

The impact of tocilizumab on physical function and quality of life in patients with rheumatoid arthritis: a systematic literature review and interpretation

Shatara V Townes¹
Daniel E Furst¹
Anuradha Thenkondar²

¹Department of Rheumatology, University of California-Los Angeles, Los Angeles, CA, USA; ²Sri Ramachandra Medical College and Research Institute, Chennai, India

Objective: To determine the impact of tocilizumab on physical function and quality of life in patients diagnosed with rheumatoid arthritis.

Methods: A systematic literature review was performed to select for trials that could be used to examine the impact of tocilizumab on patients in terms of health-related physical function, quality of life, and quality of sleep. By examining background therapy, disease duration, and remission rates, we were able to determine the impact that a dose of tocilizumab has on various patients.

Results: A total of 2617 tocilizumab-treated patients and 1271 controls were available for this study. Tocilizumab improved the Health Assessment Questionnaire Disability Index score statistically in comparison to the controls, with odds ratios from 1.4 to 7.0. Tocilizumab improved the physical function measure substantially more than the minimal clinically important difference (MCID) (5 units) – 8.9 and 9.7 – compared to 4.1 and 5.0 for controls. Seven and nine units of improvement were observed when measuring fatigue in rheumatoid arthritis patients. Using the Epworth Sleepiness Scale, we found that sleep improved (from 7.7 [3.1] to 3.4 [2.2]).

Conclusion: Tocilizumab improves function and quality of life and decreases fatigue in patients with rheumatoid arthritis.

Keywords: tocilizumab, rheumatoid arthritis, quality of life, sleep, randomized trials

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint pain, fatigue, and even loss of certain crucial physical functions. Disease-modifying antirheumatic drugs are standard care for RA. Recent studies have shown that interleukin 6 (IL-6) plays an important role in inflammation. IL-6 is a membrane receptor produced by cells such as lymphocytes and monocytes, as well as other cell types. IL-6 activates T cells and catalyses B cell proliferation. IL-6 also stimulates osteoclast differentiation, leading to joint destruction.

Tocilizumab (TCZ) is a humanized anti-IL-6 receptor (anti-IL-6R) monoclonal antibody. TCZ can bind to either soluble or membrane-bound IL-6 receptors. When bound, TCZ blocks the IL-6 receptor and prevents or decreases inflammation. It has been approved by the FDA for use in patients diagnosed with moderate to severe rheumatoid arthritis.¹ The purpose of this article is to review the effect that TCZ has on patients' physical function, quality of life (QoL), level of fatigue, and sleep patterns.^{1,2}

Correspondence: Daniel E Furst
1000 Veteran Ave, Rehabilitation
Center Room 32-59, Los Angeles,
CA 90095-1670, USA
Tel +1 310 794 9506
Fax +1 310 206 8606
Email defurst@mednet.ucla.edu

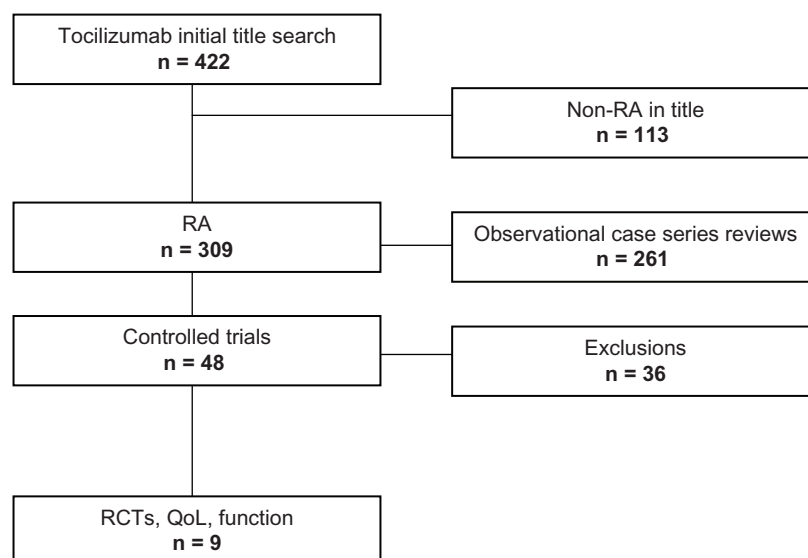


Figure 1 A systematic literature review was undertaken.

Abbreviations: RA, rheumatoid arthritis; RCTs, randomized controlled trials; QoL, quality of life.

Materials and methods

As seen in Figure 1, a systematic review of TCZ was undertaken with the following keywords used as criteria for the search: TCZ, clinical trial, rheumatoid arthritis, human, and English. Also of interest were the following: health-related quality of life, activities of daily living, quality of life, fatigue, sleep, Health Assessment Questionnaire Disability

Index (HAQ-DI), Short Form 36 (SF-36), European Quality of Life-5 Dimensions (EQ-5D), Functional Assessment of Chronic Illness Therapy (FACIT), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS). Exclusions included reviews, editorials, non-RA studies, case series, and randomized non-trials that did

Table 1 Descriptions of the most commonly used measurements of function, quality of life, fatigue, and sleep

Method	Measures	Domains	Range	MCID
HAQ-DI ³	Health-related physical function	Dressing, rising, eating, walking, hygiene, reach, grip, and daily activity	0 to 3	0.22
SF-36 ⁴	Quality of life	Physical activities, social activities, role functioning due to emotional distress, role functioning due to physical impairment, bodily pain, general mental health, general health perceptions, and vitality	0 to 100	5–10
EQ-5D ^{5,6}	Differences in health states in RA	Mobility, self-care, usual activities, pain discomfort and anxiety/depression (mood disorders)	0 to 1	–
FACIT ^{7–9}	Quality of life	Physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing	0 to 100	–
FACIT-F ^{7–9}	Fatigue	13 items on a 0–4 scale; ie, fatigue, weakness, listlessness, tiredness, energy, difficulty starting things, difficulty finishing things, able to do usual activities, need for assistance in doing usual activities, sleeping during the day, too tired to eat, frustration due to feeling too tired to do things you want, limitation of social activity due to tiredness	0 to 52	4
PSQI ¹⁰	Quality of sleep	Sleep quality, sleep latency, sleep duration, habitual sleep disturbance, sleep disturbance, use of sleep medication, daytime dysfunction	0 to 21	–
ESS ¹⁰	Sleepiness	Tendency to fall asleep in certain situations of daily life: reading, watching TV, sitting in public place, sitting in the car as passenger, resting in the afternoon, talking, sitting after lunch, sitting in car after stopping for traffic	0 to 24	–

Abbreviations: HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, Short Form 36; EQ-5D, European Quality of Life-5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

not produce quantifiable data for any one of the following factors: functionality, QoL, fatigue, or sleep. PubMed and the Cochrane databases were queried and bibliographies in all articles were examined. Two individuals extracted data independently from the final articles and any disagreements regarding whether or not the articles stayed within the criteria were discussed. An agreement was reached, resulting in eight relevant articles.

Because randomized controlled trials (RCTs) are of higher quality, this review concentrates on the RCTs, while the remaining open-label trials are used for support. For one domain, sleep, only a single, open-label study was available.

Table 1 describes the validated measures of function, quality of life, fatigue, and sleep used in this study.³⁻¹⁰

Results and discussion

Table 2 reviews the eight RCTs included in the systematic review.^{1,2,11-16} They include 2617 TCZ-treated patients and 1271 controls. Most of the patients were followed in 24-week studies, while one study was 16 weeks, one was 52 weeks, and one was 12 weeks. The patients were quite heterogeneous, with disease duration lasting from less than one year to more than eleven years. Patients had used a wide variety of background therapy and/or previous medications. The background therapies ranged from an 8 mg per week dosage of methotrexate to having had an incomplete response to two tumor necrosis factor inhibitors. Nonetheless, all of the patients' RA activity was very vigorous, with disease activity scores, using 28 joint counts, between 6.1

Table 2 Description of RCTs

Study	Trial duration	Rx (dose)	Background therapy	n	Disease duration	RF +ve	Baseline DAS28
Nishimoto et al ¹¹	24 wks	TCZ 8.00 mg/kg every 4 weeks	MTX-IR	61	8.50 yrs	NA	6.10
		Placebo + MTX 8.00 mg/week		64	8.70 yrs	NA	6.20
Maini et al ¹²	16 wks	TCZ 2.00 mg/kg	MTX-IR	53	9.19 mos	83.0%	6.48
		TCZ 4.00 mg/kg		54	9.79 mos	72.2%	6.55
		TCZ 8.00 mg/kg (every 4 weeks)		52	9.21 mos	82.7%	6.43
		TCZ 2.00 mg/kg + MTX		52	9.33 mos	88.5%	6.58
		TCZ 4.00 mg/kg + MTX		49	7.82 mos	77.6%	6.34
		TCZ 8.00 mg/kg + MTX		50	10.62 mos	80.0%	6.47
		Placebo + MTX (MTX 10.00–25.00 mg/wk)		49	11.24 mos	95.9%	6.75
Genovese et al ¹	24 wks	TCZ 8.00 mg/kg + DMARD	DMARD-IR	803	9.80 yrs	NA	6.70
		DMARD		413	9.80 yrs	NA	6.60
Jones et al ¹³	24 wks	TCZ 8.00 mg/kg every 4 weeks	Never failed MTX or biological agents in the past	288	6.40 yrs	NA	6.80
		MTX 7.50 mg/wk (titrated to 20.00 mg/kg at 8 wks)		284	6.20–6.30 yrs	NA	6.80
		Placebo (first 8 wks), then TCZ for 16 wks		101	NA	NA	NA
Emery et al ¹⁴	24 wks	TCZ 8.00 mg/kg + MTX	TNFi-IR	170	12.60 yrs	79.00%	6.79
		TCZ 4.00 mg/kg + MTX		161	11.00 yrs	73.00%	6.78
		Placebo + MTX		158	11.40 yrs	75.00%	6.80
Nishimoto et al ¹⁵	52 wks	TCZ 8.00 mg/kg every 4 weeks	DMARD-IR or failed immunosuppressant	157	2.20 yrs	NA	6.50
Smolen et al ²	24 wks	TCZ 4.00 mg/kg + MTX	MTX discontinued \geq 12 weeks before study	145	2.40 yrs	NA	6.40
		TCZ 8.00 mg/kg + MTX (every 4 wks)		214	7.40 yrs	78.00%	6.80
		Placebo + MTX (MTX 10.00–25.99 mg/wk)		205	7.50 yrs	83.00%	6.80
		Placebo + MTX (MTX 10.00–25.99 mg/wk)		204	7.80 yrs	71.00%	6.80
Nishimoto et al ¹⁶	12 wks	TCZ 4.00 mg/kg	DMARD-IR or failed immunosuppressant	54	7.30 yrs	NA	NA
		TCZ 8 mg/kg (every 4 wks)		55	8.30 yrs	NA	NA
		Placebo		53	8.40 yrs	NA	NA
Choy et al ¹⁷	8 wks	TCZ 0.1 mg/kg	DMARD-IR or failed immunosuppressant	9	17.00 yrs	NA	NA
		TCZ 1 mg/kg		9	6.00 yrs	NA	NA
		TCZ 5 mg/kg		9	14.00 yrs	NA	NA
		TCZ 10 mg/kg		7	13.00 yrs	NA	NA
		Placebo		11	14.00 yrs	NA	NA

Abbreviations: TCZ, tocilizumab; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug; RCT, randomized controlled trial.

and 6.8. This degree of heterogeneity precludes a credible meta-analysis.

Table 3 displays the results of the health questionnaires' disability index (HAQ-DI) responses in the eight RCTs, where such data were available.^{1,2,11,13–17} TCZ improved the HAQ-DI score statistically in comparison to the controls, with odds ratios from 1.4 to 7.0, favoring TCZ. The percent of patients who improved more than the MCIDs (≥ 0.22) were noted in four studies, and the TCZ groups improved by at least that amount in 60%–68% of the patients, compared to 32%–48% of the controls. It is clear that TCZ improves disease-related function significantly and more frequently than the controls, in turn making the amount of improvement clinically important. Open-label studies using TCZ supported the RCT findings. HAQ-DI normalization (< 0.5) occurred in 23%–48% of TCZ-treated patients in four trials.^{18–22}

Table 4 displays the results regarding QoL (SF-36). There were only two double-blind RCTs of TCZ that described this measure.^{1,2} The Physical Component Summary comprises⁴ the four domains of the SF-36 pertaining to physical function, and it is statistically clear that TCZ improved this measure substantially more than the MCID (5 units) – 8.9 and 9.7 – compared to 4.1 and 5.0 for controls. Unusually, TCZ also statistically improved the Mental Component Summary⁴

versus control, implying that TCZ may have a positive effect on mood and mental status. As for the HAQ-DI, it is reasonably clear that TCZ both physically and mentally improves QoL in patients diagnosed with RA. The strength of this conclusion is less than that for the HAQ-DI, because there are only two controlled studies measuring QoL.

Fatigue is very common among RA patients. The prevalence rates for fatigue in RA range from 42% to 80%. By using the Checklist of Individual Strength (CIS), persistent severe fatigue is found in 40% of RA patients (according to the FDA). Table 4 also shows the results regarding fatigue in the two double-blind RCTs in which it was measured.^{1,2} As for QoL, the patients' feelings of fatigue improved substantially more than the MCID, when compared to the control patients. The open-label studies support the conclusions stemming from the randomized trials, with 7 and 9 units of improvement.^{22,23} Overall, this important aspect of fatigue associated with RA seems to change favorably when TCZ is used.

Rheumatoid arthritis also affects patients' quality of sleep. This may be due to pain, mood changes, and/or disease activity. There was only one published study, an open-label study, that reported the effects of TCZ on sleep.²² This study used the PSQI and ESS instruments. It showed that patients

Table 3 Double-blind studies examining HAQ-DI

Study	Treatment dose	Baseline HAQ-DI	Changes from baseline	P-value	MCID (≥ 0.22)	P-value
Nishimoto et al ¹¹	TCZ	NA	NA	NA	67%	$P < 0.001$
	Control	NA	NA	NA	34%	NA
Genovese et al ¹	TCZ 8 mg/kg	1.50	-0.50	$P < 0.0001$	60%	NA
	Placebo + DMARDS	1.50	-0.20	NA	34% ^b	NA
Jones et al ¹³	TCZ	1.50	-0.70	NA	NA	NA
	MTX	1.60	-0.50	NA	NA	NA
Emery et al ¹⁴	TCZ 4	1.70	-0.31	$P = 0.003$	NA	NA
	TCZ 8	1.70	-0.39	Less than $P < 0.001$	NA	NA
Nishimoto et al ¹⁵	Control	1.70	-0.05	NA	NA	NA
	TCZ 8 mg/kg every 4 weeks	0.80	-0.50	$P < 0.001$	68%	$P < 0.001$
	DMARD	0.90 ^a	-0.30 ^a	NA	40%	NA
Smolen et al ²	TCZ 4.00 mg/kg	1.60	-0.52	$P = 0.0296$	61%	NA
	TCZ 8.00 mg/kg	1.60	-0.55	$P = 0.0082$	59%	NA
	Control	1.50	-0.34	NA	47% ^b	NA
Nishimoto et al ¹⁶	TCZ 4.00 mg/kg	1.00	-0.01	$P < 0.0100$	NA	NA
	TCZ 8.00 mg/kg	1.00	-0.25	NA	NA	NA
	Control	1.00 ^a	-0.35 ^a	NA	NA	NA
Choy et al ¹⁷	TCZ 0.10 mg/kg	2.30	-0.30	NA	NA	NA
	TCZ 1.00 mg/kg	2.40	-0.10	NA	NA	NA
	TCZ 5.00 mg/kg	2.00	-0.80	NA	NA	NA
	TCZ 10.00 mg/kg	2.60	-0.60	NA	NA	NA
	Placebo	2.60 ^a	-0.10 ^a	NA	NA	NA

Notes: ^aApproximately; ^bHAQ ≥ 0.30 .

Abbreviations: TCZ, tocilizumab; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; MCID, minimal clinically important difference.

Table 4 Double-blind studies examining SF-36 and FACIT-F

Study	Treatment Dose	Baseline FACIT-F	Changes in FACIT-F from baseline	P-value	Baseline SF-36 scores		Changes from baseline		P-value
					Physical	Mental	Physical	Mental	
Genovese et al ¹	TCZ 8.00 mg/kg	NA	8.0	P < 0.0001 (>MCID)	NA	NA	8.9	5.3	P < 0.0001
			3.6	NA	NA	4.1	2.3	P < 0.0001	
Smolen et al ²	TCZ 4.00 mg/kg DMARDs	27.0	7.3	P = 0.0063 (>MCID)	31.5	40.1	9.7	5.7	P = 0.0394
			8.6	P < 0.0001 (>MCID)	32.1	40.9	9.5	7.3	P = 0.0012
	Control	26.7	4.0	NA	32.3	39.1	5.0	2.7	NA

Abbreviations: SF-36, Short Form 36; FACIT, Functional Assessment of Chronic Illness Therapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; TCZ, tocilizumab; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug; MCID, minimal clinically important difference.

reported better quality of sleep after taking just two doses of TCZ. No prior sleeping medications were used in this study, so the results are ascribable to the use of TCZ alone. Using the ESS, sleep improved from 7.7 (3.1) to 3.4 (2.2); using the PSQI, it improved from 8.7 (3.3) to 6.7 (4.3). Both changes are more than the MCID's. Nonetheless, because these data originate from an open-label study, these results should be interpreted with caution.

Conclusion

Based on a systematic review supplemented by the RCTs and open-label studies, TCZ improves function and quality of life, and decreases fatigue, in patients with RA; all are probably as important to patients as are joint swelling counts and so forth. It must be noted that sleep, too, may be favorably affected. This supports the general efficacy of TCZ in RA, as demonstrated through conventional measures such as joint tenderness and swelling, and through combined indices such as the ACR response criteria or the 28 joint counts.^{1,2,12-16}

Acknowledgements and disclosure

Dr Furst has received consultant fees, speaking fees, and/or honoraria (usually less than \$US5000 each and rarely \$US5000–<\$US10,000) from Abbott, Actelion, Amgen, BMS, Biogen Idec, Centocor, Genentech, Gilead, GSK, NI, Nitec, Novartis, Pfizer, Roche, and UCB; serves on the advisory boards for Abbott, Amgen, BMS, Centocor, Genentech, Biogen Idec, Roche, and UCB; and serves as Director of Publications for the Consortium of Rheumatology Researchers of North America (CORRONA).

References

1. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum*. 2008;58:2968–2980.
2. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatic arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet*. 2008;371:987–997.
3. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol*. 2005;23:S14–S18.
4. Talamo J, Frater A, Gallivan S, Young A. Use of the short form 36 (SF36) for the health status measurement in rheumatoid arthritis. *Br J Rheumatol*. 1997;36:463–469.
5. Luo N, Chew LH, Fong KY, Koh DR, Ng SC, Yoon KH. Validity and reliability of the EQ-5D self-report questionnaire in Chinese-speaking patients with rheumatic diseases in Singapore. *Ann Acad Med Singapore*. 2003;32:685–690.
6. Calculating the US population-based EQ-5D Index Score. August 2005. Agency for Healthcare Research and Quality. Rockville, MD. <http://www.ahrq.gov/rice/EQ5Dscore.htm>. Accessed April 17, 2011.

7. Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1:79.
8. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis*. 2007;66:936–939.
9. FACIT.org [homepage on the Internet]. Available from: <http://www.facit.org/FACITOrg/Questionnaires>. Accessed April 17, 2011.
10. Buysse DJ, Hall ML, Strollo PJ, Kamarck TW, Owens J, Lee Laisze. Relationships between the Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), and clinical/polysomnographic measures in a community sample. *J Clin Sleep Med*. 2008;4:563–571.
11. Nishimoto N, Miyasaka N, Kamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol*. 2009;19:12–19.
12. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum*. 2006;54:2817–2829.
13. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis*. 2010;69:88–96.
14. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biological: results from a 24-week multicenter randomized placebo-controlled trial. *Ann Rheum Dis*. 2008;67:1516–1523.
15. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomized controlled trial of tocilizumab. *Ann Rheum Dis*. 2007;66:1162–1167.
16. Nishimoto N, Yosizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2004;50:1716–1769.
17. Choy EH, Isenberg DA, Garrood T, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. *Arthritis Rheum*. 2002;46(12):3143–3150.
18. Khraishi M, Alten R, Gomez-Reino JJ, et al. Long-term efficacy of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) treated up to 3.7 years [abstract]. *ACR*. 2010:S760–S761.
19. Takeuchi T, Tanaka Y, Amano K, et al. Clinical, structural and functional remission in the treatment of rheumatoid arthritis with tocilizumab in daily clinical practice-REACTION-2 study [abstract]. *ACR*. 2010:S747.
20. Kremer JM, Furst DE, Burgos-Vargas R, et al. LITHE: Tocilizumab (TCZ) inhibits radiographic progression and improves physical function in rheumatoid arthritis (RA) patients (pts) at 3 years with maintenance of clinical efficacy over time [abstract]. *Arthritis Rheum*. 2011;63(3):609–621.
21. Jones G, Sebba A, Calvo A, et al. Efficacy of tocilizumab in patients with rheumatoid arthritis who had never been exposed to or had never failed methotrexate: analysis of up to 3 years of treatment in a long-term extension study [abstract]. *Ann Rheum Dis*. 2010;69:386.
22. Fragiadaki K, Sfikakis PP. EULAR. Effect of the first and second infusion of tocilizumab on sleep and daytime sleepiness in patients with active rheumatoid arthritis [abstract]. *Ann Rheum Dis*. 2010; 69:683.
23. Burmester G, Feist E, Kellner H, Braun J, Iking-Konert C, Rubbert-Roth A. Extended report: Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). *Ann Rheum Dis*. 2011;70: 755–759.

Open Access Rheumatology Research and Reviews

Publish your work in this journal

Open Access Rheumatology Research and Reviews is an international, peer-reviewed, open access journal, publishing all aspects of clinical and experimental rheumatology in the clinic and laboratory including the following topics: Pathology, pathophysiology of rheumatological diseases; Investigation, treatment and management of rheumatological

diseases; Clinical trials and novel pharmacological approaches for the treatment of rheumatological disorders. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/open-access-rheumatology-research-and-reviews-journal>

Dovepress