Treat to target in managing inflammatory arthritis

Treating to target has been used in many areas of medicine, including diabetes mellitus and cardiovascular disease risk. This principle has now been applied to rheumatological conditions, notably inflammatory arthritis. This article discusses the role and importance of this management approach in inflammatory arthritis.

Current management of rheumatoid arthritis and other forms of inflammatory arthritis focusses on using disease-modifying anti-rheumatic drugs effectively. Most patients receive conventional disease-modifying drugs, and a minority receive biologics. The main disease-modifying anti-rheumatic drugs are summarized in *Table 1*. Conventional disease-modifying anti-rheumatic drugs were historically termed slow-acting anti-rheumatic drugs. In contrast biologics have relative rapid effects. Steroids (glucocorticoids) have some disease-modifying properties and are often given with disease-modifying anti-rheumatic drugs. Steroids have rapid effects, unlike conventional disease-modifying anti-rheumatic drugs. The long-term benefits and risks of steroids and conventional disease-modifying anti-rheumatic drugs differ substantially.

Clinical trials show that when patients with active inflammatory arthritis start disease-modifying anti-rheumatic drugs their joint inflammation is reduced. The numbers of swollen and tender joints decrease, patients' global assessments of disease activity improve and the elevated acute phase response declines. Integrated response measures such as the American College of Rheumatology (ACR) responder rates and the European League Against Rheumatism (EULAR) responder rates also show treatment is effective. These benefits have been confirmed in systematic reviews and meta-analyses (Donahue et al, 2008; Ma et al, 2010).

While it is clearly crucial for patients to receive effective treatments, simply giving patients treatments which are better than placebo cannot be an end in itself. Instead the management of inflammatory arthritis needs to deliver care that meets current quality standards. It needs to be safe, effective, patient-centred, timely, efficient and equitable. The 'treat to target' initiative reflects this approach to medical care.

The management of inflammatory arthritis focuses on two of its important characteristics: its persisting synovitis and its associated systemic inflammation, which often includes autoantibody formation involving rheumatoid factor and anti-cyclic citrullinated peptide antibody. Ongoing synovitis damages cartilage, bone and tendons. Ongoing systemic inflammation causes extra-articular complications like vasculitis and lung disease. Uncontrolled inflammatory arthritis results in disability, decreased quality of life and increased comorbidity, notably cardiovascular disease. The consequences include loss of work, major medical and social costs, and high morbidity and mortality.

Assessing inflammatory arthritis

There is general agreement on the need to measure the activity of inflammatory arthritis and to use these measures to assess the impact of treatment.

Individual measures, such as joint counts, have been used for many years. However, there has been greater emphasis on combining individual measures in composite indices. The most widely used measure is the disease

Table 1. Main disease-modifying drugs used in inflammatory arthritis

Class	Group	Agent
Conventional synthetic disease-modifying anti-rheumatic drugs	Main disease-modifying anti-rheumatic drugs	Methotrexate
		Hydroxychloroquine
	Other commonly used	Leflunomide
		Sulfasalazine
		Azathioprine
	Infrequently used	Ciclosporin
		Injectable gold
		Adalimumab
		Certolizumab pegol
	Tumour necrosis factor inhibitors	Etanercept
Biological disease-modifying anti-rheumatic drugs		Golimumab
		Infliximab
	T cell co-stimulation inhibitor	Abatacept
	Anti CD20 (B cell inhibitor)	Rituximab
	IL-6 receptor blocker	Tocilizumab

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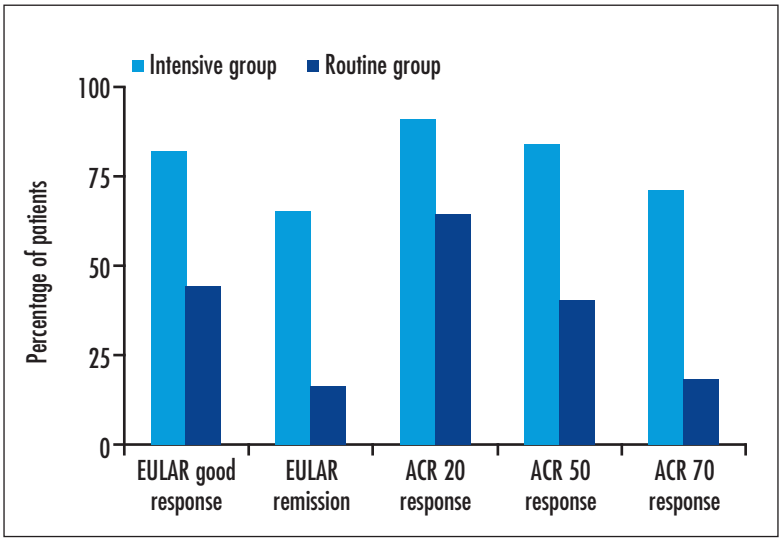
activity score for 28 joints (DAS28). This combines tender joint counts, swollen joint counts, the patient's global assessments and the erythrocyte sedimentation rate. Alternative measures include the simplified disease activity index, which incorporates physician's global assessments and replaces erythrocyte sedimentation rate with C-reactive protein levels, and the clinical disease activity index, which omits the laboratory measures (Aletaha and Smolen, 2005).

The DAS28 has become frequently used in clinical practice as it is easy to use, is relatively reproducible, and can be assessed at consecutive visits to assess changes in disease activity and monitor treatment responses. However, it has several limitations. First it omits most lower limb joints, particularly the small joints of the feet and ankles. Second it is over-reliant on subjective measures such as patient global assessments, and may particularly reflect pain and fibromyalgic features (McWilliams et al, 2012). Some experts believe more use should be made of patient self-assessment and advocate measures such as the Routine Assessment of Patient Index Data 3 (RAPID3) (Pincus et al, 2011), although this approach also emphasizes pain and fibromyalgic features.

One approach to overcoming the limitations of patient self-assessment is to incorporate objective measures such as ultrasound examination of joints within clinical assessment. Ultrasound is becoming increasingly used in clinical practice to identify synovitis by detecting power Doppler signal within the joint. It is relatively inexpensive, non-invasive and uses no radiation. However, it is not routinely available in all rheumatology clinics, training requires time, supervised development and practice, and the ultrasound machines come at a significant cost. Wakefield et al (2004) found subclinical asymptomatic synovitis in 13% of patients with early oligoarthritis arthritis on ultrasound examination, supporting the role of ultrasound in early inflammatory arthritis pathways. However, the role of ultrasound in established disease remains unclear. Wakefield et al (2012) investigated the role of ultrasound in achieving improved outcomes. The results suggested patients in clinical remission have silent synovitis on ultrasound imaging. Power Doppler signal is thought to be an independent predictor of a flare, raising the possibility of its use to decide on treatment and to risk stratify patients who may be at greater risk of active disease (Saleem et al, 2009). However, clearly more research is needed in this area to determine in which group of patients this modality should be used.

Figure 1. Improvements at 18 months in TICORA strategy trial (Grigor et al, 2004). There were significant differences in favour of the intensive group in all assessments. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.



Why 'treat to target'?

Several trials of treatment strategies in rheumatoid arthritis have established the benefits of using targeted treatments based on aiming to improve composite scores of disease activity. The first of these was the TICORA trial (Grigor et al, 2004), based in two teaching hospitals in Glasgow. Between 1999 and 2001 110 patients were enrolled who had active rheumatoid arthritis of less than 5 years' duration. Intensive treatment involved monthly specialist assessments which included measuring disease activity scores. Disease-modifying anti-rheumatic drug treatment was escalated using a standardized protocol. This approach included combination disease-modifying anti-rheumatic drugs. Active joints were injected with steroids. Treatment was escalated until disease control was achieved. Routine care involved 3-monthly reviews. No measure of disease activity was used in clinical decision making, and there was no pre-defined treatment escalation. After 18 months all assessments of disease activity were significantly better in the intensive active treatment group (*Figure 1*). Interestingly drug-related adverse events were lower in the intensive treatment group and the overall medical costs were less, mainly because more patients receiving routine care were admitted to hospital.

Several other strategy trials produced similar results. Most notable were two trials from Holland; the Behendel Strategieen (BeST) or treatment strategy Study (Goekoop-Ruiterman et al, 2007) and the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (Verstappen et al, 2007). Interestingly the CAMERA trial used a computer algorithm to guide treatment escalation instead of relying on clinician choice.

These and other strategy trials showed tighter control, using disease activity scores to guide treatment decisions, gave better outcomes in patients with active rheumatoid arthritis. A systematic review by Knevel et al (2010) identified two kinds of strategy trials. In 13 trials the reason for treatment adjustment differed between study arms, while in seven trials the same clinical outcome was used to adjust therapy with different treatments. Both approaches achieved better outcomes in early active rheumatoid arthritis.

The treat to target initiative in inflammatory arthritis built on these findings in rheumatoid arthritis. This approach is considered likely to achieve the best out-

comes. The primary goal is to fully suppress joint inflammation, which will prevent structural joint damage, reduce long-term disability and improve quality of life. Treat to target involves using a composite measure to guide treatment. The aim is to achieve remission or low disease activity. An international task force formulated a consensus and published recommendations which could form the basis for using treatment to target in routine practice (Smolen et al, 2010). The consensus balanced evidence obtained by systematically reviewing the literature with expert opinion. It has two components. First there are four overarching principles, which are summarized in *Table 2*. Second there are ten specific recommendations for achieving treat to target, which are shown in *Table 3*.

Many doubts and uncertainties surround the use of treat to target. One challenge is agreeing the best target. There are many different criteria for remission. Although complete remission leads to better overall outcomes for patients, it is only achieved by a small minority of patients. Less complete forms of remission are easier to achieve but less beneficial for patients. A second challenge is that there is uncertainty about the optimal treatments to achieve remission. Pincus and Castrejón (2013) suggest that the strategy is more important than the agent. In particular there is doubt about the best way to use high-cost biological treatments. Finally in many patients it is not possible to achieve remission or low disease activity. When patients have already developed joint damage, consequent pain and reduced function are unlikely to respond to escalation of disease-modifying anti-rheumatic drugs and immunosuppression. When patients develop significant treatment-related adverse events treatment escalation may be impractical. Co-existing comorbidities and clinician and patient choice may also limit the use of treat to target. As a consequence the best way forward is to develop an individually tailored management plan which is supported by the clinician, the managing team and the patient to achieve the best possible outcome for each individual.

There has been less research into the relationship between joint inflammation and damage in other forms of inflammatory arthritis. The tight control principle is being investigated in psoriatic arthritis. The TICOPA study (Tight Control of Psoriatic Arthritis) randomized patients to an intervention group where they were reviewed and treatment escalated as necessary every 4 weeks *vs* the standard care group where patients were seen every 3 months. Preliminary results have been positive with significantly more patients achieving responses with intensive treatments (Coates et al, 2014). Publication of the full results is awaited.

Access to treatments

When anti-tumour necrosis factor therapy first became available, there were concerns regarding the safety profile of these agents both in the long and short term. It was therefore widely accepted that anti-tumour necrosis factor therapy should be reserved for those patients in whom other treatments had failed to adequately suppress disease activity. Since then there has been increasing evidence for the role of combination disease-modifying anti-rheumatic drug therapy but the question about the benefits of initiating high-cost biological therapy earlier over trying to induce remission with a step-wise disease-modifying anti-rheumatic drug to anti-tumour necrosis factor esca-

Table 2. Principles of treat to target in rheumatoid arthritis

Principle	Concept
Rheumatoid arthritis treatment is based on shared decision making between patient and rheumatologist	The patient must be informed of the therapeutic options, understand the reasons for recommending a particular therapeutic approach by weighing benefit and risk, and participate in the decision as to which treatment should be used
The goal is to maximize health-related quality of life by controlling symptoms, preventing structural damage, normalizing function and social participation	This principle transcends all treatments and their follow up
Minimizing inflammation is the best way to achieve these goals	The inflammatory response underlying rheumatoid arthritis is responsible for the signs and symptoms of the disease and is associated with adverse outcomes in all areas
Treatment to target, including measuring disease activity and adjusting therapy accordingly, will optimize rheumatoid arthritis outcomes	Although treat to target involves a range of interventions, this general statement summarizes its key components

Table 3. Ten key recommendations on treating rheumatoid arthritis to target

1. The primary target for treatment of rheumatoid arthritis should be clinical remission
2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
3. Low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
4. Until the target is reached, drug therapy should be adjusted at least every 3 months
5. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (every 3–6 months) in those with sustained low disease activity or remission
6. Validated composite measures of disease activity, which include joint assessments, should guide treatment decisions
7. Structural changes and functional impairment should also be considered when making clinical decisions
8. The treatment target should be maintained throughout the course of the disease
9. The choice of the measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks
10. The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist

lation approach remains incompletely answered. In the UK, the current National Institute for Health and Care Excellence (2007) guidance takes into account cost effectiveness, requiring a high disease activity score of >5.1 on two occasions and demonstration of inadequate control with at least two disease-modifying anti-rheumatic drugs including methotrexate for at least 6 months.

There is significant variation between countries regarding the initiation of biological therapies in the management of rheumatoid arthritis. A study published by Pease et al (2011) explored some of these differences looking at data from America, UK, American, Australian, British, Czech, Danish, Dutch, Finnish, German, Italian, Norwegian, Spanish and Swedish rheumatoid arthritis databases. The study identified that there was more relatively more stringent prescribing of anti-tumour necrosis factor therapy in the UK and Czech databases compared with the other countries. Anti-tumour necrosis factor therapy was initiated with less severe disease in the American databases and there was a discrepancy between pubic and privately insured patients suggesting the effect of cost on treatment decisions.

Conclusions

There is considerable evidence in favour of managing inflammatory arthritis using a target-driven approach. In practice not all targets will be achieved by all patients as a result of drug toxicity, comorbidities and pre-existing joint damage. However, combining pre-defined treatment targets with regular reviews and monitoring allows a framework for safe and rapid escalation of therapy to optimize outcomes for patients with inflammatory arthritis. BJHM

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KEY POINTS

- Treatment of inflammatory arthritis is primarily aimed at reducing the number of swollen and tender joints.
- Treating to a predefined target achieves better outcomes (decreased joint inflammation and structural joint damage, reduced long-term disability and improved quality of life).
- Treating to target involves using a composite score to measure disease activity.
- Treatment should be escalated safely and as tolerated to achieve remission or low disease activity.
- Co-existing comorbidities and existing joint damage may make a target of remission more difficult or unachievable in a proportion of patients, and more realistic targets may need to be agreed for individual patients.

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