Biological therapy for rheumatoid arthritis: where are we now?

Since the introduction of targeted biological therapies, the implications of a new diagnosis of rheumatoid arthritis have changed dramatically. There are now several therapeutic options available for these patients and the target of treatment – remission – is now a realistic goal.

As recently as 15 years ago, the outcome for patients with rheumatoid arthritis in whom conventional disease-modifying anti-rheumatic drug therapy was insufficient to suppress disease activity was poor. There was increased mortality and morbidity as a result of the consequences of both long-term use of corticosteroids and uncontrolled inflammation. This included cardiovascular disease, joint destruction and extra-articular manifestations of rheumatoid. Over the last 10 years, with advances in the understanding of the immunopathogenesis of rheumatoid arthritis and biological drug development, several biologic therapies have proved effective and safe in the treatment of rheumatoid arthritis resistant to standard disease-modifying anti-rheumatic drug therapies including methotrexate (methotrexate-inadequate response) and are now licensed in Europe for this indication (*Table 1*). These include several tumour necrosis factor alpha (TNF) inhibitors, tocilizumab (an interleukin (IL)-6 receptor inhibitor), and abatacept (an inhibitor of T cell co-stimulation). Rituximab, a B cell depleting therapy, is licensed for use in patients who have had an inadequate response or intolerance to a TNF inhibitor.

After cost-effective analyses in the UK, the National Institute for Health and Clinical Excellence has approved the majority of these agents with some

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Table 1. Biologic therapies approved for use in rheumatoid arthritis by the European Medicines Agency

Mechanism of action	Name	Structure	Year of approval (by the EMA)	Route	Dose and frequency
TNFα inhibition	Etanercept	Fusion protein; extracellular domains of two 75kDA TNFα receptors and constant fragment of human immunoglobulin	2000	Subcutaneous	50 mg weekly or 25 mg twice weekly
	Infliximab	Mouse–human chimeric monoclonal antibody against TNFα	1999	Intravenous	3 or 5 mg/kg at 0, 2 and 6 weeks then every 2 months. Weekly methotrexate must be administered to decrease immunogenicity
	Adalimumab	Humanized monoclonal antibody against TNFα	2003	Subcutaneous	40 mg every 2 weeks
	Certolizumab pegol	Pegylated antibody-binding fragment of immunoglobulin against TNFα	2009	Subcutaneous	400 mg at 0, 2 and 4 weeks then maintenance dose of 400 mg every 4 weeks or 200 mg every 2 weeks
	Golimumab	Fully human monoclonal antibody against TNFα	2009	Subcutaneous	50 mg every 4 weeks
B cell depletion	Rituximab	Mouse–human chimeric monoclonal antibody against CD20	2006	Intravenous	1000 mg at 0 and 2 weeks. Retreatment regimens include retreatment on demand (at time of flare), retreatment to target (according to level of disease activity) or fixed retreatment every 6 months
Inhibition of T-cell co-stimulation	Abatacept	Fusion protein; extracellular domain of CTLA-4 and human immunoglobulin	2007	Intravenous	10 mg/kg (one of three doses) every 4 weeks
Inhibition of IL-6	Tocilizumab	Monoclonal antibody against IL-6 receptor	2009	Intravenous	400 mg every 4 weeks

CD20 = cluster of differentiation cell-surface protein 20; CTLA-4 = cytotoxic T-lymphocyte antigen 4; EMA = European Medicines Agency; IL = interleukin; TNFα = tumour necrosis factor alpha.

restrictions, for example TNF inhibitors are available for patients who have persistent high disease activity (assessed using the Disease Activity Score, DAS28, a composite measure comprising joint assessment, a laboratory marker of inflammation and patient self-assessment of health) and have failed two conventional disease-modifying anti-rheumatic drugs. Rituximab is available for use in cases of inadequate response, or contraindication to, TNF inhibitor, with other biologics being available if rituximab treatment is contraindicated or not successful.

In addition to the advances in biological drug development, greater awareness of the need for early, aggressive treatment has contributed to an improved prognosis for rheumatoid arthritis patients today. With initial trials demonstrating the benefits of biologic therapies in methotrexate-inadequate responders, and increasing evidence for a critical window in early disease in which tight control of inflammatory disease activity minimizes long-term disability and joint damage, randomized controlled trials of biologics have been conducted in methotrexate-naïve patients. Preliminary studies examined efficacy of TNF inhibitors in methotrexate-naïve patients with a poor prognosis. As a consequence, a number of TNF inhibitors are now approved for severe, progressive rheumatoid arthritis before the failure of disease-modifying anti-rheumatic drugs including methotrexate. Their impressive results have also driven several studies investigating a novel approach to management of early rheumatoid arthritis – remission induction with short-term use of these agents.

Current evidence-based guidelines for management of rheumatoid arthritis recommend 'treatment to target', i.e. step-up in treatment, on a monthly basis if necessary, according to a pre-defined target of disease activity – ideally remission but at least low disease activity (Smolen et al, 2010a). This review will explore the efficacy of biologic therapies in rheumatoid arthritis in the context of 'treatment to target' regimens as well as in the other situations previously discussed: methotrexate-inadequate response, methotrexate-naïve patients with poor prognosis and remission induction in methotrexate-naïve patients.

A concern with these drugs has been safety, particularly in respect to potential long-term effects such as malignancy, which randomized controlled studies are unable to adequately address. Data from large observational cohorts regarding safety of these therapies in the real-life clinical setting will be reviewed.

Methotrexate-inadequate response

The first biologic therapy to become available was the TNF inhibitor etanercept (initially approved by the United States Food and Drug Administration in 1998), shortly followed by infliximab (Food and Drug Administration approval in 1999). Early, pivotal phase III trials assessing efficacy of TNF inhibitors include a randomized controlled trial of etanercept *vs* placebo in patients receiving methotrexate (Weinblatt et al, 1999). Patients had disease activity (at least six swollen and tender joints) despite methotrexate. Clinical response was assessed, as it has been in trials since, using criteria defined by the American College for Rheumatology (ACR); an ACR20, 50 or 70 response pertaining to a 20%, 50% or 70% improvement in the number of tender joints, number of swollen joints, and at least three out five further criteria including patient-reported pain, global health or physical function, physician assessment of global health or a laboratory marker of inflammation (C-reactive protein or erythrocyte sedimentation rate). Patients were over twice as likely to achieve the primary outcome, an ACR20 response at 24 weeks, with etanercept in combination with methotrexate compared to methotrexate alone (71% achieving ACR20 compared to 27% respectively). Efficacy of infliximab and methotrexate in comparison to methotrexate alone was demonstrated in a similar cohort; six swollen and tender joints despite methotrexate, median disease duration between 7 and 9 years across treatment groups (Maini et al, 1999). The primary end point, ACR20 at 30 weeks, was met in 50% of patients receiving infliximab 3 mg/kg compared to 20% of controls ($P<0.001$). Approximately half of patients were functionally limited at baseline, fulfilling ACR criteria for functional class III or IV.

Biologic therapies which have since become available have been trialled in similar patient cohorts; *Table 2* illustrates a selection of such trials. Secondary outcome measures in these and other studies include radiographic outcomes and patient-reported measures, demonstrating ability of these agents to slow radiographic damage and improve patients' self-reported physical function and quality of life. Interesting post-hoc analysis of studies has shown prevention of radiographic progression occurs with TNF inhibitors even in the absence of a clinical response (unlike methotrexate). Owing to proven efficacy and safety in combination with methotrexate they are licensed for use in this combination. For a selection of biologics (etanercept, adalimuab, certolizumab pegol and tocilizumab) concomitant use of methotrexate is preferred because of the superior efficacy, but their use is also approved without methotrexate when methotrexate is not tolerated or is contraindicated.

These trials demonstrate that no agent is universally effective, with approximately one third of patients not responding, hence the continued development of alternative agents. This rate of response seems to translate into clinical practice. In 2004, results from the British Society of Rheumatology Biologics Register were reported in over 3000 rheumatoid arthritis patients treated with infliximab or etanercept in UK clinical practice: approximately two-thirds achieved at least a moderate clinical response at 6 months (Hyrich et al, 2006).

Methotrexate-naïve with poor prognosis

In the knowledge that joint damage occurs most rapidly in early disease, and with recent studies favouring early aggressive treatment for improved long-term outcomes, biologic therapy (in particular TNF inhibitors) has been trialled in early rheumatoid arthritis in patients with prognostic factors for severe, progressive disease before the use of methotrexate. Results are such that etanercept, infliximab, adalimumab and golimumab are now approved for use in Europe in patients with severe, progressive rheumatoid arthritis before the use of disease-modifying anti-rheumatic drugs. *Table 3* provides a summary of such trials involving over 500 patients.

Poor prognostic factors largely included positivity for rheumatoid factor and/or presence of radiographic erosions. Responses appear qualitatively and quantitatively superior to those seen with use in established disease (*Table 2*), with significant proportions of patients attaining the higher response levels selected as primary end points. This may be predicted as by definition, as a group, these patients have less resistant disease (being methotrexate-naïve rather than methotrexate inadequate responders), but the higher response rates seen with methotrexate as an active comparator in these patients should also be borne in mind. Less striking results were seen with golimumab in the GO-BEFORE study (Emery et al, 2009), potentially because of the low disease activity of patients at baseline (median DAS28 across groups 2.95–3.31).

Methotrexate-naïve: remission induction

Further to conferring superior response rates in early disease, early TNF inhibitor therapy may induce disease remission which, in a proportion of patients, can be sustained without relapse of disease even after drug withdrawal. This concept was initially explored with 12 weeks of high-dose infliximab (10 mg/kg) in combination with methotrexate in five patients with early, untreated rheumatoid arthritis, with poor prognostic factors such as positive rheumatoid factor (Conaghan et al, 2002). One of the five patients achieved remission, none achieved drug-free remission. The same group went on to assess remission induction with infliximab in a randomized double-blind controlled trial (Quinn et al, 2005). Twenty patients with early untreated rheumatoid arthritis with poor prognostic factors were randomly allocated to methotrexate or infliximab and methotrexate for 1 year; at 2 years (1 year after stopping infliximab) there

Table 2. Selection of major phase III trials comparing efficacy of biologic therapy in combination with methotrexate to methotrexate therapy alone

Drug and study	Inclusion criteria for disease activity	Mean disease duration	Primary/co-primary end points	Results: primary outcome(s) in active treatment group (dose used in clinical practice) *vs* controls
Adalimumab, ARMADA (Weinblatt et al, 2003)	Swollen joint count ≥6 and tender joint count ≥9 despite ≥6 months of methotrexate plus failure of one other disease-modifying anti-rheumatic drug	12 years	ACR20 at 24 weeks	67% *vs* 14% ($P<0.001$)
Certolizumab pegol, RAPID 1 (Keystone et al, 2008)	Swollen joint count ≥9 and tender joint count ≥9 despite ≥6 months of methotrexate	6 years	ACR20 at 24 weeks Mean change from baseline in mTSS at 52 weeks	59% *vs* 14% ($P<0.001$) Mean change from baseline in mTSS 0.4 *vs* 2.8 Sharp units ($P<0.001$)
Golimumab, GO-FORWARD (Keystone et al, 2009)	Swollen joint count ≥4 and tender joint count ≥4 despite ≥3 months methotrexate	5–7 years (across groups)	ACR20 at 14 weeks Median change from baseline in physical function (HAQ-DI) at 24 weeks	55% *vs* 33% ($P<0.001$) 0.38 *vs* 0.13 units ($P<0.001$)
Rituximab, DANCER (Emery et al, 2006)	Swollen joint count ≥8 and tender joint count ≥8 despite ≥12 weeks of methotrexate plus failure of one other disease-modifying anti-rheumatic drug	9–11 years (across groups)	ACR20 at 24 weeks in rheumatoid factor-positive subjects	54% *vs* 28% ($P<0.001$)
Abatacept, AIM (Kremer et al, 2006)	Swollen joint count ≥10 and tender joint count ≥12 despite ≥3 months of methotrexate	9 years	ACR20 at 6 months Clinically meaningful improvement in physical function (improvement of ≥0.3 units in HAQ-DI score) Mean change from baseline in erosion score of Genant-modified Sharp score	ACR20 in 68% *vs* 40% ($P<0.001$) Meaningful improvement in HAQ-DI in 64% *vs* 39% ($P<0.001$) Median change from baseline in erosion score 0.0 *vs* 0.3 Sharp units ($P=0.029$)
Tocilizumab, OPTION (Smolen et al, 2008)	Swollen joint count ≥6 and tender joint count ≥8 despite ≥12 weeks of methotrexate	7–8 years (across groups)	ACR20 at 24 weeks	59% *vs* 26% ($P<0.001$)

ACR20 = 20% improvement in the American College of Rheumatology clinical components of response (including tender and swollen joint counts); HAQ-DI = health assessment questionnaire disability index; mTSS = van der Heijde modified total Sharp score (measure of radiographic damage including assessment of erosions and joint space narrowing)

was a significant difference in physical function (assessed by the Health Assessment Questionnaire) and quality of life ($P<0.05$). Eight years on, 40% of patients initially treated with infliximab were still in remission, in comparison to none of the controls (Bejarano et al, 2010).

The COMET study was the first large randomized controlled trial ($n=542$) in early rheumatoid arthritis to assess remission as a primary end point (Emery et al, 2008). Methotrexate-naïve patients, with at least moderate disease activity (DAS28≥3.2) and disease duration less than 2 years, were treated with methotrexate and randomized to receive either etanercept or placebo. Half of those receiving etanercept achieved remission (DAS28<2.6) at 1 year, in comparison to 28% of controls ($P<0.001$). Sub-analysis of these patients suggests a 'window of opportunity' whereby TNF inhibitors confer superior response effects occurs very early in disease: in the etanercept group 70% of those with 'very early rheumatoid arthritis' (disease duration less than 4 months) achieved remission in comparison to 48% of those with 'early rheumatoid arthritis' (disease duration of between 4 months and 2 years; $P=0.0035$) (Emery et al, 2010). This hypothesis is further supported by observational data indicating that symptom duration of less than 6 months at time of commencement of TNF inhibitor may predict sustained remission, after withdrawal of therapy after 1 year, with an odds ratio of 13 (95% confidence interval 1.0–825, $P=0.050$) (Saleem et al, 2010).

Treatment to target strategies

Current evidence-based guidelines for management of rheumatoid arthritis recommend step-up in treatment, on a monthly basis if necessary, according to a predefined target of disease activity; ideally remission but at least low disease activity (Smolen et al, 2010a). The first disease-modifying anti-rheumatic drug usually administered is methotrexate. In the SWEFOT study (van Vollenhoven et al, 2009), patients failing to achieve low disease activity after 3 months of initial methotrexate monotherapy were randomized to addition of infliximab or addition of conventional disease-modifying anti-rheumatic drugs (sulfasalazine and hydroxychloroquine).

Table 3. Efficacy of biologic therapy in methotrexate-naïve, early rheumatoid arthritis patients with poor prognostic factors in double-blind randomized controlled trials including more than 500 participants*

	Inclusion criteria			
Drug and study	Disease activity	Disease duration	Primary/co-primary end points	Results: primary outcome(s) in active treatment group (dose used in clinical practice) *vs* controls
Etanercept monotherapy (Bathon et al, 2000)	Swollen joint count ≥10 Tender joint count ≥12 ESR ≥28 mm/h	<3 years	Clinical response over 6 months (area under the curve for ACR-N up to 6 months) Mean change in total Sharp score from baseline at 12 months	Significantly greater area under the curve for ACR-N at 6 months ($P<0.05$) 1.0 *vs* 1.6 Sharp units ($P=0.11$)
Infliximab with methotrexate, ASPIRE (St Clair et al, 2004)	Swollen joint count ≥10 Tender joint count ≥12	<3 years	Clinical response over 54 weeks (area under the curve for ACR-N up to week 54) Change in mTSS from baseline to week 54	Median ACR-N 39% *vs* 26% ($P<0.001$) 0.4 *vs* 3.7 Sharp units ($P<0.001$)
Adalimumab monotherapy and in combination with methotrexate, PREMIER (Breedveld et al, 2006)	Swollen joint count ≥8 Tender joint count ≥10 ESR ≥28 mm/h or CRP ≥15 mg/litre	<3 years	ACR50 at 1 year Mean change in mTSS from baseline at 1 year	Adalimumab in combination with methotrexate superior to adalimumab monotherapy or methotrexate alone ACR50 in 62% *vs* 41% (adalimumab monotherapy) and 46% (methotrexate controls), $P<0.001$ for both comparisons 1.3 *vs* 3.0 (monotherapy) and 5.7 (controls) Sharp units, $P<0.002$ for both comparisons
Golimumab with methotrexate, GO-BEFORE (Emery et al, 2009)	Swollen joint count ≥4 Tender joint count ≥4	>3 mths	ACR50 at 24 weeks	40% *vs* 29% ($P=0.038$)
Rituximab every 24 weeks with methotrexate, IMAGE (Tak et al, 2011)	Swollen joint count ≥8 Tender joint count ≥8 CRP ≥10 mg/litre	<4 years	Mean change in Genant-modified total Sharp score at 52 weeks	0.4 *vs* 1.1 Sharp units ($P<0.001$)
Abatacept with methotrexate (Westhovens et al, 2009)	Swollen joint count ≥10 Tender joint count ≥12 CRP ≥4.5 mg/litre	≤2 years	DAS28 remission at 1 year Mean change in Genant-modified total Sharp score from baseline at 1 year	Remission in 41% *vs* 23% ($P<0.001$) 0.6 *vs* 1.06 Sharp units ($P=0.040$)

ACR50 = American College of Rheumatology response criteria improvements of 50%; ACR-N = mean American College of Rheumatology response; CRP = C-reactive protein; DAS28 = Disease activity score, based on 28 specified joints (calculated using a mathematical formula comprising: number of swollen joints, number of tender joints patient self-assessment of global health (on a visual analogue scale), laboratory markers (CRP or ESR); A DAS28 score of 5.1 or more is classed as high disease activity, low disease activity is 3.2 or less and clinical remission is less than 2.6); ESR = erythrocyte sedimentation rate; mTSS = van der Heijde modified total Sharp score (measure of radiographic damage including assessment of erosions and joint space narrowing). *Controls were treated with methotrexate. Only groups treated with the dose currently approved for clinical practice are presented

The primary end point, a good response (as defined by the European League Against Rheumatism) at 1 year, was achieved in significantly more patients randomized to receive infliximab than in those receiving conventional disease-modifying anti-rheumatic drugs (39% compared to 25%, *P*=0.016).

A handful of studies have begun to compare strategies for treatment in early rheumatoid arthritis, including comparison of first-line use of TNF inhibitors to use in treatment to target regimens. Some indicate that faster control of inflammatory disease activity with first-line use leads to improved long-term outcomes, for example the BeST study comparing four treatment strategies in early rheumatoid arthritis demonstrated less radiographic damage at 1 year in the group receiving first-line infliximab and methotrexate (Goekoop-Ruiterman et al, 2005), while others have shown that despite better initial response, comparable clinical and radiographic results may be achieved at 1 year (Soubrier et al, 2009). The heterogeneity of such studies presents difficulty when drawing any conclusions, and research is ongoing to determine how best to use biologic agents in clinical practice.

Safety

Safety concerns with the use of biologic therapy arise not least because their targets in the immune system have a role in the body's defence against infection and malignancy. Meta-analyses of trials have been conducted, including several Cochrane reviews, but because trials may exclude patients with comorbidities, results may not apply to the general rheumatoid arthritis population. For the longest established biologics (etanercept, infliximab and adalimumab) data have become available from patient registries, for example the British Society for Rheumatology Biologics Register. Although these registries often include a control group of rheumatoid arthritis patients treated with conventional disease-modifying anti-rheumatic drugs (over 3000 such controls in the British Society for Rheumatology Biologics Register), as treatment is not allocated at random, confounding by indication is inherent within this data and must be borne in mind; for example, any potential increase in rates of malignancy and infection with biologic therapies (both of which are associated with rheumatoid arthritis) may reflect greater disease severity in this group and not biologic treatment.

Biologic therapies are contraindicated in the presence of concurrent severe infection. Data from the British Society for Rheumatology Biologics Register indicates that risk of serious infection (infection requiring intravenous antibiotics, or leading to hospitalization or death) is increased with TNF inhibitors (etanercept, infliximab and adalimumab) within the first 90 days of treatment initiation (adjusted incidence rate ratio 4.6, 95% confidence interval 1.8–11.9) (Dixon et al, 2007). There is an increased risk of tuberculosis, either reactivation of latent infection or increased susceptibility to infection; out of the 10 403 patients on TNF inhibitor therapy in the British Society for Rheumatology Biologics Register there have been 35 cases of tuberculosis, with no cases in the disease-modifying anti-rheumatic drug group (Dixon et al, 2010a). All patients should be screened (and, when appropriate, treated) for latent infection before receiving a TNF inhibitor.

Safety of B cell depleting therapy has been of concern, especially considering the potential long-lasting effect of rituximab on B cell depletion. Long-term safety data are now available for patients receiving multiple cycles of rituximab and alternative biologic therapies after rituximab. Serious infection rates were not increased with repeat cycles in pooled data from randomized controlled trials and their open-label extension studies (van Vollenhoven et al, 2010), or with subsequent alternative biologic therapies in an initial report of over two hundred patients (178 patients receiving a TNF inhibitor) despite below normal peripheral B cell concentrations in 86% of these patients at the time they received their subsequent biologic (Genovese et al, 2010).

Data from several national registries have been reassuring in that no increase in the overall incidence of malignancy, or malignancy-specific rates such as the incidence of lymphoma, has been identified in comparison to rheumatoid arthritis controls. This is with the exception of the risk of non-melanotic skin cancers which may be increased by approximately 50% with etanercept, infliximab and adalimumab compared to rheumatoid arthritis controls; an odds ratio of 1.5 (95% confidence interval 1.2–1.8) was reported in the USA (Wolfe and Michaud, 2007). Guidelines for the use of biologic therapies recommend caution in regard to patients with a history of malignancy, and avoidance of TNF inhibitors in patients with a lymphoproliferative disorder within the preceding 5 years. Again, there is no signal from observational data of an increased risk of recurrence in patients with prior malignancy, although numbers of patients are limited; for example, in 294 patients with prior malignancy (excluding non-melanotic skin cancers) in the British Society for Rheumatology Biologics Register (177 receiving TNF inhibitors), the incidence rate ratio for new or recurrent malignancy with TNF inhibitor treatment was 0.6 (95% confidence interval 0.2–1.4) compared to controls, and 0.5 (95% confidence interval 0.1–2.2) after adjusting for potential confounders including disease duration and DAS28 (Dixon et al, 2010b).

Conclusions

Several biologic therapies, with a range of mechanisms of action, are licensed for use in patients who have failed treatment with the anchor disease-modifying anti-rheumatic drug methotrexate, providing multiple treatment options for patients in whom, 15 years ago, the outlook was very different, with management frequently involving a balance of the risks of poorly controlled disease with

side effects of long-term steroid use. Indeed for patients with long-standing disease, whose disease onset preceded this current biologic era, the management of the consequences of previous poorly controlled disease constitutes a significant clinical challenge.

Evidence supporting the earlier use of TNF inhibitors, before the failure of conventional disease-modifying anti-rheumatic drugs, is increasing such that a number of these agents are now licensed for use before treatment with disease-modifying anti-rheumatic drugs. Expert consensus on the use of biologic therapies suggests the use of TNF inhibitors in combination with methotrexate as first-line therapy in patients with poor prognostic signs for rapidly progressive disease (such as early radiographic damage or very high disease activity) (Smolen et al, 2010b). Presently, however, it remains controversial whether first-line use may be cost effective, and first-line use is not approved by the National Institute for Health and Clinical Excellence. Studies suggest very early, short-term use may induce remission which may be sustained despite biologic withdrawal. It is perceivable that early, short-term use may offset the need for long-term treatment with several, sequential biologic therapies in the most resistant patients. Further research is needed to establish the optimal use of biologics in order to maximize their cost effectiveness, and to develop biomarkers which may help identify the patients who may benefit most from treatment.

More than 10 years of accumulating evidence for safety of etanercept, infliximab and adalimumab is reassuring, while long-term follow-up of patients receiving newer biologic therapies in clinical practice is still awaited. **BJHM**

Conflict of interest: Professor P Emery has provided expert advice and undertaken clinical trials for Pfizer, Merck, Abbott, UCB, BMS and Roche; Dr SC Horton: none.

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KEY POINTS

- Several biologic therapies, differing in their mechanism of action, are licensed in Europe for the treatment of patients with moderate to severely active rheumatoid arthritis in whom methotrexate treatment has failed: tumour necrosis factor inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol and golimumab), tocilizumab (an interleukin-6 receptor inhibitor), and abatacept (an inhibitor of T cell co-stimulation). Rituximab, a B cell depleting therapy, is licensed for use in patients who have had an inadequate response or intolerance to a tumour necrosis factor inhibitor.
- Etanercept, infliximab, adalimumab and golimumab are also approved for treatment of severe, progressive rheumatoid arthritis before the use of disease-modifying anti-rheumatic drugs.
- Phase III trials demonstrate these agents are effective in methotrexate-inadequate responders in achieving clinical improvement in disease activity, as well as slowing radiographic progression and improving patient-reported quality of life and disability.
- The National Institute for Health and Clinical Excellence supports tumour necrosis factor inhibitors as the first choice of biologic therapy for patients who have persistent high disease activity and have failed two conventional disease-modifying anti-rheumatic drugs.
- National Institute for Health and Clinical Excellence and international evidence-based guidelines recognize the importance of early, effective disease control to optimize long-term outcomes. Current best practice comprises a 'treatment to target' approach, in which remission should be the goal of therapy.
- Early use of tumour necrosis factor inhibitors offers improved outcomes over methotrexate monotherapy. Further research is necessary to clarify when, or in whom, first-line tumour necrosis factor inhibitor treatment may be cost-effective in comparison to 'treatment to target'.
- Safety data from large cohorts of patients in observational registries is available for the longest established biologics (etanercept, infliximab and adalimumab). Further long-term data for rare events (such as lymphoma) are needed, particularly in respect to the biologics licensed most recently.

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