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Compared Efficacy of Tocilizumab versus Rituximab in the Treatment of Refractory Rheumatoid Arthritis: A Randomized Clinical Trial study

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ABSTRACT

Background & Objective: This study was carried out to compare the efficacy of tocilizumab versus rituximab in the treatment of refractory rheumatoid arthritis.

Materials & Methods: Twenty-two women with refractory rheumatoid arthritis were randomly divided into rituximab (n= 11) and tocilizumab (n= 11) treatment groups. In the first group, rituximab was injected intravenously at a dose of 1 gram. In the second group, tocilizumab was injected subcutaneously at a dose of 20 mg /2 weeks for 6 months. Before the intervention, intensity was measured according to visual analog scale (VAS), along with vital signs and side effects. After 6 months, the clinical disease activity index (CDAI), pain intensity, tender joint count (TJC for 68 and 28 joints) and swollen joint count (SJC for 66 and 28 joints) were assessed. SPSS version 26 was used for data analysis.

Results: The mean age for rituximab and tocilizumab groups were 54.63 (±10.76) and 49.91 (±11.14) years, respectively. After 6 months of follow-up, the means of TJC (68 and 28 joints), SJC (for 66 and 28 joints), CDAI and pain intensity were not significantly different in the rituximab and tocilizumab groups (P>0.05). However, the mean of all the above-mentioned items before and 6 months after follow-up was statistically significant within each of the rituximab and tocilizumab groups (P<0.05).

Conclusion: The efficacy of tocilizumab and rituximab in the treatment of refractory rheumatoid arthritis was similar, therefore, both drugs can be used to treat these patients.

Keywords: Efficacy, Tocilizumab, Rituximab, Refractory Rheumatoid Arthritis

1. Introduction

Rheumatoid arthritis is a common autoimmune disease that is characterized by joint inflammation, cartilage involvement, and bone erosion (1). This disorder is a type of joint inflammation and destruction in an autoimmune form (2). Rheumatoid arthritis has a global prevalence of 0.5 - 1% (3). The global prevalence of rheumatoid arthritis is reported to be about 460 per 100,000 population in 2019. About 528 million people were suffering from osteoarthritis worldwide in 2019, which shows an increase of 113% compared to 1990 (4). The incidence of rheumatoid arthritis in women is three times that of men. Its incidence increases with age (5). The most obvious characteristic of the disease is chronic synovitis, which usually affects the hands and ankles and can eventually affect any joint (6). This disease is characterized by

inflammatory polyarthritis in large and small joints and general symptoms. This disease is characterized by inflammatory polyarthritis in large and small joints and general symptoms. One of its prominent clinical features is morning stiffness. The symptoms are aggravated in the morning and improve with activity, which is a classic feature of inflammatory arthropathies (2, 7). Despite the ever-increasing advances, none of the drug treatments cures this disease definitively and are used only to relieve symptoms and control attacks (8). In addition, the existence of some risk factors such as delays in treatment, inappropriate treatment, obesity, female gender, baseline disease activity and function, smoking and low socio-economic status can lead to refractory rheumatoid arthritis. This resistance to treatment can eventually lead to progressive destruction of the joint, functional disorder and increased mortality (9, 10). Since the immune mechanism plays a fundamental role, drugs that weaken the immune system are more effective in cases where other rheumatic drugs are not responsive (11). Rituximab is an immunosuppressive drug that is used for refractory rheumatoid arthritis. In addition, it is a chimeric IgG1 monoclonal antibody that is being used as a novel therapeutic agent in human lymphoma (12, 13). Rituximab binds to the CD20 antigen on B lymphocytes and causes their death. Recent evidence suggests that B-cell depletion is a safe and highly effective therapeutic option for autoimmune diseases (14, 15). Despite the good effects of rituximab in reducing symptoms, respiratory and urinary tract infections, varicella zoster, herpes simplex, and malignancies may develop following its use (16). Tocilizumab is another drug used in the treatment of refractory rheumatoid arthritis. This drug is a monoclonal antibody against the interleukin-6 receptor (IL-6R), which is used to treat various inflammatory diseases (17). Some studies have reported that tocilizumab can be effective for rheumatoid arthritis and reduce its symptoms (18, 19). However, infection, increased liver enzymes and serum cholesterol levels are listed as the most common side effects of this drug (20, 21). Limited studies have investigated and compared the advantages and disadvantages of rituximab and tocilizumab; however, contradictory results have been reported. Therefore, we designed this research with the aim of comparing the efficacy of tocilizumab and rituximab in patients with refractory rheumatoid arthritis.

2. Materials and Methods

2.1 Study Design and Subjects

We investigated 22 women with refractory rheumatoid arthritis referred to Luqman Hospital in Tehran in 2023. The convenience sampling method was implemented. A patient with positive rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) and high ESR/CRP with clinical symptoms who did not respond to the first-line treatments was defined as having refractory rheumatoid arthritis.

The inclusion criteria consisted of 1- age between 18 - 65 years 2- weight less than 100 kg 3- diagnosis of refractory rheumatoid 4- resistance to Methotrexate 5- Patients with mild and severe rheumatoid arthritis must have at least 4 painful joints and 4 swollen joints 6- ESR> 30 mm/h and CRP >10 mg/l at the time of study entry 7- Not taking DMARDS for at least 2 weeks before entering the study 8- Not belonging to functional class IV according to ACR, 9- Lack of history of rituximab injection within 2 years before entering the study 10- Not receiving tocilizumab and oral corticoid drugs at doses greater than 10 mg per day during the last 4 weeks at the time of the start of the study 11- No history of increasing the number or dose of DMARDS or immunosuppressant drugs within 4 weeks prior to the initiation of tocilizumab treatment 12- Lack of history of receiving live or attenuated vaccines 4 weeks before entering the study 13- Lack of history of performing plasmapheresis major joint and cardiovascular surgeries during the 8 weeks before entering the study until the end of the study 14-Lack of history of other rheumatic diseases and malignancy in the last 5 years 15- Lack of history of treatment with tacrolimus and cyclosporine in 1 month prior to the study 16- Normal liver enzymes 17- No history of thrombocytopenia, AIDS, hepatitis B and C 18- Not taking drugs that interact with rituximab or tocilizumab. Exclusion criteria also included 1- Death of the patient for any reason before the end of the follow-up 2- Joint surgery during the study 3- The patient's lack of satisfaction with the treatment during the study.

2.2 The intervention

Twenty-two women with refractory rheumatoid arthritis were randomly divided into two groups: rituximab (n= 11) and tocilizumab (n= 11) treatment groups. In the first group, rituximab was injected intravenously (IV) at a dose of 1 gram. In the second group, tocilizumab was injected at a dose of 20 mg /2 weeks subcutaneously for 6 months.

Clinical Disease Activity Index (CDAI) was assessed based on two criteria: physician global assessment (PGA) of disease activity and PGA of disease activity, each of which ranged from 0 -100 Pain intensity was measured based on patient's assessment of pain, which ranged from 0-100. Also, tender joint count (TJC) for 68 and 28 joints and swollen joint count (SJC) for 66 and 28 joints were measured before and 6 months after the intervention. In addition, to measure daily activities in the past week, 20 questions including the scales of dressing, getting up, eating, walking, personal hygiene, stretching and grasping were used. Each question included 4 options based on the Likert scale (No problem = 1, a little problem = 2, a lot of difficulty = 3 and I can't = 4). The score of daily activities in the past week was from 20 to 80 (No problem = 20, a little problem = 21- 40, a lot of difficulty = 41- 60 and I can't = 61-80).

2.3 Statistical Analysis

Data analysis was carried out using SPSS version 26. Means ± standard deviations and frequencies (%) were estimated for descriptive data. If there was a normal distribution, an independent t-test was performed to

compare quantitative variables in two groups, otherwise, the Mann–Whitney U test was implemented. For intra-group comparison, if the distribution was normal, the paired t-test was used; otherwise, the Wilcoxon signed-rank test was used. Chi-square test was applied to compare qualitative variables in the two groups.

3. Results

The mean age and the duration of the disease were 54.63 (±10.76) vs. 49.91 (±11.14) years and 10.82 (±1.08) vs. 11.18 (±1.25) months in the two groups, respectively. The mean daily activities in the past week were 49.36 (±3.26) and 51.00 (±11.11) in the rituximab and tocilizumab groups; respectively. Generally, the two groups were similar regarding baseline variables (P-Value>0.05) (Table 1).

Rituximab and Tocilizumab groups did not exhibit a significant difference after the intervention regarding the means of TJC (68 and 28 joints), SJC (66 and 28 joints), patient assessment of PGA of disease activity, and daily activities in the past week, as well as PGA of disease activity (P-Value>0.05) (Table 2).The means of TJC (68 and 28 joints), SJC (66 and 28 joints), PGA of disease activity, patients' assessment of pain, patients' assessment of PGA of disease activity, PGA of disease activity and daily activities in the past week after the intervention were significantly lower than before the intervention (P-Value<0.05) (Table 3).

Table 1. Comparison of the baseline and clinical variables before intervention in two groups.

Qualitative Variables		Rituximab	Tocilizumab	P-Value*
		N (%)	N (%)	
Sex	Female	11 (0)	11 (0)	1.000 *
	Male	0 (0)	0 (0)	
Daily activities in the past week	low difficulty	0 (0)	1 (9.1)	0.176*
	Very difficult	11 (100)	8 (72.2)	
	I can not	0	2 (18.2)	

Quantitative variable	Group	N	Mean	S.D	P-Value
Age (year)	Rituximab	11	54.63	10.76	0.324**
	Tocilizumab	11	49.91	11.14	
The duration of the disease (months)	Rituximab	11	10.82	1.08	0.474**
	Tocilizumab	11	11.18	1.25	
TJC 68 joints	Rituximab	11	20.36	4.03	0.670**
	Tocilizumab	11	21.54	5.11	
TJC 28 joints	Rituximab	11	20.90	2.87	0.203**
	Tocilizumab	11	18.91	4.13	
SJC 66 joints	Rituximab	11	20.72	4.27	0.229**
	Tocilizumab	11	18.37	4.65	
SJC 28 joints	Rituximab	11	20.72	4.26	0.140**
	Tocilizumab	11	17.63	5.12	
Physician global assessment of disease activity	Rituximab	11	90.91	7.00	0.797***
	Tocilizumab	11	91.81	7.50	
Patient global assessment of disease activity	Rituximab	11	91.79	6.03	0.606***
	Tocilizumab	11	90.00	7.74	
Patients assessment of pain	Rituximab	11	82.73	14.53	0.238***
	Tocilizumab	11	92.72	11.90	
Daily activities in the past week	Rituximab	11	49.36	3.26	0.654**
	Tocilizumab	11	51.00	11.11	

*: Chi square test
**: Independent sample t-test
***: Mann–Whitney U test

Table 2. Comparison of the clinical variables after intervention in two groups.

Qualitative Variables		Rituximab	Tocilizumab	P-Value*
		N (%)	N (%)	
Daily activities in the past week	Without difficulty	0 (0)	2 (18.2)	0.476
	Low difficulty	11 (100)	9 (81.8)	
Quantitative variable	**Group**	**N**	**Mean**	**S.D**	**P-Value**
TJC 68 joints	Rituximab	11	0.82	0.60	0.652**
	Tocilizumab	11	1.36	1.75	
TJC 28 joints	Rituximab	11	0.81	0.61	0.949**
	Tocilizumab	11	1.18	1.78	
SJC 66 joints	Rituximab	11	0.00	0.00	0.748**
	Tocilizumab	11	0.18	0.60	
SJC 28 joints	Rituximab	11	0.00	0.00	0.748**
	Tocilizumab	11	0.18	0.60	
Physician global assessment of disease activity	Rituximab	11	8.18	7.51	0.300**
	Tocilizumab	11	9.09	20.71	
Patient global assessment of disease activity	Rituximab	11	7.27	6.47	0.166**
	Tocilizumab	11	7.57	21.02	
Patients' assessment of pain	Rituximab	11	9.54	4.72	0.065**
	Tocilizumab	11	7.27	14.89	
Daily activities in the past week	Rituximab	11	28.45	3.83	0.130 ***
	Tocilizumab	11	25.27	5.44	

*: Chi square test
**: Mann–Whitney U test
***: Independent sample t-test

Table 3. Comparison of the clinical variables before and after intervention in rituximab group.

Variable	Group	N	Mean	S.D	P-Value
TJC 68 joints	Before	11	20.36	4.03	<0.001*
	After	11	0.82	0.60	
TJC 28 joints	Before	11	20.90	2.87	<0.001*
	After	11	0.81	0.61	
SJC 66 joints	Before	11	20.72	4.27	<0.001*
	After	11	0.00	0.00	
SJC 28 joints	Before	11	20.72	4.26	<0.001*
	After	11	0.00	0.00	
Physician global assessment of disease activity	Before	11	90.91	7.00	<0.001*
	After	11	8.18	7.51	
Patient global assessment of disease activity	Before	11	91.79	6.03	<0.001*
	After	11	7.27	6.47	
Patients' assessment of pain	Before	11	82.73	14.53	<0.001*
	After	11	9.54	4.72	
Daily activities in the past week	Before	11	49.36	3.26	<0.001**
	After	11	28.45	3.83	

*: Wilcoxon signed-rank test
**: Paired t-test

The means of TJC (68 and 28 joints), SJC (66 and 28 joints) PGA of disease activity, patients' assessment of pain, patients' assessment of PGA of disease activity, PGA of disease activity and daily activities in the past week after the intervention were significantly lower than before the intervention (P-Value<0.05) (Table 4).

The mean difference of TJC (68 and 28 joints) and SJC (66 and 28 joints) before and after the intervention was not significant in two groups (P-Value>0.05) (Table 5).

Table 4. Comparison of the clinical variables before and after intervention in tocilizumab group.

Variable	Group	N	Mean	S.D	P-Value
TJC 68 joints	Before	11	21.54	5.11	<0.001*
	After	11	0.82	0.60	
TJC 28 joints	Before	11	18.91	4.13	<0.001*
	After	11	0.81	0.61	
SJC 66 joints	Before	11	18.37	4.65	<0.001*
	After	11	0.00	0.00	
SJC 28 joints	Before	11	17.63	5.12	<0.001*
	After	11	0.00	0.00	
Physician global assessment of disease activity	Before	11	91.81	7.50	<0.001*
	After	11	8.18	7.51	
Patient global assessment of disease activity	Before	11	90.00	7.74	<0.001*
	After	11	7.27	6.47	
Patients assessment of pain	Before	11	92.72	11.90	<0.001*
	After	11	9.54	4.72	
Daily activities in the past week	Before	11	51.00	11.11	<0.001**
	After	11	25.27	5.44	

*: Wilcoxon signed-rank test
**: Paired t-test

Table 5. Comparison of mean difference of TJC (68 and 28 joints) and SJC (66 and 28 joints) before and after intervention in two groups.

Variable	Group	N	Mean difference	S.D	CI 95 %	P-Value*
Δ1	Rituximab	11	-20.72	4.27	-7.55 – 1.01	0.126
	Tocilizumab	11	-17.45	5.30	-7.56 – 1.02	
Δ2	Rituximab	11	-20.09	2.91	-5.28 – 0.55	0.106
	Tocilizumab	11	-17.72	3.60	- 5.29 – 0.56	
Δ3	Rituximab	11	-20.72	4.27	- 6.42 – 1.33	0.186
	Tocilizumab	11	-18.18	4.44	- 6.43 – 1.33	
Δ4	Rituximab	11	-19.54	4.08	- 4.50 – 5.77	0.799
	Tocilizumab	11	-20.18	7.06	- 4.58 – 5.85	

Δ1 = TJC 68 joints after - TJC 68 joints before
Δ2 = TJC 28 joints after - TJC 28 joints before
Δ3= SJC 66 joints after - SJC 66 joints before
Δ4= SJC 28 joints after - SJC 66 joints before
*: Independent sample t-test

4. Discussion

Despite the ever-increasing advances in rheumatoid arthritis, about 40% of patients have not shown a good clinical response to therapy with TNFi as a first-line treatment, which is mechanistically still unexplained

(22). Meanwhile, the drugs tocilizumab and rituximab are available treatment options and have shown good efficacy compared to placebo (23, 24). However, the studies regarding the direct comparison of the efficacy of these two drugs are limited (25). Hence, this study was carried out to compare the efficacy of tocilizumab and rituximab in the treatment of refractory rheumatoid arthritis. After the intervention, we observed that rituximab and tocilizumab had no significant differences regarding the means of TJC (68 and 28 joints), SJC (66 and 28 joints), CDAI and pain intensity (P>0.05). However, these indicators had significant differences before and after the intervention in each of the rituximab and tocilizumab groups (P<0.05). In Humby et al.'s study, the rituximab and tocilizumab groups were similar regarding CDAI 50% (45% vs. 56%, P=0.310). Also, the incidence of side effects (70% vs. 80%) and serious adverse events (7% vs. 10%) were similar in the two groups (P>0.05). However, B-cell depletion with RNA sequencing, CDAI50% in patients who received tocilizumab was significantly higher (36% vs. 63%, P= 0,035) (22). In the study of González-Vacarezza et al (26) on 6357 rheumatoid arthritis patients resistant to first-line drugs, the ACR20 response rate at 6 months in the tocilizumab group was significantly higher than in the rituximab group in patients who had failed to respond to anti-TNF drug. Also, tocilizumab showed a higher ACR70 response rate. Finally, this study concluded that tocilizumab can be a suitable treatment for those who are resistant to at least one anti-TNF drug (26). In a cohort study on 3162 adults with refractory rheumatoid arthritis, the mean survival without failure in the three groups of rituximab, abatacept, and tocilizumab was 19.8, 15.6, and 19.1 months, respectively. The three treatment groups were similar regarding major cardiovascular events, survival without death, incidence of cancer and serious infections. Finally, this study concluded that rituximab and tocilizumab compared to abatacept have better outcome and treatment response in adults (27).

However, there were also studies that did not agree with our results. For example, in another meta-analysis study conducted by Pugliesi et al (19), 19 clinical trials involving 7,835 patients were investigated. The results showed that the chances of getting a good response from ACR70 in the two groups of rituximab and abatacept did not show a significant difference. However, it was significantly higher in the abatacept group. Finally, this study states that despite the high heterogeneity in the studies, chances of getting a good response from ACR70 for refractory rheumatoid arthritis are higher than that of rituximab and tocilizumab (19). Differences in study design, sample size, drug dosage, different tools and scales for measuring pain intensity and patients' activity, and different follow-up periods can be the main reasons for the contradiction in the findings of this research with various studies conducted in this field.

Limitations

The first limitation is the low sample size. The second limitation is the possibility of selection bias due to the single-center study which makes the need for multi-center clinical trials and prospective cohort studies with a high sample size necessary in future research. The third limitation is the lack of examination of side effects and long-term serious adverse events of these drugs.

5. Conclusion

This study suggests that the efficacy of tocilizumab and rituximab in the treatment of refractory rheumatoid arthritis is similar, therefore, both drugs can be used to treat these patients. However, it seems necessary to design and implement multicenter clinical trial studies for a more detailed investigation of the efficacy, side effects, and long-term consequences of these drugs.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study began after obtaining ethics approval from Shahid Beheshti University of Medical Sciences. (ID-number: IR.SBMU.MSP.REC.1402.538).

6.3 Authors' Contributions

Lack of Response from the Corresponding Author. (**Publisher's Note:** Unfortunately, the corresponding author has not responded regarding this matter. In accordance with the publisher's policy, the article published with an editorial comment.)

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest.

6.5 Fund or Financial Support

Shahid Beheshti University of Medical Sciences was the financial sponsor of this research.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

6.7 Availability of data

Data can be obtained by request from the responsible author.

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