Rheumatoid arthritis

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Rheumatoid arthritis is a chronic inflammatory joint disease, which can cause cartilage and bone damage as well as disability. Early diagnosis is key to optimal therapeutic success, particularly in patients with well-characterised risk factors for poor outcomes such as high disease activity, presence of autoantibodies, and early joint damage. Treatment algorithms involve measuring disease activity with composite indices, applying a treatment-to-target strategy, and use of conventional, biological, and newz non-biological disease-modifying antirheumatic drugs. After the treatment target of stringent remission (or at least low disease activity) is maintained, dose reduction should be attempted. Although the prospects for most patients are now favourable, many still do not respond to current therapies. Accordingly, new therapies are urgently required. In this Seminar, we describe current insights into genetics and aetiology, pathophysiology, epidemiology, assessment, therapeutic agents, and treatment strategies together with unmet needs of patients with rheumatoid arthritis.

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Introduction

Rheumatoid arthritis is one of the most prevalent chronic inflammatory diseases. It primarily involves the joints, but should be considered a syndrome that includes extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement or vasculitis, and systemic comorbidities. A therapeutic revolution in the treatment of rheumatoid arthritis in the past decade—with the advent of novel therapeutics, introduction of early therapy, development of new classification criteria, and application of new effective treatment strategies—has transformed articular and systemic outcomes.[1–6] In this Seminar, we highlight recent insights into most aspects of rheumatoid arthritis, from diagnosis to treatment strategies, and from aetiology to novel therapies. There is still a considerable unmet need in rheumatoid arthritis; full or stringent remission is not typical, nor is it usually sustained without continuing treatment, and as such it should now be the priority of research efforts.

Epidemiology, genetics, and aetiology

Rheumatoid arthritis is a chronic disease that carries a substantial burden for both the individual and society.[7] The individual burden results from musculoskeletal deficits, with attendant decline in physical function, quality of life, and cumulative comorbid risk.[8] The socioeconomic burden, aside from major direct medical costs, is a consequence of functional disability, reduced work capacity, and decreased societal participation.[9] Efforts to establish the diagnosis early, initiate treatment promptly, and design novel treatment strategies to control inflammation and reduce or prevent consequent damage are paramount.

Rheumatoid arthritis has an incidence of 0·5% to 1%, with an apparent reduction from north to south (in the northern hemisphere) and from urban to rural areas.[10,11] Some Native American populations have a very high prevalence.[10] A positive family history increases the risk of rheumatoid arthritis roughly three to five times; concordance rates in twins are increased, implicating genetic factors in pathogenesis.[10,12] The heritability of rheumatoid arthritis is currently estimated as 40–65% for seropositive rheumatoid arthritis, but lower (20%) for seronegative disease.[13,14]

Modern genetic technologies combined with large, well-characterised clinical cohorts have advanced our understanding of the genetics of the disease. Genome-wide association studies using single nucleotide polymorphisms have characterised more than a hundred loci associated with rheumatoid arthritis risk, most of which implicate immune mechanisms (figure 1), some of which are shared with other chronic inflammatory diseases.[15] The HLA system (particularly HLA-DRB1) remains the dominant influence, strongly implicating peptide (and self-peptide) binding in pathogenesis.[16] Disease-associated alleles share common aminoacid sequences in the peptide-binding groove (the so-called shared epitope).[17] Moreover, some HLA genotypes particularly associate with more aggressive erosive disease and with higher mortality, pointing to a crucial role of peptide binding.[18]

Other genetic loci probably contribute smaller functional effects that are presumably singly or cumulatively mediated,[19] for example, via altered co-stimulatory pathways (eg, CD28, CD40), cytokine signalling, lymphocyte receptor activation threshold (eg, PTPN22), and innate immune activation (figure 1). The increased risk for rheumatoid arthritis in patients with the shared epitope is linked with seropositivity for autoantibodies against citrullinated peptides (ACPAs) and autoantibodies against IgG (rheumatoid factor [RF]). These characteristic autoantibodies for rheumatoid

Search strategy and selection criteria

We searched MEDLINE using the terms "rheumatoid arthritis" in conjunction with "diagnosis", "classification", "epidemiology", and "pathogenesis". For treatment, we used recent systematic literature searches, and updated the respective searches in October, 2015, including terms on novel therapies and "treatment strategy". Selection of articles was based on our personal judgment of relevance within the scope of this Seminar.

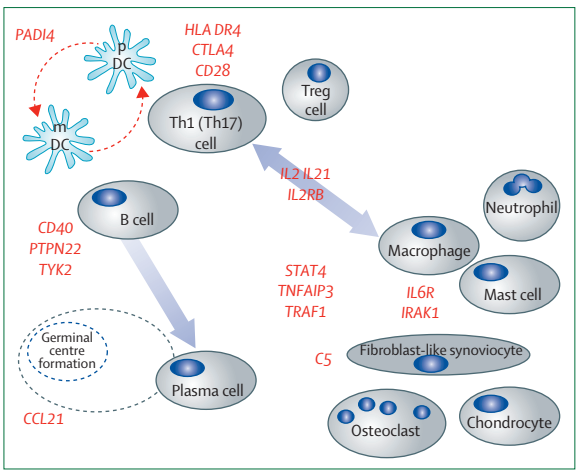


Figure 1: **Important loci associated with risk and progression of rheumatoid arthritis**

Key immune cells implicated in the pathogenesis of rheumatoid arthritis. Th1=T-helper-1. Th17=T-helper-17. Treg=regulatory T. mDC=myeloid dendritic cell. pDC=plasmacytoid dendritic cell.

arthritis are present in 50–70% of patients at diagnosis, with remarkable stability throughout the disease course.[20,21] The shared epitope has only poor association with ACPA-negative and RF-negative rheumatoid arthritis.[18]

Epigenetics contribute to pathogenesis, probably by integrating environmental and genetic effects.[22] A recent epigenome-wide association study identified ten differentially methylated positions that could promote genetic risk in rheumatoid arthritis.[23] Altered histone acetylation and DNA methylation can regulate the biology of synovial fibroblasts and leucocytes.[22] MicroRNAs represent an additional epigenetic aspect by targeting mRNA for degradation, thereby fine-tuning cellular responses.[24,25] Many microRNAs have been identified as key regulators of lymphocytes, macrophages, and synovial fibroblasts (eg, miR146a or miR155).[25] Whether microRNAs will offer therapeutic utility in rheumatoid arthritis is as yet unclear.[22]

Development of rheumatoid arthritis is associated with environmental factors. Consistently reported risk factors include smoking[26,27] and low socioeconomic status or educational attainment.[28,29] Rheumatoid arthritis is associated with periodontal disease, although the causality and nature of this relationship remains ill defined.[30] One hypothesis proposes that *Porphyromonas gingivalis* (a bacterium frequently found in periodontitis) promotes aberrant citrullination and provokes local breach of tolerance to citrullinated peptides via endogenous expression of its PADI4, which converts arginine to citrulline.[31] Indeed, other infectious agents (eg, *Proteus mirablis*, *Escherichia coli*, and Epstein-Barr virus) have been suggested to trigger rheumatoid arthritis,[32] generally via molecular mimicry; however these proposed mechanisms have not yet been substantiated.

As is the case with many autoimmune diseases, there is now considerable interest in the effect of the microbiome on disease risk and progression (figure 2).[30,35] Data from animal models of arthritis suggest an essential role for the gut microbiome in the development of disease.[35] Initial studies in humans have implicated gastrointestinal dysbiosis in rheumatoid arthritis, particularly in early disease.[30] One study[36] detected alterations in common microbial populations in oral, salivary, and gastrointestinal sites, which were associated with C-reactive protein and ACPA status, and further altered by therapy with disease-modifying antirheumatic drugs. The mechanisms underpinning such observations and their importance remain to be elucidated.

Pathophysiology of rheumatoid arthritis

Autoimmune response

Rheumatoid arthritis is pathologically heterogeneous. The presence of autoantibodies (seropositivity) is associated with more severe symptoms and joint damage, and increased mortality.[35–39] This is most likely due to formation of immune complexes by ACPAs with citrulline-containing antigens and subsequent binding of RF, which can lead to abundant complement activation.[40–42] The detection of autoimmune responses to citrullinated self-proteins is a major advance.[43,44] ACPAs can bind citrullinated residues on many self-proteins including vimentin, α-enolase, fibronectin, fibrinogen, histones, and type II collagen. The tissue in which these immune responses are activated is uncertain, but the lung is an attractive candidate, which is consistent with a role for smoking in rheumatoid arthritis and the presence of shared citrullinated peptides in lung and synovial tissue biopsies (figure 2).[45] Circulating ACPAs can be detected up to 10 years before diagnosis—so-called pre-rheumatoid arthritis.[46] Over time, the concentration and epitope diversity of ACPAs increases, as do serum cytokine concentrations, especially before onset of articular involvement. ACPAs can be of IgG, IgA, or IgM isotype, are indicative of T-cell help, and have an altered glycosylation status that confers enhanced Fc-receptor and citrullinated antigen binding.[47,48] ACPA-producing B cells are present in the synovium and in the circulation.[47,49] ACPAs themselves can be pathogenic, either by activating macrophages (eg, by ligating to toll-like receptors via the bound antigen, or by Fc-receptor engagement, or both), or by activating osteoclasts via immune complex formation and Fc-receptor engagement or, possibly, by binding membrane citrullinated vimentin,[50] thus promoting bone loss. With effective therapy, both RF and ACPA concentrations decrease, but patients rarely become ACPA negative, whereas RF decreases more profoundly and more frequently and patients may serocovert to RF negativity.[51] Anti-carbamylated and acetylated peptide autoantibodies have also been identified in patients with rheumatoid arthritis;[52] additional autoantibodies, directed against other post-translational protein modifications,

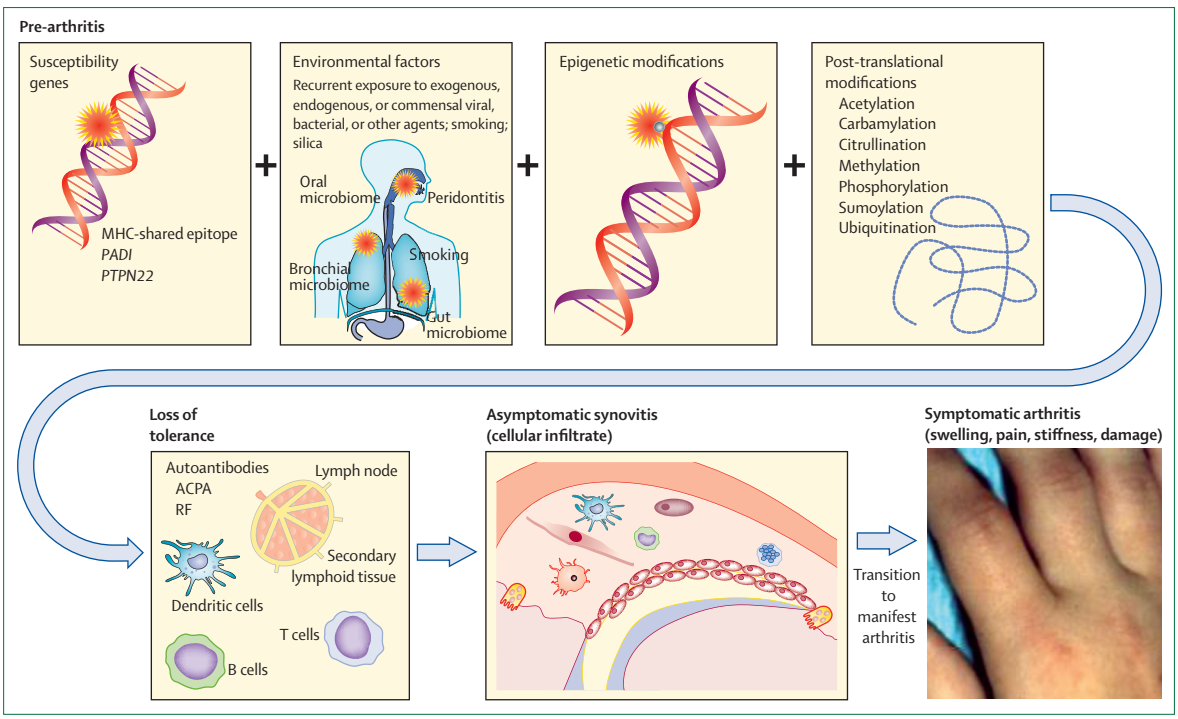


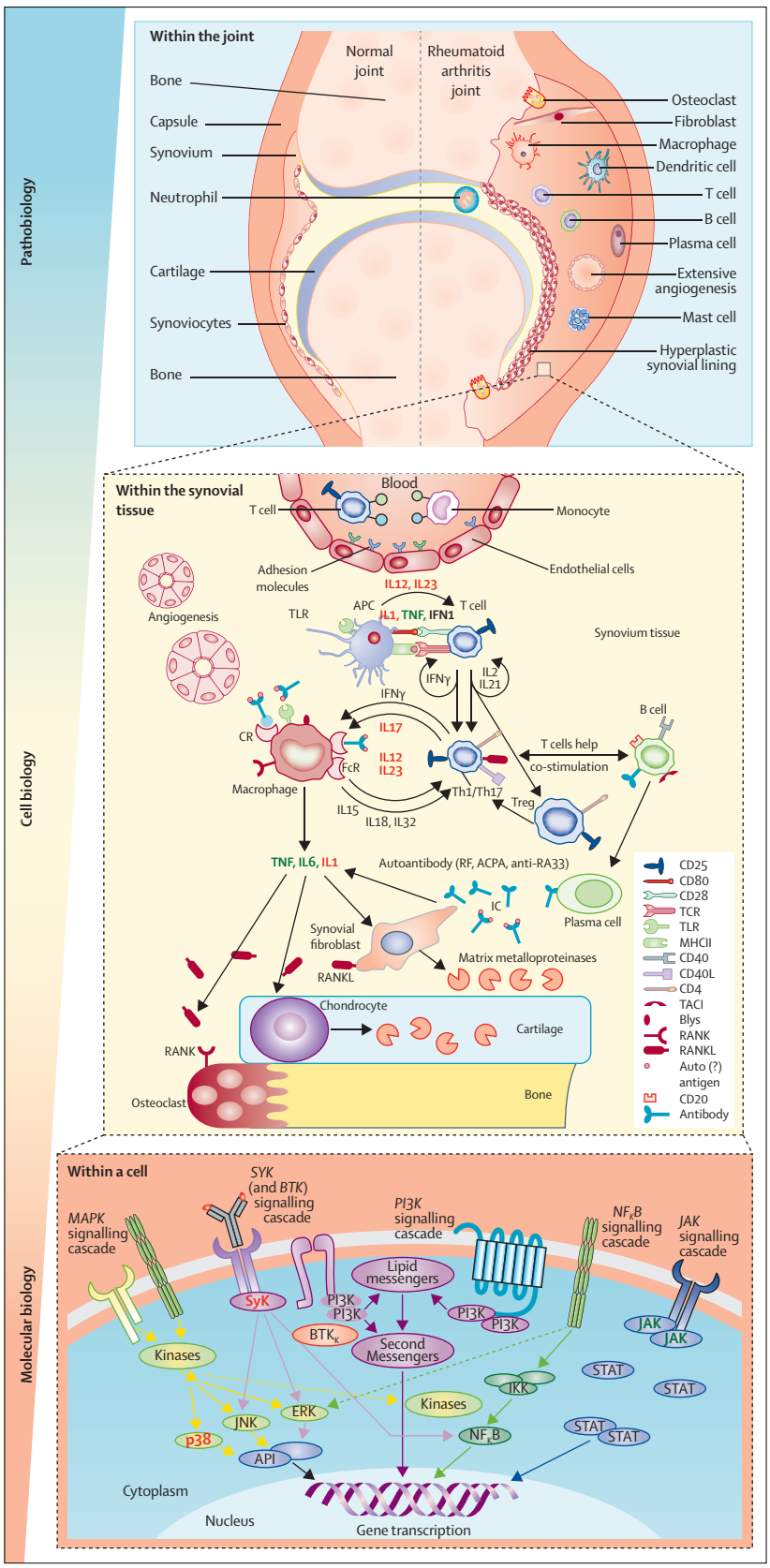
Figure 2: **Pathways to rheumatoid arthritis**
In a genetically predisposed host with susceptibility genes, environmental insults, epigenetic modifications, and post-translational modifications can lead to loss of tolerance with subsequent asymptomatic synovitis, ultimately leading to clinically overt arthritis. ACPA=autoantibodies against citrullinated peptides. RF=rheumatoid factor. Adapted from Smolen and colleagues[33] by permission of Elsevier, and McInnes and Schett[34] by permission of the Massachusetts Medical Society.

might emerge. RF is more directly involved in mechanisms of macrophage activation and induction of cytokine activation than ACPAs.[42,53] ACPAs might form immune complexes that interact with RF, thus potentiating the effect on the inflammatory and destructive response.[37,53] Less is known of the T-cell response that supports these processes.[54] Using HLA-DRB1*0401 tetramers, elevated numbers of citrulline-specific T-helper-1 cells have been found in the circulation of patients with rheumatoid arthritis, particularly in those with early disease,[55] although their contribution to autoimmune mechanisms remains uncertain. Lymph node biopsies in early rheumatoid arthritis suggest T-cell activation distant from the synovium.[56]

Inflammation

Joint swelling in rheumatoid arthritis reflects synovial membrane inflammation consequent to immune activation, and is characterised by leucocyte infiltration into the normally sparsely populated synovial compartment (figure 3). The cellular composition of synovitis in rheumatoid arthritis includes innate immune cells (eg, monocytes, dendritic cells, mast cells, and innate lymphoid cells) and adaptive immune cells (eg, T-helper-1 and T-helper-17 cells, B cells, plasmablasts, and plasma cells). A robust tissue response—whereby synovial fibroblasts assume an aggressive inflammatory, matrix regulatory, and invasive phenotype, together with enhanced chondrocyte catabolism and synovial osteoclastogenesis—promotes articular destruction.[33,34] Findings from ultrasound-guided biopsies of small joints and detailed molecular (particularly transcriptomic) analyses suggest that myeloid-dominant, lymphocytic-dominant, and fibroid-dominant synovial subtypes might exist, which could be of therapeutic significance.[59]

The inflammatory milieu in the synovial compartment is regulated by a complex cytokine and chemokine network; clinical interventions clearly demonstrate that of these components, tumour necrosis factor (TNF), interleukin 6, and probably granulocyte-monocyte colony stimulating factor are essential to the process, whereas others (such as interleukin 1 and various lymphokines) may be less important.[60] Cytokines and chemokines lead to the induction or aggravation of the inflammatory response by activating endothelial cells and attracting immune cells to accumulate within the synovial compartment. Activated fibroblasts, together with the accumulated activated T cells and B cells, and monocytes and macrophages, ultimately trigger osteoclast generation via receptor activator of nuclear factor κ B ligand (RANKL) expressed on T cells, B cells, and fibroblasts, with its receptor RANK on macrophages, dendritic cells, and pre-osteoclasts.[61,62] Bony erosions ensue, arising from the so-called bare area at the junction between cartilage, periosteal synovial membrane insertion, and bone. Cartilage undergoes damage by catabolic effects in



chrondrocytes after their stimulation by cytokines. Cartilage matrix is degraded by matrix metalloproteinases and other enzymes.[63] Cytokines bind cognate receptors to trigger various intracellular signal transduction events, the intermediaries between extracellular events and activation of an array of genes that lead to or aggravate inflammation and damage (figure 3).

Learning from success and failure of therapies

Many of these cells and molecules have been tested as therapeutic targets with notable success in rheumatoid arthritis and subsequently other inflammatory diseases, whereas targeting of other molecules rendered low or no therapeutic success. Thus, whereas the pathogenetic events initiating and mediating chronicity of synovitis are not yet fully understood, remarkable insights have arisen from genetic, epidemiological, translational biological, and therapeutic studies.

Taken together, this evidence suggests that rheumatoid arthritis probably arises from multiple hits, whereby an initial combination of environmental, lifestyle, and stochastic insults occurring in a genetically predisposed, epigenetically modified individual leads to breach of immunological tolerance. An additional trigger, perhaps infectious (facilitated particularly by pathways associated with HLA class II), drives expansion of T-cell-mediated autoimmunity, and thereafter articular localisation via currently obscure mechanisms (eg, neurological, vascular, biomechanical). This crucial transition to chronic (non-resolving) synovitis is characterised by leucocyte and stromal cell dysregulation and wider comorbidity affecting various organs, such as the heart and the bone. Importantly, this transition must occur quite early, because treatment of very early, clinically incipient but overt rheumatoid arthritis usually does not reverse arthritis, and because synovial infiltration by inflammatory cells can occur before clinical signs and symptoms.[64,65] Therefore, diagnosis of preclinical rheumatoid arthritis has become a focus of research activity,[66,67] with the goal of using preventive therapy; the term "window of opportunity" increasingly refers to preventive aspects rather than interventions in early but clinically already manifest disease.

Diagnostic approach and differential diagnosis

No diagnostic criteria exist for rheumatoid arthritis. The typical patient presents with tender and swollen joints of recent onset, morning joint stiffness, and abnormal laboratory tests such as elevated concentrations of C-reactive protein or erythrocyte sedimentation rate. Unfortunately, this presentation is not specific to

Figure 3: **Pathogenetic pathways in rheumatoid arthritis**
Green text shows molecules or cells which are successfully targeted by respective therapies. Red text relates to molecules or cells for which targeting was not effective. Adapted from Smolen and colleagues[33] by permission of Elsevier, Mavers and colleagues[57] by permission of Springer, and Smolen and Steiner[58] by permission of Nature Publishing Group.

rheumatoid arthritis. Other causes of arthritis need to be considered, such as reactive arthritis, osteoarthritis, psoriatic arthritis, infectious arthritis (viral or bacterial, and particularly Lyme disease depending on geographic region), or some rarer autoimmune conditions such as connective tissue diseases if additional suggestive signs or symptoms are present (eg, rash, mouth ulcers, alopecia, Raynaud's phenomenon, Sicca syndrome, antinuclear antibodies, elevated muscle enzymes). In fact, in many patients no specific diagnosis can be made at first presentation, and the diagnosis of exclusion is undifferentiated arthritis. Providing such preliminary diagnosis, while leaving the future evolution to a distinct diagnosis open, is important, because disease-modifying treatment is indicated and necessary for any type of chronic inflammatory arthritis.

New classification criteria for rheumatoid arthritis were presented in 2010[1] to eliminate shortcomings of the former American College of Rheumatology (ACR) criteria, particularly inclusion of features of chronicity and poor prognosis.[68] Briefly, the new criteria, developed using cohorts and case scenarios of patients with early arthritis, require at least a single clinically swollen joint as entry criterion in the absence of other diseases explaining the clinical symptoms. Thereafter, the classification criteria allow for sensitive assessment of extent of joint involvement (tender joints or joints positive by ultrasound or MRI can be classified as active joints, just as well as clinically swollen joints). Additional features are serological markers (RF and ACPA), long symptom duration, and laboratory markers of systemic inflammation. The criteria have been validated in many settings and offer 21% higher sensitivity than the former criteria, at the cost of 16% lower specificity.[69] However, classification is not synonymous with diagnosis. Whereas diagnosis has the ultimate goal of being correct at the level of the individual patient, classification aims to maximise homogeneous populations for study purposes, but can be used to support diagnosis.

Extra-articular manifestations and comorbidities

Patients with insufficiently treated rheumatoid arthritis can have various extra-articular manifestations, including vasculitis or interstitial lung disease.[69] Moreover, the chronic inflammatory state of rheumatoid arthritis has been associated with secondary amyloidosis, lymphoma,[70] and cardiovascular disease[8] and increased mortality.[71] All these risks appear to be strikingly reduced with modern therapeutic strategies.[72,73] Of note, methotrexate can induce nodulosis, which is indistinguishable from rheumatoid nodules,[74] and TNF inhibitors can elicit psoriasis-like lesions[75] that only subside after cessation of the drugs.

Disease assessment and definition of treatment targets

Assessment of disease activity is crucial in the follow-up of patients with rheumatoid arthritis.[76,77] Composite measures that include joint counts have been recommended for daily practice.[77] The ACR improvement criteria[78] distinguish a change from baseline of several defined variables by at least 20% (ACR20, minimal response), 50% (ACR50, moderate response), or 70% (ACR70, major response). They were developed to differentiate active therapy from placebo in clinical trials (in particular, ACR20), but cannot be used in practice because they are not based on a continuous scale; improvement is related to baseline values of the respective variable, which differ between individual patients or within patients at different treatment starts. By contrast with the DAS28, a disease activity score using 28 joint counts along with other components in a complex calculation (table 1),[80] the simplified disease activity index (SDAI) and clinical disease activity index (CDAI)[81,82] provide continuous numerical scales reflecting disease activity (higher is worse; table 1).[80,83] These measures can also classify disease activity states (high, moderate, low, and remission). There is an almost linear relationship between these disease activities and impairment of physical function[77,82,84] or damage progression.[82,85–87] Other disease activity measures that do not include joint counts[88]

	Components	Cutpoints			
		Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28-ESR*	Tender joint count (of 28), swollen joint count (of 28), erythrocyte sedimentation rate (in mm), global health	<2·6	2·6 to 3·2	>3·2 to ≤5·1	>5·1
DAS28-CRP†	Tender joint count (of 28), swollen joint count (of 28), C-reactive protein (in mg/dL), global health	<2·6	2·6 to 3·2	>3·2 to ≤5·1	>5·1
SDAI‡	Tender joint count (of 28), swollen joint count (of 28), patient global assessment, evaluator (physician) global assessment both in cm, C-reactive protein (in mg/dL)	≤3·3	>3·3 to 11	>11 to ≤26	>26
CDAI§	Tender joint count (of 28), swollen joint count (of 28), patient global assessment, evaluator (physician) global assessment both in cm	≤2·8	>2·8 to 10	>10 to ≤22	>22
ACR-EULAR remission[79]	Index: SDAI, CDAI; Boolean: swollen joint count (of 28), tender joint count (of 28), patient global assessment, C-reactive protein (in mg/dL)	SDAI ≤3·3, CDAI ≤2·8, Boolean all ≤1	..	..	..

Patient global assessment reflects global health in DAS28; mm in DAS28; cm in CDAI, SDAI, Boolean. ACR=American College of Rheumatology. EULAR=European League against Rheumatism. DAS28=disease activity score using 28 joint counts. SDAI=simplified disease activity index. CDAI=clinical disease activity index. TJC28=tender joint count (of 28). SJC28=swollen joint count (of 28). ESR=erythrocyte sedimentation rate (in mm). GH=global health. CRP=C-reactive protein (in mg/dL). *DAS28-ESR calculated according to the following equation: $0{\cdot}56 \times \sqrt{(TJC28)} + 0{\cdot}28 \times \sqrt{(SJC28)} + 0{\cdot}70 \times \log_e(ESR) + 0{\cdot}014 \times GH$. †DAS28-CRP calculated according to the following equation: $0{\cdot}56 \times \sqrt{(TJC28)} + 0{\cdot}28 \times \sqrt{(SJC28)} + 0{\cdot}36 \times \log_e(CRP + 1) + 0{\cdot}014 \times GH + 0{\cdot}96$. ‡SDAI calculated according to the following equation: TJC28 + SJC28 + PtGA + EGA + CRP. §CDAI calculated according to the following equation: TJC28 + SJC28 + PtGA + EGA.

***Table 1*: Composite measures of disease activity including joint counts, and ACR-EULAR remission criteria**

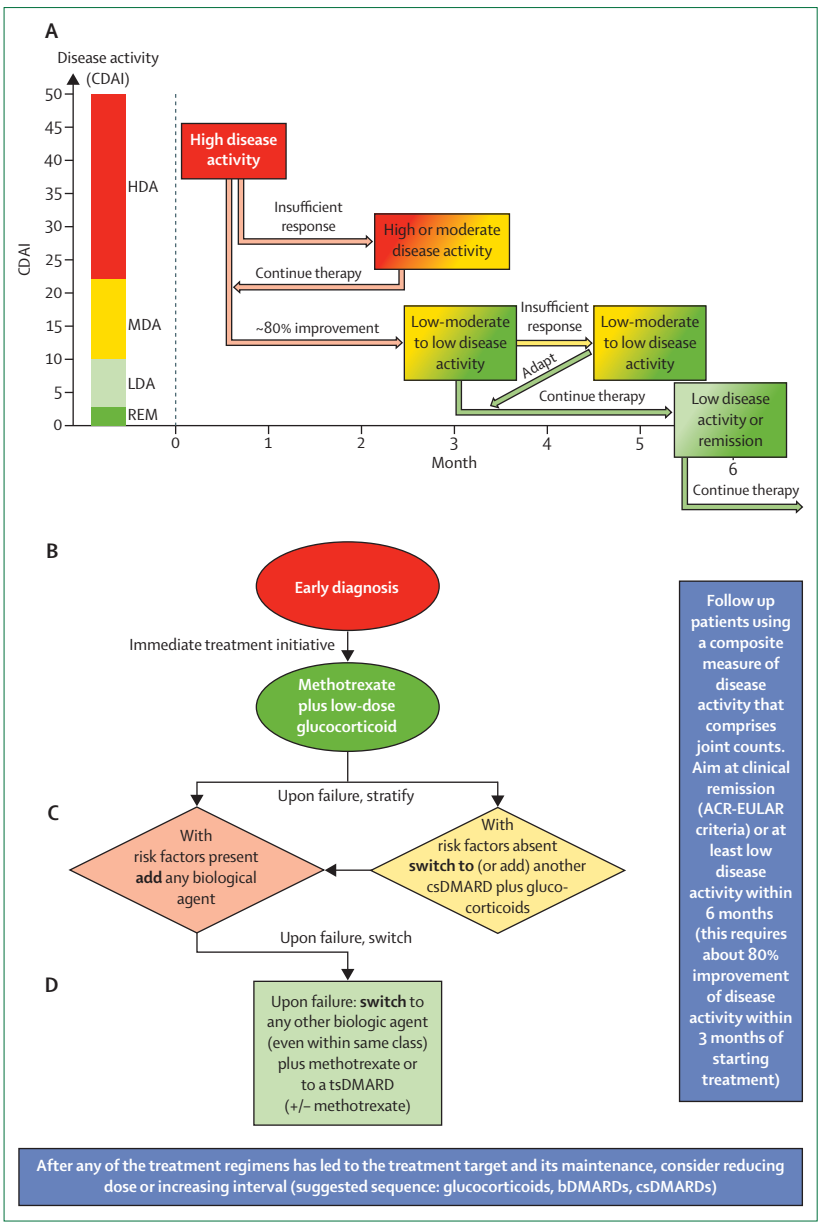


Figure 4: **Therapeutic approaches to rheumatoid arthritis**
(A) General strategy. (B) Early treatment phase. (C) Treatment approach if methotrexate (plus glucocorticoid) does not achieve the treatment target. (D) Treatment approach after a first biologic has failed. The recommendation to potentially use a TNF inhibitor after another TNF inhibitor has failed is based on the available evidence for biological DMARDs, but in some countries switching to another mode of action is recommended or mandated (against this evidence). Treatment algorithm based on EULAR recommendations.[89,100] DMARD=disease-modifying antirheumatic drug. tsDMARD=targeted synthetic DMARD. csDMARD=conventional synthetic DMARD. bDMARD=biological DMARD. ACR=American College of Rheumatology. EULAR=European League Against Rheumatism. CDAI=clinical disease activity index. HDA=high disease activity. MDA=moderate disease activity. LDA=low disease activity. REM=remission. TNF=tumour necrosis factor.

have also been developed but are not widely recommended because of insufficient evidence for reliability across all patient populations and reflection of all outcomes.

Remission (primarily for early rheumatoid arthritis) or low disease activity (especially in long-standing disease) have been established as treatment targets.[89,90] The ACR and the European League Against Rheumatism (EULAR) recently developed new remission criteria, based on a Boolean approach or on an index approach using the criteria of the SDAI or CDAI (table 1).[79] Other definitions of remission (eg, remission according to DAS28-ESR criteria; table 1) might not correspond to true remission, because they are associated with progression of joint damage,[91] presence of comorbidities,[92] and significant residual activity in many patients,[93,94] even if the established cutpoint of 2·6 is lowered.[79,95] Although this issue is controversial, our analyses[96,97] suggest that classification of remission according to DAS28-ESR or DAS28-CRP criteria (table 1) results in high frequency of false-positive responses, particularly when drugs affecting the acute-phase response are used. Indeed, sometimes major differences between DAS28-ESR and DAS28-CRP activity states are observed.[98,99] Importantly, with the development of the new remission criteria, remission—either index-based or Boolean-based—is now closely related to the absence of residual inflammatory disease activity,[100] leaving other definitions consistent with a state of low disease activity.[96,101]

Finally, it is important to evaluate structural progression of the disease. Treatment of rheumatoid arthritis should prevent or halt structural changes and thereby minimise or reverse physical disability. In routine practice, radiographs are usually done annually and evaluated semi-quantitatively. Formal scoring of radiographs for progression of erosions and joint space narrowing, as done in trials, is more accurate and sensitive.[102] Other imaging modalities are being increasingly used, especially for diagnostic purposes. MRI scans detect bone marrow oedema as a potential area of (early or future) erosions,[103] but erosions also correlate well with clinical joint swelling. Ultrasound can quantify the degree and extent of synovial inflammation by using greyscale and power Doppler measurements.[95,104,105] However, in follow-up, targeting sonographic remission does not provide any benefit over targeting clinical remission or even low disease activity, but is associated with substantial overtreatment.[106,107] Notably, many healthy people have detectable ultrasound and MRI signals of synovitis and vascularity.[108] Physical function is typically assessed using the Health Assessment Questionnaire Disability Index,[109] usually at every clinical visit.

Treatment strategies

Because inflammation is at the apex of clinical events (driving clinical symptoms, joint damage, disability, and comorbidity),[33] its reversal is the major therapeutic target; if inflammation subsides rapidly, damage or its progression are prevented, and physical function can be maximally improved without further sequelae. Treatment of rheumatoid arthritis thus requires a strategic approach whereby regular assessment of disease activity drives therapeutic adaptations or changes of drugs in accordance with such activity (treat to target).[100] Composite measures of disease activity that include joint counts are preferred

	Timepoint	Methotrexate plus glucocorticoid		Methotrexate plus other csDMARDs plus glucocorticoid, or methotrexate plus bDMARD	
		Dose	LDA (% of patients)	Dose	LDA (% of patients)
CareRA[113]	4 months	15 mg methotrexate plus 30 mg prednisone (tapered)	87%	15 mg methotrexate plus 2 g sulfasalazine plus 60 mg prednisone (tapered)	85%
tREACH[114]	6 months	25 mg methotrexate plus 15 mg prednisone (tapered)	68%	25 mg methotrexate plus 2 g sulfasalazine plus 400 mg hydroxychloroquine plus 15 mg prednisone (tapered)	71%
IDEA[115]	6 months	20 mg methotrexate plus single intravenous dose of 250 mg methylprednisolone	67%	20 mg methotrexate plus infliximab	65%
BeSt[116]	6 months	7·5 mg methotrexate (increased to 30 mg if needed) plus 2 g sulfasalazine plus 60 mg prednisone	67%	25 mg methotrexate plus infliximab	64%

LDA=low disease activity. DMARD=disease-modifying antirheumatic drug. csDMARD=conventional synthetic DMARD. bDMARD=biological DMARD.

Table 2: **Achievement of low disease activity using methotrexate monotherapy (with glucocorticoids) or combination therapy**

tools in treat-to-target approaches. In practice, if a state of low disease activity or approximately 80% improvement in SDAI or CDAI has been attained by 3 months, the likelihood of reaching the target at 6 months from therapy initiation is very high.[110] If improvement is small at 3 months (figure 4), treatment should be adapted. Likewise, if the state of low disease activity (or remission) is not attained at 6 months, treatment should be re-evaluated. However, escalation of therapy needs to be balanced against patient factors and treatment-related risks.[100]

Therapies

Therapeutic approaches

Disease-modifying antirheumatic drugs (DMARDs) target inflammation and by definition must reduce structural damage progression. Non-steroidal anti-inflammatory drugs (NSAIDs), while reducing pain and stiffness and improving physical function, do not interfere with joint damage and are thus not disease modifying. Glucocorticoids offer rapid symptomatic and disease-modifying effects,[111] but are associated with serious long-term side-effects.

There are two major classes of DMARDs: synthetic and biological. Synthetic DMARDs are further defined as conventional synthetic or targeted synthetic.[112] The use of conventional synthetic DMARDs has evolved empirically and their modes of action are still largely unknown. By contrast, targeted synthetic DMARDs have been developed to modulate a particular target implicated in the generation of inflammation. Key examples include janus kinase (JAK) inhibitors, such as tofacitinib or baricitinib (Eli Lilly, Indianapolis, IN, USA).

Conventional synthetic DMARDs and glucocorticoids

According to EULAR recommendations,[89] treatment should be initiated with a conventional synthetic DMARD, ideally methotrexate, plus low-dose glucocorticoids (figure 4). There is compelling evidence that this is the optimal approach. First, clinical trials comparing methotrexate plus glucocorticoids with combinations of methotrexate plus a biological agent have shown no significant difference in outcomes (table 2).[115,116] Clearly, the dose of all conventional synthetic DMARDs should be optimised, escalating methotrexate to 25–30 mg per week (about 0·3 mg/kg)—either orally or subcutaneously—or sulfasalazine up to 3 g per day. Second, comparing methotrexate plus glucocorticoids with combinations of conventional synthetic DMARDs plus glucocorticoids revealed similar efficacy with less toxicity (table 2).[113,114] Glucocorticoids are given at low to intermediate oral doses or parenterally as single intravenous or intramuscular applications. Low doses of glucocorticoids (<7·5 mg daily) combined with methotrexate confer additive structural protection when compared with methotrexate alone.[117] Oral glucocorticoids should be tapered and then stopped within 6 months, when conventional synthetic DMARDs should have induced significant improvement.[89] With respect to the choice of a conventional synthetic DMARD, methotrexate is considered the anchor drug that also optimises efficacy of biological DMARDs.[89,90] However, it has not yet been conclusively shown that methotrexate is superior to other conventional synthetic DMARDs clinically or structurally; rather, comparisons with sulfasalazine or leflunomide revealed similar outcomes, but the doses of methotrexate in these studies were low compared with those in current use.[118] Other conventional synthetic DMARDs include sulfasalazine, leflunomide, and (for very mild disease) hydroxychloroquine or chloroquine, although these antimalarials have few structural effects.[119] In some countries parenteral gold is still used,[120] but it can have serious side-effects.[121]

Table 2 summarises the most recent data on conventional synthetic DMARD monotherapy and combination therapy. These data suggest some uncertainty as to general use of conventional synthetic DMARD combinations. By comparison with methotrexate

	Molecule type	Usual dose*	Loading dose	Comments
Conventional synthetic DMARDs				
Methotrexate	Small chemical	25 mg once weekly*	No	Starting dose 10 mg—escalation to 25 mg within 4–8 weeks; folate use important (suggest 10 mg/week or 1 mg/day)
Sulfasalazine	Small chemical	3 g/day*	No	Starting dose 1 g, escalation to 3 g/day within 4–8 weeks
Leflunomide	Small chemical	20 mg/day	Optional	Loading dose associated with more gastrointestinal side-effects
Hydroxychloroquine	Small chemical	400 mg/day	No	For mild arthritis or as combination therapy
Biological DMARDs				
TNF inhibitors				
Adalimumab	Human monoclonal antibody	40 mg every 2 weeks subcutaneously	No	Biosimilars expected
Certolizumab pegol	F(ab') fragment of a humanised monoclonal antibody	200 mg every 2 weeks subcutaneously	Yes	
Etanercept	IgG–Fc-receptor construct (fusion protein)	50 mg/week subcutaneously	No	Biosimilar approved
Golimumab	Human monoclonal antibody	50 mg/month subcutaneously	No	
Infliximab	Chimeric monoclonal antibody	3–10 mg/kg intravenously every 4–8 weeks	Yes	Biosimilars approved
Anti-B-cell				
Rituximab	Chimeric monoclonal antibody	1000 mg intravenously every 6 months	No	Biosimilars expected
Anti-T-cell co-stimulation				
Abatacept	IgG–Fc-receptor construct (fusion protein)	125 mg/week subcutaneously	No	Intravenous dosing available
Anti-IL 6R				
Tocilizumab	Humanised monoclonal antibody	162·6 mg/week subcutaneously		Intravenous dosing available; sarilumab (anti-IL6R [Regeneron, Tarrytown, NY, USA]) and anti-IL6 cytokine antibodies (sirukumab [Janssen, Springhouse, PA, USA]) in development
Targeted synthetic DMARDs				
Janus kinase inhibitors				
Tofacitinib	Small chemical	5 mg twice daily	No	JAK1/2/3 inhibitor; once daily medication in development; baricitinib (Eli Lilly, Indianapolis, IN, USA), a JAK1/2 inhibitor, has completed phase 3 trials

IL6R=interleukin 6 receptor. IL6=interleukin 6. DMARD=disease-modifying antirheumatic drug. TNF=tumour necrosis factor. *Contraindicated or dose reductions needed with renal or hepatic impairment; for adverse events see package inserts.

Table 3: **DMARDs and recommended doses**

monotherapy, there might be no added efficacy of conventional synthetic DMARD combinations at the potential cost of more toxicity. By comparison with biological agents used after methotrexate, conventional synthetic DMARD combination confers profound responses (eg, ACR70) at only low frequencies.[122] This is a controversial issue,[118,123] and triple therapy (methotrexate plus sulfasalazine plus hydroxychloroquine) was thought to be more efficacious than monotherapy. Several reviews that addressed higher glucocorticoid doses in the triple therapy arm arrive at different conclusions.[4,124] Indeed, if the same dose of glucocorticoids is applied across both study groups, the most recent randomised controlled trials show no significant clinical, functional, or structural advantage of conventional synthetic DMARD combinations compared with methotrexate monotherapy, but more toxicity and discontinuations.[113,114]

Notably, the new ACR guidelines no longer advocate an early use of combination conventional synthetic DMARD therapy.[90] Many studies of such combination therapies were investigator initiated and these trials could have limitations, as discussed by Landewé and colleagues.[125] However, in patients with low risk of progressive disease, adding a conventional synthetic DMARD when methotrexate has not sufficiently improved disease activity is a possible therapeutic option, although switching the conventional synthetic DMARD is just as good an option.[116]

When the first treatment cycle fails, EULAR recommends stratification for predictors of severe disease as suggested by high disease activity despite the

previous therapy, autoantibodies (ACPA or RF, especially at high titres), and early joint damage on radiography (figure 4).[89] Patients with these risk factors should receive a biological DMARD, whereas those without should receive another conventional synthetic DMARD again in combination with glucocorticoids.

Biological DMARDs

Currently approved biological therapeutics for rheumatoid arthritis have four different modes of action:[3] TNF inhibition, interleukin 6 receptor inhibition, T-cell co-stimulation blockade, and B-cell depletion (table 3, figures 3, 4, 5). A small proportion of patients respond to inhibition of interleukin 1 pathways.[3] Among the TNF inhibitors, five compounds are currently approved, one for intravenous use (infliximab) and four for subcutaneous application (adalimumab, certolizumab pegol, etanercept, and golimumab). Etanercept is a TNF-receptor construct, whereas the others are monoclonal antibodies or fragments of monoclonal antibodies (certolizumab). Etanercept appears to have a lower (but not absent) risk of reactivating tuberculosis than monoclonal antibodies.[127] Patients with a positive tuberculosis test should receive appropriate prophylactic therapy. Biosimilar infliximab is already available and a biosimilar etanercept has been approved in Europe and other countries (table 3). Interleukin 6 inhibition is currently achieved by treatment with tocilizumab, a humanised monoclonal antibody directed at the interleukin 6 receptor; sarilumab (Bridgewater, NJ, USA), a human interleukin 6 receptor inhibitor, has completed phase 3 trials. Interleukin 6 itself is targeted by several monoclonal antibodies, including sirukumab (Janssen, Springhouse, PA, USA), which has completed phase 3 trials (eg, NCT01606761). Abatacept is presently the only T-cell co-stimulation inhibitor approved for rheumatoid arthritis; intriguingly its efficacy might result not only from T-cell targeting but also from inhibition of myeloid cell function.[128,129] Rituximab is the only B-cell-directed monoclonal antibody approved for the treatment of rheumatoid arthritis, targeting CD20; biosimilars are expected in the near future.

These mechanistically discrete therapies seem to convey similar efficacy.[3] Patients who have not previously received methotrexate have the highest ACR70 response rates (a surrogate for achieving low disease activity) with these therapies. Overall, ACR70 response rates to biological DMARDs in combination with methotrexate in these patients are around 30–40% (figure 5). However, embedded within this group of responders are those who would experience efficacy with methotrexate alone (20–25%). These data informed the decision of EULAR and, more recently, ACR to recommend starting treatment with methotrexate.[89,90] Importantly, despite differences in targets, all four major modes of action of targeted biologics (in combination with methotrexate) have similar response rates, decreasing with increasing previous drug experience (figures 4, 5).[3,130,131] This suggests that all these drugs might mediate their efficacy by interfering with a common final pathway—namely, proinflammatory cytokine production.[132]

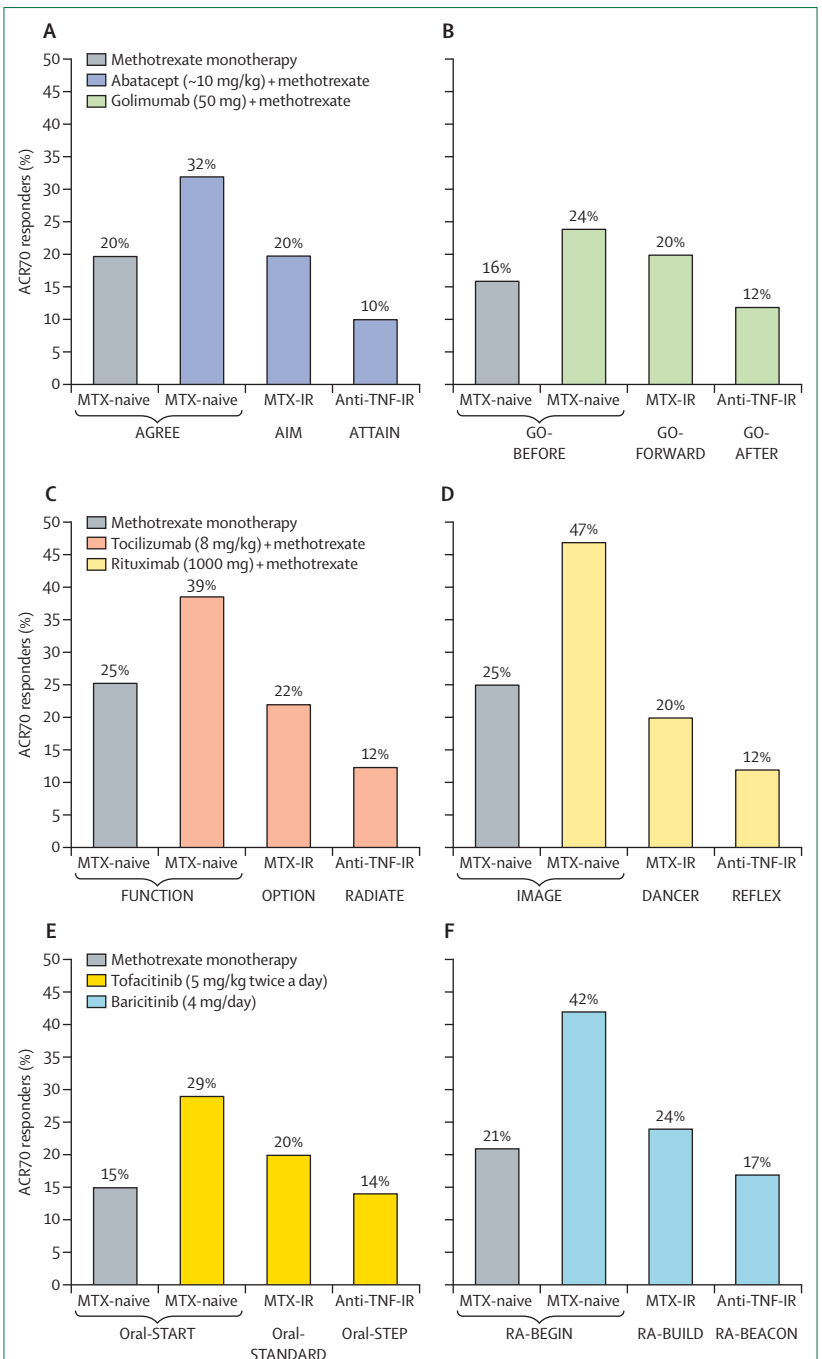


Figure 5: **Response to different DMARD therapies**
(A) Abatacept (inhibition of T-cell co-stimulation). (B) Golimumab (TNF inhibitor). (C) Tocilizumab (anti-interleukin 6 receptor antibody). (D) Rituximab (anti-CD20 mediated B-cell depletion). (E) Tofacitinib (pan-JAK inhibitor). (F) Baricitinib (JAK1/2 inhibitor; Eli Lilly, Indianapolis, IN, USA). ACR70 improvement rates as a surrogate for profound treatment responses. Baricitinib is not yet approved by regulatory authorities but has completed phase 3 trials. For the full list of references, see appendix. DMARD=disease-modifying antirheumatic drug. MTX=methotrexate. Adapted from Smolen and Aletaha[2] by permission of Nature Publishing Group.

See Online for appendix

All biological DMARDs exhibit enhanced efficacy when combined with methotrexate and presumably any other conventional synthetic DMARD, especially leflunomide.[133,134] No biological DMARD used as monotherapy has shown consistent statistically significant clinical or functional superiority compared with methotrexate.[126,135,136] Progression of structural damage is inhibited more strongly with biological monotherapy than with methotrexate monotherapy, albeit to a lesser extent than with the combination therapies. Also, combination of biologics with methotrexate has shown clinical and functional superiority to biological monotherapy.[135–138] Moreover, methotrexate (plus glucocorticoids) conveys similar clinical, functional, and structural efficacy as methotrexate plus biological agent (table 2).[115,116] However, if a monotherapy of a biological DMARD must be given because of intolerance of all conventional synthetic DMARDs, then tocilizumab would be the biologic of choice, since it has better efficacy than TNF inhibitor monotherapy[139] and also somewhat better efficacy than methotrexate.[126,140]

Clinical and structural efficacy is similar across all types of biological DMARDs. This has been shown in meta-analyses, as well as in head-to-head studies.[3,130,141] When a patient does not achieve the treatment target on a biological DMARD (plus methotrexate), then any other biological DMARD or a targeted synthetic DMARD can be used.[89] Indeed, even sequential use of TNF-inhibitors after initial lack of response appears to provide similar outcomes as biologics targeting other molecules, at least in clinical trials.[130,131,142] Of note, in most recommendations or guidelines, rituximab should be used after other biologics have failed; however, it is highly effective in early rheumatoid arthritis[143] and is often used as a first biologic when others are contraindicated.

Targeted synthetic DMARDs

The first approved targeted synthetic DMARD is tofacitinib, a pan-JAK inhibitor; JAK inhibition interferes with signal transduction and thus cell activation elicited by interleukin 6, granulocyte-monocyte colony stimulating factor, interferons (type I and type II), and common γ-chain cytokines (such as interleukin 2 or interleukin 15).[144] Tofacitinib has been approved in the USA and many other countries, but is not yet approved for use within the European Union. The efficacy of tofacitinib plus methotrexate at the approved dose of 5 mg twice a day appears to be similar to that of biologics (figure 5). Intriguingly, tofacitinib monotherapy is clinically superior to methotrexate,[145] by contrast with most biological DMARDs. In phase 3 clinical trials the JAK 1/2 inhibitor baricitinib, which is not yet approved in any jurisdiction, appears to convey a similar range of efficacy as the biological DMARDs and tofacitinib (figure 5). Interestingly, however, baricitinib plus methotrexate elicited a superior clinical and functional (although not structural) outcome compared with adalimumab plus methotrexate;[146] moreover, the roughly 15% ACR70 response rate in patients whose disease had previously not responded to or not tolerated a TNF inhibitor was similar to the response rate in patients who had not responded to multiple biologics.[147]

Tapering therapy

After the desired treatment target (low disease activity or remission) has been reached, it should be sustained over time. Maintenance of a good outcome will normalise or at least maximise physical function, quality of life, and ability to work. When remission (or a targeted low disease activity) is sustained on biological DMARDs for some time (usually about 6 months), the treating clinician should consider tapering therapeutics. Glucocorticoid should be reduced and discontinued within about 6 months, and this should be done first. For biological therapies, the risk of a flare in disease activity after halving dose or doubling the interval between doses is low, whereas complete withdrawal often leads most patients to experience a flare in disease activity; however, the rate of flares decreases with increasingly lower disease activity and longer duration of sustained response.[148–150] Importantly, when a flare occurs, patients usually respond very well to re-introduction of the same agent. However, more than 10% of the patients do not regain their original good outcome and, therefore, subjecting patients to abrupt stopping of biologics and thus risking potentially permanent deterioration of their status may be regarded as ethically unsound. Therefore, gradual dose reduction, rather than sudden stopping of biologics, should be the norm.

Adverse event profiles

The biological agents and the targeted synthetic DMARDs induce more adverse events than do conventional synthetic DMARDs. In particular, the incidence of serious infections is increased, although it decreases over time.[5,151] A special risk relates to reactivation of tuberculosis,[127] although this has not been reported with rituximab. Rituximab is also the drug of choice in patients with concomitant multiple sclerosis, because it has shown efficacy in this disease,[152] whereas TNF inhibitors can elicit flares of multiple sclerosis.[153] Patients with hepatitis B or hepatitis C, whose disease is well controlled with antiviral therapy, can be treated with biologics, but hepatologists should be consulted to introduce and monitor antiviral therapy.[154] However, the introduction of curative treatment for hepatitis C is likely to eliminate the potential risk for these patients. Biological agents (except rituximab) should be avoided within 5 years after malignant disease has been cured, although registry data do not suggest increased risks.[155] However, in patients with a history of lymphoma, rituximab or possibly tocilizumab would be drugs of choice.

During pregnancy, the drugs of choice are sulfasalazine or possibly azathioprine, which is approved for rheumatoid arthritis although it seems to have little efficacy.[4] Methotrexate and leflunomide are contraindicated.[156] The use of biological therapies in pregnancy is controversial.[157,158] Recent data suggest that use of TNF inhibitors is not associated with effects on conception or teratogenic risk. Similar data have been reported for abatacept and tocilizumab.[159,160]

Open questions, unmet needs, and future therapeutics

Despite advances made over the past two decades, many open issues remain. First, we do not understand how therapies targeting different molecules achieve such similar efficacies, and we do not even know if profound responses are elicited by these agents in the same, totally different, or overlapping patient populations. Second, we cannot predict optimal responses or toxic risk for a given treatment; molecular analyses have failed to answer this question,[161–163] although we firmly believe that predictors to permit precision medicine approaches in rheumatology will emerge. Third, although stringent remission (or at least low disease activity) is today's therapeutic goal for rheumatoid arthritis, many patients do not reach this target or achieve it but remain dependent on medication, implying that new therapies are still needed. Fourth, many patients lose responsiveness over time, the reasons for which are not known but might include immunogenicity, or non-adherence. Finally, therapeutics are not delivered via a pathogenetically coherent protocol that takes account of early dominant autoimmunity and later damage-related effector pathways. In this context, early treatment might be highly effective at preventing manifestation of rheumatoid arthritis, but how to detect pre-rheumatoid arthritis or patients at increased risk is unknown. Future diagnostic approaches and therapeutics must address these issues. We contend that there is value in studying the mechanisms of therapeutic failure—for example, interleukin 1, interleukin 12, interleukin 17, interleukin 20, interleukin 21, interleukin 23, anti-CD4, anti-BAFF, and inhibitors of p38-MAPK and SYK. The panel shows new therapeutics that are currently being developed on the basis of pathogenic insights and are being tested in early trials. The ultimate goal is to develop cause-directed, curative therapies, but this will not be possible without better understanding of the cause—or causes—of rheumatoid arthritis.

Panel: Potential future therapeutics for rheumatoid arthritis

Biologics

- Cytokine inhibitors (human, or humanised; eg, targeting interleukin 6, interleukin 21, interferons, granulocyte-monocyte colony stimulating factor or its receptor)
- Cytokine–IgG fusion proteins (eg, interleukin 4–IgG)
- Bi-specific antibodies
- miRNA targeting
- Cell-targeting agents (eg, B-cell depletion, co-stimulatory blockade)

Intracellular signal inhibitors

- Janus kinase inhibitors (eg, baricitinib [Eli Lilly, Indianapolis, IN, USA], filgotinib)
- Bruton's tyrosine kinase inhibitors
- PI3 kinase inhibitors

Cellular therapies

- Tolerogenic dendritic cell transfer
- Stem cell transfer
- T-regulatory-cell activation

Miscellaneous approaches

- Toll-like receptor inhibitors
- PADI4 inhibitors
- Epigenetic modifiers (eg, histone deacetylase inhibitors)
- GnRH antagonists
- Vagus nerve stimulation

Conclusions

The therapeutic insights presented in this Seminar constitute the basis for recommendations for the management of rheumatoid arthritis (figure 4).[89] Early diagnosis and initiation of DMARD therapy are pivotal to prevent damage from occurring or becoming clinically significant.[164] The lower the disease activity achieved at 6 months, the better the long-term outcome; reaching stringent clinical remission within 3–6 months halts damage progression independent of the type of therapy used.[85,91] Setting a treatment target of low disease activity or remission, following up patients regularly using composite disease activity measures (especially joint counts) to determine the disease activity status, and modulating DMARD therapy rapidly if the targeted state has not been achieved within a period of few months lead to better outcomes than routine care.[165,166] Adding low-dose glucocorticoids to conventional synthetic DMARDs maximises clinical, functional, and structural benefit.[117,167] In higher-risk patients, using methotrexate as a first DMARD and adding a biologic, for those who do not attain at least low disease activity within 6 months and have high progression risk, optimises benefit.[168] And finally, if a state of low disease activity or an 80% reduction of disease activity is achieved within 3 months from start of treatment, attainment of the target of low disease activity or remission at 6 months is highly likely. Rigorous attention to this regimen, coupled with the development of further therapeutic options for patients who remain unresponsive, should ensure within the next 10 years that most patients will achieve cessation of disease progression and disability, and retention of high levels of quality of life.

Contributors

JSS wrote the first versions of the introduction, the sections on treatment strategies, therapies, tapering, adverse events, failed therapies and open questions, and contributed to all other parts of the manuscript. DA performed the search and wrote the first versions of the sections on epidemiology, differential diagnosis and assessment, and contributed to all other parts of the manuscript. IBM wrote the first versions of the sections on genetics and pathophysiology, contributed to all other parts of the manuscript, and amended language aspects. All authors performed several rounds of amendments and also had a face-to-face meeting to finalise the manuscript. All authors have seen and approved of the final text.

Declaration of interests

JSS has received grants and/or personal fees from Abbvie, Lilly, MSD, Pfizer, Roche, personal fees from Amgen, AstraZeneca, Astro, Celgene, Chugai, GSK, ILTOO, Janssen, Novartis, Samsung, Sanofi, UCB, all outside the submitted work. DA has received personal fees from AbbVie, BMS, and MSD and personal fees from UCB, Janssen, AstraZeneca, Pfizer, Medac, Roche, Eli Lilly & Co, all outside the submitted work. IBM has received grants and/or personal fees from AbbVie, AstraZeneca, BMS, Celgene, Crescendo Bioscience, Janssen, MSD, Novartis, Lilly, UCB, Amgen, and Pfizer, all outside the submitted work.

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