Factors associated to long-term retention rate of Janus kinase inhibitors in a multi-failure rheumatoid arthritis population

M. Sebastiani[1], A. Zabotti[2], B. Biasi[1], S. Cacioppo[2], G. Sandri[1], I. Giovannini[2], A. Manfredi[1], L. Quartuccio[2]

[1]Rheumatology Unit, Azienda Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy; [2]Division of Rheumatology, Department of Medicine (DMED), University of Udine, Udine, Azienda Sanitaria Universitaria del Friuli Centrale (ASUFC), Italy.

Abstract

Objective

We aimed to retrospectively evaluate retention rate and causes of discontinuation of JAKi in rheumatoid arthritis (RA) patients with particular regards to difficult-to-treat subgroups.

Methods

The diffusion of Janus kinase inhibitors (JAKi) for the treatment of RA has rapidly increased in recent years due to their effectiveness, even in difficult-to-treat subgroups of patients. After the publication of the Oral Surveillance study, the labelling of JAKi was modified, advising against their use in elderly patients and those atrisk for cardiovascular events and malignancies. Demographic, clinical, serological and therapeutic characteristics of RA patients treated with JAKi were recorded, including smoking habit and comorbidities.

Results

Three hundred and thirty consecutive RA patients were enrolled in the study. Among them, 50.3% patients had previously failed at least two biologic DMARDs. Risk factors for the use of JAKi were reported in 75.5% of patients, 41.5% of them were older than 65 years, 37.6% had smoked, while 48.8% had increased cardiovascular or cancer risk. Anticitrullinated peptide antibodies (ACPA) and combination therapy with conventional synthetic DMARDs were associated with a longer drug persistence and ACPA remained independently associated to a higher retention rate of JAKi also in the subgroup of difficult-to-treat patients.

Conclusion

In conclusion, our study supports the clinical effectiveness of JAKi in RA, even in the multi-failure subgroup of patients, where the risk/benefit ratio overcomes the safety risk. The presence of ACPA and the concurrent use of + cs-DMARD may increase the survival on JAKi in the long term.

Key words

rheumatoid arthritis, anticitrullinated peptide antibodies, Janus kinase inhibitors, disease-modifying anti-rheumatic drugs, difficult-to-treat rheumatoid arthritis

Marco Sebastiani, MD
Alen Zabotti, MD
Bruno Biasi, MD
Sofia Cacioppo, MD
Gilda Sandri, MD
Ivan Giovannini, MD, PhD
Andreina Manfredi, MD, PhD
Luca Quartuccio, MD, PhD

Please address correspondence to:
Marco Sebastiani
U.O. di Reumatologia,
Azienda Ospedaliera Policlinico di Modena,
Università di Modena e Reggio Emilia,
Via del Pozzo 71,
41125 Modena, Italy.
E-mail: marco.sebastiani@unimore.it

Received on October 31, 2023; accepted in revised form on December 18, 2023.

Competing interests: none declared.

Introduction

Janus kinases-inhibitors (JAKi) have recently been introduced for the treatment of many immune-mediated diseases, such as rheumatoid arthritis (RA). Their diffusion in clinical practice rapidly increased due to their effectiveness and oral availability (1), even in a difficult-to-treat subgroup of patients (2, 3).

Since the approval of JAKi, data from registries have shown that their use in RA varies drastically worldwide. The 2019 European Alliance of Rheumatology Associations (EULAR) recommendations for the treatment of RA did not specify which biologic (b-) or targeted synthetic (ts-) disease modifying antirheumatic drugs (DMARDs) use after the failure of a conventional synthetic (cs-) DMARD and the only suggestion was to prefer inhibitors of interleukin-6 (IL6) and JAKi for monotherapy in patients who do not tolerate conventional synthetic- (cs-) DMARDs (4).

Recently, the results of the Oral Surveillance trial suggested an association between tofacitinib and cardiovascular adverse events and malignancies rather than tumour necrosis factor blockers (TNFi) in patients with RA (5). Consequently, the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) modified the labelling of JAKis. In particular, EMA recommended JAKi should only be used in patients under 65 years of age, who are not current or past smokers, without other cardiovascular risk factors, and without other malignancy risk factors if suitable treatment alternatives are available (6). In 2022, the update EULAR recommendations for the treatment of RA advised rheumatologist should consider the following risk factors for cardiovascular events and malignancies before to prescribe a JAKi: age over 65years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic disease" (7).

In Italy, the Italian Agency for the drugs (AIFA) reserved these medicines for patients who have had an inadequate response or intolerance to one or more TNFi, including the safety advices proposed by EMA (6).

In the interim period, for patients already in treatment with a JAKi, Italian rheumatologists should evaluate the opportunity to maintain or change the current therapy according with the new safety and reimbursement conditions.

The aim of the study was to retrospectively evaluate retention rate and cause of discontinuation of JAKi in an Italian cohort of RA patients with particular regards to difficult-to-treat subgroups (8).

Materials and methods

RA patients treated with JAKi were retrospectively collected in two Italian Rheumatology centres from the North of Italy. Demographic and serological data, other than combination therapy with glucocorticoids (GC) and cs-DMARDs were recorded for each patient. Moreover, data on smoking habit and comorbidities, including diabetes, renal failure, peripheral arterial disease, hearth failure, dyslipidaemia, arterial hypertension and chronic obstructive pulmonary disease were systematically investigated. Finally, the cause of drug discontinuation (primary inadequate response or secondary loss of efficacy, adverse events, remission, change in drug reimbursement by national health system) was reported. We defined as primary inadequate response the failure in achievement of a remission or a low disease activity according to EULAR recommendations (7). Secondary loss of efficacy was defined as a failure of the treatment after a first good response (7).

Statistical analysis

Continuous variables have been reported as mean ± standard deviation or median and interquartile (IQR) range; median or IQR and categorial variables were reported as absolute number or percentage. Differences among patients who discontinued or continued treatment were analysed using Mann-Whitney test for non-parametric variables and Chi-square or Fisher tests when appropriated were used for categorial variables. Global persistence in therapy and 2-year retention rate were evaluated by mean of Cox regression. Then, a multivariate analysis was performed to analyse effect of features at baseline of patients in regard to drug discontinu-

ation (10). Analyses were made using the STATA14 Software (StataCorp LLC, College Station, TX, USA), with a p-value ≤0.05 considered to be statistically significant.

Results

Three hundred and thirty patients were enrolled in the study, 263 (79.7%) females and 67 (20.3%) males, with a median age at the beginning of therapy of 62 (IQR 19) years and a median disease duration of 11.3 (IQR 12.6) years. The median age at the diagnosis was 49 (IQR 19) years. Globally, patients included in the study had received at least one previous b-DMARD in 71.5% of cases (median number of previous b-DMARDs 2, range 1–12). Patients who had failed at least two b-DMARDs were 166 (50.3%).

Overall, 62.4% had never smoked, 18.5% are current smokers and 19.1% are former smokers. Comorbidities were detected in 56.4% of cases. In details, arterial hypertension and hyperlipidaemia were the most frequent, recorded both in 38.8% and 20.3% of subjects, respectively, while diabetes was observed in 9.4% of patients. A major cardiovascular event, namely myocardial infarction and stroke, was previously reported in 3.6% and 0.9% of cases, respectively (Table I).

According to the new EULAR recommendations, 75.5% of patients reported at least one risk factor for the use of JAKi, *i.e.* 41.5% of patients were older than 65 years, 37.6% were current or former smokers, while 48.8% of them had an increased major acute cardiovascular events (MACE) or cancer risk.

Among JAKi, baricitinib was prescribed in 169/330 (51.2%) subjects, upadacitinib in 68 (20.6%), tofacitinib in 51 (15.5%), and filgotinib in 42 (12.7%) cases.

A combination therapy with a cs-DMARD, mostly methotrexate, was reported in 51.2% of patients, while glucocorticoids was associated in 43.6% of cases.

The median follow-up was 21 months (IQR 29). In particular, the median follow-up was 12.5 (IQR 8.75–16.25) months for filgotinib, 17 (13.75) for upadacitinib, 31 months for baricitinib and tofacitinib (IQR 38.5 and 39, respectively).

Table I. Characteristics of rheumatoid arthritis patients treated with Janus kinase inhibitors.

	Number (%)
Number	330
Males/Females	67/263
Rheumatoid factor	228 (69.3)
ACPA	203 (62.1)
Ever smoker	124 (37.6)
COPD	24 (7.3)
Arterial hypertension	128 (38.8)
Heart failure	16 (4.9)
Renal failure	2 (0.6)
Hyperlipidaemia	67 (20.3)
Previous myocardial infarction	12 (3.6)
Previous stroke	3 (0.9)
Diabetes mellitus	31 (9.4)
Concurrent therapies	
Glucocorticoids	144 (43.6)
Methotrexate	147 (44.5)
Leflunomide	22 (6.7)
Median age at RA diagnosis (IQR)	49 (19)
Median age at enrolment (IQR)	62 (16)

ACPA: anticitrullinated peptide antibodies; COPD: chronic obstructive pulmonary disease; ICR: interquartile range.

During the follow-up, 137 (41.5%) patients discontinued their therapy, mainly for primary (19%) or secondary (38.7%) ineffectiveness, while 36% of subjects discontinued their treatment for adverse events. Among them, infections were reported in 21 subjects (6.4%); in particular, 6 cases were classified as severe (requiring hospitalisation) and other 9 were related to herpetic infections. A solid cancer was the cause of drug discontinuation in 6 subjects (1.8%), while no haematological cancers were recorded; only one patient showed a venous thromboembolism, while no major cardiovascular events were observed.

The change in reimbursement from NHS induced the discontinuation of JAKi only in 3 cases treated with a JAKi as a first-line and an increased cardiovascular risk. For the other patients treated with a JAKi as first-line therapy, rheumatologist decided to maintain therapy with JAKi, evaluating the benefit/risk ratio of patients positive in consideration of the good disease control.

Estimated median persistence in therapy was 44 months (CI 95% 35.2–52.7), while 2-year retention rate was 66.4%. There was no difference in the 2-year retention rate between upadacitinib, tofacitinib and baricitinib, while filgotinib showed a significantly better 2-year retention rate (see Fig. 1).

At univariate analysis, renal failure was significantly associated with drug discontinuation (OR 4.9 CI 95% 1.2–20; p=0.027), while the presence

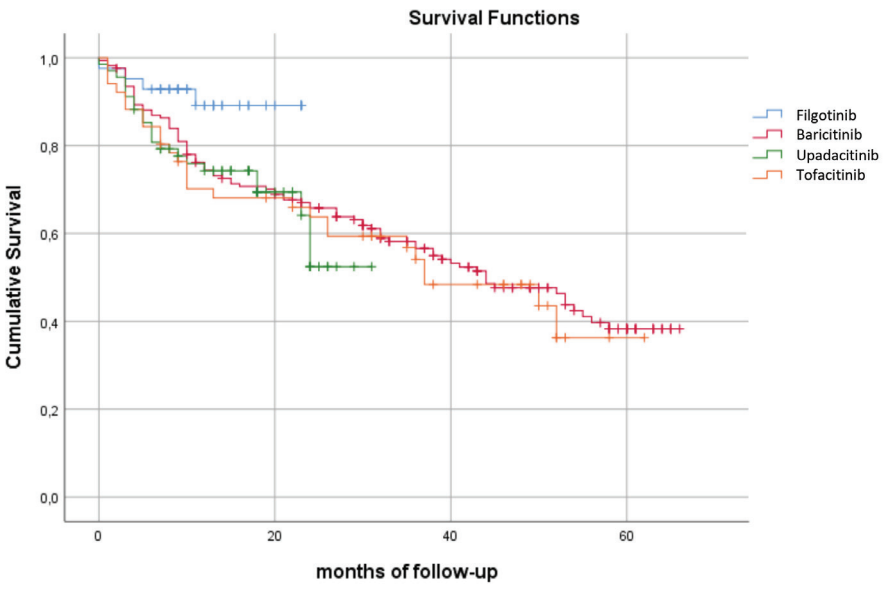

Fig. 1. Two-year retention rate for ts-DMARDs.
The overall 2-year retention rate was 66.4±2.8%, 65.8±3.7% for baricitinib, 63.8±6.8 for tofacitinib, 52.5±9.7% for upadacitinib, and 89.1±5.3% for filgotinib, with a significant difference between filgotinib and baricitinib (p=0.036), tofacitinib (p=0.021), and upadacitinib (p=0.037), respectively.

of anticitrullinated peptide antibodies (ACPA) (regardless of the titre) and combination therapy with csDMARDs were associated with a higher retention rate (odds ratio [OR] 0.67, 95% confidence interval [CI 95%] 0.48–0.94 [*p*=0.023] and OR 0.74, CI 95% 0.55–0.97 [*p*=0.035] for therapy discontinuation for ACPA and combination therapy with a cs-DMARD, respectively). These three variables were independently associated to JAKi discontinuation at multivariate regression analysis, also after correction for age and sex (Table II). Of interest, the failure of one or two previous b-/ts-DMARDs did not modify the possibility to discontinue the therapy (OR 1.35, CI 95% 0.97–1.90, *p*=0.08). The presence of ACPA remained independently associated to a lower rate of drug discontinuation (OR 0.59, CI 95% 0.38–0.92, *p*=0.02), while JAKi were withdrawn more frequently in patients with renal failure (OR 4.58, CI 95% 1.10-–9.05, *p*=0.04) also in the subgroup of multi-failure patients (at least two b- or ts-DMARDs).

Table II. Factors associated to drug discontinuation in rheumatoid arthritis patients treated with Janus kinase inhibitors.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Female gender	0.80	0.52-1.25	0.32	0.67	0.41-1.09	0.11
Rheumatoid factor	1.08	0.73-1.51	0.80			
ACPA	0.67	0.48-0.94	0.02	0.67	0.47-0.97	0.03
Ever smoker	1.00	0.71-1.41	0.59			
COPD	1.34	0.78-2.30	0.28			
Arterial hypertension	1.22	0.86-1.72	0.27			
Heart failure	1.89	0.96-3.73	0.06			
Renal failure	4.90	1.20-20	0.03	4.30	1.04-17.73	0.04
Hyperlipidaemia	1.23	0.80-1.87	0.33			
Previous myocardial infarction	1.06	0.39-2.88	0.91			
Previous stroke	1.43	0.2-10.23	0.70			
Diabetes mellitus	1.32	0.77-2.26	0.31			
Any comorbidities	1.12	0.81-1.57	0.49			
Type of JAK inhibitor	1.10	0.98-1.19	0.11			
Glucocorticoids	1.27	0.91-1.78	0.16			
Combination therapy	0.74	0.55-0.97	0.03	0.70	0.53-0.94	0.02
First-line after cs-DMARDs	1.38	0.93-2.06	0.11			
Difficult to treat patients	1.35	0.97-1.89	0.08			
Age at RA diagnosis	1.00	0.99-1.01	0.64			
Age at enrolment	1.01	0.99-.1.02	0.23	1.01	0.99-1.03	0.16
Disease duration	1.01	0.99-1.02	0.52			

ACPA: anticitrullinated peptide antibodies; COPD: chronic obstructive pulmonary disease; ICR: interquartile range; JAK: Janus kinase; cs-DMARDs: conventional synthetic disease-modifying antirheumatic drugs; RA: rheumatoid arthritis.

Discussion

JAKi have successfully expanded the armamentarium of RA, introducing a new mechanism of action and, for the first time, an effective oral treatment after failure of cs-DMARDs (11).

The results of the Oral Surveillance trial suggested that tofacitinib, the first commercialised JAKis, was associated with higher cardiovascular adverse events and malignancies than TNFi in patients with RA (2). The consequent change in labelling of JAKi introduced a transient period with RA patients already treated with a JAKi becoming off-label. For these patients, the rheumatologist could decide to maintain or change the ongoing treatment.

After the publication of the ORAL Surveillance trial, many studies from real-life and registries were published, suggesting a good safety profile for JAKi (12-17).

This is the first Italian study that analyses the retention rate of the four currently available JAKi. Our study shows a good retention rate for JAKi with no significant differences between them, even in a challenging scenario of patients who had already failed b-DMARDs. Interestingly, the presence of ACPA and the concomitant use of cs-DMARDs were linked to a lower discontinuation rate of JAKi, and ACPA remained associated to a high retention rate also in the setting of difficult-to-treat patients.

However, our study does not allow us to evaluate the safety of these drugs, even if in a median follow-up of almost 2 years (ranging from 12.5 months for filgotinib to 31 months for baricitinib and tofacitinib), the number of adverse events was low. In particular, although 56.4% of patients had at least one comorbidity and 32.5% at least two, the presence of comorbidities was not associated to an increase risk of drug discontinuations due to adverse events, including the presence of previous cardiovascular events. Similarly, smoking habit, both current or previous, did not influence either the persistence or the safety of the treatment.

Our study suggested also that the change in labelling of JAKi marginally influenced the use of these drugs in patients already treated, especially in the context of difficult-to-treat patients. Only three patients, all with high cardiovascular risk, discontinued their treatment after the change in labelling. In patients with RA within the Veterans Affairs Health System, a decrease in the number and proportion of new courses of JAKi after the release of safety data was observed, mainly for tofacitinib. In contrast, the TNFi use increased after January 2021 (18). Our study was not planned to define the variation in prescription of JAKi in Italy, but the new courses of therapy did not change significantly over time before and after 2021, although a reduction of new courses with tofacitinib and baricitinib has been recorded in our series.

The main limits of the study were the different follow-up duration for each JAKi, due to different period of commercialisation, and the inhomogeneous number of patients for each group, with a prevalence of subjects treated with baricitinib. Moreover, the number of patients enrolled in the study and the median follow-up period were significantly lower for filgotinib and upadacitinib when compared with the other ts-DMARDs. Future studies with a more homogeneous number of patients for each ts-DMARD could better evaluate possible differences between JAKi.

However, this is the first study to compare the retention rate of the four different available JAKi in RA patients in a real-world setting characterised by multi-failure patients (median of 2 previous b-DMARDs) and a higher prevalence of comorbidities including an increased cardiovascular risk. In two recent Italian studies independently evaluating RA patients treated with tofacitinib or baricitinib, the 2-year retention rates of the 2 drugs were 78.8% and 69.3%, respectively (19, 20). Only one other Italian study compared the retention rate of baricitinib and tofacitinib, reporting very high persistence in therapy after 2 years (91.1%) (21). The discrepancy between these results and our work is largely explainable by the different features of our patients. A minority of patients were treated with ts-DMARDs as first-line therapy after a cs-DMARD failure (14) and, compared with other studies, our patients were older and with a higher frequency of comorbidities (16). Another partial explanation derives from the need to withdraw JAKi in 3 patients (2 treated with tofacitinib and 1 with baricitinib) because of the change in labelling and reimbursement profile that took place in Italy in the last few months.

In a study on Japanese elderly patients (older than 65 years) there was no significant difference in the overall drug retention rate according to age, gender, methotrexate use, and ACPA status, including for patients treated with tofacitinib, upadacitinib and baricitinib (13)

In conclusion, our study supports the clinical effectiveness of JAK inhibitors in RA, even in the multi-failure subgroup of patients, where the risk/benefit ratio overcomes the safety risk. The presence of ACPA and the concomitant cs-DMARD may increase the survival on JAKi in the long term.

In the next few years, we can suppose that patients prescribed treatment with JAKi will be younger and with fewer comorbidities and, consequently, the retention rate of JAKi could furtherly increase. However, we need large studies with a long follow-up period to understand the impact of changes in labelling of these drugs and to definitively evaluate their safety profile.

References

1. CAPORALI R, GERMINARIO S, KACSÁNDI D, CHOY E, SZEKANECZ Z: Start RA treatment - biologics or JAK-inhibitors? *Autoimmun Rev* 2023:103429. https://doi:10.1016/j.autrev.2023.10342
2. DE STEFANO L, BOZZALLA CASSIONE E, BOTTAZZI F *et al*.: Janus kinase inhibitors effectively improve pain across different disease activity states in rheumatoid arthritis. *Intern Emerg Med* 2023; 18: 1733-40. https://doi:10.1007/s11739-023-03350-4
3. JUNG JY, LEE E, KIM JW, SUH CH, KIM HA: Efficacy and drug retention of tofacitinib in rheumatoid arthritis: from the nationwide Korean College of Rheumatology Biologics registry. *Clin Exp Rheumatol* 2023; 41: 1034-41. https://doi:10.55563/clinexprheumatol/6fcyza
4. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 685-99. https://doi:10.1136/annrheumdis-2019-216655
5. YTTERBERG SR, BHATT DL, MIKULS TR *et al*.: Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; 386: 316-26. https://doi:10.1056/nejmoa2109927
6. EMA/142279/2023. EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders. 2023. https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki
7. SMOLEN JS, LANDEWÉ RBM, BERGSTRA SA *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82:3-18. https://doi: 10.1136/ard-2022-223356
8. HECQUET S, COMBIER A, STEELANDT A *et al*.: Characteristics of patients with difficult-to-treat rheumatoid arthritis in a French single-centre hospital. *Rheumatology* (Oxford) 2023; 62: 3866-74. https://doi:10.1093/rheumatology/kead143
9. ALTMAN D: Practical Statistics for Medical Research. First. London: 1991.
10. TANAKA Y, LUO Y, O'SHEA JJ, NAKAYAMADA S: Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022; 18: 133-45. https://doi:10.1038/s41584-021-00726-8
11. SINGH JA: Risks and benefits of Janus kinase inhibitors in rheumatoid arthritis - past, present, and future. *N Engl J Med* 2022; 386: 387-9. https://doi:10.1056/nejme2117663
12. TEMMOKU J, MIYATA M, SUZUKI E *et al*.: Drug retention rates and the safety of Janus kinase inhibitors in elderly patients with rheumatoid arthritis. *J Clin Med* 2023; 12: 4585. https://doi:10.3390/jcm12144585
13. WENG C, XUE L, WANG Q, LU W, XU J, LIU Z: Comparative efficacy and safety of Janus kinase inhibitors and biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and network meta-analysis. *Ther Adv Musculoskelet Dis* 2021; 13. https://doi:10.1177/1759720X21999564
14. AHN SS, HAN M, JUNG I, KIM HW: Cancers and cardiovascular diseases in patients with seropositive rheumatoid arthritis treated with JAK inhibitors, biologics and conventional synthetic DMARDs. *Clin Exp Rheumatol* 2023; 41: 1908-16. https://doi:10.55563/clinexprheumatol/ins2z2
15. FAVALLI EG, CINCINELLI G, GERMINARIO S *et al*.: The impact of EMA recommendations on the real-life use of Janus kinases inhibitors for rheumatoid arthritis: the Expanded Risk Score in RA as a tool to quantify the risk of cardiovascular events. *Front Immunol* 2023; 14: 1225160. https://doi:10.3389/fimmu.2023.1225160
16. JEONG S, GEORGE MD, MIKULS TR *et al*.: Changes in patterns of use of advanced therapies following emerging data about adverse events in patients with rheumatoid arthritis from the Veterans Affairs Health System. *ACR Open Rheumatol* 2023; 5: 563-7. https://doi:10.1002/acr2.11602
17. PAROLI M, BECCIOLINI A, BRAVI E *et al*.: Long-term retention rate of tofacitinib in rheumatoid arthritis: an Italian multicenter retrospective cohort study. *Medicina* 2023; 59: 1480. https://doi:10.3390/medicina59081480
18. BALDI C, BERLENGIERO V, FALSETTI P *et al*.: Baricitinib retention rate: 'real-life' data from a mono-centric cohort of patients affected by rheumatoid arthritis. *Front Med* 2023; 10: 1176613. https://doi:10.3389/fmed.2023.1176613
19. TASSO M, BERTOLINI N, MOSTACCIUOLO E *et al*.: Effectiveness and safety profile of tofacitinib and baricitinib in rheumatoid arthritis patients: results from a 24-month real-life prospective study in Southern-Italy. *Reumatismo* 2022; 74(3). https://doi:10.4081/reumatismo.2022.1511