

# Biologics-Based Therapy for the Treatment of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) remains a major clinical problem, but treatments involving biologics have revolutionized its management. They target pathogenically relevant cytokines such as tumor necrosis factor and immune cells such as B cells. In RA, biologics reduce joint inflammation, limit erosive damage, decrease disability, and improve quality of life. Infections are the main risk associated with their use. Because of the high prices of biologics, their cost-effectiveness is a matter of debate. They are mainly coadministered with disease-modifying drugs such as methotrexate when the latter are found to achieve insufficient disease control on their own.

## CLINICAL RATIONALE FOR USING BIOLOGICS

### Clinical picture

Rheumatoid arthritis (RA) is an immunologically driven long-term condition.<sup>1</sup> It is characterized by persistent joint inflammation (synovitis), systemic inflammation, and autoantibodies, particularly the rheumatoid factors anticyclic citrullinated peptide antibodies. Ongoing joint inflammation damages cartilage, bone, and tendons. Ongoing systemic inflammation causes extra-articular complications such as lung disease. Uncontrolled active RA causes disability, decreases quality of life, and increases comorbidity, notably cardiovascular disease. These in turn result in loss of work, high medical and social costs, and substantial morbidity and mortality. The impact of RA on patients justifies treatment with high-cost biologics.

RA is not a single disease. It is probably the final common pathway for several related pathologic processes. It is therefore unlikely to be cured by one management strategy. Instead, individualized, “bespoke” approaches are needed.

### Epidemiology and costs

In industrialized countries, RA affects 0.5–1% of adults. Its incidence and prevalence are higher in women than in men, and in older adults than in younger ones.<sup>2,3</sup> Its incidence varies across populations, with 5–50 per 100,000 adults developing RA annually.<sup>4</sup> Estimates by the National Audit Office for England, which is taken to reflect the situation in other industrialized countries, suggest that there are 580,000 English adults with RA and that 26,000 new diagnoses of RA are made annually.<sup>5</sup>

The management of RA dominates specialist rheumatology services. Inflammatory arthritis, mainly RA, constitutes 10–20% of new referrals and 40–60% of follow-up visits. English Hospital

Episode Statistics data for 2009–2010 showed 1,200,000 rheumatology outpatient follow-ups, of which ~600,000 were likely to be for RA. It also involves substantial primary care workloads, including lifestyle advice such as smoking cessation, disease and drug monitoring, management of comorbidities, vaccination, and initial management of flares.

The financial impact of RA is substantial for health-care systems and national economies. The National Audit Office estimated that direct health service costs in England are £560 million/year and work-related disability costs add an additional £1,800 million/year.<sup>5</sup> Most of these costs are attributable to patients with high disability levels. As a result, there is a strong societal case for using high-cost biologic treatments, provided they have sufficient impact on changing the course of RA.

## CLINICAL ASSESSMENTS

There are several ways to assess the impact of biologic treatments and other interventions in RA. These include overall impacts on RA using combined indexes, core clinical measures, erosive damage, and quality of life. All are equally important in assessing treatment outcomes.

### Combined indexes

Combined indexes amalgamate individual assessments.<sup>6</sup> They are widely used in clinical trials and observational studies. Clinical trials have focused on the American College of Rheumatology (ACR) criteria with respect to improvement or response.<sup>6</sup> These reflect changes in status in clinical trials, including reductions in joint counts and several other assessments: patient's global, physician's global, erythrocyte sedimentation rate, pain, and health assessment questionnaire (HAQ). The ACR criteria

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are designed to record 20% (ACR20), 50% (ACR50), and 70% (ACR 70) improvement in five of the seven measures.

An alternative approach, which is used in trials as well as in routine clinical practice, is to use the Disease Activity Score–28 (DAS28). This index combines 28 swollen and 28 tender joints (hands, arms, and knees), patient's global assessment, and erythrocyte sedimentation rate. DAS28 reflects a patient's current status.<sup>6</sup> DAS28 scores range from 1 to 9. High scores indicate more active disease. DAS28 scores of 5.1 or more define active RA. Scores of 3.2 or less indicate low disease activity.

Calculating DAS28 involves applying a complex mathematical formula, and simplified variants have therefore been devised. The Simplified Disease Activity Index uses 28 tender and swollen joint counts, physician's and patient's global assessments, and C-reactive protein (CRP). The Clinical Disease Activity Index is similar but omits CRP.<sup>7</sup>

Combined indexes need careful interpretation because high scores may reflect active arthritis or high pain levels. There are also theoretical concerns about combining dissimilar measures in a single index.<sup>8</sup>

#### Core measures

These involve assessments by clinicians, self-assessments by patients, and laboratory tests.<sup>9</sup> Physician-based assessments comprise swollen and tender joint counts and global estimations of activity. Standard joint counts focus on 28 joints in the hands, upper limbs, and knees. Because these omit joints in the feet, some experts recommend extended 66- and 68-joint counts that include the feet. Laboratory measures include erythrocyte sedimentation rate and/or CRP. Patient-based measures evaluate pain, global assessment, and disability. The HAQ measures disability. Patients record other relevant factors such as fatigue and depression. Patient measures are particularly important because they measure the patient's perspective on the burden of RA.

#### Erosive damage

Juxta-articular erosions characterize progressive, established RA and are usually irreversible. They are most readily detected in X-rays of the hands and feet. Extensive erosive and other radiological damage suggests the presence of inadequately controlled RA. Rapid progression of joint damage requires intensive treatment. Several radiological scoring systems record the extent of damage seen on X-rays. The scoring systems of Larsen and of Sharp, both of which have been substantially modified, are widely used.<sup>10</sup>

Several advanced imaging modalities are used to assess RA. These include ultrasound and magnetic resonance imaging (MRI). Both can assess irreversible and reversible structural changes.<sup>11</sup> Although they are widely used in research, they are associated with marked interobserver variability. This has limited their value in both routine practice and clinical trials.

#### Quality of life

The assessment of disability using HAQ is widely used as an indicator of the ways in which RA reduces quality of life. A number of more formal patient-derived measures are used to assess quality of life.<sup>12</sup> These include the Medical Outcomes Study short

form 36 (SF-36) and the EuroQol. Although these are relevant and reproducible assessments in RA, they are not reported in most clinical trials, and, unlike HAQ, they are rarely used in routine clinical practice. Their value is therefore limited.

## CONVENTIONAL MANAGEMENT

### Overall

New therapies such as biologics need to be placed within the context of current conventional RA management. High-quality care is best delivered by multidisciplinary teams including rheumatologists, specialist nurses, and a range of therapists.<sup>13</sup> In addition to optimizing drug treatment, it must provide the patient with education, particularly self-management skills, psychological support, and advice on exercise and joint protection. Surgical intervention is needed when joints fail.

Historically, symptom reduction using nonsteroidal anti-inflammatory drugs and analgesics dominated RA management. Over the past two decades, the emphasis has shifted toward controlling RA using disease-modifying antirheumatic drugs (DMARDs). These drugs reduce synovitis, systemic inflammation, and disability.<sup>14</sup> Methotrexate is the dominant DMARD. Others include sulfasalazine and leflunomide. They are introduced as soon as possible after diagnosis in patients with active RA. They are often used in combination to maximize their efficacy. The use of DMARDs is limited by associated adverse events, ranging from symptoms of minor intolerance such as nausea to serious blood and liver toxicity.

Steroids (glucocorticoids) can be used in the short term to reduce joint inflammation. They can also be used in DMARD combination regimens to reduce joint erosion and to treat systemic disease. Their long-term use, particularly at high dosage, is limited by concerns about their toxicity.

### Treating to target and remission

A substantial and growing body of research shows that RA outcomes are improved by adopting management strategies in which patients are treated to achieve predefined targets. There is also growing recognition that the most appropriate target is remission.<sup>15</sup> There is evidence that patients with RA who achieve sustained remission have less disability, less erosive joint damage, and a better quality of life.

RA remission can be defined in several ways.<sup>16</sup> DAS28 scores of 2.6 or less are often used as surrogate indicators of remission. However, more stringent definitions are increasingly being preferred, although achieving them may be very challenging.

## BIOLOGICS FOR RA

### Background

The introduction of biologics has revolutionized RA treatment. Their success has underlined the key roles of inflammatory cytokines in the pathogenesis of inflammatory arthritis, particularly tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin (IL) 1 and 6. They have also refocused attention on T cells and B cells.<sup>17–20</sup>

Conventional drugs such as DMARDs are capable of inhibiting only small molecules. However, cytokines are large peptides.

They can be inhibited only by large molecules. The biologics that inhibit cytokines are proteins based on immunoglobulins. Although it may be possible to replace biologics with small molecules that inhibit intracellular targets of the cytokines, this has not been achieved. Such an approach may also be irrelevant if new biotechnologic approaches permanently change the way we treat inflammation.

The biologics used in inflammatory arthritis are genetically engineered proteins derived from human genes. They mainly inhibit specific components of the immune system that play pivotal roles in driving or inhibiting inflammation in arthritis. Unlike conventional drugs that modify the immune system as a whole, biologics affect specific components of the immune system. Theoretically, this targeted approach is both more specific in its effects and less likely to cause adverse events.

The complex interactions of cytokines and the multiplicity of cytokine targets make it difficult to predict the effectiveness and toxicity of cytokine-based interventions and other biologics. Several strategies have been explored to treat inflammatory diseases involving cytokines. These include neutralizing cytokines by using soluble receptors or monoclonal antibodies, receptor blockade, and activation of anti-inflammatory pathways by bioengineered versions of immunoregulatory cytokines.

There are currently five classes of biologics available for the treatment of inflammatory arthritis, each inhibiting a different aspect of the immune-driven inflammatory pathway:

- TNF inhibitors, five biologics currently available
- Interleukin-1 receptor antagonists, one biologic currently available
- B-cell inhibition, one biologic currently available
- T-cell costimulation inhibition, one biologic currently available
- Interleukin-6 inhibition, one biologic currently available

Anakinra, an interleukin-1 receptor antagonist, was developed for use in RA and had some efficacy in early trials. However, its relative effectiveness has been limited and it is now rarely used in RA, although it is effective in other disorders, particularly auto-inflammatory diseases.<sup>21</sup> We do not consider anakinra further in this review. The other four key biologics used in RA are summarized in **Table 1**. Their relationship to key pathogenic aspects of RA is summarized in **Figure 1**.

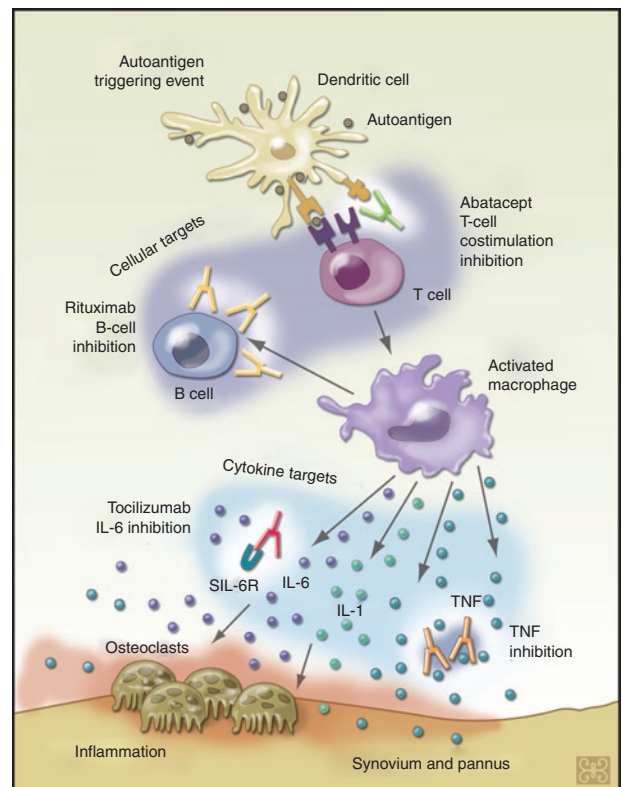
**The biological revolution**

There are three reasons, apart from observed clinical experience, to suggest that the advent of biologics has brought about a revolutionary change in RA care. First, the main clinical trials have created widespread interest, with the key trials often attracting more than 1,000 citations.<sup>22,23</sup> Second, biologics are generating very large revenues. Three of them are among the 10 leading international “best sellers” based on pharmaceutical revenue data, reflecting their high prices as well as their widespread use. Although drug costs are driven by many factors, widespread use of high-cost treatments indicates that a new treatment paradigm has developed. Third, the clinician scientists

**Table 1 Main biologics used in rheumatoid arthritis**

Biologic type	Agent	Mechanism of action
TNF inhibitors	Adalimumab	Recombinant human IgG1 monoclonal antibody
	Etanercept	Soluble TNF-receptor fusion protein
	Infliximab	Chimeric IgG1 anti-TNF- $\alpha$ antibody
	Certolizumab	Recombinant humanized Fab' fragment of a TNF-antibody coupled to polyethylene glycol
	Golimumab	Recombinant human IgG1 monoclonal antibody specific for TNF- $\alpha$
Interleukin-6 inhibitor	Tocilizumab	Recombinant humanized antihuman interleukin-6 receptor monoclonal antibody of the IgG1 subclass
B-cell inhibitor	Rituximab	Chimeric monoclonal antibody targeting cells bearing CD20 surface marker
T-cell costimulation inhibitor	Abatacept	Immunoglobulin fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4

IgG1, immunoglobulin G subclass 1; TNF, tumor necrosis factor.



**Figure 1** The relationship of biological treatments to the pathogenic aspects of rheumatoid arthritis. IL, interleukin; SIL, soluble interleukin; TNF, tumor necrosis factor.

whose research was crucial to the introduction of biologics in clinical practice have received many national and international awards. Although such awards reflect subjective assessments, they indicate major changes in practice.

Clinical revolutions, like other forms of revolutionary change, are often unstable and might not persist. The factors driving the use of biologics in RA are complex. The rationale for their

widespread use has strengths and weaknesses. Although the rise of biologics in RA has been driven by the strengths of these compounds, if their weaknesses cause concerns, the biologics revolution will cease.

### Tumor necrosis factor inhibitors

There are currently five TNF inhibitors available for the treatment of RA.<sup>24</sup> These can be classified as first-generation agents (etanercept, infliximab, and adalimumab) and second-generation agents (certolizumab and golimumab). All five TNF inhibitors are approved for use in routine clinical care.

**Infliximab.** Infliximab is a chimeric immunoglobulin 1 (IgG1) anti-TNF- $\alpha$  antibody with the antigen-binding region derived from a mouse antibody and the constant region from a human antibody. It binds to soluble and membrane-bound TNF- $\alpha$  with high affinity, thereby impairing the binding of TNF- $\alpha$  to its receptor. Infliximab also kills cells that express TNF- $\alpha$ , through antibody-dependent and complement-dependent cytotoxicity. There are considerable interpatient differences in the pharmacokinetics of infliximab. Trough concentrations, seen at 8 weeks after intravenous administration of 3 mg/kg of infliximab, vary considerably among patients. For increasing the trough levels, shortening the interval between doses may be more effective than increasing the dose. Most patients show response to a dose of 3 mg/kg once every 8 weeks. Some patients need higher doses or shorter intervals between doses.<sup>25</sup>

**Etanercept.** Etanercept is a soluble TNF-receptor fusion protein. It has two dimers, each with an extracellular, ligand-binding portion of the higher-affinity type 2 TNF-receptor (p75) linked to the Fc portion of human IgG1. This fusion protein binds to both TNF- $\alpha$  and TNF- $\beta$ . It prevents them from interacting with their receptors. Etanercept is administered as a subcutaneous injection of 25 mg twice a week or 50 mg once a week. These dosages are based on its half-life, which is ~4 days.

**Adalimumab.** This is a recombinant human IgG1 monoclonal antibody. It binds to human TNF- $\alpha$  with high affinity and, as a consequence, it inhibits the cytokine from binding to its receptors. It also lyses cells that express TNF- $\alpha$  on their surface. It is administered by subcutaneous injection and is absorbed slowly. Although there are wide variations in the pharmacokinetics of this biologic among patients, it is generally administered once every 2 weeks.

**Certolizumab.** Certolizumab pegol is a recombinant humanized Fab' fragment (the antigen-binding domain) of a TNF-antibody coupled to an ~40 kDa polyethylene glycol to enhance its plasma half-life to ~2 weeks. It binds and neutralizes membrane-bound and soluble human TNF- $\alpha$ . In contrast to the other TNF inhibitors, it lacks an Fc region. It is given by subcutaneous injection, with 80% bioavailability. It has an initial loading dose of 400 mg every 2 weeks for 6 weeks, followed by 200 mg every 2 weeks.

**Golimumab.** Golimumab is a human IgG1 monoclonal antibody specific for TNF- $\alpha$  and is produced in a transgenic mouse. It targets and neutralizes both soluble and membrane-bound TNF- $\alpha$ ; it has a half-life of 7–20 days. Golimumab is administered as a subcutaneous injection at an initial dose of 50 mg a month, to be increased to 100 mg a month if there is no response after 4 doses (provided the body weight of the patient is >100 kg).

### Interleukin-6 inhibition

IL-6 is an important pro-inflammatory cytokine in RA. It promotes inflammation through the expansion and activation of T cells, differentiation of B cells, and induction of acute-phase reactants by hepatocytes. IL-6 signal transduction is mediated by membrane-bound and soluble receptors. Currently, tocilizumab is the only available IL-6 inhibitor for the treatment of inflammatory arthritis. It is a recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1 subclass.<sup>26</sup> It binds to both membrane-bound and soluble IL-6 receptors, preventing their activation by IL-6.

### B-cell modulation

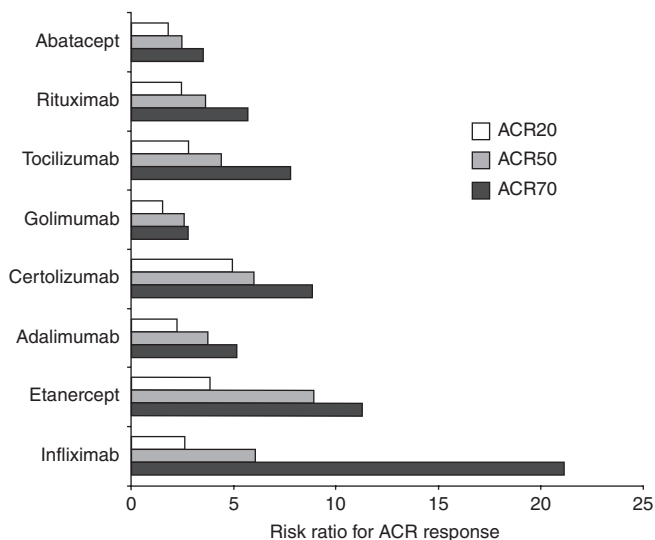
Rituximab is a genetically engineered chimeric monoclonal antibody. It depletes the B-cell population by targeting cells bearing the CD20 surface marker.<sup>27</sup> This binding interferes with the activation and differentiation of B cells. It was introduced for the treatment of lymphomas but was subsequently found to be effective in RA. The effect on B cells suggests that the prevailing view of RA as a predominantly T-cell-mediated disease is open to doubt.

The mechanism through which B-cell elimination improves RA is unclear. B cells may play several important roles in RA pathogenesis. First, they function as antigen-presenting cells, providing costimulatory signals for CD4-positive T-cell expansion and function. Second, synovial membrane B cells may produce pro-inflammatory cytokines and chemokines. Finally, synovial membrane B cells produce rheumatoid factor, which is associated with more aggressive articular disease.<sup>28</sup>

The efficacy of rituximab is superior in patients with RA who also have the rheumatoid factor (termed "seropositive" disease). Its clinical effects appear to be associated with rheumatoid factor levels; these levels fall when clinical responses are seen. Many experts are therefore of the opinion that rituximab exerts its effects in RA through reducing B-cell-driven autoantibody production alongside B-cell-related T-cell activation.

### T-cell modulation

T cells, in particular CD4-positive T cells, have well established roles in RA pathogenesis. Abatacept is a fusion protein constituting an immunoglobulin fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4. Cytotoxic T-lymphocyte antigen 4 is a molecule that binds with a high affinity to the CD80/86 ligand on antigen-presenting cells.<sup>29</sup> The abatacept molecule blocks the interaction between the antigen-presenting cell's CD80/86 ligand and the CD28 ligand on the T cell, which is necessary for T-cell activation. This results in decreases in T cell proliferation and in cytokine production. T-cell inhibition is a less focused form of immune modulating therapy than the use



**Figure 2** American College of Rheumatology (ACR) responses from Cochrane reviews of key clinical trials.<sup>30–39</sup>

of specific anticytokine agents. T-cell inhibition results in reduction of the cytokines TNF, IL-1, and IL-6. It also has implications for B-cell activation.

**OVERALL CLINICAL RESPONSES WITH BIOLOGICS**

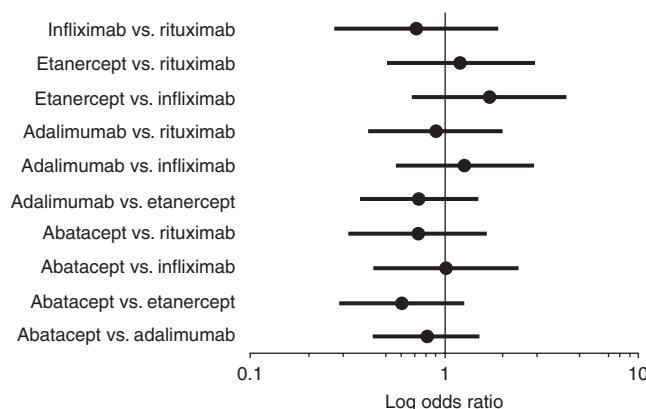
The initial trials of biologics in RA focused on patients with active disease which had failed to respond to methotrexate and other DMARDs. The trial results mainly reported ACR responses, although some also reported DAS responders and DAS remissions. Conventionally, biologics have been administered with methotrexate as a cotherapy, and therefore dissociating the specific effect of methotrexate in these trials is challenging. The overall clinical responses for each of these outcomes, collated from Cochrane and other systematic reviews,<sup>30–39</sup> are summarized in this section.

**ACR responses**

Six-month ACR responses pooled from 16 trials comparing a biological DMARD with placebo in combination with background methotrexate were evaluated in a meta-analysis by Nam *et al.*<sup>38</sup> They found that the overall relative risks of achieving ACR20, ACR50, and ACR70 responses at 6 months were 2.16 (95% confidence interval (CI): 1.83, 2.55), 3.20 (2.6, 3.95), and 4.82 (2.43, 9.57), respectively. They also considered an alternative assessment: the number needed to treat to achieve ACR20, ACR50, and ACR70 responses. These were calculated as 3.2, 4.2, and 7.7, respectively.

Comparative data from Cochrane reviews and other systematic reviews for individual biologics are shown in **Figure 2**. Risk ratios for biologics vary from 1.5 for ACR20 responses to 21 for ACR70 responses. On average, the risk ratios are in the region of 2 for an ACR20 response, 4 for ACR50, and 8 for ACR70.

There have been no head-to-head trials of the different biologics. The available clinical trials are not entirely comparable. They vary with respect to the duration of RA in the patients and the initial severity and activity of the disease. However, in an



**Figure 3** Comparative efficacy of different biologics from a Cochrane overview of systematic reviews.<sup>39</sup>

overview of Cochrane reviews, Singh *et al.*<sup>39</sup> devised a method to carry out indirect comparisons of biologics using a hierarchical generalized linear mixed model. This analysis took ACR50 responders as the key measure because it was reported in the majority of trials. Biologics were associated with a significantly higher likelihood of achieving an ACR50 response, as compared to placebo, with an overall odds ratio of 3.35 (95% CI: 2.62, 4.29), although there was substantial heterogeneity between trials. Indirect comparisons among five biologics showed no significant differences with respect to attainment of ACR50 (**Figure 3**).

**Changes in DAS**

Only a minority of trials have specifically reported changes in DAS scores; however, in general, these mirror ACR responder rates, with more patients showing DAS responses with biologics than with placebo therapy. DAS responders have been reported in more detail in observational studies. A systematic review by Lloyd *et al.*<sup>40</sup> reported that the weighted mean DAS28 responder rates were 70% (95% CI: 64, 77) in 10 studies.

**Remission**

Trials that report rates of remission focus mainly on DAS28 criteria. The early trials that evaluated biologics did not routinely report remission; only the more recent trials have included remission as one of the standard clinical outcomes. **Table 2** summarizes the risk of remission in 12 trials of four biologics. Overall, biologics were shown to increase the frequency of remission. Although the rate of remission was not significantly increased with abatacept at 6 months, there was a significant increase in remissions at 12 months (risk ratio 12.74; 95% CI: 4.76, 34.15). Nam *et al.*<sup>38</sup> evaluated DAS28 remission data from four trials (involving abatacept, certolizumab, golimumab, and rituximab) and calculated that the number required to be treated to achieve remission at 6 months was 9.1.

**Methotrexate coprescription**

Different systematic reviews provide varying perspectives on the value of coprescribing methotrexate. The overview of systematic reviews by Singh *et al.*<sup>39</sup> concluded that there was no evidence

**Table 2 Disease Activity Score (DAS28) remissions at 6 months**

Biologic	Trials	Remission risk ratio (95% CI)
Abatacept	2	2.50 (0.57, 11.03)
Certolizumab	2	3.88 (2.33, 6.45)
Golimumab	4	6.00 (1.52, 23.64)
Tocilizumab	4	11.85 (7.38, 19.02)

CI, confidence interval.

Data from Cochrane reviews (29–32).

to show that concomitant methotrexate treatment increased the probability of achieving ACR50 responses. They evaluated 20 studies that included concomitant methotrexate and 7 studies that did not. In all the studies, biologics increased the likelihood of achieving ACR50 responses as compared with placebo therapy. In trials involving concomitant methotrexate, the odds ratio for achieving ACR50 responses was 3.16 (95% CI: 2.40, 4.16) whereas in trials without concomitant methotrexate the odds ratio was 4.18 (95% CI: 2.48 to 7.06).

In contrast, Nam *et al.*<sup>38</sup> focused on trials in which patients were randomized to biologics alone or biologics in combination with methotrexate. Pooled data from three such trials yielded 12-month ACR20, ACR50, and ACR70 responses of 1.31 (95% CI: 1.05, 1.64), 1.49 (95% CI: 1.32, 1.68), and 1.77 (95% CI: 1.48, 2.12), respectively.

In addition, there is evidence that the coprescription of methotrexate with biologics improves persistence with the therapy regimen. Blum *et al.*<sup>41</sup> systematically evaluated persistence in 52 studies. Various continuation rates, which they grouped together as “persistence,” were reported, with continuation at 12 months varying from 32 to 91% across studies. Rates of persistence were generally higher when methotrexate or DMARDs were combined with biologics as part of the treatment regimen.

### THE USE OF BIOLOGICS IN SPECIFIC PATIENT GROUPS

All new treatments are initially used in patients who have failed to respond to conventional treatments. Any other approach would be unethical. Therefore, the initial trials of TNF inhibitors—the first biologics to be successfully studied in RA—were used in patients who had failed to respond to methotrexate and other DMARDs. Over time, these patients have been described as “methotrexate nonresponders.” However, there are two specific patient groups that have attracted clinical interest: patients with early RA who have not yet received methotrexate or other DMARDs and patients who have failed to respond to TNF inhibitors.

#### Early rheumatoid arthritis

Most of the data on the use of biologics in early RA is based on trials of TNF inhibitors given alongside methotrexate. These trials have been assessed in a systematic review and meta-analysis by Ma *et al.*<sup>42</sup> They identified eight such trials and showed that the combining of TNF inhibitors with methotrexate increased the rate of attainment of ACR20, ACR50, and ACR70 responses as compared to patients receiving methotrexate monotherapy. These results are summarized in **Table 3**. The odds ratios for ACR responders were all highly significant and were ~2.

**Table 3 ACR responders in trials of TNF inhibitors with methotrexate in early rheumatoid arthritis**

ACR responders	Trials	Odds ratio (95% CI)
ACR20	6	2.03 (1.63, 2.54)
ACR50	5	2.17 (1.78, 2.64)
ACR70	5	2.30 (1.89, 2.79)

ACR, American College of Rheumatology criteria; CI, confidence interval; TNF, tumor necrosis factor.

From ref. 38.

Nam *et al.*<sup>38</sup> systemically reviewed a broader range of biologics used in early RA. They identified randomized controlled trials (RCTs) pertaining to five biologics (abatacept, adalimumab, etanercept, golimumab, and infliximab) administered in combination with methotrexate. All these trials involved only methotrexate-naïve patients with early RA. Six-month ACR responses reported from a trial involving golimumab showed increases in the number of ACR20 and ACR50 responses (relative risks 1.25, 95% CI: 1.04, 1.49; and 1.31, 95% CI: 0.99–1.72, respectively). The pooled relative risks for 12-month ACR50 and ACR70 responses reported from trials of the other four biologics were 1.43 (95% CI: 1.30, 1.56) and 1.63 (95% CI: 1.45, 1.83). However, in two trials of biologic monotherapy there was no evidence that the outcomes were better than those of methotrexate monotherapy.

There are other approaches to evaluating the relevance of biologics in early RA. Yazici *et al.*<sup>43</sup> undertook a *post hoc* analysis of data from two trials in patients who had inadequate response to methotrexate and were treated with abatacept. Patients with disease duration of <2 years (considered as having early RA) were compared with those with disease duration of >10 years (considered as having long-standing RA). Of the total sample, 23% had early disease. At 12 months, a higher percentage of these patients had achieved DAS28-CRP remission as compared with patients with long-standing disease (35% as compared with 19%). A higher percentage of the subgroup with early RA also achieved ACR70 responses.

#### Preventing RA

A few studies have evaluated the role of a range of treatments including biologics, particularly T-cell modulation using abatacept, to prevent the onset of RA in patients with early undifferentiated arthritis.<sup>44</sup> At present, there is insufficient evidence for or against this approach. However, it is an area of growing clinical interest.

#### Failure of TNF inhibitors

TNF inhibition failure was evaluated by Nam *et al.*<sup>38</sup> They identified several trials that evaluated non-TNF targeted biologics after TNF inhibitors had failed. These trials included studies using abatacept, rituximab, and tocilizumab. Golimumab was also studied in patients in whom TNF inhibition had failed. Nam *et al.* calculated the overall relative probability of achieving ACR responses at 6 months on a treatment of a conventional DMARD plus a biologic as compared with a conventional DMARD alone. The relative risks of attaining ACR20, ACR50, and ACR70

responses were 2.78 (95% CI: 2.28, 3.38), 5.00 (95% CI: 3.45, 7.24), and 8.27 (95% CI: 3.65, 18.76), respectively. Although these data provided convincing evidence that non-TNF biologics are effective after TNF inhibition failure, they provide limited information about the relative merits of switching from one TNF inhibitor to another.

In clinical practice, it is necessary to evaluate the relative efficacy of switching from one TNF inhibitor to another in patients who, for one reason or another, have not responded to a particular biologic. Given the limited trial data available, this issue can be addressed only by using observational data from registries and similar studies. Lloyd *et al.*<sup>40</sup> evaluated 20 such observational studies that had examined the benefits of switching TNF inhibitors in 2,705 patients who had previously had to discontinue treatment with a TNF inhibitor. Four studies reported data comparing outcomes in patients receiving sequential TNF inhibitors with those receiving treatment with a TNF inhibitor for the first time. Three studies reported ACR20 outcomes, three reported EULAR response rates, and all four reported improvement in DAS28. A random-effects meta-analysis comparing response rates for sequential use with those for first-time use produced an odds ratio of 0.65 (95% CI: 0.56, 0.76) for ACR20 data and 0.60 (95% CI: 0.50, 0.71) for EULAR outcomes. Meta-analysis of improvement in DAS28 gave a weighted mean difference of  $-0.37$  (95% CI:  $-0.57$ ,  $-0.17$ ). One study reported comparative data for patients who switched to second or third TNF inhibitors and those who switched to rituximab (a B-cell modulator) after failing at least one TNF inhibitor. The estimated difference in DAS28 improvement between those who switched from one TNF inhibitor to another and those who switched from a TNF inhibitor to rituximab was  $-0.63$  (95% CI:  $-1.14$ ,  $-0.12$ ). This shows that response rates after sequential TNF inhibitor use were lower than for first-time use.

Although sequential use of TNF inhibitors will reduce disease activity, the probability of achieving a response is lower and the average magnitude of response is also lower than with first use of a TNF inhibitor. Although further evidence from randomized controlled trials is needed to evaluate this issue fully, the balance of evidence favors changing to a different class of biologic in most patients.

### Changing entry criteria

Rahman *et al.*<sup>45</sup> have shown that the type of patients enrolled in trials of TNF inhibitors has changed over the years. They systematically reviewed entry criteria in trials that started enrolling patients between 1993 and 1997. They identified 37 trials in which patients had previously received methotrexate and 7 trials in which they had not. In trials involving patients with prior exposure to methotrexate, the enrollment criteria, including swollen joint counts and CRP, did not change, but baseline swollen joint count, CRP, and X-ray scores decreased. However, in studies in methotrexate-naïve patients, there were decreases over the years with respect to swollen joint and tender joint inclusion criteria but not in baseline tender joint count, CRP, or X-ray scores. Overall, they concluded that the more recent trials, especially those studying patients with prior exposure to

methotrexate treatment, tended to enroll cohorts with lower disease activity.

## EFFECTS OF BIOLOGICS ON EROSIVE DAMAGE AND QUALITY OF LIFE

### Erosive damage

There is strong evidence that biologics reduce the progression of erosive damage as assessed using X-ray. This effect of biologics was evaluated in a systematic review by Graudal and Jürgens.<sup>46</sup> They examined the impact of biologics combined with methotrexate in 12 trials enrolling 4,965 patients overall. When compared to methotrexate monotherapy, biologic-treated patients had a mean difference in their percentage annual radiographic disease progression rate of  $-0.61$  (95% CI:  $-0.72$ ,  $-0.51$ ). Further analyses of these trials examined patients who were “biologic nonresistant” (i.e., those who responded to the first treatment with a biologic) and “biologic resistant” (i.e., those in whom a biologic treatment had previously failed). These groups were studied in six trials enrolling  $>2,400$  patients overall and showed similar reductions in annual progression rates with biologic treatment ( $-0.81$  and  $-0.73$  for nonresistant and resistant patients, respectively).

Kuriya *et al.*<sup>47</sup> have specifically evaluated the effect of initial combination therapy with biologics as compared with initial methotrexate monotherapy in patients with early RA with minimal or no previous exposure to methotrexate. They identified seven relevant trials. All the trials showed risk estimates that favored the use of combinations of biologics. The pooled relative risk of radiographically determined nonprogression of disease was 1.30 (95% CI: 1.01, 1.68).

### Quality of life

Most research relating to quality of life has focused on HAQ scores, which decline as disability improves. Given that not all trials report HAQ scores in the same way, not all systematic reviews have examined changes in HAQ in detail. The early trials of TNF inhibitors, which were restricted to etanercept and infliximab, were evaluated by Jobanputra *et al.*<sup>48</sup> This review showed that, after 6 months of treatment, the weighted mean difference in HAQ scores was  $-0.37$  (95% CI:  $-0.77$ , 0.03). Subsequent systematic reviews showed similar data with respect to adalimumab (mean difference  $-0.32$ ; 95% CI:  $-0.51$ ,  $-0.13$ ),<sup>32</sup> certolizumab (mean difference  $-0.39$ ; 95% CI:  $-0.45$ ,  $-0.32$ ),<sup>33</sup> and tocilizumab (mean difference  $-0.30$ ; 95% CI:  $-0.44$ ,  $-0.16$ ).<sup>35</sup> In the case of some of the biologics, there has been a greater focus on the numbers of patients who show important clinical improvements, which are generally considered to be reductions in HAQ score of 0.22 or more. With abatacept treatment, the relative risk of such a change at 6 months as compared to methotrexate treatment was 1.73 (95% CI: 1.29, 2.33).<sup>36</sup>

Changes in HAQ score can be ambiguous and are influenced by patient selection. For example, Aletaha *et al.*,<sup>49</sup> in a systematic review of 25 studies involving biologics, showed that disease duration has a major impact on changes in HAQ. The effects of biologics on HAQ scores decreased considerably as the duration of RA increased. This implies that HAQ scores are only partially

reversible by treatment; in late disease, irreversible erosive damage may have a key role in the persistence of high HAQ scores even when joint inflammation has been minimized.

The improvements in HAQ are mirrored by enhanced quality of life, measured using SF-36, EuroQol, and related measures. Overall, the changes are similar for different biologic treatments. However, the data have been collected in various ways and there is limited availability of comparable data. Observational data from population studies provide useful insights. In Sweden, Gulfe *et al.*<sup>50</sup> reported changes in 1,001 RA patients treated with TNF inhibitors. They found that EuroQol scores improved by a mean of 0.21 (95% CI: 0.19, 0.22).

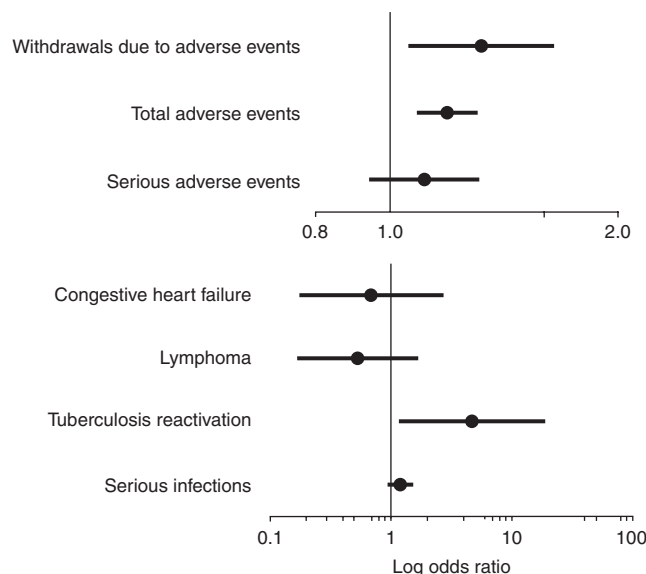
## TOXICITY

### Overall reactions

In an overview of the toxicity of biologics, Khraishi<sup>51</sup> divided them into risks of infection, infusion/injection reactions, malignancy, and a range of other concerns including lupus-like syndromes, demyelinating syndromes, and the development of blocking antibodies. There are concerns about the use of biologics in patients with congestive heart failure. Some biologics have idiosyncratic effects on lipid metabolism. Other unusual adverse effects include the triggering of interstitial lung disease and psoriasis. The toxicity of biologics has been evaluated in clinical trials and extension studies and in large national registries. Many of the studies produce conflicting results about the frequency of each of the reactions.

A network meta-analysis and Cochrane overview of toxicity caused by biologics have been reported by Singh *et al.*<sup>52</sup> Their meta-analysis compared the adverse effects of TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, and certolizumab) with those of anakinra, tocilizumab, abatacept, and rituximab therapy in patients with a range of inflammatory diseases other than human immunodeficiency disease. This meta-analysis included 163 trials involving 50,010 participants and 46 extension studies involving 11,954 participants. The median duration was 6 months for the trials and 13 months for the open-label extension studies. The review focused on overall reaction rates and toxicity arising from tuberculosis reactivation, lymphoma, and congestive heart failure. The key findings are summarized in **Figure 4**. After adjusting for dose, the authors found that biologics as a group were associated with a higher rate of total adverse events (odds ratio 1.19; 95% CI: 1.09, 1.30) than control treatments. The number needed to harm was 30. Biologics were also associated with more treatment withdrawals due to adverse events (odds ratio 1.32; 95% CI: 1.06, 1.64) and tuberculosis reactivation (odds ratio 4.68; 95% CI: 1.18, 18.60). However, serious adverse events, serious infections, lymphoma, and congestive heart failure were not seen more often in patients receiving biologics than in those receiving control treatments.

In their review, Singh *et al.* also identified specific issues relating to individual biologics. Certolizumab was associated with a significantly higher risk of serious infections as compared with the control treatment (odds ratio 3.51; 95% CI: 1.59, 7.79). Infliximab was associated with higher risks of withdrawals due to adverse events (odds ratio 2.04; 95% CI: 1.43, 2.91).



**Figure 4** Toxicity of biologics from a network meta-analysis and a Cochrane overview.<sup>52</sup>

In contrast, abatacept was associated with lower risks of serious adverse events.

### Infections

The main problem associated with the use of biologics is the occurrence of infections. RA itself increases the risk of infections, and this risk is heightened by biologics, particularly TNF inhibitors. Early meta-analyses of clinical trials by Leombruno *et al.*<sup>53</sup> and Bongartz *et al.*<sup>54</sup> produced variable findings, reflecting differences in the selection of trials evaluated and the way in which infections were classified. A subsequent report from the British Society for Rheumatology Biologics Register assessed the risk of serious infections in 11,798 TNF-inhibitor-treated patients and 3,598 patients receiving conventional DMARDs.<sup>55</sup> Patients receiving TNF inhibitors had 4.2 serious infections per 100 patient-years as compared with 3.2 per 100 patient-years in those receiving conventional DMARDs. The risk was greatest during the first 6 months of therapy. Advanced age was an independent risk factor for serious infections in both groups.

Trials and registries all show an increased risk of tuberculosis in patients receiving TNF inhibitors. The British Society for Rheumatology Biologics Register provides comprehensive data for this risk.<sup>56</sup> An analysis of data from 40 patients with tuberculosis showed that the rate of tuberculosis infection was higher with monoclonal antibody treatment (136–144 events/100,000 person-years) than with etanercept treatment (39 events/100,000 person-years). After adjustments, the relative incidence rate was >3. Interestingly, 13 of the 40 cases of tuberculosis occurred after treatment was stopped, and 25 cases were extrapulmonary. Patients of nonwhite ethnicity had a sixfold higher risk of tuberculosis infection than white patients. In view of this increased risk, appropriate screening including chest X-ray, skin testing, and immunological testing, is needed before patients are started on biologics. Clinicians should follow local guidance.



Many other infections are associated with the use of biologics. There are concerns that patients receiving biologics have greater risks of contracting viral infections, including herpes zoster.<sup>57</sup> There are similar anxieties about viral hepatitis. Patients should be screened for hepatitis B and C before being started on TNF inhibitors because the long-term safety of these biologics in patients with chronic viral hepatitis is not known.

A particular concern with rituximab treatment is the risk of progressive multifocal leukoencephalopathy due to activation of the JC polyomavirus. There have been only a few reports of this fatal progressive brain disease in RA patients treated with rituximab, and it is difficult to be certain about the risks involved.<sup>58</sup> Although the risks are small, the clinical consequences of progressive multifocal leukoencephalopathy are severe.

### Cancer

There have been concerns that biologics might be associated with an increased risk of developing cancer. However, there are complexities in assessing the frequency of cancers, particularly lymphomas, in patients treated with biologics. This is because the incidence of lymphoma is in any case higher in patients with RA, with the risk being highest in patients with active disease, the same patients who are also most likely to be receiving biologics. There is some evidence that there may be a higher rate of some solid tumors, particularly skin cancer, in patients receiving biologics. However, a recent systematic review by Solomon *et al.*,<sup>59</sup> who evaluated 11 studies of cancer risk associated with TNF inhibitors and assessed the data from an appropriate epidemiologic perspective, found little or no cancer risk associated with TNF inhibitors. The balance of recent evidence suggests that there is currently no convincing evidence of an increased cancer risk associated with the use of biologics; however, continuing caution is needed.

## SPECIFIC PROBLEMS

### Pregnancy

Most experts recommend stopping biologics and methotrexate prior to conception. There is relatively strong evidence for stopping methotrexate but less certainty about biologics. The British Society for Rheumatology Biologics Register has published experience based on 88 live births from a total of 130 pregnancies reported in patients who received TNF inhibitors before or during pregnancy.<sup>60</sup> There was evidence that the rate of spontaneous abortion was highest among patients exposed to TNF inhibitors at the time of conception. A systematic review of more than 600 pregnancies in which there was exposure to biologics found no convincing evidence of harm. However, continuing caution would appear to be a sensible approach.

### Immunization

Appropriate vaccinations should be carried out before initiating treatment with biologics. Vaccination with live attenuated vaccines is not recommended in patients receiving biologics.<sup>61</sup>

### Surgical procedures

Most experts recommend temporary stoppage of biologics therapy prior to surgery.<sup>62</sup> The evidence for this is incomplete, but

the association of biologics with infections makes a compelling case for caution. Some experts suggest that this treatment-free period prior to surgery should represent several half-lives of the relevant biologic, so as to ensure negligible exposure to biologics at the time of surgery.

### Immune reactions

All protein drugs can cause immunogenicity. Repeated injections of these drugs can trigger antibody responses, resulting in therapeutic failure and side effects. Although some experts consider antibodies to TNF inhibitors as having limited importance, the full impact of immunogenicity may be overlooked because patients are not routinely monitored for these antidrug antibodies. Antibodies affect therapeutic efficacy and can develop at all stages during treatment, including before and during remission.<sup>63</sup> Concomitant treatment with immunosuppressive drugs such as methotrexate may limit the development of antidrug antibodies. Other DMARDs may have similar roles.<sup>64</sup> The frequency of antidrug antibodies varies depending on the specific biologic that is used. Currently, there is no evidence that it would be particularly useful to look for antidrug antibodies in routine clinical practice.

### COST-EFFECTIVENESS

Some studies show that biologics are highly cost-effective in RA. Other studies show the opposite and suggest that they fall substantially outside the conventional window for cost-effectiveness. This paradox is an unresolved problem. It is an issue of crucial importance because its answer determines whether biologics should be used widely and considered as an early treatment choice or whether they should be viewed as treatments of last resort.

### Methodologies

Economic modeling needs to extend beyond conventional randomized controlled trials.<sup>65</sup> This is because such trials are short-term (months rather than years), rarely collect relevant data about costs and health-related quality of life, do not involve key head-to-head treatment comparisons, omit crucial outcomes such as employment and morbidity, and are often not generalizable to all clinical settings. Consequently, health economists use a variety of modeling methods such as simple decision trees, Markov models (which allow transitioning between finite health states without having too many branches on a simple decision tree), and individual sampling models in which each individual can be modeled separately.

Most economic studies evaluate the impact of biologics on quality-adjusted life years (QALYs), which reflect the theoretical concept of the number of years of perfect health on a scale of 0–1 (death to perfect health) added by the intervention. Because a particular treatment cannot be evaluated in isolation, biologics-based treatments are compared with conventional treatments using incremental cost-effectiveness ratios (ICERs). ICER is the ratio of the differences between costs and benefits of two interventions. Economic modeling enables QALYs to be calculated from available outcomes in clinical trials (such as changes in HAQ score) using available long-term observational data to construct likely outcomes. A crucial, unresolved issue

is whether such modeling should include nonmedical costs such as employment lost as a result of disability due to poorly controlled RA.

### Established disease

A systematic review of health economic studies in RA by Schoels *et al.*<sup>66</sup> identified 21 relevant studies of biologics. Based on society's willingness to pay ICER thresholds of US\$50,000–100,000, they were of the view that combinations of TNF inhibitors with methotrexate were a cost-effective option after failure of conventional DMARD therapy. They also concluded that there was broadly equivalent evidence for the cost-effectiveness of other types of biologics, although it is less detailed and weaker. There is very limited evidence for the cost-effectiveness of sequential use of TNF inhibitors, although Brennan *et al.*<sup>67</sup> have reported favorable ICERs for the use of second TNF inhibitors as a class as compared with DMARD treatment.

### Early disease

Schoels *et al.*<sup>66</sup> identified six studies in early RA and reported that economic evaluations provide only sparse information. However, initiating methotrexate monotherapy with the option to add biologics in the absence of a sufficient response is invariably more cost-effective than administering biologics initially along with methotrexate. It is possible that early treatment with biologics will be cost-effective in patients in whom there are high risks of poor outcomes without intensive treatment. However, this is an area in which more research is needed.

### Overall findings

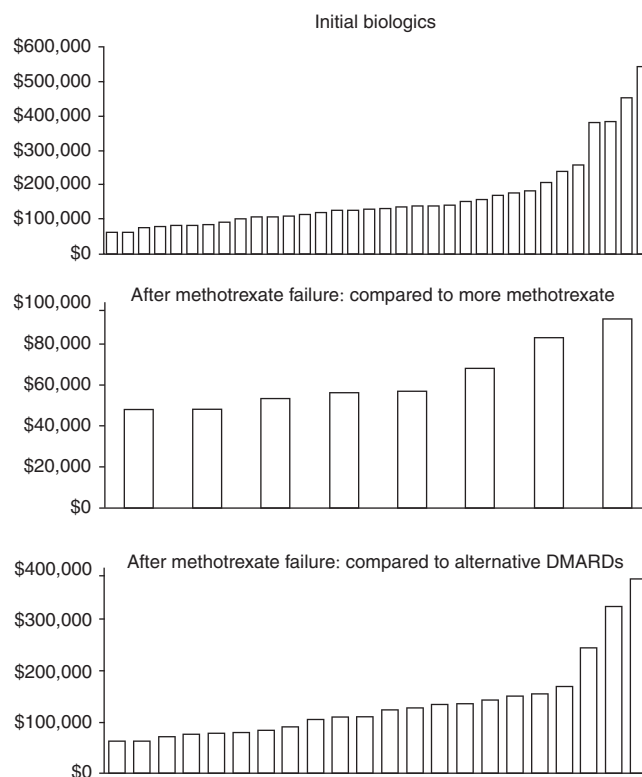
Although most overviews are broadly positive about the cost-effectiveness of biologics, there is a diversity of opinion. One recent systematic review by Van Der Velde *et al.*<sup>68</sup> evaluated published ICERs for biologics in early RA and in failed methotrexate treatments as compared with continuing with methotrexate or trying an alternative biologic (Figure 5). They concluded that the available economic evidence suggests that biologics would cease to be cost-effective as compared with DMARDs for the treatment of RA in adults at the cost-effectiveness threshold of \$50,000 (Canadian dollars) per QALY. They found mixed evidence of cost-effectiveness in selected populations at a willingness-to-pay threshold of \$100,000 (Canadian dollars) per QALY. They also found it challenging to draw definitive conclusions because of the lack of consistent, high-quality economic studies.

### LIMITATIONS

Although biologics are effective and safe, they are not ideal treatments. They have several drawbacks, which are summarized in this section.

### Noncurative

Despite the fact that biologics have been available for more than a decade, and even though some patients have already been receiving them for many years, there is no evidence that they cure RA. If disease resolution is the ultimate goal of treatment, biologics fall well short of the mark.



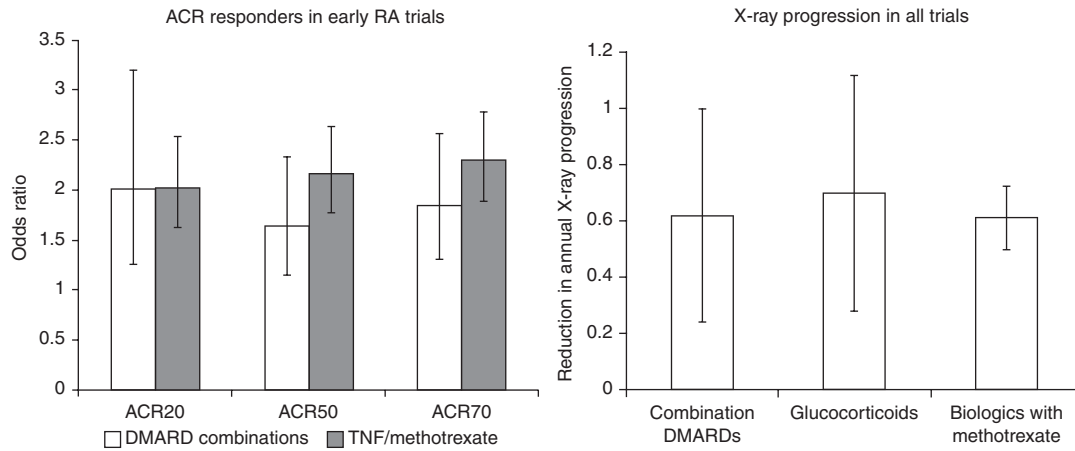
**Figure 5** Systematic review of cost-effectiveness of biologics.<sup>68</sup> The incremental cost-effectiveness ratios (ICERs) of individual studies are shown for initial biologics and for methotrexate failure compared with more methotrexate or alternative DMARDs. DMARD, disease-modifying antirheumatic drug.

### Limited comparisons with best conventional treatments

Most trials of biologics are designed to establish that these compounds are effective. There have been few trials that have compared them with best possible conventional treatment. Trials that have undertaken such comparisons, such as the BeSt treatment strategy in early RA, show no evidence of greater benefits with biologics.<sup>69</sup>

Although the benefits of biologics are undoubtedly substantial, their relative efficacy is uncertain. Comparative systematic reviews evaluating responses in early RA and the impact of treatment on erosive damage show no added benefits from treatments with biologics in these clinical settings over and above best conventional treatment using DMARDs and steroids. The key comparative findings from these systematic reviews are shown in Figure 6.

An argument in favor of using biologics is that major improvements have occurred in the clinical picture of RA since biologics came into use. Although this is a cogent argument, it has a crucial weakness: the improvements in RA outcomes started well before the era of biologics and in many ways transcend their use.<sup>1</sup> This observed improvement in outcomes makes it very challenging to compare results obtained with biologics-based treatments with historical outcomes with conventional drugs; the improvements could be attributed to biologics; alternatively, they may represent the effects of temporal improvements in RA due to many other factors.



**Figure 6** Comparison of TNF inhibitors with methotrexate or combination DMARDs against methotrexate monotherapy in trials. American College of Rheumatology (ACR) criteria responders are compared in early rheumatoid arthritis trials,<sup>42</sup> and X-ray progression is compared in all trials.<sup>46</sup> DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.

**Extending beyond the evidence base**

The trials showing that biologics are effective have enrolled patients with active disease. These patients have six or more tender joints, six or more swollen joints, and an erythrocyte sedimentation rate of 28 mm/h or higher. This level of disease activity equates with DAS28 scores of 5.1 or higher.<sup>70</sup> However, in the clinical setting, many patients with less active disease often receive biologics. In these patients, the relative benefits of biologics are likely to be substantially smaller.<sup>71</sup>

An associated problem concerns continuation of treatment beyond 12 months. Although extension studies show that biologics are safe to use in patients with RA, there is no evidence that they are clinically beneficial. The available clinical evidence suggests that biologics-based treatments can sometimes be tapered off or discontinued without major drawbacks for patients, provided that DMARDs are continued.<sup>72</sup> Tapering off of biologics in RA treatment is an area in which further research is needed.

**Incomplete evidence of cost-effectiveness**

In patients with active disease who have failed all conventional treatments and who also show marked reductions in HAQ scores and substantial improvements in quality of life, there is no doubt that biologics are cost-effective. However, that does not imply that they are universally cost-effective. It is likely that biologics will not be cost-effective in patients with early RA or in those with less active disease.

Concerns about the cost-effectiveness of biologics are driven mainly by the high costs of these treatments. Although the production of biological agents requires substantial infrastructural investments and extensive trial programs, this does not mean that their costs have to remain high indefinitely. When their costs fall, as they must inevitably do in the fullness of time, the issues about their cost-effectiveness will change substantially.

**Uncertainties about future toxicity**

When biologics were first introduced, there were genuine concerns that, over time, major toxicities would emerge. As a consequence they have been subjected to unprecedented levels of

scrutiny through national registries. Over the years these concerns have declined. Thus far no major unexpected toxicities have emerged. Nevertheless, it appears appropriate to continue to exercise caution in the use of biologics.

**GUIDANCE**

There is evidence (of varying strengths) that biologics are effective in four clinical situations:

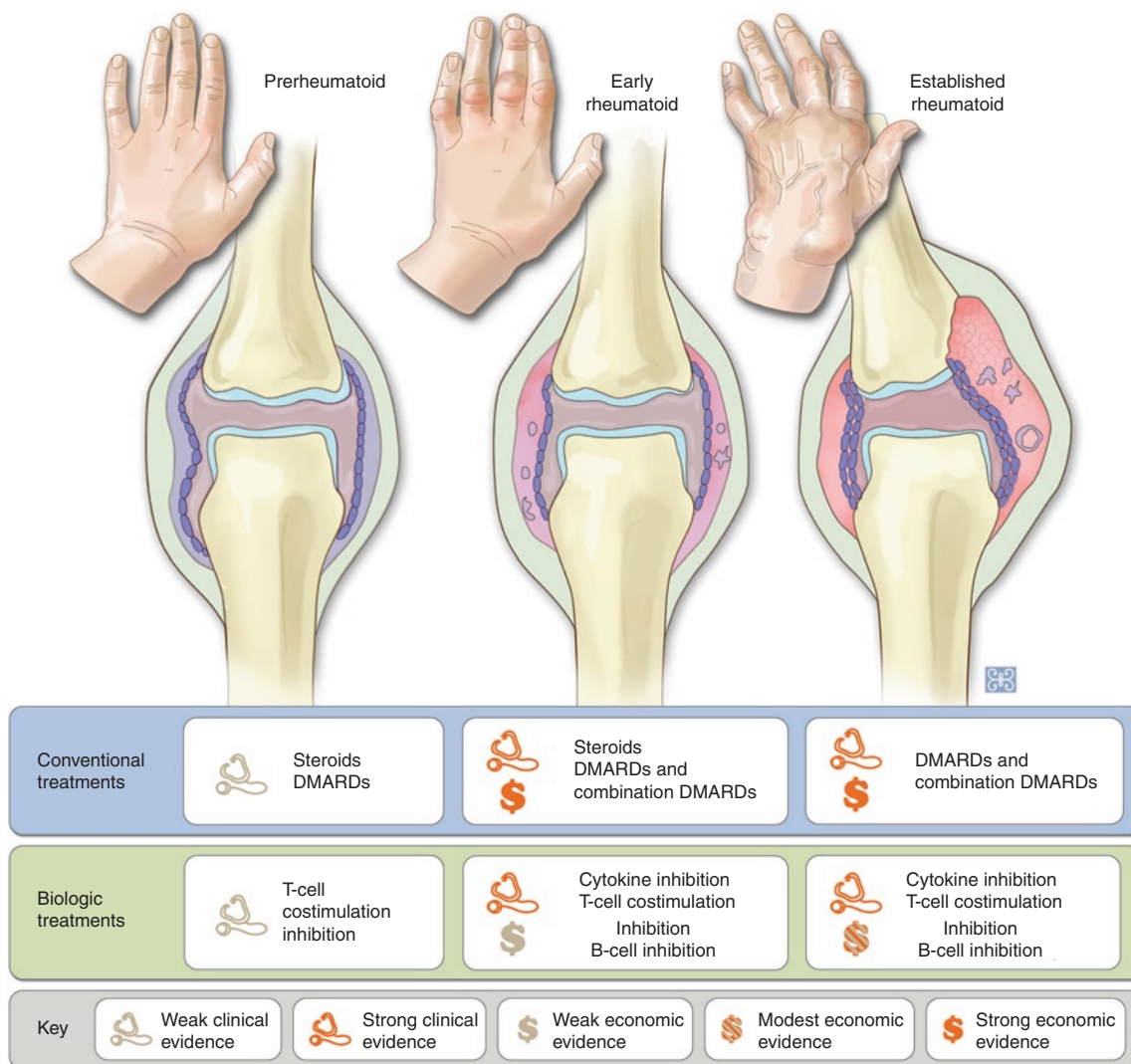
- Prevention of RA
- As first-line treatment for early active RA
- When methotrexate and other DMARDs fail to control RA
- When patients fail to respond to initial treatment with biologics, particularly TNF inhibitors

Many guidelines have been devised to ensure that biologics are used in the most effective and cost-effective manner in RA. These include North American guidance, continental European guidance, and English guidance based on reviews by the National Institute for Health and Clinical Excellence (NICE).<sup>73–75</sup> The general ethos of this guidance is similar, although it differs in points of detail.

The common points shared by most guidelines are that:

- Biologics should be reserved for use in patients with active disease who have failed to respond to methotrexate and, potentially, to other DMARDs
- It is preferable to give biologics in combination with methotrexate and, potentially, with other DMARDs
- It is advisable to start with the most established biologics, which are usually the TNF inhibitors
- If patients have active disease despite TNF inhibitors, alternative biologics should be administered until disease control is achieved or until the patient has failed to respond to all appropriate biologics

There are differences in definitions of active disease, definitions of DMARD failure, and recommendations for how



**Figure 7** The potential use of conventional treatments and biologics in the treatment pathway of rheumatoid arthritis. DMARD, disease-modifying antirheumatic drug.

biologics should be sequenced. The key issues about the place of conventional therapy and biologics in RA treatment are summarized in [Figure 7](#).

There is an interesting paradox involving the divergence of views of people receiving and delivering treatment for RA on the one hand and those funding RA care on the other. Patients and clinicians want biologics to be widely used. Funders want their use to be restricted. Although part of the pressure to use biologics will inevitably be driven by the manufacturers of these compounds, the key reason for wanting to use them is that they appear to be more effective and less toxic than conventional DMARDs.

#### FUTURE DEVELOPMENTS

The use of biologics for the treatment of RA has expanded rapidly over the past decade. Eventually this expansion will draw to a close. At present, there are at least four factors driving change: the introduction of new biologics, the rise of biosimilars, the focused use of biologics, and the introduction of alternative non-biologics-based immune modulators.

Many new biologics are being developed, including inhibitors of IL-17. Although these appear to be promising, their ultimate utility cannot currently be assessed. Biosimilars are likely to be introduced within the next few years. Although their impact is difficult to judge at present, they are likely to decrease the overall costs of biologics. This change will alter the cost-effectiveness of biologics and may increase their use.

Personalized medicine remains an unfulfilled aspiration. However, the growing availability of genetic and other biomarkers makes it a realistic medium-term aspiration. Using biologics in patients who are most likely to benefit from them will be a major step forward and has the potential to radically alter the clinical use of these compounds.

Finally, the advent of new conventional drugs that replicate some of the effects of biologics is likely to materialize in the near future. JAK and SYK kinase inhibitors may well move from clinical trials into clinical practice in the near future. Their introduction could change the current treatment paradigm for RA and have a major impact on the way we use biologics.

CONFLICT OF INTEREST

D.L.S. holds grants from several funding organizations, including Arthritis Research UK, the Medical Research Council, and the National Institute for Health Research. He has not received any personal financial support (lecture fees, consultancies, or funds for traveling to meetings) since 2009. His department has received funds for clinical research from several pharmaceutical sponsors, but he is not the primary grant holder for any of these studies.

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