

# Therapeutic advances in rheumatoid arthritis

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Cite this as: *BMJ* 2024;384:e070856  
<http://dx.doi.org/10.1136/bmj-2022-070856>

**Series explanation:** State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

## ABSTRACT

Rheumatoid arthritis (RA) is one of the most common immune mediated inflammatory diseases. People with rheumatoid arthritis present with pain, swelling, and stiffness that typically affects symmetrically distributed small and large joints. Without effective treatment, significant joint damage, disability, and work loss develop, owing to chronic inflammation of the joint lining (synovium). Over the past 25 years, the management of this condition has been revolutionized, resulting in substantially higher levels of disease remission and better long term outcomes. This improvement reflects a paradigm shift towards early and aggressive pharmacological intervention coupled with a proliferation in treatment choice, in turn related to enhanced pathobiological understanding and the advent of new drugs for rheumatoid arthritis. Following an overview of these developments from a historical perspective, and with a general audience in mind, this review focuses on newer, targeted treatments in an ever evolving landscape. The review highlights ongoing areas of debate and unmet need, including the proportion of patients with persistent, difficult-to-treat disease, despite recent advances. Also discussed are personalized, strategic approaches to individual patients, the role for imaging in clinical decision making, and the goal of sustained, drug free remission and disease prevention in the future.

## Introduction

Rheumatoid arthritis (RA) is a common immune mediated inflammatory disease (IMID) that typically presents with pain, swelling, and stiffness of synovial joints.<sup>1</sup> Early symptoms commonly affect the hands and feet, particularly across the metacarpophalangeal and metatarsophalangeal joints. Diagnosis is clinical, based on the pattern and nature of joint involvement; diagnosis is supported by, but not dependent on, the presence of autoantibodies (rheumatoid factor or anti-citrullinated peptide autoantibodies (ACPAs), or both; box 1), and evidence of systemic inflammation (increased erythrocyte sedimentation rate or C reactive protein, or both). For research purposes, the disease is classified according to the 2010 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria (table 1), which emphasize the role of joint pattern, seropositivity, and inflammation.

Rheumatoid arthritis historically resulted in significant disability, morbidity, and premature mortality, but clinical outcomes for the condition have been greatly improved over the past 25 years. Whereas previous treatment approaches at best slowed joint damage and disability at the expense of significant glucocorticoid toxicity, contemporary strategies aim to induce a state of remission, preventing damage before it occurs. This review

focuses on current and emerging pharmacological strategies, as well as future directions and challenges, in the management of this complex disease.

## Sources and selection criteria

We reviewed evidence for current and emerging treatment strategies in rheumatoid arthritis. We searched the Medline database and Cochrane Library for articles dated from January 1980 to 1 February 2023, and following initial peer review, updated the search with select articles published up to September 2023. A range of sources were used, including recent systematic literature reviews, Cochrane reviews of individual therapeutic agents, randomized controlled trial data, and observational/registry data. Priority was given to meta-analyses and primary randomized controlled trial data, where the aim was to provide an overview of current practice and directions for future development across this broad topic for a wide audience. For less common safety events, though, observational data inform much of the discussion. Case studies and case series were not considered.

## Epidemiology

Rheumatoid arthritis is estimated to affect up to 1% of the adult population.<sup>3</sup> Using the 2010 criteria applied to the Norfolk Arthritis Cohort, the incidence of rheumatoid arthritis in the UK was estimated to be 54/100 000 women and 25/100 000 men from 1990-95, although the incidence increased with

**Box 1: Autoantibodies in rheumatoid arthritis**

Autoantibodies are detected in 50-60% of newly diagnosed patients, rising to 80% of patients with longstanding/active disease; potentially reflecting increased remission rates in seronegative disease.

**Rheumatoid factor**

- First described in the 1940s.
- Detectable in about 60% of people diagnosed with rheumatoid arthritis (sensitivity); similarly, only about 60% specific, also occurring in older individuals, other immune mediated diseases, and in the context of infection.
- Typically pentameric IgM autoantibodies that bind the Fc portion of IgG (although can also occur in IgG and IgA isoforms).
- Likely has a role in perpetuating disease via immune complex formation and complement activation, leading to increased vascular permeability and immune cell chemotaxis to the joint.

**Anti-citrullinated peptide antibodies (ACPAs)**

- First fully characterized in the 1990s.
- Measured in routine practice using anti-cyclic citrullinated peptide assays.
- Present in 60-80% of patients with rheumatoid arthritis.
- >90% specific in the setting of suspected rheumatoid arthritis (less specific at low titers and in the general, asymptomatic population).
- Citrullination is a ubiquitous biochemical process catalyzed by the enzyme peptidyl arginine deiminase, leading to the post-translational modification of arginine amino acids; the presence of citrullinated (auto) antigen is not associated with pathology, but the presence of ACPAs is.
- Mucosal insult in the context of genetic risk might provide a mechanism for autoantibody production, which could in turn contribute to the initiation of joint inflammation, but this remains an active field of research.

**Other anti-modified protein autoantibodies (AMPAs)**

- Aside from ACPAs, autoantibodies to carbamylated and acetylated protein antibodies are well described and associated with rheumatoid arthritis; being unlikely to add diagnostic value, they are not routinely tested for, but remain of pathophysiological interest.

age, peaking in the sixth and seventh decades of life.<sup>4</sup> Globally, the incidence of rheumatoid arthritis is increasing.<sup>5</sup> A 2023 publication using UK general practice data estimated the incidence of rheumatoid arthritis was 58/100 000 person years between 2000 and 2002, but increased to 94/100 000 person years between 2017 and 2019.<sup>1</sup> Whether these data represent a true increase in disease, or better identification or recording, is unknown.

The burden of rheumatoid arthritis is profound.<sup>6</sup> As well as musculoskeletal symptoms and declining physical function, debilitating fatigue,<sup>7</sup> treatment burden, and increased healthcare contact for patients contribute to a deterioration in quality of life. Extra-articular manifestations, including interstitial lung disease, subcutaneous rheumatoid nodules, pericarditis, scleritis, and, rarely, vasculitis,

also contribute to the morbidity of rheumatoid arthritis; however, these manifestations, which are associated with seropositive disease, are becoming less common.<sup>8</sup> Significant comorbidities including cardiovascular disease, infection, depression, and cancer add to the disease burden.<sup>9 10</sup> Mortality rates are increased compared with the general population,<sup>11</sup> with elevated mortality from cardiovascular disease, malignancy, and respiratory diseases, including infection.<sup>12</sup> Although mortality rates have fallen in recent years, excess mortality is still observed.<sup>13 14</sup>

**Advances in treatment: a historical overview**

Until the 1990s, a diagnosis of rheumatoid arthritis implied inevitable functional decline and joint deformity. Options for treatment were limited, and

**Table 1 | 2010 EULAR/ACR rheumatoid arthritis classification criteria<sup>2</sup>**

2010 EULAR/ACR rheumatoid arthritis classification criteria	
Joint distribution (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least one small joint)	5
Serology (0-3)	
Negative rheumatoid factor AND negative anti-citrullinated peptide autoantibody (ACPA)	0
Low positive rheumatoid factor OR low positive ACPA	2
High positive rheumatoid factor OR high positive ACPA	3
Symptom duration (0-1)	
<6 weeks	0
≥6 weeks	1
Acute phase reactants (0-1)	
Normal C reactive protein AND normal erythrocyte sedimentation rate	0
Abnormal C reactive protein OR abnormal erythrocyte sedimentation rate	1
≥6 required for rheumatoid arthritis classification	
Should only be applied in the presence of ≥1 objectively swollen joint and in the absence of an alternate clinical explanation for the presentation	
Joint involvement can be confirmed using imaging (musculoskeletal ultrasound, magnetic resonance imaging)	

many patients received long term glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs), or both, with their associated toxicity. Disease modifying antirheumatic drugs (DMARDs), named to reflect their demonstrable effects in slowing joint destruction, were introduced in the 1970s and 1980s. With broad and incompletely understood modes of action, some of the earliest examples of DMARDs, including gold salts and penicillamine, have all but been abandoned owing to low efficacy and high toxicity. Now referred to as conventional synthetic DMARDs (csDMARDs), other csDMARDs found a niche for patients with rheumatoid arthritis once joint damage was established, meaning the perceived risks of treatment were warranted. Disease remission was rare.

Two parallel developments of recent decades underlie advances in rheumatoid arthritis treatment. Firstly, an expanding armamentarium of targeted treatments has been driven by improved knowledge of the disease's pathobiology, coupled with biotechnology developments. Secondly, the realization that early and effective control of inflammation improves outcomes has heralded formalized disease activity targets against which to titrate treatments: this is called the treat-to-target strategy.

#### Rational targets, designer drugs

The heterogeneity of rheumatoid arthritis precludes a single, unified description of pathogenesis. In keeping with many common, complex diseases, genetic factors such as variation at HLA loci, environmental exposures such as smoking, and the microbiome together confer disease risk.<sup>15</sup> These factors appear to exert their strongest influence on the development of seropositive disease, potentially predisposing to neoantigen presentation, and the consequent production of autoantibodies that could themselves contribute to the initiation and perpetuation of arthritis.<sup>16</sup> The fundamental importance of cytokines in orchestrating these processes is established,<sup>17</sup> and together with cellular components of the adaptive immune system, these signaling molecules therefore emerged as rational treatment targets (fig 1).

The abundance of proinflammatory mediators such as tumor necrosis factor (TNF), interleukin 1, and interleukin 6 in the rheumatoid arthritis synovium was first recognized in the 1980s.<sup>18–19</sup> Promising in vitro appraisal of a humanized, TNF targeting mouse monoclonal antibody culminated in successful phase 3 trials of infliximab in combination with methotrexate during the late 1990s, and hence, the first biologic DMARD (bDMARD) for the treatment of rheumatoid arthritis.<sup>20–21</sup> Recombinant DNA technology was similarly employed to develop a human IgG1 Fc-TNF receptor 2 fusion molecule, in an alternative but equally successful approach. The example of TNF blockade has formed the blueprint for development of other bDMARD classes since. The interleukin 1 receptor antagonist anakinra was an early example which, although licensed, is now rarely used for rheumatoid arthritis owing to lower

cost effectiveness compared with alternatives,<sup>22</sup> but targeting of the interleukin 6 alpha receptor subunit interleukin 6R has gained more traction. In addition, and reinforcing the view of rheumatoid arthritis as a disease of adaptive immune dysregulation, the B cell depleting chimeric mouse/human anti-CD20 monoclonal antibody rituximab, as well as the human cytotoxic T lymphocyte antigen 4 (CTLA4)-IgG1Fc fusion protein abatacept (which, in binding CD80/86 in preference to CD28, blocks co-stimulation to attenuate T cell activation) have both found roles in the clinic; the former is now largely reserved for patients who have had an inadequate response to a TNF inhibitor. The expiry of “innovator” bDMARD patents has brought about a welcome downward pressure on price through legal manufacture of so called “biosimilar” copies. The quality attributes, efficacy, safety, and immunogenicity of these products is tightly controlled by regulators, with demonstrable equivalence to innovator products mandated.<sup>23</sup> The first of these products, a biosimilar of the anti-TNF infliximab, was marketed in 2013 following European Medicines Agency approval, with dozens following.

bDMARDs are large proteins that currently require parenteral administration. Many also have the potential for recognition by the host immune system (immunogenicity), resulting in neutralizing antibody formation and reduced detectable drug in the serum, with associated loss of clinical response.<sup>24–26</sup> Circumventing these challenges, evolving understanding of cytokine signaling has led to the development of small molecule inhibitors of intracellular components downstream of cytokine receptors on immune cells, called Janus kinases (JAKs). The JAK family comprises four members, JAK1, JAK2, JAK3, and Tyk2, which in homodimeric or heterodimeric combinations facilitate intracellular signaling by phosphorylating signal transduction and activation of transcription (STAT) monomers; consequent STAT dimerization, nuclear translocation, and DNA binding then modulates gene expression.<sup>27</sup> The range of possible JAK family pairings and their STAT associations defines the combination of cytokines that will be blocked by inhibition of any individual JAK.<sup>28</sup> JAK inhibitors represent the most recently licensed new class of targeted synthetic DMARDs (tsDMARDs), with tofacitinib receiving US Food and Drug Administration approval in 2012; baricitinib, filgotinib, and upadacitinib have followed. Their varying relative specificity for JAK family members is predicted to determine the extent to which they inhibit different combinations of cytokines; hence their immunomodulatory profile (fig 2).

#### Treating to target in early disease

Efforts to quantify the inflammatory burden of rheumatoid arthritis culminated in the development and widespread adoption of the DAS (disease activity score) in the early 1990s.<sup>29</sup> This composite clinical metric takes account of joint tenderness and swelling across 44 peripheral joints, the erythrocyte

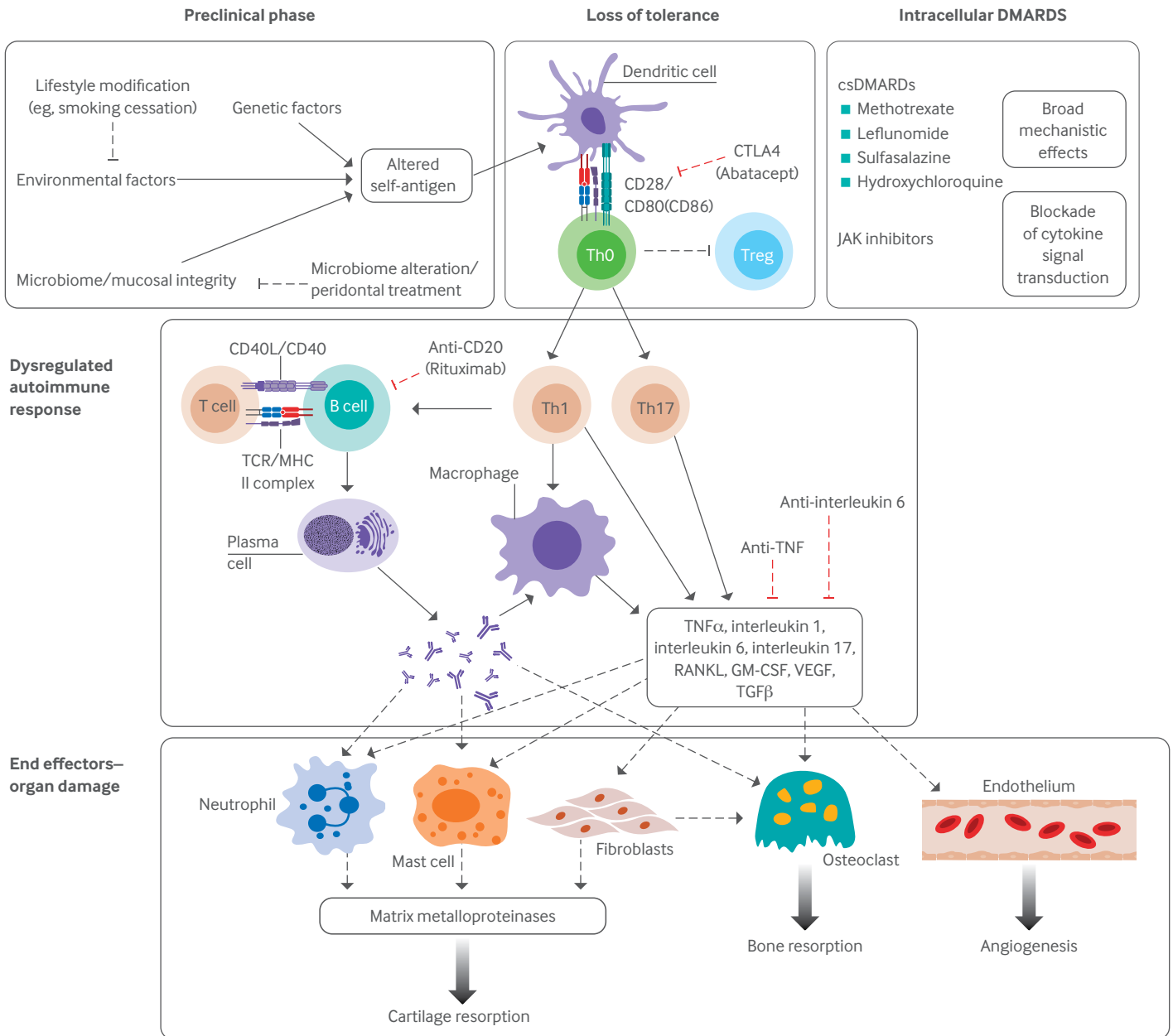


Fig 1 | Pathobiological schema of rheumatoid arthritis and rational drug design. csDMARD=conventional synthetic disease modifying antirheumatic drug; CTLA4=cytotoxic T lymphocyte antigen 4; DMARD=disease modifying antirheumatic drug; GM-CSF = granulocyte macrophage colony stimulating factor; JAK=Janus kinase; RANKL=receptor activator of nuclear factor kappa β ligand; TCR/MHC=T cell receptor/major histocompatibility complex; TGFβ = transforming growth factor β; Th=T helper cell; TNFα=tumor necrosis factor alpha; Treg=regulatory T cell; VEGF=vascular epidermal growth factor

sedimentation rate, and a patient reported global assessment of disease activity (recorded on a visual analog scale). This work laid the foundation for the notion that a window of opportunity might exist in early rheumatoid arthritis, during which prompt, csDMARD induced suppression of the DAS is associated with reduced radiographic joint damage. Support for such a strategy was galvanized over the next decade following several landmark trials, including the tight control for rheumatoid arthritis (TICORA) trial of 2004.<sup>30-33</sup> Here, an intensive “step-up” treatment approach, in which a disease activity score indicating moderate disease activity

or greater, recorded at any monthly assessment, prompted incremental csDMARD escalation, and led to significantly improved outcomes over 18 months compared with standard care.

Numerous studies,<sup>34</sup> sometimes using an abbreviated form of the DAS known as the DAS28-ESR (disease activity score 28 for rheumatoid arthritis with erythrocyte sedimentation rate),<sup>35</sup> have since reinforced the validity of treat-to-target strategies in improving outcomes for newly diagnosed rheumatoid arthritis. Now the subject of consensus management recommendations,<sup>36</sup> the treat-to-target approach has become embedded in clinical practice and drives

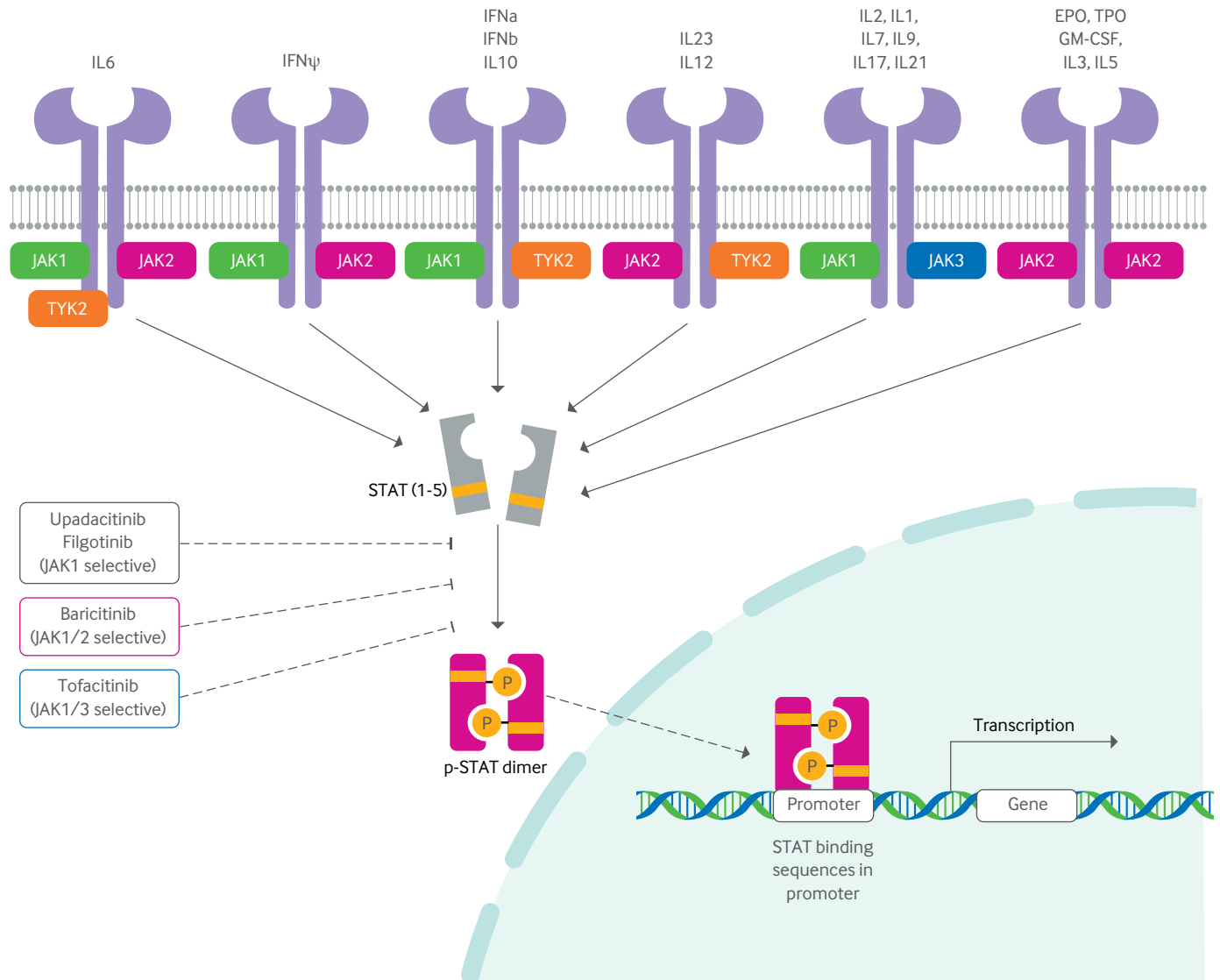


Fig 2 | Cytokine signaling through the JAK/STAT signaling pathway. EPO=erythropoietin; IFN=interferon; IL=interleukin; GM-CSF=granulocyte macrophage colony stimulating factor; JAK=Janus kinase; p-STAT=phosphorylated signal transducer and activator of transcription; STAT=signal transducer and activator of transcription; TPO=thrombopoietin; TYK=tyrosine kinase

modern service delivery models, including the increasingly common early arthritis clinic. Indeed, and as discussed later, ongoing debate is less about the principle of treat-to-target as such, than the selection and sequence of DMARDs and adjunctive glucocorticoids employed to achieve it, as well as the depth of clinical remission considered desirable. Critical to any such consideration is the balance between the likelihood that individual treatment selections will have the desired effect on disease control and the risk of adverse reactions. These themes will be considered in the next section.

#### Current treatments Glucocorticoids

Glucocorticoids exert their predominant actions at a genomic level, readily passing through the cell membranes to bind cytosolic glucocorticoid

receptors present in nearly all tissues, before translocating to the nucleus. Via transactivation of genes that encode immunoregulatory factors, or trans-repression at nuclear factor  $\kappa$ B (NF $\kappa$ B) responsive elements to restrain proinflammatory gene expression, glucocorticoids influence about 1% of the genome, explaining their extremely rapid and broad spectrum immunosuppressive effects. The potency of glucocorticoids has afforded them a continued short term adjunctive role (either orally or by intramuscular injection) alongside DMARDs in achieving symptom control and inhibiting joint damage in early rheumatoid arthritis, as advocated by many rheumatoid arthritis management guidelines. Recently, the glucocorticoid low dose in rheumatoid arthritis (GLORIA) trial in patients aged  $\geq 65$  years showed that low dose (5 mg/day) prednisolone over two years was superior to placebo for disease control, suggesting benefits of



Agent	Structure	Proposed mechanism of action	Route
Methotrexate	Folate derivative and antagonist of DHFR	Potiation of anti-inflammatory adenosine signaling	Oral, subcutaneous
Sulfasalazine	Prodrug of 5-aminosalicylic acid and sulphapyridine	Antagonism of NF- $\kappa$ B signaling	Oral
Leflunomide	Isoxazole derivative	Depletion of uridine resulting in cell cycle arrest in autoreactive lymphocytes	Oral
Hydroxychloroquine	Synthetic quinine analog	Antagonism of autophagy and TLR signaling through increase in endosomal/lysosomal pH	Oral

prolonged glucocorticoids; however, this finding was tempered by an increased risk of infection (although most infections were non-serious).<sup>37 38</sup> The wide range and potential seriousness of adverse effects from glucocorticoids (which include infections, osteoporosis, cataracts, and diabetes) demand that any longer term use is carefully considered.<sup>39</sup>

### csDMARDs

Despite the advances in biotechnology and the expansion of available treatments, csDMARDs remain the standard first line treatment for rheumatoid arthritis (table 2). Clinical trials and observational data have shown that methotrexate, which is considered the csDMARD of choice in early rheumatoid arthritis, has at least comparable if not better efficacy, faster onset of action, and better treatment persistence than other csDMARD monotherapy.<sup>40-42</sup> Combined with a short bridging course of prednisolone, methotrexate monotherapy can induce early and sustained remission in approximately 40% of newly diagnosed patients.<sup>43</sup> Other csDMARDs, primarily sulfasalazine, leflunomide, and hydroxychloroquine,<sup>44-46</sup> are most often used when methotrexate is contraindicated or poorly tolerated, or in combination with or subsequent to methotrexate, especially when a trial of more than one csDMARD is obligated before initiation of bDMARDs or tsDMARDs. Hydroxychloroquine monotherapy is an option for patients who present with mild or palindromic disease.<sup>22 47 48</sup>

Serious adverse events, that is, those resulting in death or hospitalization, are uncommon with methotrexate and other csDMARDs, although many patients report less severe adverse effects.<sup>49-51</sup> Gastrointestinal intolerance, including nausea or abdominal discomfort, is estimated to affect over 40% of patients receiving methotrexate,<sup>52</sup> and all patients require frequent monitoring for cytopenias and liver enzyme abnormalities. Taking methotrexate with folic acid is thought to help to reduce adverse effects without sacrificing clinical response.<sup>50</sup> Nonetheless, up to one third of methotrexate recipients have discontinued the drug within a year of initiation for a variety of reasons.<sup>53</sup> Most patients will start methotrexate orally, aiming for a weekly dose of 15-25 mg, but where an adequate clinical response is not achieved or they have gastrointestinal intolerance, many patients will switch to subcutaneous methotrexate before escalating or changing treatment.

### Efficacy of biologic and targeted synthetic DMARD treatments

Despite an array of advanced therapeutic options in terms of molecular structure, biological target, and formulation, most placebo controlled trials suggest similar efficacy across the different classes of bDMARDs and tsDMARDs as well as between individual drugs within each class. Table 3 describes the currently available b/tsDMARDs, as well as evidence of their efficacy from pivotal placebo controlled or active comparator clinical trials. Pooled data from methotrexate inadequate responders starting a combination of biologics (abatacept, adalimumab, etanercept, golimumab, infliximab, or rituximab) with methotrexate showed an American College of Rheumatology 50% response rate (ACR50) of 38% and a remission rate of 18%.<sup>54</sup>

Although most clinical trials have not performed direct head-to-head comparisons between different bDMARD and tsDMARD treatments, network meta-analyses have not identified any significant differences in efficacy,<sup>54-56</sup> and a recent observational study of pooled national registry data could not identify any difference in effectiveness (including remission rates or treatment persistence).<sup>57</sup> Similarly, switching between formulations of the same drug (eg, from intravenous to subcutaneous tocilizumab or abatacept) has not resulted in any significant loss of clinical benefit.<sup>58 59</sup>

Many studies have found better clinical outcomes among patients who receive most (but not all) b/tsDMARDs in combination with methotrexate, even among those for whom methotrexate has otherwise been insufficiently effective.<sup>60</sup> Some bDMARDs (eg, infliximab, golimumab, abatacept, and rituximab) only have regulatory approval for use in combination with methotrexate (table 3). The reasons for this advantage of combination treatment with methotrexate are unclear. Biologically, methotrexate could reduce the immunogenicity seen with some bDMARD treatments.<sup>61</sup> Some studies have also suggested that seropositive patients respond better to rituximab than seronegative patients, although the benefit was modest.<sup>62</sup>

### Safety of biologic DMARD treatments

With generally comparable efficacy, the safety of individual treatments must also be considered. For most patients, targeted treatments are well tolerated, and serious adverse events are uncommon.<sup>63</sup> Injection site or infusion reactions have been

**Table 3 | Details of currently licensed biologic and targeted synthetic DMARDs including structure, formulation, and clinical trial efficacy (ordered by approval date of first drug treatment in class)\***

Agent	First year of EU marketing authorization	Structure and target	Route	ACR50 response rates in methotrexate inadequate response (versus placebo) as monotherapy	ACR50 response rates in methotrexate inadequate response (versus placebo) in combination with methotrexate	ACR50 response rates in TNFi inadequate response (versus placebo) in combination with methotrexate	Licensed for use as monotherapy, in combination with methotrexate, or both	Reference
Anti-TNF treatments								
Infliximab	1999	Chimeric mAb against TNF $\alpha$	Intravenous, subcutaneous	—	26% versus 5%	—	Combination only	173
Etanercept	2000	Fusion protein of human Fc and human TNFR2	Subcutaneous	—	48% versus 10%	—	Both	174
Adalimumab	2003	Fully human mAb against TNF $\alpha$	Subcutaneous	22% versus 8%	36% versus 11%	—	Both	175, 176
Golimumab	2009	Fully human mAb against TNF $\alpha$	Subcutaneous	20% versus 14% (GO-FORWARD)	38% versus 15%	16% versus 4%	Combination only	177-179
Certolizumab pegol	2009	PEGylated Fab fragment of human mAb against TNF $\alpha$	Subcutaneous	23% versus 4% (FAST4WARD)	36% versus 9%	—	Both	180, 181
Anti-interleukin 1R								
Anakinra†	2002	Modified recombinant human interleukin 1 receptor agonist	Subcutaneous	—	18% versus 7%	—	Combination only	182
Anti-CD20								
Rituximab	2006	Chimeric mAb against CD20	Intravenous	—	29% versus 9%	27% versus 5%	Combination only	183, 184
Anti-CTLA4								
Abatacept	2007	Fusion protein of CTLA4 and human IgG1 Fc	Intravenous, subcutaneous	—	37% versus 17%	20% versus 4%	Combination only	185, 186
Anti-interleukin 6R								
Tocilizumab	2009	Humanized mAb against interleukin 6 receptor	Intravenous, subcutaneous	—	30% versus 10%	29% versus 4%	Both	187, 188
Sarilumab	2017	Fully human mAb against interleukin 6 receptor	Subcutaneous	—	46% versus 17%	37% versus 18%	Both	189, 190
JAK inhibitors								
Tofacitinib	2017	JAK1, JAK2, JAK3 antagonist	Oral	31% versus 12%‡	32% versus 8%	26% versus 8%	Both	191-193
Baricitinib	2017	JAK1, JAK2 antagonist	Oral	—	51% versus 19%	23% versus 13%	Both	194, 195
Upadacitinib	2019	JAK1 antagonist	Oral	—	54% versus 21%	34% versus 12%‡	Both	196, 197
Filgotinib	2020	JAK1 antagonist	Oral	44% versus 11%‡	58% versus 33%	46% versus 19%	Both	198-200

\*For a full list of drug effects, including reported adverse effects, the reader is referred to the summary of product characteristics for each drug.

†Not currently approved by the National Institute for Health and Care Excellence for the treatment of rheumatoid arthritis in the UK, owing to lower cost effectiveness; use in rheumatoid arthritis is uncommon.

‡Assessed at week 12.

Fc=fragment crystallizable region; mAb=monoclonal antibody; JAK=Janus kinase; TNF $\alpha$ =tumor necrosis factor alpha; TNFR2= tumor necrosis factor receptor 2; CTLA4=cytotoxic T lymphocyte associated protein 4; ACR50=American College of Rheumatology 50% response rate.

experienced with bDMARDs, but are a rare reason for treatment discontinuation. This section considers reported risks of infection and malignancy associated with bDMARDs. Limited space precludes a detailed discussion of each drug, and full prescribing information should be consulted for further details.

### Serious infections

One of the most important serious adverse events across all agents is infection. Analyses of real world anti-TNF datasets suggest rates of serious infection resulting in hospitalization or death of 4-5/100 person years of treatment.<sup>64 65</sup> A recent meta-analysis of pooled observational cohort and treatment register data estimated an overall increased infection risk of 1.48 (95% confidence interval 1.18 to 1.85) with anti-TNF compared with csDMARDs.<sup>66</sup> Individual studies have shown this risk varies over time, being highest during the first six months of treatment, and reducing considerably thereafter.<sup>65 67</sup> Importantly, the risk of serious infection is associated with

individual patient factors, including higher doses of concurrent glucocorticoids, higher disability and disease activity, and comorbidity<sup>67 68</sup>; it can be estimated for the individual using an online calculator (<https://biologika-register.de/en/rabbit/rabbit-risk-score-of-infections/>). A network meta-analysis of randomized controlled trial data suggested the anti-TNF certolizumab pegol could incur a higher rate of infection than other bDMARDs, but this analysis could not allow for differences in patient infection risk across the various studies.<sup>69</sup> Observational studies, which could adjust for these differences using alternative statistical approaches, have not confirmed this finding.<sup>64</sup>

Rates of serious infection are thought to be similar across different classes of bDMARDs. The well recognized and almost universal suppression of the acute phase response induced by anti-interleukin 6R monoclonal antibodies (eg, tocilizumab, sarilumab) makes identification of infection more challenging, demanding heightened suspicion from the clinician.

Some observational studies have suggested an increased risk of infection with tocilizumab than with other bDMARDs, but interpretation is complicated considering that tocilizumab came after anti-TNF in the sequence of agents tried. Perhaps more pertinently, a recent large observational national cohort study looking specifically at the risk of infection by bDMARD class has not identified important differences when used at comparable disease stages.<sup>70</sup>

A concern regarding rituximab has been whether repeated courses can increase the risk of infection over time, through depletion of IgG and IgM; however, in most patients, the risk of infection appears to be stable in this setting.<sup>71</sup> Owing to its B cell mechanism of action, rituximab has been shown to attenuate the response to vaccination. This attenuation was particularly evident during the covid-19 pandemic, when rituximab showed ablated humeral responses to SARS-CoV-2 vaccination,<sup>60</sup> as well as increased mortality rates from SARS-CoV-2 infection,<sup>72</sup> compared with other DMARDs.

Most serious infections in patients receiving bDMARDs are caused by common bacterial and viral pathogens. Opportunistic infections are rare, occurring at rates no higher than csDMARD recipients,<sup>73</sup> although vigilance for specific pathogens is warranted. TNF signaling is known to play a key role in granuloma maintenance,<sup>74-77</sup> and latent tuberculosis reactivation among patients treated with anti-TNF monoclonal antibodies is of particular concern. Widespread pretreatment screening has greatly reduced rates of tuberculosis.<sup>64</sup> Whether the risk of tuberculosis reactivation is similarly increased with other b/tsDMARD classes in the absence of screening is unknown. Reactivation of hepatitis B virus infection following bDMARD treatment is recognized, and all patients are recommended to be screened before starting bDMARD treatment.<sup>78</sup>

#### *Malignancy*

Rheumatoid arthritis is associated with a small but significant increase in the risk of cancer. A recent meta-analysis found a pooled standardized incidence ratio of 1.09 (95% confidence interval 1.06 to 1.13) compared with the general population.<sup>79</sup> This risk was not constant across all cancers, being increased for lung cancer (pooled standardized incidence ratio 1.64, 95% confidence interval 1.51 to 1.79), in part related to the shared risk factor of cigarette smoking,<sup>80</sup> and lymphoma (2.26, 1.82 to 2.81). The pooled standardized incidence ratio for colon cancer was reduced (0.78, 0.71 to 0.86), often thought to be related to the common use of NSAIDs in rheumatoid arthritis.<sup>79</sup> The increased lymphoma risk was observed even before widespread DMARD use, and has been linked with chronic inflammation<sup>81</sup>; however, there remains significant interest as to whether bDMARDs can influence this risk, through immunosuppression or other pathways. Reassuringly, no study of anti-TNF has yet confirmed an increased malignancy risk compared with csDMARDs during the short to

medium term.<sup>66 79 82</sup> Limited evidence suggests this is also the case among patients with a history of cancer.<sup>83</sup> Most data in this field focus on lymphoma, solid organ cancers, and keratinocyte skin cancers (eg, basal cell carcinoma). An observational study set in the Swedish population suggested an increased risk of malignant melanoma with anti-TNF compared with patients with rheumatoid arthritis who have never received bDMARDs (hazard ratio 1.5, 95% confidence interval 1.0 to 2.2); however, the absolute observed risk was low (20 additional cases per 100 000 person years). A subsequent large Europe-wide meta-analysis of observational data did not find evidence to support an increase of melanoma in patients receiving anti-TNF compared with patients receiving csDMARDs only (pooled relative risk 1.1, 95% confidence interval 0.8 to 1.6).<sup>84</sup>

Data regarding risk of cancer with other classes of bDMARDs are limited, but a meta-analysis of observational studies, which have the advantage of larger sample sizes, did suggest a small but significant increased risk of cancer with abatacept (pooled relative risk 1.13, 95% confidence interval 1.02 to 1.24), but no increased risk observed for rituximab or tocilizumab, compared with csDMARDs or anti-TNF.<sup>85</sup> The clinical significance of this small but increased risk observed with abatacept is unknown, and should be validated in further populations.

#### *Safety of tsDMARDs*

Janus kinase inhibitors (JAKi) (the first class of tsDMARDs) are the most recent DMARDs to be approved for rheumatoid arthritis, and knowledge of their safety is evolving. In 2022, the results of a large safety trial of the JAKi tofacitinib versus anti-TNF (adalimumab and etanercept) were published.<sup>86</sup> The ORAL Surveillance trial was a postmarketing non-inferiority safety trial mandated by the FDA following observations of higher-than-expected rates of major adverse cardiovascular events (MACE), malignancy and infection in the tofacitinib clinical trial program (albeit largely among those receiving tofacitinib 10 mg twice daily, twice the licensed dose for rheumatoid arthritis). Patients aged  $\geq 50$  years receiving background methotrexate and with at least one cardiovascular risk factor were recruited. The trial randomized 4362 patients in a ratio of 1:1:1 to tofacitinib 5 mg twice daily (current licensed dose for rheumatoid arthritis), tofacitinib 10 mg twice daily, or anti-TNF (either adalimumab (US) or etanercept (rest of world)). Two primary co-endpoints were included: MACE (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) and cancer (excluding non-melanoma skin cancer). Other key trial endpoints included serious infections, opportunistic infections, including herpes zoster, and venous thromboembolism. Non-inferiority of tofacitinib would be shown if the upper limit of the 95% confidence interval of the hazard ratio for the comparison between combined tofacitinib doses versus anti-TNF did not exceed 1.8 for the primary endpoints.



During a median of four years of follow-up, the trial failed to show that tofacitinib was not worse (not non-inferior) than anti-TNF with respect to both primary endpoints (MACE and malignancy). More endpoints were observed in the combined tofacitinib group (MACE n=98 (3.4%); malignancy n=122 (4.2%)) than in the anti-TNF group (MACE n=37 (2.5%); malignancy n=42 (2.9%)). The hazard ratio for MACE was 1.33 (95% confidence interval 0.91 to 1.94) and the hazard ratio for malignancy was 1.45 (1.04 to 2.09); neither analysis showed non-inferiority of tofacitinib, and in the case of malignancy, superiority was shown (higher risk with tofacitinib). Tofacitinib also had higher rates of serious infections, herpes zoster infections, non-melanoma skin cancer, and venous thromboembolism than anti-TNF. The findings were relatively consistent across both doses of tofacitinib, although the rates of venous thromboembolism were higher with the higher dose of tofacitinib (5 mg twice daily 1.2%; 10 mg twice daily 2.3%; anti-TNF 0.7%). The number of patient years needed to harm for tofacitinib 5 mg twice daily (the current approved dose for rheumatoid arthritis) compared with anti-TNF was 567 years for MACE and 276 years for cancer.

Post hoc exploratory analyses of these data have also been published, and offer further insight.<sup>87-90</sup> The risk of MACE was substantially higher in those patients with a history of atherosclerotic cardiovascular disease (ASCVD) (14.7% of the trial population) than in those without. Patients receiving tofacitinib without a history of ASCVD history had rates of MACE, similar to anti-TNF.<sup>87</sup> A further analysis suggested that the risk of MACE and malignancy was increased with tofacitinib (compared with anti-TNF) in a high risk group of patients characterized as being aged >65 years or ever smokers. No difference was identified in risk of MACE or malignancy between tofacitinib and anti-TNF in low risk patients who were aged <65 and never smokers.<sup>88</sup> Herpes zoster infections were increased with both doses of tofacitinib compared with anti-TNF, although most cases were graded as mild to moderate (95%, 92.7%, and 96.6% for 5 mg tofacitinib, 10 mg tofacitinib, and anti-TNF, respectively) rather than severe.<sup>89</sup>

In the absence of a biological explanation for these findings, the trial has prompted much discussion and debate, particularly regarding whether these observations are a tofacitinib dose effect, a tofacitinib specific effect versus a class effect, or are limited to the enrolled subset of patients already at higher a priori risk for these outcomes. For example, observational datasets have not confirmed an increased risk of MACE with tofacitinib compared with anti-TNF,<sup>91-93</sup> albeit in a different population using a less robust study design. One challenge in understanding further the results of the ORAL Surveillance trial is that as it (appropriately) had no placebo arm, it showed a relative increase in rates of these events with JAKi compared with TNFi in this trial population (aged ≥50 years with at least one cardiovascular risk factor). It has been shown,

using observational data, that MACE events might be decreased in patients receiving anti-TNF (compared with csDMARDs).<sup>94</sup> Similarly, signals for increased malignancy with tofacitinib have not been observed in real world cohorts<sup>93 95</sup> or over longer follow-up in an integrated analysis of the clinical trial program.<sup>96</sup> That said, and while meta-analyses of trial data, including all four currently available JAKi, did not identify an increased venous thromboembolism risk (compared with placebo), a recent large analysis across 14 real world datasets has suggested a risk of venous thromboembolism with baricitinib,<sup>97</sup> as well as with the higher dose of tofacitinib. Until further data become available, regulatory warnings from the European Medicines Agency<sup>98</sup> and the FDA<sup>99</sup> restricting the drug to lower risk patients are now in place, and should be followed.

### The pharmacological approach in patients with rheumatoid arthritis

Evolving understanding of optimal treatment strategies, and the growing array of available drugs, inform a generally accepted approach for targeting remission in early rheumatoid arthritis. Although not always successful, this current pharmacological approach is summarized here.

#### Early disease

The aim of the treat-to-target approach is to achieve rapid and sustained suppression of inflammatory disease activity, preventing joint damage in a manner that is both acceptable to the patient and cost effective for the healthcare provider. To achieve this optimally, national and international treatment recommendations currently converge on the use of low dose methotrexate as an anchor drug, accompanied by (discretionary) use of “bridging”: short term glucocorticoids at the time of diagnosis (box 2).<sup>22 47 48</sup> The target is sustained remission (ideally), or low disease activity, using a composite measure of disease activity that incorporates tender and swollen joint counts.<sup>36</sup> While recognizing their strategic niche, these guidelines place emphasis on limiting the duration of glucocorticoid treatment to the bridging period (that is, for no longer than is commensurate with concomitant DMARD pharmacokinetics). A recent meta-analysis of clinical trials suggested that most patients can stop their glucocorticoids over this period.<sup>100</sup> The ideal frequency of regular disease activity assessments required to guide subsequent escalation decisions is suggested to range between monthly and trimonthly if inadequate disease control persists, falling to every six months or longer once the disease activity target achieved.<sup>36</sup>

Treatment intensification involving csDMARD or b/tsDMARD permutations will invariably be indicated where the prespecified target is not met, and questions regarding optimal first line drug and dose selection, and the virtues of a “step-down” combination drug approach, have accompanied the accumulation of available drugs in recent years. A

**Box 2: British, American, and European guidelines for pharmacological management of early rheumatoid arthritis<sup>22 47 48 172</sup>****UK National Institute for Health and Care Excellence (NICE), 2020**

Methotrexate, leflunomide, or sulfasalazine as first line treatment for patient newly diagnosed with rheumatoid arthritis.

Consider short term bridging treatment with glucocorticoids alongside initial csDMARD.

Offer additional csDMARDs (oral methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) in combination in a step-up strategy when the treatment target has not been achieved with first csDMARD.

In patients who do not reach their treatment target\* following  $\geq 2$  csDMARDs, b/tsDMARDs should be started.

**American College of Rheumatology, 2021**

Methotrexate as first line treatment for patient newly diagnosed with rheumatoid arthritis.

Initiation of a csDMARD without bridging glucocorticoid treatment is conditionally recommended.

In patients who do not reach their treatment target with methotrexate, b/tsDMARDs should be started.

**European Alliance of Associations for Rheumatology (EULAR), 2022**

Methotrexate as first line treatment for patient newly diagnosed with rheumatoid arthritis.

Consider short term bridging treatment with glucocorticoids alongside initial csDMARD.

In patients who do not reach their treatment target with methotrexate, bDMARDs should be started in those with poor prognostic factors. Janus kinase inhibitors can also be considered, but pertinent risk factors must be taken into account. In patients without poor prognostic factors, further csDMARDs should be considered.

\*Until recently, NICE stipulated that bDMARDs were reserved for patients with a DAS28-ESR  $>5.1$ , indicating high disease activity. In recent years, for many b/tsDMARDs, this threshold dropped to DAS28-ESR  $>3.2$ , indicating moderate disease.

meta-analysis of randomized trials identified no convincing advantage to the first line use of anti-TNF over csDMARD regarding long term radiographic damage, disability, or disease activity, assuming treat-to-target adherence.<sup>101</sup> The recent NORD-STAR trial further highlighted the efficacy and safety of active conventional treatment based on methotrexate combined with corticosteroids when compared with first line anti-TNF or anti-interleukin 6R; superiority of first line abatacept was suggested (9% increase in clinical remission rate at six months),<sup>43</sup> but this superiority was considered nominal given the non-inferiority of csDMARD in all other/secondary outcome domains, and should be balanced against cost.

Another area of debate has been whether initiating a combination of csDMARDs (usually a second csDMARD alongside methotrexate) at the time of diagnosis, as opposed to a primary escalation intervention, is beneficial. In this approach, other csDMARDs are added to or replace methotrexate over time, should initial treatment targets remain unmet. Objective evidence provides little support for an initial combination approach.<sup>102-104</sup> Treatment guidelines that allow discretionary consideration of combination csDMARD use ahead of b/tsDMARD initiation nonetheless reflect real world constraints. For example, failure of two csDMARDs is required ahead of b/tsDMARD consideration in the UK.<sup>22</sup>

All guidelines agree that where csDMARDs are ineffective or not tolerated, all patients should be escalated as soon as possible to b/tsDMARDs (where safe). Currently, which b/tsDMARDs should be used in which individual patients is unknown, as is the

order, given the observations of very similar efficacy overall. These decisions are often, therefore, a careful balance of efficacy with safety and cost.

**Difficult to treat rheumatoid arthritis**

Recently, EULAR has proposed a definition of difficult-to-treat rheumatoid arthritis (box 3), recognizing that a significant proportion of patients still fail to attain an adequate treatment target following initiation of csDMARDs and then b/tsDMARDs.<sup>105</sup> Most patients will be offered subsequent b/tsDMARDs on inadequate response to their first but, for some, disease remission remains elusive. A 2022 UK study describing patients who had received up to 10 sequential b/tsDMARDs illustrates this point.<sup>106</sup> Although the full definition of the EULAR difficult-to-treat definition is difficult to apply to existing research databases, a UK publication including 13 502 patients starting their first anti-TNF treatment found that 29% went on to receive two different classes of bDMARDs, and 6% received three different classes.<sup>107</sup> The reasons patients had received multiple treatments were multifactorial, and included serial non-response, serial adverse events, or a combination of the two.

As with the choice of first b/tsDMARD for patients with inadequate response to methotrexate, no evidence based strategy for selecting subsequent lines of b/tsDMARD exists. Evidence indicates that for some patients, particularly those who do not respond to a first anti-TNF treatment, switching to an alternative class of bDMARD is preferable to cycling through alternative anti-TNF agents, with many studies comparing rituximab with a second anti-TNF.<sup>108 109</sup> This advantage was more pronounced

**Box 3: European Alliance of Associations for Rheumatology (EULAR) definition of difficult to treat rheumatoid arthritis<sup>106</sup>**

- Treatment according to EULAR recommendation and failure of  $\geq 2$  b/tsDMARDs (with different mechanisms of action)\* after failing csDMARD treatment (unless contraindicated).†
- Signs suggestive of active/progressive disease, defined as  $\geq 1$  of:
  - At least moderate disease activity (according to validated composite measures including joint counts; eg, DAS28-ESR  $>3.2$  or CDAI (Clinical Disease Activity Index)  $>10$ ).
  - Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
  - Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
  - Rapid radiographic progression (with or without signs of active disease).
  - Well controlled disease according to above standards, but still having rheumatoid arthritis symptoms that cause a reduction in quality of life.
- The management of signs and/or symptoms is perceived as problematic by the rheumatologist or the patient, or both.

All three criteria need to be present in difficult to treat rheumatoid arthritis.

\*Unless restricted by access to treatment owing to socioeconomic factors.

†If csDMARD treatment is contraindicated, failure of  $\geq 2$  b/tsDMARDs with different mechanisms of action is sufficient.

when patients stopped their first anti-TNF drug for ineffectiveness rather than an adverse event.

Potential reasons for the development of difficult-to-treat rheumatoid arthritis are poorly understood. At one level, the clinical composites used to define the adequacy of treatment responses, such as the DAS28-ESR, might be questioned: their reliance on subjective components (patient visual analog scale, joint tenderness) could in some cases lead to inappropriate DMARD escalation in patients with non-inflammatory or complex pain or fatigue.<sup>110</sup> On the other hand, the direct pharmacodynamic effect of anti-interleukin 6R and JAKi on C reactive protein might flatter the efficacy of these agents in some patients despite persistent disease activity,<sup>111</sup> leading to a failure to identify difficult-to-treat disease when present.

In all patients, as per the EULAR 2022 guidelines on the management of difficult-to-treat rheumatoid arthritis,<sup>112</sup> the first step should be to reconfirm the diagnosis of rheumatoid arthritis. Assuming the diagnosis is correct, sociodemographic factors (eg, smoking, obesity) and adherence to drug treatment can also influence response,<sup>113</sup> and these potentially modifiable factors should be investigated. Comorbidity can limit the choice or tolerability of DMARDs for some patients owing to relative contraindications, an increased risk of serious infections, or other chronic health problems. For example, symptomatic interstitial lung disease, seen in approximately 10% of patients, poses particular challenges with respect to b/tsDMARD choice, owing to concerns about the safety of anti-TNF treatments in this patient subgroup.<sup>114</sup> Some guidelines (eg, British) suggest rituximab or abatacept as preferred treatment options in these patients.<sup>115</sup> Finally, immunogenicity and subtherapeutic serum drug concentrations appear to drive secondary loss of bDMARD response for some patients. Measurement of trough drug and antidrug antibody monitoring to

guide decisions around dose titration and therapeutic switches are starting to be explored.<sup>24-26</sup>

Currently, and in the absence of a robust biologic and holistic understanding of difficult-to-treat rheumatoid arthritis, risk factor modification, prompt intervention, and judicious use of targeted treatment are considered the best means to avoid its development.

### New concepts and controversies

In light of transformed treatment strategies hitherto discussed, remarkable strides in outcomes have been achieved for people with rheumatoid arthritis. Illustrative of this improvement, and coincident with the advent of both treat-to-target and bDMARD availability, observational data identify a sharp increase in the proportion of patients in clinical remission between 2004 and 2015, from 6% to 32%.<sup>116</sup> Indeed, clinical remission (DAS28-ESR  $<2.6$ ) has become a readily achievable treatment outcome for well over 50% of patients within six months of their initial diagnosis, according to recent UK National Audit data.<sup>102 117</sup> Such metrics, however, mask ongoing uncertainties and considerable unmet need. Many patients do not experience disease control sufficient to prevent progressive joint damage, while for others, doing so comes at the cost of unacceptable side effects; and all patients are affected by the burden of frequent hospital visits and safety monitoring. Moreover, patients with rheumatoid arthritis who are seronegative for ACPA and rheumatoid factor autoantibody, long considered a subset with good prognosis, have not been subject to the same improvements in long term outcomes as their seropositive counterparts is increasingly apparent, likely reflecting divergent etiologies and a need for deeper pathophysiological understanding.<sup>118 119</sup> Overall, the need to optimize and innovate rheumatoid arthritis management in the coming years demands consideration of a range

of emerging concepts considered here (see also questions for future research).

#### Refining the treatment target and the role of imaging

The presence of damaging subclinical inflammation cannot necessarily be excluded even when clinical remission has been determined. Radiographic evidence of synovitis is readily identifiable in at least half of such individuals undergoing musculoskeletal ultrasound or MRI (magnetic resonance imaging),<sup>120 121</sup> with progressive bone damage observed in a substantial minority.<sup>122</sup> Evaluating the role of musculoskeletal ultrasound as part of a strategy targeting imaging remission, two recent clinical trials failed to confirm a benefit over standard treat-to-target approaches, including in terms of radiographic progression over up to two years,<sup>123 124</sup> and analogous findings were reported in respect of MRI.<sup>125</sup> Further work could yet carve out a niche for these modalities as adjunctive tools for targeting remission in clinical practice,<sup>126 127</sup> and imaging can also prevent treatment escalation among patients confirmed to lack synovitis, despite subjective disease activity.<sup>128</sup>

#### Personalizing treatment decisions using biomarkers

The heterogeneity of rheumatoid arthritis extends from its complex genetics and synovial pathobiology, through clinical presentation to treatment responsiveness. As patient tailored, targeted treatments become increasingly established in oncology, equivalent advances in precision medicine for rheumatoid arthritis (as with other IMiDs) lag behind, with no biomarkers yet ready for use in the clinical setting.<sup>129</sup> Efforts to improve on trial-and-error treatment selection by defining robust endotypes for which individual drugs will be most effective are therefore intense, with considerable resources focused on stratifying newly diagnosed patients according to their subsequent response to methotrexate.<sup>130</sup> On the premise that endotypes could themselves be more evident at the level of synovial pathobiology, increased availability of synovial tissue from well characterized patient cohorts has illuminated this field, aided by the development of safe, minimally invasive synovial biopsy approaches guided by musculoskeletal ultrasound.<sup>132</sup> For example, a study of a large, observational inflammatory arthritis inception cohort identified a poor prognosis gene signature from synovium at baseline, which was linked to the presence of lymphoid rich infiltrates and a need for bDMARD treatment after 12 months of follow-up.<sup>131</sup> In a separate, stratified, biopsy driven randomized trial of rituximab versus tocilizumab among patients with rheumatoid arthritis with an inadequate response to anti-TNF, a gene signature developed to identify B cell poor synovial tissue was predictive of a favorable outcome with tocilizumab (63% clinical response *v* 36% among rituximab recipients; *p*=0.035).<sup>132</sup>

Musculoskeletal ultrasound guided synovial biopsy is currently a research procedure. Whether or not synovial tissue analysis becomes routine care in the future, we hope that such efforts will ultimately yield tractable stratification tools for the clinic from peripheral blood, which have thus far remained elusive. Studies have often been restricted by size and replication challenges, but recent data from the UK Rheumatoid Arthritis Methotrexate Study (RAMS) initiative seem to emphasize the predictive value of short term methotrexate induced perturbations in molecular readouts (determined through measurements before and shortly after drug initiation) over single, pretreatment snapshot assays as efficacy biomarkers.<sup>133-135</sup> As technology applications become cheaper and more reliable, improved biomarkers of disease, remission, and response to individual treatments should emerge perhaps as a liquid biopsy stratification tool for this and later phases in the natural history of rheumatoid arthritis.<sup>136</sup> Such tools, robustly validated for clinical application, have yet to be developed.

#### Tapering and drug free remission

How should rheumatoid arthritis be managed once remission has been achieved and sustained over time? The question is far from hypothetical. Drug free remission has become a reality for a minority of patients—up to 23% of those who stop treatment according to one recent meta-analysis of studies in which patients on bDMARDs were predominantly included—with as much as double this rate observed in cohorts limited to patients stopping csDMARDs only, and flares increasingly unlikely beyond one year from cessation.<sup>137-139</sup> Incomplete tapering could be preferable for some patients in stable remission; among those on csDMARDs it did not incur significant risk of flare,<sup>140</sup> with flare rates lower among targeted treatment recipients.<sup>141</sup> Whether preferential discontinuation of conventional versus targeted DMARDs is safer for people taking combinations remains unknown.<sup>142 143</sup> All these considerations raise important risk-benefit questions, in which the advantages of remission must be balanced against the side effects, risks, and costs of indefinite therapeutic intervention. Expert consensus on whether, when, and how DMARDs should be tapered or discontinued in people with stably controlled disease has only recently begun to emerge<sup>137</sup>; the consensus will be informed by ongoing work in a fast moving field to identify clinical and biomolecular predictors of successful drug cessation. Thus far, an absence of circulating autoantibodies, a shorter disease duration, a more stringent definition of remission (with a possible role for imaging<sup>144 145</sup>), and male sex have emerged as favorable factors from a range of studies, which are not always consistent in their findings.<sup>138 139 146</sup> Most studies have found that a state of remission can be regained promptly after reversion to pre-flare DMARD dose(s), where tapering or withdrawal proves unsuccessful.



### Can rheumatoid arthritis be prevented?

Environmental factors including smoking, dietary, and microbial exposures together provoke a phase of autoimmunity characterized by ACPA formation many years before clinically overt joint inflammation occurs.<sup>147</sup> The fact that symptomatic individuals on this pathway are identifiably at risk of rheumatoid arthritis development in the absence of objective inflammation,<sup>148</sup> has fueled interest in studies seeking to intercept the disease. Several placebo controlled interventional trials have aimed to delay or even prevent the onset of rheumatoid arthritis, using agents including hydroxychloroquine, rituximab, and abatacept.<sup>149-154</sup> An early example, the PRAIRI study, appraised rituximab versus placebo in arthritis free people with a range of musculoskeletal symptoms, who were seropositive for both ACPA and rheumatoid factor, and had detectable C reactive protein on laboratory testing; the intervention appeared to delay disease onset by approximately 12 months but did not prevent rheumatoid arthritis.<sup>151</sup> Meanwhile, the recently reported TREAT-EARLIER study found that methotrexate plus an intramuscular steroid bolus improved MRI appearances of inflammation and patient reported outcomes versus placebo, in arthritis free patients with clinically suspect arthralgia who had MRI evidence of joint inflammation—77% of whom were ACPA seronegative—but did not prevent progression to rheumatoid arthritis.<sup>149</sup> While encouraging, these studies illustrate the challenges to be tackled by future research. Firstly, heterogeneous and overlapping enrolment criteria that map to differential a priori rheumatoid arthritis progression risk are challenging to interpret, particularly in respect of comparisons between interventions. Secondly, a lack of consensus in determining primary endpoints and limited or varying follow-up presents difficulties. Finally, as interest in the field accelerates, the logistical challenges of identifying sufficient people at risk of rheumatoid arthritis, naive to immunomodulation, for enrolment into potentially competing studies, is only likely to increase. A coordinated strategy, such as that published by a recent EULAR taskforce,<sup>155</sup> is needed to overcome these challenges and accelerate progress towards preventing rheumatoid arthritis.

### Emerging treatments

Evolving pathobiological insights continue to fuel drug development for rheumatoid arthritis. For example, enhanced surface expression of the co-inhibitory immune checkpoint receptor programmed cell death protein 1 (PD1) on infiltrating synovial T cells is thought to reflect accumulation of so called peripheral T helper cells, in turn supporting tertiary lymphoid structure development and autoantibody production. Ligation of PD1 can suppress lymphocyte activation, whereas blockade of PD1 signaling in cancer patients can lead to the development of inflammatory arthritis.<sup>156</sup> These observations provided rationale for a promising phase 2 trial of

PD1 agonism for rheumatoid arthritis<sup>157</sup>; this and other development programs are ongoing.

Agents that target alternative co-stimulatory components of the immune checkpoint system such as CD40/CD40L signaling or inducible co-stimulator ligand, are also in development.<sup>142 201</sup> Aside from mitigating unwanted T cell activation, approaches to bolster the number and/or function of regulatory T cells (Tregs) have also been proposed. In particular, administration of low dose recombinant interleukin 2 over six months has been shown to expand and activate Tregs (but not effector T cells) across a range of IMIDs, including rheumatoid arthritis, without raising safety concerns.<sup>158</sup>

The importance of stromal cells as mediators of organ specific pathology is increasingly recognized; stromal cells mediate fibrosis, inflammation, and immune cell accumulation. As such, these cells represent potentially attractive and common cellular targets for the treatment of IMIDs, especially rheumatoid arthritis, where synovial fibroblasts have long been understood to adopt a hyperproliferative and invasive phenotype.<sup>159</sup> Efforts to target the synovial fibroblast in rheumatoid arthritis remain in their infancy, recently exemplified by the deployment of a cyclin dependent kinases for difficult-to-treat disease.<sup>160</sup>

Finally, the potential for advanced and cellular treatments to restore immune tolerance in rheumatoid arthritis underpins active research programs. For example, administration of autologous antigen presenting cells manipulated ex vivo to suppress immunogenicity has shown promise in early trials.<sup>161 162</sup>

### Guidelines

The treatment of rheumatoid arthritis covers a broad range of considerations, from management of early disease, choice of treatment, including advanced treatments, and management of difficult-to-treat disease. For the most part, clinicians are supported by evidence based treatment guidelines when considering these aspects, many of which have been discussed in this review; they are summarized here for quick reference:

Management of early and established rheumatoid arthritis, including choice of treatment (box 2)<sup>22 47 48</sup>

Management of difficult-to-treat rheumatoid arthritis<sup>112</sup>

Screening and prophylaxis of chronic and opportunistic infections.<sup>78 163</sup>

Although not a focus of this review, the equally important role of allied health professionals and patient self-management in the treatment of rheumatoid arthritis is recognized, and the reader is also referred to recent reviews and guidelines on these topics for further information.<sup>164-167</sup>

### Conclusion

A person diagnosed with rheumatoid arthritis today can expect a radically different journey compared with what would have been expected just a few decades



### QUESTIONS FOR FUTURE RESEARCH

- **Disease prevention:** Which non-pharmacological and/or pharmacological interventions should be deployed, and for how long, during various preclinical phases to prevent rheumatoid arthritis in people at risk of developing the disease?
- **Imaging:** What role should musculoskeletal ultrasound and magnetic resonance imaging play in guiding real world management decisions for people with rheumatoid arthritis?
- **Personalized medicine:** To what extent can molecular or cellular biomarkers in synovial biopsies and/or peripheral blood help guide the selection of treatments of maximal efficacy for individual patients, to optimize outcomes in rheumatoid arthritis?
- **Drug free remission:** When should drugs be stopped in patients with rheumatoid arthritis experiencing sustained disease remission, and when should they be re-initiated to prevent flares?

ago. The expectation of effective disease control and prevention of joint damage and disability is now the norm, driven by an ever expanding repertoire of targeted treatments and the understanding that early and aggressive disease control improves long term outcomes. Now, the focus of attention is on how best to employ these treatments to achieve the most cost effective control of the disease process, considering patient factors and comorbidities to reduce the still important proportion of patients who have difficult-to-treat rheumatoid arthritis and progressive disability, despite recent developments. Nonetheless, continued advances in treatment offer hope in this regard, with the once aspirational goals of disease prevention and sustained drug free remission becoming a reality for a minority of individuals.

**Contributors:** All authors participated in the literature search, reviewing the literature, as well as conception, drafting, and revising the manuscript. All authors accept full responsibility for the work, had access to the data, and controlled the decision to publish. All authors are the guarantors. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

**Funding:** No specific grant for preparing and writing this review was received from any funding agency in the public, commercial, or not-for-profit sector. KLH and AGP are supported by the National Institute for Health and Care Research Biomedical Research Centres at Manchester and Newcastle, respectively. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

**Competing interests:** KLH has received honorariums from Abbvie for speaking at educational meetings, and grant funding from Pfizer and BMS. AGP is in receipt of grant funding from Pfizer, Gilead, and GSK.

**Provenance and peer review:** Commissioned; externally peer reviewed.

**Patient involvement:** No patient or public involvement was included in the writing of this review article.

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