Safety and Efficacy of Infliximab Therapy in a Sample of Iraqi Patients with Rheumatoid Arthritis

Dr. Rana Jabar Mahdi[1,] 1,2 Alfurat general hospital, Baghdad-Alkarkh health directorate, Ministry of health, Iraq
1Email: rjbar6067@gmail.com

Dr. Ahmed Salahuddin M. Rhida[2] 1,2 Alfurat general hospital, Baghdad-Alkarkh health directorate, Ministry of health, Iraq
2Email: salaha798@yahoo.com

ABSTRACT

Background: Rheumatoid arthritis is a chronic inflammatory disease characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations. Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor- α.It has been used as an effective treatment in rheumatoid arthritis because of its substantial benefits on the signs and symptoms of the disease, as well as its ability to significantly retard the radiographic progression of joint damage.

Objective: To assess the safety and efficacy of infliximab in a sample of Iraqi patients with rheumatoid arthritis.

Patients and methods: A clinical trial consisted of 47 active rheumatoid arthritis patients, who fulfilled the revised 1987American College of Rheumatology criteria for RA and the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis. All the patients received Infliximab 3mg/kg intravenously and were followed up for disease activity using DAS28, complete blood count, ESR, liver and renal function during the period of the study at base line, after 2 ,6,14,22 weeks respectively, due to limited time specified for the study , in each follow up session there had been a number of patients did not complete the follow-up .

Results: There was statically significant improvement in the disease activity score in the 2nd and in the 6th week of treatment (p value <0.001). There were obvious differences in disease activity score between the patients at the 6th week and 14th week and between patients at 14th week and 22nd week, but these results did not reach statistical significance. There were no significant differences in liver enzymes, blood urea, serum creatinine, WBC count and hemoglobin during follow up sessions. There were no obvious adverse effects recorded throughout the follow up period.

Conclusion: Infliximab is effective and relatively safe in treatment of Iraqi patients with rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Infliximab

Introduction

Rheumatoid arthritis is a chronic inflammatory disease characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations involving eyes, skin, lungs, and heart, as well as rheumatoid vaculitis. The characteristic feature of established RA is persistent inflammatory

synovitis, usually involving peripheral joints in a symmetric distribution (1 - 3).

Epidemiology The prevalence of RA is practically constant worldwide at about 1%.The annual incidence of rheumatoid arthritis is approximately 3 cases per 10,000 population .Women are affected more frequently than men, in a proportion of two to one. The disease starts most often between the ages of 35 and 50, but it can appear at any age (4- 6).

Risk factors of rheumatoid arthritis Genetic factors and environmental exposures predispose to the development of rheumatoid arthritis (7).

1. Genetic element: • The studies revealed that concordance of RA in monozygotic twins (8- 10).
2. Non genetic element:

a. Sex: females are 2-3 times higher than males due to hormonal effect of estrogen (7).

b. Tobacco: smoking enhances the risk of developing anti-CCP positive rheumatoid arthritis in patients with the shared epitope(7).

c. Bacteria and viruses: infectious agents are considered as initiating factors for RA(7).

Pathophysiology

In rheumatoid arthritis the synovium shows increased angiogenesis, cellular hyperplasia, influx of inflammatory cells(12).

Pathogenesis T cell activation When T cells become activated by antigen presenting cell, can be differentiated into Th1 and Th2 phenotypes, and secrete characteristic effectors cytokines (IFN-gamma and IL-2 by Th1 cells, IL-4 and IL-10 by Th2 cells), IL4 and IL-10 inhibit Th1 cells, while IFN-gamma suppresses Th2 function (13). B cell activation and auto antibodies B cells become activated through interactions with T cells and through soluble cytokines that enhance their proliferation and differentiation to antibodyforming plasma cells. Macrophage and fibroblast cytokines in rheumatoid arthritis Synovial macrophages and fibroblasts are primary sources of cytokines in the rheumatoid synovium, which produce a plethora of proinflammatory factors in the joint involved in the cytokine network including IL-1, IL-6, IL-8, IL-12, IL- 15, IL-16, IL-18, IL-32, TNF-alpha, granulocyte macrophage colony-stimulating factor, and multiple chemokines . These cytokines can participate in paracrine and autocrine networks that enhance and perpetuate synovial inflammation.

Clinical features

The start of the disease is usually insidious with polyarthritis affecting small and large joints. The swelling and pain in the joints must occur for at least 6 weeks before the diagnosis. The hallmark symptom of rheumatoid arthritis is morning stiffness that lasts for at least an hour. Constitutional symptoms including malaise, fatigue, weight loss, fever are also present (16) .Extra-articular manifestations occur in seropositive patients and include rheumatoid nodules, , Sjögren's syndrome, interstitial lung disease and vasculitis(17).

Diagnosis

The diagnosis of rheumatoid arthritis based on symptoms, physical examination and the results of x-rays and blood tests (18). The American Rheumatism Association revised criteria for rheumatoid arthritis classification (19). and the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for Rheumatoid arthritis score. were used.

Treatment: The classes of drugs used for treatment of RA include: 1. Nonsteroidal anti-inflammatory drugs: For example: ibuprofen, diclofenac, naproxen. They reduce pain and stiffness. (20) 2. Corticosteroids: Low-dose oral corticosteroids can be used in combination with 3. Disease-modifying anti rheumatic drugs Include azathioprine, ciclosporin,,

hydroxychloroquine,leflunomide, methotrexate, sodiumaurothiomalate, sulfasalazine. 4. Biological therapies The biologic agents have revolutionized for the treatment of RA because of their substantial benefits on the signs and symptoms of the disease, as well as their ability to significantly retard the radiographic progression of joint damage (23). The following medications are approved for treatment of rheumatoid arthritis(24)

Tumour necrosis factor (TNF) inhibitors: adalimumab, certolizumab pegol, etanercept,golimumab and infliximab. Infliximab Infliximab is a chimeric (human-mouse) monoclonal antibody to human tumour necrosis factor-α (24). Mechanism of action inhibits binding of TNFα with its receptors (27).

Side effects (28,29)

1.Infusion reaction: like headache, dyspnea , hypotension , transient fever ,chills ,gastrointestinal symptoms, skin rashes.

2. Serious infections: Including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis) .

3. Reactivation of tuberculosis.

4. Reactivation of hepatitis B virus. 5. Reports of serious liver injury, including acute liver failure. 6. Lethal hepatosplenic T-cell lymphoma. 7. Drug-induced lupus. Dose of infliximab By intravenous infusion for rheumatoid arthritis (in combination with methotrexate) 3mg/kg, repeated 2weeks and 6weeks after initial infusion, then every 8 weeks (31).

Contraindications

Severe infection, pregnancy, breast feeding and heart failure (moderate and severe) (31). Aim of the study To assess the safety and efficacy of infliximab in Iraqi patients with rheumatoid Arthritis.

Patients and Methods:

Patients An open labeled single group observational clinical trial consisted of 47 Iraqi patients with active rheumatoid arthritis, defined as a Disease Activity Score in 28 joints (DAS28) of at least 3.6 (at the screening visit), despite maximal tolerable doses of disease modifying anti rheumatic drugs.

All patients fulfilled the revised 1987 American College of Rheumatology criteria for RA ,and the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for Rheumatoid arthritis The study subjects were chosen from the patients who attended the Rheumatology Unit of Baghdad Teaching Hospital in Medical City between 3 Rd of October 2012 to 1st of April 2013, 83% of them were females, 17% were males and their age range between 23-65 years. All the patients received Infliximab 3mg/kg intravenously and were followed up during the period of the study at base line, after 2, 6, 14, 22 weeks respectively, due to limited time specified for the study, in each follow up session there had been a number of patients did not complete the follow-up .

Methods

Data was collected using a structured questionnaire form, constructed by the researcher and revised by supervisor; the questionnaire sheet was filled by the researcher after measuring weights and heights of patients. The questionnaire sheet consists of

1. The first part includes the demographic data of the patients regarding their age, sex, occupation, address, disease duration, smoking status, body mass index and drug history.

2. The second part includes assessment of the patients at each follow up session including complete blood count, ESR , liver and renal function , and assessment of disease activity using DAS28.

3. The third part includes assessment of side effects at each follow up Session .

Results:

The total number of the study sample included 47 Iraqi patients affected by rheumatoid arthritis (83% female, 17% male), and 31 (66.0%)were testing positive for rheumatoid factor , 42(89.4%)were not smoker.

47 cases received the first dose of treatment at baseline (start of the study), and were evaluated after 2 weeks for effect on DAS28. After 2 weeks, the DAS28 was reduced by a

mean of 0.91 point compared to the baseline .This effect was statistically significant (p value <0.001) .This beneficial effect of treatment was evaluated as strong effect (Cohen's d: 0.88).p value

Table (1) Effect of infliximab on disease activity after 2 weeks of treatments .

	DAS-28-at basline	DAS-28-after 2weeks	P	Mean difference	Cohen's d
Range	(3.6-7.9)	(3.2-7.6)	<0.001	-0.91	-0.88
Mean	6.05	5.14			
SD	0.93	1.13			
SE	0.19	0.17			
N	47	46			

In table (2) 39 cases received the second dose of treatment and were evaluated after 4 weeks from the previous dose (6 weeks from the base line) for effect on DAS28. After 4 weeks, the DAS28 was reduced by a mean of 0.61 point compared to the previous dose .This effect was statistically significant (p value <0.001). This beneficial effect of treatment was evaluated as moderately strong effect (Cohen's d: 0.50)

Table (2) Effect of infliximab on disease activity after 6 weeks of treatments.

	DAS-28-after 2weeks	DAS-28-after 6weeks	P	Mean difference	Cohen's d
Range	(3.2-7.6)	(3.2-7.6)	<0.001	-0.61	-0.50
Mean	5.13	4.52			
SD	1.20	1.13			
SE	0.14	0.17			
N	39	39			

As shown in table(3)18 cases received the third dose of treatment and were evaluated after8 weeks from the previous dose(14 weeks from baseline dose) for effect on DAS28.After8 weeks, the DAS28 was reduced by a mean of 0.15)

Table (3) Explained correlation between disease activity score and response to treatment.

	DAS-28-after 6weeks	DAS-28-after 14weeks	P	Mean difference	Cohen's d
Range	(3.2-7.6)	(2.7-5.9)	0.58[NS]	0.15	0.15
Mean	5.13	4.52			
SD	1.20	0.90			
SE	0.19	0.21			
N	39	18			

18 As shown in table(4) 6 cases received the fourth dose of treatment and were evaluated after 8 weeks from the previous dose(22 weeks from baseline dose) for effect on DAS28.After8 weeks, the DAS28 was reduced by a mean of 0.18 point compared to the previous dose .This effect of treatment was ineffectual (p value0.29) evaluated as (Cohen's d:0.25).

Table (4) Effect of infliximab on disease activity after 22 weeks.

	DAS-28-after 14weeks	DAS-28-after 22weeks	P	Mean difference	Cohen's d
Range	(3.9-5.6)	(3.5-5.7)	0.29[NS]	-0.61	-0.50
Mean	4.55	4.37			
SD	0.61	0.80			
SE	0.25	0.33			
N	6	6			

6 As shown in table (5) evaluating the difference of DAS28 of the patients at baseline dose and after 22 weeks, theDAS28 was reduced by a mean of 1.37 from the baseline, this effect was statistically significant (p vlue0.013) evaluated as (Cohen's d: 1.63)

Table (5) Explained correlation between disease activity score and response to treatment.

	DAS-28-after 14weeks	DAS-28-after 22weeks	P	Mean difference	Cohen's d
Range	(4.3-7)	(3.5-5.7)	0.013	-1.37	-1.63
Mean	5.73	4.37			
SD	0.88	0.80			
SE	0.36	0.33			
N	6	6			

Discussion

Treatment with infliximab showed significant improvement in disease activity. The study results showed that infliximab was an effective treatment option for patients with rheumatoid arthritis, and showed statically significant improvement in the disease activity score in the 2nd and 6th weeks of treatment , this results is in agreement with another study done by Smeets T J et al(35) , indicating that clinical improvement has, for instance, been described as early as 1 week after initiation of treatment with the chimeric anti-TNFα monoclonal antibody infliximab resulted from decreased synovial cellularity early after initiation of infliximab treatment. Conclusion Infliximab is relatively safe and effective treatment option in a sample of Iraqi patients with rheumatoid arthritis.

Recommendations

1. We emphasize the need to focus on improvement in registration of patients on biological agents.
2. The finding in this study need to be confirmed using larger study samples and longer duration for follow up.
3. Estimating the level of Anti ccp ,RF and monitor their effects on response to the treatment.
4. Utilizing ultrasound or MRI in assessing effect of infliximab on disease Progression.

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