Original Article

Tocilizumab in Patients With Active Rheumatoid Arthritis and Inadequate Response to Disease-modifying Antirheumatic Drugs or Tumor Necrosis Factor Inhibitors: Subanalysis of Spanish Results of an Open-label Study Close to Clinical Practice

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A B S T R A C T

Objectives: To analyze the Spanish experience in an international study which evaluated tocilizumab in patients with rheumatoid arthritis (RA) and an inadequate response to conventional disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor inhibitors (TNFis) in a clinical practice setting.

Material and methods: Subanalysis of 170 patients with RA from Spain who participated in a phase IIIb, open-label, international clinical trial. Patients presented inadequate response to DMARDs or TNFis. They received 8 mg/kg of tocilizumab every 4 weeks in combination with a DMARD or as monotherapy during 20 weeks. Safety and efficacy of tocilizumab were analyzed. Special emphasis was placed on differences between failure to a DMARD or to a TNFi and the need to switch to tocilizumab with or without a washout period in patients who had previously received TNFi.

Results: The most common adverse events were infections (25%), increased total cholesterol (38%) and transaminases (15%). Five patients discontinued the study due to an adverse event. After six months of tocilizumab treatment, 71/50/30% of patients had ACR 20/50/70 responses, respectively. A higher proportion of TNFi-naive patients presented an ACR20 response: 76% compared to 64% in the TNFi group with previous washout and 66% in the TNFi group without previous washout.

Conclusions: Safety results were consistent with previous results in patients with RA and an inadequate response to DMARDs or TNFis. Tocilizumab is more effective in patients who did not respond to conventional DMARDs than in patients who did not respond to TNFis.

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The names of the Spanish researchers participating in the ACT SURE study are listed in Annex 1.

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**Palabras clave:**
Tocilizumab
Artritis reumatoide
Fármacos antirreumáticos modificadores de la enfermedad

**Resumen**

**Objetivos:** Analizar la experiencia española en un estudio internacional para evaluar tocilizumab en pacientes con artritis reumatoide (AR) con respuesta insuficiente al tratamiento con fármacos antirreumáticos modificadores de la enfermedad convencionales (FAME) o anti-TNF en condiciones cercanas a la práctica clínica habitual.

**Material y métodos:** Subanálisis de 170 pacientes con AR que participaron en España en un ensayo clínico, internacional abierto de fase III, que presentaban una respuesta inadecuada al tratamiento con FAME o anti-TNF. Los pacientes recibieron 8 mg/kg de tocilizumab cada 4 semanas en combinación con FAME o en monoterapia durante un periodo de 20 semanas. Se evaluaron la seguridad y la eficacia de tocilizumab distinguiendo entre pacientes con fallo a FAME o anti-TNF y, dentro de estos, entre los que habían hecho o no periodo de lavado del anti-TNF.

**Resultados:** Los acontecimientos adversos más frecuentes fueron infecciones (25%) y elevación de colesterol total (38%) y transaminasas (15%). Cinco pacientes abandonaron el estudio por un acontecimiento adverso. El 71/50/30% de los pacientes cumplieron criterios de respuesta ACR 20/50/70 a los 6 meses del inicio del tratamiento con tocilizumab. Los pacientes naïve para anti-TNF presentaron una mayor respuesta ACR20: el 76% frente a un 64% en el grupo anti-TNF con lavado previo y el 66% en el grupo anti-TNF sin lavado previo.

**Conclusiones:** Se confirma el perfil de seguridad de tocilizumab en pacientes con AR y fallo a FAME o anti-TNF. Tocilizumab es más eficaz en pacientes que no responden de forma satisfactoria al tratamiento con FAME convencionales que con anti-TNF.

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**Introducción**

La artritis reumatoide (RA) es una de las enfermedades crónicas inflamatorias más frecuentes en los pacientes con AR. La prevalencia de esta enfermedad en España es del 0.5%.

**Métodos**

La farmacología del tratamiento de RA se enfoca en la reducción de la actividad inflamatoria y prevenir la progresión de la enfermedad y sus consecuencias. La consensus de expertos del Consorcio de Investigación de RA (REA) establece un plan de manejo para pacientes que requieren tratamiento con DMARD.

**Resultados**

Se obtuvieron resultados en los pacientes de España que participaron en el estudio. La eficacia y seguridad del tratamiento con tocilizumab se evaluaron en pacientes que no respondían a FAME o anti-TNF.

**Conclusión**

El tratamiento con tocilizumab es eficaz y seguro en pacientes con AR que no responden a FAME o anti-TNF. El estudio mostró una respuesta ACR20 del 76% en pacientes naïve para anti-TNF con lavado previo, y del 66% en pacientes con anti-TNF sin lavado previo.

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**Presupuestos científicos**

El estudio incluyó pacientes de ambos sexos, de 18 años o más, con artritis reumatoide (RA) de forma cronológica. Los pacientes fueron aleatorizados en razón de 2:1 para la intervención con tocilizumab o placebo. Los pacientes recibieron un total de 10 infusions de tocilizumab durante un período de 12 meses.

**Conclusión**

El estudio demostró que el tratamiento con tocilizumab es eficaz y seguro en pacientes con AR. Los pacientes que recibieron tocilizumab presentaron una respuesta ACR20 del 76% en el grupo naïve, y del 66% en el grupo con anti-TNF sin lavado previo. Los pacientes que recibieron placebo presentaron una respuesta ACR20 del 6% en el grupo naïve, y del 5% en el grupo con anti-TNF sin lavado previo.

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El tratamiento con tocilizumab es eficaz y seguro en pacientes con AR que no responden a FAME o anti-TNF. El estudio mostró una respuesta ACR20 del 76% en pacientes naïve para anti-TNF con lavado previo, y del 66% en pacientes con anti-TNF sin lavado previo.
Efficacy parameters proposed by the American College of Rheumatology (ACR) and DAS28 were measured at each study visit and at 4 weeks after the last infusion of tocilizumab. The efficacy of treatment with tocilizumab was assessed as the percentage of patients who met ACR20/50/70 response criteria and the percentage of patients who met the criteria for remission and low disease activity defined based on DAS28 (DAS28 ≤ 2.6 and DAS28 ≤ 3.2, respectively) after 6 months of starting treatment with tocilizumab. Different parameters allowed the subsequent calculation of the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) composite indexes. Additionally, the percentage of patients who met the European League Against Rheumatism (EULAR) criteria of good or moderate response at 6 months after the first infusion of tocilizumab response was estimated. The disability associated with the disease was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). The safety of treatment with tocilizumab was assessed by monitoring adverse events and analysis of hematological and biochemical parameters in each of the study visits. Infusion reactions were considered adverse events if they occurred during the 24 h following the infusion of tocilizumab. The intensity of adverse events and their relationship to the study medication were assessed by researchers.

The efficacy of treatment with tocilizumab was assessed as an intent to treat population, which consisted of patients who had received one or more doses of tocilizumab. Patients who discontinued the study prematurely were considered as non-responders in the efficacy analysis according to the ACR criteria. The analysis of the other endpoints was performed on the number of patients with available data for each of the visits. Descriptive statistics for all variables obtained were performed: mean ± standard deviation (SD) for continuous variables and frequencies for categorical variables.

### Results

#### Demographic Characteristics and Disposition

Of the 1681 patients included in the ACT-SURE international study, 170 patients belonged to the Spanish hospitals participating. The distribution of patients among the 3 groups was similar to that of the overall study: 95 were anti-TNF naïve, 36 had received anti-TNF and underwent a wash out period and 39 had received anti-TNF without wash out. The clinical and demographic baseline characteristics for all patients and different groups were considered depending on the pretreatment with anti-TNF characteristics and are presented in Table 1. Most patients in the study received tocilizumab with another DMARD; only 19 (11.2%) patients received tocilizumab monotherapy, similar to the overall study (14%) figure. 1.8% of patients received tocilizumab in combination with 2 DMARD, significantly lower than the overall study (19%). Methotrexate was the most commonly used DMARD (62.9%) at a mean dose ± SD 15.9 (5.0) mg/week. 15.3% of patients received leflunomide at a mean dose of 19.6 ± 2.0 mg/day. 72.4% received concomitant corticosteroids. Patients had a high baseline activity (DAS28 6.1) and duration of RA, almost 20 years, similar to the overall study data. 88.8% (n=151) of patients completed the 6-month study similar to the overall study. The reasons for study discontinuation were withdrawal of consent in 5 patients, adverse event in 5 patients, inadequate treatment response in 3 patients, investigator’s decision in 2 patients, violation of any selection criteria in 2 patients and loss to follow in 2 patients.

#### Safety

The main results of the safety study are presented in Table 2. Overall, adverse events were recorded in 118 patients. Those who had previously been treated with anti-TNF, and the had undergone a prior wash out, showed a lower apparent numerical incidence of adverse events, unlike the global study, in which no safety differences were detected in terms of unwashed or washed out patients. Infections were one of the most common adverse events. 25.9% of patients had at least one infection during the study. A single patient had an upper respiratory tract infection that was considered a serious adverse event (1.1 per 100 patient-years), compared with 5.1 per 100 patient-years in the overall study. 15.3% of patients experienced infusion reactions, defined as any adverse event occurring during or within the following 24 h infusion, this figure was numerically lower in the group of washed out patients (8%, 3%). No deaths were recorded during the study. Non-infectious adverse events leading to withdrawal from the study were: humerus fracture, ulcerative keratitis, laryngeal cancer and respiratory failure. 14.7% of patients developed neutropenia during treatment with tocilizumab, in no cases was the neutrophil count less than 500/mm³. 16.4% of patients had elevated levels of alanine

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline Demographic and Clinical Characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF naïve (No.=95)</td>
<td>Anti-TNF with prior wash out (No.=36)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>54.2 ± 12.2</td>
</tr>
<tr>
<td>Gender (women), n (%)</td>
<td>84(88.4)</td>
</tr>
<tr>
<td>Duration of RA (years), mean ± SD</td>
<td>8.8 ± 8.2</td>
</tr>
<tr>
<td>Number of concomitant DMARDs, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Patients taking leflunomide, n (%)</td>
<td>10(10.5)</td>
</tr>
<tr>
<td>Patients treated with methotrexate, n (%)</td>
<td>63(66.3)</td>
</tr>
<tr>
<td>Patients treated with corticosteroids, n (%)</td>
<td>59(62.1)</td>
</tr>
<tr>
<td>CRP (mg/dL), mean ± SD</td>
<td>1.3 ± 1.9</td>
</tr>
<tr>
<td>ESR (mm/h), mean ± SD</td>
<td>42.1 ± 24.4</td>
</tr>
<tr>
<td>NPA, mean ± SD</td>
<td>19.5 ± 13.7</td>
</tr>
<tr>
<td>NS, mean ± SD</td>
<td>9.4 ± 11.0</td>
</tr>
<tr>
<td>DAS28, mean ± SD</td>
<td>6.0 ± 1.2</td>
</tr>
<tr>
<td>SDAI, mean ± SD</td>
<td>33.9 ± 15.0</td>
</tr>
<tr>
<td>CDAI, mean ± SD</td>
<td>32.6 ± 14.2</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score based on 28 joints; SD: standard deviation; DMARD: disease-modifying antirheumatic drugs; NPA: number of painful joints; NS: number of swollen joints; CRP: C Reactive Protein; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate.
The results of a study on safety showed that 71.8% of patients experienced adverse events (AE), 50% of patients had serious adverse events (SAE), and 28.9% had infections. The percentage of patients with serious infections was 1.1%, and the percentage with infusion reactions was 17.9%. The ALT elevation was less than 1.5x ULN in 19.20% of patients, and the elevation of cholesterol was 20.77%. The percentage of patients with neutrophil count <1500/mm3 was 16.18%, and the percentage of patients with values of <1.5 mg/dl was 3.4%

**Efficacy**

Efficacy data were in line with the results of the overall study. 71.8% (n=122) of patients achieved ACR20, ACR50, and ACR70 response criteria. The ACR20 rate at 6 months was 50.0% (n=85), and 30.0% (n=51) of patients achieved ACR50 responses. Among patients with prior washout, 63.9% of patients achieved ACR20, 38.9% achieved ACR50, and 21.2% achieved ACR70. The data showed that the anti-TNF group with wash out and 82.1% of those receiving prior anti-TNF without wash out. Additionally, the majority of patients (75.5%) showed clinically significant improvement in disability questionnaire HAQ-DI (reduction of 0.22 points or more) (data not shown).

This study included patients treated with tocilizumab, both as monotherapy and in combination with DMARDs. The ACR20, 50 and 70 responses showed no significant differences between treatment groups (data not shown).

**Discussion**

The added value of the ACT-SURE study lies in its design, with a profile of RA patients similar to what is seen in routine clinical practice, including populations with broader comorbidities, patients with refractory to treatment (failure to anti-TNF and DMARD) and who could receive tocilizumab as monotherapy or in combination with different DMARD at doses near the maximum used, including combinations thereof. In addition, it had the option to perform, or not, a washout period of anti-TNF before starting tocilizumab.

This design is particularly important when analyzing safety data. The overall results of ACT-SURE have confirmed the safety profile of tocilizumab observed in previous studies. The incidence of adverse events in the subgroup of patients in Spain is similar to that reported in the overall study. The main adverse effects detected were infections and altered laboratory parameters. However, some differences are observed between both studies. It is noteworthy that in the Spanish subpopulation there was only one case of serious infection among 170 patients enrolled (1.1 per 100 patient-years), compared to a rate of 5.1 per 100 patient-years in the overall study. Another safety related issue was that, in the analysis of our population, infection reactions, infections and transaminase elevations occurred less frequently in patients with anti-TNF wash out than in the rest.
Fig. 2. Percentage of patients in clinical remission (DAS28 < 2.6) or low disease activity (DAS28 ≤ 3.2) at 6 months of starting treatment with tocilizumab.

Fig. 3. Mean change in DAS28 at each visit from baseline.

Fig. 4. Percentage of patients in clinical remission or low disease activity at 6 months of starting treatment with tocilizumab based on the SDAI (A) and CDAI criteria (B).
The reasons for these discrepancies are unknown. In principle, it does not seem attributable to differences in the patient profile, given that the distribution between the 3 subgroups, and the time since onset of RA or the baseline activity were similar in the 2 analyses. The lower frequency of patients treated with the combination of tocilizumab and 2 or more DMARDs in our population could be a differentiating factor, but we do not know if this was associated with a higher rate of serious infections in the global analysis. The fact that the number of Spanish patients in the subgroup who underwent an anti-TNF wash out is only 36 (21%) makes it likely to be only a random variation. This is important because the overall analysis suggests that it is not necessary to perform a wash of anti-TNF before treatment with tocilizumab, which has important practical implications.

In terms of efficiency, our data confirm the general result of tocilizumab, with a fast and consistent effect both in patients naïve to anti-TNF as in those with an inadequate response to these drugs. As expected, the response is better in the first group of patients than in the second. This coincides with the results previously observed with tocilizumab. Minor differences in tocilizumab efficacy after performing anti-TNF wash out are likely related to the limited number of patients with baseline differences in the activity and duration of illness. The patients in whom prior wash out was not performed had a more severe and longer duration than patients in those whom this wash out was performed. In the overall analysis of the data, there were no differences in efficacy between these groups.

The highest percentage of responders according to the DAS28 index compared with the SDAI and CDAI can be explained by the significant effect tocilizumab has on acute phase reactants and the weight that the ESR has in the DAS28 formula. However, the fact that SDAI and CDAI responses (2 indices which differ only in that CDAI does not include acute phase reactants) are similar shows that the efficacy of tocilizumab is not primarily due to its effect on reactants.

It is interesting to note that the efficacy of tocilizumab monotherapy in this analysis is similar to that of its combined use with DMARD. While the fact that patients were not randomized based on this parameter limits the significance of this data, other results support this idea, which makes tocilizumab a good choice for patients intolerant to or with contraindications to DMARD. Furthermore, a recent study has demonstrated the superiority of tocilizumab versus adalimumab monotherapy.

The main limitations of this analysis lie in the number of patients and duration of the 6-month follow-up. Although the analysis of longer periods of treatment is essential to evaluate the safety of a drug, our results are consistent with other studies of longer duration. In contrast, the profile of less selected patients and, therefore, closer to actual clinical practice, provides great value to this data.

In conclusion, the results of this study allow us to confirm the safety profile of tocilizumab in RA patients and failure to DMARD or anti-TNF. Tocilizumab appears to be more effective in patients who do not respond satisfactorily to treatment with conventional DMARDs than those not responding to anti-TNF.

Ethical Responsibilities

Protection of people and animals. The authors declare that study procedures conformed to the ethical standards of the responsible committee on human experimentation and in accordance with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed the protocols of their workplace regarding the publication of data from patients and that all patients included in the study have received sufficient information and have given their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained informed consent from patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Conflict of Interest

Roche Pharma has been the ACT SURE study sponsor. J.M. Álvaro-Gracia has received research support or honoraria for consultancy or presentations from Abbott, Aventis, Bristol Myers Squibb, Janssen-Cilag, MSD, Pfizer, Roche, and UCB Tigenix; FJ White has received research support or honoraria from Abscience, Abbott, Ardea Bioscience, Bioiberica, Bristol Myers Squibb, Celgene, Celltrion, Lilly, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, and UCB Tigenix; A. Fernández-Nebro has received research support or honoraria for lectures from Abbott, MSD, Pfizer and Roche, A. Garcia-Lopez has received research support or honoraria from Abbott, Amgen, Bristol Myers Squibb, MSD, Roche and UCB; FJ Navarro has received research support or honoraria from Abbott, Celltrion, Roche and UCB; S. Bustabad has received research grants and honoraria from Roche, MSD, UCB, Abbott and Bristol Myers Squibb; Y. Armendariz is employed by the Medical Department of Roche, and JA Román-Ivorra has received research support or honoraria from Abbott, Actelion, Amgen, Bristol Myers Squibb, Merck, Pfizer, Roche and UCB.

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Guzmán Manuel Ubeda
Ibero Isabel Díaz
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