



## The Efficacy of Infliximab plus Methotrexate in Patients with Active Rheumatoid Arthritis in North of Iraq: 5-Year Extended Study

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### Abstract

**Objective:** To evaluate the role of infliximab plus methotrexate given for up to 5 years in patients with active longstanding rheumatoid arthritis.

**Methods:** patients responding inadequately to methotrexate and at least one other disease-modifying anti-rheumatic drug were enrolled into a 24 week, controlled study with infliximab plus methotrexate or placebo plus methotrexate and some were enrolled in a subsequent open label extension. The efficacy were evaluated.

**Results:** Among 250 patients in the original trial, 220 received at least one dose of infliximab and were evaluated. At the time of analysis 160/ 220 (72.7%) patients had remained in the study and received treatment for a mean of 4.5 years. Withdrawals were for lack of efficacy (24%), adverse events (36%), and other reasons(50%). In 160 patients who completed 5 years treatment efficacy achieved of 6 month was maintained at 5 years. 45% achieved clinical remission (DAS28<2.6), and 27% had no physical function abnormalities (HAQ=0). Results were similar for 160 patients who received treatment for 3-5 years.

**Conclusions:** Infliximab plus methotrexate sustained clinical response and remission in patients with rheumatoid arthritis during 5 years

### Introduction

Rheumatoid arthritis is a chronic inflammatory autoimmune disease of unknown etiology that occurs in approximately 0.8% of population.<sup>1</sup> although the pathophysiology of rheumatoid rheumatoid arthritis is not completely understood ,tumor necrosis factor (TNF) a proinflammatory cytokine, appears to have a key role in its aetiology<sup>1,2</sup>. Use of TNF antagonists as a highly effective and targeted therapeutic strategy that directly alters the biological processes underlying rheumatoid arthritis synovial inflammation and

progressive structural destruction.<sup>3,4</sup> Infliximab is a monoclonal antibody that binds with high affinity and specificity to human TNF and neutralizes its biologic activity<sup>5</sup>

### Patients and Methods

Patients were eligible to enroll in the randomized, controlled trial if they were aged >18 years, met ACR criteria for the diagnosis of rheumatoid arthritis,<sup>6</sup> and had at least nine tender joints and six swollen joints. patients were required to have been treated with methotrexate and at least one

other disease modifying anti-rheumatic drugs for a minimum of 6 months before screening and to have been receiving a stable weekly dose of 12.5-25mg/week for at least 8 weeks before screening. During the 6 months, blinded trial, patients were randomized to receive either placebo or infliximab at dose of 3mg/kg body weight at weeks 0,2 and 6, then every 8 weeks. Methotrexate and corticosteroid doses and routes of administration were required to remain unchanged. Once patients completed the 24 weeks, blinded portion of the trial. All patients (including those originally receiving placebo) were permitted to enter an open label extension study and receive the standard infliximab dose in combination with methotrexate. In addition patients whether they had received infliximab or placebo who had failed to achieve clinical improvement at or after 16 weeks in the blinded trial could enter the open label extension at that time. Efficacy outcomes were regularly evaluated and assessed as observed data. Baseline values for the patients group analyzed in this study reflects the values at entry of patients randomized to either placebo or infliximab in the controlled period of the trial. Consequently, changes from baseline in the efficacy were measured by using clinical evaluations on the 28 joint count disease activity score (DAS28) using C reactive protein(CRP) based formula, useful for continual assessments of efficacy. A DAS28 cut off value <2.6 was used to define clinical remission based on published sensitivity and specificity analysis in clinical setting.<sup>8</sup> Physical function was evaluated by measuring changes in the disability index of the health assessment questionnaire (HAQ). Patients who had remained in the study and had completed visit (visit every 3months) reports within pre specified frames since study entry were analyzed. A paired t test was employed to detect statistically significant difference in disease activity and functional outcomes from baseline in patients available for analyses at 5 years.

## Results

A total of 220 patients were randomized into the trial and 160 patients completed 24 weeks. All patients completing weeks 24, including those in the placebo arm, as well as any patients who failed to meet or maintain an DAS28 response at week 16, were eligible to roll over into an open label extension study.<sup>9</sup> All patients received the standard dose of infliximab 3mg/kg 0, 2 weeks then 6week and then every 8 week of 220 patients originally enrolled in this study 60 (27.27%) of them withdrew from the study, among the 60 patients who withdrew from the study, 12(24%) withdrew for lack of efficacy, 18(36%) for adverse side effects and 30 (50%) for other reasons. The mean age of all 220 patients treated with infliximab and evaluated in this study was 55 years and the majority were women (75%) table (1). The mean duration of disease was 12.4 years. Baseline mean tender joint count (TJC), swollen joint count (SJC) and HAQ values were all indicative of significant disease activity, which occurred despite previous use of various antirheumatic drugs. At the time of enrolment the majority of patients (74%) had been treated previously with two or three traditional disease modifying drugs, including methotrexate. The demographic and baseline disease characteristics (TJC, SJC, HAQ, CRP and DAS28) of the 160 patients who had reached 5 years of treatment (table 2). These patients showed a statistically significant reduction of mean TJC by more than 70%, while mean SJC and DAS28 score had decreased by 40-60% compared with baseline values. the mean HAQ was 0.7 among these patients, indicative of a significantly improved physical functioning status v base line table (2). Similarly, results for the 160 patients who had 3-5 years treatment with infliximab confirmed that clinical benefits achieved during the 1st 6 months of treatment, either in the blinded period of the study or in the first 6 months of the open label trial for patients originally receiving placebo, were sustained with infliximab treatment throughout the continuation study.

The percentage of patients who had achieved clinical remission using the DAS28<2.6 criterion. 19,23 were 32% at 6 months and 43% at 5 years .mean DAS28 had declined from 5.8 at base line to 3.3 at 6 months of treatment and 3.2, 3.1, 3.1, 3.0 and 3 at years 1,2,3,4,5, respectively. Mean CRP concentration had decreased from 25mg/l at base line to 7 mg/l after 1 year of continuous treatment, indicative normalization in this biomarker of systemic inflammation. This reduction was sustained in patients who received infliximab from 2 through 5 years. as shown by CRP concentrations <10 mg/l. In addition reductions in the mean TJC and SJC were seen at 6 months of treatment and sustained over time in completers. The

reduction seen in TJC was from a mean of 28.1 at baseline to 8.3 joints at years 1 through 5. Mean SJC had declined from 17.7 affected joints to 5.4 joints at years 1 through 5. During the first 6 months of treatment, the mean HAQ score had decreased from 1.5 to 0.8. this improvement was sustained for up to 5 years, with a HAQ score of 0.8 at years 1 through 3 and a score of 0.7 at year 5. this mean 80-82% achieved a clinically meaningful improvement in their HAQ score > 0.22).24 and 19 -27 % of patients had reached and sustained a completely normal physical function status while receiving infliximab treatment , assessed by a HAQ score of 0 table (3).

**Table (1)** baseline disease characteristics of patients with rheumatoid arthritis who received infliximab at any time during the blinded period or open label extension study n=160

Characteristics	Value	Range
Age	55(11.8)	25-74
Female(%)	75	
Disease duration(years)	12.4(9.5)	0.33- 56.92
Tender joint count(0-68 joints)	28.4(14.2)	9-65
Swollen joint count (0-68 joints)	17.2(8.6)	6-43
Patients global assessment of pain(0-100)mm VAS	52.6(23)	0- 99
Patients global assessment of disease activity(0-100) mm VAS	55.6(23.5)	0-99
HAQ disability index (0-3 scale)	1.55(0.62)	0.1- 2.7
DAS 28	5.8(1.0)	2.9- 8.1
C reactive protein (mg/l) normal <10	25(23)	0.5 - 165
Number of previous DMARDs (mean)	2	1-3

Values are mean (SD), the (VAS) for pain ranges from 0=no pain to 100=severe pain, VAS for disease activity ranges from 0=no disease activity to 100= extreme disease activity, the health assessment Questionnaire (HAQ) scale range from 0=no difficulty to 3= unable to perform activity. DAS28 is based on a 28 joint assessment for pain, swelling using the CRP based formula.

**Table (2)** shows the efficacy assessment of patients with rheumatoid arthritis in the closed and open label extension who completed 5 years of continuous treatment with infliximab.

Criterion	Baseline	5 years	Absolute change	Percentage change
Tender joint count(0-68)	28.1(13.8)	8.3 (12.5)	-19.7(13.8)	-70.8
Swollen joint count(0-68)	17.7(8.6)	5.4 (6.7)	- 12.3(10.8)	- 60.7
HAQ (0-3)	1.5(0.6)	0.8 (0.7)	- 0.7(0.6)	- 52.1
CRP (mg/l) (normal<10mg/l)	25(23)	7(12)	- 18(23)	- 58
DAS28 (remission<2.6)	5.8(0.9)	3.0(1.2)	-2.7(1.4)	-46.5

results are shown as mean (SD) of each individual patient result for each criterion, values for absolute change and percentage changes from baseline are based on actual data from patients of 5 years (n=160 patients) had TJC, SJC, and CRP data available ,A negative absolute or percentage change indicates an improvement in the response criterion.

p<0.001 paired t test (last result compared with baseline).

**Table (3)** No(%) patients with rheumatoid arthritis during the study with no signs of joint involvement (TJC=0, SJC= 0), normal CRP< 10, clinical remission based on DAS28<2.6 and normal functional status(HAQ=0).

Variables	Month					
	6	12	24	36	48	60
TJC=0	40(25)	36(22.5)	48(30)	43(26.87)	42(26.25)	47(29.37)
SJC=0	33(20.62)	37(23.12)	52(32.5)	42(26.25)	39(24.37)	46(28.75)
CRP<10mg/l	146(91.25)	141(88.12)	144(90)	149(93.12)	127(79.37)	139(86.87)
DAS<2.6	51(32)	63(39.37)	72(45)	69(43.12)	76(47.5)	68(43)
HAQ=0	31(19.37)	34(21.25)	38(23.75)	41(25.62)	40(25)	44(27.5)

## Discussion

The present study demonstrated that the majority of patients with longstanding rheumatoid arthritis who had continued to receive the standard treatment of infliximab plus methotrexate for up to 5 years experienced significant, sustained improvement in sign and symptoms, disease activity, and functional status. The results of this study are consistent with those seen in patients treated with etanercept in combination with methotrexate for 3 years.<sup>9</sup> Although methotrexate is considered the anchor drug of rheumatoid arthritis treatment, in some studies methotrexate monotherapy may lead to decreased efficacy and reduced patients compliance over time.<sup>10-13</sup> On the other hand the long term efficacy observed when methotrexate is combined with a TNF antagonist may lead to sustained patient compliance. In randomised studies, initiation of a TNF antagonist in combination with methotrexate has shown the combination to be more efficacious than either methotrexate<sup>8,10,11,14</sup> or TNF antagonist as monotherapy,<sup>6-13,15-25</sup> without being necessarily more toxic.

The reduction of HAQ to an average mean score of 0.7-0.8 for up to 5 years seen in this study is important for the long term prognosis of these patients. Although functional improvements achieved with TNF antagonists mostly depend on baseline joint destruction in individual patients,<sup>26</sup> the direct correlation between physical function and radiographic progression is stronger for patients with longstanding, active rheumatoid arthritis than for patients in the early stages of the disease.<sup>27</sup> The functional improvements seen in this study need to be complemented with studies

confirming long term inhibition of radiographic progression in patients with longstanding rheumatoid arthritis.

## Conclusion

The majority of patients with rheumatoid arthritis who entered this study of infliximab in combination with methotrexate achieved substantial improvement in disease activity, including improvement in swollen and tender joints, global assessment of disease activity, functional status, and CRP concentration. These improvements were sustained for 5 years, with many patients achieving clinical remission and functional normality with continuous infliximab treatment. To acquire even longer term information about drug response and tolerability, these patients with rheumatoid arthritis will need continuous follow up over time.

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