ISSN 2181-7812
(2010-2025 yillar “Toshkent tibbiyot axborotnomasi” bo’lib chiqgan)

O‘ZBEKISTON TIBBIYOT AXBOROTNOMASI

Medical herald of Uzbekistan Медицинский вестник Узбекистана

ISSN 2181-7812

"ONLY ENGLISH"

YOSH OLIMLAR XALQARO ILMIY-AMALIY ANJUMANIGA BAG'ISHLANGAN

MAXSUS SON

Toshkent shahar,
Farobiy ko‘chasi 2

+998781507825
fax: +998781507828

www.tashmeduni.uz

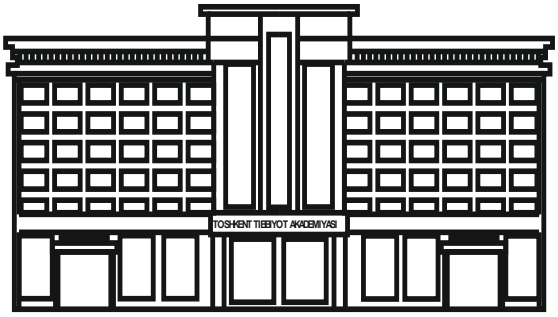
TOSHKENT

O‘ZBEKISTON RESPUBLIKASI SOG‘LIQNI SAQLASH VAZIRLIGI
TOSHKENT DAVLAT TIBBIYOT UNIVERSITETI

2026

*2011 yildan "Toshkent tibbiyot akademiyasi axborotnomasi"
nomi bilan chiqa boshlagan*

O'ZBEKISTON TIBBIYOT AXBOROTNOMASI



МЕДИЦИНСКИЙ ВЕСТНИК УЗБЕКИСТАНА

“ONLY ENGLISH”

YOSH OLIMLAR XALQARO ILMIY-AMALIY

ANJUMANIGA BAG'ISHLANGAN

MAXSUS SON

Toshkent

Выпуск набран и сверстан на компьютерном издательском комплексе

редакционно-издательского отдела Ташкентской медицинской академии

Начальник отдела: М. Н. Аслонов

Редактор русского текста: О.А. Козлова

Редактор узбекского текста: М.Г. Файзиева

Редактор английского текста: А.Х. Жураев

Компьютерная корректура: З.Т. Алюшева

Учредитель: Ташкентская медицинская академия

Издание зарегистрировано в Ташкентском Городском управлении печати и информации
Регистрационное свидетельство 02-00128

Журнал внесен в список, утвержденный приказом № 201/3 от 30 декабря 2013года

реестром ВАК в раздел медицинских наук

Рукописи, оформленные в соответствии с прилагаемыми правилами, просим направлять по адресу: 100109, Ташкент, ул. Фароби, 2, Главный учебный корпус ТМА,

4-й этаж, комната 444.
Контактный телефон: 214 90 64
e-mail: rio-tma@mail.ru
rio@tma.uz

Формат 60x84 1/8. Усл. печ. л. 9,75.

Гарнитура «Cambria».
Тираж 150.
Цена договорная.

Отпечатано на ризографе редакционно-издательского отдела ТМА.
100109, Ташкент, ул. Фароби, 2.

Медицинский вестник Узбекистана 2026

Journal edited and printed in the computer of Tashkent Medical Academy editorial department

Editorial board of Tashkent Medical Academy

Head of the department: M.N. Aslonov

Russian language editor: O.A. Kozlova

Uzbek language editor: M.G. Fayzieva

English language editor: A.X. Juraev

Corrector: Z.T. Alyusheva

Organizer: Tashkent Medical Academy

Publication registered in editorial and information department of Tashkent city

Registered certificate 02-00128

Journal approved and numbered under the order 201/3 from 30 of December 2013 in Medical Sciences department of supreme attestation comission

COMPLITED MANSCIPTS PLEASE SENd following address:

2-Farobiy street, 4 floor room 444. Administration building of TMA. Tashkent. 100109, Toshkent, ul. Farobi, 2, TMA bosh o'quv binosi, 4-qavat, 444-xona.

Contact number:71- 214 90 64

e-mail: rio-tma@mail.ru. rio@tma.uz

Format 60x84 1/8. Usl. printer. l. 9.75.

Listening means «Cambria».

Circulation 150.

Negotiable price

***Printed in TMA** editorial and publisher department risograph*

2 Farobiy street, Tashkent, 100109.

TOFACITINIB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: RESULTS FROM A 104-WEEK PROSPECTIVE COHORT STUDY

Anorboev M, Akhmedov Kh., Khujanazarov I., Mullokulov J.

Tashkent state medical university, Tashkent, Uzbekistan

Background: *Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial inflammation, progressive joint destruction, and disability. Despite biologic DMARDs, many patients remain uncontrolled. Tofacitinib, an oral Janus kinase (JAK) inhibitor, offers an alternative mechanism with convenient oral dosing.* ***Objectives:*** *To assess the long-term efficacy and safety of tofacitinib in patients with RA inadequately controlled by conventional synthetic DMARDs (csDMARDs).* ***Methods:*** *Sixty-five RA patients fulfilling 2010 ACR/EULAR criteria and DAS28-CRP ≥3.2 were enrolled in a single-center, 104-week, prospective cohort. Patients received tofacitinib 5 mg twice daily with background csDMARDs. Primary endpoints were ACR20/50/70 responses. Secondary endpoints included DAS28-CRP, CDAI, HAQ-DI, and patient-reported outcomes. Safety was monitored with exposure-adjusted incidence rates.* ***Results:*** *At 104 weeks, 78% achieved ACR20, 60% ACR50, and 32% ACR70. Mean DAS28-CRP decreased from 5.6 ± 0.9 at baseline to 2.6 ± 0.6 ($p<0.001$). Clinically meaningful improvement (ΔDAS28 ≥1.2) was observed in 86% of patients, and 48% achieved DAS28 remission (<2.6). CDAI improved from 32 ± 8.4 to 8 ± 3.2, with 42% achieving CDAI remission (<2.8). HAQ-DI decreased from 1.4 ± 0.5 to 0.6 ± 0.2 ($p<0.001$). Safety was consistent with prior reports: any treatment-emergent AE occurred at 90/100 patient-years, serious AEs at 14/100, infections at 38/100, herpes zoster at 6/100, venous thromboembolism at 2.5/100, and major adverse cardiovascular events at 2/100 patient-years.* ***Conclusion:*** *Over 104 weeks, tofacitinib produced sustained improvements in disease activity, function, and remission rates, with a manageable safety profile. These findings support tofacitinib as a durable oral option for RA patients with inadequate csDMARD response.*

Introduction: Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory disease that affects approximately 0.5–1% of the global population. It is characterized by persistent synovitis, systemic inflammation, autoantibody production, and progressive joint destruction, ultimately leading to disability, reduced quality of life, and increased mortality. The disease burden extends beyond articular involvement, as RA is associated with comorbidities such as cardiovascular disease, osteoporosis, pulmonary complications, and increased risk of malignancy, contributing to its substantial socioeconomic impact. The therapeutic landscape of RA has evolved significantly over the past three decades. The introduction of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly methotrexate, marked the first major milestone, enabling disease control in many patients. Subsequently, the development of biologic DMARDs (bDMARDs), including TNF inhibitors, IL-6 receptor blockers, anti-CD20 therapy, and CTLA-4Ig, revolutionized RA management, allowing many patients to achieve remission or low disease activity. Despite these advances, a substantial proportion of patients remain inadequately controlled. Studies have shown that 30–40% of patients either fail to respond or lose response over time to bDMARDs, while others encounter challenges related to parenteral administration, immunogenicity, cost, and treatment fatigue. In recent years, targeted synthetic DMARDs (tsDMARDs) have emerged as an innovative therapeutic class designed to overcome some of these limitations. Among them, Janus kinase (JAK) inhibitors have garnered particular interest due to their oral administration and broad immunomodulatory effects. JAKs are intracellular tyrosine kinases that mediate signaling of multiple pro-inflammatory cytokines implicated in RA pathogenesis, including IL-2, IL-4, IL-6, IL-7, IL-15, and interferons. By inhibiting JAK1 and JAK3, tofacitinib interrupts the JAK–STAT signaling cascade, thereby reducing synovial inflammation, autoantibody production, and joint destruction. Tofacitinib was the first JAK inhibitor approved for the treatment of RA and has since demonstrated efficacy and safety across diverse patient populations in multiple phase 3 trials. The ORAL Scan, ORAL Sync, and ORAL Strategy trials confirmed its ability to improve disease activity and inhibit structural damage progression, both as monotherapy and in combination with methotrexate. Furthermore, long-term extension studies and real-world observational data suggest durable efficacy and manageable safety. However, regulatory authorities and clinicians remain cautious due to emerging safety signals, particularly regarding infection risk (notably herpes zoster), venous thromboembolism, and cardiovascular events, as highlighted in the ORAL Surveillance trial. Despite these concerns, tofacitinib continues to represent a valuable option in RA, particularly for patients with inadequate response or intolerance to csDMARDs and bDMARDs. Long-term, real-world prospective data are critical to better define its sustained effectiveness, remission rates, functional outcomes, and safety beyond the confines of randomized controlled trials. The present study reports the results of a 104-week prospective cohort evaluating the efficacy and safety of tofacitinib in RA patients refractory to csDMARDs. By focusing on clinical responses (ACR20/50/70, DAS28-CRP, CDAI), functional outcomes (HAQ-DI), and patient-reported measures, alongside long-term safety, this study contributes valuable insights into the role of tofacitinib as a durable oral therapy in the comprehensive management of RA.

Materials and Methods: This was a 104-week, prospective, single-center, observational cohort study conducted at a tertiary academic rheumatology department to evaluate the long-term efficacy and safety of tofacitinib in patients with active rheumatoid arthritis (RA) who had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Eligible patients were adults fulfilling the 2010 ACR/EULAR classification criteria for RA, with baseline disease activity defined as DAS28-CRP ≥3.2 despite treatment with at least one csDMARD. Patients were required to have been on a stable regimen of csDMARDs and/or corticosteroids for at least four weeks before enrollment, while those with prior JAK inhibitor exposure, active or latent tuberculosis, chronic viral infection, malignancy, or other uncontrolled comorbidities were excluded. All enrolled patients received tofacitinib 5 mg orally twice daily, in addition to stable background therapy with methotrexate, sulfasalazine, hydroxychloroquine, low-dose glucocorticoids (≤10 mg/day prednisone equivalent), or NSAIDs when indicated. Temporary dose interruptions were allowed in the event of adverse events, with

re-initiation at investigator discretion. Patients were assessed at baseline and at weeks 12, 24, 36, 52, 72, and 104 with standardized evaluations that included 28-joint tender and swollen joint counts, patient and physician global assessments, C-reactive protein, and functional questionnaires. Laboratory monitoring consisted of complete blood count, renal and liver function tests, lipid profile, and CRP, performed at every visit. The primary efficacy endpoints were the proportions of patients achieving ACR20, ACR50, and ACR70 responses at weeks 52 and 104. Secondary outcomes included changes in DAS28-CRP, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), remission and low disease activity rates defined by DAS28-CRP <2.6 and CDAI <2.8 or ≤10, improvement in Health Assessment Questionnaire Disability Index (HAQ-DI), and patient-reported outcomes measured by Short Form-36 (SF-36). Safety assessments comprised treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), infections, herpes zoster, venous thromboembolism (VTE), major adverse cardiovascular events (MACE), malignancies, and laboratory abnormalities, with all events coded according to MedDRA and reported as exposure-adjusted incidence rates per 100 patient-years. Analyses were conducted in the intention-to-treat population. Categorical outcomes were expressed as percentages with 95% confidence intervals, and continuous variables were reported as mean ± standard deviation or standard error. Comparisons between baseline and follow-up were performed using paired t-tests, and missing efficacy data were imputed using non-responder imputation. Statistical analyses were carried out with SPSS version 26.0, and a two-sided p value <0.05 was considered significant. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision) and Good Clinical Practice, with approval from the Institutional Ethics Committee, and all patients provided written informed consent prior to enrollment.

Results: A total of 65 patients were enrolled, of whom 72% were female, with a mean age of 47 ± 10 years and a mean disease duration of 8.1 ± 4.5 years. At baseline, the mean DAS28-CRP was 5.6 ± 0.9, mean CDAI was 32 ± 8.4, and mean HAQ-DI was 1.4 ± 0.5. Seventy-five percent of patients had failed at least two csDMARDs, and 28% had prior exposure to biologic therapy. Treatment with tofacitinib resulted in rapid and sustained clinical improvements. By week 52, ACR20, ACR50, and ACR70 response rates were 74%, 56%, and 28%, respectively, and these continued to increase modestly through week 104, reaching 78%, 60%, and 32%. Disease activity indices showed significant and durable reductions, with mean DAS28-CRP declining from 5.6 at baseline to 2.8 at week 52 and further to 2.6 at week 104 (p<0.001 for all comparisons vs baseline). Clinically meaningful improvement defined as ΔDAS28 ≥1.2 was observed in 81% of patients at week 52 and 86% at week 104, and remission defined as DAS28-CRP <2.6 was achieved in 42% and 48% of patients at these time points. Consistent findings were seen with CDAI, which declined from 32 at baseline to 9 at week 52 and 8 at week 104, corresponding to remission in 36% and 42% of patients and low disease activity (CDAI ≤10) in 64% and 68%, respectively. Functional status improved significantly, as HAQ-DI scores decreased from 1.4 at baseline to 0.7 at week 52 and 0.6 at week 104 (p<0.001), with 72% of patients achieving a clinically meaningful improvement of at least 0.22 points. Patient-reported outcomes reflected parallel improvements, with SF-36 physical component scores increasing by +13.2 points at week 52 and +15.4 points at week 104. Safety outcomes over 104 weeks were consistent with the established safety profile of tofacitinib. The exposure-adjusted incidence of any treatment-emergent adverse event was 90 per 100 patient-years, and that of serious adverse events was 14 per 100 patient-years. Infections occurred at a rate of 38 per 100 patient-years, with herpes zoster reported in 6 per 100 patient-years; all cases were non-disseminated and resolved with antiviral therapy. Venous thromboembolism occurred at a rate of 2.5 per 100 patient-years, and major adverse cardiovascular events were observed at a rate of 2 per 100 patient-years. Lipid elevations were reported in 14 per 100 patient-years, and mild reversible elevations of liver enzymes were noted in 6% of patients. No malignancies or deaths were recorded during the study period.

Overall, tofacitinib provided sustained clinical benefit over two years, with continuous improvement in disease activity, remission rates, physical function, and patient-reported outcomes, while maintaining a manageable safety profile in line with previous randomized controlled trials and extension studies.

Table 1.

Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Value
Number of patients	65
Mean age, years (±SD)	47 ± 10
Female, %	72%
Mean disease duration, years (±SD)	8.1 ± 4.5
RF positive, %	78%
ACPA positive, %	74%
Baseline DAS28-CRP (±SD)	5.6 ± 0.9
Baseline CDAI (±SD)	32 ± 8.4
Baseline HAQ-DI (±SD)	1.4 ± 0.5
Prior ≥2 csDMARD failures, %	75%
Prior biologic exposure, %	28%

Discussion: In this 104-week prospective cohort, treatment with tofacitinib demonstrated rapid, sustained, and clinically meaningful improvements in disease activity, physical function, and remission rates in patients with rheumatoid arthritis who had an inadequate response to csDMARDs, with a manageable safety profile consistent with previous trials. ACR20, ACR50, and ACR70 responses were achieved by 78%, 60%, and 32% of patients, respectively, at two years, while mean DAS28-CRP decreased from 5.6 to 2.6, and nearly half of the patients achieved DAS28-CRP remission. Improvements in CDAI and HAQ-DI paralleled these findings, confirming durable disease control and functional restoration.

Table 2.

Efficacy Outcomes with Tofacitinib at Baseline, Week 52, and Week 104

Outcome	Baseline	Week 52	Week 104
ACR20 response, %	-	74%	78%
ACR50 response, %	-	56%	60%
ACR70 response, %	-	28%	32%
DAS28-CRP, mean (±SD)	5.6 ± 0.9	2.8 ± 0.6	2.6 ± 0.6
DAS28-CRP remission (<2.6), %	-	42%	48%
CDAI, mean (±SD)	32 ± 8.4	9 ± 3.6	8 ± 3.2
CDAI remission (<2.8), %	-	36%	42%
HAQ-DI, mean (±SD)	1.4 ± 0.5	0.7 ± 0.3	0.6 ± 0.2
HAQ-DI improvement ≥0.22, %	-	68%	72%

Table 3.

Exposure-Adjusted Incidence Rates of Adverse Events During 104 Weeks of Tofacitinib Treatment

Adverse Event	Incidence (per 100 pt-yrs)
Any TEAE	90
Serious AE	14
Infections	38
Herpes Zoster	6
Venous thromboembolism (VTE)	2.5
Major adverse cardiovascular events (MACE)	2
Lipid elevations	14

Our results align with pivotal randomized controlled trials of tofacitinib, including ORAL Scan, ORAL Sync, and ORAL Strategy, which demonstrated significant efficacy across diverse patient populations, and are also consistent with long-term extension studies reporting sustained improvements beyond three years of follow-up. Importantly, the trajectory of CDAI and DAS28-CRP in our cohort closely mirrors findings from these trials, reinforcing the reproducibility of tofacitinib's disease-modifying effects in real-world practice. Compared with biologic DMARDs, such as TNF inhibitors or IL-6 receptor blockers, the magnitude and durability of clinical responses observed here suggest that oral JAK inhibition can achieve equivalent long-term efficacy while offering the convenience of oral administration.

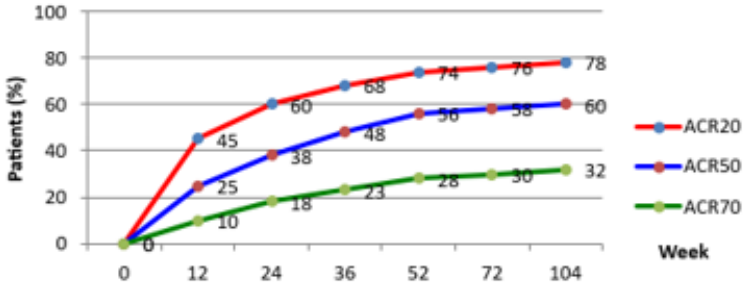


Figure 1. ACR20/50/70 Responses Over 104 Weeks. Proportion of patients achieving ACR20, ACR50, and ACR70 responses increased progressively throughout the study. By Week 12, 45%, 25%, and 10% of patients reached ACR20, ACR50, and ACR70, respectively. Rates continued to rise, reaching 74%, 56%, and 28% at Week 52, and 78%, 60%, and 32% at Week 104, indicating rapid onset, steady improvement, and sustained clinical efficacy with tofacitinib.

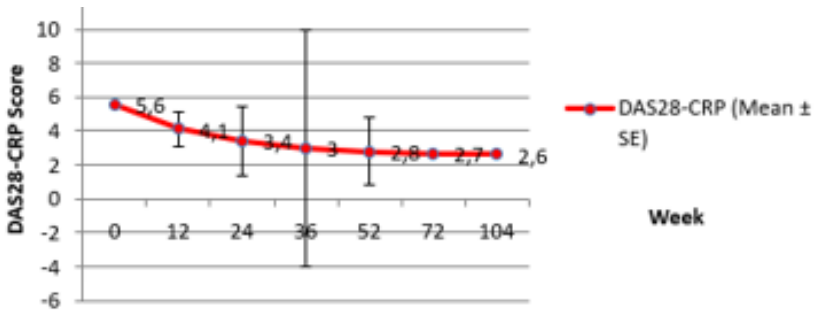


Figure 2. DAS28-CRP Trajectory Over 104 Weeks. Mean DAS28-CRP values declined rapidly from 5.6 at baseline to 4.1 at Week 12 and 3.4 at Week 24, reaching 2.8 at Week 52 and further improving to 2.6 at Week 104. Error bars represent standard error of the mean. These results demonstrate a sustained and progressive reduction in disease activity with tofacitinib, with nearly half of patients achieving DAS28-CRP remission (<2.6) by Week 104.

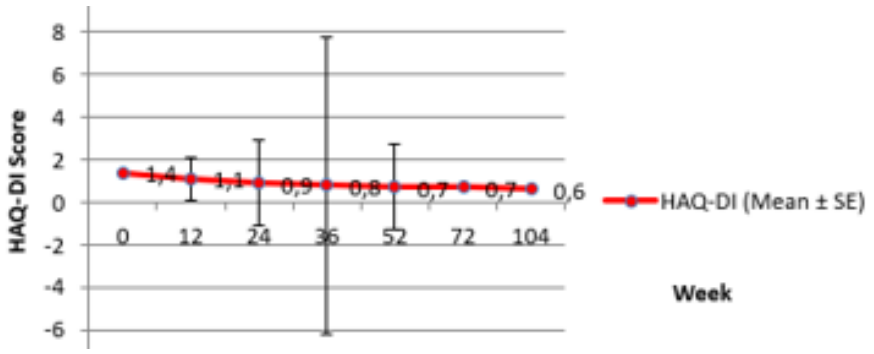


Figure 3. ***HAQ-DI Trajectory Over 104 Weeks. Mean HAQ-DI score improved steadily from 1.4 at baseline to 1.1 at Week 12, 0.9 at Week 24, 0.7 at Week 52, and 0.6 at Week 104. Error bars represent standard error of the mean. These findings indicate significant and durable improvements in physical function, with more than 70% of patients achieving a clinically meaningful reduction (≥0.22) by Week 104.***

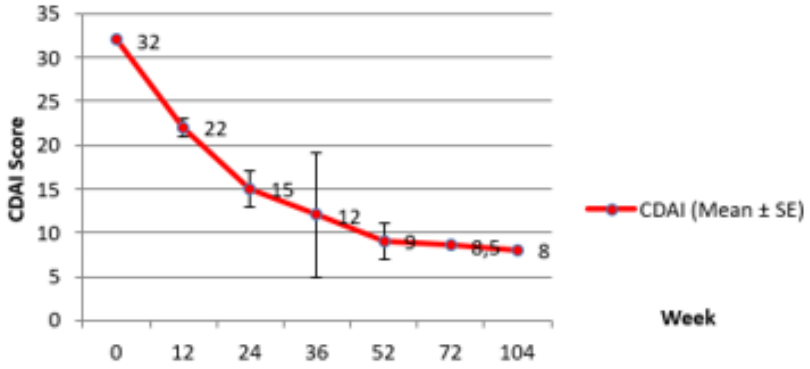


Figure 4. ***CDAI Trajectory Over 104 Weeks. Mean CDAI score decreased markedly from 32 at baseline to 22 at Week 12, 15 at Week 24, 12 at Week 36, and 9 at Week 52, with further stabilization at 8.5 at Week 72 and 8 at Week 104. Error bars represent standard error of the mean. These results demonstrate sustained and clinically meaningful reductions in disease activity, with remission (CDAI <2.8) achieved in 42% of patients and low disease activity (CDAI ≤10) in 68% by Week 104.***

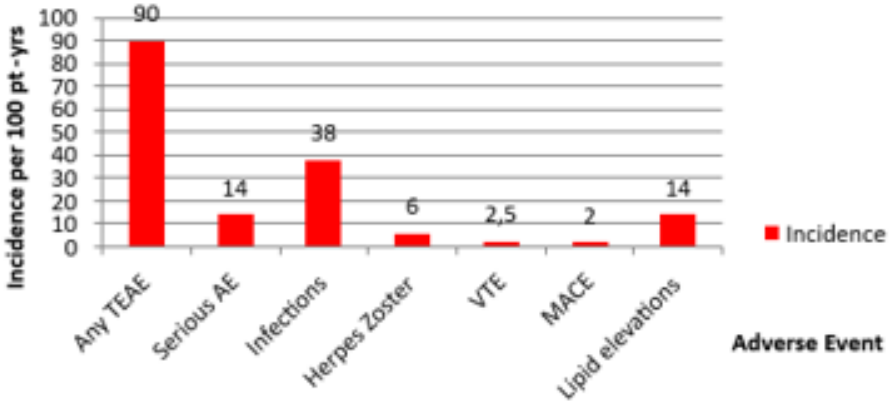


Figure 5. Safety Outcomes Over 104 Weeks. Exposure-adjusted incidence rates of adverse events observed during tofacitinib treatment. The incidence of any treatment-emergent adverse event (TEAE) was 90 per 100 patient-years, with serious adverse events occurring at 14 per 100 patient-years. Infections were reported at a rate of 38 per 100 patient-years, including herpes zoster at 6 per 100 patient-years. Venous thromboembolism (VTE) and major adverse cardiovascular events (MACE) occurred at rates of 2.5 and 2 per 100 patient-years, respectively. Lipid elevations were observed at 14 per 100 patient-years. These findings are consistent with the known long-term safety profile of tofacitinib.

Functional outcomes are of particular relevance in RA, as they directly impact quality of life and work productivity. In our cohort, HAQ-DI scores improved from 1.4 to 0.6, with more than 70% of patients achieving clinically meaningful functional gains. These improvements are comparable to those seen in long-term biologic cohorts and support the hypothesis that sustained suppression of inflammation with JAK inhibition translates into durable functional benefits. The safety profile observed over 104 weeks was consistent with previous tofacitinib studies. The incidence of serious adverse events was 14 per 100 patient-years, and infections were the most frequent adverse events, with herpes zoster occurring at a rate of 6 per 100 patient-years, in line with pri-

or Asian and global studies. VTE and MACE rates were low but underscore the need for careful risk stratification, particularly in older patients with cardiovascular risk factors. Notably, no malignancies or deaths were observed in this cohort, which is reassuring, although larger and longer-term registries remain necessary to fully evaluate the malignancy risk associated with JAK inhibition. The lipid elevations observed were modest and manageable, consistent with known JAK inhibitor pharmacodynamics. The findings of this study contribute to the ongoing debate regarding the optimal positioning of JAK inhibitors in the RA treatment algorithm. While regulatory agencies have recommended caution in high-risk populations, the sustained efficacy and manageable safety observed in our study reinforce the value of tofacitinib as a viable option for patients refractory to csDMARDs, and potentially as an alternative to biologic DMARDs in appropriate patients. Furthermore, the oral route of administration addresses issues of treatment burden and adherence that are often encountered with parenteral biologics.Limitations of this study include the single-center design, modest sample size, and lack of a comparator arm, which restrict the generalizability and preclude definitive head-to-head comparisons with biologic agents. Nevertheless, the prospective design, systematic follow-up, and consistency with larger clinical trial data strengthen the validity of our findings. In conclusion, this 104-week prospective cohort confirms that tofacitinib provides sustained and clinically meaningful improvements in disease activity, remission, and physical function in RA patients with prior csDMARD failure. The safety profile remained consistent with prior evidence and manageable over long-term follow-up. Together, these results support the role of tofacitinib as a durable oral therapeutic option in the comprehensive management of RA, while highlighting the importance of individualized patient selection and ongoing pharmacovigilance.

References:

1. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Soma K, Bradley J, Mebus C; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381(9865):451–460.
2. Burmester GR, Kremer JM, Van den Bosch F, Kivitz AJ, Bessette L, Li Y, Zhou Y, Zwillich SH, Fleischmann R. Safety and efficacy of up to 9.5 years of tofacitinib treatment in patients with rheumatoid arthritis: final results of a global open-label, long-term extension study. *Lancet Rheumatol*. 2021;3(5):e347–e357.
3. Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, Boy M, Zuckerman A, Soma K, Kwok K, Benda B. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. *Arthritis Rheumatol*. 2016;68(5):1045–1055.
4. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, Winthrop KL. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open*. 2020;6(3):e001395.
5. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, Wallenstein GV, Zwillich SH, Kanik KS. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):495–507.
6. Gladman DD, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, Kudlacz E, Wang C, Menon S, Hendrikx T, Pangan AL, Mease PJ. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors: a randomized phase 3 trial. *Lancet*. 2017;391(10125):227–239.
7. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, Krishnaswami S, Burgos-Vargas R, Wilkinson B, Zerbini CA, Zwillich SH. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of tofacitinib. *Arthritis Rheum*. 2009;60(7):1895–1905.
8. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, Gruben D, Kanik KS, Krishnaswami S, Pascual-Ramos V, Wallenstein GV, Zwillich SH, Fleischmann R. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study of tofacitinib monotherapy in patients with active rheumatoid arthritis. *Arthritis Rheum*. 2012;64(10):3255–3265.
9. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, Koncz T, Krishnaswami S, Wallenstein GV, Zang C, Zwillich SH, van Vollenhoven RF; ORAL Start investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370(25):2377–2386.
10. Mease PJ, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, Curtis JR. Incidence of venous thromboembolism and cardiovascular events in patients with rheumatoid arthritis receiving tofacitinib: analysis from the US Corrona registry. *Ann Rheum Dis*. 2020;79(9):1184–1191.
11. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, McInnes IB, Sepriano A, van Vollenhoven RF, De Wit M, Aletaha D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685–699.
12. Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney TP, Chen L, Dickson CL, Camp HS, Cardillo TE, Wu J, Manoukian R, Hsia EC, Riese RJ. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 years: an updated integrated safety analysis. *Lancet Rheumatol*. 2022;4(5):e348–e357.
13. Strand V, Kremer J, Wallenstein G, Kanik KS, Connell C, Gruben D, Zwillich SH, Krishnaswami S, Wilkinson B. Tofacitinib in combination with conventional disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: patient-reported outcomes from a phase III randomized controlled trial. *Arthritis Care Res*. 2015;67(4):475–483.
14. van der Heijde D, Tanaka Y, Fleischmann R, Keystone EC, Kremer J, Zerbini C, Cardillo T, Chen L, Gruben D, Mebus C, Pangan AL, Wallenstein G, Smolen JS. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum*. 2013;65(3):559–570.
15. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, Germino R, Menon S, Sun Y, Wang C, Wisniewski LM, Bradley JD, Connell C, Kanik KS, Johnsen A, Gruben D, de Bono S, Pangan AL, Winthrop KL. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386(4):316–326.

СОДЕРЖАНИЕ

I. SECTION - THERAPY