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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

Background and objectives Anti-Tumor necrosis factor agents are among the most effective therapies for Rheumatoid Arthritis, however, their optimal use is yet to be determined .In this 5 year open labeled study attempted remission induction using standard therapy with infliximab in patients with poor response to ordinary disease modifying anti-Rheumatic drugs. **Methods:** Patients responding inadequately to methotrexate and at least one other disease-modi - fying 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 by measuring the disease activity by using DAS-28(disease activity score in 28joints) and functional evaluation by using the health assessment questioner (HAQ). **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 in 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:** In Patients with persistently active Rheumatoid Arthritis despite Methotraxate therapy, repeated doses of infliximab in combination with methotraxate provided clinical remissions with functional and quality of life benefits were sustained.

Keywords: Infleximab; Methotroxate; Rheumatoid Arthritis.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology that occurs in approximately 0.8% of population[1]. is the most common, potentially treatable cause of disability in the western world[2]. Evidence supports the early use of disease-modifying antirheumatic drugs (DMARDs) in RA, however the optimal treatment strategy is uncertain[3]. Ideally, effective therapy would produce rapid and sustained suppression of inflammatory disease, resulting in preserved function and prevention of joint damage, without risk of long-term toxicity. A hypothesis in RA research is that early in the disease process, a window of opportunity exists, where therapeutic intervention has a disproportionate impact on outcome[4-6]. Proof of this concept for an anti-tumor necrosis factor (anti-TNF) agent would require maintenance of response after cessation of treatment. The development of biologic agents, in particular, those that target TNF, has heralded a new era in the management of chronic inflammatory disease. Data from studies of patients with longstanding RA showed that these agents are effective in improving clinical, functional outcomes[7]. Anti-TNF& agents have been successfully used in a number of other inflammatory conditions, including Crohn's diseases[8], ankylosing spondylitis[9] and psoriasis and psoriatic arthritis[10]. In Crohn's diseases, intermittent short courses or single infusions can be sufficient to suppress disease activity for long periods[11]. However, in RA, which is characterized by a chronic progressive course, sustained therapy is required, and when therapy with anti-TFN is withdrawn, the only published evidence suggests that diseases activity rapidly returns (within 12 weeks)[12].

Patients and Methods The study started in 2009, included 160 RA patients from north of Iraq 120 out of 160 patients were female (75 %) and only 40 out of 160 patients were male (25 %), the study includes RA patients who didn't responde to ordinary treatment which is combination of methotrexate who received a stable weekly dose of 12.5 - 25 mg/week with leflunomide 20 mg/day and or one of the non-cytotoxic drug like Anti-malarial drugs for at least 6 months before starting the study and still the disease was active according to DAS-28 who have at least 9 tender joints and 6 swelling joints. Patients were eligible to enroll in the randomized, controlled trial if they were aged >18 years, and met ACR criteria for the diagnosis of rheumatoid arthritis,[13]. During the first 6 months (blinded trial), patients were sub divided into 2 subgroups the first subgroup remained on the same treatment as before the study while the second subgroup we stopped placebo drugs (Leflunomide and or Anti-malarial drug) we added infleximab at dose of 3 mg/Kg body weight at weeks 0, 2 and 6, then every 8 weeks. Methotrexate and corticosteroid doses and routs of administration were required to remain unchanged. Once patients completed the 24 weeks blinded portion of the trial, all patients (including the first and second subgroups) were permitted to enter an open label extension study and receive the standard infiliximab dose in combination with methotrexate. 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

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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[14]. A DAS28 cut off value <2,6 was used to define clinical remission based on published sensitivity and specificity analysis in clinical setting[15]. Physical functions were evaluated by measuring changes in the disability index of the health assessment questionnaire (HAQ). Patients who had remained in the study and had completed follow up (every 3 months) 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.[16] 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 majorities were women (75%), Table 1.

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

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 are shown in 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): The efficacy assessment of patients with rheumatoid arthritis in the closed and open label extension that are 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 (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

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 infilximab treatment throughout the continuation study.

The percentage of patients who had achieved clinical remission using the DAS 28<2.6 criteria.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 7mg/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 (3): Frequency distribution of patients with rheumatoid arthritis during the study with no signs of joint involvement

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)

(TJC=0, SJC= 0), normal CRP< 10, clinical remission based on DAS28<2.6 and normal functional status (HAQ=0).

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.

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).

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[17]. Although methotrexate is considered the anchor drug of rheumatoid arthritis treatment, in some studies methotrexate monotherapy may lead to decreased efficacy and reduced patient's compliance over time[18-20]. on the other hand the long term efficacy observed when methotrexate is combined with a TNF antagonist may lead to sustained patient compliance. In randomized studies, initiation of a TNF antagonist in combination with methotrexate has showed the combination to be more effective than either methotrexate[15,18,19,21] or TNF antagosist as monotherapy,[13-20, 22-32] 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,[33] 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[34]. 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.

The combination of infliximab and methotrexate was well tolerated and safe. Although the frequency of serious infections was no greater than with methotrexate alone, the frequency of infectious complications will have to be carefully monitored when a large number of patients are treated with infliximab and methotrexate. Cancers did occur in patients treated with infliximab and methotrexate, all in

those receiving the dose of infliximab of 10 mg per kilogram. However, the overall frequency of cancers was similar to that predicted from the Surveillance, Epidemiology, and End Results data base[35]. Finally, the administration of TNF-&-neutralizing agents is clearly associated with the development of autoantibodies. This finding has been reported with both infliximab and etanercept and in patients with Crohn`s disease as well as in those with rheumatoid arthritis[36-38]. The mechanisms of these phenomena are uncertain. But the development of these antibodies was only rarely associated with symptoms suggestive of an autoimmune disease.

Conclusions

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 in the future.

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