Efficacy and safety of tocilizumab in refractory rheumatoid arthritis: a real life cohort from a single centre

O. Addimanda, N. Possemato, P. Macchioni, C. Salvarani

Rheumatology Unit, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, Italy.

Abstract

Objective

Tocilizumab (TCZ) is an effective treatment in patients with rheumatoid arthritis (RA) refractory to anti-tumour necrosis factor-α. However, only few studies in real life have evaluated the efficacy of TCZ in long-standing rheumatoid arthritis (LSRA). Our aim was to evaluate the efficacy and safety of tocilizumab in refractory LSRA.

Methods

Twenty-seven consecutive patients with refractory LSRA treated with at least one biologic agent were enrolled in a 19-month study in a single centre. Demographic [age, gender, disease duration, body mass index (BMI), previous therapies], clinical [total swollen and tender joints count (SJC-TJC) on 28, 44 and 68 joints, DAS28, Health Assessment Questionnaire (HAQ), infections, cardiovascular, renal, pulmonary and metabolic comorbidities], and serological [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies] data were collected. Patients were evaluated at baseline, and after three and six months.

Results

Mean disease duration was 16.75±9.94 years. Seventeen out of 27 (62.9%) were RF positive and 13/27 (48.1%) were CCP positive. All of them experienced at least one previous biological agent (mean value 1.9±1.15; range 1–6). We observed a progressive reduction in all clinical and clinimetric features evaluated as well as a progressive reduction in steroids use. The EULAR response also improved. By analysing the RF positive subgroup we found that there is a better clinical response both at the 3rd and 6th month.

Conclusion

TCZ is an effective and safe treatment in refractory LSRA.

Key words

rheumatoid arthritis, long-standing disease, biologic agents, tocilizumab

Olga Addimanda, MD
Niccolò Possemato, MD
Pierluigi Macchioni, MD
Carlo Salvarani, MD

Please address correspondence to:
Carlo Salvarani, MD,
Rheumatology Unit,
Arcispedale Santa Maria Nuova,
Viale Risorgimento 80,
42123 Reggio Emilia, Italy.
E-mail: salvarani.carlo@asmn.re.it

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Introduction

Tocilizumab (TCZ) is a fully humanised anti-interleukin-6 receptor monoclonal antibody licensed for the treatment of rheumatoid arthritis (1), which is effective in patients with rheumatoid arthritis (RA), both as first-line treatment (2-3) and after the failure of other biological drugs (refractory rheumatoid arthritis (4-8); a recent one-week substudy of a randomised controlled trial by Yazici *et al*. has also demonstrated its rapidity of action (9); however, only few studies *in real life* have evaluated the efficacy of TCZ in long-standing rheumatoid arthritis (LSRA) (10-12) In addition, TCZ has been shown to be effective not only in reducing joint inflammation, but also in decreasing cardiovascular risk in patient achieving clinical remission, as recently published by Benucci *et al*. (13) Nowadays, an established definition of LSRA is still lacking: many works have recently been published on LSRA, and patients' disease duration ranges from more than 3 to 12 years (14-18) In our study we enrolled patients with LSRA and persistent high disease activity, refractory to both conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents (tumour necrosis factor alpha (TNF-α) antagonists, Rituximab, Abatacept, Anakinra). Furthermore, it is important to consider the social and economic burden of RA which must be taken into account when estimating the overall impact on society (19). The objective of our study was to assess the response rate and safety of TCZ in refractory LSRA from a real life cohort of patients in a single centre.

Patients and methods

Twenty-seven consecutive patients refractory to both conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents (tumour necrosis factor alpha (TNF-α) antagonists, Rituximab, Abatacept, Anakinra) were enrolled in a 19-month period in a single centre in order to perform an observational study of real-life patients. All patients satisfied the 1987 American College of Rhematololgy Criteria for Rheumatoid Arthritis (20). Refractoriness was intended as a lack of adequate response to DMARDs and biologic agents, as described in published international guidelines on therapeutic approach in rheumatoid arthritis management (6-21).

Patients were considered on high disease activity when DAS28 was higher than 5.1, that is defined according to the ACR/EULAR core set measures (21, 22-23).

Demographic [age, gender, disease duration, body mass index (BMI), previous therapies], clinical [total swollen and tender joints count (SJC-TJC) on 28, 44 and 68 joints, DAS28, Health Assessment Questionnaire (HAQ), EULAR response, infections, cardiovascular, renal, pulmonary and metabolic comorbidities], and serological [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies] data were collected. Patients were evaluated at baseline, and after three and six months.

All of the subjects gave written informed consent and approval from the ethics committees of the institution involved was obtained.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc., Chicago, USA).

Chi-squared and Student's *t*-test were used to perform all statistical analyses. For all tests, $p<0.05$ was considered significant.

Results

Mean age at enrolment was 60.6±16.5 and mean disease duration was 16.75±9.94 years. Among them 4/27 patients (14.8%) were male and 23/27 (85.2%) were female. Seventeen out of the 27 patients (62.9%) were RF positive and 13/27 (48.1%) were CCP positive. Only two of them (7.40%) were current smokers. Mean value of BMI was 22.7±3.57. All of them experienced at least one previous biological agent (mean value 1.9±1.15; range 1–6). TCZ in combination with conventional DMARDs [Methotrexate - MTX, 16 patients (80%) or Leflunomide - LEF (20%)] was prescribed in 20 out of 27

(74.1%), the remaining ones (7 out of 27, 25.9%) were on TCZ monotherapy, due to previous adverse reactions/intolerance to conventional DMARDs.

All patients were screened at baseline for HIV, HCV, HBV and none of them was found positive.

Tuberculosis (TB) infection was also evaluated at baseline, none of the patients was positive for active infection or latent TB. (See Table IA)

No significant new comorbidities were detected since TCZ was started among chronic ischaemic heart disease (CHD), congestive heart failure (CHF), dyslipidaemia, arterial hypertension, chronic obstructive pulmonary diseases (COPD), interstitial lung disease (ILD), chronic renal failure (CRF), diabetes mellitus, cerebrovascular diseases, demyelinating diseases and neoplasia; 7 patients of our cohort had already been diagnosed as affected by osteoporosis and among them six had already experienced a pathologic bone fracture.

Only one of the patients previously experienced severe infections: it is worthnoting that he was the only patient who had been already treated with six different biologic agents. (see Table IB)

We observed a progressive and statistical significant reduction in all clinical and clinimetric features evaluated (DAS28, Health Assessment Questionnaire [HAQ], Global Health [GH], Tender and Swollen Joint Count [TJC and SJC], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]; Table IIA) as well as a progressive reduction in steroids use: prednisone using patients at baseline were 15 out of 27 (55.5%), 11 out of 26 (42.3%) at the 3rd month follow-up and 9 out of 26 (34.6%) at the 6th month follow-up; furthermore, the mean daily prednisone dose was reduced from 5.6±2.4 mg per day at baseline to 2.78±4.78 mg per day at the 6th month (p=0.01).

When comparing patients RF-positive (Table IIB) with RF-negative (Table IIC) we found that RF-positive patients showed a better clinical and serological response; the remission was achieved at the 3rd month and maintained at 6th month evaluation. In RF-negative patients we observed a good serological response but a less clear clinical response moreover we did not find any significant improvement between the 3rd and 6th month follow-up.

We also compared all clinical and clinimetric features between RF-positive and RF-negative patients at baseline, 3rd month follow-up and 6th month follow-up and we did not find any significant differences at baseline or at the 3rd month follow-up (data not shown); at the 6th month follow-up we found greater improvement in RF-positive patients limited to HAQ values and tender joint count (RF-positive HAQ = 0.6±0.5, RF-negative HAQ = 1.3±1.1, p=0.03; RF-positive TJC-28 = 1.9±2.3, RF-negative TJC-28 = 6.2±5.7, p=0.01; RF-positive TJC-44 = 3.1±4.5, RF-negative TJC-44 = 8.5±8.0, p=0.03; RF-positive TJC-68 = 3.1±4.5, RF-negative TJC-68 = 8.5±8.0, p=0.03).

The EULAR response also improved as shown in Figure 1: at baseline 21 patients (77.8%) were on high disease activity (HDA), 5 (18.5%) on medium disease activity (MDA) and only one (3.70%) on low disease activity (LDA). No patients were on remission. At the 3rd month 2 (7.40%) were on HDA, 8 (29.6%) on MDA, 4 (14.8%) on LDA and 10 (37.0%) were in remission. At the 6th month, no patients were on HDA,

Table IA. Demographic features.

Demographic features	Values (percentages or mean values)
Female sex, % (n°)	85.2 (23/27)
Age, years (mean ± SD)	60.6 ± 16.5
Disease duration, years (mean ± SD)	16.7 ± 9.9
RF positivity, % (n°)	62.9 (17/27)
anti-CCP positivity, % (n°)	48.1 (13/27)
BMI, kg/m² (mean ± SD)	22.7 ± 3.57
Smoking habits, % (n°)	7.4 (2/27)
Previous biologic agents, (mean ± SD; range)	1.9 ± 1.1; 1-6
TCZ + DMARD, % (n°)	74.1 (20/27)
TCZ + MTX, % (n°); TCZ + LEF, % (n°)	80 (16/20); 20 (4/20)
TCZ monotherapy, % (n°)	25.9 (7/27)
Chronic infections – HIV, HCV, HBV, latent TB	0 pts

Table IB. Baseline comorbidities.

Comorbidities	no. of patients	%	
Chronic ischaemic disease (CHD)	1/27	3.70	
Congestive heart failure (CHF)	1/27	3.70	
Dyslipidaemia	8/27	29.60	
		Mean ± SD	Units of measurement
	Total cholesterol	208.4 ± 34.0	mg/dl
	Triglycerides	100.4 ± 48.8	mg/dl
Arterial hypertension	11/27	40.7	
Chronic obstructive pulmonary disease (COPD)	3/27	11.1	
Interstitial lung disease (ILD)	2/27	7.4	
Chronic renal failure (CRF)	1/27	3.70	
Diabetes mellitus (DM)	4/27	14.80	
Cerebrovascular diseases	None		
Demyelinating diseases	None		
Neoplasia	None		
Osteoporosis	7/27	25.9	
	Number of patients	%	
Pathologic osteoporotic bone fractures	6/7	85.7	
Previous severe infections	1/27*	3.7	

*It is worth noting that this was the only patient who had already been treated with six different biologic agents.

Table IIA. Clinical and clinimetric features.

	Baseline (A)	3rd month follow-up (B)	6th month follow-up (C)	*p*-value (A *vs*. B)	*p*-value (B *vs*. C)	*p*-value (A *vs*. C)
DAS 28	5.8 ± 1.1	3.1 ± 1.6	2.5 ± 1.1	<0.005	0.038	<0.005
HAQ	1.4 ± 0.8	1.0 ± 0.8	0.9 ± 0.9	0.018	<0.005	0.009
GH	63.4 ± 26.2	40.4 ± 27.9	32.7 ± 28.2	0.002	0.005	0.001
TJC-28	14.6 ± 8.1	6.7 ± 7.8	3.5 ± 4.5	0.038	0.041	<0.005
TJC-44	16.6 ± 9.2	8.5 ± 9.9	5.5 ± 6.7	0.001	0.01	<0.005
TJC-68	16.6 ± 9.2	8.5 ± 9.9	4.9 ± 6.2	0.001	0.007	<0.005
SJC-28	6.0 ± 4.6	3.2 ± 4.1	1.9 ± 2.4	0.642	0.018	0.001
SJC-44	6.6 ± 5.8	3.9 ± 5.9	2.3 ± 3.1	0.11	0.01	0.007
SJC-68	6.6 ± 5.8	3.9 ± 5.9	2.0 ± 3.1	0.11	0.074	0.009
ESR (mm/h)	39.0 ± 24	7.4 ± 10.3	8.0 ± 15	<0.005	0.57	<0.005
CRP (mg/dl)	1.5 ± 1.5	0.005 ± 0.06	0.3 ± 0.8	<0.005	0.72	<0.005

Table IIB. Clinical and clinimetric features in RF-positive patients.

	RF+ (n=17) Baseline	RF+ (n=17) 3rd month follow-up	*p*-value	RF+ (n=17) 6th month follow-up	*p*-value
DAS 28	5.8 ± 1.2	3.3 ± 1.7	<0.0005	2.3 ± 0.9	0.02
HAQ	1.3 ± 0.7	0.9 ± 0.6	0.04	0.6 ± 0.5	0.06
GH	65.2 ± 24.3	41.9 ± 26.5	0.006	27.4 ± 25.6	0.06
TJC-28	14.1 ± 7.3	6.8 ± 8.5	0.006	1.9 ± 2.3	0.02
TJC-44	17 ± 9.3	8.3 ± 9.9	0.006	3.1 ± 4.5	0.03
TJC-68	17 ± 9.3	8.3 ± 9.9	0.006	3.1 ± 4.5	0.03
SJC-28	6.2 ± 4.5	2.6 ± 2.7	0.005	1.4 ± 1.8	0.07
SJC-44	7 ± 6.1	3.3 ± 4.7	0.03	1.5 ± 1.9	0.08
SJC-68	7 ± 6.1	3.3 ± 4.7	0.03	1.5 ± 1.9	0.08
ESR (mm/h)	42.2 ± 28.8	9.4 ± 12.6	0.0001	10.5 ± 18.3	0.58
CRP (mg/dl)	1.3 ± 1.2	0.05 ± 0.06	0.0003	0.2 ± 0.8	0.77

Table IIC. Clinical and clinimetric features in RF-negative patients.

	RF- (n=10) Baseline	RF- (n=10) 3rd month follow-up	*p*-value	RF- (n=10) 6th month follow-up	*p*-value
DAS 28	5.8 ± 0.8	2.9 ± 1.5	<0.0005	2.9 ± 1.3	NS - 1
HAQ	1.6 ± 0.9	1.2 ± 1.1	0.02	1.3 ± 1.1	0.58
GH	63.5 ± 28.8	38.1 ± 31.5	0.04	43.3 ± 31.1	0.64
TJC-28	13.7 ± 9.5	6.6 ± 7.2	0.04	6.2 ± 5.7	0.45
TJC-44	15.7 ± 9.4	8.7 ± 10.3	0.06	8.5 ± 8.0	0.48
TJC-68	15.7 ± 9.4	8.7 ± 10.3	0.06	8.5 ± 8.0	0.48
SJC-28	5.8 ± 4.3	4.1 ± 5.7	0.24	2.7 ± 2.9	0.24
SJC-44	6.2 ± 4.6	4.8 ± 7.7	0.32	3.5 ± 4.0	0.32
SJC-68	6.2 ± 4.6	4.8 ± 7.7	0.32	3.5 ± 4.0	0.32
ESR (mm/h)	31.1 ± 10.4	4.3 ± 3.4	0.0007	4.3 ± 7.3	NS - 1
CRP (mg/dl)	1.9 ± 1.8	0.05 ± 0.05	0.005	0.3 ± 0.7	0.85

7 (25.9%) were on MDA, 5 (18.5%) on LDA and 11 (40.7%) were in remission. No significant clinical and clinimetric differences were found when comparing patients treated with TCZ monotherapy and patients treated with TCZ associated with DMARDs (data not shown).

At the 3rd month follow-up we did not find any variations in BMI values (22.8±3.69; p=0.090) as also at the 6th month follow-up (22.8±3.84; p=0.090). We also found a slight increase in percentages of dyslipidaemic patients from baseline (8 out 27, 29.6%) to the 3rd month follow-up (15 out of 27, 55.5%), while the percentage remained the same at the 6th month follow-up. Statistical analyses of mean values of total cholesterol and triglycerides showed a slight increase, although it did not reach statistical significance [total cholesterol from baseline, to the 3rd and 6th month follow-up (mean ± SD) was: 208.4±34.0 at baseline, 225.9±38.5 at the 3rd month follow-up and 210.9±25.3 at the 6th month follow-up (p=0.050 and 0.083; triglycerides from baseline, to the 3rd and 6th month follow-up (mean ± SD) were 100.4±48.8 at baseline, 138.8±96.6 at the 3rd month follow-up and 117.7±75.6 (p=0.078 and 0.095)].

Prevalence of other comorbidities remained unchanged (no increase in CHD, CHF, COPD, ILD, renal failure, arterial hypertension, diabetes and osteoporosis); at the 6th month follow-up two patients experienced severe infections (herpes zoster and infected ulcerated wound without osteomyelitis), one patient only a minor infection (urinary tract infection). It is worth noting that one of the two patients with severe infection had already experienced infectious adverse events with previous biologic therapies; two of these patients were on monotherapy and did not use DMARDs.

Discussion

TCZ is an effective treatment in patients with rheumatoid arthritis (RA): studies performed on TCZ as a first-line biologic treatment (2-3) demonstrated its efficacy and its safety if started in early phase of disease and as a first-line drug. Due to its mechanism of action, which blocks inflammation mediators, it has been argued that TCZ might be effective also in patients with LSRA and among them also in patients with a previous history of treatments with biologic drugs (4-8).

The results of our observational study were in accordance with data and hypotheses presented in previous works, showing high response to therapy both at three and at six months of follow-up. Our study population showed high disease duration and almost all patients experienced many biological therapies before starting TCZ. Despite that, we observed a significant clinical response since the third month evaluation and a sustained efficacy till the end of the study.

As reported in previous works about differences in treatment responses between seronegative and seropositive patients for RF antibodies (24), we analysed our patients comparing seropositive with seronegative ones. Besides a good serological and clinical response

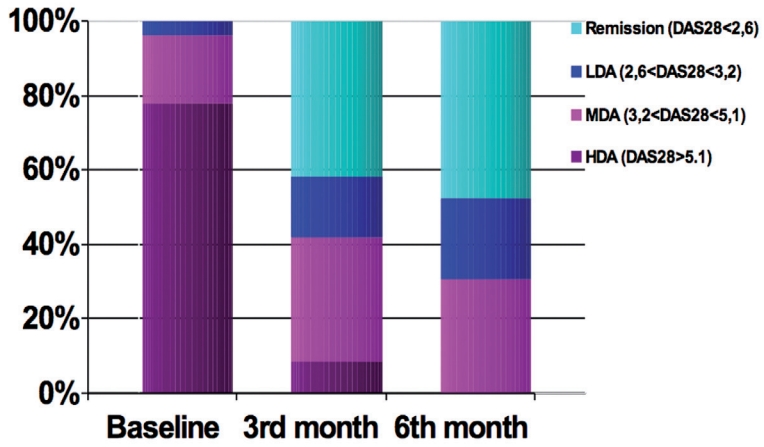

Fig. 1. EULAR esponse.

in both groups (DAS 28), we found that seronegative patients have a worse outcome. In particular, swollen and tender joint count did not reach significant improvement in RF-negative patients.

Obviously our study has some limitations: first of all, the small sample of patients which could reduce the significance of the results; likewise, the small sample of patients on TCZ monotherapy might reduce significance of the subanalysis which compares patients in TCZ monotherapy and patients on combination therapy (TCZ plus DMARDs). Our data suggest that TCZ is an effective drug for LSRA patients who have already been treated with other biological drugs before. RF positivity seems to be predictive of a rapid and sustained response.

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