



ORIGINALS

Bilingual edition English/Spanish

Baricitinib and tofacitinib in patients with rheumatoid arthritis: results of regular clinical practice

Baricitinib y tofacitinib en pacientes con artritis reumatoide: resultados de práctica clínica habitual

Lara González-Freire^{1,2}, Rosa María Giménez-Candela¹, Susana Castro-Luaces^{1,2}, Ana Belén Veiga-Villaverde¹, Carlos Crespo-Diz^{1,2}

¹Servicio de Farmacia, Complejo Hospitalario Universitario de Pontevedra, Pontevedra. Spain. ²Instituto de Investigación Sanitaria Galicia Sur, Fundación Biomédica Galicia Sur. Spain.

Author of correspondence

Lara González Freire
Servicio de Farmacia
Hospital Montecelo
Avenida Mourente, s/n
36071 Pontevedra. Spain.

Email:
lara.gonzalez.freire@sergas.es

Received 31 October 2020;
Accepted 29 March 2021.
DOI: 10.7399/fh.11586

How to cite this paper

González-Freire L, Giménez-Candela RM, Castro-Luaces S, Veiga-Villaverde AB, Crespo-Diz C. Baricitinib and tofacitinib in patients with rheumatoid arthritis: results of regular clinical practice. *Farm Hosp.* 2021;45(4):165-9.

Abstract

Objective: Main objective: Describe the effectiveness and safety of baricitinib and tofacitinib in patients diagnosed with rheumatoid arthritis in our hospital. Secondary objective: Analyse whether there are differences between the two drugs in routine clinical practice.

Method: Two-year retrospective study of patients diagnosed with rheumatoid arthritis treated in our hospital with baricitinib and tofacitinib for at least 6 months. Databases: Electronic medical record and outpatient medication dispensing software. Variables collected: Demographic variables, poor prognosis factors, previous treatment, duration of treatment, concomitant treatment, DAS28, number of swollen and painful joints, pain visual analogy scale, treatment discontinuation, and adverse reactions. Effectiveness evaluation: Decreases in the DAS28 scale, the number of swollen and painful joints, and the pain Visual Analogy Scale at 6 months and 12 months after starting treatment. Safety evaluation: Detection of adverse reactions. Statistical analysis: Student *t*-test.

Results: A total of 44 patients were evaluated. Of these, 20 (70% women) received treatment with baricitinib and 24 (95.8% women) received tofacitinib. Baricitinib reduced the DAS28 by 2.3 and 1.7 at 6 months and 12 months, respectively, and tofacitinib reduced the scale by 2 and 1.9 at 6 months and 12 months, respectively. Baricitinib reduced the number of swollen and painful joints by 7 at both 6 months and 12 months, and

Resumen

Objetivo: Objetivo principal: describir la efectividad y seguridad de baricitinib y tofacitinib en pacientes diagnosticados de artritis reumatoide en nuestro centro. Objetivo secundario: analizar si existen diferencias entre ambos fármacos en práctica clínica real.

Método: Estudio observacional retrospectivo de 2 años de duración que incluyó pacientes diagnosticados de artritis reumatoide en tratamiento con baricitinib o tofacitinib en nuestro centro durante al menos 6 meses. Bases de datos: historia clínica electrónica, aplicativo informático de dispensación a pacientes externos. Variables recogidas: demográficas, factores de mal pronóstico, tratamiento previo, duración de tratamiento, tratamiento concomitante, escala DAS28, número de articulaciones inflamadas y dolorosas, escala visual analógica del dolor, suspensión del tratamiento y reacciones adversas. Evaluación de la efectividad: disminución en la escala DAS28, articulaciones inflamadas y dolorosas y escala visual analógica del dolor a los 6 y 12 meses de iniciado el tratamiento. Evaluación de la seguridad: detección de reacciones adversas. Análisis estadístico: prueba *t*-student.

Resultados: Se evaluaron 44 pacientes, 20 (70% mujeres) recibieron tratamiento con baricitinib, 24 (95,8% mujeres) con tofacitinib. Baricitinib redujo la puntuación en la escala DAS28 en 2,3 y 1,7 a los 6 y 12 meses. Tofacitinib en 2 y 1,9 respectivamente. Baricitinib redujo el número de

KEYWORDS

Rheumatoid arthritis; Drug therapy; Janus kinase inhibitors; Tofacitinib; Baricitinib; Drug effectivity; Drug safety; Adverse reactions.

PALABRAS CLAVE

Artritis Reumatoide; Tratamiento; Inhibidores JAK Kinasa; Tofacitinib; Baricitinib; Efectividad; Seguridad; Reacciones adversas.



Los artículos publicados en esta revista se distribuyen con la licencia
Articles published in this journal are licensed with a
Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.
<http://creativecommons.org/licenses/by-nc-sa/4.0/>
La revista Farmacia no cobra tasas por el envío de trabajos,
ni tampoco por la publicación de sus artículos.

tofacitinib reduced the number of swollen and painful joints by 4 and 6 at 6 months and 12 months, respectively. Baricitinib reduced the Visual Analogy Scale score by 7.8 and 6.8 at 6 months and 12 months, respectively, and tofacitinib reduced the score by 5 and 6 at 6 months and 12 months, respectively. Corticosteroid treatment was needed in 40% of patients treated with baricitinib and 62.5% of patients treated with tofacitinib. Treatment was discontinued due to loss of effectiveness in 10% of patients receiving baricitinib and 25% of patients treated with tofacitinib. Adverse reactions were experienced by 10% of patients treated with baricitinib and 12.5% of patients treated with tofacitinib. Adverse reactions led to treatment discontinuation in only 1 patient in each group. No statistically significant differences were observed between the two drugs.

Conclusions: The results show that baricitinib and tofacitinib were effective and safe in relation to all the variables analysed. Moreover, both drugs were similar in terms of effectiveness and safety for the treatment of rheumatoid arthritis in real-world clinical practice.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease that mainly affects the synovial membrane leading to the destruction of joint structures^{1,2}.

Typical symptomatology includes joint pain, swelling, and stiffness, together with functional limitation of the affected joints². It also manifests in general symptoms such as fatigue, malaise, morning stiffness, and weakness and depression which, in association with possible extra-articular involvement, reduce quality of life and life expectancy¹.

In Spain, the prevalence of RA in adults is 1.07% (95% Confidence Interval [95%CI]: 0.70-1.44), and it is higher in women and persons older than 60 years^{3,4}.

In recent years, we have witnessed a genuine revolution in the treatment of RA. The therapeutic approach includes the use of drugs aimed at short-term symptom control (anti-inflammatory drugs and corticosteroids) and the simultaneous initiation of the use of disease-modifying antirheumatic drugs (DMARDs). DMARDs are slow-acting drugs that target molecules directly involved in the pathogenesis of the disease. They are classified into three groups: conventional synthetic DMARDs (cDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs)^{5,6}.

Some drugs are currently available that block cytokines and cell costimulation, act as cell surface antagonists, and target intracellular Janus Kinase (JAK) enzymes involved in the transmission of cellular signals essential for the production of inflammatory cytokines. These drugs are known as JAK inhibitors (JAKi), which are small synthetic molecules for oral administration^{2,5,7}.

The development of these new drugs has led to the implementation of treatment strategies for patients with RA, such as early treatment, targeted treatment, and close monitoring, and the development of tools that allow better monitoring of the disease at each of its stages⁵.

Baricitinib (BAR) is a reversible selective JAK1 and JAK2 inhibitor and tofacitinib (TOF) is a selective JAK1 and JAK3 inhibitor. Both drugs are indicated as monotherapy or in combination with methotrexate for the treatment of moderate-severe active RA in adults with inadequate response or intolerance to one or more DMARDs^{2,6}.

Both drugs have undergone extensive phase III clinical trials and have demonstrated rapid improvements in disease activity, function, and patient-reported outcomes^{2,6,8}. Several studies and meta-analyses have assessed the effectiveness and safety in real-world clinical practice of BAR and TOF in the treatment of RA in patients who have failed previous treatments with other cDMARDs and bDMARDs^{9,16}.

JAKi are still a relatively novel RA treatment option, thus there is a need to utilize the experience gained with these drugs in real-life clinical settings to further evaluate their safety and utility¹¹.

The main objective of this study was to investigate the effectiveness and safety of BAR and TOF in patients diagnosed with RA receiving treatment with them in our hospital. A secondary objective was to identify any differences between them in real-world clinical practice.

articulaciones inflamadas y dolorosas en 7 a los 6 y 12 meses, tofacitinib en 4 las inflamadas y 6 las dolorosas. Baricitinib redujo la puntuación en la escala visual analógica del dolor en 7,8 y 6,8; tofacitinib en 5 y 6 a los 6 y 12 meses. El 40% de los pacientes con baricitinib y el 62,5% con tofacitinib precisaron tratamiento con corticoides. El 10% de los pacientes con baricitinib y el 25% de los pacientes con tofacitinib suspendieron el tratamiento por ineficacia. El 10% de los pacientes de baricitinib y el 12,5% de tofacitinib experimentaron reacciones adversas. Sólo un paciente de cada grupo suspendió el tratamiento por reacciones adversas. No se observaron diferencias estadísticamente significativas entre ambos fármacos.

Conclusiones: Según nuestros resultados, baricitinib y tofacitinib han demostrado ser efectivos y seguros en todas las variables analizadas. Además, ambos fármacos resultaron similares en efectividad y seguridad en la práctica clínica habitual del tratamiento de la artritis reumatoide.

Methods

A single-centre, observational, retrospective study was carried out. We included patients diagnosed with RA who met the funding criteria established by the Central Autonomous Commission for Pharmacy and Therapeutics (CACFT) and who started treatment with BAR and TOF between January 2018 and December 2019 with a minimum period of 6 months of treatment.

The criteria established by the CACFT for the use of BAR and TOF are as follows¹⁷:

- In the case of primary failure to an anti-tumour necrosis factor (anti-TNF) drug.
- In the case of loss of efficacy of previous treatment with cDMARDs or bDMARDs, based on efficiency criteria and the characteristics of each patient.

The electronic medical record (IANUS version 04.53.0102) and the software application for outpatient dispensing (Silicon version 10.5.0) were used as sources of demographic, analytical, pharmacotherapeutic, and clinical data.

The following variables were collected: age and sex as demographic variables, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) as poor prognostic factors, previous treatment with cDMARDs and bDMARDs, treatment duration, concomitant treatment with corticosteroids, concomitant treatment with cDMARDs, number of swollen joints (NSJ) and painful joints (NPJ), visual analogue scale for pain (VAS) score, disease activity score of 28 joints (DAS28), adverse reactions (AR), discontinuation of treatment, and reason for discontinuation.

The primary endpoint used to assess effectiveness was decreases in the DAS28 at 6 months and 12 months of treatment. Secondary endpoints were decreases in the NSJ and NPJ and in VAS scores at 6 and 12 months after initiation of treatment.

Safety was assessed by reviewing the clinical manifestations of ARs recorded in medical records. Qualitative variables are expressed as absolute frequency and percentage, and quantitative variables are expressed as median and range. The Shapiro-Wilk normality test was performed to determine whether the dependent variables followed a normal distribution. Differences between BAR and TOF were analysed using the student *t*-test. A *P*-value of < 0.05 was used as a cutoff for statistical significance. All statistical analyses were performed using the R-Commander software package (version R x64 3.6.1). All data were anonymised by the elimination of personal information.

Results

Patient characteristics

Between January 2018 and December 2019, 48 patients started treatment with BAR and TOF in our hospital. Four patients were excluded because they had not been on treatment for at least 6 months.

A total of 44 patients were evaluated, of whom 20 (45.5%) received treatment with BAR at 4 mg/24 h and 24 (54.5%) received TOF at 5 mg/12 h. Monotherapy was received by 95.0% of BAR patients and

70.8% of TOF patients. Table 1 shows the demographic characteristics of the patients, poor prognostic factors, and prior treatment with cDMARDs or bDMARDs.

Patients in the BAR and TOF groups received a median of 2 (0-7) and 2 (1-6) previous lines of bDMARD therapy, respectively. The following bDMARDs were used: etanercept in 23 (47.9%) patients, adalimumab in 17 (35.4%), abatacept in 15 (31.2%), certolizumab in 13 (27.1%), infliximab in 13 (27.1%), tocilizumab in 13 (27.1%), rituximab in 8 (16.7%), golimumab in 7 (14.6%), ustekinumab in 3 (6.3%), and secukinumab in 2 (4.2%).

Effectiveness

The DAS28 decreased in the BAR group by 2.3 points at 6 months and 1.7 points at 12 months and decreased in the TOF group by 2 points at 6 months and 1.9 points at 12 months. No statistically significant differences were found between groups ($P = 0.074$) (Table 2).

The NSJ decreased in the BAR group by 7 and in the TOF group by 4 at both 6 months and 12 months with no statistically significant differences between groups ($P = 0.42$) (Table 3).

The NPJ decreased in the BAR group by 7 and in the TOF group by 6 at both 6 months and 12 months with no significant differences between groups ($P = 0.67$) (Table 3).

The VAS score decreased in the BAR group by 7.8 points at 6 months and 6.8 points at 12 months and decreased in the TOF group by 5 points at 6 months and 6 points at 12 months. No statistically significant differences were found between the 2 groups ($P = 0.66$) (Table 4).

Concomitant corticosteroid treatment was required in 8 (40.0%) BAR patients and in 15 (62.5%) TOF patients. No statistically significant differences were found between the 2 drugs ($P = 0.17$).

Median treatment duration was 14 (7-24) months in BAR patients and 14 (7-27) months in TOF patients. Treatment was discontinued because of a lack of effectiveness due to secondary failure in 10% (2) of BAR patients and 25% (6) of TOF patients.

Safety outcomes

Adverse reactions were experienced by 2 (10%) BAR patients. In 1 patient (50%), blood analysis showed increased LDL-cholesterol and transaminase concentrations as moderate ARs leading to discontinuation of

Table 1. Patient characteristics, poor prognostic factors, and prior treatment

	BARICITINIB n (%) n = 20	TOFACITINIB n (%) n = 24
Age, years; median (range)	61 (41-79)	56 (38-79)
Sex (women)	14 (70.0%)	23 (95.8%)
Positive RF	17 (85.0%)	10 (41.7%)
Presence of ACPA	16 (80.0%)	16 (66.7%)
Prior treatment with cDMARDs	20 (100.0%)	24 (100.0%)
Pre-treatment with bDMARDs	15 (75.0%)	22 (91.7%)

ACPA: anti-citrullinated protein antibodies; bDMARDs: biological disease-modifying antirheumatic drugs; cDMARDs: conventional disease-modifying antirheumatic drugs; n: number of patients; RF: rheumatoid factor.

Table 2. Scores on the DAS28 scale

	BARICITINIB Median (range)	TOFACITINIB Median (range)
DAS28 score t0	4.4 (2.7-6.3)	4.9 (3.6-6.2)
DAS28 score t6	2.1 (0.6-4.1)	2.9 (0.9-5.3)
DAS28 score t12	2.7 (1.1-3.5)	3 (1.3-5.3)

DAS28: Disease Activity Score; t0: at baseline; t6: at 6 months; t12: at 12 months.

Table 3. Evolution of the number of swollen and painful joints

	BARICITINIB Median (range)	TOFACITINIB Median (range)
NSJ t0	7 (2-10)	4.5 (0-12)
NSJ t6	0 (0-0)	0 (0-4)
NSJ t12	0 (0-0)	0 (0-1)
NPJ t0	7 (2-12)	6 (0-10)
NPJ t6	0 (0-0)	0 (0-1)
NPJ t12	0 (0-0)	0 (0-1)

NPJ: number of painful joints; NSJ: number of swollen joints; t0: at baseline; t6: at 6 months; t12: at 12 months.

Table 4. Visual Analogue Scale for Pain scores

	BARICITINIB Median (range)	TOFACITINIB Median (range)
VAS score t0	8.8 (7-10)	8 (3-10)
VAS score t6	1 (0-5)	3 (2-8)
VAS score t12	2 (2-4)	2 (1-10)

t0: at baseline; t6: at 6 months; t12: at 12 months; VAS: Visual Analogue Scale for Pain.

treatment. The other patient (50%) experienced mild gastrointestinal disturbances.

Adverse reactions were experienced by 3 (12.5%) TOF patients. One patient (33.3%) experienced diffuse interstitial lung disease as a severe AR leading to discontinuation of treatment. The other 2 patients experienced mild ARs. One (33.3%) experienced asthenia and 1 (33.3%) experienced gastrointestinal disturbances.

Moderate-severe ARs led to treatment discontinuation in 5.0% (1) of BAR patients and 4.2% (1) of TOF patients. The safety results showed that there were no statistically significant differences between the two groups ($P = 0.5$).

Discussion

Rheumatoid arthritis is the most prevalent form of chronic polyarthritis and has a major social and health impact in Spain. It can lead to varying degrees of disability, loss of quality of life, and even increased mortality¹.

In Spain, current treatment guidelines and the CACFT treatment protocol recommend the use of cDMARDs as initial treatment as soon as RA is diagnosed. If the therapeutic target is not reached using this initial strategy, other cDMARDs can be used in sequential or combined therapy or a bDMARD can be added depending on the patients' characteristics and the presence of poor prognostic factors. If treatment with the first bDMARD is unsuccessful, it is recommended that patients are treated with another bDMARD or a targeted synthetic drug^{1,17,18}.

In the present study, all patients received treatment with cDMARDs. Of these patients, the majority (75% of the TOF group and 91.7% of the BAR group) received more than 1 previous bDMARD. The patients received a median of 2 treatment lines, the most frequent being etanercept. These results are similar to those obtained in a study by Mueller *et al.*¹¹, in which 84.7% of patients had received at least 1 previous bDMARD with a median of 2.2 treatment lines.

Regarding demographic data, patients were slightly younger and had fewer poor prognostic factors in the TOF group than patients in the BAR group: however, there were more women in the TOF group than in the BAR group. These results differ from those published in previous studies, in which the majority of patients were female: however, the patients were older in the TOF groups than patients in the BAR groups^{11,16}.

Although the baseline DAS28 and VAS scores were similar in the two groups, the BAR group had a higher NSJ and NPJ. These results are similar

to those described in a study by Guidelli *et al.*, in which they evaluated the efficacy and safety of BAR. The patients had a baseline DAS28 score of 4.67 ± 1.05 , NPJ of 7.6 ± 5.7 , and NSJ of 5.5 ± 4.5 (mean \pm standard deviation [SD])¹⁴.

The doses administered were those described in the summary of product characteristics (SPC). Although the SPC specifies that 2 mg/d BAR may be appropriate in patients aged at least 75 years¹⁹, it should be noted that all BAR patients, including older patients, received 4 mg/d. This dose is the same as that administered in previous studies, although the patients had a mean age of less than 75 years^{13,14,16}. Although some patients received a higher dose than that recommended for their age in the SPC, no related adverse drug reactions were observed.

Since JAKi were launched, several real-life studies have assessed the effectiveness and safety of BAR and TOF and have obtained similar results to those obtained in the two study groups.

Iwamoto *et al.* conducted a study to evaluate the effectiveness and safety of TOF. They observed a decrease in the DAS28 (mean \pm SD) from 5.04 ± 1.33 to 3.83 ± 1.11 at 4 weeks, to 3.69 ± 1.19 at 12 weeks, and to 3.53 ± 1.17 at 24 weeks¹².

Spinelli *et al.* conducted a study to assess the effectiveness and safety of BAR over 48 weeks in 59 patients diagnosed with RA. At weeks 4, 12, 24, and 48, the results (median [interquartile range]) showed a reduction in the DAS28 from an initial 4.68 (1.5) to 3.41 (1.6), to 2.79 (1.52), to 2.79 (1.66), and to 2.77 (1.55), respectively. At the same time points, the NPJ decreased from 8 (7) to 4 (5), to 2 (4), to 1 (5.5), and to 1 (4.5) and the NSJ decreased from 4 (4) to 1 (3), to 0 (2.25), to 0 (4), and to 0 (1), respectively. In addition, the VAS scores showed significant improvements in patient-reported outcomes¹³. These results are similar to the DAS28 and VAS scores observed in our study. The baseline NSJ was higher in our sample than that in their study, and so the reduction was greater; however, the results on the NPJ were similar in both studies.

In the present study, treatment was discontinued due to loss of effectiveness in 10% of the BAR patients and 25% of the TOF. These results are similar to those reported for both drugs in previous studies^{3,15}. However, fewer patients discontinued treatment for this reason in the BAR group in the present study than in the study by Fitton *et al.*¹⁶, in which 14 out of 54 patients in the TOF group and 15 out of 69 patients in the BAR group discontinued treatment due to inefficacy.

Glucocorticoids are among the most commonly used anti-inflammatory and immunosuppressive drugs for RA. In other developed countries, patients with active RA use concomitant glucocorticoids and cDMARDs in percentages ranging from 38% to 55%. Spinelli *et al.*¹³, reported that 78.0% of patients were taking concomitant corticosteroids at the start of treatment with BAR. By the end of the study period, this percentage had decreased to 34.8%. Guidelli *et al.*¹⁴ found that the percentage of patients taking concomitant corticosteroids decreased from 70% at the beginning of the study

period to 32% at the end of the period. These results are similar to those described in our study. In addition, we found no significant differences in the need for corticosteroids during treatment with both drugs.

The aforementioned studies and the pivotal studies investigated the safety of BAR and TOF. The most frequently described ARs to TOF were infections followed by headache, nausea, hypertension, and diarrhoea, and the ARs to BAR were increased LDL concentrations, elevated liver enzymes, and nausea^{1,2,6,11-18,20}. We observed similar ARs to the two drugs in our study population. Nevertheless, it is striking that we observed no signs of infection, despite this AR being one of the most common in this type of treatment. Moreover, only a small percentage of patients discontinued treatment due to severe ARs.

However, in 2019, the Spanish Agency for Medicines and Health Products published a recommendation on restrictions to the use of TOF due to the increased risk of dose-dependent venous thromboembolism in patients with at least one risk factor²¹. No such effect was observed in our study population.

Our study is limited by its having a retrospective observational design, being a single-centre study with a small number of patients, and having possible biases due to the absence of data in the medical records. However, it was conducted in the setting of real-world clinical practice, and thus the results can be extrapolated to other hospital settings.

Based on our results, BAR and TOF have been shown to be effective and safe for use in decreasing DAS28, NSJ, NPJ, and VAS scores. In addition, both drugs demonstrated similar effectiveness and safety in real-world clinical practice in the treatment of RA.

Funding

No funding.

Conflicts of interests

No conflict of interest.

Contribution to the scientific literature

Rheumatoid arthritis is a chronic inflammatory disease with high prevalence. It causes significant disability and reduced quality of life and has a major social and health impact in Spain. In recent years, we have witnessed a revolution in the treatment of this disease due to the development of drugs targeting molecules directly involved in the pathogenesis of disease.

The evaluation of the effectiveness and safety of these drugs in real-world clinical practice will help us gain a better understanding of the different therapeutic alternatives for this disease and their beneficial or harmful effects on patients.

Bibliography

- Grupo GUIPCAR de trabajo de la GPC para el manejo de pacientes con Artritis Reumatoide. Sociedad Española de Reumatología. Guía de práctica clínica para el manejo de pacientes con Artritis Reumatoide. 2019 [accessed 10/15/2020]. Available at: <https://www.ser.es/wp-content/uploads/2018/09/Gu%C3%ADa-de-Pr%C3%A1ctica-Cl%C3%ADnica-para-el-Manejo-de-Pacientes-con-Artritis-Reumatoide.pdf>
- Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicios Sociales e Igualdad. Informe de posicionamiento terapéutico de Baricitinib (Olumiant®) en artritis reumatoide. 2017 [accessed 10/14/2020]. Available at: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-baricitinib-Olumiant-artritis-reumatoide.pdf>
- Silva-Fernández L, Macía-Villa C, Seoane-Mato D, Cortés-Verdú R, Romero-Pérez A, Quevedo-Vila V, *et al.* The prevalence of rheumatoid arthritis in Spain. *Sci Rep.* 2020;10(1):1-9. DOI: 10.1038/s41598-020-76511-6
- Puig L, Ruiz de Morales JG, Dauden E, Andreu JL, Cervera R, Adán A, *et al.* La prevalencia de diez enfermedades inflamatorias inmunomediadas (IMID) en España. *Rev Esp Salud Pública.* 2018 [accessed 01/12/2021];93:e1-19. Available at: <https://www.scielosp.org/article/resp/2019.v93/e201903013/>
- Castañeda S, González-Álvoro I. Novedades en el panorama terapéutico de la artritis reumatoide. *Rheumatol Clin.* 2017;13(2):63-5. DOI: 10.1016/j.reuma.2017.02.001
- Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicios Sociales e Igualdad. Informe de posicionamiento terapéutico de Tofacitinib (Xeljanz®) en artritis reumatoide. 2017 [accessed 10/14/2020]. Available at: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-tofacitinib-Xeljanz-artritis-reumatoide.pdf?x18703>
- Movasat Hajkhan A, Turrión Nieves A, Bohórquez Heras C, Pérez Gómez A. Tratamiento de la artritis reumatoide. *Medicine.* 2017;12(28):1626-38. DOI: 10.1016/j.med.2017.02.011
- Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology.* 2019;58:i17-26. DOI: 10.1093/rheumatology/key225
- Bae SC, Lee YH. Comparison of the efficacy and safety of tofacitinib and baricitinib in patients with active rheumatoid arthritis: a bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol.* 2019;78(6):559-67. DOI: 10.1007/s00393-018-0531-5
- Young HL, Song GG. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib as monotherapy for active rheumatoid arthritis. *J Clin Pharm Ther.* 2020;45:674-81. DOI: 10.1111/jcpt.13142
- Mueller RB, Hasler C, Popp F, Mattow F, Durmisi M, Souza A, *et al.* Effectiveness, tolerability, and safety of tofacitinib in Rheumatoid Arthritis: A retrospective Analysis of Real-world data from the St. Gallen and Aarau Cohorts. *J. Clin Med.* 2019;8(10):1-14. DOI: 10.3390/jcm810548

12. Iwamoto N, Tsuji S, Takatani A, Shimizu T, Fukui S, Umeda M, *et al*. Efficacy and safety at 24 weeks of daily clinical use of tofacitinib in patients with rheumatoid arthritis. *PLoS One*. 2017;12(5):1-13. DOI: 10.1371/journal.pone.0177057
13. Spinelli FR, Ceccearelli F, Garufi C, Duca I, Mancuso S, Cipriano E, *et al*. Effectiveness and safety of baricitinib in rheumatoid arthritis: a monocentric, longitudinal, real-life experience. *Clin Exp Rheumatol*. 2020. Epub ahead of print. PMID: 33337992
14. Guidelli GM, Viapiana O, Luciano N, De Santis M, Boffini N, Quartuccio L, *et al*. Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study. *Clin Exp Rheumatol*. 2020. Epub ahead of print. PMID: 33338001
15. García García S, Cardona Pascual I, Larrosa García M, Montoro Ronsano JB, Caparrós Ruiz R, Alonso Martínez C, *et al*. 4CPS-119 Real World experience of tofacitinib and baricitinib in the treatment of rheumatoid arthritis: effectiveness and safety evaluation. *Eur J Hosp Pharm*. 2020;27(1):A103-4. DOI: 10.1136/ejhpharm-2020-eahoconf.220
16. Fitton J, Melville AR, Emery P, Nam JL, Buch MH. Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway. *Rheumatology*. 2020. Epub ahead of print. PMID: 33331938. DOI: 10.1093/rheumatology/keaa858.
17. Comisión Autonómica Central de Farmacia y Terapéutica. Servicio Gallego de Salud. Xunta de Galicia. Dictamen Sarilumab y actualización protocolo Artritis Reumatoide. 2019 [accessed 10/29/2020]. Available at: <https://www.sergas.es/Asistencia-sanitaria/Documents/1118/SARILUMAB%20e%20Actualizaci%C3%B3n%20protocolo%20Artrite%20Reumatoide.pdf>
18. Sanmartí R, García-Rodríguez S, Álvaro-Gracia JM, Andreu JL, Balsa A, Cáliz R, *et al*. Actualización 2014 del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la artritis reumatoide. *Reumatol Clin*. 2015;11(5):279-94. DOI: 10.1016/j.reuma.2015.05.001
19. Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicios Sociales e Igualdad. Ficha técnica de Baricitinib (Olumiant®). 2017 [accessed 01/16/2021]. Available at: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_es.pdf
20. Cid Boza N, Velloso Feijoo ML, Pérez Quintana MJ, Marenco De la Fuente JL. RC020- Seguridad de los inhibidores JAK en pacientes con artritis Reumatoide en condiciones de práctica clínica diaria. *Reumatol Clin*. 2020;16(Espec Cong):376 [accessed 01/15/2021]. Available at: <https://www.reumatologiaclinica.org/en-congresos-xlvi-congreso-nacional-sociedad-espanola-111-sesion-trabajos-aceptados-solo-para-publicacion-6096-seguridad-de-los-inhibidores-jak-72677-pdf>
21. Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicios Sociales e Igualdad. Nota informativa Tofacitinib (Xeljanz®): nuevas restricciones de uso. 2019 [accessed 01/12/2021]. Available at: https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2019/docs/NI_MUH_FV-18-2019-Tofacitinib.pdf?x34225