Evidence-based Rheumatology

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In early rheumatoid arthritis the combination of methotrexate and infliximab over 2 years reduces the progression of radiological lesions more than methotrexate alone

Authors: F.C. Breedveld *et al.*
Source: *Ann Rheum Dis* 2004;63:149-55
Title: Infliximab in active early rheumatoid arthritis

Background and aims
In recent years, treatment of early rheumatoid arthritis (RA) with traditional disease modifying anti-rheumatic drugs (DMARDs), especially in combination therapy, has shown to clearly improve clinical response and structural damage. In two preliminary reports, infliximab, an anti-TNF monoclonal antibody, was found to be effective for the treatment of early RA(1, 2).
The results of the Anti-TNF Therapy in RA with Concomitant Therapy (ATTRACT) study (3-5) showed that infliximab plus methotexate (MTX) increases the clinical and radiographic benefit in patients with active RA unresponsive to treatment with MTX. Patients with RA of duration ≤ 3 years treated with any of the infliximab plus MTX regimens resulted in significantly greater improvement in radiographic scores than the MTX-only group (4). However, the longer term radiographic benefit in patients with early RA has not been reported. Thus, the primary objective of the subanalyses reported in this study and carried out in the early RApatients of the ATTRACT study was to evaluate the effects of the combination of infliximab plus methotrexate (MTX) on the progression of structural damage over 2 years in this subgroup of patients.
Methods
Subanalyses were carried out on patients with early RA participating in the ATTRACT. 428 patients with active RA despite MTX therapy received placebo with MTX (MTX-only) or infliximab 3 mg/kg or 10 mg/kg every (q) 4 or 8 weeks with MTX (infliximab plus MTX) for 102 weeks (3-5). Early RA was defined as a disease duration ≤ 3 years; 82 of the 428 patients enrolled (19%) met this definition. Structural damage was assessed with the modified van der Heijde-Sharp score (6) by readers scoring the radiographs "blindly" and in random order. The changes from baseline to week 102 in the total modified van der Heijde-Sharp score were compared between the infliximab plus MTX groups and the MTX-only group.
Results
Of the 82 patients with early RA, 61 (74%) had radiographs suitable for analysis. At week 102, substantial progression in structural damage was observed in patients with early RA treated with MTX only, whereas the change from baseline in radiographic scores for the infliximab plus MTX groups was significantly lower. Treatment with infliximab plus MTX inhibited radiographic damage comparably in the early RA group and the overall infliximab treated population of the ATTRACT study. In early RA patients, a consistent benefit was also seen in the erosion and joint space narrowing scores of the hands and feet at week 102 in each of the four infliximab treatment groups compared with that of the MTX-only group. Interestingly, the lowest infliximab dosage regimen (3 mg/kg q 8 weeks) produced results comparable with all the infliximab groups collectively.
Conclusions
In patients with early RA, 2 years of combination therapy with infliximab and MTX inhibited the progression of structural damage, by preventing radiographic damage and preserving joint integrity and provided long-term benefits. The ATTRACT subgroup analysis of patients with rapidly progressive disease despite MTX therapy suggests that early infliximab therapy may produce better results than treatment begun later in the course of the disease.

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In early rheumatoid arthritis combination therapy with methotrexate and infliximab is more efficacious than methotrexate alone

Authors: E.W. St. Clair *et al.*
Source: *Arthritis Rheum* 2004; 50: 3432-3443
Title: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis. Arandomized, controlled trial

Background and aims
In rheumatoid arthritis (RA), there is only a brief time lapse between the onset of joint inflammation and the development of bone erosions and cartilage injury, events in which the increased expression of tumor necrosis factor α (TNFα) plays a prominent role. This role is confirmed by the improvement in joint inflammation and physical function and by the slowing of radiographic damage in established RAinduced by TNFα blockers shown in many clinical trials.

Early treatment with a TNFα blocker may be efficacious in suppressing joint inflammation and preventing joint damage in RA.

In early RA, combination therapy with 2 or more disease-modifying anti-rheumatic drugs (DMARD) produces greater clinical, radiographic, and functional benefits than less intensive regimens. The aim of this 54-week multicentric, double-blind study was to compare the benefits of the combination of methotrexate (MTX) and infliximab (anti-TNFα monoclonal antibody) with those of MTX alone in patients with active early RA.

Methods

RA patients were eligible if they had active disease (persistent synovitis for ≥ 3 months and ≤ 3 years, ≥ 10 swollen joints, and ≥ 12 tender joints and one or more of the following: a positive rheumatoid factor, radiographic erosions of the hands or feet, or CRP levels ≥ 2.0 mg/dl) and no preceding treatment with MTX or a TNFα inhibitor.

1,049 patients (out of the 1,490 screened) were randomly assigned in a 4:5:5 ratio to 3 treatment groups: MTX–placebo (289 patients), MTX–3 mg/kg infliximab (373 patients), and MTX–6 mg/kg infliximab (378 patients). MTX dosages were rapidly escalated to 20 mg/week, and infliximab or placebo infusions were given at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. MTX tapering was allowed only for toxicity. Oral corticosteroids (≤ 10 mg/day prednisone or its equivalent) and nonsteroidal anti-inflammatory drugs were maintained at baseline dosages. Other DMARDs were not permitted during the study.

Joint examinations were performed by an assessor unaware of the patient's treatment. Other assessments included the patient's self-evaluation of pain, fatigue, functional status (HAQ Disability Index), and quality of life (SF-36) and patient's and evaluator's global disease assessment. Blood samples were obtained to measure ERS, CRP, anti-nuclear and anti-double-stranded DNA antibodies (ANAs and anti-dsDNA), and antibodies to infliximab. Radiographs of the hands and feet were obtained within 4 weeks of the first dose of the study drug and at weeks 30 and 54, or upon premature withdrawal of the patient from the study.

The primary end point for reduction of signs and symptoms was the percentage of ACR improvement (ACR-N) from baseline to week 54 (1). The clinical improvement was also evaluated by the ACR20, 50 and 70 criteria (2) and DAS28 (3). The primary endpoint for radiographic progression of joint damage was the change from baseline to week 54 in the van der Heijde modification of the total Sharp score (vdH-S) (4), evaluated independently by 2 readers blinded to the treatment, clinical response, and the order of the radiographs. The endpoints for improvement in physical function and quality of life were the changes from baseline over weeks 30–54 in the HAQ and SF-36 scores, respectively.

Results

The baseline characteristics of the RA patients were similar among the 3 treatment groups. Premature discontinuation occurred in similar proportions among the 3 treatment groups, but more patients from the MTX–placebo group than from the MTX–3 mg/kg infliximab and MTX–6 mg/kg infliximab groups withdrew due to lack of efficacy (9.6% versus 1.9% and 3.3%, respectively), while withdrawals due to adverse events were more frequent in the MTX–3 mg/kg infliximab and MTX–6 mg/kg infliximab groups than in the MTX-placebo group (9.5% and 9.6% versus 3.2% respectively).

At week 54, the median percentage of ACR-N was higher for the MTX–3 mg/kg infliximab and MTX–6 mg/kg infliximab groups than for the MTX–placebo group (38.9% and 46.7% versus 26.4%, respectively; $P < 0.001$ for both comparisons). There were no significant differences in clinical efficacy between the 3 mg/kg and 6 mg/kg infliximab groups.

ACR20, ACR50, and ACR70 response rates were significantly higher in the MTX–infliximab groups than in patients receiving MTX alone as well as greater reductions in DAS28 scores were observed in the MTX–infliximab groups.

Patients in the MTX–3 mg/kg infliximab and MTX–6 mg/kg infliximab groups also showed lower radiographic progression than those receiving MTX alone (mean ± SD changes in van der Heijde modification of the total Sharp score at week 54: 0.4 ± 5.8 and 0.5 ± 5.6 versus 3.7 ± 9.6, respectively; $P < 0.001$ for each comparison). Radiographic progression of joint damage was not significantly different between the 2 infliximab dosage groups.

In addition, physical function evaluated by HAQ improved significantly more in the MTX–infliximab groups than in the MTX–placebo group as well as Improvement in the SF-36 physical component summary score was higher in MTX–infliximab groups than in MTX therapy alone.

Infliximab therapy was associated with a significantly higher incidence of serious infections, especially pneumonia. The development of ANAs was higher in MTX-infliximab groups than in the MTX group ($P < 0.001$ for both comparisons with the MTX–placebo group).

Conclusions

This study demonstrates that in patients with active early RA, treatment over 1 year with a combination of MTX and infliximab improves the signs and symptoms of disease activity, inhibits the radiographic progression of joint damage, and improves physical function better than therapy with MTX alone.

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Comment

Both of these studies focus on treatment with the combination of MTX and infliximab in RA of less than 3 years' duration, defined as "early RA".

The first report is a retrospective analysis of the "early RA" cohort of the ATTRACT study consisting of partial responders to MTX. As stated by the authors, the original design of ATTRACT did not anticipate the carrying out of this sub-analysis and the "early RA" subgroup was not generated by random assignment. Furthermore the cohort analyzed was very small: only 12 patients receiving MTX plus placebo and and 10 receiving MTX plus 3 mg/Kg q 8 weeks infliximab. Finally, radiographs were available for only 53% (10/19) of the patients receiving 3 mg/kg q 8 weeks of infliximab, the first choice dose in clinical practice. Due to the above limitations, this study does no more than suggest that infliximab could produce incremental radiographic benefits even in an early phase of RA when added to background MTX therapy.

The second study was specifically designed to compare the initiating combination treatment MTX plus infliximab with MTX alone in patients with persistently active "early RA" not previously exposed to MTX. This study demonstrates that the combination of MTX and infliximab improves the signs and symptoms of disease activity, inhibits the radiographic progression of joint damage, and improves physical function better than MTX. This appears to represent an important step toward a better understanding of the benefits of early aggressive therapy for active RA.

Several points remain to be addressed however, if we are to take into account the increased toxicity (e.g. serious infections) and costs related to the combination of MTX and infliximab. First, the patients in the study by St. Clair et al. had rather severe RA characterized by persistent synovitis in at least 10 joints and either a positive test for RF, radiographic erosions, or high CRP levels. Thus the results from this trial, as well as from other clinical trials with similar inclusion criteria, may not necessarily be generalizable to the patients with less severe, early RA usually seen in private rheumatology practice.

Secondly, there were no significant differences in the inhibition of radiographic joint damage and the ACR response criteria between the 3 mg/kg and 6 mg/kg infliximab dosage groups. However, only 6 mg/Kg q 8 weeks proved to be significantly superior to MTX alone with regard to the remission rate, i.e. DAS < 1.6. If our goal in early RA is now remission, the most effective infliximab dosage still remains to be determined.

Thirdly, we are waiting for the results of further controlled studies that compare starting combination treatment with MTX plus TNF alpha blockers with a step-up approach leading to tight disease control, including the prompt introduction of TNF-alpha blockade in poor responders to MTX.

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