Role of biologics in early arthritis

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ABSTRACT

Recent advances in the management and treatment of rheumatoid arthritis (RA) have provided evidence for the importance of early diagnosis and treatment of the disease. Biological therapy with monoclonal antibodies, including anti-tumor necrosis factor (TNF) agents have shown major efficacy in terms of disease activity and outcome of inflammatory arthritis in trials. Interest has focused on the treatment of early rheumatoid arthritis with anti-TNF agents to induce long-term impact on outcome. A major study of etanercept versus methotrexate (MTX) showed some benefit at one year for the etanercept group, but long-term data have shown greater benefit. Two double-blind placebo-controlled studies of infliximab in patients with early RA yielded promising data, showing the possibility of a true 'window of opportunity' with long-term benefit from a short term treatment period. Aggressive treatment by anti-TNF agents as well as combination therapies of disease modifying anti-rheumatic drugs (DMARDs) in patients with very early disease would be a logical approach to be investigated in the future.

Introduction

The management of patients with early rheumatoid arthritis (RA) has focused on the early stage of disease. As a consequence, management of the early phase of disease has moved from being a neglected area to being probably the most studied and important time for the care of a patient with RA. The evidence supporting the importance of the early phase of disease can be summarized in the following way.

First, a body of evidence has demonstrated that untreated inflammation leads inevitably to damage of one sort or another, and that the longer a patient is left with untreated inflammation the greater the cumulative damage (1-3). As most damage is believed to be irreversible, if persistent this damage will inevitably translate into disability, and thus a large direct cost to both the individual and society. Objective measures of damage have been developed to document these effects and include the measurement of bony erosions detected by radiographs (4) and more recently evidence from high-resolution ultrasound (5) and magnetic resonance imaging (MRI) (6). Both these latter techniques show that damage occurs early in the disease process and is much more extensive than revealed by conventional radiographs. The loss of function, which is conveniently measured by the Health Assessment Questionnaire (HAQ), has also been demonstrated to occur early in the disease process and to correlate with inflammation (7). Finally, the use of dual-energy X-ray absorptiometry has been adopted as a quantitative measure of the impact of inflammation on bone and again has shown that very rapid bone loss occurs in the early phase of disease, with a close correlation between the amount of inflammation present both locally and systemically. Thus, by every assessment damage occurs early in the disease process and is associated predominantly with the degree of inflammation (8).

An important issue is the concept that the reversibility of damage is transitory. For example, it has been shown that the rapid treatment of inflammation can reverse functional loss in RA if done early, and that this improvement is sustained provided that the inflammation remains suppressed (7). Likewise, bone densitometry has demonstrated that bone loss can be improved in the early phases of disease when inflammation is adequately treated (8). This (temporary ?) reversibility adds urgency to the management of patients with RA. A final crucial and perhaps related point is the suggestion that the outcome of treatment is qualitively different if therapy is given within a narrow therapeutic window. This concept was derived originally from animal models (9), but is supported by the evidence from an

open intervention study which suggests that a 50% chance of remission can be obtained with early therapy in patients with a diagnosis of RA with a duration of less than 12 weeks (10). Care is needed in interpretation of these data, but by analogy with oncology even if early therapy only achieves a reduction in disease bulk, this alone can have a profound difference in outcome. The quantitative reduction in bulk may produce differences, which amount to an almost qualitative difference.

It is reasonable to conclude that the early phase of disease is the crucial time for therapy and the time when most care should be given to optimizing therapy.

Biological therapy

Biological therapy with tumor necrosis factor (TNF) blocking agents represents the most effective therapy so far available to patients with RA. Patients experience relatively few adverse reactions and this combined with the efficacy of the therapy mean that more patients remain on active treatment. Most of the studies have been conducted in patients who had failed to respond to conventional disease-modifying antirheumatic drugs (DMARDs). This group of patients was thought to be largely untreatable and therefore it is important to note that these drugs were as effective in DMARD failure patients as conventional DMARDs had been in DMARD naïve patients. What these studies could not reveal was whether the early use of such biologics would provide a much greater level of response than that seen with conventional DMARDs. Furthermore, there was no indication as to whether the level of improvement in an individual patient would be qualitatively different from that seen with existing treatments given early.

Despite the above caveats, it was believed by most rheumatologists that early use of these agents would provide unequivocal evidence of significant advantage over existing treatments.

Use of etanercept in early RA

It was on this basis that a study was undertaken that compared etanercept with methotrexate (MTX) in patients with RA (11). In the protocol 632 MTX-naïve patients were randomised to either twice-weekly etanercept (10 or 25 mg) or oral weekly MTX up to 20 mg. Etanercept (25 mg) and MTX were equally effective in preventing joint space narrowing and reducing the Sharp score over one year; etanercept (25 mg) significantly slowed the rates of erosion compared to MTX. The American College of Rheumatology improvement criteria (ACR 20) response rates at 12 months were 75% and 65% in the etanercept (25 mg) and MTX groups, respectively. However, functional disability as assessed by HAQ did not differ significantly in the two groups. It was concluded that etanercept was at least as effective as MTX in preventing overall structural damage and superior to MTX in preventing erosions (the latter was not the primary end point). It was clear that etanercept produced more clinical improvement that was sustained over one year.

Importantly, follow-up has shown that at two and three years the patients who received etanercept did increasingly well compared to those who received MTX (12). Interestingly, those who were initially assigned to MTX and later switched to etanercept never caught up in terms of the response rate with patients who had been treated with etanercept from the outset. In the latest and longer-term follow-up data presented at the ACR 2002 Annual Scientific Meeting, among patients who had been randomized initially to etanercept 25 mg, 79% had ACR20, 58% had ACR50, and 31% ACR70 response after four years of continuous etanercept therapy. In addition, 27% of patients had no tender joints, 21% had no swollen joints, 23% had a HAQ score of zero, 73% had a normal C-reactive protein (CRP) level, and radiographic progression had slowed throughout the study: i.e., 0.90 Sharp unit/year in the first year and 0.57 and 0.37 Sharp unit/year in the second and third years, respectively (13).

Explanation of early RA data

The explanation for the surprisingly small differences between the therapies over one year may lie in two critical areas: the MTX regimen and the patient population. The MTX regimen involved the use of MTX earlier in disease and at a higher dose than had ever previously been administered (starting with rapid escalation to 20 mg per week in the first three months). As these were 'early patients' they were much less systemically unwell, and perhaps because of this tolerated the regime in a way that most rheumatologists would not have predicted from their experience of the drug in patients with longer disease duration. This is when therapy with MTX is most frequently given. Therefore patients had a very effective dose of MTX given early and responded better than had ever previously been seen.

As the patient population was naive to MTX, the group contained within it a large population of responders. It is known that patients respond better to their first therapy than they do to later therapies. Interestingly, within the responder population it did not appear to make a great difference whether patients received MTX or etanercept. These patients appeared to do as well with MTX as with etanercept, and thus the effective difference between the two therapies was confined to the higher number of MTX non-responders. This represents a much smaller proportion of the total population than would have been predicted. Thus the above may explain the data at 12 months which did not show any significant difference in several outcome measures.

However, as is now known, over the second and third years patients who took etanercept were more likely to maintain their improvement than patients who took MTX and the difference between the two groups increased with time. The implications of this study are still being assessed. However, what is clear is that therapy did not produce compelling evidence for the use of biologic therapies as first line treatments in every patient with early RA.

Infliximab in early RA

Within the pivotal Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study there were 82 patients who had a disease duration of less than three years (14).

These patients were divided into four dosing regimens; there were small numbers in each group and therefore conclusions must be limited, especially as it was a retrospective analysis. The major findings were that the improvements in radiological progression seen in the whole group were also seen in this sub-group. In fact those who received MTX alone actually deteriorated faster than patients who had disease of longer duration. Thus it appears that infliximab worked equally well in preventing damage in early and late disease, in those patients who had partial responses to MTX prior to entry into this study.

High dose anti-TNF as potential remission-induction therapy

A mode-of-action study was undertaken in 5 patients with very poor prognosis RA treated at presentation (15). This study addressed the questions of whether the heterogeneous response seen in disease was due to insufficient drug levels, and whether a high-dose regimen could induce a disease remission state which could then be sustained without the biologics. These patients received induction with a high dose (infliximab, 10 mg/kg at 0, 2, 6 and 14 weeks)< At the end of this induction, if their disease was not in remission by imaging criteria they underwent re-induction with a further identical high dose induction regimen. The results showed that one patient did not respond at all and one patient achieved clinical remission; however, no patient achieved remission as judged by imaging with high-resolution ultrasound or MRI. By the protocol agreed to at the onset, all patients were eligible for re-induction with a further series of high-dose infusions. One patient did not receive this because of side effects. The re-induction did not produce any further response either in the non-responsive patients or in the others who had not achieved remission. Eventually all patients required further therapy.

It was concluded from the study that the variable response to anti-TNF therapy was not due to insufficient drug. Furthermore, a true remission was rarely obtained with these therapies and a drug-free state could not be sustained; all patients required further anti-TNF therapy. Finally the study demonstrated that there was a close correlation between the synovitis observed with the imaging techniques and the development of new bony defects. No defects were seen without synovitis. Thus, it appeared that the inter-relationship between synovitis and bony damage, which had been observed in other mode of action studies with conventional DMARDs and steroids, also applied to infliximab.

Double-blind placebo-controlled studies of infliximab in early RA

A multicenter, double-blind, placebo-controlled study was undertaken, in which 24 patients with early RA of less than 3 years' duration receiving a stable dose of MTX (mean 15 mg/wk), were randomized to treatment with infliximab, 5 mg/kg, or placebo for 46 weeks. Sonographic measurements of metacarpophalangeal joints at 18 weeks revealed a significantly greater reduction in synovial thickening and vascularity in patients receiving combination therapy compared with those receiving MTX alone, with a significant difference in the serum level of vascular endothelial growth factor (16). Radiographs of the hands and feet at 54 weeks showed greater progression in the total Sharp score in the group receiving MTX alone as compared to the group which received infliximab (17)

Another double-blind placebo-controlled study (18) has shown that early treatment with infliximab may possibly induce clinical remission when administered to patients with a very early stage of RA. This study included patients with untreated RA with poor prognostic features, whose mean symptom duration was 6 months. Patients were randomized to receive MTX plus either placebo or infliximab at presentation. These patients received a year's treatment with frequent assessment by MRI and ultrasound in order to examine the impact of infliximab on the early phase of disease, in particular the time course of response, and furthermore to establish the long-term outcome of these patients. Twenty patients were recruited, one of whom withdrew early due to a vasculitic rash. The infliximab treated patients demonstrated an almost immediate improvement in systemic symptoms. There was a very rapid reduction in synovitis and in the swollen and tender joint counts; the improvements seen at 2 weeks with infliximab were equivalent to those seen at 14 weeks with MTX. At 14 weeks a 50% greater reduction in the joint count was seen in the infliximab patients; slightly delayed but also rapid were the improvements in quality of life and function. At one year an ACR50 was achieved in 77% of the patients treated with infliximab, and ACR70 in 66%. There was also a significant reversal of bony lesions as well as synovitis demonstrated on MRI. More importantly, at two years follow up (mean one year after the last infusion), no patient achieving ACR50 at one year had a flare of disease; the median disease activity score (DAS) 28 was < 2.6, indicating remission, and the quality-of-life improvement had been maintained. This study provides information on the possibility of a true 'window of opportunity' with long-term benefit from a short-term treatment period. Since combination therapies of conventional DMARDs have demonstrated benefit in the disease activity score and radiographic progression but not in the HAQ score or quality of life over time, anti-TNF therapy in the very early stage of disease represents the most successful treatment approach to date in these types of patients.

Currently two very large studies are being undertaken by Centocor and Abbot that are examining infliximab and adalimumab, respectively, compared to MTX (and in one case a combination of TNF blockade with MTX) in early disease. In the Active controlled Study of Patients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset (ASPIRE) trial – a randomized, double-blind, controlled clinical trial of MTX plus infliximab – more than 1000 patients with early RA have been randomly assigned to receive MTX plus infliximab (either 3 mg/kg, 6 mg/kg) or placebo at weeks 0, 2, and 6 and every 8 weeks thereafter

through week 46. The first preliminary results are to be disclosed at the EULAR 2003 Annual European Congress (19). Findings from the PREMIER trial, a study with the fully human anti-TNF agent adalimumab, will also soon be disclosed. In this trial approximately 750 patients with RA of less than 3 years' duration were randomized into treatment groups with MTX plus adalimumab, adalimumab alone, or MTX alone. Assessments include DAS, structural joint damage, and physical disability in a two-year follow-up. These studies should give much clearer evidence of the efficacy and cost-effectiveness of the early use of TNF blocking agents, particularly in combination with MTX. Critical to these studies will be the cost-effectiveness analysis. The alternative approach would be to use the biological agents as step-up therapy for patients who have shown an incomplete response to MTX at an early stage of disease.

Conclusion

Biological therapy with anti-TNF is the most effective therapy available for patients with RA. There is no doubt that it works at least as well as DMARDs in early disease and for sub-populations unresponsive to DMARDs it is considerably more efficacious. This difference appears to increase over time. Studies now in progress will reveal whether there is a significant difference between patients treated with biologics and those receiving monotherapy or combination therapy with conventional DMARDs. However, this research will not clarify whether early anti-TNF therapy will be cost effective, either in terms of the direct or indirect costs both to society and to patients who are exposed to biologics and who may not have required them. These questions will be debated for some time. In the meantime, if costs were not an issue the use of early anti-TNF would be supported by most data. At present a pragmatic approach would be to treat patients initially with conventional DMARD but to rapidly induce biologics if there was evidence of no or an incomplete response. However, if the results of anti-TNF treatment at presentation can be shown to be qualitatively different, this will rapidly change the treatment paradigm.

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