**EFFICACY OF USTEKINUMAB IN CROHN’S DISEASE WITH AND WITHOUT CONCURRENT AUTOIMMUNE SKIN DISEASE**

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**Brief Summary:** Ustekinumab was approved for autoimmune skin disease prior to being approved for IBD; this retrospective case-control study in patients with Crohn’s disease demonstrates an association between concurrent autoimmune skin disease and a more robust clinical response to ustekinumab.

**Abstract**

Background: Approximately 33% of Crohn’s disease (CD) patients have associated autoimmune skin disease. The pathophysiology of the latter frequently involves IL-12/IL-23 signaling pathways that may also play a role in gut inflammation. Even though ustekinumab is an anti-IL-12/23 biologic that is FDA-approved for psoriasis (2008), CD (2016), and ulcerative colitis (2019), its relative efficacy has never been studied in CD with vs. without skin manifestations.

Methods: This is a retrospective single-center case-control study comparing markers of disease activity between patients with CD and skin disease (SKIN) and CD without cutaneous involvement (NOSKIN) from prior to drug initiation to the same markers after 6 months of treatment: fecal calprotectin (FCP), C-reactive protein (CRP), and 5-point Likert scoring of endoscopic, pathologic, and imaging reports by two blinded observers.

Results: Manual review of the 595 CD patients receiving ustekinumab revealed 79 SKIN and 316 NOSKIN patients similar in age, gender, ethnicity, amount of tobacco use, and steroid use. There were statistically significant improvements in FCP and CRP in SKIN compared to NOSKIN with p = 0.0167 and p = 0.039, respectively. SKIN showed significantly better outcomes than NOSKIN in Likert scores of endoscopy (p = 0.0138 and p = 0.0264), histopathology (p = 0.0305 and p = 0.0506), and numerically more improvement in imaging reports. Additional sub-analyses for surgeries, ulcers, abscesses, fistulas, and colitis were conducted.

Conclusion: Greater ustekinumab effectiveness in controlling intestinal inflammation in Crohn’s disease is associated with concurrent autoimmune skin disease.

**Key Words:**

Ustekinumab, Crohn’s, IBD, Autoimmune, Treatment

**Introduction**

Approximately 33% of patients with Crohn’s disease develop dermatologic manifestations [1]. These can be subdivided into three categories: disease-specific lesions that have identical histopathology, reactive inflammatory lesions, and Crohn’s-associated HLA-linked conditions with sequelae of chronic inflammation. Reactive lesions include erythema nodosum, pyoderma gangrenosum, and the rarer manifestations: pyostomatitis vegetans, Sweet’s syndrome, granulomatous vasculitis, and leukocytoclastic vasculitis. The most common associated autoimmune diseases are psoriasis, eczema, and alopecia areata – all of which can worsen or even present after treatment with TNF- α inhibitors. Literature search reveals elevated levels of interleukins IL-12 and IL-23 in patients with most of the aforementioned lesions, often irrespective of any association with inflammatory bowel disease.

The pathogenesis of several autoimmune diseases that are linked with Crohn’s appear to be dependent on Il-12/IL-23 signaling. One of the proposed mechanisms of psoriatic inflammation involves dermal dendritic cells secreting IL-23, which is important in the differentiation and activation of pro-inflammatory T helper 17 (Th17) cells [2]. Th17 cells are found in large numbers in psoriatic plaques underscoring their significance in its pathogenesis [3]. In alopecia areata lesions, IL-23 transcription was found to be upregulated using microarray analysis and reverse-transcriptase PCR [4] implying its significance. Patient with eczema, otherwise known as atopic dermatitis, also have elevated serum levels of IL-23 [5].

Ustekinumab has been FDA approved for the treatment of psoriasis since 2008; it was recently approved for the treatment of Crohn's disease in 2016 and ulcerative colitis in 2019. Ustekinumab acts through binding to the p-40 subunit of both IL-12 and IL-23 making them unable to bind to their receptors and trigger downstream pro-inflammatory signaling. To our knowledge, there have been no direct comparison studies for the efficacy of ustekinumab in patients with and without autoimmune skin disease. We hypothesized that, given ustekinumab’s efficacy in treating skin disease, including psoriasis, the pathophysiology of Crohn’s with skin disease may be different than its other subtypes and therefore more susceptible to targeted IL12/23 treatment.

In this paper we investigated whether patients who have autoimmune skin disease (atopic dermatitis, eczema, psoriasis, and alopecia) or cutaneous manifestations of Crohn’s (erythema nodosum, pyoderma gangrenosum, pyostomatitis vegetans, Sweet’s syndrome, granulomatous vasculitis, and leukocytoclastic vasculitis) are more likely to have a good clinical response to ustekinumab than patients without skin disease.

**Materials and Methods**

**Study Design**

This is a retrospective single-center case-controlled study of clinical outcomes in patients at the University of Michigan with Crohn’s disease on a standard dose of ustekinumab with a goal of comparing the clinical efficacy of the drug in patients with and without skin disease. It investigates whether patients who have autoimmune skin disease or cutaneous manifestations of Crohn’s disease are more likely to have a clinical response to ustekinumab than patients without skin disease. For our purposes, autoimmune skin diseases included: atopic dermatitis, eczema, psoriatic disease (psoriasis, psoriatic arthritis, psoriasiform dermatitis, and psoriasiform epidermal hyperplasia), and alopecia (areata or universalis); and cutaneous manifestations of Crohn’s disease included: erythema nodosum, pyoderma gangrenosum, pyostomatitis vegetans, sweet syndrome, granulomatous vasculitis, epidermolysis bullosa acquisita, and leukocytoclastic vasculitis.

Patients from ages 16 to 85 after IV induction and on the standard ustekinumab dose of 90mg administered subcutaneously every 8 weeks for at least 6 months were included in the study. In order to track changes over time, each patient’s data before treatment (from 12 months prior to drug initiation date) was compared to the same variable (in the same patient) after initiation with adequate treatment duration (from about 6 months to 2 years after start or from about 6 months until ustekinumab was discontinued).

**Data Collection**

Several electronic health record (EHR) data tables were used for the collection of clinical data, including diagnoses, encounters, procedures, medications (ordered and administered), pathology, and laboratory values. Users accessing these databases for research must have protocols that have received either approval or exemption from the IRB. All of the data in these databases is extracted from University of Michigan’s EHR, EPIC. Health Systems Data Warehouse (HSDW) and the Clinical Data Repository (CDR) can be queried using Structured Query Language (SQL) commands; DataDirect is a web-based tool that allows for querying Clarity, a proprietary EPIC database. All information was gathered on a password protected University of Michigan computer and all patient data were recorded with direct identifiers removed.

Patient from age 16 to 85 with Crohn’s disease were identified by querying HSDW. This list of patients was then uploaded into the DataDirect data warehouse to obtain ustekinumab prescription information. The chart of each patient with a prescription for ustekinumab listed in DataDirect was then manually reviewed to obtain exact dosing and treatment interval. From this manually verified list of patients, a query was run in HSDW for the skin diagnoses listed above. Patient demographics including age, gender, ethnicity, and smoking status were also extracted from DataDirect.

Further queries in DataDirect, HSDW, and CDR databases were performed to extract fecal calprotectin (FCP) and C-reactive protein (CRP) levels. The databases were also queried for endoscopic, pathologic, computer tomography (CT), and magnetic resonance imaging (MRI) reports, as well as for the use of steroids (budesonide, prednisone, or methylprednisolone). Data were extracted into HSDW tables and Excel workbooks with specific coded identifiers correlating to each patient stored in a separate “key” file. Each individual patient’s results were matched pre- and post- ustekinumab initiation. Only patients who had both pre- and post- values for a variable of interest were included in the corresponding analysis. Values from 12 months to the initiation date were included in the pre group and values from 6 months to 2 years after initiation date were included in the post group. Care was taken to ensure that all post- values were obtained during the interval when the patient was actively receiving ustekinumab. If the medication was discontinued in less than 2 years, then the discontinuation date was made the final date for available values.

Treatment-associated improvements in FCP and CRP levels were compared between SKIN and NOSKIN. Additionally, written endoscopy, imaging, and pathology reports were divided into before ustekinumab initiation and after 6 months of ustekinumab treatment and then paired by patient. These pairs were then manually reviewed by two blinded observers, who were unaware of whether the individual being assessed had skin disease. Each observer then assigned each patient a numeric value based on the Likert score for the degree of change: (1 – severely worsening, 2 – slight worsening, 3 – no change, 4 – some improvement, and 5 – complete resolution of severe disease). When differences occurred, these were resolved in a consensus meeting which included reference to the original reports and images.

Pathology reports before and after ustekinumab treatment were investigated to ascertain whether the patient required surgery. All patients who had surgery before ustekinumab initiation were removed. The analysis then compared the relative percentage of surgeries in both SKIN and NOSKIN for patients with previously intact colons and small bowels.

Smaller sub-analyses were performed on the written reports for two variables: ulceration and penetrating complications. After ascertaining the presence of a variable on patient reports obtained prior to ustekinumab initiation, the same patients’ reports obtained after 6 months of treatment were queried for the same variable. The reports were then manually reviewed for accuracy. The first assessment evaluated for presence of ulceration on endoscopy. The extracted endoscopy reports were screened for the words: ulcer, erosion, or aphtha. The second sub-analysis ascertained whether there was a differential effect of ustekinumab on fistulas, sinus tracts, and abscesses between SKIN and NOSKIN based on imaging reports. The third sub-analysis assessed for presence of inflammation on pathology reports, by searching for the key words: colitis, ileocolitis, ileitis, and enteritis. The reports were then manually reviewed to ensure that the inflammation was active and not quiescent.

**Statistical Design**

For the continuous variables CRP and FCP paired T-testing was used to compare improvements within each of the two groups, SKIN and NOSKIN. Unpaired T-tests assuming unequal variances were used to compare SKIN to NOSKIN for the end-of-study continuous variables and for the Likert score of pathology, endoscopy, and imaging reports. Cronbach Alpha (raw) inter-rater reliability (IRR) scores were used to assess for similarities between the two blinded observers’ scores.

For SKIN versus NOSKIN, chi-squared analyses were performed on all binary outcomes listed below. These outcomes include: the use of steroids at 6 months of ustekinumab therapy, the use of steroids at one year of ustekinumab therapy, and surgery within 6 months of initiation of ustekinumab therapy in surgery-naïve patients. They also included the resolution of ulcers, fistulas, abscesses or active inflammation after 6 months of therapy based on imaging, endoscopy, or pathology reports.

**Ethical Considerations**

The University of Michigan IRB-MED granted a waiver on September 9, 2019 for this retrospective study HUM 00166791, as record review is regarded as minimal risk to patients.

**Results**

**Characteristics of Study Participants**

From database queries, 7,190 patients were identified as having CD; of these, 558 had skin disease and 595 were listed as taking ustekinumab. Manual chart review was performed on the 595 patients: 445 were on the standard dose of ustekinumab, 395 of them on it for 6 months or longer. 79 of these patients had skin disease in addition to Crohn’s (SKIN) and 316 did not (NOSKIN).

Among the 79 SKIN patients, the following diseases were seen: 55 had psoriatic disease (psoriasis, psoriatic arthritis, psoriasiform dermatitis, and psoriasiform epidermal hyperplasia), 20 had eczema (eczema, eczematous dermatitis), 1 had atopic dermatitis, 1 had alopecia, 8 had pyoderma (pyoderma gangrenosum/gangrenosa), 11 had erythema nodosum, and 1 had leukocytoclastic vasculitis as well as psoriasis. 16 patients had two or more skin diseases including combinations of two autoimmune skin diseases, such as psoriasis and eczema or combinations of an autoimmune disease and inflammatory skin lesion such as psoriasis and pyoderma gangrenosum. The other skin manifestations queried were not seen in this population.

Demographics of the study population above were similar across the two groups. 66% of the SKIN patient were female and 34% were male. 58% of NOSKIN were female and 42% were male. The ethnic breakdown was similar in the two groups as well with 87% of SKIN and 90% of NOSKIN being Caucasian. Among the non-white ethnicities, 7.6% of SKIN and 7.6% of NOSKIN were African American, 3.8% of SKIN and 0.6% of NOSKIN were Hispanic. SKIN had no Asian patients and NOSKIN had only 5 (1.6%). The average age at ustekinumab initiation was near 40 in both groups (40.6 years in SKIN and 40.3 years in NOSKIN) [Table 1]. Two possible confounders, tobacco use and treatment with systemic steroids, were evaluated in the two groups. Tobacco use was similar across the two groups with 54% of SKIN patients being never smokers and 57% of NOSKIN patients being never smokers. There was no statistically significant difference in steroid prescriptions across the two groups SKIN and NOSKIN: at 6 months 1.3% in SKIN (N = 79) vs 1.6% NOSKIN (N = 316) with p = 0.837 and at 1 year SKIN 1.6% (N = 62) vs. NOSKIN 4.2% (N = 240) with p = 0.339.

**Laboratory Values**

In terms of laboratory values there was a statistically significantly decrease in FCP in the SKIN group, but not in the NOSKIN group. Each group had a large decrease in FCP after treatment, with SKIN showing statistical significance and NOSKIN almost reaching it. FCP in the SKIN group decreased by 58% from mean of 394.0 (SD = 165.6) to 164.1 (SD = 142.5), N = 7, P = 0.0015, whereas FCP in the NOSKIN group decreased by 27.5% from a mean of 364.9 (SD = 277.3) to 264.7 (SD = 412.5), N = 37, P = 0.052. The percentage reduction was significantly different between the two groups, with p = 0.0167.

CRP followed a similar trajectory to FCP with a statistically significantly decrease in CRP in the SKIN group and in the NOSKIN group. Both SKIN and NOSKIN showed statistical significance in CRP decreases after 6 months of treatment. For SKIN, CRP decreased by 49.2% from a mean of 3.58 (SD = 3.02) to 1.81 (SD = 1.74), N =34, P = 8.13 x 10^-4. For NOSKIN, the CRP decreased by 46.0% from a mean of 2.54 (SD = 2.59) to 1.37 (SD = 1.81), N = 105, P = 7.25 x 10^-6. The percentage reduction was not significantly different between the two groups.

**Endoscopy**

The SKIN group showed a statistically significantly degree of disease improvement compared to NOSKIN based on Likert endoscopy scores according to both observers with a Cronbach Alpha (raw) inter-relator reliability (IRR) of 96.1%. Reviewer A’s SKIN had a mean Likert score of 3.91 (SD = 0.97, N = 22) and NOSKIN 3.37 (SD = 0.94, N = 73), with P = 0.0138. Reviewer B’s SKIN had a mean Likert score of 3.95 (SD = 0.95, N = 22) and NOSKIN 3.49 (SD = 0.93, N = 73), with P = 0.0264.

An additional analysis was performed on the endoscopic assessment of disease progression, evaluating whether patients who had ulcers, aphthae, or erosions prior to starting ustekinumab still had any of these lesions after treatment. This analysis did not assess for the degree of lesion improvement, but rather for the presence of any lesions. SKIN had a larger improvement (68.2%, N = 22) than NOSKIN (42.4%, N = 59) with a statistically significant difference in the percentage with ulcers present after treatment in the two groups with P = 0.0187.

**Imaging**

There was numerically greater improvement in disease activity based on Likert assessments of imaging (CT and MRI) reports in the SKIN group compared to NOSKIN according to both observers with an IRR of 95.7%, but neither reached statistical significance. Reviewer A’s SKIN had a mean Likert score of 3.64 (SD = 1.28, N = 14) and NOSKIN 3.09 (SD = 0.90, N = 47), with P = 0.073. Reviewer B’s SKIN had a mean Likert score of 3.57 (SD = 1.22, N = 14) and NOSKIN 3.06 (SD = 0.87, N = 47), with P = 0.083.

Two separate analyses were performed on the imaging data, one evaluated for resolution of abscesses after ustekinumab therapy and the other evaluated for resolution of fistulas and sinus tracts. The analyses showed a numerically greater effect of ustekinumab on patients with skin disease, but without statistical significance. The total number of patients who had abscesses or fistulas on imaging before ustekinumab initiation was quite small in both groups. Only one out of the 4 SKIN patients who had abscesses prior to ustekinumab initiation had ongoing abscesses after ustekinumab treatment (25% lesions left). 50% of the NOSKIN patients still had abscesses after 6 months of ustekinumab therapy based on imaging (N=6). The p value for this difference in percentage of persistent abscesses was 0.43. For fistulas and sinus tracts, 33.3% remained in the SKIN group (N = 6) and 53.8% remained in the NOSKIN group (N = 26) with p = 0.37.

**Pathology**

The Likert score for pathologic improvement was significantly larger in the SKIN group than in the NOSKIN group for reviewer A and almost significant for reviewer B with an IRR of 95.8%. Reviewer A’s SKIN had a mean Likert score of 3.77 (SD = 1.15, N =22) and NOSKIN had a mean of 3.24 (SD = 1.0, N =70), with P = 0.0305. Reviewer B’s SKIN had a mean Likert score of 3.73 (SD = 1.16, N =22) and NOSKIN had a mean of 3.27 (SD = 0.88, N =70), with P = 0.0506.

A separate assessment was performed for presence of colitis, ileitis, enteritis, or ileocolitis on pathology reports from endoscopies performed before and after treatment. Pathology reports from patients were compared to the same patient’s reports after 6 months of ustekinumab therapy. SKIN showed greater improvement, with only 25% still having any form of inflammation on imaging (N = 20); 69.8% of NOSKIN patients had ongoing inflammation (N = 53). The P value for the difference was statistically significant at 5.51 x 10^-4.

**Surgery**

This study also evaluated whether there was a difference in percentage of patients requiring major abdominal surgery after 6 months of treatment. To reduce confounders, patients who had previous colon or small bowel surgery were excluded. A slightly lower percentage of patients in the SKIN group needed surgery (4.4%, N = 45) than in the NOSKIN group (5.7%, N = 193) with p = 0.739.

**Discussion: (Do I repeat too much of the paper in this section)**

Crohn’s disease has been shown to be linked to skin disease in 33% of cases – some of which are thought to have the same pathophysiology as the gut inflammation and others that are associated with the autoimmune bowel inflammation. IL-23 signaling has been shown to play a role in at least three of the Crohn’s associated skin diseases: psoriasis, eczema, and alopecia. In 2008 ustekinumab was approved for the treatment of psoriasis and, more recently, in 2016 for Crohn’s disease and 2019 for ulcerative colitis. There are many inflammatory mechanisms that have been proposed to play a role in Crohn’s pathogenesis including, but not limited to TNF-α related immune activation, leukocyte homing via integrin α₄β₇, and IL-23 related downstream signaling. Given that IL-23 signaling related inflammation is prevalent in many cutaneous lesions, it is possible that IL-23 signaling is particularly important in the subset of CD patients who have concurrent skin disease.

In this study we investigated whether patients aged 16 to 85 with Crohn’s disease and autoimmune skin disease or cutaneous manifestations of Crohn’s are more likely to have a stronger clinical response to ustekinumab than patients without skin disease.

Due to the desire for longitudinal evaluation of each patient, only patients who had before and after values for each variable were included in the respective analysis. While this decreased the number of patients available for each analysis, it ensured that the before population for each group, SKIN or NOSKIN, was identical to the after population for that group. It removed confounders, such as patients in the before group having more active disease than the patients in the after group, making the overall efficacy of ustekinumab seem greater.

The majority of the data were either statistically significant or trended in a direction that supported an association between a more robust treatment effect of ustekinumab for Crohn’s disease and concurrent automimmune skin disease. This held true across laboratory biomarkers (FCP, CRP) and blinded Likert score evaluations of imaging, endoscopy, and pathology reports comparing disease activity before and after ustekinumab therapy.

To complement the Likert data, a series of objective small sub-analyses were performed on the subset of patients with active lesions prior to treatment. These sub-analyses were performed to exclude human judgement as they only evaluated for presence or absence of a feature not its severity or degree of improvement. These results mirrored the Likert data, further validating it.

Another important metric of Crohn’s medication efficacy is whether it obviates the need for surgery. A separate analysis was performed to ascertain whether patients in the SKIN or NOSKIN group had fewer surgeries with treatment. Again, SKIN had a lower percentage of surgeries than NOSKIN, but the number of events was low.

**Limitations**

Some limitations of this study stem from its retrospective design. In order to have pre- and post- values for all the variables, large time ranges had to be used. The before group included all values from up to a year prior to ustekinumab initiation. The patient’s CRP and FCP values could fluctuate significantly over this time. In addition, the after- values could also span large time ranges with some people having FCPs obtained after 6 months and others after 1 year of treatment. In order to limit the noise from multiple measurements, each patient’s FCPs in the pre group were averaged to obtain a single pre value per patient. Post FCP, pre CRP, and post CRP were also averaged by patient. Since the report-based results could not be averaged as simply as numerical values, the overall severity of illness in the pre group was compared to the overall severity in the post group based on all the reports in each section. Another limitation of the Likert analysis was that different imaging modalities were sometimes used; while MRIs were generally used for patients under 35 years old, and CTs for patients over 35, CTs were occasionally compared to MRIs. These comparisons were allowed as long as the imaging was of the same regions of the body.

While there overall seems to be a trend for improved response in the SKIN group, several of the individual metrics did not show statistical significance. This is possibly due to type II error as the event rates for many of the complications were small. This is a single-center pilot study of a medication that was relatively recently introduced, thereby partially accounting for the small numbers. Furthermore, in order to help control for confounders all results were matched by patient for each analysis. This also decreased the sample size.

**Future directions**

Further studies could be performed to determine the mechanism of the differential effect of ustekinumab upon SKIN and NOSKIN patients; further work with genetic data and cytokine profiles of patients with Crohn’s disease could identify a subset particularly responsive to ustekinumab. In the future it would be beneficial to extend this study to a larger group of patients in multiple centers. If the analyses used in this study show significance with a larger number of patients, then it may affect Crohn’s disease management with earlier introduction of ustekinumab treatment for patients with concurrent skin disease.

**Conclusion:**

This study has demonstrated an association between a robust response to ustekinumab in Crohn’s disease and the presence of concurrent cutaneous manifestations of Crohn’s disease or concurrent autoimmune skin disease.

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TABLES and FIGURES

TABLE 1: Demographics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | SKIN | SKIN % | NOSKIN | NOSKIN % |
| FEMALE | 52 | 0.658227848 | 184 | 0.582278 |
| MALE | 27 | 0.341772152 | 132 | 0.417722 |
|  |  |  |  |  |
| CAUCASIAN | 70 | 0.886075949 | 285 | 0.901899 |
| ASIAN | 0 | 0 | 5 | 0.015823 |
| AFRICAN AMERICAN | 6 | 0.075949367 | 24 | 0.075949 |
| HISPANIC | 3 | 0.037974684 | 2 | 0.006329 |
|  |  |  |  |  |
| SMOKER | 36 | 0.455696203 | 136 | 0.43038 |
| NONSMOKER | 43 | 0.544303797 | 180 | 0.56962 |
|  |  |  |  |  |
| AGE | 40.58 |  | 40.18 |  |
|  |  |  |  |  |
| TOTAL PATIENTS | 79 |  | 316 |  |