# Role of infliximab in the treatment of early rheumatoid arthritis

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**ABSTRACT**

*Data has been generated that infliximab may be more effective when initiated earlier in the course of disease. A subset analysis of the Attract trial has demonstrated better efficacy of infliximab in reducing joint damage in an early rheumatoid arthritis (RA) population. Recently a randomized double-blind controlled trial revealed that infliximab in combination with methotrexate (MTX) in an early RA population improved signs and symptoms as well as inhibition in radiographic progression compared with patients receiving infliximab or MTX alone. The possibility of withdrawing infliximab after induction of remission with a combination of infliximab and MTX has been shown in a small pilot trial. Taken together, the results support the early use of infliximab in the treatment of patients with moderate to severe disease.*

## Introduction

A recent paradism shift in the treatment of RA has evolved with early aggressive therapy using high dose methotrexate, combination DMARDs, and earlier use of biologic therapies. The concept of aggressive therapy early in the disease course has been formulated based on data demonstrating that: (i) joint damage occurs early at a rapid rate; (ii) a brief delay in therapy appears to have long term consequences on the promotion of joint damage; and (iii) combination DMARD therapy is more effective than mono-therapy.

One TNF antagonist, infliximab, has been shown to substantially improve signs and symptoms of RA as well as significantly inhibit radiographic progression in patients with long standing DMARD refractory RA when used in combination with methotrexate.

Recently, data have been generated suggesting that infliximab may be more effective when initiated earlier in the course of disease. We would like to discuss the preliminary results of the Attract study regarding this issue.

## Adding infliximab to methotrexate

In the Attract study of infliximab, 428 patients with active RA and an incomplete response to methotrexate (MTX) therapy received either infliximab at 3 mg/kg or 10 mg/kg every 4 or 8 weeks in combination with MTX, or MTX alone for 102 weeks (1). Entry criteria for this study included patients with RA according to the 1987 ACR criteria who had 6 or more swollen and tender joints plus 2 of the following: morning stiffness greater than or equal to 45 minutes, ESR > 28 mm/h, and CRP > 2 mg/dl. These criteria reflect a population with rather severe disease. Patients must also have been receiving methotrexate for at least 3 months with a stable dose at 12.5 mg per week or more for at least 4 weeks before screening. Patients using oral corticosteroids or NSAIDs must have been on a stable dose for at least 4 weeks before screening.

## Infliximab and joint damage progression

A subset analysis of patients with early RA (disease duration ≤ 3 years) was carried out to evaluate the effect of infliximab on progression of joint damage in this cohort (2). In this early RA subset, 82 out of 428 patients (17 placebo, 19 in each of the q 4 and q 8 weeks, 3 mg/kg infliximab group, 20 in the 10 mg/kg q 8 week group and 7 in the 10 mg/kg q 4 week group) had less than 3 years of disease. Structural damage was assessed using the Van der Heijde modification of the Sharp score with x-rays of hands and feet obtained at baseline and after 30, 45 and 102 weeks. The changes in total Sharp score from baseline to week 102 were compared between the infliximab and placebo groups.

With respect to the clinical response, the early RA patients treated with infliximab demonstrated a numerically superior ACR20 response relative to the placebo group; however, the results did not reach statistical significance.

**Table I.** Change in mean total Sharp Score in patients in the Attract study who had less than 3 years of disease at baseline comparing radiographic progression in patients treated with MTX alone (placebo) versus patients who received different doses of infliximab therapy.

| | Placebo | 3 q 8 wks | 3 q 4 wks | 10 q 8 wks | 10 q 4 wks | All Infliximab |
|---|---|---|---|---|---|---|
| Total patients | 88 | 86 | 86 | 87 | 81 | 340 |
| Early RA pts | 17 | 19 | 19 | 20 | 7 | 65 |
| Patients evaluated | 12 | 10 | 16 | 17 | 6 | 49 |
| Change in TSS (mean) | 25.0 | -0.6 | -2.5 | 1.7 | -1.4 | -0.5 |
| SD | 26.8 | 8.3 | 9.8 | 5.0 | 3.5 | 7.5 |
| Median | 14.5 | -1.4 | 0.4 | 0.50 | -0.8 | 0.5 |
| p-value | | < 0.001 | < 0.001 | 0.004 | 0.001 | < 0.001 |

The ACR 20 response for the early RA patients receiving infliximab was 44.6% at 102 weeks while patients receiving MTX only had an ACR 20 response of 29.4%.

The radiographic data demonstrated more rapid progression of joint damage in the MTX only group in patients with early RA compared to the entire MTX treated group (early and late). A substantial reduction in radiographic progression was observed with infliximab in early disease – even lower than that seen in the entire infliximab population (early and late disease). The statistical differences noted between the infliximab combination group and the MTX only population in early RA were all the more significant given the small sample size evaluated. The results suggest the possibility of a better efficacy of infliximab in reducing joint damage in an early RA population compared to patients with late disease. Confirmation is required with a randomized controlled trial.

**Infliximab and ultrasonographic markers of poor prognosis**

A subsequent study was carried out to determine the ultrasonographic markers of poor prognosis in patients with early RA treated with infliximab (2). In this study, 24 patients with disease of less than 3 years' duration were randomized in a double-blind fashion to receive infliximab 5 mg/kg in combination with MTX or MTX only at weeks 0, 2, 6 and thereafter every 8 weeks to week 46. High resolution ultrasound (H.2VS) imaging and power doppler imaging of the metacarpalphalangeal joints was carried out to assess vascularity and synovial thickening.

The results revealed greater progression in the total Sharp score (TSS) in the groups receiving MTX alone compared with the infliximab group (median 14, versus 3.3, $p = 0.056$). While a strong positive correlation was seen in the MTX group only between radiographic progression and baseline synovial thickening (0.69, $p = 0.02$) and vascularity (0.78, $p = 0.003$), no significant correlation existed in the infliximab treated patients. Furthermore, in the cohort as a whole there was a significant correlation between changes in synovial vascularity and progression of joint damage over 54 weeks.

Data has accumulated suggesting that once initiated, treatment with disease modifying agents must be life-long and withdrawal leads to a flare of disease (3). However, a recent preliminary study was carried out to examine the possibility of withdrawing infliximab once significant improvement was achieved in early RA, with the initiation of combination therapy with methotrexate and infliximab (4). Ten patients each (all naïve to MTX therapy) were randomized to infliximab 3 mg/kg or placebo in addition to MTX with a standardized dose escalation. After 54 weeks, infliximab therapy or placebo were withdrawn and the patients were followed prospectively for flare, defined as an increase in clinical disease activity with an increase in CRP leading to additional DMARD or corticosteroid therapy. Baseline demographics revealed that patients had a mean age of 52 years, mean duration of symptoms of 6 months, mean CRP 42 mg/l and 65% rheumatoid factor positivity. There were no significant differences in baseline disease activity between the groups. At 54 weeks the infliximab treated group had a greater percentage of patients achieving a ACR50 response 77% versus 40% ($p < 0.05$) as well as an ACR70 response of 66% versus 30% ($p < 0.005$). At 54 weeks the infliximab group had significantly less synovitis, bone edema and bone erosions on MRI imaging.

Nineteen patients were followed for a mean of 81 weeks, 35 weeks after the last infusion. No patient demonstrating an ACR50 response after 12 months of therapy with infliximab has flared while receiving methotrexate maintenance therapy. The data suggest for the first time that a prolonged therapeutic response with a short course of a biologic agent may be achieved in early RA using an induction and maintenance therapeutic strategy. Studies of larger numbers of patients for a longer duration are clearly required to confirm this concept.

**Conclusion**

While most evidence indicates that early aggressive treatment of RA improves outcomes, the optimal approach for intervening has not been defined. Recently a randomized double blind controlled trial (the Aspire trial) was conducted on 1051 RA patients to compare the efficacy and safety of initiating therapy with infliximab in combination with MTX versus MTX alone in patients with early RA diagnosed within 3 years. The primary clinical endpoint was sustained improvement in signs and symptoms of disease at 54 weeks, defined as the percentage improvement from baseline in ACR-N. The results of the trial are still pending. Taken together, the data outlined above

supports the early use of infliximab in the treatment of patients with moderate to severe RA.

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