Can we cure rheumatoid arthritis?

Rheumatoid arthritis is a chronic multisystem autoimmune disorder associated with significant morbidity and premature mortality. The management of rheumatoid arthritis has undergone a sea change over the last century from nihilistic beginnings using bed rest and analgesia to the aggressive interventional management course pursued today.

The current goal in the treatment of rheumatoid arthritis is long-term remission and a number of key developments have allowed us to achieve this end point. Owing to a greater understanding of the pathophysiology of rheumatoid arthritis, including characterizing the pivotal pro-inflammatory cells and cytokines involved in the disease, targeted biologic therapies have been developed to switch off the inflammatory process.

This underscores the imperative in rheumatoid arthritis treatment, to suppress inflammation as rapidly and comprehensively as possible, in order to maximize outcomes. In the clinic we attempt to do this by seeing patients as early in their disease process as possible, treating them aggressively with combinations of drugs and monitoring them frequently to allow a change in therapy if the disease remains active. The so-called 'treat to target' paradigm evolved from this, dictating that we strive for remission according to a rheumatoid arthritis disease activity score (DAS) (see below).

Apart from the biologic agents, the appropriate use of traditional disease-modifying anti-rheumatic drugs, specifically methotrexate, has produced excellent results and allowed us to consider whether cure of disease is possible. Owing to the heterogeneity of rheumatoid arthritis, however, it seems likely that the true key to curing rheumatoid arthritis will be to fully characterize the genetic, immunological, hormonal and environmental factors which perpetuate disease. This will eventually allow therapy to be focused on the individual leading to an even more sophisticated therapeutic approach than that used now.

Key advances

Early diagnosis

Many believe that a 'window of opportunity' exists in early rheumatoid arthritis during which therapeutic intervention is more effective than in later disease. A European task force concluded that patients should be treated if they have joint symptoms for >6 weeks, including morning stiffness (>30 minutes' duration) and joint swelling (Combe et al, 2007). Patients with these features should be reviewed urgently by a rheumatologist and thus many centres in the UK have developed early inflammatory arthritis clinics to facilitate the process.

The National Institute for Health and Clinical Excellence (2009) rheumatoid arthritis guidelines have endorsed this rapid referral paradigm. Early diagnosis has been greatly aided by the serological identification of anti-citrullinated peptide antibodies (ACPA) which are equally sensitive but more specific for rheumatoid arthritis than rheumatoid factors. Furthermore ACPA-positive patients have a poorer prognosis with more rapid joint destruction (Rönnelid et al, 2005).

Intensive treatment with combination therapy

A major therapeutic advance has been use of disease-modifying anti-rheumatic drug combinations. One of the first studies to show this was the FIN-RACo trial (Möttönen et al, 1999) in early arthritis comparing sulphasalazine monotherapy with sulphasalazine, methotrexate, hydroxychloroquine and prednisolone combination therapy. The researchers found higher rates of remission and less radiological damage in the combination group which was sustained for 11 years of follow up.

These findings were echoed by the Combination therapy in daily practice (COBRA) (Landewe et al, 2002) and Dutch Behandel Strategieen (BeSt) (Goekoop-Ruiterman et al, 2005) trials which showed sustained benefit using early combination therapy. As a consequence of these and other studies, the National Institute for Health and Clinical Excellence (2009) recommends the use of combination therapy especially in early disease.

The benefit of early intensive intervention, however, needs to be weighed against the potential risk of over-treatment in a given individual. Patient factors such as level of disease activity, age, co-morbidity and medication use must be considered when formulating a management plan.

Early intervention with biologic disease-modifying anti-rheumatic drugs

A wealth of evidence exists showing that patients who do not respond adequately to traditional disease-modifying anti-rheumatic drugs (e.g. methotrexate) should be treated with biologic agents. These targeted medications include those which inhibit tumour necrosis factor-alpha (TNF-α) (infliximab, adalimumab, etanercept, certolizumab, golimumab), B-cells (rituximab), T cell co-stimulation (abatacept) and interleukin-6 (tocilizumab). Studies have demonstrated superiority of biologic agents combined with methotrexate compared with methotrexate alone in moderate to severe active rheumatoid arthritis. Furthermore early intervention with a biologic disease-modifying anti-rheumatic drug may be the optimal therapeutic approach (Klarenbeek et al, 2009).

Target-driven therapy

However, perhaps the most important message to emerge from the literature has been the benefit of tight control and target-driven therapy in maximizing outcomes. The approach is similar to that used in controlling diabetes and hypertension. The Tight Control for Rheumatoid Arthritis (TICORA) (Grigor et al, 2004) and BeSt trials clearly showed the benefits of treating to a target DAS. The DAS is a semi-objective measure which is easily integrated into routine clinical practice (*Table 1* and *Figure 1*). Ideally the DAS should be documented for every rheumatoid arthritis patient at every outpatient visit.

Can we cure rheumatoid arthritis currently?

The BeSt study has given great insight into answering the question of whether it is yet possible to cure rheumatoid arthritis. The

results demonstrated that methotrexate combined with an anti-TNF agent (infliximab), when introduced early, allowed a significant proportion of patients to enter remission which was sustained without further medication. Indeed 50% and 19% of those initially treated with the above combination were in biologic-free and total drug-free remission respectively after 5 years (Klarenbeek et al, 2006). This suggests that currently drug-free remission is achievable in a proportion of patients which contrasts sharply with therapeutic paradigms and outcomes even a decade ago. Despite this patients in remission need to be monitored in the long term as truly curing disease remains elusive.

Will we be able to cure rheumatoid arthritis in future?

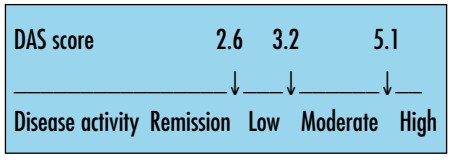
The search continues apace for novel therapeutic targets in rheumatoid arthritis. Since the identification of TNF-α as a key pro-inflammatory cytokine in rheumatoid arthritis pathogenesis, translational research has identified other cytokines important in the disease such as IL-6 and IL-17 and thus therapies have been developed to block their activity. Furthermore agents which inhibit T cell co-stimulation and cause B cell destruction have been highly successful although further research is required to ascertain exactly how best to use these interventions to optimize prognosis. Another approach, adapted from oncology, is to block the signalling pathways activated during the inflammatory process although this strategy is still very much in the development phase.

Table 1. Components of the disease activity score (DAS)

Component	Value
Swollen joint count	__/28
Tender joint count	__/28
Patient's global assessment of disease activity (visual analogue score)	__/100 mm
erythrocyte sedimentation rate	__mm/hr

Enter values into an online DAS calculator, e.g. www.das-score.nl, to derive score

Figure 1. Disease activity score (DAS) explanation.



Huge variation exists between individuals with rheumatoid arthritis in aspects such as severity of disease and response to treatment. It is highly likely that the disease currently classified as rheumatoid arthritis is in fact several distinct conditions with differing pathogeneses. When treating patients we frequently find that while one individual will respond to a specific biologic agent a phenotypically similar patient will fail to respond to the same biologic. A major milestone in the bid to cure this disease would be the identification of markers, genetic or otherwise, which would allow us to predict disease severity and response to a particular therapeutic intervention. An insight into this is that patients seropositive for rheumatoid factors or ACPAs are more likely to respond to rituximab than those who are negative for these antibodies.

Conclusions

These are truly exciting times in rheumatology with management strategies constantly being refined and myriad therapeutic targets on the horizon. We cannot yet cure rheumatoid arthritis but remission is a realistic goal provided appropriate management strategies are used. If advances continue at the current rate it seems likely that a cure will soon be within our sights. BJHM

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KEY POINTS

- Early recognition of rheumatoid arthritis is vital and must be considered in any patient with ≥6 weeks of joint pain and swelling and >30 minutes of morning stiffness.
- Referral to a rheumatologist should occur as rapidly as possible.
- Treatment should commence immediately, often with combination therapy.
- Regular review is essential with driven treatment to optimize outcomes.
- Following failure of traditional disease-modifying anti-rheumatic drugs patients should be started on biologic agents (usually anti-tumour necrosis factor first line).
- When used early anti-tumour necrosis factor treatment can result in drug-free remission.
- Studies are ongoing in many areas including genetics and translational research looking for new therapeutic targets which may one day allow us to cure rheumatoid arthritis.