Biologic treatments for rheumatoid arthritis

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Biologic disease-modifying antirheumatic drugs (bDMARDs) have made a significant difference to the lives of people with rheumatoid arthritis (RA), in particular those who do not respond to conventional drugs. In this article the authors review the place in therapy of bDMARDs for RA and consider a range of factors that could contribute to further improvements to patient otucomes.

Rheumatoid arthritis (RA) is an aggressive destructive inflammatory disease that is principally focussed on synovial joints, with the capacity to cause immense harm. The UK prevalence of RA is approximately 1% of the general population, with a male to female ratio of 1:3.

The immune response in RA leads to synovial inflammation and joint damage so that within a few months of symptom onset patients may be constrained from functioning or working, with long-lasting effects on mental and physical wellbeing. Its persistence also results in non-musculoskeletal consequences, including accelerated atherosclerosis and cardiovascular morbidity, sepsis, some cancers (including lymphoma), and chronic mental ill health – all adding to a lifetime burden and increased mortality.

Score	SJC	TJC	ESR/ CRP	Patient global	Physician global	Pain	Function
DAS[32]	x	x	x	x			
DAS28[32]	x	x	x	x			
CDAI[32]	x	x		x	x		
SDAI[32]	x	x	x	x	x		
ACR-EULAR Boolean[33]	x	x	x	x			
RAPID 3[32]				x		x	x
Score	**Pain**	**Functional disability**	**Fatigue**	**Sleep**	**Physical well-being**	**Emotional well-being**	**Coping**
RAID[34]	x	x	x	x	x	x	x

SJC = swollen joint count; TJC = tender joint count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

DAS = Disease Activity Score (based on 44 joint counts: remission score <1.6 [range 0–10.43]); DAS28 = Disease Activity Score (based on 28 joint counts: remission score <2.6 [range 0–9.4]); CDAI = Clinical Disease Activity Index (remission score ≤2.8 [range 0–76]); SDAI = Simplified Disease Activity Index (remission score ≤3.3 [range 0–86]); ACR-EULAR Boolean (SJC, TJC, CRP [mg/L], patient global [0–10] all ≤1); RAPID 3 = Routine Assessment of Patient Index Data 3 (remission score ≤1 [range 0–10]); RAID = Rheumatoid Arthritis Index of Disease (patient acceptable state <2 [range 0–10])

Table 1. Treat to target composite disease activity measures in rheumatoid arthritis and contributing components

Principles of rheumatoid arthritis management

The strategy that underpins management of RA is to rapidly suppress inflammation in newly diagnosed patients and to maintain this indefinitely in all patients. The recommended way to achieve this follows the principle of 'treat to target' (T2T), which requires the selection of an objective measurement of remission or low disease activity (the target), and treatment optimisation to achieve and maintain this.[1,2,3] T2T in everyday practice means that when a patient is reviewed the chosen 'target' is measured. If the target is not achieved a treatment change is instituted, with follow up four to six weeks later, whereupon the target is reassessed and treatment escalated again if necessary. This cycle is repeated until the T2T goal is achieved, after which follow up can become much less frequent (6–12 months), with rapid patient-initiated access available if the disease flares. The chosen 'target' may be inflammation or patient-outcome oriented, but generally a composite disease activity score such as the DAS28 is used (see Table 1).

Current guidelines place importance on the involvement of patients in their care, with education and shared decisions made between the patient, rheumatologist and multidisciplinary team (MDT).[2,3] There is also an important role for patient organisations, such as the UK National Rheumatoid Arthritis Society, to support the process by providing written and telephone advice about all aspects of the disease and the therapies available.

Treatment choices

Conventional synthetic DMARDS

The foundations of pharmacological treatment for all RA patients are conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). These include methotrexate (MTX) 7.5–25mg weekly oral or subcutaneous; hydroxychloroquine (HCQ) up to 5mg/kg daily orally; sulfasalazine (SSZ) 1–3g daily orally; and leflunomide (LEF) 10–20mg daily orally. Because all csDMARDs have a slow onset of action, corticosteroids are used for rapid suppression of inflammation at first diagnosis or to control flares, but adverse effects mean they are not favoured as part of a long-term treatment strategy.[2,3] Depomedrone 120mg intramuscularly (repeated at 4–6 weeks), or tapering oral prednisolone starting at 15–20mg daily reducing to zero over 8–12 weeks would be typical practice.

Biologic DMARDs

Approximately 40% of newly diagnosed RA patients fail to achieve a low disease activity or remission target with csDMARDs, either due to lack of efficacy or poor tolerability. Furthermore, given the relentless relapsing nature of RA, patients who initially achieve remission lose control during the course of their disease and, despite combination csDMARDs and corticosteroids, fail to maintain good outcomes. In this situation a biological medicine, referred to as biologic DMARD (bDMARD), is used.

Four classes of bDMARDs are licensed, targeting tumour necrosis factor alpha (TNFi: anti-TNFα antibody and soluble TNF receptor), B cells (anti-CD20 antibody), IL-6 (anti-IL6 receptor antibody) and T cell co-stimulation (CTLA4-Ig) (see Table 2). Recently, the patents for some bDMARDs expired, enabling biosimilar products to be licensed in the UK. Currently there are biosimilars for three TNFi and the anti-CD20 antibody bio-originator products (see Table 3).

The value that bDMARDs have brought to RA management and disease outcomes cannot be overstated. Since the introduction of TNFi in 1999, the natural history of RA has been radically changed, with some features now rarely seen, such as rheumatoid vasculitis, corneal melt, metacarpophalangeal ulnar deviation, swan neck, Boutonniere deformities and gross destructive disease. The inhibition of erosions has reduced the subsequent need for arthroplasty, and joint rheumatology-orthopaedic clinics have been disbanded through lack of necessity. Adverse cardiovascular outcomes linked to the accelerated atherogenesis of inflammation have also diminished, with the increased standardised mortality rate of RA being brought back to that seen in the general population in those who achieve sustained low disease activity.[4,5]

All classes of bDMARDs have proven efficacy in RA patients who have failed to respond to MTX, with clinical, functional and structural benefits demonstrated.[6-8] A few studies have compared one bDMARD against another: within class, EXXELERATE demonstrated non-superiority of one TNFi over the other (certolizumab and adalimumab) in RA patients with prognostic factors for severe disease progression.[9] Between-class trials include ORBIT, which demonstrated non-inferiority of rituximab in comparison with TNFi (adalimumab or etanercept) in seropositive biologic-naive patients,[10] while AMPLE demonstrated non-inferiority of adalimumab to abatacept in MTX-IR patients with early RA.[11] In

Target	Structure	Generic name			
TNF	Anti-cytokine mAb	Adalimumab BO, BS	Certolizumab BO	Golimumab BO	Infliximab BO, BS
TNF	Soluble receptor-Ig construct	Etanercept BO, BS			
CD20	Anti-B cell surface receptor	Rituximab BO, BS			
IL-6	Anti-cytokine receptor	Sarilumab BO	Tocilizumab BO		
CD28	CTLA4-Ig construct	Abatacept BO			
JAK 1&2	Chemical inhibitor	Baricitinib			
JAK 1&3	Chemical inhibitor	Tofacitinib			

TNF = tumour necrosis factor; IL = interleukin; JAK = Janus kinase; mAb = monoclonal antibody; Ig = immunoglobulin; BO = bio-originator; BS = biosimilar

Table 2. Biologic DMARDs and targeted synthetic DMARDs and their targets for the treatment of rheumatoid arthritis

general, all bDMARDs exhibit better efficacy when co-prescribed with MTX, but poor tolerability of the latter in some patients has led to bDMARDs being used either with other csDMARDs or as monotherapy in up to a third of patients. In this context, ADACTA and MONARCH have demonstrated superiority of anti-IL-6 receptor antibody (tocilizumab and sarilumab, respectively) monotherapy over adalimumab monotherapy in MTX-IR patients.[12,13]

There are a number of stratifiers that permit optimal use of some bDMARDs over others in particular situations.[14] To avoid toxicity, TNFi are not favoured in patients with interstitial lung disease, severe cardiac failure or multiple sclerosis, whereas rituximab and abatacept appear safer in these situations. Similarly, tocilizumab is not favoured in patients with diverticular disease. Rituximab is also favoured over TNFi in patients with a recent history of lymphoma or malignancy; however, observational studies, while limited in terms of duration of follow up and methodological difficulties, have failed to establish an increased risk of cancer (except non-melanoma skin cancer) in TNFi-treated patients.[14] Seropositivity for rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (ACPA) stratifies an optimal response to rituximab (especially in those with high total Ig) and abatacept (especially in those with high titre ACPA), but does not influence response to tocilizumab, and has a less clear impact on response to TNFi.[14] Smoking adversely affects outcomes with TNFi and abatacept but seems to have less impact on the efficacy of rituximab and tocilizumab. Obesity also adversely affects outcomes across TNFi but less so for anti-CD20, IL6 and CTLA4-Ig classes of bDMARDs.

The success of the T2T strategy, with many patients achieving remission or low disease activity, has led to some patients tapering treatment. It is now commonplace in clinical practice to attempt dose reduction of csDMARD and bDMARDs. However, this remains somewhat arbitrary as there are few or no biomarkers of optimum doses across the bDMARD classes to guide likelihood of success. One exception is adalimumab and certolizumab where a therapeutic dose range has been established. In practice, many patients (almost 40%) have supratherapeutic drug levels following fixed dosing of TNFi drugs according to their licence.[15] For those in remission, where the drug level is in the supratherapeutic range, it is logical to predict a high likelihood of maintained good disease control following dose tapering.[16] Dose reduction of bDMARDs is achieved by prolonging the interval between doses of subcutaneously delivered therapies, or using lower doses if commercially available, such as 25mg of etanercept. The next major advance in RA management will come from personalised medicine, enabling selection of the right class of bDMARD at the correct dose first time for individual patients.

Generic name	Bio-originator brand name	Biosimilar brand name(s)
Abatacept	Orencia	
Adalimumab	Humira	Amgevita, Hulio, Hyrimoz, Imraldi
Certolizumab	Cimzia	
Etanercept	Enbrel	Benepali
Golimumab	Simponi	
Infliximab	Remicade	Remsima/Inflectra, Flixabi/ Renflexis, Zessly
Rituximab	Mabthera	Truxima
Sarilumab	Kevzara	
Tocilizumab	RoActemra	

Table 3. Generic and brand names of bio-originator and biosimilar biologic agents licensed for treatment of rheumatoid arthritis in the European Union

Targeted synthetic DMARDS

A new therapeutic class of DMARDs that inhibit Janus kinases (JAK) have recently been licensed. JAKs are intracellular enzymes that enable cytokines, hormones or growth factors to bind to their cell surface receptors to mediate effects at the nucleus, so-called intracellular signalling. Baricitinib (Olumiant) preferentially inhibits JAK1 and 2, and tofacitinib (Xeljanz) preferentially inhibits JAK1 and 3 (see Table 2). These inhibitors are synthetic chemical compounds that inhibit JAK phosphorylation and thereby perturb the intracellular signalling that follows cytokine binding to cell surface receptors. They have been given the nomenclature targeted synthetic DMARD (tsDMARD), as their structure and mechanism of action are distinct from csDMARDs and bDMARDs. Clinical trials have demonstrated efficacy of tsDMARDs across composite disease activity and structural outcomes in csDMARD-naïve, csDMARD IR and bDMARD IR patients. They appear to have a similar order of magnitude of efficacy to bDMARDs.[17,18] The place of tsDMARDs in the RA treatment pathway remains uncertain, and has been influenced by cost in comparison with bDMARDs. The unique mode of action, oral bioavailability, efficacy as monotherapy (without MTX), rapid onset of action and short half-life make them an

attractive treatment option. However, as with bDMARDs, observational postmarketing surveillance will be necessary to confirm trial data and long-term tolerability.

Gender

In many RA analyses female gender has been found to be associated with higher disease activity parameters and poorer prognosis than men. For patients treated with biologics, the outcomes with TNFi in meta-analysis[19] support female gender as a poor prognosis marker, significantly predicting discontinuation for any cause (inadequate response or intolerance), hazard ratio 1.18 (95% CI 1.03, 1.36). Clinical outcomes with TNFi are reported in randomised trials and registry studies to be significantly better in men, including composite disease activity scores and pain.[20,21] The duration of disease may be a factor, as the Danish DANBIO registry found better clinical outcomes among men only in those with early RA, up to two years,[22] and no gender effect was seen in the South Swedish registry, which reported outcomes in patients with mean disease duration of 11 years.[23] In rituximab-treated patients, the UK BSRBR and French AIR registries have reported male gender to be associated with better clinical outcomes in patients previously failing to respond to TNFi.[24,25] In contrast, clinical and functional outcomes with tocilizumab and abatacept treatment have not been found to be associated with gender.[20,26,27]

Other considerations

Notwithstanding the challenge of monitoring and achieving sustained low disease activity or remission in RA, an important part of disease management includes awareness and monitoring of toxicity across the spectrum of DMARDs. All licensed agents – csDMARD, bDMARD and tsDMARD – have clearly defined toxicities and monitoring requirements to detect and minimise these.

Increased risk of sepsis is of paramount concern, and prompt recognition and treatment is vital for those who manage RA patients. Some agents have specific toxicities and monitoring requirements fully explained in the product characteristics, with guidelines on how to manage these recently updated for csDMARDs[28] and bDMARDs.[29]

Whereas guidelines indicate that bDMARDs/tsDMARDs should be prescribed in a T2T model of care in all patients failing to achieve low disease activity or remission with csDMARDs,[2,3] in some countries, including England and Wales, an additional threshold of having a high DAS28 score of at least 5.1 is required. This is contentious as it denies access to bDMARDs/tsDMARDs for a group of patients with moderate DAS28 scores. These patients have not achieved the least stringent recommended T2T goal of DAS 3.2 (low disease activity) and have been shown to have poor outcomes, including high rates of orthopaedic surgery with continued csDMARD treatment.[30,31] It is hoped that falling costs will make the use of bDMARDs/tsDMARDs sufficiently cost effective to enable NICE to change eligibility criteria to permit access to bDMARDs/tsDMARDs for such patients.

Although the large number of licensed csDMARD and bDMARDs used in a robust T2T strategy will achieve remission for many, a proportion of RA patients will demonstrate a lack of sustained response. There are many reasons that contribute to this unwelcome outcome, including lack of disease biomarkers to permit optimal DMARD choice, delayed treatment escalation according to the principles of T2T, non-adherence, restricted access to care or therapies (*eg* eligibility criteria mandated by NICE) and the adverse effects of comorbidities, including obesity and smoking. Every time there is a flare, or an episode of increased inflammatory activity, quality of life may be affected and joint damage may progress with functional and mental health consequences. RA management therefore requires lifelong support for patients from their rheumatologist and MDT. Patient involvement, education, measures to enhance adherence to treatment, prompt intervention to control flares and access to programmes to stop smoking and weight reduction are all key components of the holistic care required.

RA remains a complex and challenging disease to manage, but changes in our treatment strategy to ensure rapid and sustained disease suppression, supported by more and more therapeutic options, make the outlook immeasurably better. Nonetheless, it is sobering that despite the advances that T2T and new therapies have brought to clinical practice, the autoimmune processes that leads to RA remain incurable and management for the majority depends upon chronic immune suppression, physical and psychological support.

Declaration of interests

Patrick Kiely has been involved in educational support, speaker meetings, consultancy and advisory board attendance for Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Eli Lilly, Gilead, Pfizer, Roche, Sanofi, UCB.

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