Clinical Rheumatology (2019) 38:2109–2117
https://doi.org/10.1007/s10067-019-04508-2

ORIGINAL ARTICLE

Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis

Samah Hamdy Elmedany[1] · Aly Elsayed Mohamed[2] · Sahar Mahfouz Abdel Galil[3,4]

Received: 22 November 2018 / Revised: 6 February 2019 / Accepted: 7 March 2019 / Published online: 26 March 2019

Abstract

Objectives To compare the efficacy and safety of tocilizumab with those of abatacept in patients with active rheumatoid arthritis not responding to anti-tumor necrosis factor therapy.

Methods A prospective, open-label study was carried out on adult females with moderate-to-severe rheumatoid arthritis. Patients were randomly assigned to receive either intravenous tocilizumab or abatacept treatment. History taking, clinical examination, and laboratory evaluation were done at baseline and during a 24-week period of follow-up. Disease activity was calculated using the DAS28-ESR score. The incidence of accompanying adverse events was evaluated and all statistical analyses were performed by InStat.

Results One hundred thirty-two patients were enrolled and classified randomly into the tocilizumab ($n = 68$) and abatacept ($n = 64$) groups. By week 24, the mean DAS28-ESR was significantly reduced in both groups ($P < 0.0001$) in association with significant reductions in CRP, ESR, and HAQ scores. No significant difference in the incidence rate of adverse effects appeared between both study groups. However, there were marked declines in the hemoglobin levels ($P = 0.003$) and neutrophil count ($P = 0.002$) together with significant elevations in systolic blood pressure ($P = 0.002$), liver enzymes ($P = 0.001$), total cholesterol ($P = 0.001$), and high-density lipoproteins ($P = 0.002$) in the tocilizumab group compared with the abatacept group.

Conclusion Both intravenous abatacept and tocilizumab significantly decreased the disease activity and improved the physical function in rheumatoid arthritis patients who failed to respond to anti-tumor necrosis factor therapy. Although the efficacy of both drugs was similar, abatacept showed a more promising short-term safety profile since it was associated with less adverse effects and better laboratory outcomes.

Keywords Abatacept · Adverse effects · Disease activity · Rheumatoid arthritis · Tocilizumab

Introduction

Rheumatoid arthritis (RA) is a chronic disabling disease that requires a long-term therapy. Biological agents are novel effective drugs used in the treatment of RA and can significantly decrease the subsequent disability, improve the quality of life, and inhibit structural damage [1]. Although many clinical trials have shown that combination therapy of methotrexate (MTX) plus anti-tumor necrosis factor (anti-TNF) agents for treating early RA can induce clinical remission in about half of the patients [2], the remaining patients cannot achieve a clinical remission or may develop adverse effects and may need to switch to other more effective biological agents [3–5]. However, there are several debates regarding choosing the next suitable biologic drug for managing a patient who has failed to respond to anti-TNF therapy [6].

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody (mAb) that has been approved for the treatment of RA patients who have failed to achieve remission with at least one anti-TNF therapy [7]. TCZ is an anti-IL-6 receptor

✉ Sahar Mahfouz Abdel Galil
dr_saharmahfouz@yahoo.com

[1] Physical Medicine, Rheumatology and Rehabilitation Department, Tanta University, El-Giesh Street, Tanta 31111, Egypt

[2] Physical Medicine, Rheumatology and Rehabilitation Department, Suez Canal University, Ismailia, Egypt

[3] Rheumatology & Rehabilitation Department, Faculty of Medicine, Zagazig University, University Street, Zagazig 44519, Egypt

[4] Medicine Department, College of Medicine, Umm Al-Qura University, El-Abdia, Makkah province 21955, Saudi Arabia

that inhibits the signaling of IL-6 by binding to both the soluble and membrane-bound IL-6 receptors [8]. It has demonstrated efficacy in the treatment of active RA by decreasing the acute phase reactants as well as beneficial effects on radiographic progression [9–11].

Another recently approved drug is abatacept (ABA). It is composed of two parts: the CTLA-4 ligand-binding domain and a modified IgG1-derived Fc portion domain. CTLA-4 has a high avidity for binding with CD80 and CD86 than binding to CD28; thus, it acts as a negative regulator of CD28-mediated T cell co-stimulation. Then, ABA blocks the engagement of CD28 with its ligand and inhibits T cell activation [12, 13]. The US Food and Drug Administration (FDA) had approved ABA as having a low toxicity profile for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis [14].

From the clinical point of view, for any novel medication to be widely accepted, its safety is ultimately important. The primary objective of this study was to determine the efficacy and compare the clinical outcomes together with the alterations in the laboratory markers (e.g., hemoglobin levels, leucocyte, neutrophil, lymphocyte and platelet counts, lipid profile, liver enzymes, and kidney function) following intravenous biologic therapy with either TCZ or ABA in patients who suffer from active RA and have failed to respond to anti-TNF therapy. The secondary objective was to evaluate the safety profile of both drugs by assessing the incidence rates of complications and adverse effects that may develop during a period of 24-week follow-up.

Patients and methods

Patient selection and enrollment

Adult females diagnosed with active RA according to the current criteria set by the American College of Rheumatology/European League Against Rheumatism (EULAR), 2010 for the classification of rheumatoid arthritis [15] and who failed to respond to anti-TNF drugs, were recruited from the rheumatology outpatient clinics located in multiple tertiary care institutes, Holly Makkah, Saudi Arabia. Initially, 185 RA patients were consecutively screened then only 132 were subsequently randomized and treated in this trial according to the following inclusion and exclusion criteria and the equation of sample-size calculation previously described by Sakpal [16].

Sample-size calculation

The calculator uses the following formula for calculating the sample size (n):

$$n = (Z\alpha/2 + Z\beta)^{2^*}\, 2^*\, \sigma 2/d2$$

where $Z\alpha/2$ is the critical value of the normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), $Z\beta$ is the critical value of the normal distribution at β (e.g., for a power of 80%, β is 0.2 and the critical value is 0.84), $\sigma 2$ is the studied variance (= 4.3), and d is the difference between two interventions (= 1); n = 68 subjects per group.

Inclusion criteria

We have selected adult female RA patients, > 18 years of age, with moderate-to-severe disease activity (based on the Disease Activity Score-28 (DAS-28) ≥ 3.2) [17], free from other comorbidities, and had failed to improve or achieve remission with at least one anti-TNF drug.

Exclusion criteria

We had excluded patients with other comorbidities as diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, end-stage renal failure, or any other autoimmune diseases as systemic lupus erythematosus. Also, we excluded any patients with evidence or history of significant infection within the previous 6 months (hepatitis B or C virus, human immunodeficiency virus; ruled out by clinical examination and serological markers) and patients with evident or suspected latent tuberculosis (ruled out by tuberculin purified protein derivative skin testing). Patients giving a history of gastrointestinal bleeding and patients reporting existing or history of malignancy, patients reporting altered laboratory investigations such as elevated liver aminotransferases (AST and/or ALT), 1.5 times upper limit of normal, decreased hemoglobin (Hb) < 10.0 g/dl, a total leukocytic cell count < 3.0×10^3/mm^3, an absolute neutropenia < 1200 cells/ml, or lymphopenia < 750 cells/ml, and decreased glomerular filtration rate [GFR] < 40 ml/min were all also excluded from our study. Male patients were excluded as their number was so small (14/185) when compared with the relatively large number (132/185) of female patients, in addition to having other exclusion criteria.

Study design

This is a prospective, open-label study. Patients were randomly assigned to two treatment groups using a simple randomization method with a computer-generated randomization number. The first group (n = 68) comprised IV TCZ infusion in a dose of 8 mg/kg every 4 weeks, according to the summary of product characteristics and as previously documented in several clinical trials [6, 18–21]. The second group (n = 68) comprised IV ABA infusion in a dose of 500 mg for patients less than 60 kg body weight, 750 mg for 60–100 kg, and

1000 mg for patients more than 100 kg body weight. ABA treatment was applied on days 1, 15, and 29 and then every 4 weeks, as previously applied in several studies [6, 18, 19, 22]. Four patients in the ABA group lost follow-up; therefore, they were excluded from final analysis after the 24-week period, leaving the ABA group to be composed of 64 patients only.

All patients of both groups also received oral MTX as 15 mg once weekly. When needed, concomitant treatment with full doses of non-steroidal anti-inflammatory drugs (NSAIDs) and/or low-dose oral steroids (< 10 mg/day of prednisone) were allowed in both treatment groups.

Data collection and assessment of efficacy and safety

Epidemiological and clinical characteristics data of all patients before the initiation of TCZ or ABA treatment including age, disease duration, seropositivity for rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs), disease activity according to DAS28-ESR score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) serum level, nature of previous treatments, and either disease-modifying antirheumatic drugs (DMARDs) or biologics were all recorded.

The following laboratory investigations were performed: complete blood count (CBC), fasting blood sugar (FBS), lipid profile, and liver and kidney function tests. Both clinical and laboratory analyses were assessed at baseline and at routine monthly follow-up visits through a 24-week duration. The incidence, frequency, and severity of any adverse events (AEs) associated with each therapy were also reported and evaluated.

The clinical improvement criteria (e.g., decreased tender and/or swollen joint count, decreased duration of morning stiffness, health assessment questionnaire (HAQ) scores) and laboratory improvement markers (e.g., decrease level of ESR, CRP, decreased platelet count) were all recorded. The outcome measures were set for a clinical improvement and achieving remission as defined by a DAS28-ESR score ≤ 2.6.

Statistical analysis

Characteristics of patients and their baseline disease activity features are described with statistical comparisons overall and according to sub-classified treatment groups.

Quantitative variables were presented as mean ± SD, while qualitative variables were described as number and percentage. We used the unpaired *t* test to compare between the two groups regarding the quantitative variables. The qualitative variables were compared between both groups by using the χ^2 test. Cox proportional hazard model was used to evaluate the incidence of the most common and most serious AEs during the study period. InStat was used to perform all analyses, and the *P* value was considered as statistically significant if it was ≤ 0.05.

Results

A total of 132 RA patients who failed in controlling the disease activity following one or more anti-TNF therapy were enrolled in this study. There was no significant difference ($P = 0.306$) in the mean age ± SD between the TCZ group (51.12 ± 16.11 years) and the ABA group (47.91 ± 15.12 years).

Before study initiation, patients of the TCZ group received anti-TNF drugs in a mean ± SD number of previous applications of 1.4 ± 0.35, while those of the ABA group received anti-TNF drugs in a mean ± SD number of previous applications of 1.3 ± 0.36. Anti-TNF therapies were discontinued due to primary inefficacy in 58% of the patients, secondary loss of efficacy in 32%, and intolerance in 10%.

All patients enrolled in this study were established and advanced RA cases. The mean disease duration was 6.97 ± 6.33 and 8.00 ± 6.16 years in the TCZ and ABA groups, respectively. When the TCZ was initiated, the mean ± SD of DAS28-ESR score was 5.76 ± 1.04, and the mean ± SD of CRP was 2.51 ± 2.68 mg/dl. Tender joint count (TJC) mean ± SD was 4.347 ± 2.391 joints and the swollen joint count (SJC) mean ± SD was 3.32 ± 1.71 joints. In the group treated with ABA, the mean ± SD of DAS28-ESR was 5.44 ± 1.26 and that of the CRP was 2.60 ± 3.49 mg/dl. TJC mean ± SD was 4.49 ± 2.26 joints and the SJC mean ± SD was 3.57 ± 1.64 joints, which denotes high disease activity in all patients (Table 1).

Notably, MTX was concomitantly used in all patients. Overall, about 15% of the patients required a low-dose corticosteroid therapy. Baseline clinical characteristics of all patients are detailed in Table 1, where there were no statistically significant differences between both groups of patients in all parameters.

Clinical efficacy and laboratory outcomes of both groups

By week 24, both the TCZ and ABA groups achieved a highly significant reduction in all the parameters of disease activity including TJC, SJC, ESR, CRP, and DAS28-ESR scores, as well as in the mean HAQ-visual analogue score (HAQ-VAS score) (Table 2). However, the mean change (mean of 24-week scores − mean of baseline scores) of DAS28-ESR was significantly higher ($P = 0.049$) in the TCZ group (− 3.3) compared with that of the ABA group (− 2.6) (data not shown).

The TCZ group showed a highly significant elevation in systolic blood pressure, total cholesterol, high-density lipoproteins (HDL), and liver enzymes, while it showed significant reductions in hemoglobin level, neutrophil count, and homeostasis model assessment-insulin resistance (HOMA-IR). On the other hand, ABA group showed only a significant elevation in liver enzymes together with a significant reduction in neutrophil count and HOMA-IR (Table 2).

Table 1 Baseline clinical and laboratory characteristics of the patients with RA

Characteristics	Tocilizumab, no = 68	Abatacept, no = 64	*P* value
Medical profile			
Mean of systolic Bl. Pressure (SD)	115.6 ± 15.95	118.55 ± 14.66	0.250
Body mass index, kg/m^2 mean (SD)	29.51 ± 5.16	29.08 ± 5.89	0.856
Total cholesterol mg/dl mean (SD)	176.95 ± 36.65	178.24 ± 32.36	0.160
Triglycerides mg/dl mean (SD)	108.06 ± 46.68	110.16 ± 56.67	0.940
HDL mg/dl mean (SD)	48.56 ± 10.83	49.89 ± 11.85	0.765
LDL mg/dl mean (SD)	121.79 ± 39.60	115.43 ± 37.49	0.988
Hemoglobin g/dl mean (SD)	11.99 ± 2.02	11.60 ± 1.27	0.189
Leukocytes 10^3/l mean (SD)	7.00 ± 2.34	7.10 ± 2.40	0.581
Neutrophil 10^3/l mean (SD)	2.2 ± 0.35	2.3 ± 0.32	0.237
Lymphocyte 10^3/l mean (SD)	1.410 ± 0.67	1.367 ± 0.62	0.267
Platelet 10^9/l mean (SD)	32.6 ± 9.2	33.3 ± 10.0	0.749
FBS mg/dl mean (SD)	111.50 ± 36.1	108.09 ± 32.45	0.197
S. insulin (uIU/ml) mean (SD)	12.82 ± 10.02	12.72 ± 6.33	0.945
HOMA-IR mean (SD)	4.95 ± 1.11	4.53 ± 1.64	0.085
ALT mean (SD)	20.4 ± 3.25	19.6 ± 3.85	0.198
AST mean (SD)	20.2 ± 2.75	18.35 ± 2.45	0.178
Total bilirubin mean (SD)	0.616 ± 0.325	0.588 ± 0.388	0.653
Serum urea mean (SD)	30.2 ± 5.56	31.4 ± 4.95	0.194
Serum creatinine mean (SD)	0.666 ± 0.24	0.625 ± 0.26	0.348
RA characteristics			
RA duration (years) mean (SD)	6.97 ± 6.33	8.00 ± 6.16	0.346
DAS28 mean (SD)	5.76 ± 1.04	5.44 ± 1.26	0.113
CRP mg/dl mean (SD)	2.513 ± 2.680	2.604 ± 3.491	0.866
ESR mm 1st h mean (SD)	38.695 ± 24.27	40.388 ± 25.16	0.695
HAQ (VAS) mean (SD)	44.842 ± 9.878	45.714 ± 9.574	0.608
HAQ DI mean (SD)	0.905 ± 1.168	1.020 ± 1.436	0.674
Tender joint count mean (SD)	4.347 ± 2.391	4.490 ± 2.265	0.817
Swollen joint count mean (SD)	3.326 ± 1.713	3.579 ± 1.641	0.277
RF positive, *n* (%)	52 (76.470%)	48 (75%)	0.8891
ACCP antibody positivity, *n* (%)	50 (73.52%)	46 (71.87%)	0.5670
Medication profile			
Concomitant MTX use, *n* (%)	68 (100%)	64 (100%)	0.892
Concomitant corticosteroids, *n* (%)	6 (8.823%)	4 (6.25%)	0.692
Previous biologic (anti-TNF), mean (SD)	1.4 ± 0.35	1.3 ± 0.36	0.108

Values are given as mean ± SD or *n* (%)

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *HOMA-IR* homeostasis model assessment-insulin resistance, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *RA* rheumatoid arthritis, *DAS28* disease activity score 28, *HAQ* health assessment questionnaire, *HAQ DI* disability index, *RF* rheumatoid factor, *ACCP* anti-cyclic citrullinated peptide

Comparison of the outcomes between both groups

When comparing the outcomes of both groups at the 24th week, patients of the TCZ group achieved a lower DAS28-ESR score compared to the ABA group, albeit the difference between groups is not statistically significant (2.4 ± 0.84 versus 2.8 ± 0.78; respectively, $P = 0.055$). As regards to ESR and CRP, a statistically highly significant reduction in their levels was found in patients treated with TCZ compared to patients treated with ABA ($P = 0.0001$). Besides, there was a significant reduction in the HAQ-VAS scores ($P = 0.001$) and the TJC ($P = 0.001$) that also denoted a much better improved disease activity in the TCZ than the ABA group (Table 3).

However, the notable different outcomes between both groups were the significant reduction in hemoglobin level

Table 2 Clinical efficacy and laboratory changes through the 24 weeks of follow-up in both groups of patients

Characteristics	Tocilizumab (no = 58)			Abatacept (no = 60)		
	BL	W24	*P* value	BL	W24	*P* value
Mean of sys. Bl. Pressure (SD)	115.6 ± 15.9	129.3 ± 17.3	0.001*	118.5 ± 14.6	120.8 ± 13.9	0.356
TC mg/dl mean (SD)	176.95 ± 36.7	209.3 ± 30.2	0.0006*	178.24 ± 32.4	182.3 ± 24.6	0.421
Triglycerides mg/dl mean (SD)	108.06 ± 46.7	117.4 ± 36.5	0.204	110.16 ± 56.7	116.6 ± 48.2	0.526
HDL mg/dl mean (SD)	48.6 ± 10.83	60.3 ± 12.61	0.0004*	49.89 ± 11.9	52.6 ± 9.5	0.152
LDL mg/dl mean (SD)	121.8 ± 39.6	126.7 ± 40.3	0.482	119.43 ± 37.5	126.5 ± 26.5	0.215
Hemoglobin g/dl mean (SD)	11.99 ± 2.02	10.88 ± 1.38	0.0004*	11.60 ± 1.27	11.8 ± 2.11	0.507
Leucocytes 10^3/l mean (SD)	7.00 ± 2.34	6.6 ± 2.15	0.309	7.10 ± 2.4	7.2 ± 2.2	0.804
Neutrophil 10^3/l mean (SD)	2.2 ± 0.35	1.9 ± 0.36	0.001*	2.3 ± 0.32	2.1 ± 0.38	0.001*
Lymphocyte 10^3/l mean (SD)	1.410 ± 0.67	1.22 ± 0.58	0.084	1.367 ± 0.62	1.336 ± 0.48	0.749
Platelet 10^9/l mean (SD)	32.6 ± 9.2	32.2 ± 8.9	0.800	33.3 ± 10.0	32.9 ± 9.8	0.817
FBS mg/dl mean (SD)	111.50 ± 36.1	109.6 ± 35.8	0.762	108.09 ± 32.5	110.2 ± 34.6	0.718
S. insulin (uIU/ml) mean (SD)	12.82 ± 10.02	10.62 ± 8.66	0.180	12.72 ± 6.33	11.24 ± 7.98	0.238
HOMA-IR mean (SD)	4.95 ± 1.11	2.45 ± 1.22	< 0.0001*	4.53 ± 3.64	3.11 ± 1.05	0.003*
ALT mean (SD)	20.4 ± 3.25	37.73 ± 6.84	< 0.0001*	19.6 ± 3.85	22.75 ± 4.66	0.001*
AST mean (SD)	20.2 ± 2.75	35.44 ± 6.41	< 0.0001*	18.35 ± 2.45	20.68 ± 3.85	0.002*
Total bilirubin mean (SD)	0.616 ± 0.325	0.82 ± 0.25	0.001*	0.588 ± 0.388	0.766 ± 0.16	0.008*
Serum urea mean (SD)	30.2 ± 8.56	32.3 ± 7.22	0.131	31.4 ± 4.95	32.8 ± 4.87	0.104
Serum creatinine mean (SD)	0.666 ± 0.24	0.682 ± 0.18	0.667	0.625 ± 0.26	0.633 ± 0.17	0.836
RA characteristics						
DAS28 mean (SD)	5.76 ± 1.04	2.4 ± 0.84	< 0.0001*	5.44 ± 1.26	2.8 ± 0.78	< 0.0001*
HAQ (VAS) mean (SD)	44.842 ± 9.88	15.95 ± 7.86	< 0.0001*	45.714 ± 9.57	20.74 ± 8.82	< 0.0001*
HAQ DI mean (SD)	0.905 ± 1.168	0.89 ± 1.12	0.940	1.020 ± 1.436	1.01 ± 1.24	0.966
Tender joint count mean (SD)	4.347 ± 2.39	1.5 ± 1.02	< 0.0001*	4.490 ± 2.265	2.33 ± 1.46	0.0001*
Swollen joint count mean (SD)	3.326 ± 1.713	0.8 ± 1.34	< 0.0001*	3.579 ± 1.641	1.24 ± 1.23	< 0.0001*
CRP, mg/dl mean (SD)	2.513 ± 2.680	0.56 ± 0.12	< 0.0001*	2.604 ± 3.491	1.21 ± 0.64	0.002*
ESR mm 1st h mean (SD)	38.695 ± 24.3	18.44 ± 3.65	< 0.0001*	40.388 ± 25.2	25.3 ± 2.89	< 0.0001*

Values are given as mean ± SD

BL baseline, *W24* week 24, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FBS* fasting blood sugar, *HOMA-IR* homeostasis model assessment-insulin resistance, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DAS28* disease activity score 28, *HAQ* health assessment questionnaire, *HAQ DI* disability index

*$P < 0.05$; significant

($P = 0.003$), neutrophil count ($P = 0.002$), and HOMA-IR ($P = 0.001$), in the TCZ group in comparison with the ABA group. Additionally, there were significant elevations in systolic blood pressure ($P = 0.002$), the liver enzymes ($P = 0.001$), total cholesterol ($P = 0.001$), and HDL ($P = 0.002$) in the TCZ group compared with the ABA group (Table 3).

Adverse effects and safety evaluation

By week 24, we found that 60.29% of the patients in the TCZ group and 28.13% in the ABA group had AEs. Upper respiratory tract infections—nasopharyngitis, sinusitis, oral herpes, and rhinitis, were the most common AEs reported with no significant differences between both groups (Table 4).

However, serious adverse effects (SAEs) were reported in ten patients (14.7%) following treatment with TCZ compared with four patients (6.25%) following treatment with ABA. The most incident serious infection was pneumonia which affected eight patients (6.06%). Additionally, urinary tract infection was reported as SAEs in two patients from each study group. Moderate-to-severe abdominal pain was observed in two patients treated with TCZ that necessitated discontinuation of the treatment. No gastrointestinal perforation, major adverse cardiovascular events, or new cancer incidence were observed in either groups until the end of the study. The incidence rates of AEs showed non-significant differences between both groups of patients all over the period of follow-up (Table 4).

Table 3 Comparison of the clinical and laboratory outcomes at week 24 between both treatment groups

	Tocilizumab (no = 58)	Abatacept (no = 60)	*P* value
Mean of sys. Bl. Pressure (SD)	129.3 ± 17.3	120.8 ± 13.9	0.002*
TC mg/dl mean (SD)	209.3 ± 30.2	182.3 ± 24.6	0.001*
Triglycerides mg/dl mean (SD)	117.4 ± 36.5	116.6 ± 48.2	0.914
HDL mg/dl mean (SD)	60.3 ± 12.61	52.6 ± 9.5	0.002*
LDL mg/dl mean (SD)	126.7 ± 40.3	126.5 ± 26.5	0.973
Hemoglobin m/dl mean (SD)	10.88 ± 1.38	11.8 ± 2.11	0.003*
Leukocytes 103/l mean (SD)	6.6 ± 2.15	7.2 ± 2.2	0.116
Neutrophil 103/l mean (SD)	1.9 ± 0.36	2.1 ± 0.38	0.002*
Lymphocyte 103/l mean (SD)	1.22 ± 0.58	1.336 ± 0.48	0.239
Platelet 109/l mean (SD)	32.2 ± 8.9	32.9 ± 9.8	0.668
FBS mg/dl mean (SD)	109.6 ± 35.8	110.2 ± 34.6	0.922
S. insulin (uIU/ml) mean (SD)	10.62 ± 8.66	11.24 ± 7.98	0.677
HOMA-IR mean (SD)	2.45 ± 1.22	3.11 ± 1.05	0.001*
ALT mean (SD)	37.73 ± 6.84	22.75 ± 4.66	0.001*
AST mean (SD)	35.44 ± 6.41	20.68 ± 3.85	0.001*
Total bilirubin mean (SD)	0.82 ± 0.25	0.766 ± 0.16	0.145
Serum urea mean (SD)	32.3 ± 5.22	32.8 ± 4.87	0.571
Serum creatinine mean (SD)	0.682 ± 0.18	0.633 ± 0.17	0.111
RA characteristics			
DAS28 (ESR)	2.4 ± 0.84	2.8 ± 0.78	0.055
HAQ (VAS)	15.95 ± 7.86	20.74 ± 8.82	0.001*
HAQ DI	0.89 ± 1.12	1.01 ± 1.24	0.560
Tender joint count	1.5 ± 1.02	2.33 ± 1.46	0.001*
Swollen joint count	0.8 ± 1.34	1.24 ± 1.23	0.052
CRP, mg/dl	0.56 ± 0.12	1.21 ± 0.64	0.0001*
ESR, mm/h	18.44 ± 3.65	25.3 ± 2.89	0.0001*

Values are given as mean ± SD

BL baseline, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FBS* fasting blood sugar, *HOMA-IR* homeostasis model assessment-insulin resistance, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DAS28* disease activity score 28, *HAQ* health assessment questionnaire, *HAQ DI* disability index

*$P < 0.05$; significant

Regarding the incidence rate of allergic reactions (e.g., shortness of breath, lip and tongue swelling, chest pain, feeling faint or dizzy, and injection site reactions), there was not any significant difference between the patients who received TCZ and those who received ABA treatment (Table 4).

The most highly incident laboratory abnormalities were hyperlipidemia, especially HDL, in 28 patients (41.18%) following TCZ versus 20 patients (31.25%) following ABA treatment, which is considered protective from atherosclerotic changes. Additionally, decreased hemoglobin level by 1–3 g/dl, neutropenia, and lymphopenia were more prevalent in the TCZ group, although did not reach a critical level. However, elevated hepatic transaminases were significantly more frequent following TCZ treatment (4 patients with an AST level ≥ 2 upper limit of normal (ULN), and 4 patients with an ALT level ≥ 2 ULN). Discontinuation of treatment due to serious AEs was more prevalent in the TCZ group.

Discussion

The efficacy and safety of biologics such as TCZ and ABA in treating moderate-to-severe RA were reported by several randomized clinical trials and confirmed by other different clinical practice studies. However, the paucity of data on the use of both drugs with Saudi patients had led us to carry out this prospective comparative trial of intravenous TCZ versus intravenous ABA in RA patients who failed to respond to at least one anti-TNF drug from our real world of rheumatology field.

Depending on the hypothesis that the blockage of T cell activation or inhibition of IL-6 signaling might impact the pathogenesis of RA disease, we compared the changes in the disease activity and achievement of low disease activity/remission as well as meaningful improvement in physical functions in the two treatment groups.

Table 4 Incidence of most common adverse events (AEs) and serious AEs (SAEs) during the period of follow-up

	Tocilizumab ($N = 68$)	Abatacept ($N = 64$)	Odd ratio, 95% CI	P value
AEs				
Nasopharyngitis	16 (23.53%)	8 (12.5%)	2.2 (0.6–8.0)	0.25
Upper respiratory tract infection	12 (17.65%)	4 (6.25%)	3.2 (0.6–17)	0.26
Sinusitis	6 (8.82%)	2 (3.125%)	3.0 (0.3–30)	0.61
Oral herpes	4 (5.88%)	0 (0.0%)	–	0.49
Rhinitis	2 (2.94%)	4 (6.25%)	0.45 (0.04–5)	0.61
SAEs				
Urinary tract infection	2 (2.94%)	2 (3.125%)	0.9 (0.06–16)	1.0
Pneumonia	6 (8.82%)	2 (3.125%)	3.0 (0.3–30)	0.61
Cellulitis	0 (0.0%)	0 (0.0%)	–	–
Herpes zoster	0 (0.0%)	0 (0.0%)	–	–
Moderate to severe abdominal pain	2 (2.94%)	0 (0.0%)	–	
Gastrointestinal perforation	0 (0.0%)	0 (0.0%)	–	–
New cancer incidence	0 (0.0%)	0 (0.0%)	–	–
Major adverse cardiovascular event	0 (0.0%)	0 (0.0%)	–	–
Allergic reactions				
Shortness of breathing	8 (11.76%)	8 (12.5%)	0.9 (0.2–4.1)	1.0
Lip and tongue swelling	4 (5.88%)	6 (9.375%)	0.6 (0.09–3.9)	0.67
Chest pain	4 (5.88%)	4 (6.25%)	0.9 (0.1–7.1)	1.0
Feeling faint or dizzy	8 (11.76%)	6 (9.375%)	1.3 (0.3–6.3)	1.0
Injection site reaction	12 (17.65%)	10 (15.62%)	1.1 (0.3–4.2)	1.0
Laboratory data				
Hypercholesterolemia	28 (41.18%)	20 (31.25%)	1.5 (0.6–4.2)	0.40
Decreased hemoglobin, *n* (%)				
Decrease 1–3 g/dl	8 (11.76%)	4 (6.25%)	2.0 (0.3–11.8)	0.67
Decrease ≥ 3 g/dl	0 (0.0%)	0 (0.0%)	–	–
Neutropenia *n* (%)				
1500–2000 cells/mm^3	16 (23.53%)	4 (6.25%)	4.6 (0.9–24)	0.08
500–1500 cells/mm^3	8 (11.76%)	0 (0.0%)	–	0.11
< 500 cells/mm^3	0 (0.0%)	0 (0.0%)	–	–
Lymphopenia *n* (%)				
500–1500 cells/mm^3	8 (11.76%)	2 (3.125%)	4.1 (0.4–39)	0.36
< 500 cells/mm^3	0 (0.0%)	0 (0.0%)	–	–
Aminotransferases *n* (%)				
AST ≥ 2 ULN with normal baseline	4 (5.88%)	0 (0.0%)	–	0.49
ALT ≥ 2 ULN with normal baseline	4 (5.88%)	0 (0.0%)	–	0.49
Serum creatinine *n* (%)				
>50% increase from baseline	0 (0.0%)	0 (0.0%)	–	–
Discontinuations due to SAEs	10 (14.71%)	4 (6.25%)	5.3 (0.6–49)	0.20

AEs adverse events, *SAEs* serious adverse events, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal, *CI* confidence interval

One hundred thirty-two adult Saudi female patients with established moderate-to-severe RA, according to DAS28-ESR score ≥ 3.2, were randomized to receive monthly IV TCZ or ABA and were followed up for 24 weeks.

Our results showed a comparable efficacy for both drugs on the disease activity and physical functions. Both drugs achieved a highly significant reduction in all disease activity parameters that agrees with several previous studies [23–26]. There was a rapid descent of CRP levels in patients under TCZ therapy than those under ABA treatment, as previously documented [23], where the hepatic synthesis of CRP is under the control of IL-6; hence, the anti-IL-6 action of TCZ has a particular efficacy in decreasing the levels of CRP [9]. To avoid such a possible disproportionate effect of TCZ,

DAS28-ESR was preferred as the efficacy outcome in our study. However, similarly as reported in a previous study [20], there was also a highly significant decrease in the mean ESR levels in the TCZ group compared with ABA group, by the end of follow-up period.

Although TCZ resulted in more improving effects on disease activity in the present study, some clinical and laboratory outcomes of the TCZ group were significantly worse than those of the ABA group. Consequently, we are in accordance with multiple previous studies that clarified the safety of ABA is much better than that of TCZ either on the short- or the long-term follow-up periods [27–30]. In further details, TCZ was associated with significant elevations in systolic blood pressure and hepatic transaminases (even though they are still within the normal range), through the 24-week period of follow-up, which could be alarming for more progression to much higher levels with the prolonged therapeutic duration.

Similarly, the AMBITION study has reported that a tripled elevation of ALT is more common with methotrexate-TCZ combination therapy and may lead to liver toxicity [31]. In addition, other studies confirmed that patients on TCZ therapy may stop treatment due to significant increases in ALT or AST levels, where they showed a threefold ULN increase, in 7.6 and 2.4% of patients, respectively, after about 1.5 years of treatment, and in 9.8% and 6.3% of patients, respectively, after 5 years of treatment [11]. Thus, a more prolonged close follow-up is a must in such cases under TCZ treatment, for avoidance and early detection of hepatic toxicity. However, it is worth mentioning that most elevations were transient and self-remitting [11].

Our results demonstrated a significant elevation in the total cholesterol level in the TCZ group, which may be due to the significant increase in the HDL levels. The increased HDL levels have a significant protective effect from subsequent atherosclerotic changes, especially that the low-density lipoproteins (LDL) and triglycerides were not significantly elevated; hence, there is no increased atherogenic index (ratio LDL/HDL). As previously explained, a greater increase in the atherogenic index may arise in patients under TCZ treatment [31] and could be counter-balanced by a marked decrease in CRP level, which is an independent risk factor for cardiovascular diseases [21], and that is the state of our sample of patients. The resultant hyperlipidemia, with TCZ treatment, may due to its anti-inflammatory effect (as an anti-IL-6) and could be explained by the potential role of IL-6 on the lipid metabolism [32].

Although there was a significant reduction in hemoglobin level and neutrophil count in the TCZ group, these alterations are still in the safe side (not less than 8 g/dl for hemoglobin and not less than 500 cells/mm^3 for neutrophils) that do not need interference but just close follow-up to avoid hazardous more reduction with long-term therapy. Previously, it was reported that decreased neutrophil count is not associated with serious infections [33] and has occurred in a dose-dependent fashion during TCZ treatment [21].

Our present findings are derived from a randomized study, which is a subject to well-known limitations by their strict inclusion criteria and their restricted time span. These limitations may be overcome by meta-analysis, which combines the results of several randomized controlled trials and increases the statistical power to detect significant differences. Detection of the true incidence of AEs was adequately limited in the present study by its small sample size, short duration of follow-up, and strict inclusion and exclusion criteria.

Conclusion

This study provides an evidence that either IV tocilizumab or abatacept treatments are efficient second-line regimens for a significant proportion of RA patients following failure of the initial anti-TNF drugs. Compared to abatacept, tocilizumab yielded a higher reduction in DAS28-ESR and CRP as well as a higher percentage of patients who achieved low disease activity/remission. However, abatacept treatment presented less significant adverse effects and better laboratory outcomes; thus, it gave a more promising short-term efficacy and safety data. Additional long-term safety data are needed for better characterization of the risk-benefit profile of both drugs.

Compliance with ethical standards

Disclosures None.

Ethical approval Our study was approved according to the local ethical committee inside all hospitals that participated in this study. All selected patients have given written informed consents, before being enrolled in the study.

References

1. Giles J, Bathon JM (2010) Management of rheumatoid arthritis: synovitis. Rheumatology 1:955–963
2. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B (2008) Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomized, double-blind, parallel treatment trial. Lancet 372:375–382
3. Finckh A, Simard JF, Gabay C, Guerne PA (2006) Evidence for differential acquired drug resistance to anti-tumor necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis 65:746–752
4. Du Pan SM, Dehler S, Ciurea A et al (2009) Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 61:560–568
5. Buch MH (2010) Sequential use of biologic therapy in rheumatoid arthritis. Curr Opin Rheumatol 22:321–329
6. Harrold LR, Reed GW, Solomon DH, Curtis JR et al (2016) Comparative effectiveness of abatacept versus tocilizumab in

rheumatoid arthritis patients with prior TNFi exposure in the US Corrona registry and Joel M. Kremer 5,6. Arthritis Res Ther 18:280
7. Moots RJ, Sebba A, Rigby W, Ostor A, Porter-Brown B, Donaldson F, Dimonaco S, Rubbert-Roth A, van Vollenhoven R, Genovese MC (2017) Effect of tocilizumab on neutrophils in adult patients with rheumatoid arthritis: pooled analysis of data from phase 3 and 4 clinical trials. Rheumatology 56:541–549
8. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T (2008) Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood 112:3959–3964
9. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, Woodworth T, Alten R (2008) Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double blind, placebo-controlled, randomized trial. Lancet 371:987–997
10. Nishimoto N, Hashimoto J, Miyasaka N et al (2007) Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor—evidence of clinical and radiographic benefit from an X-ray reader-blinded randomized controlled trial of tocilizumab. Ann Rheum Dis 6:1162–1167
11. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J (2009) Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis 68:1580–1584
12. Bluestone J, St. Clair E, Turka L (2006) CTLA4Ig: bridging the basic immunology with clinical application. Immunity 24:233–238
13. Cron RQ (2005) A signal achievement in the treatment of arthritis [editorial]. Arthritis Rheum 52:2229–2232
14. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, Seo P, Moreland LW, Weisman M, Koening CL, Sreih AG, Spiera R, McAlear C, Warrington KJ, Pagnoux C, McKinnon K, Forbess LJ, Hoffman GS, Borchin R, Krischer JP, Merkel PA, Vasculitis Clinical Research Consortium (2017) A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of Takayasu arteritis. Arthritis Rheumatol 69(4):846–853
15. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JMW, Hobbs K, Huizinga TWJ, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G (2010) Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62:2569–2581
16. Sakpal TV (2010) Sample size estimation in clinical trial. Perspect Clin Res 1(2):67–69
17. Prevoo ML, van't Hof MA, Kuper HH et al (1995) Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 38(1):44–48
18. Kubo S, Nakayamada S, Nakano K et al (2015) Comparison of the efficacies of abatacept and tocilizumab in patients with rheumatoid arthritis by propensity score matching. Ann Rheum Dis. https://doi.org/10.1136/annrheumdis-207784
19. Pascart T, Philippe P, Drumez E, Deprez X, Cortet B, Duhamel A, Houvenagel E, Flipo RM (2016) Comparative efficacy of tocilizumab, abatacept and rituximab after non-TNF inhibitor failure: results from a multicenter study. Int J Rheum Dis 19(11):1093–1102
20. Jones G, Ding C (2010) Tocilizumab: a review of its safety and efficacy in rheumatoid arthritis. Clin Med Insights Arthritis Musculoskelet Disord 3:81–89
21. King-Konert C, von Hinüber U, Richter C et al (2016) ROUTINE—a prospective, multicenter, non-interventional, observational study to evaluate the safety and effectiveness of intravenous tocilizumab for the treatment of active rheumatoid arthritis in daily practice in Germany. Rheumatology 55:624–635
22. Schiff M, Poncet C, Le Bars M (2010) Efficacy and safety of abatacept therapy for rheumatoid arthritis in routine clinical practice. Int J Clin Rheumatol 5(5):581–591
23. Leffers HC, Ostergaard M, Glintborg B, Krogh NS et al (2011) Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 70(7):1216–1222
24. Hirabara S, Takahashi N, Fukaya N, Hiroyuki H et al (2014) Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. Clin Rheumatol 33:1247–1254
25. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J, Kremer J (2008) IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicenter randomized placebo-controlled trial. Ann Rheum Dis 67(11):1516–1523
26. Genovese MC, Schiff M, Luggen M, Becker JC et al (2008) Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 67(4):547–554
27. Schiff M, Pritchard C, Huffstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, Li T, Bahrt K, Kelly S, le Bars M, Genovese MC (2009) The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis 68:1708–1714
28. Westhovens R, Kremer JM, Emery P, Russell AS, Alten R, Barré E, Dougados M (2014) Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. Clin Exp Rheumatol 32:553–562
29. Gottenberg JE, Morel J, Constantin A et al (2016) Long-term registry data in 4498 patients with rheumatoid arthritis indicate a similar safety but a different drug retention between abatacept, rituximab and tocilizumab. Arthr Rheumatol. 68(Suppl 10):2550–2553
30. Gottenberg JE, Morel J, Constantin A et al (2016) Similar rates of death, serious infections, cancers, major cardiovascular events in patients treated with abatacept, rituximab and tocilizumab: long-term registry data in 4498 patients with rheumatoid arthritis. Arthr Rheumatol 68(Suppl 10):3536–3537
31. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, Siri DA, Tomsic M, Alecock E, Woodworth T, Genovese MC (2010) Comparison of TCZ monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 69:88–96
32. Choy E, Sattar N (2009) Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 68:460–469
33. Kremer JM, van Vollenhoven RF, Ridley DJ et al (2008) Relationship between patient characteristics and the development of serious infections in patients receiving tocilizumab: results from long-term extension studies with a follow-up duration of 1.5 years. Arthritis Rheum 58:S783–S784