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REVIEW

Drug delivery options to increase patient adherence and satisfaction in the management of rheumatoid arthritis – focus on subcutaneous tocilizumab

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Abstract: Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease associated with joint destruction. Tocilizumab (TCZ) is a humanized monoclonal anti-interleukin-6 receptor antibody that was initially developed for use as an intravenous (IV) infusion. Previous studies have shown that TCZ-IV is an important treatment option in patients with moderate-to-severe RA. A subcutaneous (SC) formulation of 162 mg TCZ that was recently developed and approved provides an additional treatment option for RA patients. In the present review, we provide an update on the efficacy and safety of TCZ-SC, compared with TCZ-IV. The TCZ-SC doses of 162 mg every 2 weeks (q2w) or weekly (qw) were selected based on pharmacokinetic and pharmacodynamic studies. Both TCZ-SC q2w and qw regimens showed equivalent effects to TCZ-IV in most patients; however, the TCZ-SC qw regimen consistently showed a more rapid effect in terms of C-reactive protein normalization. Randomized controlled studies showed that TCZ-SC monotherapy or combined with disease-modifying antirheumatic drugs demonstrated comparable efficacy to TCZ-IV in patients who were both biologic-naïve and refractory to tumor necrosis factor inhibitors. TCZ-SC at both qw and q2w were generally well-tolerated for up to 24 weeks. There was a low rate of withdrawal due to adverse events, and their incidence was comparable with that seen with TCZ-IV. An injection site reaction was seen in approximately 10% of patients who received the subcutaneous formulation. In conclusion, although clinical results are still limited, the currently available evidence suggests that TCZ-SC is a promising treatment for moderate-to-severe RA, both as monotherapy and combination therapy. More data is needed to determine the optimal dosing schedule.

Keywords: rheumatoid arthritis, tocilizumab, subcutaneous injection, review

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease associated with joint destruction.[1] The inflammation in RA is in part due to proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha. Biological agents against these cytokines have dramatically changed the management of patients with RA.[2–5] The recent consensus is that patients with progressive joint destruction should be treated with biologics to achieve tight disease control and remission. Recent studies showed that the concomitant administration of anti-TNF biologics and methotrexate led to remission in a significant percentage of patients.[6–8] Such biologics induce a rapid therapeutic response and now play an essential role in the treatment of RA; however, not all patients respond to existing biologics and must switch to other drugs. Therefore, new drugs that target other molecules are needed.

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Interleukin-6 (IL-6) is an inflammatory cytokine that is abundantly expressed in the serum and inflamed synovial tissue of RA patients.[9–11] IL-6 acts on a wide range of cells that are strongly activated in RA, such as neutrophils, T-cells, B-cells, monocytes, and osteoclasts. The IL-6 blockade was, therefore, considered a promising candidate for the treatment of RA. Tocilizumab (TCZ) is a humanized monoclonal anti-IL-6 receptor (IL-6R) antibody that was developed to inhibit the action of IL-6.[12–14] TCZ blocks IL-6 signaling by binding to both soluble and membrane-bound IL-6R; it was initially developed for use as an intravenous infusion (TCZ-IV). The efficacy and safety of TCZ-IV were previously demonstrated as monotherapy and in combination with disease-modifying antirheumatic drugs (DMARDs) in adult patients with RA.[15–28] Accumulated clinical data on TCZ-IV suggested that TCZ is an important treatment option in patients with moderate-to-severe RA as both an initial biologic and for use following the failed trials of other drugs.

To achieve clinical, functional, and structural remission or the lowest disease activity state possible, each patient's disease status should be considered, along with the efficacy, safety, and route of administration of each therapy. Some patients prefer subcutaneous (SC) injection of biologic agents rather than intravenous administration and may favor self-administration.[29–31] An SC formulation of TCZ (TCZ-SC) would provide an additional treatment option for patients with RA. A TCZ-SC dose of 162 mg every 2 weeks (q2w) or weekly (qw) was selected based on pharmacokinetic and pharmacodynamic studies and was approved in 2013.[32–34] At present, only limited data on the efficacy and safety of TCZ-SC are available. This article reviews the use of TCZ-SC in adult patients with active RA.

Pharmacokinetic and pharmacodynamic properties of TCZ-SC

This section discusses the pharmacokinetic and pharmacodynamic properties of TCZ-SC, focusing on the data from the MATSURI study, a report by Zhang et al, and the SUMMACTA study.[33–35] The details are shown in Table 1. We must take into consideration the differences in the subjects' body weights and the evaluation periods in each study. Ohta et al (MATSURI study) reported that 3 weeks after a single SC administration of TCZ, the area under the serum TCZ concentration (AUC) values following 81 mg and 162 mg doses were 513.6 μgh/mL and 2,320.8 μgh/mL, and the maximum TCZ concentration (C_{max}) values were 3.4 μg/mL and 10.9 μg/mL, respectively, demonstrating the nonlinear pharmacokinetics of TCZ-SC.[34] The serum trough TCZ concentration was under the detectable level until the dosing frequency was increased to qw at week 9 in the 81 mg q2w group. In contrast, the mean serum trough TCZ concentrations of ≥1 μg/mL were maintained in 88% of 162 mg q2w patients and 100% of 162 mg qw patients. Both doses had exposures comparable to the approved TCZ-IV dose of 8 mg/kg. Although the C-reactive protein (CRP) normalization rate increased over time, not all patients in the 81 mg q2w group achieved normalized CRP levels. In contrast, all patients in the 162 mg q2w group achieved normalized CRP levels by week 7, which were subsequently maintained. All patients in the 162 mg qw group achieved normalized CRP levels by week 3. The study authors concluded that the appropriate TCZ-SC dose was 162 mg q2w for Japanese patients whose mean body weight was about 53 kg.

Zhang et al compared TCZ-SC doses of 162 mg SC qw and q2w at 12 weeks after initiation in patients with RA whose mean body weight was about 80 kg.[33] After final dosing, TCZ-SC qw and q2w were associated with AUC values of 5,505 μgh/mL and 2,332 μgh/mL, and C_{max} values of 39.4 μg/mL and 10.7 μg/mL, respectively. The median CRP levels decreased in both groups after the first dose of TCZ-SC. Normal CRP levels were achieved after single administration in the qw group. In the q2w group, median CRP levels fluctuated after the first three doses, with the elevations occurring

Table 1 Pharmacokinetic and pharmacodynamic properties of TCZ-SC and TCZ-IV

	MATSURI study[34]		Zhang et al[33]		SUMMACTA study[35]	
	TCZ-SC 81 mg q2w (day 21) n=8	TCZ-SC 162 mg q2w (day 21) n=12	TCZ-SC 162 mg qw (day 78) n=13	TCZ-SC 162 mg q2w (day 71) n=14	TCZ-SC 162 mg qw (week 20–24) n=13	TCZ-IV 8 mg/kg q4w (week 20–24) n=13
AUC (μgh/mL)	513±799	2,320±1,288	5,505±2,632	2,332±1,696	30,168	41,304
C_{max} (μg/mL)	3.4±4.3	10.9±5.6	39.4±18.1	10.7±6.57	52.7±27.3	223±117
t_{max} (days)	1.5–6.0	2.0–7.2	2	3	NA	NA
$t_{1/2}$ (days)	NA	1.6±0.24	8±3	3.5±2.21	NA	NA

Abbreviations: TCZ, tocilizumab; SC, subcutaneous; IV, intravenous; q2w, every 2 weeks; qw, every week; q4w, every 4 weeks; AUC, area under the serum TCZ concentration; C_{max}, maximum TCZ concentration; $t_{1/2}$, half-life; NA, not available; t_{max}, time to maximum concentration.

between the dosing weeks. However, normal CRP levels were achieved consistently after three doses. They concluded that both TCZ-SC regimens demonstrated clinical benefit, although greater soluble IL-6R levels and more rapid normalization of CRP levels were observed with the qw regimen than the q2w regimen. It is suggested that TCZ-SC qw could be considered in patients with greater body weight.

Burmester et al (SUMMACTA study) found that at 20–24 weeks following the administration of TCZ-SC 162 mg qw and TCZ-IV 8 mg/kg q4w, the AUC values were 30,168 μgh/mL and 41,304 μgh/mL, and the C_{max} values were 52.7 μg/mL and 223 μg/mL, respectively.[35] The CRP levels decreased in both groups after the first dose of TCZ and, subsequently, remained below the upper limit of normal until week 24. The time course of CRP levels for TCZ-SC was comparable to that for TCZ-IV.

Summary

Based on the MATSURI study, it is clear that TCZ-SC 81 mg q2w does not reach sufficient concentrations to result in clinical efficacy even in Japanese patients whose mean body weight was thought to be small. Two other studies[33,35] showed that both TCZ-SC 162 mg q2w and qw showed equivalent effects to TCZ-IV in most patients; however, TCZ-SC 162 mg qw regimens consistently showed more rapid effects in terms of CRP normalization.

Efficacy

At present, five studies have reported the efficacy of TCZ-SC in patients with RA. They are: a report by Zhang et al;[33] the MATSURI study (2013); the BREVACTA study (2013); the MUSASHI study (2014); and the SUMMACTA study (2014).[33–37] The first two were open-label studies to determine TCZ-SC doses in small numbers of patients. The last three were large (n>100), randomized, controlled, and multicenter studies of up to 24 weeks' duration, using doses of 162 mg q2w or qw. The TCZ-SC efficacy findings obtained in these studies are summarized in Table 2. Importantly, there were differences in the doses of TCZ-SC and concomitant DMARDs used in each study. For TCZ-SC, the dose was 162 mg q2w in the BREVACTA and the MUSASHI studies; in the SUMMACTA study, it was 162 mg qw.

The MATSURI study was designed as a multicenter, open-label, dose-escalation study to determine the optimal TCZ-SC dose that would result in exposure comparable to the approved 8 mg/kg TCZ-IV dose in patients with RA.[34] No concomitant conventional DMARDs were allowed in this study. Patients received TCZ-SC at 81 mg q2w, 162 mg q2w, or 162 mg qw for 25 weeks. As described previously, the CRP normalization rate (patients achieving levels <1 mg/dL) was 2/8 patients (25%) at 3 weeks in the 81 mg q2w group. In contrast, all of the patients in the 162 mg q2w and qw groups achieved normalized CRP levels by week 7 and subsequently maintained normal levels. In the 81 mg q2w group, the American College of Rheumatology (ACR) 20 response rate was 13% (one of eight patients) through week 9. No patients in this group achieved an ACR 50 response. After the dosing frequency was increased to qw at week 9 in the 81 mg q2w group, the ACR 20 and ACR 50 response rates increased and reached 38% (three of eight patients). The ACR 20 and ACR 50 response rates did not differ significantly between the 162 mg q2w and 162 mg qw groups after week 7. The ACR 20 response rate increased to 83% (ten of 12 patients) at week 13 in both groups. The ACR 50 response rate increased to 75% (nine of 12 patients) by week 17 in the 162 mg qw group and to 83% (ten of 12 patients) by week 21 in the

Table 2 Efficacy of TCZ-SC and TCZ-IV in patients with active RA

Study	Mean duration of RA (years)	Previous failed TNF-i therapy	# of patients	Study duration (weeks)	TCZ treatment	Combined DMARDs	ACR 20 (%)	ACR 50 (%)	ACR 70 (%)	DAS remission rate (%)
MATSURI[34]	7.8	18.75%	32	25	SC 81 mg q2w*	No (mono)	38	38	38	50
					SC 162 mg q2w		83	83	50	83
					SC 162 mg qw		92	92	67	100
BREVACTA[37]	NA	21%	437	24	SC 162 mg q2w	Yes	61	40	20	NA
					Placebo		NA	NA	NA	NA
MUSASHI[36]	7.6	21.2%	348	24	SC 162 mg q2w	No (mono)	79.2	63.5	37.1	49.7
					IV 8 mg/kg q4w		88.5	67.3	41.0	62.2
SUMMACTA[35]	8.7	21%	1,262	24	SC 162 mg qw	Yes	69	47	24	38
					IV 8 mg/kg q4w		73	49	28	36

Notes: Data are from a report by the MATSURI study,[34] the BREVACTA study,[37] the MUSASHI study,[36] and the SUMMACTA study.[35] *Dosing frequency was increased to qw at week 9 in the 81 mg q2w group.

Abbreviations: RA, rheumatoid arthritis; TCZ, tocilizumab; SC, subcutaneous; IV, intravenous; TNF, tumor necrosis factor; TNF-i, TNF inhibitor; DMARDs, disease-modifying antirheumatic drugs; ACR, American College of Rheumatology; DAS, disease activity score; DAS remission, DAS <2.6; mono, TCZ monotherapy; q2w, every 2 weeks; qw, every week; q4w, every 4 weeks; NA, not available.

162 mg q2w group; they remained at this level until the last observation. The ACR 20, ACR 50, and ACR 70 response rates as well as the disease activity score (DAS) 28 remission (DAS 28<2.6) rate at week 25 were not significant between the 162 mg q2w and 162 mg qw groups; however, the 162 mg qw group constantly showed the slightly better results.

The MUSASHI study was designed as a double-blind, parallel-group, double-dummy, comparative Phase III study for Japanese patients.[36] No concomitant conventional DMARDs were allowed. The primary endpoint was the noninferiority of TCZ-SC to TCZ-IV as determined by ACR 20 response rates. Patients were randomized to receive TCZ-SC 162 mg q2w or TCZ-IV 8 mg/kg q4w. At week 24, ACR 20 response was achieved in 79.2% of the TCZ-SC group and in 88.5% of the TCZ-IV group. DAS 28 remission at week 24 was 49.7% in the TCZ-SC group and 62.2% in the TCZ-IV group. ACR 50 and ACR 70 response rates at week 24 were also similar between the groups. The authors concluded that TCZ-SC monotherapy 162 mg q2w demonstrated comparable efficacy to TCZ-IV monotherapy. However, logistic regression analyses showed that baseline body mass index in the fourth quartile (23.4–29.6 kg/m^2) was associated with a significantly lower ACR 20 response rate (63.4%; odds ratio [OR] 0.31; *P*=0.0048), ACR 50 response rate (51.2%; OR 0.47; *P*=0.0444), and ACR 70 response rate (24.4%; OR 0.39; *P*=0.0271). This result was not unexpected since TCZ-SC monotherapy was administered as a fixed dose (162 mg); whereas, the TCZ-IV monotherapy formulation was dosed by body weight (8 mg/kg). Although no significant differences in efficacy were observed between the two groups, TCZ-IV consistently showed slightly better results. These trends might indicate lower efficacy in patients with greater body weight. The BREVACTA study also showed that treatment with TCZ-SC 162 mg q2w plus concomitant DMARDs was clinically effective, resulting in ACR 20, 50, and 70 response rates of 61%, 40%, and 20%, respectively.[37]

In contrast, therapy with TCZ-SC 162 mg qw and concomitant DMARDs was assessed in the SUMMACTA study, a randomized, double-blind, parallel-group study of TCZ-SC versus TCZ-IV in patients with moderate to severe RA.[35] Patients (n=1,262) were randomly assigned to receive TCZ-SC 162 mg qw or TCZ-IV 8 mg/kg q4w in combination with conventional DMARDs. The primary outcome was the noninferiority of TCZ-SC to TCZ-IV with regard to the proportion of patients achieving an ACR 20 response at week 24. At week 24, 69.4% of the TCZ-SC group versus 73.4% of the TCZ-IV group achieved an ACR 20 response. ACR 50/70 responses, DAS 28, and physical function improvements were comparable between the two groups. The authors concluded that TCZ-SC 162 mg qw was noninferior to TCZ-IV 8 mg/kg q4w.

Summary

Based on the MATSURI study, it could be concluded that the TCZ-SC 81 mg q2w regimen was not sufficient for clinical efficacy. Both TCZ-SC 162 mg q2w and qw were not inferior to TCZ-IV 8 mg/kg q4w; however, the MUSASHI study revealed that the greater body mass index resulted in the lower ACR 20 response rate. In contrast, TCZ-SC 162 mg qw seemed to have the equivalent efficacy with the TCZ-IV 8 mg/kg q4w.

Safety

TCZ-SC qw or q2w was generally well-tolerated when administered as monotherapy or in combination with DMARDs for up to 24 weeks (Table 3). The rates of withdrawal due to adverse events were generally low: 4.8% in the BREVACTA study; 1.7% in the MUSASHI study; and 4.8% in the SUMMACTA study.[35–37] These were comparable to or slightly better than the rates in the groups treated with TCZ-IV 8 mg/kg. The wide variety of adverse events reported falls into several basic categories: infection; lipid level; liver enzyme; hematological parameters; and injection site reactions (ISR). Incidences of adverse events are summarized in Table 3.

Infection

The incidence of serious infections associated with TCZ-SC was generally low and was comparable with TCZ-IV. The MUSASHI study reported two serious infections (1.2%), cellulitis, and gastroenteritis.[36] In the SUMMACTA study, serious pneumonia occurred in two patients in each group and bacterial arthritis occurred in two patients in the TCZ-IV group.[35] The most common reason for withdrawal due to adverse events in both groups was infection (1.1% TCZ-SC and 1.3% TCZ-IV). No obvious difference in the incidence of serious infections was observed between the treatment groups.

Lipid levels

Moderate increases in serum total cholesterol and triglyceride had been reported in the treatment of TCZ-IV.[15] TCZ-SC treatment also showed the variable value of elevated total cholesterol. The MUSASHI study showed 18.5% of the patients with the shift in total cholesterol from baseline <200 mg/dL to >240 mg/dL; whereas, in the SUMMACTA study, that number was 7.0%. The proportion

Table 3 Incidence of adverse events receiving TCZ-SC and TCZ-IV

	BREVACTA study[37]	MUSASHI study[36]		SUMMACTA study[35]	
	TCZ-SC 162 mg q2w n=437	TCZ-SC 162 mg q2w n=173	TCZ-IV 8 mg/kg q4w n=173	TCZ-SC 162 mg qw n=631	TCZ-IV 8 mg/kg q4w n=631
Discontinuation rate due to AEs	21 (4.8%)	3 (1.7%)	9 (5.2%)	30 (4.8%)	42 (6.7%)
Serious AEs	25 (5.7%)	13 (7.5%)	10 (5.8%)	34 (5.4%)	43 (6.8%)
Serious infection	12 (2.7%)	2 (1.2%)	5 (2.9%)	9 (1.4%)	9 (1.4%)
Shift in total cholesterol from baseline <200 mg/dL to >240 mg/dL	NA	32 (18.5%)	35 (20.2%)	44 (7.0%)	26 (4.1%)
Shift in ALT normal at baseline to value >3× ULN	NA	5 (2.9%)	9 (5.2%)	30 (4.8%)	32 (5.1%)
Shift in AST normal at baseline to value >3× ULN	NA	2 (1.2%)	6 (3.5%)	6 (1.0%)	8 (1.3%)
Shift in neutrophil normal at baseline to value <1,000/mm^3	NA	5 (2.9%)	5 (2.9%)	18 (2.9%)	20 (3.2%)
ISR	57 (10.3%)	21 (12.1%)	9 (5.2%) (placebo)	61 (10.1%)	15 (2.4%) (placebo)

Notes: Data are from a report by BREVACTA study,[37] MUSASHI study.[36] All values are expressed as number of the patients (%). Data adapted from Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis*. 2014;73(1):69–74.[35]

Abbreviations: TCZ, tocilizumab; SC, subcutaneous; IV, intravenous; AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ISR, injection site reaction; q2w, every 2 weeks; qw, every week; q4w, every 4 weeks; NA, not available.

of patients with an increase in total cholesterol was slightly higher in the TCZ-SC group than in the TCZ-IV group in the SUMMACTA study; however, this trend was not noted in the MUSASHI study.[36] No patients withdrew from the study due to elevated total cholesterol or triglycerides.

Liver enzymes

The mild-to-moderate elevation of hepatic transaminases, which were not associated with hepatic injury, has been commonly reported in patients receiving TCZ-IV.[15] More than 20% of patients receiving TCZ-SC experienced elevations of alanine aminotransferase and aspartate aminotransferase from normal at baseline to < three times the upper limit of normal, while 1%–5% showed elevations to > three times this level. No patients withdrew from the MUSASHI study due to liver dysfunction.[36] In the SUMMACTA study, five patients (0.8%) in the TCZ-SC group and seven patients (1.1%) in the TCZ-IV group withdrew due to elevated liver transaminases.[35]

Hematological parameters

Treatment with TCZ-IV was associated with the transient decrease of neutrophils.[15] In the MUSASHI group, the proportion of patients who experienced a decrease in neutrophils (<1,000–500 cells/mm^3) was 2.9% (five of 173 patients) in both the TCZ-SC and TCZ-IV groups; one patient in the TCZ-SC group withdrew from the study for this reason.[36] No grade 4 neutropenia (<500 cells/mm^3) was reported. In the SUMMACTA study, about 3% of the patients showed a decrease in neutrophils to <1,000–500 cells/mm^3. No differences were observed between the groups.[35] One patient in the TCZ-SC group experienced a sustained consecutive neutrophil decline.

ISR

The ISR site reaction in BREVACTA study,[37] MUSASHI study,[36] and SUMMACTA study[35] was 10.3%, 12.1%, and 10.1%, respectively. The incidence of ISR was more compared to patients with placebo in both the MUSASHI and SUMMACTA studies. Among the reported ISR, the common events were injection site erythema, injection site hemorrhage, pruritus, swelling, and pain. All the ISRs were mild, and no cases withdrew from the studies due to the ISR.

Summary

The rate of withdrawal from TCZ therapy due to adverse events was generally low in all studies, and similar profiles were observed in the TCZ-SC and TCZ-IV groups. TCZ-SC qw or q2w was generally well-tolerated when administered as monotherapy or in combination with DMARDs for up to 24 weeks. ISRs thought to be specific to the SC formulation were seen in approximately 10% of patients.

Conclusion

TCZ-SC monotherapy or in combination with DMARDs demonstrated comparable efficacy and safety to TCZ-IV in patients with active RA who previously had an inadequate response to conventional DMARDs or biologics. A SC

formulation of TCZ would provide an additional treatment option for patients with RA and could save time and reduce the frequency of hospital visits. Determining the optimal TCZ-SC dose requires further comparative investigation.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Boissier MC, Semerano L, Challal S, Saidenberg-Kermanac'h N, Falgarone G. Rheumatoid arthritis: from autoimmunity to synovitis and joint destruction. *J Autoimmun*. 2012;39(3):222–228.
2. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. 2002 Update. *Arthritis Rheum*. 2002;46(2):328–346.
3. Müller N, Döring F, Klapper M, et al. Interleukin-6 and Tumour Necrosis Factor-α differentially regulate lincRNA transcripts in cells of the innate immune system in vivo in human subjects with rheumatoid arthritis. *Cytokine*. 2014;68(1):65–68.
4. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol*. 2001;19:163–196.
5. Alghasham A, Rasheed Z. Therapeutic targets for rheumatoid arthritis: Progress and promises. *Autoimmunity*. 2014;47(2):77–94.
6. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying anti-rheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis*. 2010;69(6):976–986.
7. Smolen JS, Aletaha D, Bijlsma JW, et al; T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69(4):631–637.
8. Schipper LG, Vermeer M, Kuper HH, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis*. 2012;71(6):845–850.
9. Wang J, Platt A, Upmanyu R, et al. IL-6 pathway-driven investigation of response to IL-6 receptor inhibition in rheumatoid arthritis. *BMJ Open*. 2013;3(8):e003199.
10. Nishimoto N. Interleukin-6 as a therapeutic target in candidate inflammatory diseases. *Clin Pharmacol Ther*. 2010;87(4):483–487.
11. Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. *Arthritis Rheum*. 2011;63(1):43–52.
12. Brandão FM, Coelho P, Pinto P, Combe B. Tocilizumab – a new step in rheumatoid arthritis treatment. *Acta Reumatol Port*. 2010;35(3): 302–312.
13. Schoels MM, van der Heijde D, Breedveld FC, et al. Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement. *Ann Rheum Dis*. 2013;72(4): 583–589.
14. Smolen JS, Schoels MM, Nishimoto N, et al. Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions. *Ann Rheum Dis*. 2013;72(4):482–492.
15. Oldfield V1, Dhillon S, Plosker GL. Tocilizumab: a review of its use in the management of rheumatoid arthritis. *Drugs*. 2009;69(5):609–632.
16. Nishimoto N, Miyasaka N, Yamamoto 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(1):12–19.
17. Smolen JS, Beaulieu A, Rubbert-Roth A, et al; OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet*. 2008;371(9617):987–997.
18. 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(1):88–96.
19. 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 biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis*. 2008;67(11):1516–1523.
20. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum*. 2011;63(3):609–621.
21. 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(10):2968–2980.
22. Yazici Y, Curtis JR, Ince A, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann Rheum Dis*. 2012;71(2):198–205.
23. Maini RN, Taylor PC, Szechinski J, et al; CHARISMA Study Group. 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(9):2817–2829.
24. Dougados M, Kissel K, Sheeran T, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis*. 2013;72(1):43–50.
25. Gabay C, Emery P, van Vollenhoven R, et al; ADACTA Study Investigators. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013;381(9877):1541–1550.
26. 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 randomised controlled trial of tocilizumab. *Ann Rheum Dis*. 2007;66(9):1162–1167.
27. Nakashima Y, Kondo M, Fukuda T, et al. Remission in patients with active rheumatoid arthritis by tocilizumab treatment in routine clinical practice: results from 3 years of prospectively registered data. *Mod Rheumatol*. 2014;24(2):258–264.
28. Nakashima Y, Kondo M, Harada H, et al. Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. *Mod Rheumatol*. 2010;20(4):343–352.
29. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. *Patient Prefer Adherence*. 2009;3:335–344.
30. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. *Musculoskeletal Care*. 2008;6(1):1–14.

31. Williams EL, Edwards CJ. Patient preferences in choosing anti-TNF therapies-R1. *Rheumatology (Oxford)*. 2006;45(12):1575–1576.
32. Zhang X, Georgy A, Rowell L. Pharmacokinetics and pharmacodynamics of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, following single-dose administration by subcutaneous and intravenous routes to healthy subjects. *Int J Clin Pharmacol Ther*. 2013;51(6):443–455.
33. Zhang X, Chen YC, Fettner S, et al. Pharmacokinetics and pharmacodynamics of tocilizumab after subcutaneous administration in patients with rheumatoid arthritis. *Int J Clin Pharmacol Ther*. 2013;51(8):620–630.
34. Ohta S, Tsuru T, Terao K, et al. Mechanism-based approach using a biomarker response to evaluate tocilizumab subcutaneous injection in patients with rheumatoid arthritis with an inadequate response to synthetic DMARDs (MATSURI study). *J Clin Pharmacol*. 2014;54(1):109–119.
35. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis*. 2014;73(1):69–74.
36. Ogata A, Tanimura K, Sugimoto T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2014;66(3):344–354.
37. Burmester GR, Rubbert-Roth A, Cantagrel AG, et al. A randomized, double-blind, parallel group study of the safety and efficacy of tocilizumab SC versus tocilizumab IV, in combination with traditional Dmards in patients with moderate to severe RA. *Arthritis Rheum*. 2012;64(10):S1075–S1075.