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Original Article

Effectiveness of intravenous tocilizumab in routine clinical practice in a cohort of Costa Rican patients with rheumatoid arthritis[☆]



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ABSTRACT

Objective: To determine the effectiveness and the incidence of severe adverse events in a cohort of Costa Rican patients with Rheumatoid Arthritis (RA) treated with intravenous (IV) tocilizumab (TCZ).

Patients and methods: A retrospective analysis was carried out in 45 patients that were unresponsive to disease-modifying antirheumatic drugs (DMARDs). The study included patients who received IV TCZ every 4 weeks (4 mg/kg) along with methotrexate or leflunomide. Effectiveness was measured through the incidence of clinical remission according to a disease activity score – erythrocyte sedimentation rate (DAS28-ESR) less than 2.6. Safety was assessed by the incidence rate of serious adverse events. An univariate and multivariate logistic regression analysis was performed to assess the association of potential variables with the probability of achieving remission during the first 3 months of TCZ therapy.

Results: During the 3rd month of TCZ therapy, a total of 22 patients (48.9%; 95% Confidence Interval (CI) 34.3%–63.5%) achieved remission. The cumulative incidence of patients with remission at month 12 was 75.0% (n = 34) (95% CI: 62.3%–87.6%). A total of 18 patients (40%; 95% CI: 25.7%–54.3%) were switched to a 8 mg/kg dose due to the absence of remission. The incidence rate of serious adverse events was .98 per 100 patients/year, all of them due to infectious diseases with no fatal events reported. Only basal DAS28-ESR was associated with the probability of achieving remission at month 3.

Conclusions: IV TCZ (4 mg/kg) is an effective and safe treatment for RA patients in a clinical setting in Costa Rica.

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Efectividad del tocilizumab intravenoso en la práctica clínica usual de una cohorte de pacientes costarricenses con artritis reumatoide

RESUMEN

Objetivo: Determinar la efectividad y la incidencia de eventos adversos graves del tocilizumab (TCZ) en una cohorte de pacientes costarricenses con artritis reumatoide (AR).

Pacientes y métodos: Se realizó un análisis retrospectivo de 45 pacientes con AR, refractarios al uso previo de fármacos modificadores de la enfermedad reumática (FAME), que utilizaron TCZ a una dosis inicial de 4 mg/kg intravenoso (IV) cada 4 semanas en asociación con metotrexato o leflunomida. La medida de efectividad fue la incidencia de remisión clínica, determinada cada 3 meses y definida por un puntaje de actividad de la enfermedad en 28 articulaciones con velocidad de sedimentación globular (DAS28-VSG) menor de 2,6. La seguridad del fármaco se evaluó mediante la tasa de incidencia de eventos adversos severos. Se realizó un modelo de regresión logística uni- y multivariado para determinar las variables asociadas con la probabilidad de remisión a los 3 meses de iniciado el tratamiento.

Palabras clave:

Anticuerpo monoclonal humanizado

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Efectividad

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Resultados: A los 3 meses de tratamiento un total de 22 pacientes (48,9%; intervalo de Confianza [IC] del 95%: 34,3–63,5%) alcanzaron remisión, en tanto que a los 12 meses de terapia con TCZ el valor aumentó a 34 pacientes (75%; IC 95%: 62,3–87,6%). Un total de 18 pacientes (40%; IC 95%: 25,7–54,3%) requirieron aumento de dosis del TCZ de 4 a 8 mg/kg ante la ausencia de remisión. La tasa de incidencia de eventos adversos severos fue de 0,98 por 100 pacientes/año, correspondiendo todos ellos a cuadros infecciosos que resolvieron sin ningún desenlace fatal. Solo el DAS28-VSG inicial se asoció de forma independiente con la probabilidad de remisión a los 3 meses.

Conclusiones: El uso de TCZ IV a una dosis inicial de 4 mg/kg en pacientes costarricenses con AR es efectivo y seguro en la práctica clínica.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that predominantly affects the joints, causing damage and leading to functional impairment in patients, in some cases irreversible.¹ Treatment of RA includes low-dose prednisone and non-steroidal anti-inflammatory drugs (NSAIDs), in conjunction with disease-modifying antirheumatic drugs (DMARDs), which have been shown to improve physical function and slow joint damage.¹ Although the incorporation of biologic and synthetic therapies against tumour necrosis factor, B cells or T cells has resulted in higher clinical response rates, 30%–40% of patients fail to achieve and maintain a major clinical response according to the American College of Rheumatology (ACR) criteria, or a good response according to the criteria defined by the European League Against Rheumatism (EULAR).^{2,3} These limitations have led to the development of new drugs such as tocilizumab (TCZ). This drug is a humanised monoclonal antibody that inhibits the activity of interleukin-6 (IL-6) by preventing this cytokine binding to its receptor, blocking the classical activation, trans-signalling, and trans-presentation pathways.⁴ TCZ has been shown in several clinical trials^{5–7} to be safe and effective in reducing acute phase protein concentrations, inflammatory symptoms and progression of joint damage when used as monotherapy.⁸

TCZ has been shown in several clinical trials^{5–11} to be a safe and effective drug in the treatment of RA, reducing acute-phase protein concentrations, inflammatory symptoms, and progression of joint damage in patients who have been exposed¹⁰ or not exposed¹¹ to prior treatment with biologic DMARDs. Furthermore, the efficacy of TCZ has been proven in both subcutaneous and intravenous (IV) administration⁹ and in various monotherapy⁸ or combined treatment regimens.⁷ TCZ is currently approved for the treatment of RA that has responded inadequately to prior use of biologic or synthetic DMARDs.¹² Despite the demonstrated efficacy and safety of TCZ in the abovementioned clinical trials, most of these trials did not include a significant proportion of patients of Latin American origin. Recent studies have highlighted ethnic differences in the progression and response to treatment of RA patients, with individuals of Hispanic origin reported to have higher rates of disease activity and lower rates of clinical remission.^{13,14} This study, therefore, sought to evaluate the effectiveness of IV TCZ in Costa Rican RA patients refractory to prior use of synthetic or biologic DMARDs, in a context of usual clinical practice and dose optimisation using 4 mg/kg every 4 weeks as the initial dose.

Patients and methods

We undertook a retrospective analytical study of medical records of the Hospital Rafael Ángel Calderón Guardia, San José, Costa Rica (Caja Costarricense de Seguro Social). The analysis included the entire population of RA patients treated since the drug became available in Costa Rica (January 2013) until December 2016. Subjects over 18 years of age with a diagnosis of RA accord-

ing to the ACR/EULAR 2010 criteria, who received TCZ treatment for at least one year during the study period, were included. The indication for TCZ treatment was not having responded to treatment with DMARDs (methotrexate, leflunomide, sulfasalazine or hydroxychloroquine, in combined regimens and at the maximum dose described for each drug), defined by a 28-joint disease activity score with erythrocyte sedimentation rate (DAS28-ESR) greater than 5.1.

Patients with rheumatological or inflammatory diseases other than RA, and patients with a follow-up of less than 12 months were excluded. Variables of interest were collected from the clinical records and included age, sex, smoking, presence of comorbidities, age at diagnosis and duration of RA, time between RA diagnosis and initiation of TCZ, and use of DMARDs. The dose of TCZ (IV) used was 4 mg/kg every 4 weeks, which was used in combination with methotrexate and/or leflunomide at the discretion of the treating physician. In case of documented failure to respond during the follow-up period, defined as a DAS28 score greater than 2.6, the TCZ dose was modified to 8 mg/kg every 4 weeks IV. Patients were assessed by the rheumatologist at least every 3 months. The effectiveness of TCZ was determined by EULAR criteria according to the change in DAS28-ESR score, assessed every 3 months. Patients were classified according to the response obtained with TCZ into remission (DAS28-ESR < 2.6), low-disease activity (2.6 < DAS28-ESR < 3.2), moderate disease activity (3.2 < DAS28-ESR < 5.1) and severe disease activity (> 5.1). Drug safety was assessed by the incidence of severe adverse events occurring during the entire follow-up of the patients analysed. An adverse event was defined as severe when it resulted in hospitalisation of the patient, use of IV antibiotic treatment or death.

The study was approved by the Scientific Ethical Committee of the Caja Costarricense de Seguro Social and adhered to best clinical practice.

Statistical analysis

Continuous variables are expressed as means and standard deviation. Categorical variables are expressed as absolute frequencies and percentages. The 95% confidence interval (95% CI) was calculated for each effectiveness and safety variable. The DAS28-ESR value at study entry and at week 52 was compared using the Student's t-test for paired data, previously checking the statistical assumptions of normality and homoscedasticity. A univariate and multivariate logistic regression model was performed to identify variables associated with remission (according to a DAS28-ESR score < 2.6) at 3 months as a binary dependent variable. The analysis was performed on all patients who completed the expected follow-up period (per-protocol analysis). A *P*-value of less than .05 was considered statistically significant. The analysis was performed using SPSS 21.0 for Mac (Chicago, USA).

Table 1
Clinical characteristics of the patients included.

Variable	n (%)
Sex	
Female	38 (84.4)
Male	7 (15.6)
Age (years, SD)	54.2 ± 10.8
Mean age on diagnosis of RA (years, SD)	40.3 ± 11
Comorbidities (%)	
Arterial hypertension	27 (60)
Diabetes mellitus	7 (15.5)
Dyslipidaemia	13 (28.9)
Smoking	
Positive	9 (20)
Active	2 (4.4)
Inactive	7 (15.5)
Negative	36 (80)
Treatments (%)	
Synthetic DMARDs prior to TCZ	
Methotrexate	45 (100)
Leflunomide	44 (97.7)
Hydroxychloroquine	45 (100)
Sulfasalazine	44 (97.7)
Cyclosporin A	30 (66.6)
Mean N used (SD)	4.6 ± .49
Biological DMARDs prior to TCZ	
Total patients using biological treatment	8 (17.7)
Etanercept	3 (6.7)
Etanercept/rituximab	4 (8.9)
Rituximab	1 (2.2)
Prednisone	
Use	45 (100)
Mean dose (SD) (mg)	7.56 ± 2.67
Oral methotrexate	
Use	33 (73.3)
Mean dose prior to use of TCZ (mg)	19.7 ± 4.25
Clinical variables	
DAS28 (SD)	5.33 ± 1.15
Mean ESR (mm/h)	40.35 ± 21.6
Positive rheumatoid factor	38 (86.3)
Anti-cyclic citrullinated peptides	
Positive	30 (66.7)
Indeterminate	15 (33.3)
Mean duration of RA (years, SD)	13.9 ± 8.5
Mean time between diagnosis and starting TCZ (years, SD)	12.5 ± 8.5

DAS28: 28-joint disease activity score; DMARDs: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis; SD: standard deviation; TCZ: tocilizumab.

Results

Patient characteristics

During the study period, 45 patients taking IV TCZ were identified who met the inclusion criteria. The general characteristics of the included patients are summarised in Table 1. Most of the patients were female and rheumatoid factor and anti-cyclic citrullinated peptide positive.

Effectiveness of tocilizumab

Fig. 1 shows the course of the DAS28-ESR score over the 52 weeks of clinical follow-up. According to the DAS28-ESR score, at 3 months after starting treatment, a total of 22 patients (48.9%; 95% CI: 34.3%–63.5%) achieved remission. This score gradually increased at the 6- and 12-month follow-up where the proportion of patients with remission was 62% (95% CI: 47.8%–76.2%) (n = 28) and 75% (95% CI: 62.3%–87.6%) (n = 34), respectively (Fig. 2). A statistically significant difference was detected between the mean basal DAS28-ESR score and that obtained at 52 weeks (5.33 vs. 2.18; $p < .001$). The percentage of remission at 3 months was not significantly different between the subgroup of patients who had received prior biologic

treatment and those naive to biologic therapy (71.4% vs. 45.5%; respectively; $p = .20$).

According to EULAR response criteria, by the third month of treatment, 22 patients (48.9%) had a good response, 18 patients (40%) a moderate response and only 5 patients (11.1%) did not respond to therapy. A total of 18 patients (40%; 95% CI 25.7%–54.3%) required an increase in drug dose to 8 mg/kg, which occurred at month 6.5 ± 4.48 from starting TCZ. There was persistent treatment failure in only 2 patients after increasing the dose.

The univariate and multivariate analysis of potential determinants of remission at the third month of treatment (according to DAS28-ESR score < 2.6) is shown in Tables 2 and 3. While female sex was associated with a higher probability of remission in the univariate analysis, only the basal DAS28-ESR was independently associated with the probability of remission at 3 months after multivariate analysis adjusted for the other confounding variables.

Incidence of severe adverse events

Over the entire follow-up period (median follow-up: 12 months), 6 severe infectious events affecting 4 patients were counted, for a cumulative incidence of 8.8% (95% CI: .05%–17.1%) and an incidence rate of .98 events per 100 patients/year. To be specific, three events of community-acquired pneumonia, two complicated urinary tract infections and one Fournier's gangrene were diagnosed. None of these complications had a fatal outcome and all cases were resolved with the use of antibiotic therapy.

Discussion

The present study describes for the first time the effectiveness and safety results of IV TCZ at an initial dose of 4 mg/kg every 4 weeks in a Costa Rican population. The use of TCZ was associated with a reduction in RA activity parameters by both clinical and analytical variables. Specifically, the cumulative incidence of remission at 6 months was 62%, a much higher percentage than that obtained in the clinical trial published by Smolen et al., which reported a remission rate of 13% at 6 months with the same TCZ dose and administration route as used in this group of patients.⁷ Although the objective of the above-mentioned clinical trial was remission according to ACR20 and not DAS28-ESR, the differences in remission rates are very wide. These discrepancies may be explained by the different basal characteristics of the patients included, the main differences being ethnicity and the presence of younger patients with higher exposure to DMARDs in the present study.

The remission rate reported at 6 months was also higher than that described in a Canadian observational study, which reported a remission rate of 36.3% when TCZ (8 mg/kg) was used as monotherapy or combined therapy in a group of patients previously treated with a DMARD.¹⁵ However, other authors have reported 6-month remission rates that are more in line with those described in this study. More specifically, the remission rates, published for a cohort of Spanish,¹⁶ Italian¹⁷ and Japanese¹⁸ patients, were 75.5%, 52.3% and 47.6%, respectively, although a TCZ dose of 8 mg/kg was used in these scenarios.

Although some pharmacological studies have shown that TCZ pharmacokinetics are not affected by ethnicity or RA inflammatory conditions,¹⁹ the variability observed in the pharmacological response to TCZ in different populations suggests a non-uniform distribution of certain predictive variables among the groups analysed, such as age, duration of RA and DAS28-ESR score at start of treatment. Several authors agree in identifying young age and low initial DAS28-ESR score as predictors of response to TCZ. Pers et al. described that younger patients had better response rates to TCZ compared to older individuals.²⁰ Narvaez et al. reported that an

Table 2
Univariate analysis of potential predictors of remission (DAS28 < 2.6) at 3 months.

Variable	No remission	Remission	P Value
Female sex (%)	16 (42.4)	22 (57.6)	.04*
Age	52.8 ± 11.3	55.1 ± 11.3	.53
Duration of RA	15.5 ± 10.44	13.44 ± 7.25	.46
Time from diagnosis to starting TCZ	14.10 ± 10.19	12.00 ± 7.18	.45
Prior use of biologic (%)	2 (28.6)	5 (71.4)	.22
Initial DAS28	5.78 ± 1.19	4.88 ± 1.01	.01*
Initial ESR	43.95 ± 23.79	35.55 ± 18.47	.22

DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate; TCZ: tocilizumab.

* Statistically significant p < .05.

Table 3
Multivariate analysis of potential predictors of remission (DAS28 < 2.6) at 3 months.

Variable	OR	95% CI		P Value
		Inferior	Superior	
Female sex	.111	.010	1.294	.079
Age	1.037	.955	1.127	.382
Duration of RA	.803	.252	2.557	.710
Time from diagnosis to starting TCZ	1.176	.362	3.821	.788
Prior use of biologic (%)	3.226	.297	35.081	.336
Initial DAS28	.409	.171	.974	.044*
Initial ESR	1.002	.953	1.053	.949

CI: confidence interval; DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate; OR: odds ratio; TCZ: tocilizumab.

* Statistically significant p < .05.

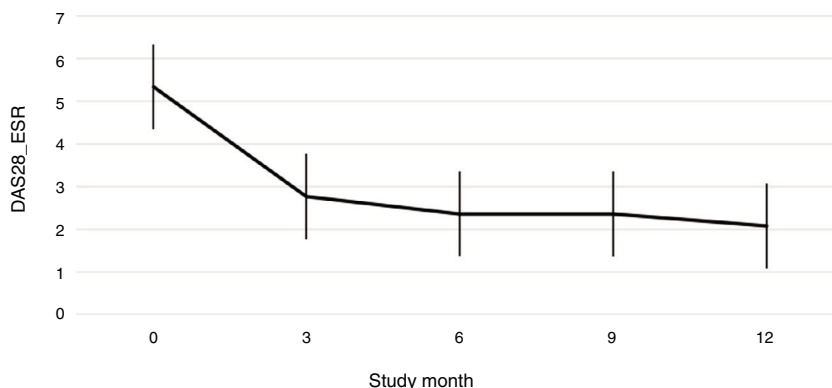


Fig. 1. Progression of the DAS28-ESR in the population studied during the follow-up period under treatment with tocilizumab. DAS28-ESR: disease activity score in 28 joints with erythrocyte sedimentation rate.

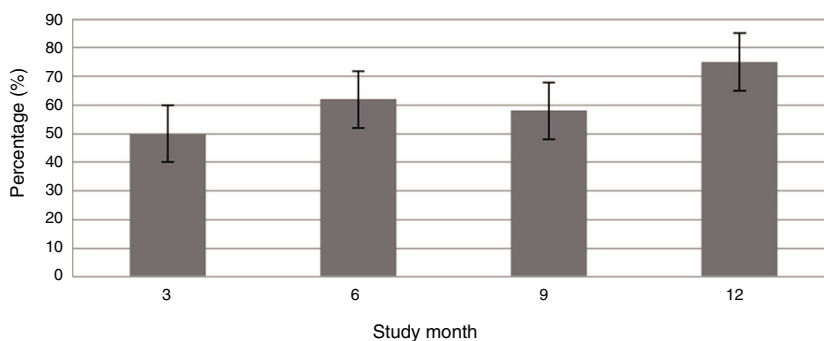


Fig. 2. Patients in remission (DAS28-ESR < 2.6) during clinical follow-up visits. DAS28-ESR: disease activity score in 28 joints with erythrocyte sedimentation rate.

elevated DAS28-ESR score at the start of biologic therapy was associated with early remission failure with IV TCZ.²¹ In line with these reports, our findings identified basal DAS28-ESR score as the only independent variable associated with remission failure. It is clinically useful to identify this prognostic variable as it could select a group of patients in whom starting with a dose of 4 mg/kg is not

the most recommended approach. Other recently described predictors are high basal IL-6 concentrations and low levels of soluble IL-6 receptor, which could identify a subgroup of patients who will benefit particularly from this therapy.²²

This study reports the experience of a group of patients of a different ethnicity than those studied in the clinical trials that

demonstrated the efficacy and safety of IV TCZ.¹⁸ This finding is of relevance as recent epidemiological studies have shown that the Hispanic population is characterised by high rates of RA activity and lower clinical response rates in similar settings, related to the low socioeconomic status and difficult access to health services of this ethnic group, compared to other populations in developed countries.²³

However, the present study demonstrates that despite these socio-cultural factors, the use of TCZ gives similar or superior responses of effectiveness than those described in other populations in industrialised countries.

Few studies have published the clinical effectiveness of an initial dose of 4 mg/kg IV TCZ. Although some clinical trials have reported that this dose could be lower than 8 mg/kg every 4 weeks,^{7,24} data from the present analysis show that this approach may be effective when used as a starting dose in patients with previous failure of synthetic DMARDs. Furthermore, other clinical trials have not shown such differences in the efficacy of TCZ according to the dose used.⁶ However, the findings of this observational study need to be confirmed prospectively and supported by scientific evidence from clinical trials comparing both doses of TCZ in search of an optimal regimen of maximum cost-effectiveness, especially in populations with limited access to financial resources. In addition, longer follow-up of this cohort of patients will be particularly useful clinically to understand the long-term effects of the TCZ dosage used.

In terms of safety, similar behaviour was found to that described in other pharmacovigilance studies. For example, Morel et al.²⁵ described a French cohort of nearly 1500 patients in which most of the serious infectious complications occurring RA patients exposed to TCZ were in the lower airway and soft tissues (35% and 32% of all documented infectious events), with an incidence rate of 4.7/100 patients/year.

The findings of this study should be interpreted with caution due to the retrospective and uncontrolled design of the study, which may have resulted in selection bias. In addition, the sample size and the single-centre nature of the analysis diminish the external validity of the findings. Another limitation of this study was that no other drug response variables were determined such as functionality and quality of life scales, which were not routinely used in the clinical practice of the hospital studied. The omission of these variables may have left out of the analysis other factors that have been linked to the effectiveness of TCZ, such as psychosocial variables, depression, and fatigue.²⁶

However, despite the above limitations, the results obtained are encouraging in that they show the effectiveness of an optimised dose in a usual clinical setting. Furthermore, even though we used a per-protocol analysis, no patients were lost to follow-up, and therefore this type of analysis did not bring information bias to the study results.

In conclusion, the present study demonstrates the effectiveness and safety of IV TCZ (4 mg/kg every 4 weeks) in a particular group of Costa Ricans and suggests the usefulness of an optimised dosing regimen that could mean a reduction in the costs associated with the treatment of RA patients.

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Conflict of interests

A Ramos-Esquivel has participated on Advisory Boards for Roche, Bayer, Stein and Astrazeneca.

M. Cordero-Alfaro has no conflict of interests to declare.

C. León-Céspedes has no conflict of interests to declare.

References

- Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet*. 2009;373:659–72.
- Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med*. 2000;343:1586–92.
- Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. The therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor a monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*. 1998;41:1552–63.
- Garbers C, Heink S, Kom T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. *Nat Rev Drug Discov*. 2018;17:395–412.
- Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, 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;66:1162–7.
- Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröll J, Balint G, 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;54:2817–29.
- Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovinsky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet*. 2008;371:987–97.
- Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, 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.
- Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). *Ann Rheum Dis*. 2016;75:68–74.
- Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, 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;67:1516–23.
- Ishiguro N, Atsumi T, Harigai M, Mimori T, Nishimoto N, Sumida T, et al. Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naïve patients with rheumatoid arthritis: the FIRST Bio study. *Mod Rheumatol*. 2017;27:217–26.
- Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76:960–77.
- Greenberg JD, Spruill T, Shan Y, Reed G, Kremer JM, Potter J, et al. Racial and ethnic disparities in disease activity in rheumatoid arthritis patients. *Am J Med*. 2013;126:1089–99.
- Bruce B, Fries JF, Murtagh KN. Health status disparities in ethnic minority patients with rheumatoid arthritis: a cross-sectional study. *J Rheumatol*. 2007;34:1475–9.
- Haraoui B, Jamal S, Ahluwalia V, Fung D, Manchanda T, Khraishi M. Real-world tocilizumab use in patients with rheumatoid arthritis in Canada: 12-month results from an observational, noninterventional study. *Rheumatol Ther*. 2018;5:551–65.
- Mena-Vázquez N, Manrique-Ariza S, Rojas-Giménez M, Ureña-Garnica I, Jiménez-Núñez FG, Fernández-Nebro A. Analysis of effectiveness, safety and optimization of tocilizumab in a cohort of patients with rheumatoid arthritis in clinical practice. *Reumatol Clin*. 2019;15:21–6.
- Iannone F, Ferraccioli G, Sinigaglia L, et al. Real-world experience of tocilizumab in rheumatoid arthritis: sub-analysis of data from the Italian biologics' register GISEA. *Clin Rheumatol*. 2018;37:315–21.
- Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J Rheumatol*. 2014;41:15–23.
- Zhang X, Peck R. Clinical pharmacology of tocilizumab for the treatment of patients with rheumatoid arthritis. *Expert Rev Clin Pharmacol*. 2011;4:539–58.
- Pers YM, Fortunet C, Constant E, Lambert J, Godfrin-Valnet M, De Jong A, et al. Predictors of response and remission in a large cohort of rheumatoid arthritis patients treated with tocilizumab in clinical practice. *Rheumatology*. 2014;53:76–84.
- Narváez J, Magallares B, Díaz-Torné C, Hernández MV, Reina D, Corominas H, et al. Predictive factors for induction of remission in patients with active rheumatoid arthritis treated with tocilizumab in clinical practice. *Semin Arthritis Rheum*. 2016;45:386–90.
- Díaz-Torne C, Ortiz MA, Moya P, Hernandez MV, Reina D, Castellvi I, et al. The combination of IL-6 and its soluble receptor is associated with the response of rheumatoid arthritis patients to tocilizumab. *Semin Arthritis Rheum*. 2018;47:757–64.

23. Massardo L, Pons-Estel BA, Wojdyla D, Cardiel MH, Galarza-Maldonado CM, et al. Early rheumatoid arthritis in Latin America: low socioeconomic status related to high disease activity at baseline. *Arthritis Care Res.* 2012;64:1135–43.
24. Fleischmann RM, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. *J Rheumatol.* 2013;40:113–26.
25. Morel J, Constantin A, Baron G, Dernis E, Flipo RM, Rist S, et al. Risk factors of severe infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry Regate. *Rheumatology (Oxford).* 2017;56:1746–54.
26. Corominas H, Alegre C, Narváez J, Fernández-Cid CM, Torrente-Segarra V, Gómez MR, et al. Correlation of fatigue with other disease related and psychosocial factors in patients with rheumatoid arthritis treated with tocilizumab. *ACT-AXIS study. Medicine (Baltimore).* 2019;98:e15947.