Efficacy, Safety and Predictors of Response to Rituximab in Treatment of Iraqi Patients with Active Rheumatoid Arthritis

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ABSTRACT

Background: Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody which effectively depletes B cells and is used for treating rheumatoid arthritis (RA).
Objectives: To assess the efficacy and safety of RTX and to evaluate the predictors of response to RTX in the treatment of Iraqi patients with active RA.
Materials and methods: An open-labeled single group study that was conducted over 13 months in 65 patients with RA diagnosed according to a 1987 American College of Rheumatology (ACR) criteria. All patients were given 4 doses RTX by intravenous infusion over 6 months 1gm/dose. Each patient was followed at each visit of disease activity, including the Clinical Disease Activity Index (CDAI) and functional class (F Class). Also, we assess 9 different patients' characteristics (age, gender, disease duration, the presence of RF, presence of ACPA, smoking status, previous use of TNF-blocker, the use of methotrexate and BMI) as predictors to RTX.
Results: Data analysis showed significant improvement in CDAI (P value=0.005) and functional disability (P-value =0.001), and ESR (P-value =0.005) with RTX use over 6 months. The analysis also showed that smoking has a negative correlation with response to treatment (p-value = 0.005). A better response was seen in RF-positive group. The other variables had no effects on the response to treatment. The patients who switched from TNF-blocker were (29), and the patients who started on RTX were 36 (either due to positive Purified Protein Derivative of a tuberculin test (PPD) or unavailability of TNF-blocker), results showed same RTX efficacy in both groups.
Conclusion: RTX is effective both clinically (CDAI and F Class) and laboratory (ESR). It is more effective in patients who are not smokers, and in those who are seropositive for RF. RTX is relatively safe with few side effects, tolerable by most patients. The most common side effect is a transfusion reaction in the form of a sore throat.

Keywords: Rheumatoid arthritis; Rituximab; active, Iraqi patients, efficacy.

INTRODUCTION

RA is a chronic, systemic inflammatory disease that affects the synovium, leading to synovial inflammation and proliferation, loss of articular cartilage, and erosion of juxta-articular bone. The natural history of the disease is one of progressive joint damage and deformity and, in a few people, the development of extra-articular manifestations, and premature death. RA follows a disease course of remissions and exacerbations [1]. The current therapeutic strategies, particularly if the disease is diagnosed and treated early, resulting in a substantial clinical benefit for most patients [2].

Epidemiology

RA affects approximately 1% of the adult population worldwide and is more common in female (female: male, 3:1). The typical age of onset in women is the late childbearing years; in men, RA develops more often in the sixth to 8 decades [1]. The prevalence can differ between different

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ethnic groups as it may drop to 0.3% in the Chinese [3] and increase to 5% in Pima Indians of Arizona [4]. Definite RA was observed in 1% of population samples in Iraq [5]. The pathogenesis RA remains vague and more than 30 loci conferring risk genetics for RA have been identified. The most potent genetic risk factor is HLA DR1, HLA DR4. The shared epitope (SE) is associated with the production of specific antibodies, especially anti-cyclic citrullinated peptide (CCP) antibodies [1]. The highest incidence of RA in women occurs after menopause when the level of sex hormones decreases and pregnancy is often associated with disease remission. Bacterial and viral components were isolated from the synovial fluid of the affected joints by polymerase chain reaction technique. EBV and parvovirus B19 are most infections associated with RA. Smoking is significantly enhancing the risk of developing RA, this association has been strong in men and in those with RF and ACPA positive disease [6]. The multiple criteria used for the diagnosis of RA depend on clinical history, physical examination, and Lab. tests. These criteria are not for diagnostic purposes, but they are mainly used in Classifying patients for clinical research [7]. There is the 1987 American College of Rheumatology (ACR) Criteria for RA and the new classification system which has been proposed by ACR and European League against Rheumatism (EULAR) and useful in the diagnosis of early disease [8].

Rheumatoid factor (RF) is an autoantibody directed against the Fc portion of IgG. RF is positive in about 50% of cases at presentation and 85% of cases positive in the first 6 months after diagnosis and is about 70% sensitive and 80% specific for RA. Anti-cyclic citrullinated peptide antibodies are key autoantibody in RA. It has a sensitivity of up to 80% and a specificity of 98% for RA [2].

Treatment needs teamwork for patient care between physicians, nurses, physiotherapists, occupational therapists, social workers, and surgeons. The treatment aims:

1. To decrease the inflammation and damage.
2. To decrease long term disability.
3. To prevent extra-articular morbidity and mortality [9].

There are four classes of medications used in RA:

1. All patients should be received analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Side-effects can be avoided by concomitant use of a gastro-protectant.
2. Earlier use of disease-modifying anti-rheumatic drug (DMARD) therapy to optimally inhibit synovitis and reduce disease activity and slowing joint destruction [10].
3. Corticosteroids are potent anti-inflammatory drugs and long-term use is associated with significant morbidities, such as osteoporosis and vertebral fracture. Its use as bridge the time until DMARDs are effective [11].
4. Biologic agents, the advent of biologics has brought a revolutionary change in RA care.

The biological drugs act by one of the following mechanisms:

- Cytokine modulation.
- Targeting T cells.
- Targeting B cells.

The B lymphocyte depletion as a technique to therapy has been established in RA patients seropositive for RF and/or anti-CCP antibodies using the anti-CD20 chimeric monoclonal antibody, RTX. It is successfully depleted B cells for up to 6−12 months, which is associated with improvement in RA disease activity and re-treatment when the B cell compartment repopulates [10]. RTX is used for resistant cases and for special cases of RA. It is standard as a second line after anti-TNF failure, for the treatment of severe RA. Use 1000 mg intravenous (IV) infusion, repeated after 2 weeks (2 infusions separated by 2 weeks (one course). Repeat the course after 24 weeks, according to clinical examination

Use acetaminophen and antihistamine before rituximab dose 375 mg/m^2 IV per Week for 4 weeks. Use methylprednisolone 1 g IV/day for 1−3 days, oral prednisone 1 mg/kg/day; maximum 80 mg/day and taper according to clinical assessment [12].

Common side effects of RTX which occurred in 10% of patients like abdominal pain, systemic hypertension, headache, and dizziness. While others like hypercalcemia, spontaneous bone fracture, and coagulation disorders occurred in less than 1% [13]. RTX has shown to be safe, although the lake of long-term efficacy and safety data limit its use. More studies are needed [14].

The aims of this study were:

1. To assess the efficacy and safety of RTX in Iraqi patients with active RA.
2. To assess the predictors of response to RTX in treatment of patients with active RA.

MATERIALS AND METHODS

This was an open-labeled single group longitudinal study that was conducted over 13 months period. The study was conducted on Iraqi patients with RA who visited the Rheumatology Ward in Baghdad Teaching Hospital from June 2015 to July 2016.

Characters of patients

1. The patient should meet the 1987 American College of Rheumatology criteria for the classification of RA.
2. The CDAI should be equal to or greater than 13 (moderately to severely active disease).
3. The age of more than 16.
4. Patients do not have other CTD overlaps with RA During the study period, 65 patients with RA were identified and enrolled in the study. All of them successfully completed the study.

Methods

All the included patients were given RTX 1g (2 vials 500mg) IV infusion for 2 cycles (6 months apart), each cycle has 2 doses (2 weeks apart). Methylprednisolone 100 mg infusion in 250 cc N/S, all ermine ampoule 10 mg and paracetamol tablet 1gm half an hour before the RTX. For each patient, baseline data were collected during the first visit and after 2 weeks and all the participants were seen after 6 months and after 2 weeks (4 visits). During these subsequent visits, further data were taken. The data were collected by the researcher and registered in a patient information sheet that was designed by the researcher and revised by the supervisor.

The collected data include 1. Demographic data of patients regarding their age and sex as well as smoking status. These data were collected at the first visit. 2. Medical data, including the disease duration, previous and current RA medications (MTX and biologic). These data were also collected during the first visit. 3. Lab data which include RF, ACPA and Hemoglobin level(Hb), white blood cell (WBC) count.

Table 1. The baseline characteristics of the study group (No.=65).

Variable		No.	%
Sex	Male	7	10.8
	Female	58	89.2
Smoking	Smoker	16	24.6
	Not	49	75.3
MTX use	Use	49	75.3
	Not	16	24.6
Previous biology	Use	29	44.6
	Not	36	55.3
RF	+	41	82
	−	9	18
ACPA	+	50	80.6
	−	12	19.3
Age	Mean 49.5 year	Range 27-70 year	
Disease duration	Mean 9.909 year	Range 1-32 year	
BMI	Mean 31.987	Range 21.6-42	

4. Assessment of disease activity by clinical disease activity index (CDAI) and functional class performed at each visit.

Statistical analysis

The data of the 65 patients in this study were entered into and analyzed by the statistical package for social science (SPSS) software version 17. Descriptive statistics were presented as mean, standard deviation, frequencies, and percentage. The efficacy of RTX was tested by comparing the mean difference of CDAI and the mean difference of ESR between the baseline and the last visit using a paired t-test. The efficacy of RTX was also assessed by comparing the change in the functional class in RA patients with time. This was tested using the Chi-square test (χ^2).

Student's t-test was used to assess the effect of patient characteristics (as predictors) on the response to treatment. The percentage of mean difference in CDAI between baseline and the last visit was used as the dependent variable to assess the difference between these factors and the response to treatment. The correlation test is used to assess the relationship between patient characteristics [age, BMI, disease duration] and percentage of mean difference in CDAI between baseline and last visit [as the response to treatment]. A level of significance (P value) of 0.05 was considered significant.

RESULTS

There were 65 patients enrolled in this longitudinal study with a mean age of (49.5) years and a range of $(27-70)$ years. Female patients were 58 (89.2%) and males were 7(10.8%). Smokers were 16 patients (24.6%), RF was positive in 41 patients (82%) (data available in 50 patients only), ACPA was positive in 50 patients (80.6%) (data obtained for 62 patients), 49 patients (75.3%) were taking MTX., 29 patients took TNF-blocker before RTX (4 developed S/E and 25 failed to respond), while 36 started on RTX (9 were PPD positive and the reminder started on RTX because none available TNF-blocker for about 4 months during the study) Table 1.

The efficacy of RTX was tested by comparing mean difference of CDAI between the first visit (37.54+6.42) and the last visit (18.98+10.14) by using Paired t-test, which revealed a highly significant difference (p<0.005). As shown in Figure 1.
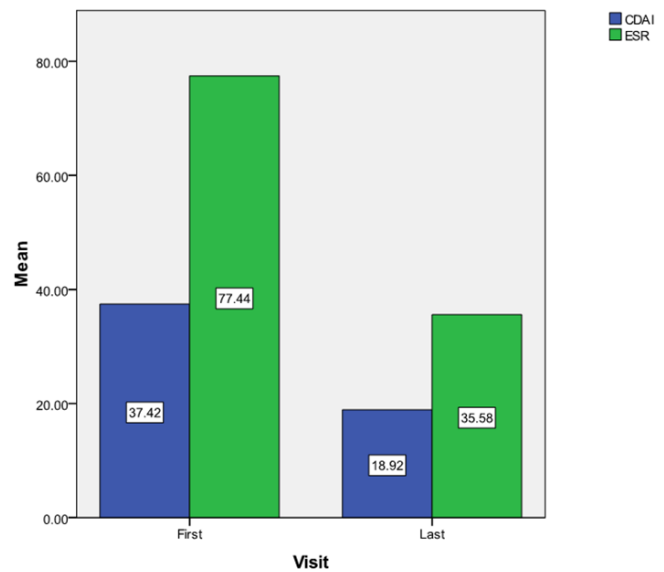

Figure 1. Comparison between mean CDAI /and mean ESR before and after 6 months of treatment among the study group.

In Figure 2 we used the Chi-square test (χ^2) to compare the changes in the functional class of RA patients during the follow-up period. There was a significant improvement in functional class with advancing treatment time. At baseline, 2 patients (3%) were FC I, 11 patients (17%) were class II, 26 patients (40%) were both class III and IV After sixth month of follow up the figures were changed to 26 patients (40%) in class I and only 3 patient (5%) in class IV which is significant (P= 0.0001).

To assess the effect of patients' characteristics on response to treatment, students t-test was conducted using 6 variables as predictors, These include the gender, smoking status and the concomitant use of methotrexate, previous biological use, the presence of RF, and the presence of ACPA. And the corre-
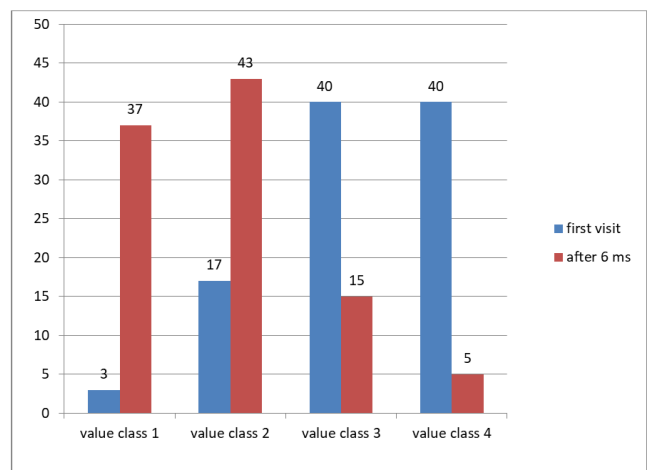

Figure 2. Comparison of F Class at baseline and after 6 months of treatment among the study group(N =65).

Table 2. The correlation between the patients' characteristics and the response to treatment.

	Gender	N	%Mean diff.of CDAI	SD	Std. Error Mean	P value
Gender	Male	7	−48.6391	34.69537	15.51624	0.906
	Female	58	−49.1927	24.75430	3.36863	
Smoking	+ve	16	−15.3973	20.29536	10.14768	0.005
	−ve	49	−51.5816	23.94436	3.17151	
MTX	+ve	49	−49.3971	24.45437	3.64544	0.973
	−ve	16	−49.4093	29.30615	7.83240	
Previous biology	+ve	29	−39.9093	26.80325	6.50074	0.071
	−ve	36	−53.5253	24.78337	3.91860	
RF	+ve	41	−53.6841	23.82826	4.27968	0.183
	−ve	9	−41.2704	26.12977	8.70992	
ACPA	+ve	50	−46.4652	26.49982	3.90719	0.297
	−ve	12	−55.9786	21.97460	6.94898	
Age (years)			49.5	9.1		0.077
Disease duration (years)			9.906	8.644		0.112
BMI (kg/m^2)			31.987	6.361		0.218

Table 3. The side effects of RTX on the patients during the study.

Side effects	No.	%
Transfusion reaction	17	26.15
Nasopharyngitis	2	3.07
Abdominal pain	1	1.53
Chest infection	1	1.53
Generalized itching	1	1.53

lation test was conducted using 3 variables, age, disease duration, and BMI The percentage of mean difference of CDAI between the baseline and the last visit was used as a dependent variable in the student's t-test model. The analysis showed that smoking has a significant effect on response to treatment with the non -smoker being more respondent to treatment than the smoker group (P-value = 0.005). From the statistical point of view, there was a great decrease in CDAI in RF-positive group (−53.6%) compared for the RF-negative group (−41.2%), it was not proved statistically probably because of the big difference in the No. of these groups (41 vs 9). The other variables (including age, gender, disease duration, presence of ACPA, MTX use, previous biological use and BMI) had no significant effect on response to treatment (p>0.05). The finding is shown in Table 2. The most common side effects reported in this study was infusion reaction(sore throat, flushing, nasal congestion) documented in 17 patients (26.15%). Other side effects are shown in Table 3. No one develops hypotension, no one develops anaphylaxis.

DISCUSSION

In patients with RA, evaluation of joint synovitis and its response to treatment is based on clinical findings and acute phase reactants. Many DMARDs and biological agents are available for the treatment of RA. Because biological agents are costly, finding the characteristics of the groups of patients who respond more to these agents is of great interest [14–16] RTX is one of the biological agents used for resistant and special cases of moderately to severely active RA. Clinical, and Lab. factors have been associated with early response

(6ms) to RTX therapy in RA [15, 16].

This study is the first observational study about the efficacy and safety of RTX conducted on RA patients in Iraq. Data analysis showed significant improvement in disease activity CDAI (p= 0.005), functional class (p=0.001) and ESR (p<0.005) with RTX use over a period of 6 months. Richter A. et al (2014) proved in his study in Germany that RTX treatment led to improvements in disease activity and functional state that were sustained over multiple courses [17]. Ronald F. et al (2015) wrote the final report of the RA Global Clinical Trial Program over 11 years and he confirmed that RTX has a consistent safety and efficacy profile over time and multiple courses up to 11 years of observation [18].

In this study, we evaluated the correlation between nine patient characteristics (age, gender, diseases duration, the presence of RF, the presence of ACPA, previous anti-TNF use, smoking status, the concomitant use of methotrexate and BMI) and the response to RTX. There was a significant inverse correlation between smoking and a reduction in disease activity (CDAI) (P=0.005). This was proved by Abdul Khan1.[19] in his study: smoking, RF status and responses to RTX, non-smokers have a very high response rate to RTX irrespective of their RF/ACPA status, in comparison, the smokers only achieve the response rate of 50

This study showed that there was more response in the RF-positive group from the RF-negative group. The RF positivity also was significant both by Luca Q. et al study (p=0.0001) [16], Lopez-Olivo [20], Isaacs JD [21] and Wendler J 2014 [22]. This study found (as in Wendler J.study) that the age did not affect RTX efficacy, while Luca Q. et al found that the older the age, the more response to RTX (p=0.01). We found MTX use was not related to the efficacy of RTX, this also proved by Richter A in German biologics register (2014) [17]. This study showed no difference between patients who started on RTX (n=36) and those who switched to RTX after use of TNF-blocker (n=29), while the previous failure to TNF blockers was positively related to RTX efficacy as proved by Lopez-Olivo [20].

This study and Wendler J. [22] did not prove that seropositivity for ACPA was associated with a superior clinical response to RTX, while Lopez-Olivo [20] did, and Jeremie S. in a Multicenter, Open-Label Study showed ACPA may be used

to predict the clinical response to a single course of RTX in patients with refractory RA [23]. In this study we did not found a relation between the gender, disease duration, and body mass index and response to treatment. The reported adverse effects of RTX in this study were in the form of descriptive statistics to give an idea about the most common side effects experienced by the patients. Unfortunately, the inferential statistic regarding drug safety was not possible due to the lack of a control group.

The most common side effect which occurs during RTX infusion is transfusion reaction in form of sore throat and nasal congestion with flushing(occur in 17 (26.17%) patients), although this was transient and was relieved by stopping the infusion for about an hour, and use of chlorpheniramine injection and acetaminophen oral. Non-serious infections developed in 3 out of 65 patients including 1 with a chest infection (1.5%) and 2 with pharyngitis (3.07%). A study of RTX safety (n=3595) published by Ronald F. at August 2015 stated that RTX has a consistent safety profile over time and multiple courses up to 11 years of observation, the patients in this update did not register increase rate of serious infections [18]. One of our patients developed severe abdominal pain and diarrhea 6hrs after RTX infusion(1.5%), she was admitted to the emergency unit, another patient had generalized itching (1.5%) at the day of infusion.

Van Vollenhoven et al. have recently reported a pooled analysis of the long-term safety of RTX in global clinical trials over 11 years [24]. The initial published data included 3194 patient. Overall, infections (5%) reported in the RTX-treated patients were upper respiratory infections, nasopharyngitis, urinary tract infection, bronchitis, sinusitis, diarrhea, and gastroenteritis, risk of serious infections was stable over time, even with multiple courses of treatment, 2 TB cases, no report on HBV, or HCV reactivation [24], increased risk of hospitalized infection [25].

Progressive multifocal leukoencephalitis (PML) is a progressive infection caused by the JC virus, and cases of PML have been reported in RA patients treated with RTX (0.001%)[25] RTX was not associated with an increased risk of any malignancy in RA pt. [24] RTX was not available from August 2015November 2015. It is to be noted that during this period the patients did not come for follow up. Also, the prolonged period between two cycles of RTX (6ms) made difficult contact with the patients.

CONCLUSION
- RTX is effective both clinically, functionally and lab. measures.
- It is most effective in those patients who are not smokers compared to smokers.
- It is more effective in a patient who is seropositive for RF (there was a great decrease in CDAI in RF-positive group (53.6%) from the RF-negative group (41.2).
- RTX is relatively safe with few side effects, tolerable by most patients. The most common side effect is transfusion reaction (26.15%).

CONFLICT OF INTEREST
The authors declare there is no conflict of interest.

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