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Is there a place for initial treatment with biological DMARDs in the early phase of RA?

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A B S T R A C T

The use of biological disease-modifying antirheumatic drugs (bDMARDs) has changed the face of rheumatoid arthritis (RA). Achieving remission, normal function and prevention of joint damage are now possible for many patients with RA. In clinical practice, however, particularly with cost considerations, bDMARDs are usually prescribed after failure of one or more conventional synthetic DMARDs. With evidence that early treatment has a greater impact than later on, the question regarding initial bDMARD therapy and their potential role within a window of opportunity to influence disease outcomes remain. The increasing emphasis on early diagnosis and research into the preclinical phase of the disease also heralds the question, 'Can bDMARDs prevent the development of RA?'
The aim of this review is to review randomised controlled trials with bDMARDs as initial therapy in early RA and to discuss their role in early disease.

Introduction

Since the introduction of the first tumour necrosis factor alpha inhibitor (TNFi), infliximab, for the treatment of RA in the 1990s [1], there has been a rapid expansion of biological disease-modifying anti-rheumatic drugs (bDMARDs) in this area. Within the TNFi class of agents, these include the monoclonal TNFi, adalimumab and the soluble recombinant TNF receptor fusion protein, etanercept, as well as two newer agents, golimumab (another fully human antibody) and certolizumab-pegol (a humanised

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recombinant antibody conjugated with a polyethylene glycol chain). Two other bDMARD cytokine inhibitors are the interleukin (IL)-1 receptor antagonist, anakinra and the IL-6 receptor blocking monoclonal antibody, tocilizumab. Those targeting alternative pathways include the anti-CD20 B-cell depleting agent, rituximab and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) fusion protein, abatacept.

The use of these bDMARDs has changed the face of rheumatoid arthritis (RA) with remission and prevention of joint damage progression being an achievable goal in a large proportion of patients. For many rheumatologists, the use of bDMARD therapy has become part of routine clinical practice. The cost of these drugs, however, remains an important point of consideration [2] and many guidelines place them after failure of one or more conventional synthetic DMARDs (csDMARDs) [3,4]. However, the question, 'Is there a place for initial treatment with biological DMARDs in the early phase of RA?' still remains.

This review will aim to

- address the rationale for early DMARD therapy,
- review randomised controlled trials (RCTs) with bDMARDs in early RA as first-line therapy compared to csDMARD and as part of different treatment strategies,
- address RCTs aiming at the potential to step down or stop DMARD therapy following remission induction and
- review RCTs with bDMARDs in early inflammatory arthritis.

A. Rationale for early therapy

The concept of the 'window of opportunity' suggests that there is a phase early in the disease during which there may be the opportunity to potentially alter the course of the disease or possibly even reverse this with a complete return to normality [5]. Treatment during this period is thought to have a much more profound effect in terms of halting disease progression and achieving remission than therapy at a later stage.

From clinical studies, the disease duration at the time of DMARD initiation has been found to be a significant predictor of response to treatment [6]. A meta-analysis of 12 trials examined the effect of early synthetic DMARD therapy on the long-term radiographic progression in patients with early RA (<2 years at presentation). The average delay between early and late therapy was 9 months. After a median of 3 years of observation, those patients who received early treatment had 33% less radiographic progression compared to those with delayed treatment [7].

It has been suggested that the window for early treatment is much shorter than this, possibly within the first 12 weeks of symptom onset [8]. In a study by Green et al. in which a single dose of corticosteroid was administered to patients with mild early inflammatory arthritis, a disease duration <12 weeks at the time of therapy was noted to be the strongest predictor of remission at 6 months [9]. A systematic literature review by Nies et al. [10] has also shown radiographic progression to be lower with shorter symptom duration. In addition, a meta-analysis of three early arthritis data sets showed symptom duration to be independently associated with DMARD-free sustained remission (the outcome chosen as deemed the closest proxy of cure in (RA) with a hazard ratio (HR) 0.989 (95% CI 0.983–0.995)) and an HR 0.88 using 12 weeks at treatment initiation. In a sub-analysis of the COMET study, an RCT of 417 early RA patients, etanercept + methotrexate (MTX) use in patients with disease duration <4 months was associated with significantly higher proportions reaching remission and low disease activity (LDA) than when the same treatment was used with a longer disease duration [11]. Interestingly, this increased remission rate with very early treatment was not seen in the MTX monotherapy group although radiographic non-progression was higher in the group that was treated early.

B. Clinical trials with biological DMARDs as first-line therapy in early RA

Early DMARD therapy is therefore one of the key principles in the treatment of RA [3]. Whilst this recommendation is widely agreed upon, initial treatment strategies particularly those which include bDMARDs are still a matter of debate.