDAC9	NA	NA	NA	NA

Gene	scRNA-Seq Cohort		Replication Cohort				Meta-Analysis				
Log2FC	L95	U95	pValue	Log2FC	L95	U95	pValue	Log2FC	L95	U95	pValue	
PLCB1	1.21	0.75	1.67	0.0003	1.36	–0.43	3.15	0.1307	1.22	0.77	1.67	8.43 × 10–8
PPP1R9B	1.00	0.40	1.60	0.0051	0.10	–0.33	0.53	0.6402	0.53	–0.36	1.41	2.44 × 10–1
CD300A	1.03	0.38	1.69	0.0068	–0.18	–1.22	0.86	0.7278	0.50	–0.68	1.67	4.08 × 10–1
HDAC9	1.12	0.38	1.86	0.0086	1.27	–0.76	3.30	0.2111	1.14	0.44	1.83	1.41 × 10–3
ABCA1	1.95	0.78	3.11	0.0050	0.32	–0.62	1.26	0.4872	1.10	–0.49	2.68	1.77 × 10–1
PIK3AP1	1.30	0.07	2.52	0.0404	–2.35	–4.53	–0.16	0.0363	–0.41	–3.97	3.16	8.23 × 10–1

TLR3	1.39	0.02	2.75	0.0469	1.98	0.17	3.79	0.0331	1.60	0.51	2.69	3.91 × 10–3
CD8B	–1.58	–2.34	–0.82	0.0018	–0.72	–3.72	2.28	0.6281	–1.53	–2.26	–0.79	4.85 × 10–5
CRTAM	–1.34	–2.34	–0.34	0.0159	–1.58	–4.27	1.11	0.2370	–1.37	–2.31	–0.43	4.15 × 10–3
CD38	–1.56	–2.54	–0.59	0.0069	–0.32	–1.62	0.98	0.6190	–1.02	–2.23	0.19	9.97 × 10–2
THEMIS2	–2.03	–3.12	–0.94	0.0032	0.07	–0.57	0.71	0.8162	–0.93	–2.99	1.13	3.76 × 10–1
DUSP10	–1.14	–2.17	–0.11	0.0351	–0.38	–1.29	0.52	0.3926	–0.72	–1.45	0.02	5.58 × 10–2
CCR7	–2.14	–3.40	–0.88	0.0053	0.13	–0.31	0.58	0.5422	–0.92	–3.15	1.30	4.15 × 10–1

scRNA-Seq COHORT	Replication Cohort									
dbSNP ID	Gene	A1	OR	AdjP Value	dbSNP ID	D′	A1	pValue	OR	CI95
rs60999716	CRTAM	T	4.12	0.0043	rs10892897	1	T	0.01781	3.42	1.22–9.569
/	/	/	/	/	rs10892893	0.9397	T	0.03554	3.02	1.091–8.383
/	/	/	/	/	rs10892894	0.9354	T	0.00923	3.85	1.374–10.77
rs2327025	PLCB1	T	5.21	0.0079	rs2327025	NA	T	0.01166	4.71	1.339–16.58
rs62446605	HDAC9	A	4.13	0.0233	rs212671	0.5312	G	0.03246	2.93	1.053–8.131
rs4579763	DUSP10	A	5.83	0.0091	rs6673674	1	T	0.04575	3.05	1.062–8.748
rs35242513	HDAC9	G	5.09	0.0144	rs212671	0.6932	G	0.03246	2.93	1.053–8.131

scRNA-Seq Cohort	Replication Cohort	Meta-Analysis									
dbSNP ID	OR	L95	U95	dbSNP ID	OR	L95	U95	OR	L95	U95	pValue
rs60999716	4.12	1.56	10.89	rs10892897	3.42	1.22	9.57	3.77	1.86	7.65	0.0002
/	/	/	/	rs10892893	3.024	1.091	8.38	3.56	1.76	7.19	0.0004
/	/	/	/	rs10892894	3.846	1.374	10.77	3.99	1.97	8.09	0.0001
rs2327025	5.21	1.54	17.59	rs2327025	4.71	1.34	16.58	4.96	2.07	11.90	0.0003
rs62446605	4.13	1.45	11.75	rs212671	2.93	1.05	8.13	3.46	1.67	7.19	0.0009
rs4579763	5.83	1.55	21.93	rs6673674	3.05	1.06	8.75	3.92	1.72	8.94	0.0012
rs35242513	5.09	1.64	15.75	rs212671	2.93	1.05	8.13	3.76	1.76	8.01	0.0006

dbSNP ID	Gene	Tissue	NES	SE	pValue
rs10892893	CRTAM	Blood	–0.079	0.039	0.0427
rs10892897	CRTAM	T cells	0.13	0.072	0.0646
rs10892894	CRTAM	T cells	0.15	0.073	0.0417
rs212671	HDAC9	NA	NA	NA	NA
rs6673674	DUSP10	Blood	0.03	0.014	0.0339

Title: Highly stable epigenome-wide peripheral blood DNA methylation signatures accurately predict endoscopic response to adalimumab, vedolizumab and ustekinumab in Crohn's disease patients: The EPIC-CD study

Publication Date: nan

Authors: Joustra V.; Li Yim A.; Hageman I.; Levin E.; Noble A.; Chapman T.; McGregor C.; Adams A.; Satsangi J.; De Jonge W.; Henneman P.; D'Haens G.

Journal: nan

Abstract: Background: Despite the proven efficacy of biological treatments in Crohn's disease (CD), many patients fail to respond or lose response over time. Therefore, predictive biomarkers for treatment efficacy would be of extreme value. Previous epigenome-wide association studies associated differential DNA methylation with CD-specific phenotypes suggesting a potential use in classification and prediction of response to treatment Methods: We prospectively collected and measured longitudinal peripheral blood DNA methylation profiles of 184 adult CD patients prior to (T1) and after a median of 28 weeks (T2) following biological treatment with Adalimumab (ADA), Vedolizumab (VEDO) or Ustekinumab (USTE) in a discovery (n=88) and independently collected internal validation cohort (n=96) using the Illumina EPIC BeadChip array. Response (R) was defined as the combination of endoscopic response (>50% reduction in SES-CD score) and steroid- free clinical response (>3 point drop in HBI or HBI <=4 AND no systemic steroids) and/or biochemical response (>50% reduction in C-reactive protein (CRP) and fecal calprotectin or a CRP <=5 g/mL and fecal calprotectin <=250 betag/g). Biomarker identification and classification analyses were performed using stability selection gradient boosting on samples taken at T1 whereas samples taken at T2 and intraclass correlation (ICC) data were used to assess long-term stability of our identified CpG loci1 Results: A total of 58 ADA-patients (NR=29, NNR=29), 64 VEDOpatients (NR=36, NNR=28) and 62 USTE-patients (NR=30, NNR=32) were included. Prior to treatment, at T1, we identified distinct panels of 100 ADA-, 22 VEDO- and 68 USTE-associated CpG loci that, in combination predict clinical- and endoscopic response with high accuracy (AUC ADA=0.73, VEDO=0.89 and USTE=0.94) upon validation Notably, for these CpG loci, methylation levels did not significantly differ between T1 and T2, implicating stability during both induction and maintenance treatment, irrespective of inflammatory status and therapeutic intervention. In addition, the majority of these CpG loci (>60%) demonstrated long-term hyper stability (ICC-values >0.90) Furthermore, genes annotated to the CpGs of interest suggest drug specific involvement in TNF-signaling, endothelial cell-cell adhesion, integrin dependent T-cell homing, the innate immune system and Th17/ Treg differentiation, corroborating to the mode of action of each drug (Figure Presented) . Conclusion(s): Here, we report on 3 validated panels of highly stable, epigenetic biomarkers that predict clinical and endoscopic response in CD patients treated with ADA, VEDO or USTE. Additional external- and clinical validation as part of EPIC-CD and the OMICROHN clinical trial are currently ongoing .

DOI: /10.1093/ecco-jcc/jjac190.0003

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjac190.0003

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Genome-wide association study of baseline disease characteristics and response to Ustekinumab in moderate to severe Crohn's disease

Publication Date: nan

Authors: Hart A.; Li K.; Gasink C.; Jacobstein D.; Brodmerkel C.

Journal: nan

Abstract: Background: Both genetic & environmental risk factors contribute to Crohn's disease (CD) susceptibility, & genetic biomarkers may allow for the characterization of disease activity & severity as well as response to therapeutic agents. Here, we evaluated the association of genetic polymorphisms with baseline disease characteristics & the response to ustekinumab (UST), an anti-IL12/23p40 monoclonal an-tibody, in the phase 3 UNITI program. Method(s): The UNITI studies assessed the safety & efficacy of UST induction & maintenance therapy in patients (pts) with moderate-severe CD who had previously failed TNF-antagonist therapy (UNITI-1) or who had previously failed conventional therapy & were largely TNF antagonist-naive (UNITI-2). Pts that responded in the induction studies were re-randomized in IM-UNITI maintenance study. 902 pts were genotyped genome-wide on the Illumina Infinium Omni5Exome platform (UNITI-1 n=479, UNITI-2 n=423). We evaluated genetic associations with baseline disease, induction wk8 response, & maintenance wk44 response phenotypes using linear or logistic regression models. Analyses were conducted separately within each study & meta-analyzed. We performed both targeted & genome-wide analyses, where the targeted analyses evaluated asso-ciations with 185 candidate SNPs in the IL12/23 pathway or previously associated with IBD risk. Significance thresholds were set at 2.7x10-4 for candidate gene analyses & 5x10-8 for the GWAS to account for multiple testing. Result(s): We did not identify any statistically significant associations with IL12/23 candidate SNPs, suggesting that pts respond equally well to UST regardless of genotype or that we did not have the power to detect these associations given our limited sample size. GWAS analyses identified two associations with response phenotypes that met statistical significance. The first was an association at a locus upstream of the TWSG1 gene on chromosome 18;these SNPs were associated with change in CDAI & remission at wk8, where pts carrying the minor allele had better response to UST. Interestingly, SNPs at this locus have been associated with TWSG1 expression within the GTEx dataset (www.gtexportal.org), suggesting a possible functional link. The second association was between change in CDAI at wk8 & an intergenic locus on chromosome 8 located between the SFRP1 & GOLGA7 genes, where pts carrying two copies of the minor allele had the greatest decrease in CDAI after treatment. Conclusion(s): These results suggest that SNPs in the IL12/23 pathway & SNPs associated with IBD disease risk may not influence responses to UST. Additionally, the genome-wide analyses nominate new candidate genes that may be influencing UST response, although these results must be replicated in an independent cohort.

DOI: /10.1093/ecco-jcc/jjx002.083

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjx002.083

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Exploration of Predictive Biomarkers of Early Infliximab Response in Acute Severe Colitis: A Prospective Pilot Study.

Publication Date: Feb 2018

Authors: Beswick, Lauren; Rosella, Ourania; Rosella, Gennaro; Headon, Belinda; Sparrow, Miles P; Gibson, Peter R; van Langenberg, Daniel R

Journal: Journal of Crohn's & colitis

Abstract: The outcomes of acute severe ulcerative colitis [ASUC] appear to be dependent on early intervention with the first and/or further infliximab [IFX] doses, although parameters to guide decision-making remain uncertain.

DOI: 10.1093/ecco-jcc/jjx146

PMID: 29121178.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjx146

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Omics data integration identifies ELOVL7 and MMD gene regions as novel loci for adalimumab response in patients with Crohn's disease.

Publication Date: Mar 2021

Authors: Gorenjak, Mario; Zupin, Mateja; Jezernik, Gregor; Skok, Pavel; Poto■nik, Uroš

Journal: Scientific reports

Abstract: Response to anti-TNF therapy is of pivotal importance in patients with Crohn's disease (CD). Here we integrated our and previously reported PBMC derived transcriptomic and genomic data for identification of biomarkers for discrimination between responders and non-responders to anti-TNF therapy. CD patients, who were naïve with respect to the treatment with biologicals, were enrolled in the study. DNA and RNA were extracted from peripheral blood mononuclear cells. RNA-seq was performed using BGISEQ-500. Genotyping was performed using Infinium Global Screening Array. Association regressions were carried out with 12 week response to adalimumab as an outcome variable. RNA-seq analysis confirmed 7 out of 65 previously suggested genes involved in anti-TNF response. Subsequently, analysis of single nucleotide variants in regions of confirmed genes identified 5 variants near MMD and two in ELOVL7 intronic regions associated with treatment response to anti-TNF. Functional analysis has shown that rs1465352, rs4422035 and rs78620886 are listed at H3K9ac_Pro histone modification epigenetic mark. The present study confirmed MMD and ELOVL7 involvement in anti-TNF response and revealed that the regulation of MMD and ELOVL7 gene regions in ADA response may be a part of a complex interplay extending from genetic to epigenetic and to transcriptomic level.

DOI: 10.1038/s41598-021-84909-z

PMID: 33750834.0

Full Article: https://doi.org/10.1038/s41598-021-84909-z

Methods:

The present study was evaluated and approved by Slovenian National Committee for Medical Ethics (KME 80/10/07, 21p/12/07). Differential expression was considered for genes with adjusted p-value < 0.05.Association analysisSamples obtained from 84 enrolled individuals were genotyped using Infinium Global Screening Array (GSA_24v1) (Illumina, San Diego, California, USA). Condition SNP and SNPs, which remained significant after conditioning, were included in subsequent Mendelian randomization analysis. eQTLs based on the study data were estimated for SNPs where chromatin state assignment was listed.

Results:

ResultsRNA-seq analysisUsing our RNA sequencing data we performed an expression study using previously suggested candidate genes discriminating anti-TNF response in CD patients. The analysis has confirmed 10 differentially expressed genes out of which 4 (GPR84, EPSTI1, IFI6, MX1) remained significantly up-regulated after correction for multiple comparison in responders relative to non-responders (Table 2, Fig. The plots were constructed using ggplot2 R package23.Full size imageIntegration to genomicsUsing an integrative transcriptomic-genomic approach we analyzed single nucleotide variants ranging ± 100 kb from previously identified differentially expressed genes in 84 patients with CD. Identified rs9892429, rs9893820 and rs11656799 have shown higher linkage disequilibrium with rs1465352 (D′: 1.0; r2: 0.96; p < 10–4) as in comparison to most significant rs4422035, which is also evident from the Table 3.

Discussion:

Thus, the targeted expression panel consisted altogether of 65 genes, which were previously identified in 2126 individuals with IBD and 34 individuals with RA as potential predictors for different anti-TNF therapy (ADA, IFX, golimumab) responses in peripheral blood of CD, UC, unclassified IBD or RA patients18,20,21,22.First, using RNA-seq and using 3 responders and 3 non-responders to ADA we confirmed differentially expressed genes from previously identified gene panel. The results have shown that in deconvoluted analysis MMD, ELOVL7 and BMP6 remained significantly differentially expressed after correction for multiple comparisons. Additionally, the implication of aforementioned SNPs in ADA response was also confirmed using random forest machine learning algorithm and ROC analysis, which has additionally confirmed the association of these three SNPs with ADA response in patients with CD. This knowledge could be further translated into new clinical non-invasive baseline biomarkers for adalimumab response in patients with CD.

Conclusion:

None available

Title: Baseline Expression of Immune Gene Modules in Blood is Associated With Primary Response to Anti-TNF Therapy in Crohn's Disease Patients.

Publication Date: Mar 2024

Authors: Bai, Benjamin Y H; Reppell, Mark; Smaoui, Nizar; Waring, Jeffrey F; Pivorunas, Valerie; Guay, Heath; Lin, Simeng; Chanchlani, Neil; Bewshea, Claire; Goodhand, James R; Kennedy, Nicholas A; Ahmad, Tariq; Anderson, Carl A; ,

Journal: Journal of Crohn's & colitis

Abstract: Anti-tumour necrosis factor [anti-TNF] therapy is widely used for the treatment of inflammatory bowel disease, yet many patients are primary non-responders, failing to respond to induction therapy. We aimed to identify blood gene expression differences between primary responders and primary non-responders to anti-TNF monoclonal antibodies [infliximab and adalimumab], and to predict response status from blood gene expression and clinical data.

DOI: 10.1093/ecco-jcc/jjad166

PMID: 37776235.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjad166

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Endoscopic Activity and Serum TNF-α Level at Baseline Are Associated With Clinical Response to Ustekinumab in Crohn's Disease Patients.

Publication Date: Oct 2020

Authors: Murate, Kentaro; Maeda, Keiko; Nakamura, Masanao; Sugiyama, Daisuke; Wada, Hirotaka; Yamamura, Takeshi; Sawada, Tsunaki; Mizutani, Yasuyuki; Ishikawa, Takuya; Furukawa, Kazuhiro; Ohno, Eizaburo; Honda, Takashi; Kawashima, Hiroki; Miyahara, Ryoji; Ishigami, Masatoshi; Nishikawa, Hiroyoshi; Fujishiro, Mitsuhiro

Journal: Inflammatory bowel diseases

Abstract: The therapeutic efficacy and safety of ustekinumab for Crohn's disease (CD) have been reported from randomized controlled trials and real-world data. However, there are few studies describing the identification of patients most suitable for ustekinumab therapy. The aim of this study was to prospectively evaluate the patients receiving ustekinumab and identify predictors of the treatment efficacy.

DOI: 10.1093/ibd/izaa086

PMID: 32405651.0

Full Article: https://doi.org/10.1093/ibd/izaa086

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Evaluation of responsive gene expression as a sensitive and specific biomarker in patients with ulcerative colitis.

Publication Date: Feb 2013

Authors: Román, Juan; Planell, Núria; Lozano, Juan J; Aceituno, Montserrat; Esteller, Miriam; Pontes, Caridad; Balsa, Dolors; Merlos, Manuel; Panés, Julián; Salas, Azucena

Journal: Inflammatory bowel diseases

Abstract: Clinical trials in ulcerative colitis (UC) rely on certain parameters to evaluate responses that are highly subjective or of low sensitivity. Here, using a select group of genes, we tested the accuracy of gene expression analysis as a biomarker of clinical, endoscopic, and histologic improvements.

DOI: 10.1002/ibd.23020

PMID: 22605655.0

Full Article: https://doi.org/10.1002/ibd.23020

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Accuracies of fecal calprotectin, lactoferrin, M2-pyruvate kinase, neopterin and zonulin to predict the response to infliximab in ulcerative colitis.

Publication Date: Jan 2017

Authors: Frin, Anne-Claire; Filippi, Jérôme; Boschetti, Gilles; Flourie, Bernard; Drai, Jocelyne; Ferrari, Patricia; Hebuterne, Xavier; Nancey, Stéphane

Journal: Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver

Abstract: Fecal markers might predict the response to anti-TNFα in ulcerative colitis (UC).

DOI: 10.1016/j.dld.2016.09.001

PMID: 27693318.0

Full Article: https://doi.org/10.1016/j.dld.2016.09.001

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Correlation Between Concentrations of Fecal Calprotectin and Outcomes of Patients With Ulcerative Colitis in a Phase 2 Trial.

Publication Date: 2016 Jan

Authors: Sandborn WJ; Panes J; Zhang H; Yu D; Niezychowski W; Su C

Journal: nan

Abstract: BACKGROUND & AIMS: Accurate biomarkers of disease activity and therapeutic response can be valuable for clinical trials. We performed a post hoc analysis of data from a phase 2 trial to assess the relationship between the concentration of fecal calprotectin (FCP) and clinical and endoscopic outcomes of patients with moderate to severe ulcerative colitis receiving tofacitinib.

DOI: /10.1053/j.gastro.2015.09.001

PMID: nan

Full Article: https://doi.org//10.1053/j.gastro.2015.09.001

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Correlation Between Concentrations of Fecal Calprotectin and Outcomes of Patients With Ulcerative Colitis in a Phase 2 Trial.

Publication Date: Jan 2016

Authors: Sandborn, William J; Panés, Julian; Zhang, Haiying; Yu, Dahong; Niezychowski, Wojciech; Su, Chinyu

Journal: Gastroenterology

Abstract: Accurate biomarkers of disease activity and therapeutic response can be valuable for clinical trials. We performed a post hoc analysis of data from a phase 2 trial to assess the relationship between the concentration of fecal calprotectin (FCP) and clinical and endoscopic outcomes of patients with moderate to severe ulcerative colitis receiving tofacitinib.

DOI: 10.1053/j.gastro.2015.09.001

PMID: 26376350.0

Full Article: https://doi.org/10.1053/j.gastro.2015.09.001

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Biological characteristics of molecular subtypes of ulcerative colitis characterized by ferroptosis and neutrophil infiltration.

Publication Date: Apr 2024

Authors: Sun, Shaopeng; Mao, Yuqing; Le, Sihua; Zheng, Mingxu; Li, Menglin; Chen, Yifei; Chen, Jiajia; Fan, Yihong; Lv, Bin

Journal: Scientific reports

Abstract: Clinical ulcerative colitis (UC) is a heterogeneous condition. Moreover, medical interventions are nonspecific, and thus, treatment responses are inconsistent. The aim of this study was to explore the molecular subtypes and biological characteristics of UC based on ferroptosis and neutrophil gene sets. Multiple intestinal mucosa gene expression profiles of UC patients in the Gene Expression Omnibus (GEO) database were downloaded. Unsupervised clustering methods were used to identify potential molecular subtypes based on ferroptosis and neutrophil gene sets. Multiple immune infiltration algorithms were used to evaluate the biological characteristics of the molecular subtypes. Machine learning identifies hub genes for molecular subtypes and analyses their diagnostic efficacy for UC and predictive performance for drug therapy. The relevant conclusions were verified by clinical samples and animal experiments. Four molecular subtypes were identified according to the ferroptosis and neutrophil gene sets: neutrophil, ferroptosis, mixed and quiescent. The subtypes have different biological characteristics and immune infiltration levels. Multiple machine learning methods jointly identified four hub genes (FTH1, AQP9, STEAP3 and STEAP4). Receiver operating characteristic (ROC) curve analysis revealed that the four hub genes could be used as diagnostic markers for UC. The clinical response profile data of infliximab treatment patients showed that AQP9 and STEPA4 were reliable predictors of infliximab treatment response. In human samples the AQP9 and STEAP4 protein were shown to be increased in UC intestinal samples. In animal experiments, the ferroptosis and neutrophil phenotype were confirmed. Dual analysis of ferroptosis and neutrophil gene expression revealed four subgroups of UC patients. The molecular subtype-associated hub genes can be used as diagnostic markers for UC and predict infliximab treatment response.

DOI: 10.1038/s41598-024-60137-z

PMID: 38664443.0

Full Article: https://doi.org/10.1038/s41598-024-60137-z

Methods:

Transmission electron microscopy (TEM) was used to observe the mitochondrial morphology of intestinal mucosal cells. All methods for animals were performed in accordance with the relevant guidelines and regulations. These analyses were completed using the R package “CIBERSORT”.Biological characteristics of the molecular subtypesWeighted correlation network analysis (WGCNA) can be used to identify cocorrelated genes, identify gene sets with potential coregulatory patterns, and divide genes into different modules. In this study, we constructed a weighted gene coexpression network using the R “WGCNA” package29 with approximately scale-free properties30.

Results:

(A) Heatmap depicting the consensus clustering solution (k = 3) for ferroptosis and neutrophil genes in UC samples (n = 298). (B) Scatter plot showing the median expression levels of ferroptosis (x-axis) and neutrophil (y-axis) genes in each UC sample. Diagnostic gene selection was performed using the Boruta (A), LASSO (B), SVM (C), random forest (D) and XGBoost (E) models. 5A), the protein levels of AQP9 and STEAP4 were also significantly upregulated in UC patients compared with HC individuals

(Fig.

Discussion:

The pathophysiological mechanism is complex, and medical interventions are nonspecific, which leads to inconsistent treatment responses46,47. We were particularly interested in the mixed phenotype because this group had high expression of both iron death-related and neutrophil signature genes. We carried out human sample and animal experiments to demonstrate the reliability of our conclusions. In the future, a large number of clinical samples are still needed for heterogeneity verification.

Conclusion:

None available

Title: Proteomics for prediction and characterization of response to infliximab in Crohn's disease: a pilot study.

Publication Date: Aug 2008

Authors: Meuwis, Marie-Alice; Fillet, Marianne; Lutteri, Laurence; Marée, Raphaël; Geurts, Pierre; de Seny, Dominique; Malaise, Michel; Chapelle, Jean-Paul; Wehenkel, Louis; Belaiche, Jacques; Merville, Marie-Paule; Louis, Edouard

Journal: Clinical biochemistry

Abstract: Infliximab is the first anti-TNFalpha accepted by the Food and Drug Administration for use in inflammatory bowel disease treatment. Few clinical, biological and genetic factors tend to predict response in Crohn's disease (CD) patient subcategories, none widely predicting response to infliximab.

DOI: 10.1016/j.clinbiochem.2008.04.021

PMID: 18489908.0

Full Article: https://doi.org/10.1016/j.clinbiochem.2008.04.021

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Machine learning using clinical data at baseline predicts the efficacy of vedolizumab at week 22 in patients with ulcerative colitis.

Publication Date: Aug 2021

Authors: Miyoshi, Jun; Maeda, Tsubasa; Matsuoka, Katsuyoshi; Saito, Daisuke; Miyoshi, Sawako; Matsuura, Minoru; Okamoto, Susumu; Tamura, Satoshi; Hisamatsu, Tadakazu

Journal: Scientific reports

Abstract: Predicting the response of patients with ulcerative colitis (UC) to a biologic such as vedolizumab (VDZ) before administration is an unmet need for optimizing individual patient treatment. We hypothesized that the machine-learning approach with daily clinical information can be a new, promising strategy for developing a drug-efficacy prediction tool. Random forest with grid search and cross-validation was employed in Cohort 1 to determine the contribution of clinical features at baseline (week 0) to steroid-free clinical remission (SFCR) with VDZ at week 22. Among 49 clinical features including sex, age, height, body weight, BMI, disease duration/phenotype, treatment history, clinical activity, endoscopic activity, and blood test items, the top eight features (partial Mayo score, MCH, BMI, BUN, concomitant use of AZA, lymphocyte fraction, height, and CRP) were selected for logistic regression to develop a prediction model for SFCR at week 22. In the validation using the external Cohort 2, the positive and negative predictive values of the prediction model were 54.5% and 92.3%, respectively. The prediction tool appeared useful for identifying patients with UC who would not achieve SFCR at week 22 during VDZ therapy. This study provides a proof-of-concept that machine learning using real-world data could permit personalized treatment for UC.

DOI: 10.1038/s41598-021-96019-x

PMID: 34385588.0

Full Article: https://doi.org/10.1038/s41598-021-96019-x

Methods:

Subjects who terminated VDZ treatment (switching to other medications) or needed surgery because of insufficient control of UC disease activity before week 22 were regarded as not achieving clinical remission at week 22.Machine learning and prediction toolsTo investigate clinical features related to SFCR during VDZ treatment at week 22, the data of 49 clinical features at week 0 were obtained from the Kyorin medical record system for patients in Cohort 1. The examined features included sex, age, height, body weight, body mass index (BMI), disease duration, disease type (inflammation distribution), treatment history for UC, clinical activity, endoscopic activity, and 25 blood test items (Table 1). Colonoscopy performed within 3 months before starting VDZ therapy was employed to obtain the baseline endoscopic findings. Next, logistic regression was used to develop a prediction tool in this study.

Results:

The results of 25 blood test items at week 0 are presented in Table 2. SFCR at week 22 was achieved in 13 patients (37.1%; seven men and six women). When the top 8 features (pMayo score, MCH, BMI, BUN, concomitant use of AZA, Lympho fraction, height, and CRP) were employed, the predictive accuracy was 100% in Cohort 1, versus 68.6% in Cohort 2. MCH mean corpuscular hemoglobin, BMI body mass index, BUN blood urea nitrogen, AZA azathioprine, CRP C-reactive protein, MCV mean corpuscular volume, UCEIS ulcerative colitis endoscopic index of severity, eGFR estimated glomerular filtration rate, ALT alanine amino transferase, GGT gamma-glutamyl transpeptidase, MCHC mean corpuscular hemoglobin concentration, 5-ASA 5-aminosalicylic acid, TAC tacrolimus, TNF tumor necrosis factor, TOF tofacitinib, PSL prednisolone, GMA granulocyte and monocyte apheresis.Full size

imageTable 4 Predictive accuracy of logistic regression models for steroid-free clinical remission at week 22 comprising the top 10 contributing clinical features.Full size tableThe calculated value of y and the accuracy of the prediction in each patient in Cohorts 1 and 2 are presented in Supplemental Table 1.

Discussion:

Logistic regression was employed in this study to develop a prediction tool with clinical features using the eight largest contributors; pMayo score, MCH (pg), BMI, BUN (mg/dL), concomitant use of AZA, Lympho fraction (%), height (cm), and CRP (mg/dL). Higher MCH levels suggest that bleeding attributable to UC and iron, vitamin B12, or folic acid deficiency are less severe. Barré et al. reviewed several reports on the predictors of VDZ treatment for UC and noted that severe disease activity at induction is a negative predictor6. Together with these reports and our findings, we speculate that adjusting the dose of VDZ depending on BMI could increase its efficacy.

Conclusion:

None available

Title: Crohn's Patient Serum Proteomics Reveals Response Signature for Infliximab but not Vedolizumab.

Publication Date: Feb 2024

Authors: Gonzalez, Carlos G; Stevens, Toer W; Verstockt, Bram; Gonzalez, David J; D'Haens, Geert; Dulai, Parambir S

Journal: Inflammatory bowel diseases

Abstract: Crohn's disease is a chronic inflammatory bowel disease that affects the gastrointestinal tract. Common biologic families used to treat Crohn's are tumor necrosis factor (TNF)-α blockers (infliximab and adalimumab) and immune cell adhesion blockers (vedolizumab). Given their differing mechanisms of action, the ability to monitor response and predict treatment efficacy via easy-to-obtain blood draws remains an unmet need.

DOI: 10.1093/ibd/izae016

PMID: 38367209.0

Full Article: https://doi.org/10.1093/ibd/izae016

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Machine learning gene expression predicting model for ustekinumab response in patients with Crohn's disease.

Publication Date: Dec 2021

Authors: He, Manrong; Li, Chao; Tang, Wanxin; Kang, Yingxi; Zuo, Yongdi; Wang, Yufang

Journal: Immunity, inflammation and disease

Abstract: Recent studies reported the responses of ustekinumab (UST) for the treatment of Crohn's disease (CD) differ among patients, while the cause was unrevealed. The study aimed to develop a prediction model based on the gene transcription profiling of patients with CD in response to UST.

DOI: 10.1002/iid3.506

PMID: 34469062.0

Full Article: https://doi.org/10.1002/iid3.506

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: A metabolomics-driven model for early remission prediction following vedolizumab treatment in patients with moderate-to-severe active ulcerative colitis.

Publication Date: Feb 2024

Authors: Jiang, Leilei; Liu, Xiaoming; Su, Yue; Chen, Yujie; Yang, Shaozhi; Ke, Xiquan; Yao, Kunhou; Guo, Zhiguo

Journal: International immunopharmacology

Abstract: To predict early remission following anti-integrin therapy (vedolizumab [VDZ]) in patients with moderate-to-severe active ulcerative colitis (UC) using non-invasive biomarkers. The clinical data of a cohort of 33 patients with moderate-to-severe active UC admitted to the Department of Gastroenterology at Suzhou Municipal Hospital between January 2021 and December 2022 were collected. Of these, 9 patients declined VDZ treatment, and 21 received VDZ at doses of 300 mg weeks 0, 2, and 6, each administered within a 30-minute infusion period. The treatment regimen aimed to induce remission of clinical symptoms; hence, the same dose was administered every 8 weeks. At weeks 0 and 14, serum C-reactive protein (CRP) and erythrocyte sedimentation rate were measured using a modified Mayo score. In addition to clinical assessment, stool samples at baseline and weeks 14 were collected and evaluated using 16SrRNA gene sequencing and gas chromatography-mass spectrometry (GC-MS). Clinical remission was determined based on the clinical symptoms and partial Mayo scores. In patients who received VDZ, the strains of bifidobacterium longum (P = 0.022) and bacteroides sartorii (P = 0.039) significantly increased after treatment than before treatment. GC-MS analysis showed that taurine (P = 0.047) and putrescine (P = 0.035) significantly decreased after treatment. Furthermore, while acetamide exhibited a notable increase (P = 0.001), arachidic acid (P < 0.001) and behenic acid (P = 0.005) demonstrated statistically significant elevations. The combined prediction model of acetamide, taurine, and putrescine demonstrated a high predictive value of early remission in patients with moderate-to-severe active UC following VDZ treatment (area under the curve = 0.911, P = 0.014).

DOI: 10.1016/j.intimp.2024.111527

PMID: 38215655.0

Full Article: https://doi.org/10.1016/j.intimp.2024.111527

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Noninvasive biomarkers as surrogate predictors of clinical and endoscopic remission after infliximab induction in patients with refractory ulcerative colitis.

Publication Date: 2017

Authors: Hassan, Elham A; Ramadan, Haidi K; Ismael, Ali A; Mohamed, Khaled F; El-Attar, Madiha M; Alhelali, Ihab

Journal: Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association

Abstract: Treatment of refractory ulcerative colitis (UC) is a clinical challenge, and after biological therapy, monitoring clinical and endoscopic responses is fundamental. We aimed to investigate and compare the predictive power of different noninvasive parameters for clinical remission and mucosal healing after infliximab induction therapy in refractory UC patients.

DOI: 10.4103/sjg.SJG_599_16

PMID: 28721978.0

Full Article: https://doi.org/10.4103/sjg.SJG_599_16

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Differences in Whole-Blood Transcriptional Profiles in Inflammatory Bowel Disease Patients Responding to Vedolizumab Compared with Non-Responders.

Publication Date: Mar 2023

Authors: Haglund, Sofie; Söderman, Jan; Almer, Sven

Journal: International journal of molecular sciences

Abstract: Vedolizumab is efficacious in the treatment of Crohn's disease (CD) and ulcerative colitis (UC). However, a significant proportion of patients present with a non-response. To investigate whether differences in the clinical response to vedolizumab is reflected in changes in gene expression levels in whole blood, samples were collected at baseline before treatment, and at follow-up after 10-12 weeks. Whole genome transcriptional profiles were established by RNA sequencing. Before treatment, no differentially expressed genes were noted between responders (

DOI: 10.3390/ijms24065820

PMID: 36982892.0

Full Article: https://doi.org/10.3390/ijms24065820

Methods:

None available

Results:

However, the serum concentration of C-reactive protein (CRP) was higher in responders compared with non-responders at both time points. Response to TreatmentThere was no difference in the plasma concentrations of VDZ between responders and non-responders at T1 (Table 1). Gene-Expression in Responders Compared with Non-RespondersNo DEGs were observed between responders (n = 9) and non-responders (n = 11), neither when analysing transcriptional profiles at baseline (T0), nor were any detected at follow-up (T1) under treatment (Table S3: Sheets 1–2). The pathways uniquely downregulated in responders (n = 184) were represented by, e.g., “actin dynamics for phagocytic cup formation”, “FCGR3A-mediated phagocytosis”, “Toll-like receptor activating cascades”, “platelet activation and degranulation”, and “detoxification of reactive oxygen species”.In non-responders, 156 pathways in total (including the 22 above) were uniquely downregulated at follow-up (e.g processes of the “cell cycle” and “DNA replication”, “anaphase promoting complex mediated degradation of cell cycle proteins” and “interferon signaling”), but only one pathway (“protein–protein interactions at synapses”) was uniquely upregulated (Table S4, Sheet 5).

Discussion:

We did not find any individual DEGs in the whole blood of non-responders at follow-up when compared with baseline. Indeed, VDZ binds to $\alpha 4\beta 7$ on B cells [30], but little is known about the effect of this binding. Therefore, it has been suggested that $\alpha 4\beta 7$-directed therapy alone may leave additional compensatory homing mechanisms active [39,40], which merits further investigation. Even though our pathway analyses showed promising results, our data also indicated that the use of blood as matrix is not suitable for identifying single or a few candidate genes able to predict response to VDZ already at baseline.

Conclusion:

None available

IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn's disease
VDZ	vedolizumab
sHBI	simplified Harvey Bradshaw index
SCCAI	Simple Clinical Colitis Activity Index
PGA	physician global assessment
DEGs	differentially expressed genes
FC	fold-change
FDR	false discovery rate
ORA	over-representation analysis
GSEA	gene set enrichment analysis
NES	normalized enrichment score
CRP	C-reactive protein
Hb	haemoglobin
Alb	albumin

		Responders (n= 13)	p-Value T0-T1	Non-Responders (n= 11)	p-Value T0–T1	p-Value at T0 or T1
Disease UC/CD		6/7		3/8		0.42
Gender (female/male)		4/9		3/8		1.00
Age (years)		30.2 (16.6)		37.6 (30.2)		0.28
Disease duration (years)		10.2 (13.5)		16.3 (15.2)		0.26
Days since last anti-TNF-α drug†		77 (1593)		99 (763)		0.98
Duration last anti-TNF-α drug (days)†		202 (356)		267 (903)		0.10
Disease activity UC	T0	11 (3)		10 (5)		0.52
	T1	6 (6)	0.02	8 (9)	1.00	0.52
	6 months‡	3 (4)	0.09	8 (15)	0.79	1.00
Disease activity CD	T0	10 (5)		7 (5)		0.14
	T1	4 (4)	0.03	8 (6)	0.55	0.28
	6 months§	6 (3)	0.07	6 (9)	0.11	0.91
Clinical remission	T0	1		2		0.57
	T1	4		2		0.65
PGA	T0	2 (0)		2 (0)		0.69

	T1	1 (1)	0.04	2 (1)	0.11	1.00
f-Calprotectin (mg/kg feces)	T0¶	1390 (2112)		549.5 (877)		0.11
	T1††	191 (1417)	0.06	266 (269)	0.58	0.96
s-CRP (mg/L)	T0	9.0 (21.0)		3.0 (5.0)		0.02
	T1	13.0 (14.0)	0.23	3.0 (1.0)	0.83	0.01
b-Leukocyte count (×109/L)	T0	9.2 (4.1)		9.2 (4.0)		0.86
	T1‡‡	8.35 (3.0)	0.16	7.8 (3.4)	0.32	0.98
b-Hb (g/L)	T0	130 (17)		133 (22)		0.57
	T1§§	125 (25)	0.39	140 (25)	0.79	0.35
s-Alb (g/L)	T0	35 (6)		37 (6)		0.57
	T1	35 (1)	0.48	36 (4)	0.62	0.46
Dose VDZ (mg/kg body weight)						
		4.1 (0.47)		3.9 (1.2)		0.65
p-VDZ at follow-up (T1) (µg/mL)		10.5 (9.9)		16.2 (8.1)		0.19

Pathway Enrichment	Reactome	
	Up	Down
T0 Responders vs. Non-responders	279	46
T1 Responders vs. Non-responders	33	7
Responders T1 vs. T0	51	221
Non-responders T1 vs. T0	1	193

Pathways Upregulated in Responders	Size	NES	FDRp-Value
Amino acid transport across the plasma membrane	19	2.30	2.44 × 10–4
Regulation of actin dynamics for phagocytic cup formation	61	2.27	8.12 × 10–5
FCGR3A-mediated phagocytosis	58	2.27	4.87 × 10–5
Glycosaminoglucan metabolism	70	2.18	3.65 × 10–4
EPH-Ephrin signaling	66	2.13	8.33 × 10–4
Pathways Downregulated in Responders			
Mitochondrial translation initiation	82	–2.41	<1.00 × 10–5
Mitochondrial translation termination	82	–2.40	<1.00 × 10–5
Mitochondrial translation	88	–2.40	<1.00 × 10–5
tRNA processing	93	–2.26	3.10 × 10–5
rRNA processing in the nucleus and cytosol	171	2.05	<1.00 × 10–5

Pathways Upregulated in Responders	Size	NES	FDRp-Value
L13-mediated translational silencing of ceruloplasmin expression	107	2.28	2.67 × 10–4
GTP hydrolysis and joining of the 60S ribosomal subunit	108	2.26	2.26 × 10–4
Eukaryotic translation elongation	87	2.25	2.42 × 10–4
Peptide chain elongation	85	2.24	2.04 × 10–4
Viral mRNA translation	85	2.21	2.35 × 10–4
Pathways Downregulated in Responders			
Interferon alpha beta signaling	49	–2.11	1.03 × 10–2
Antigen processing cross-presentation	94	–1.98	5.31 × 10–2
Interferon gamma signaling	75	–1.97	4.15 × 10–2
ADP signaling through P2Y purinoceptor	14	–1.90	7.14 × 10–2
ER-phagosome pathway	80	–1.89	7.01 × 10–2

Title: Multi-alleles predict primary non-response to infliximab therapy in Crohn's disease.

Publication Date: Oct 2021

Authors: Zhang, Cai-Bin; Tang, Jian; Wang, Xue-Ding; Lyu, Kun-Sheng; Huang, Min; Gao, Xiang

Journal: Gastroenterology report

Abstract: Infliximab (IFX) is the first-line treatment for patients with Crohn's disease (CD) and is noted for its relatively high cost. The therapeutic efficacy of IFX has noticeable individual differences. Known single-gene polymorphisms (SNPs) are inadequate for predicting non-response to IFX. In this study, we aimed to identify new genetic factors associated with IFX-therapy failure and to predict non-response to IFX by developing a multivariate predictive model.

DOI: 10.1093/gastro/goaa070

PMID: 34733528.0

Full Article: https://doi.org/10.1093/gastro/goaa070

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Comparison of fecal calprotectin and serum C-reactive protein in early prediction of outcome to infliximab induction therapy.

Publication Date: Sep 2019

Authors: Engström, Johanna; Lönnkvist, Maria; Befrits, Ragnar; Ljung, Tryggve; Diaz-Tartera, Hetzel; Holst, Mikael; Hellström, Per M

Journal: Scandinavian journal of gastroenterology

Abstract: nan

DOI: 10.1080/00365521.2019.1660402

PMID: 31499013.0

Full Article: https://doi.org/10.1080/00365521.2019.1660402

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Predictors of Response to Vedolizumab in Patients with Ulcerative Colitis: Results from the Greek VEDO-IBD Cohort.

Publication Date: Mar 2022

Authors: Bamias, Giorgos; Kokkotis, Georgios; Gizis, Michalis; Kapizioni, Christina; Karmiris, Konstantinos; Koureta, Evgenia; Kyriakos, Nikolaos; Leonidakis, Georgios; Makris, Konstantinos; Markopoulos, Panagiotis; Michalopoulos, Georgios; Michopoulos, Spyridon; Papaconstantinou, Ioannis; Polymeros, Dimitrios; Siakavellas, Spyros I; Triantafyllou, Konstantinos; Tsironi, Eftychia; Tsoukali, Emmanouela; Tzouvala, Maria; Viazis, Nikos; Xourafas, Vassileios; Zacharopoulou, Eirini; Zampeli, Evanthia; Zografos, Konstantinos; Papatheodoridis, George; Mantzaris, Gerasimos

Journal: Digestive diseases and sciences

Abstract: Optimization of treatment with biologics is currently an unmet need for patients with ulcerative colitis (UC). Real-world studies provide neutral estimates of drug efficacy and safety within unselected patient populations and allow for the recognition of specific characteristics that affect response to therapy.

DOI: 10.1007/s10620-021-06907-5

PMID: 33751325.0

Full Article: https://doi.org/10.1007/s10620-021-06907-5

Methods:

MethodsPatient PopulationThis was a collaborative, prospective observational study in adult patients with regular follow-up in 9 Greek tertiary GI-IBD centers and established active UC (Mayo score ≥ 3), who commenced treatment with vedolizumab between November 2015 and May 2019. Dose escalation (shorter infusion intervals) due to suboptimal response was also recorded. Univariate logistic regression models were performed for the identification of potential clinical predictors with a cut-off P-value = 0.1. Factors of potential significance were later included in a multiple logistic regression to identify independent associations.

Results:

Thus, final data analysis was performed for the cohort of 96 patients who received vedolizumab due to active disease at baseline and had appropriate follow-up. c Secondary loss of response (LOR) among patients with or without endoscopic improvement at week 14. Among those, 9 patients completed therapy to week 54, of whom 6 patients were in clinical remission and 5 in corticosteroid-free clinical remission (data not shown).Figure 4Kaplan–Meier curve of vedolizumab persistence for the total study population as well as for anti-TNF-naïve and anti-TNF-exposed patientsFull size imageRegarding PROs (Fig. In the multivariate analysis, only corticosteroid-refractory (OR = 0.11, 95% CI = 0.02–0.71) and anti-TNF refractory disease (OR = 0.16, 95% CI = 0.03–0.8) remained independently associated with poorer prognosis, while a tendency was also observed for history of tonsillectomy (OR = 0.21, 95% CI = 0.04–1.06).Table 3 Univariate and multivariate analysis models for prediction of primary study outcomes and clinical remission at week 54Full size tablePersistence of vedolizumab administration was not associated with any factor in the univariate model, but a tendency was observed with concomitant azathioprine use at baseline.

Discussion:

For example, the French OBSERVE study that reported much lower rates of steroid-free clinical remission at week 54 (40.5%) included only anti-TNF-exposed patients, with 71% having failed more

than two agents [15]. Alternatively, musculoskeletal problems may affect scoring on the Global Medical Assessment indicator, leading to higher final PMS readings.Our study has limitations. First, unlike most published trials that have included both CD and UC cases, ours was focused on the latter exclusively. Second, our study is in line with the highly accepted treat-to-target dogma by systematically combining PROs and ClinROs evaluations.

Conclusion:

None available

Title: Association of C-reactive Protein and Partial Mayo Score With Response to Tofacitinib Induction Therapy: Results From the Ulcerative Colitis Clinical Program.

Publication Date: Jan 2023

Authors: Dubinsky, Marla C; Magro, Fernando; Steinwurz, Flavio; Hudesman, David P; Kinnucan, Jami A; Ungaro, Ryan C; Neurath, Markus F; Kulisek, Nicole; Paulissen, Jerome; Su, Chinyu; Ponce de Leon, Dario; Regueiro, Miguel

Journal: Inflammatory bowel diseases

Abstract: Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of ulcerative colitis (UC). These post hoc analyses assessed associations between C-reactive protein (CRP), partial Mayo score (PMS), and efficacy outcomes during tofacitinib induction in UC.

DOI: 10.1093/ibd/izac061

PMID: 35380664.0

Full Article: https://doi.org/10.1093/ibd/izac061

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Changes in cytokine profile may predict therapeutic efficacy of infliximab in patients with ulcerative colitis.

Publication Date: Oct 2015

Authors: Sato, Shoko; Chiba, Toshimi; Nakamura, Shotaro; Matsumoto, Takayuki

Journal: Journal of gastroenterology and hepatology

Abstract: Infliximab is an established therapy for ulcerative colitis (UC). The aim of this study was to examine various serum cytokine levels and to identify possible markers predictive of therapeutic efficacy of infliximab for UC patients.

DOI: 10.1111/jgh.13008

PMID: 25968585.0

Full Article: https://doi.org/10.1111/jgh.13008

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Matrix Metalloproteinase 3 Predicts Therapeutic Response in Inflammatory Bowel Disease Patients Treated With Infliximab.

Publication Date: Apr 2020

Authors: Barberio, Brigida; D'Incà, Renata; Facchin, Sonia; Dalla Gasperina, Marianna; Fohom Tagne, Cedric Arsenè; Cardin, Romilda; Ghisa, Matteo; Lorenzon, Greta; Marinelli, Carla; Savarino, Edoardo Vincenzo; Zingone, Fabiana

Journal: Inflammatory bowel diseases

Abstract: Inflammatory bowel diseases (IBDs) are treated with anti-TNF agents. Strategies to monitor response to therapy may improve clinical control of the disease and reduce economical costs. Previous evidence suggests cleavage of infliximab (IFX) by Matrix Metalloproteinase 3 (MMP3) as a mechanism leading to loss of response. Our study aimed to evaluate if MMP3 serum levels could be considered an early marker of anti-TNF nonresponse and to analyze the correlation with other biochemical markers of treatment failure such as IFX trough levels and anti-IFX antibodies, inflammatory markers, and albumin levels.

DOI: 10.1093/ibd/izz195

PMID: 31504536.0

Full Article: https://doi.org/10.1093/ibd/izz195

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I.

Publication Date: 2012 Mar

Authors: Reinisch W; Wang Y; Oddens BJ; Link R

Journal: nan

Abstract: BACKGROUND: Secondary loss of response to anti-TNF-alpha therapy is observed in Crohn's disease patients.

DOI: /10.1111/j.1365-2036.2011.04987.x

PMID: nan

Full Article: https://doi.org//10.1111/j.1365-2036.2011.04987.x

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Predictors of Sustained Response With Tofacitinib Therapy in Patients With Ulcerative Colitis.

Publication Date: Sep 2022

Authors: Sandborn, William J; Armuzzi, Alessandro; Liguori, Giuseppina; Irving, Peter M; Sharara, Ala I; Mundayat, Rajiv; Lawendy, Nervin; Woolcott, John C; Danese, Silvio

Journal: Inflammatory bowel diseases

Abstract: Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of ulcerative colitis. We evaluate baseline characteristics as predictors of sustained response and remission in patients with ulcerative colitis receiving tofacitinib maintenance therapy.

DOI: 10.1093/ibd/izab278

PMID: 34958359.0

Full Article: https://doi.org/10.1093/ibd/izab278

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Histological Outcomes and Predictive Value of Faecal Markers in Moderately to Severely Active Ulcerative Colitis Patients Receiving Infliximab.

Publication Date: Dec 2016

Authors: Magro, Fernando; Lopes, Susana Isabel; Lopes, Joanne; Portela, Francisco; Cotter, José; Lopes, Sandra; Moreira, Maria João; Lago, Paula; Peixe, Paula; Albuquerque, Andreia; Rodrigues, Susana; Silva, Mário Rui; Monteiro, Pedro; Lopes, Castro; Monteiro, Lucília; Macedo, Guilherme; Veloso, Luís; Camila, Claudia; Afonso, J; Geboes, Karel; Carneiro, Fátima; ,

Journal: Journal of Crohn's & colitis

Abstract: Histological healing has emerged as a promising therapeutic goal in ulcerative colitis. This is especially important in the context of biological therapies. The objectives of the present study were to investigate the ability of infliximab to induce histological remission in ulcerative colitis [UC] patients and to explore the utility of faecal calprotectin and lactoferrin in predicting histological activity.

DOI: 10.1093/ecco-jcc/jjw112

PMID: 27226417.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjw112

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Serum protein profile of Crohn's disease treated with infliximab.

Publication Date: Nov 2013

Authors: Gazouli, Maria; Anagnostopoulos, Athanasios K; Papadopoulou, Aggeliki; Vaiopoulou, Anna; Papamichael, Konstantinos; Mantzaris, Gerassimos; Theodoropoulos, George E; Anagnou, Nicholas P; Tsangaris, George Th

Journal: Journal of Crohn's & colitis

Abstract: The infliximab (IFX) has dramatically improved the treatment of Crohn's disease (CD). However, the need for predictive factors, indicative of patients' response to IFX, has yet to be met. In the current study, proteomics technologies were employed in order to monitor for differences in protein expression in a cohort of patients following IFX administration, aiming at identifying a panel of candidate protein biomarkers of CD, symptomatic of response to treatment. We enrolled 18 patients, who either had achieved clinical and serological remission (Rm, n=6), or response (Rs, n=6) and/or were PNRs (n=6), to IFX. Serum samples were subjected to two-dimensional Gel Electrophoresis. Following evaluation of densitometrical data, protein spots exhibiting differential expression among the groups, were further characterized by MALDI-TOF-MS. Identified proteins where evaluated by immunoblot analysis while functional network association was carried out to asses significance. Proteins apolipoprotein A-I (APOA1), apolipoprotein E (APOE), complement C4-B (CO4B), plasminogen (PLMN), serotransferrin (TRFE), beta-2-glycoprotein 1 (APOH), and clusterin (CLUS) were found to be up-regulated in the PNR and Rs groups whereas their levels displayed no changes in the Rm group when compared to baseline samples. Additionally, leucine-rich alpha-2-glycoprotein (A2GL), vitamin D-binding protein (VTDB), alpha-1B-glycoprotein (A1BG) and complement C1r subcomponent (C1R) were significantly increased in the serum of the Rm group. Through the incorporation of proteomics technologies, novel serum marker-molecules demonstrating high sensitivity and specificity are introduced, hence offering an innovative approach regarding the evaluation of CD patients' response to IFX therapy.

DOI: 10.1016/j.crohns.2013.02.021

PMID: 23562004.0

Full Article: https://doi.org/10.1016/j.crohns.2013.02.021

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Assessment of the response of patients with Crohn's disease to biological therapy using new non-invasive markers: lactoferrin and calprotectin.

Publication Date: Apr 2013

Authors: Nogueira, Islaine Martins; Miszputen, Sender Jankiel; Ambrogini, Orlando; Artigiani-Neto, Ricardo; Carvente, Cláudia Teresa; Zanon, Maria Ivani

Journal: Arquivos de gastroenterologia

Abstract: The use of fecal markers to monitor Crohn's disease is crucial for assessing the response to treatment.

DOI: 10.1590/s0004-28032013000200022

PMID: 23903623.0

Full Article: https://doi.org/10.1590/s0004-28032013000200022

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

VARIABLE	Frequency	Percentage (%)
GENDER		
Male	8	47.1
Female	9	52.9
ETHNICITY		
East Asian	1	5.9
Pardo	5	29.4
White	11	64.7
SMOKING		
No	16	94.1
Yes	1	5.9
EXTENT**Montreal classification L1-ileum; L2-colon; L3-ileum-colon; B1-non-stenosing/non-fistulising; B2-stenosing; B3-fistulising		

L1	2	11.8
L2	7	41.2
L3	8	47.1
BEHAVIOUR**Montreal classification L1-ileum; L2-colon; L3-ileum-colon; B1-non-stenosing/non-fistulising; B2-stenosing; B3-fistulising		
B1	9	52.9
B2	4	23.5
B3	4	23.5
EXTRA-INTESTINAL SYMPTOMS		
No	11	64.7
Yes (joint pain****one patient with joint pain and erythema nodosum)	6	35.3
SURGERY		
No	8	47.1
Yes	9	52.9

TIME	N	Mean	Standard deviation	Standard error	95% CI lower	95% CI upper	Minimum	Maximum
0	17	682.5294	294.32043	71.38319	531.2038	833.8550	202.00	1199.00
8	16	414.5000	230.41007	57.60252	291.7231	537.2769	93.00	935.00
32	15	646.6667	364.63223	94.14764	444.7401	848.5933	83.00	1130.00

(I) time	(J)time	Mean difference (I-J)	Standard error	95% CI lower	95% CI upper	P
0	8	268.0294	104.4135	8.3759	527.6829	0.041
0	32	35.86275	106.1913	-228.211	299.9373	1.000
8	32	-232.1666	107.7356	-500.081	35.7482	0.110

	Time 0n (%)	Time 8n (%)	Time 32n (%)
Negative	1 (5.9%)	4 (25%)	4 (26.7%)
Positive	16 (94.1%)	12 (75%)	11 (73.3%)
Total	17 (100%)	16 (100%)	15 (100%)

	Time 0n (%)	Time 8n (%)	Time 32n (%)
Inactive	0 (0.0%)	0 (0.0%)	3 (18.75%)
Mild	4 (25.0%)	8 (50.0%)	5 (31.25%)
Moderate	3 (18.75%)	3 (31.25%)	6 (37.50%)
Severe	9 (56.25%)	3 (18.75%)	2 (12.50%)

Total	16 (100%)	16 (100%)	16 (100%)

		Number	Percentage
Histological progression	No change	5	33.3%
Improvement	9	60.0%	
Worsening	1	6.7%	

	Time 0Mean	Time 8Mean	Time 32Mean
CDAI	231.5606	123.6306	104.8750
CDEIS	8.0000	5.6250	6.1250
PCR	15.7712	8.6324	5.8337
VHS	28.7647	21.6471	23.9375
Alpha 1-acid glycoprotein	98.5412	79.8353	79.8813
HB	12.6235	12.8882	13.4375
HT	38.6529	38.9000	40.0250
Platelet	344.4118	316.2941	303.1875

	Lactoferrin 0Pearson correlation/P	Lactoferrin 8Pearson correlation/P	Lactoferrin 32Pearson correlation/P
CDAI	-0,158/0,545	-0,189/0,483	0,124/0,659
CDEIS	-0.474/0,054	0,183/0,514	0,368/0,177
Histology	0,491/0,054	-0,208/0,456	0,193/0,490
PCR	-0,772/0,000	0,231/0,388	0,198/0,479
VHS	-0,562/0,019	-0,187/0,489	-0,233/0,403
Alpha 1-acid glycoprotein	-0,857/0,000	0,116/0,670	0,554/0,032
Hb	0,152/0,560	0,115/0,672	-0,024/0,932
HT	0,170/0,515	0,219/0,415	0,097/0,730
Platelet	-0,347/0,172	-0,254/0,342	0,110/0,698

	CDEIS 0Pearson/Pcorrelation	CDEIS 8Pearson/Pcorrelation	CDEIS 32Pearson/Pcorrelation
Histology	0,167/0,535	0,507/0,045	0,445/0,084
CDAI	0,289/0,261	-0,097/0,722	0,367/0,163

	Calprotectin 0Pearson/Pcorrelation	Calprotectin 8Pearson/Pcorrelation	Calprotectin 32Pearson/Pcorrelation
CDAI	0,094/0,721	-0,288/0,280	0,003/0,991

Lactoferrin	0,421/0,093	0,420/0,105	0,789/0,000
CDEIS	0,255/0,323	0,032/0,910	0,597/0,019
Histology	0,471/0,066	-0,262/0,346	0,416/0,123
PCR	-0,305/0,234	0,357/ 0,174	0,188/0,503
Alpha 1-acid glycoprotein	-0,386/0,126	0,428/ 0,098	0,385/0,156
Hb	0,089/0,734	0,085/0,754	0,126/0,654
Ht	0,104/0,691	0,110/0,686	0,231/0,408
Platelet	-0,068/0,796	-0,165/0,541	0,144/0,610

Model	Coefficient	Coefficient standard error	t
Constant	3.768	5.567	.677
calprotectin 0	.011	.005	2.154
lactoferrin 0	-5.553	6.235	-.891

Mean difference (I-J)	standard error	95% CI lower	95
107.93000**Montreal classification L1-ileum; L2-colon; L3-ileum-colon; B1-non-stenosing/non-fistulising; B2-stenosing; B3-fistulising	23.70159	49.0862	
126.68559	24.06908	66.9294	
18.75559	24.06908	-41.0006	

Model	Coefficient	Standard error	P	Odds ratio
calprotectin 0	0.02	.002	.337	1.002
lactoferrin 0	20.778	40192.982	1.000	1.056E9
Constant	-21.634	40192.982	1.000	.000

Title: Genetic variation within the NKG2D pathway may influence the response to anti-NKG2D therapy in Crohn's disease

Publication Date: nan

Authors: Hart A.; Neiman E.; Perrigoue J.; Hao L.-Y.; Tomsho L.; Schultz W.; Di Narzo A.; Hao K.; Skolnick B.; Ort T.; Curran M.; Plevy S.; Allez M.

Journal: nan

Abstract: Background: Crohn's disease (CD) is a chronic inflammatory disease associated with dysregulated immune responses in the gastrointestinal tract. Despite advances in treatments for CD, there remains a significant unmet need both for novel therapeutics and the ability to identify individuals most likely to benefit from them. In a double-blind, placebo controlled clinical trial (n = 78) anti-NKG2D, an antagonistic human monoclonal antibody, showed a significant drop in Crohn's disease activity index (CDAI) in the overall population at week 12, but not week 4 (Allez et al, Gut 2017:66:1918-1925). The aim of this work was to identify predictive genetic biomarkers of response to anti-NKG2D. Method(s): Potential clinical response stratification markers were identified from 16 candidate genes within the NKG2D pathway with focus placed on non-synonymous coding single-nucleotide polymorphisms (SNPs) and SNPs associated with expression of the candidate genes in data from intestine, PBMC, B-cells and monocytes. SNPs associated with NKG2D or its ligands were subsequently prioritised for response association testing based on the strength of their associations with gene expression. A subset of placebo (n = 24) and anti-NKG2D-treated (n = 28) subjects from the anti-NKG2D clinical trial were genotyped at the five prioritised SNPs and association with response was tested. Further evaluation of the association of candidate biomarkers with gene expression was performed using data from the CERTIFI phase 2b CD ustekinumab trial (n = 54) and a cross-sectional cohort of CD, ulcerative colitis, and non-IBD control subjects (n = 432). Result(s): Two SNPs within the NKG2D pathway, rs2255336 and rs2239705, were associated with gene expression and showed trends for association with response to anti-NKG2D. The rs2255336 SNP is a missense coding variant that leads to a Thr72Ala substitution in NKG2D protein while rs2239705 is located 34 kb downstream from MICB within the second intron of ATP6V1G2. Subjects heterozygous (A/G) or homozygous for the NKG2D SNP minor allele (A/A) or homozygous for the MICB major allele (G/G) demonstrated a greater decrease in CDAI (mean DELTACDAI: NKG2D A/G or A/A,-102; MICB G/G,-133; both NKG2D A/G or A/A and MICB G/G,-158) compared with subjects without these genotypes (mean DELTACDAI-46) at week 4. We replicated the association of rs2239705 with MICB expression in intestine in the CERTIFI cohort (beta = 0.53, p = 0.001) as well as in the cross-sectional cohort (beta = 0.33, p = 2.9E-12). Conclusion(s): We have identified SNPs within NKG2D and the MICB locus that are associated with enhanced responses to anti-NKG2D therapy. These SNPs will be evaluated as response biomarkers in future studies.

DOI: /10.1093/ecco-jcc/jjx180.976

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjx180.976

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Level of Tumor Necrosis Factor Production by Stimulated Blood Mononuclear Cells Can Be Used to Predict Response of Patients With Inflammatory Bowel Diseases to Infliximab.

Publication Date: Apr 2021

Authors: Jessen, Bosse; Rodriguez-Sillke, Yasmina; Sonnenberg, Elena; Schumann, Michael; Kruglov, Andrey; Freise, Inka; Schmidt, Franziska; Maul, Jochen; Kühl, Anja A; Glauben, Rainer; Lissner, Donata; Siegmund, Britta

Journal: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association

Abstract: A substantial proportion patients with inflammatory bowel disease (IBD) have a primary non-response to infliximab; markers are needed to identify patients most likely to respond to treatment. We investigated whether production of tumor necrosis factor (TNF) by peripheral blood mononuclear cells (PBMCs) can be used as a marker to predict response.

DOI: 10.1016/j.cgh.2020.03.066

PMID: 32272247.0

Full Article: https://doi.org/10.1016/j.cgh.2020.03.066

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: USE OF FAECAL CALPROTECTIN AS A PROGNOSTIC MARKER OF RESPONSE TO TREATMENT WITH FILGOTINIB: POST HOC ANALYSIS FROM THE SELECTION STUDY

Publication Date: nan

Authors: Louis E.; Feagan B.; Hisamatsu T.; Taliadouros V.; Jongen R.; Oortwijn A.; Van Der Donckt C.; Peyrin-Biroulet L.

Journal: nan

Abstract: Introduction: Filgotinib (FIL) is a once-daily, oral, preferential JAK1 inhibitor approved for the treatment of ulcerative colitis (UC). In SELECTION, FIL 200 mg (FIL200) was efficacious in inducing and maintaining clinical remission vs placebo (PBO) in patients with moderately to severely active UC.1 Increased faecal calprotectin (FC) has been associated with the risk of relapse and is broadly used as a non-invasive monitoring tool in patients with UC. We assessed the operating properties of FC as a prognostic marker of the response to treatment with FIL200. Aims & Methods: SELECTION was a phase 2b/3, double-blind, randomized, PBO-controlled trial (NCT02914522) comprising two induction studies and one maintenance study.1 Using Mann-Whitney U tests and receiver operating characteristic (ROC) curves with comparison of areas under the curve (AUC), these post hoc analyses evaluated the ability of median FC concentration and FC concentration thresholds vs histological and endoscopic assessments to discriminate Mayo Clinic Score (MCS) response, endoscopic response and endoscopic remission after induction (week 10), and clinical remission after maintenance (week 58) treatment with FIL200. Result(s): FC concentration at baseline was not a strong prognostic factor for MCS response at week 10 (median [interquartile range (IQR)] mug/g, yes: 1450 [561-3056] vs no: 1211 [455-2734], p=0.0938), whereas FC concentration at week 10 was associated with MCS response (median [IQR] mug/g, yes: 209 [68-720] vs no: 1133 [347-2101], p<0.0001), endoscopic response (yes: 102 [41-301] vs no: 756 [211-1741], p<0.0001) and endoscopic remission (yes: 59 [29-186] vs no: 527 [148-1598],p<0.0001) at week 10. Using a cut-off of 250 mug/g to create a binary outcome, FC <250 mug/g (FC250) at week 10 was associated with a MCS response at week 10 (yes: n=340 [positive predictive value (PPV): 75.9%]; no: n=454 [negative predictive value (NPV): 61.5%]). Combining FC250 with symptomatic outcomes (partial MCS [pMCS] remission) improved both the PPV (79.8%) and NPV (73.5%) for MCS response at week 10. FC250 was associated with an endoscopic response at week 10 (PPV: 42.2%; NPV: 90.4%; ROC curve AUC: 0.724 [95% confidence interval: 0.693-0.754]). The combination of FC250 with pMCS remission at week 10 was prognostic for clinical remission at week 58 with a higher AUC than that of either endoscopic response, Geboes histological remission, FC250 or pMCS remission alone (Table 1). Conclusion(s): FC concentration following induction with FIL200 is associated with a short-term response. The combination of FC250 and pMCS remission at week 10 may be a good, non-invasive prognostic marker of clinical remission at week 58. These findings raise the possibility that some patients could avoid undergoing endoscopy at early time points with the use of close biomarker and symptom monitoring. (Table Presented).

DOI: /10.1002/ueg2.12290

PMID: nan

Full Article: https://doi.org//10.1002/ueg2.12290

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Predictive value of epithelial gene expression profiles for response to infliximab in Crohn's disease.

Publication Date: Dec 2010

Authors: Arijs, Ingrid; Quintens, Roel; Van Lommel, Leentje; Van Steen, Kristel; De Hertogh, Gert; Lemaire, Katleen; Schraenen, Anica; Perrier, Clémentine; Van Assche, Gert; Vermeire, Séverine; Geboes, Karel; Schuit, Frans; Rutgeerts, Paul

Journal: Inflammatory bowel diseases

Abstract: Infliximab (IFX) has become the mainstay of therapy of refractory Crohn's disease (CD). However, a subset of patients shows incomplete or no response to this agent. In this study we investigated whether we could identify a mucosal gene panel to predict (non)response to IFX in CD.

DOI: 10.1002/ibd.21301

PMID: 20848504.0

Full Article: https://doi.org/10.1002/ibd.21301

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Association of rs1568885, rs1813443 and rs4411591 polymorphisms with anti-TNF medication response in Greek patients with Crohn's disease.

Publication Date: Apr 2014

Authors: Thomas, Diamantis; Gazouli, Maria; Karantanos, Theodoros; Rigoglou, Stella; Karamanolis, Georgios; Bramis, Konstantinos; Zografos, George; Theodoropoulos, George E

Journal: World journal of gastroenterology

Abstract: To investigate the correlation between rs1568885, rs1813443 and rs4411591 polymorphisms and response to infliximab in a cohort of Greek patients with Crohn's disease (CD).

DOI: 10.3748/wjg.v20.i13.3609

PMID: 24707144.0

Full Article: https://doi.org/10.3748/wjg.v20.i13.3609

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

2563Tables (1-2)146Sum=3251Loading…	Item	Item		Count	Count		PDF	338	WORD	204	HTML	2563	Tables (1-2)	146
Item	Item		Count	Count										
Item														
Count														
PDF	338													
WORD	204													
HTML	2563													
ables (1-2)	146													
	Sum=3251													
	Loading…													

Item	Item		Count	Count	

Item					
Count					
PDF	338				
WORD	204				
HTML	2563				
Tables (1-2)	146				
	Sum=3251				

Item

Count

Loading…

tBrowse1058Download982Sum=2040Loading…	Item	Item		Count	Count		Browse	1058	Download	982		Sum=2040		L
Item	Item		Count	Count										
Item														
Count														
Browse	1058													
Download	982													
	Sum=2040													
	Loading…													

Item	Item		Count	Count	
Item					
Count					
Browse	1058				
Download	982				
	Sum=2040				

Item

Count

Loading…

Characteristics	Complete responders	Partial responders	Primary non-responders	Pvalue
	80 (63.49)	32 (25.39)	14 (11.11)	
Age (yr, mean ± SD)	28.42 ± 12.85	26.65 ± 14.21	27.32 ± 13.88	0.807
Gender (%)				
Male	62 (77.5)	19 (58.37)	8 (57.14)	0.082
Female	18 (22.5)	13 (40.63)	6 (42.86)	
CRP levels (mg/dL, mean ± SD)				
Pre-treatment (0 wk)	3.47 ± 0.85	5.62 ± 3.44	4.48 ± 2.15	< 0.0001
Post-treatment (12 wk)	1.07 ± 0.72	3.55 ± 1.49	1.61 ± 1.4	< 0.0001
δCRP levels (%)	75.27 ± 36.23	81.03 ± 32.05	63.91 ± 32.73	0.311
Disease years	8 ± 6.48	7.47 ± 5.11	8.18 ± 4.32	0.987
Infliximab dosing (mg/kg)	5	5	5	1.000
Localization (%)				
Colitis	26 (32.5)	4 (12.5)	2 (14.28)	0.295
Ileocolitis	50 (62.5)	27 (84.75)	12 (85.72)	
Upper gastroenteric	4 (5)	1 (2.75)	0	
Behaviour (%)				
Inflammatory	34 (42.5)	10 (31.25)	5 (35.71)	0.016
Stricturing	14 (17.5)	9 (28.13)	2 (14.29)	
Penetrating	32 (40)	13 (40.62)	7 (50)	

Genotype	Complete responders (n= 80)	Partial responders (n= 32)	Pvalue; OR (95%CI)	Non-responders (n= 14)	Pvalue; OR (95%CI)
rs1568885					
AA	57 (71.25)	14 (43.75)	1.0 (reference)	4 (28.57)	1.0 (reference)
AT	21 (26.25)	14 (43.75)	0.035; 2.71 (1.11-6.64)	7 (50)	0.032; 4.75 (1.26-17.9)
TT	2 (2.5)	4 (12.5)	0.024; 8.14 (1.3549.05)	3 (21.43)	0.007; 21.37 (2.73-167.2)
rs1813443					
GG	46 (57.5)	10 (31.25)	1.0 (reference)	4 (28.57)	1.0 (reference)
GC	28 (35)	14 (43.75)	0.09; 2.3 (0.9-5.87)	4 (28.57)	0.7; 1.64 (0.38-7.1)
CC	6 (7.5)	8 (25)	0.005; 6.13 (1.74-21.63)	6 (42.86)	0.002; 11.5 (2.5-52.84)
rs4411591					
GG	54 (67.5)	17 (53.12)	1.0 (reference)	10 (71.43)	1.0 (reference)

GA	24 (30)	12 (37.5)	0.34; 1.58 (0.66-3.84)	4 (28.57)	1; 0.9 (0.26-3.16)
AA	2 (2.5)	3 (9.37)	0.11; 4.76 (0.73-30.94)	0	1; 1.04 (0.05-23.23)

crosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials.Clin Gastroenterol Hepatol. 2008;6:644-653.[PubMed][DOI][Cited in This Ar

LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.Lancet. 200

cione R, Schreiber S, Byczkowski D, Li J, Kent JD. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM t

ik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease.Clin Gastroenterol Hepatol. 2006;4:1017-1024; quiz 976.[PubMe

lisease shows high levels of remission to therapy with adalimumab: sub-analysis of charm.Gastroenterology. 2007;132:A-147.[PubMed][DOI][Cited in This Article

M, Rattan S, Lewis JD, Su C, Katzka DA, Deren J. Strictures and response to infliximab in Crohn's disease.Am J Gastroenterol. 2002;97:S255.[PubMed][DOI][Cited

ariente JM, López-Vázquez A, de Francisco R, Rodrigo L. High serum tumor necrosis factor-alpha levels are associated with lack of response to infliximab in fistu

, Reynaert H, D'Haens G. A positive response to infliximab in Crohn disease: association with a higher systemic inflammation before treatment but not with -308 T

, Rotter JI, Targan SR. ANCA pattern and LTA haplotype relationship to clinical responses to anti-TNF antibody treatment in Crohn's disease.Gastroenterology. 2

, Rutgeerts P. Tumour necrosis factor-alpha receptor 1 and 2 polymorphisms in inflammatory bowel disease and their association with response to infliximab.Alim

isms of tumour necrosis factor alpha (TNF-α) promoter gene and response to TNF-α inhibitors in Spanish patients with inflammatory bowel disease.Int J Immuno

ölsch UR, Schreiber S. Pharmacogenetic investigation of the TNF/TNF-receptor system in patients with chronic active Crohn's disease treated with infliximab.Pha

lymorphism predicts response to treatment in Crohn's disease--first steps to a personalized therapy.Dig Dis Sci. 2012;57:879-886.[PubMed][DOI][Cited in This Art

z D, Weintraub I, Eliakim R, Karban A. NOD2/CARD15 mutation analysis and genotype-phenotype correlation in Jewish pediatric patients compared with adults w

ssum A, Belaiche J, Pescatore P, Fiasse R, Pelckmans P, Vlietinck R. NOD2/CARD15 does not influence response to infliximab in Crohn's disease.Gastroenterolo

morphisms and TNF and IL1β serum concentration on the infliximab response in Crohn's disease and ulcerative colitis.Eur J Clin Pharmacol. 2013;69:431-438.[Pu

A. Genome-wide association analysis of anti-TNF drug response in patients with rheumatoid arthritis.Ann Rheum Dis. 2013;72:1375-1381.[PubMed][DOI][Cited in

e K. Novel neural adhesion molecules in the Contactin/F3 subgroup of the immunoglobulin superfamily: isolation and characterization of cDNAs from rat brain.N

19. Podolsky DK. Inflammatory bowel disease.N Engl J Med. 2002;347:417-429.[PubMed][DOI][Cited in This Article:]

Lennard-Jones JE. Classification of inflammatory bowel disease.Scand J Gastroenterol Suppl. 1989;170:2-6; discussion 16-19.[PubMed][DOI][Cited in This Arti

21. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity.Lancet. 1980;1:514.[PubMed][DOI][Cited in This Article:]

, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine.Gastrointest Endosc. 1999;50:667-671.[PubMed][DOI][Cite

ikou E, Mantzaris JG. Association of TNF and FcγRIIIA gene polymorphisms with differential response to infliximab in a Greek cohort of Crohn's disease patients.

immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial.Lancet. 2008;371:660-667.[PubMe

nterventions in patients with inflammatory bowel disease: a systematic review and meta-analysis.Inflamm Bowel Dis. 2013;19:2098-2110.[PubMed][DOI][Cited in T

nte CT, Zanon MI. Assessment of the response of patients with Crohn's disease to biological therapy using new non-invasive markers: lactoferrin and calprotecti

luation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease.Health Technol Assess. 2011;15:1-244.[Pub

High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment.J Crohns Colitis. 2014;8:129-136.[PubMed][DOI][Cited in This Art

Sanromán A, Martín Arranz MD. Role of TNFRSF1B polymorphisms in the response of Crohn's disease patients to infliximab.Hum Immunol. 2014;75:71-75.[PubM

lymorphism influences the biological response to infliximab in Crohn's disease through affecting the ADCC activity.Immunogenetics. 2013;65:265-271.[PubMed][

ollo Z, Horvath A, Steiner L, Zahuczky G, Podani J. Peripheral blood derived gene panels predict response to infliximab in rheumatoid arthritis and Crohn's diseas

ssment of endoscopic activity index and biological inflammatory markers in clinically active Crohn’s disease with normal C-reactive protein serum level.Inflamm

mond RH, Broussard DL. Infliximab, azathioprine, or combination therapy for Crohn’s disease.N Engl J Med. 2010;362:1383-1395.[PubMed][DOI][Cited in This Artic

ue J, Gallardo E, Illa I. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy.Ann Neurol. 2013;73:370-380.[PubMed][DOI][Cited in This

irected autoimmunity is identified in multiple sclerosis patients and mediates gray matter pathology in animals.Proc Natl Acad Sci USA. 2009;106:8302-8307.[Pub

Title: Association between tumor necrosis factor-alpha and Fc-gamma receptor polymorphisms with infliximab in Crohn's disease.

Publication Date: 2010

Authors: Tomita, Kazumitsu; Chiba, Toshimi; Sugai, Tamotsu; Habano, Wataru

Journal: Hepato-gastroenterology

Abstract: The associations between tumor necrosis factor-alpha (TNF-alpha) and Fcgamma receptor (FcgammaR) polymorphisms with infliximab (IFX) treatment of Crohn's disease (CD) are not well known. The aim of this study was to evaluate the association between these polymorphisms and IFX treatment of CD.

DOI: nan

PMID: 20698223.0

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Predicting the Course of Disease in Hospitalized Patients With Acute Severe Ulcerative Colitis.

Publication Date: Feb 2019

Authors: Bernardo, Sónia; Fernandes, Samuel Raimundo; Gonçalves, Ana Rita; Valente, Ana; Baldaia, Cilénia; Santos, Paula Moura; Correia, Luís Araújo

Journal: Inflammatory bowel diseases

Abstract: Up to one-third of patients with acute severe ulcerative colitis (ASUC) will fail intravenous steroid (IVS) treatment, requiring rescue therapy with cyclosporin (Cys), infliximab (IFX), or colectomy. Although several scores for predicting response to IVS exist, formal comparison is lacking.

DOI: 10.1093/ibd/izy256

PMID: 30085135.0

Full Article: https://doi.org/10.1093/ibd/izy256

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Colonic MicroRNA Profiles, Identified by a Deep Learning Algorithm, That Predict Responses to Therapy of Patients With Acute Severe Ulcerative Colitis.

Publication Date: Apr 2019

Authors: Morilla, Ian; Uzzan, Mathieu; Laharie, David; Cazals-Hatem, Dominique; Denost, Quentin; Daniel, Fanny; Belleannee, Genevieve; Bouhnik, Yoram; Wainrib, Gilles; Panis, Yves; Ogier-Denis, Eric; Treton, Xavier

Journal: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association

Abstract: Acute severe ulcerative colitis (ASUC) is a life-threatening condition managed with intravenous steroids followed by infliximab, cyclosporine, or colectomy (for patients with steroid resistance). There are no biomarkers to identify patients most likely to respond to therapy; ineffective medical treatment can delay colectomy and increase morbidity and mortality. We aimed to identify biomarkers of response to medical therapy for patients with ASUC.

DOI: 10.1016/j.cgh.2018.08.068

PMID: 30223112.0

Full Article: https://doi.org/10.1016/j.cgh.2018.08.068

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: SEROLOGICAL BIOMARKERS OF TYPE VI AND XXII COLLAGEN FORMATION PREDICT AND MONITOR INFLIXIMAB TREATMENT RESPONSE IN PATIENTS WITH CROHN'S DISEASE

Publication Date: nan

Authors: Alexdottir M.S.; Bourgonje A.R.; Karsdal M.A.; Bay-Jensen A.-C.; Pehrsson M.; Loveikyte R.; Dullemen H.M.V.; Visschedijk M.C.; Festen E.A.; Weersma R.K.; Faber K.N.; Dijkstra G.; Mortensen J.H.

Journal: nan

Abstract: Background: Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract characterized by excessive protease activity and extracellular matrix (ECM) remodeling. Although biologics such as TNF-a-antagonists have improved the management of disease, up to 30-50% of patients still experience non-response to treatment. Biomarkers may be useful to improve therapeutic decision-making and monitor treatment response, thereby optimizing biological therapy and decreasing the risk of surgical intervention. This study aimed to assess whether serological biomarkers of ECM turnover could monitor or predict response to TNF-a-antagonists in patients with and without a surgical history. Method(s): Using protein fingerprint technology, serum biomarkers of type VI (PRO-C6) and XXII (PRO-C22) collagen formation were measured in 63 patients with CD undergoing infliximab (IFX) induction therapy. Disease activity was defined by the Harvey-Bradshaw Index (HBI) together with physician's global assessments (PGA). Response to treatment was defined as steroid-free clinical remission (HBI<5) at week 14. Patients were stratified according to the history of prior surgery. Patients with a history of prior surgery (n=18) consisted of 10 responders and 8 non-responders. Patients without a history of prior surgery (n=45) consisted of 40 responders and 5 non-responders. Differences in biomarker levels between response groups were determined using Mann-Whitney U-tests. Area under the curve (AUC) values were generated using receiver operating characteristics (ROC) statistics. Result(s): In patients with a prior history of surgery, PRO-C22 levels were increased at baseline in responders compared with non-responders (P=0.004). At week 14, responders had higher levels of PRO-C6 than non-responders (P=0.037). The PRO-C6 and PRO-C22 biomarkers demonstrated predictive value at baseline (AUC [95% CI]: PRO-C6 0.78 [0.55-1.0], P= 0.012; PRO-C22 0.90 [0.73-1.0], P<0.001). At week 14, PRO-C6 was also able to discriminate between responders and non-responders (AUC [95% CI]: 0.82 [0.54-1.0], P=0.006). No significant differences were observed in marker levels within patients without history of prior surgery (Figure 1). Conclusion(s): In patients with a history of prior surgery, higher baseline levels of PRO-C22 predict treatment response to IFX, whereas PRO-C6 levels were higher at week 14 after treatment initiation. These biomarkers demonstrated promising results in predicting response to anti-TNFalpha treatment, as well as separating responders from non-responders at week 14. Together, these markers could be used to predict and monitor treatment response to IFX in patients with CD having surgical history and may shed light on different profiles of ECM turnover. Future studies are warranted to further validate the potential utility of these biomarkers in larger patient cohorts.(Figure Presented)

DOI: /10.1016/S0016-5085%2822%2961896-1

PMID: nan

Full Article: https://doi.org//10.1016/S0016-5085%2822%2961896-1

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: B cells repertoire repartition predicts response to methotrexate at 6 and 12 months in naive RA: A machine learning driven approach

Publication Date: nan

Authors: Najm A.; Sarda S.; Toro M.; Pickle L.; Ostresh S.; Morton F.; Lowman G.; Felton A.; Goodyear C.

Journal: nan

Abstract: Background/Purpose: The adaptive immune system plays a central role in Rheumatoid Arthritis (RA) pathogenesis. Moreover, the composition of the B cell repertoire and its perturbation are known to exist across disease phenotypes (i.e., ACPA positive versus ACPA negative). However, the influence of underlying B-cell repertoire changes in RA according to their response to treatment, and the ability of these to constitute as predictive biomarkers of response to Methotrexate (MTX) are not yet known. The objective of this analysis was to create a nomogram capable of predicting response to MTX at 6 and 12 months based on properties of the baseline B cell repertoire. Method(s): Peripheral blood leukocytes (PBL) from patients from the Scottish Early Rheumatoid Arthritis SERA cohort (1) were included in the analysis and classified into 3 categories according to their response to MTX measured by CDAI or DAS 28 at 6 and 12 months: responders (n=36), non-responders (n=35) and relapsing responders (n=28). BCR sequence repertoires were explored through IGH sequencing via the IGH-LR assay and the Gene Studio S5, sequencing to a target of 1.5M reads per sample. Data were analyzed via Ion Reporter 5.12 and 5.16. A gradientboosting supervised learning method was used to build a prediction model of MTX response at 6 months and 1 year. Result(s): 99 patients, with a mean age of 60.5 (SD 13.72) were included for analysis. Of interest, differences in classswitching and repartition of naive B cells were observed across all groups. Notably, untreated patients displayed higher levels of IgA, IgE and IgG clones compared to after 12 months of MTX (p=0.003). At baseline, isotypes were more frequently switched towards IgA, IgE and IgG in non-responders than responders (p=0.008). Baseline levels of circulating IgD+ B cells clones were more frequent in responders compared to non-responders (p=0.004) while IgA1+ and IgA2+ clones tended to be more frequently represented in non-responders (p=0.069 and p=0.001 respectively). Over the course of the treatment with MTX, responders and non-responders tended to show an increased frequency of IgM+IgD+ clones whilst a depletion in IgG1+ clones was observed only in responders (p=0.034). In the relapsing responders' group, no significant depletion at both 6 and 12 months was observed. When analyzing somatic hypermutation (SHM) levels in the BCR variable regions, the levels of SHM were consistently lower in non-responders compared with responders, although the number of SHM tended to increase over time for most isotypes. The top 7 baseline features were selected from a preliminary random forest model: IgM, IgD, IgG3, IgG4 and IgA clone frequency, frequency of IgM and IgG clones with >10% SHM and CDAI. Additional training and optimization of a new gradient boosting model, revealed that the response to MTX in the cohort could be predicted with a sensitivity of 0.78, a specificity of 0.786 and an area under the curve of 0.88 (Figure 1). Conclusion(s): This model, based on an innovative machine learning approach in conjunction with a cutting-edge B cell repertoire analysis in RA, constitute the first immunology-based prediction model for response to MTX to our knowledge. This could be further used for personalized therapy in RA.

DOI: /10.1002/art.41966

PMID: nan

Full Article: https://doi.org//10.1002/art.41966

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serological biomarkers of type VI and XXII collagen formation predict and monitor infliximab treatment response in patients with Crohn's disease

Publication Date: nan

Authors: Sorokina Alexdottir M.; Bourgonje A.R.; Karsdal M.A.; Bay-Jensen A.C.; Pehrsson M.; Loveikyte R.; Van Dullemen H.M.; Visschedijk M.C.; Festen E.A.M.; Weersma R.K.; Faber K.N.; Dijkstra G.; Mortensen J.H.

Journal: nan

Abstract: Background: Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract characterized by excessive protease activity and extracellular matrix (ECM) remodeling. Although biologics such as TNF- alpha antibodies have improved the management of disease, up to 30-50% of patients still experience non-response to treatment. Biomarkers may be useful to improve therapeutic decision-making and monitor treatment response, thereby optimizing biological therapy and decreasing the risk of surgical intervention. This study assessed whether serological biomarkers of ECM turnover could monitor or predict response to TNF-alpha- antagonists in patients with and without surgical history. Method(s): Using protein fingerprint technology, serum biomarkers of type VI (PRO-C6) and XXII (PRO-C22) collagen formation were measured in 63 patients with CD undergoing infliximab (IFX) induction therapy. Disease activity was defined by a composite of the Harvey-Bradshaw Index (HBI) and physician's global assessments (PGA). Response to treatment was defined as steroid-free remission (HBI<5) at week 14. Patients were stratified according to history of prior surgery. Patients with history of prior surgery (n=18) were 10 responders and 8 non-responders. Patients without history of prior surgery (n=45) were 40 responders and 5 non-responders. Differences in marker levels between groups were determined using Mann-Whitney U-tests. Area under the curve (AUC) values were generated using receiver operating characteristics (ROC) statistics. Result(s): In patients with history of prior surgery, PRO-C22 was higher at baseline in responders than non-responders (P=0.004). At week 14, responders had higher levels of PRO-C6 than non-responders (P<0.05). Biomarkers PRO-C6 and PRO-C22 demonstrated predictive value at baseline (AUC [95% CI]: PRO-C6 0.78 [0.55-1.0], P=0.012; PROC22 0.90 [0.73-1.0], P<0.001). At week 14, PRO-C6 was also able to discriminate between responders and non-responders (AUC [95% CI]: 0.82 [0.54-1.0], P<0.01). No significant differences were observed in patients without history of prior surgery (Figure 1). Conclusion(s): In patients with a history of prior surgery, higher baseline levels of PRO-C22 predict treatment response to IFX, whereas PRO-C6 levels were higher at week 14 after treatment initiation. These biomarkers demonstrated promising results in predicting response to anti-TNFalpha treatment, as well as separating responders from nonresponders at week 14. Together, these markers could be used to predict and monitor treatment response to IFX in patients with CD with surgical history and may shed light on different profiles of ECM turnover. Future studies are warranted to further validate the potential utility of these biomarkers in larger patient cohorts.

DOI: /10.1093/ecco-jcc/jjab232.737

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjab232.737

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Predictors of response to infliximab in luminal Crohn's disease.

Publication Date: Feb 2005

Authors: Laharie, David; Salzmann, Mélanie; Boubekeur, Hamida; Richy, Frédérique; Amouretti, Michel; Quinton, André; Couzigou, Patrice; Lamouliatte, Hervé; Zerbib, Frank

Journal: Gastroenterologie clinique et biologique

Abstract: To identify predictive factors of response to infliximab in luminal Crohn's disease (CD).

DOI: 10.1016/s0399-8320(05)80718-3

PMID: 15795662.0

Full Article: https://doi.org/10.1016/s0399-8320(05)80718-3

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Faecal calprotectin measurement and infliximab trough levels predict therapeutic evolution CD patients in clinical remission

Publication Date: nan

Authors: Roblin X.; Duru G.; Clavel L.; Rinaudo M.; Cuilleron M.; Jarlot C.; Phelip J.M.; Peyrin Biroulet L.; Paul S.

Journal: nan

Abstract: Background: The deep remission notion (clinical remission and mucosal healing) is an important objective for patients under treatment. The appearance of inflammation and pharmacological biomarkers could be a non-harmful way of predicting the evolution of Crohn's disease (CD). The aim of our study was to offer a predictive model for relapse in CD patients presenting clinical remission undergoing infliximab (IFX) treatment. Method(s): It was a prospective monocentric study that included all CD patients on IFX maintenance treatment (5mg/kg) and in clinical remission (CDAI< 150) for at least 16 weeks, between 2011 and 2014. On the day of the IFX infusion, all of these patients underwent a faecal calprotectin assay (Buhlmann technique), a CRP assay and pharmacological assays of IFX (ELISA, Theradiag). TLI (> 2mug/ml) were considered therapeutic as well as CRP levels < 5mg/l and faecal calprotectin levels < 250 mg/g of stools. All of the patients included were followed up for a minimum of nine months. A CDAI score was calculated at each IFX infusion. A patient was defined in loss of response to IFX (LOR) when the CDAI was above 220, resulting in a change of treatment deemed necessary by the physician (IFX optimisation, change of medical treatment including the use of corticosteroids, surgery). Result(s): 119 patients (mean age: 34 years, M:F sex ratio 1.2, mean duration of the disease 7.8 years) were included. The mean follow-up period was 20.4 months. 17% of the patients were on com-botherapy (IFX and azathioprine). During follow-up, 37 patients (31.1%) out of the 119 relapsed, 78% within the first 6 months (mean period: 4.6 months). While the clinical characteristics of the relapsed and non-relapsed patients were similar, a univariate analysis isolated four significant factors predicting LOR: (CRP > 5mg/l (p=0.043), ATI > 20ng/ml (p< 0.001), LTI > 2 mug/ml (p< 0.001) and calprotectin > 250 mug/g stools (p<0.001)). After logistic regression, two independent factors were linked to a loss of clinical response: LTI < 2mug/ml (OR: 4,34 ; 95% CI: 1.28-10.7; p=0.001) and faecal calprotectin > 250mug/g stools (OR: 3.5; 95% CI: 1.5-8.7; p=0.001). In light of these results, a training cohort of 55 patients was isolated randomly in order to implement a predictive model for LOR in patients on IFX and in clinical remission. The combination of calprotectin > 250mug/g stools and TLI < 2mug/ml enabled to be predicted LOR in 95% of the cases within 6 months. This model was validated on the test cohort of 64 patients with a PPV of 95% and an NPV of 95%. Conclusion(s): In IFX-treated CD patients and in clinical remission, a combination of TLI (< 2mug/ml) and faecal calprotectin (>250mug/g of stools) enable the prediction of LOR within 6 months in 95% of cases.

DOI: /10.1093/ecco-jcc/jju027

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jju027

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Outcomes of maintenance ustekinumab therapy for Crohn's disease based on inflammatory burden: A post-hoc analysis of the UNITI trials

Publication Date: nan

Authors: Ghosh S.; Sattin B.; Tornatore V.; Gasink C.; Gao L.-L.; Sloan S.; Rutgeerts P.; Sands B.; Hanauer S.; Feagan B.

Journal: nan

Abstract: Background: Patient inflammatory burden has been postulated to predict response to anti-inflammatory therapies. Ustekinumab(UST) is the only approved anti-IL-12/23 mAb for the treatment of Crohn's disease (CD) and the PBO-controlled UNITI registration trials present an opportunity to test this hypothesis. We evaluated clinical outcomes to 90 mg q8 and q12wk SC treatment strategies based on inflammatory biomarkers C-reactive protein (CRP) and fecal calprotectin (fCal). Method(s): In UNITI 1 (anti-TNF therapy failures) and UNITI 2 (conventional therapy failures), patients were randomised to PBO, UST 130 mg IV, or UST ~6 mg/kg IV. At 8 weeks, all responders to IV induction therapy participated in IM-UNITI and were randomised to SC maintenance treatment with PBO, UST 90 mg q8wks, or UST 90 mg q12wks. Clinical endpoints were assessed after 44 weeks of maintenance therapy. Results were stratified by inflammatory burden based on CRP and fCal. For CRP, inflammatory burden categories used were <=5, >5 and <=10, and >10 mg/l. For fCal, inflammatory burden categories used were <250 and >=250 mg/kg. Result(s): When patients were stratified by inflammatory burden at baseline (BL) of induction (i.e. before IV dose), CRP thresholds discriminated patients in the 90 mg q12wk group into those more or less likely to achieve clinical endpoints at wk44 of maintenance. This finding is also supported by fCal stratification at BL of induction (i.e. before IV dose).Stratification at BL of maintenance provides greater distinction between UST doses. Maintenance week44 results stratified by CRP are shown in Figure 1. They suggest that a CRP >10 mg/l at maintenance BL (i.e. before first SC dose) discriminates a high inflammatory burden population that benefited from UST 90 mg SC q8wk dosing vs. q12wk dosing. Response and remission rates were similar between UST SC q8wk and q12wk dosing in patients with maintenance BL CRP <=5mg/l and between 5and10 mg/l. Similar effects were seen at maintenance wk44 endpoints using fCal (Figure 2). Those with a higher inflammatory burden(fCal >250 mg/kg) at maintenance BL more clearly separated from PBO in q8wk group(56.4% vs. 33.8% remission, p = 0.002) vs. q12wk group (46.1% vs. 33.8% remission, p = 0.065). Conclusion(s): CD patients with low inflammatory burden based on biomarkers CRP and fCal at BL and/or at initiation of maintenance therapy can benefit from q8 or q12wk maintenance dosing with UST, while those with high inflammatory burden are likely to need q8wk to maintain benefit.

DOI: nan

PMID: nan

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Faecal calprotectin measurement and infliximab trough levels predict therapeutic evolution cd patients in clinical remission

Publication Date: nan

Authors: Roblin X.; Duru G.; Clavel L.; Deltedesco E.; Phelip J.M.; Peyrin biroulet L.; Paul S.

Journal: nan

Abstract: Introduction: The deep remission notion (clinical remission and mucosal healing) is an important objective for patients under treatment. The appearance of inflammation and pharmacological biomarkers could be a non-harmful way of predicting the evolution of Crohn's disease (CD). The aim of our study was to offer a predictive model for relapse in CD patients presenting clinical remission undergoing infliximab (IFX) treatment. Aims & Methods: It was a prospective monocentric study that included all CD patients on IFX maintenance treatment (5mg/kg) and in clinical remission (CDAI < 150) for at least 16 weeks, between 2011 and 2014. On the day of the IFX infusion, all of these patients underwent a faecal calprotectin assay (Buhlmann technique), a CRP assay and pharmacological assays of IFX (ELISA technique, Theradiag). TLI (>2mug/ml) and ATI (<20ng/ml) were considered therapeutic as well as CRP levels < 5mg/l and faecal calprotectin levels < 250 mug/g of stools. All of the patients included were followed up for a minimum of nine months. A CDAI score was calculated at each IFX infusion. A patient was defined in loss of response to IFX (LOR) when the CDAI was above 220, resulting in a change of treatment deemed necessary by the physician (IFX optimisation, change of medical treatment including the use of corticosteroids, surgery). Result(s): 119 patients (mean age: 34+/- 12 years, M:F sex ratio 1.2, mean duration of evolution of the disease 7.8 years) were included. The mean follow-up period was 20.4 months. 17% of the patients were on combotherapy (IFX and azathioprine). During follow-up, 37 patients (31.1%) out of the 119 relapsed, 78% within the first 6 months (mean period: 4.6 months). While the clinical characteristics of the relapsed and non-relapsed patients were similar, a univariate analysis isolated four significant factors predicting LOR: (CRP>5mug/l (p=0.043), ATI>20ng/ml (p<0.001), LTI>2 mug/ml (p<0.001) and calprotectin>250 mug/g stools (p<0.001)). After logistic regression, two independent factors were linked to a loss of clinical response: LTI < 2mug/ml (OR: 4.34; 95% CI: 1.28-10.7; p=0.001) and faecal calprotectin >250mug/g stools (OR: 3.5; 95% CI: 1.5-8.7; p=0.001). In light of these results, a training cohort of 55 patients was isolated randomly in order to implement a predictive model for LOR in patients on IFX and in clinical remission. The combination of calprotectin >250mug/g stools and TLI<2mug/ml enabled to be predicted LOR in 95% of the cases within 6 months. This model was validated on the test cohort of 64 patients with a PPV of 95% and an NPV of 95%. Conclusion(s): In IFX-treated CD patients and in clinical remission, a combination of TLI (<2mug/ml) and faecal calprotectin (<250mug/g of stools) enable the prediction of clinical recurrence within 6 months in 95% of cases. Intervention studies are needed to assess the impact of treatment modification in this group of patients.

DOI: /10.1177/2050640615601611

PMID: nan

Full Article: https://doi.org//10.1177/2050640615601611

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: In early rheumatoid arthritis patients with non-response to methotrexate monotherapy the change in multi-biomarker disease activity score is differentially associated with subsequent response to non-biological versus biological therapy

Publication Date: nan

Authors: Hambardzumyan K.; Bolce R.J.; Saevarsdottir S.; Forslind K.; Petersson I.F.; Geborek P.; Sasso E.H.; Chernoff D.; Cruickshank S.; Van Vollenhoven R.F.

Journal: nan

Abstract: Background/Purpose: For patients with early RA (eRA), methotrexate (MTX) is recommended as first-line treatment and in nonresponders both the addition of conventional non-biological disease modifying anti-rheumatic drug therapy (triple DMARD therapy) and of biological (anti-TNF) therapy are supported by data. Identification of patients with a higher likelihood of responding to one or the other of these options would lead to more personalized medicine and an increased effectiveness of therapy. The objective of this study was to evaluate the change in the multi-biomarker disease activity (MBDA) score (Vectra DA) during MTX therapy as a predictor of response to subsequent non-biological triple versus biological therapy. Method(s): Patients with eRA and DAS28 >3.2 entered the Swedish Farmacotherapy (SWEFOT) clinical trial and received MTX monotherapy for 3 months, at which time clinical non-responders (DAS28 >3.2) were randomized to receive non-biological triple DMARD therapy (arm A) or anti-TNF (infliximab) therapy with MTX (arm B). For this study, 129 non-responders at month 3 (n=62 from arm A and n=67 from arm B) were analyzed by MBDA score at baseline (BL) and month 3. The assessment of changes in the MBDA score (DELTAMBDA) from BL to month 3 as a predictor for response (according to DAS28 and EULAR response criteria) to triple or anti-TNF therapy at year 1 was done by defining small (<=6), moderate (7-20) and large (>20) decreases by tertiles. Small and moderate decreases were combined together (small/moderate) and compared versus large decreases for arms A and B. The proportion of patients in arm A versus arm B with response at year 1 was evaluated by the odds ratio (OR) for patients with small/moderate versus large decreases. Homogeneity of the odds ratios between the two cohorts was assessed by Breslow-Day test. Result(s): The mean (median) decreases in MBDA score from BL to month 3 for year 1 responders (n=66) and non-responders (n=63) were 12.9 (10) and 10.8 (9), respectively (p=0.431), and Month 3 mean (median) MBDA scores were 47.1 (45) and 50.3 (47), respectively (p=0.336). Of patients who had small/moderate decreases in MBDA score during MTX monotherapy, 43% responded to subsequent triple therapy and 57% responded to anti-TNF (OR=0.577). In contrast, among patients with a large decreases in MBDA score from BL to month 3, 67% responded to subsequent triple therapy and 37% to anti-TNF treatment (OR=3.33). Thus the relative treatment effect of arm A versus arm B differed according to the degree of change in the MBDA score from BL to 3 months (p=0.032). Similarly, good EULAR response was achieved by the majority (67%) of patients from arm A, who had large decrease in MBDA score and also the majority (57%) of patients from arm B, who had small/moderate decrease of the MBDA score. Conclusion(s): Among patients with early RA who did not achieve low disease activity on MTX monotherapy, those patients with the greatest decrease in MDBA score were more likely to respond to triple therapy whereas patients with lesser decrease of the MBDA score were more likely to respond to anti-TNF therapy. These findings suggest that in MTX nonresponders, the changes in MBDA score may help guide subsequent therapy.

DOI: /10.1002/art.38914

PMID: nan

Full Article: https://doi.org//10.1002/art.38914

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: In early RA patients with non-response to methotrexate monotherapy the change in multi-biomarker disease activity score is differentially associated with subsequent response to non-biological versus biological therapy

Publication Date: nan

Authors: Hambardzumyan K.; Bolce R.; Saevarsdottir S.; Forslind K.; Petersson I.F.; Geborek P.; Ernestam S.; Sasso E.H.; Chernoff D.; Cruickshank S.E.; Van Vollenhoven R.F.

Journal: nan

Abstract: Background For patients with early RA (eRA), methotrexate (MTX) is recommended as first-line treatment and in non-responders both the addition of conventional non-biological disease modifying anti-rheumatic drug therapy (triple DMARD therapy) and of biological (anti-TNF) therapy are supported by data. Identification of patients with a higher likelihood of responding to one or the other of these options would lead to more personalised medicine and an increased effectiveness of therapy. Objectives To evaluate the change in the multi-biomarker disease activity (MBDA) score during MTX therapy as a predictor of response to subsequent triple versus biological therapy. Methods Patients with eRA and DAS28>3.2 entered the SWEFOT clinical trial and received MTX monotherapy for 3 months, at which time clinical non-responders (DAS28>3.2) were randomised to receive non-biological triple DMARD therapy (arm A) or anti-TNF (infliximab) therapy with MTX (arm B). For this study, 129 non-responders at month 3 (n=62 from arm A and n=67 from arm B) were analysed by MBDA score at baseline (BL) and month 3. The assessment of changes in the MBDA score (DELTAMBDA) from BL to month 3 as a predictor for response to triple or anti-TNF therapy at year 1 was done by defining small (<=6), moderate (7-20) and large (>20) decreases by tertiles. Small and moderate decreases were combined together (small/moderate) and compared versus large decreases for arms A and B. The proportion of patients in arm A versus arm B with response at year 1 was evaluated by the odds ratio (OR) for patients with small/moderate versus large decreases. Homogeneity of the odds ratios between the two cohorts was assessed by Breslow-Day test. Results The mean (median) decreases in MBDA score from BL to month 3 for year 1 responders (n=66) and non-responders (n=63) were 12.9 (10) and 10.8 (9), respectively (p=0.431), and month 3 mean (median) MBDA scores were 47.1 (45) and 50.3 (47), respectively (p=0.336). Patients who had small/moderate decreases in MBDA score during MTX monotherapy, 43% responded to subsequent triple therapy and 57% responded to anti-TNF (OR=0.577). In contrast, among patients with a large decreases in MBDA score from BL to month 3, 67% responded to subsequent triple therapy and 37% to anti-TNF treatment (OR=3.33). Thus the relative treatment effect of arm A versus arm B differed according to the degree of change in the MBDA score from BL to 3 months (p=0.032). Conclusions Among patients with eRA who did not achieve low disease activity on MTX monotherapy, those patients with the greatest decreases in MDBA score were more likely to respond to triple therapy whereas patients with lesser decreases of the MBDA score were more likely to respond to anti-TNF therapy. These findings suggest that in MTX non-responders the changes in MBDA score may help guide subsequent therapy.

DOI: /10.1136/annrheumdis-2014-eular.4231

PMID: nan

Full Article: https://doi.org//10.1136/annrheumdis-2014-eular.4231

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Infliximab in the treatment of Crohn's disease: predictors of response in an Italian multicentric open study.

Publication Date: Aug 2005

Authors: Orlando, A; Colombo, E; Kohn, A; Biancone, L; Rizzello, F; Viscido, A; Sostegni, R; Benazzato, L; Castiglione, F; Papi, C; Meucci, G; Riegler, G; Mocciaro, F; Cassinotti, A; Cosintino, R; Geremia, A; Morselli, C; Angelucci, E; Lavagna, A; Rispo, A; Bossa, F; Scimeca, D; Cottone, M; ,

Journal: Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver

Abstract: Almost 20% of patients with active Crohn's disease are refractory to conventional therapy. Infliximab is a treatment of proven efficacy in this group of patients and it is not clear which variables predict a good response. AIMS.: To evaluate the role of infliximab looking at the predictors of response in a large series of patients with Crohn's disease.

DOI: 10.1016/j.dld.2005.01.019

PMID: 15886081.0

Full Article: https://doi.org/10.1016/j.dld.2005.01.019

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Ustekinumab in Crohn's disease: real-world outcomes and predictors of response.

Publication Date: May 2022

Authors: Lorenzo González, Laura; Valdés Delgado, Teresa; Vázquez Morón, Juan María; Castro Laria, Luisa; Leo Carnerero, Eduardo; Maldonado Pérez, María Belén; Sánchez Capilla, Damián; Pallarés Manrique, Héctor; Sáez Díaz, Antonia; Argüelles Arias, Federico; ,

Journal: Revista espanola de enfermedades digestivas

Abstract: ustekinumab is a monoclonal antibody that inhibits interleukins IL-12 and IL-23, and is approved for the treatment of Crohn's disease (CD) and, more recently, also ulcerative colitis (UC). The aim of this study was to evaluate the effectiveness and safety of ustekinumab, as well as to identify possible predictive factors of response in a real-life setting.

DOI: 10.17235/reed.2020.7352/2020

PMID: 33393332.0

Full Article: https://doi.org/10.17235/reed.2020.7352/2020

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

ercookies	Makes it possible to display the notice on the use of cookies.	Logout / End of project	Ses

Title: In early RA patients with non-response to methotrexate monotherapy the change in multi-biomarker disease activity score is differentially associated with subsequent response to non-biological vs. Biological therapy

Publication Date: nan

Authors: Hambardzumyan K.; Bolce R.; Saevarsdottir S.; Forslind K.; Petersson I.; Geborek P.; Ernestam S.; Sasso E.; Chernoff D.; Cruickshank S.; Van Vollenhoven R.

Journal: nan

Abstract: Background: For patients with early RA (eRA), methotrexate (MTX) is recommended as first-line treatment, and in non-responders the addition of both conventional non-biological disease-modifying anti-rheumatic drug therapy (triple DMARD therapy) and biological (anti- TNF) therapy is supported by data. The objective was to evaluate the change in the multi-biomarker disease activity (MBDA) score during MTX therapy as a predictor of response to subsequent triple vs. biological therapy. Method(s): Patients with eRA and DAS28 > 3.2 entered the SWEFOT clinical trial and receivedMTXmonotherapy for 3 months, at which time clinical non-responders (DAS28 > 3.2) were randomized to receive non-biological triple DMARDtherapy (arm A) or anti-TNF(infliximab) therapy with MTX (arm B). For this study, 129 non-responders at month 3 (n= 62 from arm A and n = 67 from arm B) were analysed by MBDA score at baseline (BL) and month 3. The assessment of changes in theMBDA score (DMBDA) from BL to month 3 as a predictor for response to triple or anti-TNF therapy at year 1 was done by defining small (<= 6), moderate (7-20), and large (>20) decreases by tertiles. Small and moderate decreases were combined (small/moderate) and compared vs. large decreases for arms A and B. The proportion of patients in arm A vs. arm B with response at year 1 was evaluated by the odds ratio (OR) for patients with small/moderate vs. large decreases. Homogeneity of the ORs between the two cohorts was assessed by the Breslow-Day test. Result(s): The mean (median) decreases in MBDA score from BL to month 3 for year 1 responders (n = 66) and non-responders (n = 63) were 12.9 (10) and 10.8 (9), respectively (NS), and month 3 mean (median) MBDA scores were 47.1 (45) and 50.3 (47), respectively (NS). Among patients who had small/moderate decreases in MBDA score during MTX monotherapy, 43% responded to subsequent triple therapy and 57% responded to anti- TNF (OR 0.577). By contrast, among patients with a large decrease in MBDA score from BL to month 3, 67% responded to subsequent triple therapy and 37% to anti-TNF treatment (OR 3.33). Thus the relative treatment effect of arm A vs. arm B differed according to the degree of change in the MBDA score from BL to 3 months (p = 0.032). Conclusion(s): Among patients with eRA who did not achieve low disease activity on MTX monotherapy, those patients with the greatest decreases in MDBA score were more likely to respond to triple therapy whereas patients with lesser decreases of the MBDA score were more likely to respond to anti-TNF therapy. These findings suggest that, inMTX non-responders, the changes inMBDA score may help guide subsequent therapy.

DOI: /10.3109/03009742.2014.946235

PMID: nan

Full Article: https://doi.org//10.3109/03009742.2014.946235

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Nomogram to predict primary non-response to infliximab in patients with Crohn's disease: A multicenter study

Publication Date: nan

Authors: Ye X.-Q.; Cai J.; Yu Q.; Cao X.-C.; Chen Y.; Rao M.-X.; Chen B.-L.; He Y.; Zeng Z.-R.; Chen H.; Lin Y.-M.; Cao Q.; Chen M.-H.; Zhang S.-H.

Journal: nan

Abstract: Background: Infliximab (IFX) is effective at inducing and maintaining clinical remission and mucosal healing in patients with Crohn's disease (CD); however, 9%-40% of patients do not respond to primary IFX treatment. This study aimed to construct and validate nomograms to predict IFX response in CD patients. Method(s): A total of 343 patients diagnosed with CD who had received IFX induction from four tertiary centers between September 2008 and September 2019 were enrolled in this study and randomly classified into a training cohort (n = 240) and a validation cohort (n = 103). The primary outcome was primary non-response (PNR) and the secondary outcome was mucosal healing (MH). Nomograms were constructed from the training cohort using multivariate logistic regression. Performance of nomograms was evaluated by area under the receiver-operating characteristic curve (AUC) and calibration curve. The clinical usefulness of nomograms was evaluated by decision-curve analysis. Result(s): The nomogram for PNR was developed based on four independent predictors: age, C-reactive protein (CRP) at week 2, body mass index, and non-stricturing, non-penetrating behavior (B1). AUC was 0.77 in the training cohort and 0.76 in the validation cohort. The nomogram for MH included four independent factors: baseline Crohn's Disease Endoscopic Index of Severity, CRP at week 2, B1, and disease duration. AUC was 0.79 and 0.72 in the training and validation cohorts, respectively. The two nomograms showed good calibration in both cohorts and were superior to single factors and an existing matrix model. The decision curve indicated the clinical usefulness of the PNR nomogram. Conclusion(s): We established and validated nomograms for the prediction of PNR to IFX and MH in CD patients. This graphical tool is easy to use and will assist physicians in therapeutic decision-making.

DOI: /10.1093/gastro/goaa069

PMID: nan

Full Article: https://doi.org//10.1093/gastro/goaa069

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Development and Validation of a Clinical Decision Support Tool That Incorporates Pharmacokinetic Data to Predict Endoscopic Healing in Patients Treated With Infliximab.

Publication Date: 2021 06

Authors: Vande Casteele N; Jairath V; Jeyarajah J; Dulai PS; Singh S; Shackelton LM; Feagan BG; Sandborn WJ

Journal: nan

Abstract: BACKGROUND & AIMS: Infliximab is an effective treatment for moderate to severe ulcerative colitis (UC). Little is known about patient-related factors that might be used to predict endoscopic healing with infliximab therapy.

DOI: /10.1016/j.cgh.2020.04.078

PMID: nan

Full Article: https://doi.org//10.1016/j.cgh.2020.04.078

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Peripheral blood derived gene panels predict response to infliximab in rheumatoid arthritis and Crohn's disease.

Publication Date: 2013

Authors: Mesko, Bertalan; Poliska, Szilard; Váncsa, Andrea; Szekanecz, Zoltan; Palatka, Karoly; Hollo, Zsolt; Horvath, Attila; Steiner, Laszlo; Zahuczky, Gabor; Podani, Janos; Nagy, And Laszlo

Journal: Genome medicine

Abstract: Biological therapies have been introduced for the treatment of chronic inflammatory diseases including rheumatoid arthritis (RA) and Crohn's disease (CD). The efficacy of biologics differs from patient to patient. Moreover these therapies are rather expensive, therefore treatment of primary non-responders should be avoided.

DOI: 10.1186/gm463

PMID: 23809696.0

Full Article: https://doi.org/10.1186/gm463

Methods:

Co-medication was given after blood was taken.Table 1 Summary of the clinical parameters of patients with Crohn's diseaseFull size tableTable 2 Summary of the clinical parameters of patients with rheumatoid arthritisFull size tableClinical parameters, including Crohn's disease activity score (CDAI), C-reactive protein (CRP), hemoglobin, leukocyte and neutrophil counts in CD; and Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), CRP and disease-modifying anti-rheumatic drugs (DMARDs) in RA were assessed at the time of the first infliximab infusion (baseline), at the second infusion (week 2), and at week 6 or 14 when the responder statuswas determined based on clinicians' assessment.The inclusion criteria in RA were fulfillment of the 2010 European League Against Rheumatism/ACR classification criteria; age between 20 and 60 years; failure to respond to at least two DMARDs; active disease (DAS28 >3.2);and anti-TNFα therapy-naive patients or previous anti-TNFα use at least 3 months prior to blood sampling.Prednisone therapy ≤10 mg per day was allowed provided that the dosage had been stable for at least 2 months before entryand non-steroidal anti-inflammatory drugs were allowed in doses stable for at least 1 month before baseline.Patients were on maximal-tolerable methotrexate treatment (5 to 30 mg per week), which had to be stable for at least 4 weeks before baseline.Exclusion criteria were pregnancy or breastfeeding; current or recent cancer; active infectious disease; a history of an acute inflammatory joint disease of different origin; and smoking.Inclusion criteria in CD were clinically diagnosed CD; age between 20 and 60 years; CDAI >250; anti-TNFα therapy-naive patients; and prednisolone therapy with a dosage of less than 10 mg/day.Exclusion criteria were pregnancy or breastfeeding; current or recent cancer; active infectious disease; and smoking.Responder status was determined by a CDAI decrease of 100 points compared to baseline in CD at week 6; and by ACR categories at week 14 in RA (ACR0% and ACR20% improvement represent the non-responder; ACR50% and ACR70% represent the responderstatus).Peripheral blood mononuclear cell and RNA isolationVenous peripheral blood samples were collected (10 ml) in Venous Blood Vacuum Collection Tubes containing EDTA (BD Vacutainer K2EDTA, Becton Dickinson, New Jersey, United States). Total RNA was extracted from PBMCs using Trizol reagent (Invitrogen, Carlsbad, California, United States), according to the manufacturer's protocol. RT-quantitative PCR amplification was performed using an ABI Prism 7900HT instrument (Life Technologies).Relative gene expression levels were calculated by a comparative Ct method that results in normalizing to PPIA(PeptidylprolylIsomerase A (Cyclophilin A))expression for each sample.Multivariate data analysis: canonical variates analysis or linear discriminant analysisSeparation between predefined groups of objects is best revealed by canonical variates

analysis (CVA). The area under the ROC curve (AUC) is a diagnostic measure indicating how a parameter can distinguish between two groups (responder and non-responder).Automated gene panel generationLDA [18]and ROC analyses were performed using R software (R Development Core Team [19]) with packages MASS[20] and ROCR[21], respectively, to automatically generate gene panels according to thefollowing algorithm (Figure 2):Figure 2Schematic flowchart of automatic gene panel generation.

Results:

There were no significant differences regarding age, CDAI, CRP, hemoglobin, leukocytes or neutrophils between the responders and non-responders (Table 1).In RA, we used a binary outcome variable to assess clinical responder status: patients with ACR0% or ACR20% scores were classified as non-responders; and patients with ACR50% or ACR70% scores were classified as responders. There were no significant differences regarding age, DAS28, HAQ, CRP, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP)antibody status or DMARDs between respondersand non-responders (Table 2).Global gene expression analyses identify differentially expressed genes between responders and non-responders in Crohn's disease and rheumatoid arthritisIn CD, global gene expression analysis resulted in a list of 48 genes through filtering steps based on expression levels, fold-change cut-off at 1.5 and statistical significant analyses differentiating responders from non-responders at baseline. Analysis of samples obtained at week 2 identified 12differentially expressed genes with statistically significant differences between respondersand non-responders. Three gene lists scored by linear discriminant analysisin (A) Crohn's disease and (B) rheumatoid arthritis.

Discussion:

The detection of gene panels including genome classifiers discriminating between future responders and non-responders through the minimally invasive peripheral blood sampling either in CD or RA is clearly a yet unmet medical and diagnostic need. Univariate analyses may disregard potential interactions among genes,but LDA can reveal underlying differences by using genes simultaneously as a gene panel, providing perfect segregation in the multidimensional space.The high number of gene panels with 100% segregation and gene panels with accuracy of over 90% after cross-validation show that it is likely to find such panels when testing on larger cohorts. This could also mean that, regarding the development of a diagnostic assay predicting response to infliximab therapy in RA and CD, using a gene set containing 20 to 24 genes seems to be more reasonable than selecting individual gene lists consisting of typically 5 to 8 genes, provided that an LDA-based approach is used.To provide compact gene panels resulting in a perfect segregation between responders and non-responders, as well as a success rate of over 90% after cross-validation, we detected and visualized these prominent gene panels - in which many of the genes overlapped in the different groups. The final conclusion of our study was that, althoughan ultimate gene panel might have been expected to be found, there is no such panel but instead a pool of genes with high statistical power that could be tested in further cohorts using LDA.

Conclusion:

ConclusionsIn this work, we provided twopieces of proof of concept to show that peripheral blood gene expression profiles are suitable for determining gene panels with the highest discriminatory power that can differentiate responders from non-responders at baseline in CD and RA patient cohorts and can also be validated in independent cohorts; and despite the similar pathogenetic background of CD and RA, distinct, non-overlapping gene panels predict the responder status in these conditions.Such gene panels couldcontribute to the solution of unmet needs in clinical decision making by determining in advance whether a patient willrespond to a specific and expensive biologic therapy by analyzing the gene expression patterns of the least invasively obtained peripheral blood samples, therefore prevent the patient from receiving an inefficient therapy and then cycling to an efficient one that could not then achieve the same efficacy as it would have done if used in the first place.

Title: Serum PR3-ANCA Is a Predictor of Primary Nonresponse to Anti-TNF-α Agents in Patients with Ulcerative Colitis.

Publication Date: May 2021

Authors: Yoshida, Atsushi; Matsuoka, Katsuyoshi; Ueno, Fumiaki; Morizane, Toshio; Endo, Yutaka; Hibi, Toshifumi

Journal: Inflammatory intestinal diseases

Abstract: Anti-tumor necrosis factor-α (TNF-α) agents are effective for moderately to severely active ulcerative colitis (UC). Nonetheless, a proportion of patients fail to respond to these agents as therapy for induction of remission. Recent studies indicated that perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) may predict response to anti-TNF-α agents in UC patients. However, whether PR3-ANCA can predict primary nonresponse (PNR) to anti-TNF-α agents has not yet been evaluated. The aim of this study was to examine whether PR3-ANCA can predict PNR to anti-TNF-α in UC patients.

DOI: 10.1159/000515361

PMID: 34124183.0

Full Article: https://doi.org/10.1159/000515361

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Response to infliximab treatment in Crohn's disease is not associated with mutations in the CARD15 (NOD2) gene: an analysis in 534 patients from two multicenter, prospective GCP-level trials.

Publication Date: Oct 2002

Authors: Mascheretti, Silvia; Hampe, Jochen; Croucher, Peter J P; Nikolaus, Susanna; Andus, Tilo; Schubert, Silvia; Olson, Allan; Bao, Weihang; Fölsch, Ulrich Robert; Schreiber, Stefan

Journal: Pharmacogenetics

Abstract: Infliximab induces remission in 30-40% of patients with active Crohn's disease. Treatment response is a stable trait over repeated doses yet the clinical predictors of response are still unknown. Recently, three variants in the CARD15 gene have been identified as major genetic risk factors for Crohn's disease. Single nucleotide polymorphisms (SNPs) 8, 12 and 13, have been shown to be independently associated with Crohn's disease susceptibility. The aim of the present study was to investigate these variants in relation to the therapeutic efficacy of infliximab. SNPs were genotyped (TaqMan) in two cohorts (n= 90 and n= 444 (ACCENT I)) of active Crohn's disease patients (CDAI 220-450). The patients were recruited from independent multicenter trials conducted according to GCP. At the start of both trials, patients received a single infusion of open label infliximab (5 mg/kg bodyweight). The genotypic and allelic frequencies of each SNP were significantly associated with Crohn's disease in comparison to 370 healthy controls as reported previously. Response to infliximab (drop in CDAI 70 points or remission, respectively) was not associated with the genetic variants in the CARD15 gene in either cohort. The subsequent negative findings in a two-cohort model exclude SNPs 8, 12 and 13 of the CARD15 gene as predictors for therapeutic response to infliximab treatment.

DOI: 10.1097/00008571-200210000-00002

PMID: 12360101.0

Full Article: https://doi.org/10.1097/00008571-200210000-00002

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serum microRNA levels in patients with Crohn's disease during induction therapy by infliximab.

Publication Date: Jun 2014

Authors: Fujioka, Shin; Nakamichi, Ikuo; Esaki, Motohiro; Asano, Kouichi; Matsumoto, Takayuki; Kitazono, Takanari

Journal: Journal of gastroenterology and hepatology

Abstract: microRNAs (miRNAs) have been suggested to be candidates for biomarkers in various diseases including Crohn's disease (CD). To identify possible biomarkers predictive of the therapeutic effect of infliximab in CD, we investigated serum miRNA levels during the induction therapy by the medication.

DOI: 10.1111/jgh.12523

PMID: 24447044.0

Full Article: https://doi.org/10.1111/jgh.12523

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Comparison of serum biomarkers across rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patient populations prior to and following treatment with golimumab, a human anti-TNF antibody

Publication Date: nan

Authors: Wagner C.; Fan H.; Rahman M..U.; Beutler A.; Hsu B.; Elashoff M.; Visvanathan S..

Journal: nan

Abstract: Purpose: To compare and contrast biomarker profiles prior to and following golimumab (GLM) treatment across 3 populations of pts with rheumatic disease: active rheumatoid arthritis (RA) despite MTX; psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Method(s): Sera were collected at wks0, 4 and 14 from a subset (approx. 100) pts from each of the GLM Phase 3 trials: GO-FORWARD (active RA despite MTX), GO-REVEAL (active PsA despite conventional treatment) and GO-RAISE (active AS despite conventional treatment). Across the 3 studies, pts were randomized to either PBO, 50mg or 100mg GLM in the presence or absence of MTX or other conventional medications. Samples were tested for select inflammatory markers (Quintiles Laboratories) and bone and cartilage markers (Pacific Biometrics) and protein profiling using multi-analyte profiles (Rules Based Medicine). Change from baseline in markers was compared between GLM+/-MTX and PBO+MTX using ANOVA on the van der Waerden normal scores and t-tests. Pathway analysis comparisons were made using Ingenuity software and data were compared using the Fisher Exact test. Result(s): Prior to treatment, there were no biomarkers that were significantly different between the GLM+/-MTX and the PBO+/-MTX treatment groups that were consistently observed across the 3 pt populations. In the GLM+/-MTX groups at wk4, there were 7 biomarkers (haptoglobin, CRP, serum amyloid P, thyroxine binding globulin, MMP-3, ICAM-1, TNFRII) that showed significant changes from baseline ($p<0.05$) relative to PBO+/-MTX that were similarly modulated across the 3 populations. At wk4 following GLM+/-MTX treatment, there were 4 other commonly modulated biomarkers between the AS and PsA populations, 3 more markers similarly modulated between RA and PSA, and one more commonly modulated marker between the AS and RA populations. At wk14, in the GLM+/-MTX groups there were 9 markers (CRP, MIP1beta, haptoglobin, MMP-3, alpha1anti-trypsin, thyroxine binding globulin, serum amyloid P, PAI-1 and TIMP-1) that were significantly ($p<0.05$) changed from baseline relative to PBO+/-MTX across all populations. In the PsA and AS populations, 5 other markers were commonly changed from baseline at wk14 compared with only 1 additional marker for each population relative to the RA pts. Signaling pathways significantly impacted in response to treatment with GLM+/-MTX at wk4 and 14 across the different populations included the acute phase response, TREM1, hepatic fibrosis, coagulation system, and leukocyte extravasation. Conclusion(s): GLM impacts multiple proteins and signaling pathways associated with TNFalpha in the RA, PsA and AS disease processes. Principal component analysis indicates all 3 diseases are notably different from normal individuals, and pts with RA have a somewhat distinct overall profile compared with AS and PsA. Select markers were modulated across all populations of pts treated with GLM+/-MTX, with some overlap of modulated markers across all diseases.

DOI: /10.1002/art.25866

PMID: nan

Full Article: https://doi.org//10.1002/art.25866

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Correlation Between Anti-TNF Serum Levels and Endoscopic Inflammation in Inflammatory Bowel Disease Patients.

Publication Date: Mar 2019

Authors: Chaparro, María; Barreiro-de Acosta, Manuel; Echarri, Ana; Almendros, Rosendo; Barrio, Jesús; Llao, Jordina; Gomollón, Fernando; Vera, Maribel; Cabriada, José Luis; Guardiola, Jordi; Guerra, Iván; Beltrán, Belén; Roncero, Oscar; Busquets, David; Taxonera, Carlos; Calvet, Xavier; Ferreiro-Iglesias, Rocío; Ollero Pena, Virginia; Bernardo, David; Donday, María G; Garre, Ana; Godino, Ana; Díaz, Ana; Gisbert, Javier P

Journal: Digestive diseases and sciences

Abstract: (a) To evaluate the diagnostic accuracy of anti-TNF trough levels to predict mucosal healing in inflammatory bowel disease (IBD); (b) to determine the best cut-off point to predict mucosal healing in IBD patients treated with anti-TNF.

DOI: 10.1007/s10620-018-5362-3

PMID: 30426297.0

Full Article: https://doi.org/10.1007/s10620-018-5362-3

Methods:

MethodsPatientsOne hundred eighty-two consecutive patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) based on clinical, radiological, endoscopic, and histological evaluations were included. Patients were under anti-TNF treatment in stable doses for at least 6 months and underwent a colonoscopy due to clinical practice. The principal variable was mucosal healing (see Endoscopic activity assessment section for definition).Data CollectionData were prospectively obtained from medical records. Each 10-mL tube was centrifuged for 10 min (3000 rpm at 25 °C), and the supernatant cryopreserved following the kit manufacturer's instructions at a maximum temperature of − 20 °C until centrally analyzed by SMART ELISAs in Sanquin Laboratories (Amsterdam, The Netherlands).Statistical AnalysisQuantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range, depending on whether or not they followed a normal distribution.

Results:

ROC analysis showing the optimal cutoff values of both infliximab and adalimumab trough levels to predict mucosal healing is included in Fig. 1. 1Receiver operating characteristic curves (ROCs) showing the correlation between infliximab levels (a) or adalimumab levels (b) and the presence of mucosal healingFull size imageTable 2 Accuracy of anti-TNF trough serum levels to predict mucosal healing in inflammatory bowel disease patientsFull size tableIn the univariate analysis, several variables, such as tobacco consumption, having CD instead of UC, or previous infliximab therapy, were significantly associated with mucosal healing (Table 3). 2).Table 3 Factors associated with mucosal healing (a) in patients under infliximab (b) and adalimumab (c) treatmentFull size tableFig. Therefore, it was not possible to analyze the effect of anti-drug antibodies on anti-TNF serum concentration.

Discussion:

The diagnostic accuracy of anti-TNF levels for mucosal healing reported in those studies has been generally poor, with AUCs between 0.6 and 0.7 in most cases.Table 4 Published studies assessing the correlation between infliximab and adalimumab serum levels and mucosal healing in inflammatory bowel disease patients under maintenance treatmentFull size tableThe highest accuracy of anti-TNF

levels able to predict mucosal healing was reported by Morita et al. [22]. Taking all these limitations into account, authors suggested that their results should be interpreted with caution.In our study, the best cutoff value for infliximab was 3.4 μg/mL. Some authors have also suggested that severe UC patients might need higher load of anti-TNF drugs during the induction [23]. This observation needs to be confirmed in further studies.In our study we also found that smoking habit was associated with a lower probability of mucosal healing.

Conclusion:

None available

Title: Serum survivin predicts treatment response in active rheumatoid arthritis

Publication Date: nan

Authors: Levitsky A.; Erlandsson M.; Van Vollenhoven R.F.; Bokarewa M.I.

Journal: nan

Abstract: Background: Survivin is an oncological biomarker. In rheumatoid arthritis (RA), elevated serum survivin is common and has been used to predict disease onset and progressive joint damage. Objective(s): We investigated the predictive capacity of survivin in clinical disease activity and/or response to various antirheumatic treatments in patients with early RA. Method(s): Survivin levels from serum were measured using ELISA at baseline in 302 patients enrolled in the Swedish pharmacotherapy (SWEFOT) trial with follow-up at 3, 12 and 24 months. After methotrexate (MTX) monotherapy for 3 months, responders (DAS28<=3.2) remained on MTX, while non-responders were randomized to triple therapy (MTX+sulfasalazine+hydroxychloroquine) or anti-TNF (MTX+infliximab). Survivin levels >0.45 ng/mL were considered positive. Based on survivin status over 24 months, core-set outcomes (i.e. DAS28, HAQ, pain & global VAS) were evaluated at 3, 12, and 24 months. Result(s): Over one-third of all patients (n=114) were survivin-positive at baseline. Survivin-positive ever-smokers (51/71 vs. 64/112, OR 1.91 [95% CI 1.01-3.62], p=0.045) and survivin-negative patients who converted to positive over 24 months (13/161 vs. 2/100, OR 4.39 [0.97, 19.88], p=0.037) responded seldom to MTX. At 3 months, survivin-positive patients who converted negative (n=11) had greater reductions in DAS28 (p=0.002), HAQ (p=0.011) and global VAS (p=0.025) vs. those who remained positive (n=28), which were maintained over 24 months. At 12 months, survivin-positive MTX-responders who continued monotherapy had a higher risk of disease re-activation on MTX compared to the survivinnegative patients (12/36 vs. 7/52, OR 3.21 [1.12-9.24], p=0.032) and showed no improvement in HAQ over 24 months. Survivin-positive MTX non-responders who converted to negative (n=32) or remained negative (n=83) had greater improvements from 3 to 12 months than those who converted to positive (n=13) (DELTADAS28>1.2, 63% & 60% vs. 31%, p=0.053, p=0.046, respectively). Among survivin-positive patients on triple therapy, converting to negative (n=19) yielded a lower DAS28 at 12 months (2.34 vs. 4.12, p=0.046) and a high frequency of DAS<=3.2 (86% vs. 37%, p=0.056) at 24 months vs. converting to positive (n=7). They also had lower pain (p=0.048) and global VAS (p=0.015) at 24 months compared to the same subgroup, which was not observed among anti-TNF - where no differences in core-set outcomes were observed between the survivin groups. Survivin-positive patients on anti-TNF had a higher risk to have active disease at 24 months compared to those on triple therapy (16/29 vs. 9/32, OR 3.15 [1.09-9.10], p=0.037). Conclusion(s): Survivin-positive patients have worse 24-month outcomes than survivin-negative patients if treated with MTX monotherapy, but conversion to survivin-negative is associated with a good and stable response to MTX monotherapy. For survivin-positive patients with early RA who fail MTX, triple therapy is associated with a better likelihood for response than anti-TNF therapy.

DOI: /10.1136/annrheumdis-2015-eular.3151

PMID: nan

Full Article: https://doi.org//10.1136/annrheumdis-2015-eular.3151

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: Results from the GO-FORWARD study

Publication Date: nan

Authors: Visvanathan S.; Rahman M.U.; Keystone E.; Genovese M.; Klareskog L.; Hsia E.; Mack M.; Buchanan J.; Elashoff M.; Wagner C.

Journal: nan

Abstract: Introduction: The goal of this study was to identify serum markers that are modulated by treatment with golimumab with or without methotrexate (MTX) and are associated with clinical response. Method(s): Sera were collected at weeks 0 and 4 from a total of 336 patients (training dataset, n = 100; test dataset, n = 236) from the GO-FORWARD study of patients with active rheumatoid arthritis despite MTX. Patients were randomly assigned to receive placebo plus MTX; golimumab, 100 mg plus placebo; golimumab, 50 mg plus MTX; or golimumab, 100 mg plus MTX. Subcutaneous injections were administered every 4 weeks. Samples were tested for select inflammatory, bone, and cartilage markers and for protein profiling using multianalyte profiles. Result(s): Treatment with golimumab with or without MTX resulted in significant decreases in a variety of serum proteins at week 4 as compared with placebo plus MTX. The American College of Rheumatology (ACR) 20, ACR 50, and Disease Activity Score (DAS) 28 responders showed a distinct biomarker profile compared with nonresponding patients. Conclusion(s): ACR 20 and ACR 50 responders among the golimumab/golimumab + MTX-treated patients had a distinct change from baseline to week 4 in serum protein profile as compared with nonresponders. Some of these changed markers were also associated with multiple clinical response measures and improvement in outcome measures in golimumab/golimumab + MTX-treated patients. Although the positive and negative predictive values of the panel of markers were modest, they were stronger than C-reactive protein alone in predicting clinical response to golimumab. © 2010 Wagner et al.; licensee BioMed Central Ltd.

DOI: /10.1186/ar3188

PMID: nan

Full Article: https://doi.org//10.1186/ar3188

Methods:

The protocol was reviewed and approved by each site's institutional review board or ethics committee. All patients provided written informed consent before undergoing study-related procedures.Sites were randomly chosen for biomarker testing. The individual markers selected for these analyses included bone alkaline phosphatase, COL 2-3/4C long neoepitope, deoxypyridinoline, hyaluronic acid, IL-6, IL-8, ICAM-1, MMP-3, N-terminal propeptide of type 1 procollagen (P1NP), osteocalcin, pyridinoline, TNF-α, and vascular endothelial growth factor (VEGF). Pearson correlation was used to measure the association between biomarker levels and clinical response.

Results:

As discussed in more detail later, we found significant relations to efficacy for biomarkers in the following general categories: acute phase reactants (α1-antitrypsin, CRP, haptoglobin, serum amyloid P, von Willebrand factor), bone metabolism factors (hyaluronic acid, pyridinoline, P1NP), coagulation factors (lipoprotein(a), plasminogen activator inhibitor-1 (PAI-1), factor VII), hematologic factors (complement 3, ferritin, myoglobin), inflammatory markers (CD40, ENRAGE (S100A12),

epithelium-derived neutrophil-activating protein 78 (ENA-78), IL-1 receptor agonist, IL-6, IL-16, ICAM-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, MMP-3, monocyte chemotactic protein-1 (MCP-1), monocyte/macrophage-derived chemokine (MDC or CCR-4), myeloperoxidase, tissue inhibitor of metalloproteinases-1 (TIMP-1), TNF receptor 2, VEGF), metabolic factors (adiponectin, apolipoprotein A1, apolipoprotein C3, leptin), and other factors (thyroxine-binding globulin, basic fibroblast growth factor (bFGF), carcinoembryonic antigen, stem cell factor, insulin, cancer antigen 125, serum glutamic oxaloacetic transaminase (SGOT), sex hormone-binding globulin (SHBG)).Baseline characteristicsBaseline characteristics for the training and test subsets are displayed in Table 1. Log2 transformed values for these markers at baseline and week 4 are shown in Figure 1a. Significant differences between responders and nonresponders also were found in the test dataset for seven of these markers. ESR analyses were slightly less predictive of ACR 20 or ACR 50 responses than was CRP (data not shown).Table 3 Logistic regression predictive models results by using changes in biomarker levels from baseline to week 4 and clinical response at week 14.

Discussion:

Markers such as CRP [16], haptoglobin, apolipoprotein C3 [17], and ENRAGE [18] have been associated with the early, acute phase responses that occur in RA. Further, fibroblast-like synoviocytes under hypoxic conditions exhibit elevated MMP-3 levels [25], and a polymorphism in the MMP-3 gene has been shown to be associated with radiographic progression [26]. Elevated levels of hyaluronic acid have been observed in serum from RA patients, and this correlated with clinical parameters [27, 28]. Results published by Hueber et al. [29] identified a 24-serum marker signature that was also weakly predictive of response to etanercept treatment.

Conclusion:

ConclusionsClearly, a clinical response to golimumab involves modulation of several RA disease processes, including those involved in the acute and inflammatory phase of disease, as well as downstream aspects relating to bone and cartilage metabolism and destruction. The results of this study from two separate datasets showed strong associations between selected biomarker levels and improvement in a variety of clinical-response measures after treatment with golimumab. Baseline levels of markers were not consistently associated with future response to golimumab therapy. Thus, additional testing of serum and other types of markers from other studies will be needed to identify additional molecules that can either be added to strengthen this panel or be used independently as predictive markers in the management of patients with RA who are treated with anti-TNF-α therapies.

Title: Predictors of Primary Response to Biologic Treatment [Anti-TNF, Vedolizumab, and Ustekinumab] in Patients With Inflammatory Bowel Disease: From Basic Science to Clinical Practice.

Publication Date: Jun 2020

Authors: Gisbert, Javier P; Chaparro, María

Journal: Journal of Crohn's & colitis

Abstract: Inflammatory bowel diseases [IBD]-ulcerative colitis and Crohn's disease-are commonly treated with biologic drugs. However, only approximately two-thirds of patients have an initial response to these therapies. Personalised medicine has the potential to optimise efficacy, decrease the risk of adverse drug events, and reduce costs by establishing the most suitable therapy for a selected patient.

DOI: 10.1093/ecco-jcc/jjz195

PMID: 31777929.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjz195

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Biomarkers identify radiographic progressors and clinical responders among patients with early rheumatoid arthritis

Publication Date: nan

Authors: Mozaffarian N.; Smolen J.S.; Devanarayan V.; Hong F.; Kavanaugh A.

Journal: nan

Abstract: Background Biomarkers that could predict or track disease progression among patients (pts) with rheumatoid arthritis (RA) are of great interest. Objectives To evaluate several biomarkers for association with radiographic and clinical outcomes in early RA pts treated with adalimumab (ADA)+methotrexate (MTX) vs. MTX alone. Methods OPTIMA was a phase 4, double-blind, randomized, controlled trial in MTX-naive pts with early RA (<1 yr). Pts were treated for 26 weeks (wks) with ADA (40 mg every other wk)+MTX or placebo (PBO)+MTX. Radiographic progression (RP) was defined as change in modified total Sharp score (DELTAmTSS) >0.5 units/yr; rapid RP (RRP) as DELTAmTSS >=3 units/yr. Immunologic biomarkers measured include CRP, soluble E-selectin (sE-sel), soluble intercellular adhesion molecule-1 (sICAM), soluble vascular cell adhesion molecule-1 (sVCAM), anti-CCP antibodies (ACPA), and rheumatoid factor (RF); metabolic biomarkers include albumin, glucagon, insulin, and leptin; cardiovascular (CV) markers include apolipoprotein A-1 (ApoA1), apolipoprotein B (ApoB), total cholesterol, HDL, LDL, and triglycerides. Association of baseline (BL) biomarkers with radiographic outcomes was evaluated using univariate analyses. A mixed-effects model was used to compare biomarker changes in clinical responders (pts achieving DAS28(CRP) <3.2 at wks 22 and 26) vs. non-responders in each treatment group; BL DAS28(CRP) and biomarker levels were adjusted as covariates. Significance was assigned where P<.05. Corrections were made for multiple comparisons. Results 515 pts were randomized to ADA+MTX and 517 to PBO+MTX; after 26 wks, rates of RP and RRP were 25%/7% among ADA+MTX pts vs. 38%/20% among PBO+MTX pts, respectively. Regardless of treatment, pts who had poor radiographic outcomes had significantly higher BL CRP levels and lower BL mean leptin. Elevated ACPA and RF levels at BL were also associated with poor radiographic outcomes, but only for PBO+MTX pts. At wk 26, 44% of pts on ADA+MTX were clinical responders vs. 24% of pts on PBO+MTX. Eventual responders had significantly lower BL body mass index, regardless of treatment received. In the ADA+MTX group, responders had significantly larger increases in albumin, ApoA1, cholesterol and HDL, and significantly larger decreases in CRP, ET-1, sE-sel, sICAM, RF, and insulin compared to non-responders. Similarly, within the PBO+MTX group, responders had significantly larger increases in cholesterol and HDL, with significantly larger decreases in CRP, sE-sel, sVCAM, and RF. When comparing ADA+MTX responders to PBO+MTX responders, pts on ADA+MTX had significantly larger increases in albumin and ApoA1, and significantly larger decreases in CRP, lipoprotein, RF, sE-sel, and sICAM. Conclusions Overall, treatment of early RA in OPTIMA was associated with a decrease in inflammatory markers and an improvement in markers of metabolic function and CV risk. These changes were more pronounced in pts receiving ADA+MTX compared to PBO+MTX, even when analyzing only clinical responders in each group. Moreover, several immunologic biomarkers, high CRP, ACPA and RF, identified early RA pts destined for poor radiographic outcomes, and thus, pts for whom more aggressive initial therapy may be considered. The data also suggest that leptin may be an important prognostic biomarker in RA.

DOI: /10.1136/annrheumdis-2013-eular.1213

PMID: nan

Full Article: https://doi.org//10.1136/annrheumdis-2013-eular.1213

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Serum Neutrophil Gelatinase B-associated Lipocalin and Matrix Metalloproteinase-9 Complex as a Surrogate Marker for Mucosal Healing in Patients with Crohn's Disease.

Publication Date: Dec 2015

Authors: de Bruyn, Magali; Arijs, Ingrid; De Hertogh, Gert; Ferrante, Marc; Van Assche, Gert; Rutgeerts, Paul; Vermeire, Séverine; Opdenakker, Ghislain

Journal: Journal of Crohn's & colitis

Abstract: Although costly and uncomfortable for the patient, the current standard to assess mucosal healing in Crohn's disease [CD] patients is endoscopy. The aim of this study was to evaluate NGAL-MMP-9 as surrogate marker for mucosal healing in CD patients.

DOI: 10.1093/ecco-jcc/jjv148

PMID: 26351381.0

Full Article: https://doi.org/10.1093/ecco-jcc/jjv148

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Genotypic and haplotypic effects of 7 single-nucleotide polymorphisms in the CRP gene on levels of c-reactive protein and DAS28 in a cohort of 180 untreated newly diagnosed rheumatoid arthritis patients (opera study)

Publication Date: nan

Authors: Ammitzboll C.G.; Steffensen R.; Junker P.; Ostergaard M.; Johansen J.; Podenphant J.; Hetland M.L.; Lindegaard H.M.; Ellingsen T.; Stengaard-Pedersen K.

Journal: nan

Abstract: Background/Purpose: Single nucleotide polymorphisms (SNPs) in the CRP gene are implicated in the regulation of the basal C-reactive protein (CRP) expression and its response to pro-inflammatory stimuli. Previous reports suggest these effects may have an impact on clinical decision-making based on CRP, e.g. DAS28 (1). We aimed to investigate for the first time the possible association between 7 SNPs in the CRP and the serum level of CRP/ DAS28 in a cohort of 180 untreated inflammatory active early RA patients Methods: 180 DMARD naive RA patients with disease duration >=6 months were included in a randomized double blind placebo-controlled trial (OPERA-study,NCT00660647) of methotrexate, intraarticular glucucorticoids + either adalimumab or placebo. SNPs were analyzed by the TaqMan OpenArray system. The 7 SNPs (Table 2) were selected based on previously reported effects on CRP levels(1). CRP was measured using CRP QUICK-READ (range 8-160 mg/l). The associations between SNPs (and haplotypes of SNPs) and CRP and DAS28 levels were evaluated using linear regression analysis adjusted for age, sex and treatment. For the analysis of genotypic and haplotypic effects, the common allele homozygous genotype/haplotype was selected as reference, and the effects are presented as percentage. 'Haplo.stats' package for R was used Results: Baseline characteristics were similar in the two groups, Table 1. There were no significant genotypic or haplotypic effects of the 7 SNPs on CRP levels at baseline or one year (P>=0.080). Homozygosity for the minor allele of rs2808632 reduced borderline significant the baseline DAS28 levels to 54% P=0.055, and heterozygosity for rs1800947 increased DAS28 levels at one year to 158% P=0.03. Six haplotypes were constructed encompassing 94% of the cohort, Table 3. The H4 haplotype reduced baseline DAS28 score to 51% P=0.009, and the H6 haplotype increased the DAS28 score at one year to 168% P=0.02. No further haplotypic effect on DAS28 were observed at baseline or one year. (Table Presented) Conclusion(s): Seven selected CRP gene SNPs had no impact on preand one year post-treatment levels of CRP. Minor genotypic and haplotypic effects on DAS28 scores were observed, but these were not consistent between baseline and one year. This study shows that DAS28 can be used for clinical decision-making without adjustment for CRP gene variants.

DOI: /10.1002/art.38216

PMID: nan

Full Article: https://doi.org//10.1002/art.38216

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Different Biomarkers of Response to Treatment with Selective Jak-1 Inhibitors in Rheumatoid Arthritis.

Publication Date: Aug 2023

Authors: Benucci, Maurizio; Gobbi, Francesca Li; Fusi, Paola; Damiani, Arianna; Russo, Edda; Guiducci, Serena; Manfredi, Mariangela; Grossi, Valentina; Infantino, Maria; Amedei, Amedeo

Journal: Frontiers in bioscience (Landmark edition)

Abstract: Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes progressive joint damage. The Janus kinase (JAK) inhibitors (JAK-I) represent a new therapeutic option for RA patients, blocking the intracellular JAK-STAT pathway. Today, no studies have been conducted to determine whether new biomarkers could better reflect disease activity in patients treated with JAK-I than traditional disease activity indicators. Thus, the aim of our study was to determine additional disease activity biomarkers in RA patients receiving selective JAK-1 inhibitors.

DOI: 10.31083/j.fbl2808176

PMID: 37664943.0

Full Article: https://doi.org/10.31083/j.fbl2808176

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Combination of serological biomarkers and clinical features to predict mucosal healing in Crohn's disease: a multicenter cohort study.

Publication Date: May 2022

Authors: Tang, Nana; Chen, Han; Chen, Ruidong; Tang, Wen; Zhang, Hongjie

Journal: BMC gastroenterology

Abstract: Mucosal healing (MH) has become the treatment goal of patients with Crohn's disease (CD). This study aims to develop a noninvasive and reliable clinical tool for individual evaluation of mucosal healing in patients with Crohn's disease.

DOI: 10.1186/s12876-022-02304-y

PMID: 35538410.0

Full Article: https://doi.org/10.1186/s12876-022-02304-y

Methods:

In the present study, serological indicators were used to construct mucosal healing model of CD patients. All patients in the study gave their informed consent for reviewing their clinical data.Blood assessment and endoscopic documentationBaseline blood values had been collected at the time of CD diagnosis when patients were admitted to hospital before administration of any treatment. Venous blood specimens were drawn into sterile standard tubes containing ethylene diamine tetraacetic acid (EDTA) as an anticoagulant and evaluated within 1 h after venipuncture using a Beckman Coulter UniCel DxH800 hematology analyzer. R software (version 3.3.2) was used to build the nomogram and evaluation of model performance (“rms” package).

Results:

Shapiro–Wilk test showed that data of diagnosis age, disease course and HBI score were with abnormal distributions (all $p < 0.001$). Furthermore, these significant factors were selected to further perform multivariate regression analysis and only PLR was associated with MH after treatment ($p = 0.037$). The simple model (model-1) only contains serum biomarkers including PLR, CAR and ESR. 2Nomogram for evaluation of MH rate in a given patient, constructed using as weights the coefficients derived from multivariate analysis.

Discussion:

Based on this, we developed prediction model with the above significant variables to evaluate MH in patients with CD.The routine blood test is the most fundamental and accessible examination, which has long been proposed as an essential assistant tool for disease assessment [20]. Reliable nomogram based on aforementioned factors was constructed and showed excellent evaluation abilities for MH among patients with CD. This nomogram can predict MH probability in patients with CD after one year of treatment and provide reference for doctors to perform endoscopic review. The present model still could be improved by follow-up study and improved to broaden the scope in evaluation of CD.In summary, this study provides comprehensive insights into serum inflammatory index and clinical information to evaluate MH after treatment in patients with CD.

Conclusion:

None available

Title: Systematic Review and External Validation of Prediction Models Based on Symptoms and Biomarkers for Identifying Endoscopic Activity in Crohn's Disease.

Publication Date: Jul 2020

Authors: Brand, Eelco C; Elias, Sjoerd G; Minderhoud, Itta M; van der Veen, Julius J; Baert, Filip J; Laharie, David; Bossuyt, Peter; Bouhnik, Yoram; Buisson, Anthony; Lambrecht, Guy; Louis, Edouard; Pariente, Benjamin; Pierik, Marieke J; van der Woude, C Janneke; D'Haens, Geert R A M; Vermeire, Séverine; Oldenburg, Bas; ,

Journal: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association

Abstract: Endoscopic healing, an important target of treatment for Crohn's disease (CD), requires ileocolonoscopy, which is costly and burdensome. We investigated whether published noninvasive models (based on symptoms and biomarkers) to evaluate CD activity have sufficient accuracy to replace ileocolonoscopy.

DOI: 10.1016/j.cgh.2019.12.014

PMID: 31881273.0

Full Article: https://doi.org/10.1016/j.cgh.2019.12.014

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: The multi-biomarker disease activity score in a tnf inhibitor tapering study in rheumatoid arthritis patients: Predictive value for successful tapering, flaring and radiographic progression

Publication Date: nan

Authors: Bouman C.A.M.; Van Der Maas A.; Van Herwaarden N.; Sasso E.H.; Van Den Hoogen F.H.J.; Den Broeder A.A.

Journal: nan

Abstract: Background/Purpose: We evaluated the predictive value of the multi-biomarker disease activity (MBDA) score for clinical outcomes and radiographic progression in a TNFi tapering study in RA patients with sustained low disease activity. Method(s): DRESS is an 18-month randomised trial on non-inferiority of tapering of adalimumab or etanercept compared with usual care (UC). TNFi was tapered every 3 months until stopping or clinical flare (DELTADAS28-CRP >1.2 or >0.6 if current DAS28-CRP >=3.2; major flare: >3 months). Patients were assessed every 3 months and at flare. For flares, TNFi was restarted or escalated. X-rays of hands and feet were scored with modified Sharp-van der Heijde score (mSHS) at baseline (BL) and 18 months. Correlations between MBDA score and DAS28-CRP were determined at BL, 9, 18 months and first flare. MBDA scores at BL, 9 and 18 months and DELTAMBDA score from BL to 9 months were analysed for successful stopping, successful tapering, and no tapering possible. AUROC evaluated the predictive value of: 1) BL MBDA score for a) successful tapering vs. no tapering possible, b) stopping vs. no tapering possible, c) occurrence of (major) flares, d) incidence of radiographic progression (RP); 2) DELTAMBDA score from BL to 9 months for clinical outcomes and RP; 3) MBDA scores at first and second visits preceding a flare for occurrence of that flare; 4) DELTAMBDA score between first and second visits preceding a flare for occurrence of that flare. Result(s): Of 180 patients, 171 (115 tapering, 56 UC) had serum and month 18 outcomes available: 64% female, mean disease duration 12.1 (SD 8.3) years, 73.3% ACPA positive. TNFi had been successfully stopped in 19%, tapered in 44%, and re-escalated to baseline dose in 37%. MBDA scores and DAS28-CRP are summarized in Figure 1. Correlation of DAS28-CRP and MBDA score was greatest at 18 months (Spearman's r=0.45, p<0.01) and lowest at BL (r=0.19, p<0.01). AUROCs for predicting successful stopping, tapering and flare by BL MBDA score were not significant. AUROC for major flare by BL MBDA score was significant in the UC group (10% flared; AUROC 0.72, 95% CI 0.56-0.88) and not the taper group (12% flared). RP (DELTAmSHS >0.5 from BL to 18 months) occurred in 26% of 167 patients with available data and was not predicted by MBDA score. DELTAMBDA score from BL to 9 months was not predictive for clinical outcomes or RP. MBDA scores at first and second visit preceding a flare were not predictive for any flare. AUROC for DELTAMBDA score between first and second visit preceding a flare was borderline significant (0.56, 95% CI 0.50-0.63). Conclusion(s): Neither BL MBDA score nor DELTAMBDA score from BL to 9 months was predictive for successful stopping; tapering; occurrence of flare; or radiographic progression. However, exploratory analyses showed that: 1) BL MBDA score was predictive for flare in patients who received UC and 2) DELTAMBDA score between visits preceding a flare was borderline significant for predicting flare. (Table Presented).

DOI: /10.1002/art.39448

PMID: nan

Full Article: https://doi.org//10.1002/art.39448

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: A Noninvasive Method to Assess Mucosal Healing in Patients* With Crohn's Disease.

Publication Date: May 2018

Authors: Sandborn, William J; Abreu, Maria T; Dubinsky, Marla C

Journal: Gastroenterology & hepatology

Abstract: Ongoing inflammation in the gastrointestinal tract and loss of the mucosal barrier are key components of Crohn's disease. Current treatment paradigms, including treat-to-target, are based on improvement of both clinical and endoscopic symptoms. Endoscopy is an essential tool for the evaluation of mucosal healing, but patients may be reluctant to undergo repeated procedures. Surrogate markers of inflammation, such as C-reactive protein and fecal calprotectin, are being used, yet they have several limitations in the assessment of mucosal healing. A new strategy, known as the Monitr test, assesses mucosal healing status by evaluating serum levels of 13 biomarkers in patients with Crohn's disease. The 13 biomarkers are associated with cell adhesion, inflammation, angiogenesis, extracellular matrix remodeling, cell proliferation and repair, and immune cell recruitment. Monitr testing yields a mucosal healing index score that reflects disease severity. Validation of the test showed an overall accuracy of 90%, with a negative predictive value of 92% and a positive predictive value of 87% for identifying patients with endoscopic evidence of Crohn's disease. Use of this noninvasive test may aid in the monitoring and management of patients with Crohn's disease, while potentially reducing the need for repeated endoscopy.

DOI: nan

PMID: 29991933.0

Full Article: https://doi.org/nan

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Trefoil factor-3 is not a useful marker of mucosal healing in Crohn's disease treated with anti-TNF-α antibodies.

Publication Date: Jan 2017

Authors: Eder, Piotr; Stawczyk-Eder, Kamila; Korybalska, Katarzyna; Czepulis, Natasza; Luczak, Joanna; Lykowska-Szuber, Liliana; Krela-Kazmierczak, Iwona; Linke, Krzysztof; Witowski, Janusz

Journal: World journal of gastroenterology

Abstract: To evaluate whether repeated serum measurements of trefoil factor-3 (TFF-3) can reliably reflect mucosal healing (MH) in Crohn's disease (CD) patients treated with anti-tumor necrosis factor-α (anti-TNF-α) antibodies.

DOI: 10.3748/wjg.v23.i1.135

PMID: 28104989.0

Full Article: https://doi.org/10.3748/wjg.v23.i1.135

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

06Tables (1-2)164Sum=4090Loading…	Item	Item		Count	Count		PDF	392	WORD	216	HTML	3112	Figures (1-3)	206
	Item		Count	Count										
	392													
	216													
	3112													
	206													
	164													
	Sum=4090													
	Loading…													

Item	Item		Count	Count	
Item					
Count					
PDF	392				
WORD	216				
HTML	3112				
Figures (1-3)	206				
Tables (1-2)	164				
	Sum=4090				

Item	

Count	

	Loading…

ntBrowse644Download889Sum=1533Loading…	Item	Item		Count	Count		Browse	644	Download	889		Sum=1533		Lo
Item	Item		Count	Count										
Item														
Count														
Browse	644													
Download	889													
	Sum=1533													
	Loading…													

Item	Item		Count	Count	
Item					
Count					
Browse	644				
Download	889				
	Sum=1533				

Item	

Count	

Loading…	

tBrowse902Download1541Sum=2443Loading…	Item	Item		Count	Count		Browse	902	Download	1541		Sum=2443		L
Item	Item		Count	Count										
Item														
Count														
Browse	902													
Download	1541													
	Sum=2443													
	Loading…													

Item	Item		Count	Count	
Item					
Count					
Browse	902				
Download	1541				
	Sum=2443				

Item	

Count	

Loading…	

	Simple endoscopic score for Crohn’s diseasevsbiochemical parameters								
Al	Albumin	WBC	PLT	CRP	Hb	Ferritin	Fibrinogen	ESR	
ue	0.66	-0.62	0.3500	0.4400	0.57	-0.40	0.12	0.59	0.5
ue	< 0.0001	< 0.0001	0.0071	0.0005	< 0.0001	0.0018	0.41	< 0.0001	< 0.0

Feature	All (n= 29)	MH-group (n= 18)	Non-MH group(n= 11)	MHvsnon-MH
Change in Simple Endoscopic Score for Crohn’s disease over time (%)	-55 [-72-(-37)]	-70 [-81-(-56)]	-33 [-38-(-8)]	P< 0.0001

Age (yr)	27 (21-35)	22 (21-30)	35 (27-39)	P= 0.02
Men	21 (72)	15 (83)	5 (45)	P= 0.04
Disease duration (yr)	6 (3-11)	6 (5-10)	6 (3-12)	P= 0.77
Baseline Crohn's disease Activity Index (n)	319 (298-420)	310 (240-397)	348 (301-440)	P= 0.26
Baseline Simple Endoscopic Score for Crohn's disease (n)	15 (8-21)	16 (8-23)	12 (8-20)	P= 0.36
Baseline C-reactive protein (mg/L)	9.8 (2.8-31.2)	8.7 (2.3-18.2)	18.6 (3.7-34.5)	P= 0.15
Baseline hemoglobin (g/dL)	12.9 (10.1-14)	12 (9.9-13.5)	13.1 (10.2-14.8)	P= 0.60
Baseline albumin (mg/dL)	4.2 (3.6-4.4)	4.1 (3.5-4.4)	4.2 (3.7-4.4)	P= 0.84
Disease location				
L1 (ileal)	3/29 (10)	1/18 (5)	2/11 (18)	P= 0.53
L2 (colonic)	9/29 (31)	5/18 (28)	4/11 (36)	P= 0.69
L3 (ileocolonic)	17/29 (59)	12/18 (67)	5/11 (46)	P= 0.43
Disease behavior				
B1 (inflammatory)	24/29 (83)	14/18 (78)	10/11 (91)	P= 0.62
B2 (stricturing)	1/29 (3)	1/18 (5)	0/11 (0)	P= 1.00
B3 (penetrating)	4/29 (14)	3/18 (17)	1/11 (9)	P= 1.00
Medications				
Steroids	19/29 (65)	10/18 (55)	9/11 (82)	P= 0.23
Azathioprine	15/29 (52)	12/18 (67)	3/11 (27)	P= 0.06
Aminosalicylates	28/29 (96)	18/18 (100)	10/11 (91)	P= 0.37
Anti-TNF-α agent used: adalimumab/infliximab	17/12 (59/41)	11/7 (61/39)	6/5 (55/45)	P= 0.51

s in Crohn's - up, down or something else?Best Pract Res Clin Gastroenterol. 2014;28:473-483.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 23][Cited

natory bowel diseases: a systematic review.Gut. 2012;61:1619-1635.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 531][Cited by in F6Publishing: 587]

cations of mucosal healing for the management of IBD.Nat Rev Gastroenterol Hepatol. 2010;7:15-29.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 328

and deep remission: what does it mean?World J Gastroenterol. 2013;19:7552-7560.[PubMed][DOI][Cited in This Article:][Cited by in CrossRef: 49][Cited by in F6

erg M, Khanna R. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials.Gut. 2016;65:1447-1455.[PubMed][DOI][Cited in This Article:][Cit

s in inflammatory bowel disease.World J Gastroenterol. 2014;20:3223-3230.[PubMed][DOI][Cited in This Article:][Cited by in CrossRef: 67][Cited by in F6Publishin

an trefoil factor 3 is a biomarker for mucosal healing in ulcerative colitis patients with minimal disease activity.J Crohns Colitis. 2015;9:575-579.[PubMed][DOI][Cit

nd European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management.J Crohns Colitis. 2010;4:28-62.[PubMed][D

f treatment of inflammatory bowel disease from clinical trials and practice.Gastroenterology. 2015;148:37-51.e1.[PubMed][DOI][Cited in This Article:][Cited by in C

in inflammatory bowel disease.Clin Exp Gastroenterol. 2016;9:21-29.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 37][Cited by in F6Publishing: 74][A

D: objective measures, but when, how and how often?BMC Gastroenterol. 2015;15:178.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 25][Cited by in F

or IBD: practical insights.Nat Rev Gastroenterol Hepatol. 2015;12:537-545.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 204][Cited by in F6Publishing

n trefoil factors in patients with inflammatory bowel disease.Digestion. 2006;74:33-39.[PubMed][DOI][Cited in This Article:][Cited by in Crossref: 31][Cited by in F6

nke K. Is faecal calprotectin equally useful in all Crohn's disease locations? A prospective, comparative study.Arch Med Sci. 2015;11:353-361.[PubMed][DOI][Cited

inflammatory bowel disease.World J Gastroenterol. 2015;21:11246-11259.[PubMed][DOI][Cited in This Article:][Cited by in CrossRef: 110][Cited by in F6Publishing

Impact of disease location on fecal calprotectin levels in Crohn's disease.Scand J Gastroenterol. 2015;50:841-847.[PubMed][DOI][Cited in This Article:][Cited by i

e M, Loftus EV. Mucosal healing in inflammatory bowel disease-a true paradigm of success?Gastroenterol Hepatol (N Y). 2012;8:29-38.[PubMed][DOI][Cited in Thi

Title: Novel pathway-centric analysis reveals variants associated with toxicity and response to thiopurines in patients with inflammatory bowel disease

Publication Date: nan

Authors: Blaker P.A.; Fong S.; Walker J.; Lewis C.M.; Marinaki A.M.; Sanderson J.D.; Irving P.M.

Journal: nan

Abstract: Introduction Thiopurines remain the first line immunosuppressants recommended in the management of inflammatory bowel disease (IBD). Unfortunately, 30-40% of patients prescribed these agents develop adverse drug reactions or fail to derive therapeutic benefit. Candidate gene studies have identified loci that explain some of these treatment failures; however a substantial fraction of the genetic contribution remains undefined. Using whole thiopurine pathway analysis the aim of this study was to identify novel loci associated with toxicity and response to azathioprine (AZA)/mercaptopurine (MP) in patients with IBD. Methods Genomic DNA was extracted from EDTA blood samples of 472 well-characterised IBD patients treated with AZA/MP. We examined exome array data using the Illumina HumanExome Beadchip and restricted the analysis to variants associated with the thiopurine pathway as defined by the KEGG database (100 genes, 639 single nucleotide polymorphisms). Using a case-control design we firstly tested for genetic associations between patients with (n = 154) and without (n = 258) adverse drug reactions, and secondly for polymorphisms differentiating patients with (n = 188) and without (n = 141) response to thiopurines after 12 months of treatment. One year intervention-free clinical response was defined by 3 investigators (PB, PI, JS). Results Following adjustment for principal components, the minor alleles at ADK rs946185 (p = 0.0078; OR 1.675), SLC28A1 rs2242046 (p = 0.0168; OR 1.600) and ABCA1 rs4149268 (p = 0.033; OR 1.487) were associated with the development of drug toxicity, whereas the minor alleles at ABCB5 rs2301641 (p = 0.0170; OR 0.608), ABCC4 rs4148549 (p = 0.027; OR 0.652) and AOX1 rs55754655 (p = 0.038; OR 0.549) protected against it. The minor allele at RRM2 rs1130609 (p = 3.80 x 10-5; OR 0.461), which codes a subunit of ribonucleotide reductase involved in the conversion of thioguanine nucleotide to deoxy-thioguanine nucleotide, and a higher normalised dose of AZA/MP were associated with protection from non-response. Conversely, the minor allele at ABCA1 rs2230808 (p = 0.008; OR 2.585) and Crohn's disease (p = <0.001; OR 5.007) were associated with non-response to treatment at 12 months. Conclusion High-throughput sequencing using exome array technology has revealed new loci, other than thiopurine-S-methyltransferase, explaining toxicity and response to thiopurines. Validation of these markers in separate cohorts will allow the development of biomarker panels to predict outcomes prior to the start of treatment.

DOI: /10.1136/gutjnl-2014-307263.5

PMID: nan

Full Article: https://doi.org//10.1136/gutjnl-2014-307263.5

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Incorporating HLADQA1*05 in pre-biologic screening in IBD patients initiating biologic therapies

Publication Date: nan

Authors: Aleman Gonzalez H.; Ramachandran S.; Whitehead E.; Pattinson A.; Stamp K.; Turnbull J.; Myers S.; Talbot A.; Sebastian S.

Journal: nan

Abstract: Background: The PANTS study reported high risk of immunogenicity and loss of response in anti Tumor Necrosis Factor (anti-TNFs) treated Crohn's disease (CD) patients carrying HLADQA1*05 allele. The proposed biomarker stratified trial to evaluate the usefulness of HLA testing prior to initiation of anti-TNFs is not yet available. We aimed to evaluate the use of HLADQA1*05 as part of pre-biologic screening in IBD patients initiating biologics on MDT decision on drug choice and disease outcomes Methods: We prospectively included all IBD patients who had HLADQA1*05 tested prior to initiation of biologics over a period of, 12 months. Patients with definitive indication for one class of drug or drug strategy (perianal fistula, acute severe colitis, contraindications to infliximab, co-existent EIMs) were excluded. Primary outcome was treatment persistence at, 6 and, 12 months. Secondary outcomes were steroid free remission at, 6 and, 12 months, use concomitant immunosuppression and proportion needing dose escalation. Result(s): Seventy-six patients were included in analysis (UC=, 32, CD=43, IBD-U =1). HLADQA1*05 was positive in, 46.7% of patients. The therapy class choice was as recorded in figure 1. Concomitant immunosuppression was used in, 44% of the whole cohort and in, 100% of HLADQA1*05 positive patients started on anti-TNF agents. Primary non-response was recorded in, 8 patients and secondary loss of response in, 3 patients. Among patients started on anti-TNFs, anti-drug antibodies were detected in, 10 (15.6%) patients with, 7 out of, 10 positive for HLADQA1*05. However, only, 3 (4.6%) had undetectable drug levels in the presence of antibody and all three were HLADQA1*05 positive. Two patients had reactions during induction therapy both were HLADQA1*05 positive and were on combination therapy with Infliximab. Therapy persistence with initial drug strategy and steroid free remission at, 6 months was recorded in, 77.1% and, 78% respectively. There was no significant difference in drug persistence rates at, 6 months and, 12 months in patients with HLADQA1*05 variant or those with variant absent (Figure, 2). Steroid free remission at, 6 and, 12 months was also similar irrespective of the variant status (Figure 3) Conclusion(s): Choice of therapy incorporating HLADQA1*05 status may allow anti-TNF monotherapy and tailoring of therapy in IBD patients. A randomised stratified biomarker trial is required to determine the utility of pre-treatment testing. (Figure Presented).

DOI: /10.1093/ecco-jcc/jjab232.446

PMID: nan

Full Article: https://doi.org//10.1093/ecco-jcc/jjab232.446

Methods: None available

Results: None available

Discussion: None available

Conclusion: None available

Title: Incorporating hladqa1*05 in pre-biologic screening in ibd patients initiating biologic therapies

Publication Date: nan

Authors: Gonzalez H.A.; Ramachandran S.; Whitehead E.; Pattinson A.; Stamp K.; Turnbull J.; Myers S.; Talbot A.; Sebastian S.

Journal: nan

Abstract: Introduction The PANTS study reported high risk of immunogenicity and loss of response in anti Tumor Necrosis Factor (anti-TNFs) treated Crohn's disease (CD) patients carrying HLADQA1*05 allele. The proposed biomarker stratified trial to evaluate the usefulness of HLA testing prior to initiation of anti-TNFs is not yet available. Aim To evaluate the use of HLADQA1*05 as part of pre-biologic screening in IBD patients initiating biologics on MDT decision on drug choice and disease outcomes Methods We prospectively included all IBD patients who had HLADQA1*05 tested prior to initiation of biologics over a period of 12 months. Patients with definitive indication for one class of drug or drug strategy (perianal fistula, acute severe colitis, contraindications to infliximab, co-existent EIMs) were excluded. Primary outcome was treatment persistence at 6 and 12 months. Secondary outcomes were steroid free remission at 6 and 12 months, use concomitant immunosuppression and proportion needing dose escalation. Results Seventy-six patients were included in analysis (UC= 32, CD=43, IBD-U =1). HLADQA1*05 was positive in 46.7% of patients. The therapy class choice was as recorded in figure 1. Concomitant immunosuppression was used in 44% of the whole cohort and in 100% of HLADQA1*05 positive patients started on anti-TNF agents. Primary nonresponse was recorded in 8 patients and secondary loss of response in 3 patients. Among patients started on anti-TNFs, anti-drug antibodies were detected in 10 (15.6%) patients with 7 out of 10 positive for HLADQA1*05. However, only 3 (4.6%) had undetectable drug levels in the presence of antibody and all three were HLADQA1*05 positive. Two patients had reactions during induction therapy both were HLADQA1*05 positive and were on combination therapy with Infliximab. Therapy persistence with initial drug strategy and steroid free remission at 6 months was recorded in 77.1% and 78% respectively. There was no significant difference in drug persistence rates at 6 months and 12 months in patients with HLADQA1*05 variant or those with variant absent (Figure 2). Steroid free remission at 6 and 12 months was also similar irrespective of the variant status (Figure 3) Conclusions Choice of therapy incorporating HLADQA1*05 status may allow anti-TNF monotherapy and tailoring of therapy in IBD patients. A randomised stratified biomarker trial is required to determine the utility of pre-treatment testing.

DOI: /10.1136/gutjnl-2021-BSG.180

PMID: nan

Full Article: https://doi.org//10.1136/gutjnl-2021-BSG.180

Methods:

None available

Results:

None available

Discussion:

None available

Conclusion:

None available

Title: Ulcerative colitis immune cell landscapes and differentially expressed gene signatures determine novel regulators and predict clinical response to biologic therapy.

Publication Date: Apr 2021

Authors: Penrose, Harrison M; Iftikhar, Rida; Collins, Morgan E; Toraih, Eman; Ruiz, Emmanuelle; Ungerleider, Nathan; Nakhoul, Hani; Flemington, Erik F; Kandil, Emad; Shah, Shamita B; Savkovic, Suzana D

Journal: Scientific reports

Abstract: The heterogeneous pathobiology underlying Ulcerative Colitis (UC) is not fully understood. Using publicly available transcriptomes from adult UC patients, we identified the immune cell landscape, molecular pathways, and differentially expressed genes (DEGs) across patient cohorts and their association with treatment outcomes. The global immune cell landscape of UC tissue included increased neutrophils, T CD4 memory activated cells, active dendritic cells (DC), and M0 macrophages, as well as reduced trends in T CD8, Tregs, B memory, resting DC, and M2 macrophages. Pathway analysis of DEGs across UC cohorts demonstrated activated bacterial, inflammatory, growth, and cellular signaling. We identified a specific transcriptional signature of one hundred DEGs (UC

DOI: 10.1038/s41598-021-88489-w

PMID: 33907256.0

Full Article: https://doi.org/10.1038/s41598-021-88489-w

Methods:

Materials and methodsData sources of ulcerative colitis patient transcriptomesUlcerative colitis (UC) colonic tissue microarray and RNAseq gene expression datasets used in this study were obtained from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO) data repository using the following GEO accession numbers listed in Table 3. Only those genes expressed at a minimum threshold of > |2.0|-fold change as compared to healthy control (with an adjusted $p < 0.05$) were used for pathway analysis. Generation of biologic resistance signatures were accomplished using two microarray datasets from UC patients treated with anti-TNFα (GSE12251, GSE73661) or anti-α4β7 (GSE73661). DEGs were identified in non-responders compared to responders at various time points using the limma R differential expression analysis package and mean calculation was performed for gene-level summarization.

Results:

(C) Presence of the UC100 signature represented as a score in inflamed UC compared to uninflamed matched control transcriptomes from an independent cohort (GSE107593) ($p = 4.65e-08$). Several of them encoded protein with established roles in UC pathobiology such as hypoxia (HIF1A), nitric oxide (NOS2), inflammation (TNIP3, TNFRSF6B, CXCL, IL1RN, IRAK3, IRF1, IFITM1, OMSR), matrix metallopeptidases (MMP1, 3, 10, 12), and calcium signaling (S100A8)6,18,19,20,21. We utilized publicly available transcriptomes of UC tissue acquired from patients (GSE73661) before anti-TNFα and anti-α4β7 treatments that were later classified as non-responders or responders by clinical endoscopic assessment for disease remission status22,23. Specifically, we found the top four significantly increased transcripts, IGFBP5 (Insulin Like Growth Factor Binding Protein 5), SELE (Selectin E), STC1 (Stanniocalcin 1), and VNN2 (Vanin 2), in non-responders.

Discussion:

Limited studies showed that increased lipid droplets may drive intestinal inflammation40,44 and LPCAT1 could play an important function in the synthesis of inflammatory lipids45. In IBD intestine, mitochondrial gene expression is aberrant leading to reduced respiratory activity and energy depletion, associated with bacterial signaling53,54,55,56,57. Thus, we anticipate that transcriptional signatures found in UC patient tissue may guide selection of therapy and more personalized therapeutic approaches. Our results could provide insight into disease pathogenesis and mechanistic reasons why certain patients do not respond to mainstay therapy.

Conclusion:

None available