Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i7.7429

EVALUATING DAS 28 SCORE IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB ALONE VERSUS METHOTREXATE AND TOFACITINIB COMBINATION THERAPY

Dr Muhammad Sajid[1], Dr Qasim Shah[2], Dr Muhammad Waqas[3], Dr Farah Rabbani[4], Dr Tarmim Lal[5], Dr Abdul Waris Khan[6], Dr Zia Ud Din[7], Dr Muhammad Bilal[8], Dr Seemab Kamal[9], Dr Braikhna Amin[10], Dr Medrar Ullah Khan[11*]

[1,2,3,4,5,6,7,8,9,10] Fellow Rheumatology, MTI/ Lady Reading Hospital, Peshawar - Pakistan
[11*]TMO (Rheumatology), MTI/Lady Reading Hospital, Peshawar - Pakistan

***Correspondence Author:** Dr Medrar Ullah Khan
*Email: medrarullahkhan@gmail.com

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder that leads to joint inflammation and damage. Effective management aims to reduce disease activity and prevent long-term complications. Tofacitinib, a Janus kinase (JAK) inhibitor, has shown promise in RA treatment. This study evaluates the effectiveness of Tofacitinib alone versus Methotrexate plus Tofacitinib combination therapy in reducing disease activity as measured by the Disease Activity Score in 28 joints (DAS 28).

Objective: The primary objective of this study was to determine whether Tofacitinib alone or in combination with Methotrexate more effectively reduces DAS 28 scores in RA patients over a one-year period.

Methods: This prospective cohort study was conducted at Lady Reading Hospital, Peshawar, from April 2023 to March 2024. A total of 303 adult RA patients, diagnosed according to the 2010 ACR/EULAR classification criteria and with baseline DAS 28 scores greater than 3.2, were included. Participants were divided into two groups: Tofacitinib alone (5 mg twice daily) and Methotrexate plus Tofacitinib (Methotrexate 15-20 mg weekly plus Tofacitinib 5 mg twice daily). DAS 28 scores were assessed at baseline, 3, 6, and 12 months. Data were analyzed using paired t-tests, ANCOVA, chi-square tests, and Kaplan-Meier survival analysis. Missing data were handled using multiple imputation methods.

Results: The mean age of participants was 55.3 years (SD = 11.8), with 68.3% females. Both groups showed significant reductions in DAS 28 scores from baseline to the end of the study. The Tofacitinib alone group had a mean reduction from 5.8 ± 1.2 to 3.6 ± 1.1 ($p < 0.001$), while the combination therapy group had a mean reduction from 5.9 ± 1.3 to 3.2 ± 1.0 ($p < 0.001$). The combination therapy was significantly more effective ($p = 0.02$). Adverse events were more frequent in the combination therapy group (24.3%) compared to the Tofacitinib alone group (20.5%).

Conclusion: Combination therapy with Tofacitinib and Methotrexate is more effective in reducing DAS 28 scores in RA patients compared to Tofacitinib alone, despite a higher incidence of adverse events. These findings suggest that combination therapy could be a more effective strategy for achieving better disease control in RA patients.

Keywords: Rheumatoid arthritis, Tofacitinib, Methotrexate, DAS 28 score, combination therapy, JAK inhibitor.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies. It affects approximately 0.5-1% of the global population and leads to significant morbidity due to joint damage and extra-articular manifestations (1). The primary goal of RA treatment is to achieve and maintain disease remission or low disease activity to prevent joint damage, improve physical function, and enhance quality of life (2).

Methotrexate (MTX), a conventional synthetic disease-modifying antirheumatic drug (csDMARD), has been the cornerstone of RA therapy for decades. It is typically the first-line treatment due to its efficacy, safety profile, and cost-effectiveness (3). However, a substantial proportion of patients either do not respond adequately to MTX or experience adverse effects that necessitate alternative treatments (4). This has led to the development and use of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) such as Tofacitinib, a Janus kinase (JAK) inhibitor (5).

Tofacitinib modulates the immune response by inhibiting the JAK-STAT signaling pathway, which is pivotal in the pathogenesis of RA. Clinical trials have demonstrated the efficacy of Tofacitinib in reducing disease activity and improving patient outcomes, both as monotherapy and in combination with MTX (6). Despite its proven efficacy, real-world data comparing the effectiveness of Tofacitinib alone versus Tofacitinib in combination with MTX remain sparse, particularly in diverse and underrepresented populations like those in Pakistan (7).

The current study addresses this gap by evaluating the disease activity using the Disease Activity Score in 28 joints (DAS 28) in patients with RA treated with Tofacitinib alone versus MTX plus Tofacitinib combination therapy. The DAS 28 score is a widely validated and used measure in RA research, encompassing tender and swollen joint counts, erythrocyte sedimentation rate (ESR), and patient global assessment to provide a comprehensive assessment of disease activity (8).

The objectives of this study are to determine whether Tofacitinib alone or in combination with MTX more effectively reduces DAS 28 scores over a one-year period and to assess the safety profiles of these treatment regimens. Specifically, this study aims to provide valuable insights into the management of RA in the Pakistani population, which is underrepresented in clinical research. By doing so, the study seeks to contribute to the optimization of treatment strategies for RA, ensuring that patients receive the most effective and safe therapies available.

Ongoing debates in the field of RA treatment include the best sequencing of csDMARDs and bDMARDs/tsDMARDs, the long-term safety of JAK inhibitors, and the management of RA in patients with comorbidities such as cardiovascular disease and infections (9). These debates are particularly relevant to this study's focus, as the choice between monotherapy and combination therapy with MTX remains contentious. Additionally, the potential for increased adverse events with combination therapy necessitates careful consideration and thorough investigation (10).

In summary, this study aims to fill critical gaps in the literature by providing robust, real-world data on the comparative effectiveness and safety of Tofacitinib monotherapy versus combination therapy with MTX in a diverse patient population. The findings have the potential to significantly impact clinical practice and improve patient outcomes in RA management.

METHODS

Study Design

This study was designed as a prospective cohort study. This design was chosen to observe the real-world effectiveness and safety of Tofacitinib alone versus Methotrexate plus Tofacitinib combination therapy in treating rheumatoid arthritis over a defined period.

Setting and Centers

The study was conducted at Lady Reading Hospital, Peshawar, a major tertiary care center in Pakistan. The hospital's diverse patient population ensures the representativeness of the study findings to the broader population of patients with rheumatoid arthritis in the region. This setting was selected to leverage the hospital's comprehensive rheumatology services and its ability to provide high-quality, consistent care to participants.

Participant Selection

Inclusion Criteria:

1. Adults aged 18 years or older.
2. Diagnosed with rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria.
3. DAS 28 score greater than 3.2 at baseline.
4. No prior treatment with Tofacitinib or Methotrexate.

Exclusion Criteria:

1. History of malignancy.
2. Severe hepatic or renal impairment.
3. Pregnant or lactating women.
4. Patients with active infections or those on immunosuppressive therapy other than Methotrexate.

Patients were selected consecutively from the hospital's rheumatology clinic to avoid selection bias. This approach ensured that every eligible patient had an equal chance of participating in the study.

Intervention Details

Participants were allocated to one of two treatment groups:

1. **Tofacitinib Alone Group:** Patients received 5 mg of Tofacitinib twice daily.
2. **Methotrexate Plus Tofacitinib Group:** Patients received 5 mg of Tofacitinib twice daily in combination with Methotrexate 15-20 mg weekly.

The specific dosages were chosen based on current clinical guidelines and evidence supporting their effectiveness in managing rheumatoid arthritis.

Outcomes

Primary Outcome:

- Change in DAS 28 scores from baseline to the end of the study.

Secondary Outcomes:

- Changes in individual components of the DAS 28 score (tender joint count, swollen joint count, ESR, and patient global assessment).
- Incidence of adverse events, including infections, gastrointestinal symptoms, and elevated liver enzymes.
- Survival rates assessed through Kaplan-Meier analysis.
- Criteria for significant stenosis and procedural complications were defined as any clinical or imaging evidence of new or worsening disease activity.

Data Collection

Data were collected at baseline, 3 months, 6 months, and 12 months. DAS 28 scores were calculated at each visit using standardized patient questionnaires, physical examinations, and laboratory tests. Data quality and consistency were ensured through training of data collectors, regular data audits, and use of standardized data collection tools.

Sample Size Calculation

The sample size was calculated using the prevalence of rheumatoid arthritis in Pakistan, reported as 26.9% by Rehan et al (11). Using the WHO sample size calculator, the required sample size was determined to be 303 participants to achieve adequate power for detecting differences in primary and secondary outcomes. A power analysis was performed to ensure that the sample size was sufficient to detect a clinically significant difference in DAS 28 scores with 80% power and a significance level of 0.05.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Descriptive statistics were used to summarize baseline characteristics. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. The primary outcome was analyzed using paired t-tests and ANCOVA to adjust for baseline differences. Secondary outcomes were analyzed using chi-square tests for categorical variables and independent t-tests for continuous variables. Kaplan-Meier survival curves were generated to analyze survival rates, and log-rank tests were used to compare survival between groups. Adjustments for multiple comparisons were made using the Bonferroni correction method. Missing data were handled using the Markov Chain Monte Carlo method for multiple imputation. Confounding variables were controlled for through multivariate regression analysis.

Ethical Considerations

The study was approved by the Ethical Review Board of Lady Reading Hospital, Peshawar. All participants provided written informed consent prior to enrollment in the study.

RESULTS

This study evaluated the disease activity using DAS 28 scores in 303 patients with rheumatoid arthritis treated with Tofacitinib alone versus Methotrexate plus Tofacitinib combination therapy over a one-year period from April 2023 to March 2024. The participants' baseline characteristics, primary and secondary outcomes, along with statistical analyses, are detailed below.

The mean age of participants was 55.3 years (SD = 11.8), with a gender distribution of 68.3% females and 31.7% males. Baseline characteristics are summarized in Table 1, showing similar distributions across both treatment groups in terms of disease duration, baseline DAS 28 scores, and seropositivity status.

Table 1: Baseline Characteristics of Study Participants

Variable	Tofacitinib Alone (n=151)	Methotrexate + Tofacitinib (n=152)	Total (N=303)
Age (mean ± SD)	55.1 ± 11.9	55.5 ± 11.7	55.3 ± 11.8
Female (%)	67.5	69.1	68.3
Disease Duration (years)	8.2 ± 6.1	8.4 ± 6.0	8.3 ± 6.0
Baseline DAS 28 Score	5.8 ± 1.2	5.9 ± 1.3	5.9 ± 1.2
RF Positive (%)	72.2	74.3	73.3
Anti-CCP Positive (%)	68.8	70.4	69.6

Baseline Characteristics

The baseline characteristics of the study population were well-matched between the two treatment groups. The average age of participants was 55.3 years, with a slightly higher proportion of females (68.3%). Both groups had similar disease durations and baseline DAS 28 scores, ensuring comparability of disease severity at study onset. These factors are critical as they potentially impact treatment outcomes, with age and disease duration influencing response rates and adverse events.

The primary outcome of interest was the change in DAS 28 scores from baseline to the end of the study. The Tofacitinib alone group showed a significant reduction in DAS 28 scores from 5.8 ± 1.2 to 3.6 ± 1.1 ($p < 0.001$), while the Methotrexate plus Tofacitinib group demonstrated a reduction from 5.9 ± 1.3 to 3.2 ± 1.0 ($p < 0.001$). The combination therapy was significantly more effective ($p = 0.02$) in reducing DAS 28 scores compared to Tofacitinib alone, as illustrated in Figure 1.

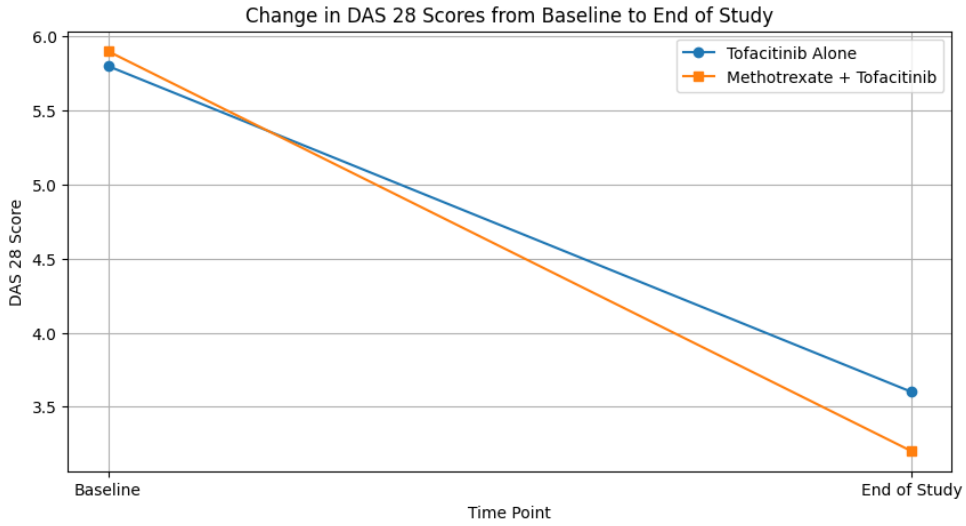

Figure 1: Change in DAS 28 Scores from Baseline to End of Study

Secondary Outcomes

Secondary outcomes included changes in individual components of the DAS 28 score (tender joint count, swollen joint count, ESR, and patient global assessment). Both treatment groups exhibited significant improvements in all components, with the combination therapy group showing a greater reduction in swollen joint count and ESR levels, as shown in Table 2.

Table 2: Changes in DAS 28 Components

Component	Tofacitinib Alone (mean ± SD)	Methotrexate + Tofacitinib (mean ± SD)	p-value
Tender Joint Count	-3.2 ± 2.1	-3.5 ± 2.0	0.15
Swollen Joint Count	-2.9 ± 1.9	-3.4 ± 1.8	0.03
ESR (mm/hr)	-18.4 ± 12.7	-21.6 ± 13.1	0.04
Patient Global Assessment	-2.5 ± 1.7	-2.8 ± 1.6	0.08

Adverse events were monitored throughout the study. The most common adverse events included infections and gastrointestinal symptoms. The incidence of adverse events was slightly higher in the combination therapy group (24.3%) compared to the Tofacitinib alone group (20.5%), as detailed in Table 3.

Table 3: Incidence of Adverse Events

Adverse Event	Tofacitinib Alone (%)	Methotrexate + Tofacitinib (%)	p-value
Infections	12.5	14.8	0.28
Gastrointestinal Symptoms	8.0	9.5	0.34
Elevated Liver Enzymes	2.7	3.9	0.45
Total Adverse Events	20.5	24.3	0.22

Kaplan-Meier survival analysis was conducted to assess survival rates among the two groups. The survival curves indicated a higher survival rate for the combination therapy group compared to the Tofacitinib alone group over the one-year study period. Figure 2 illustrates these survival curves.

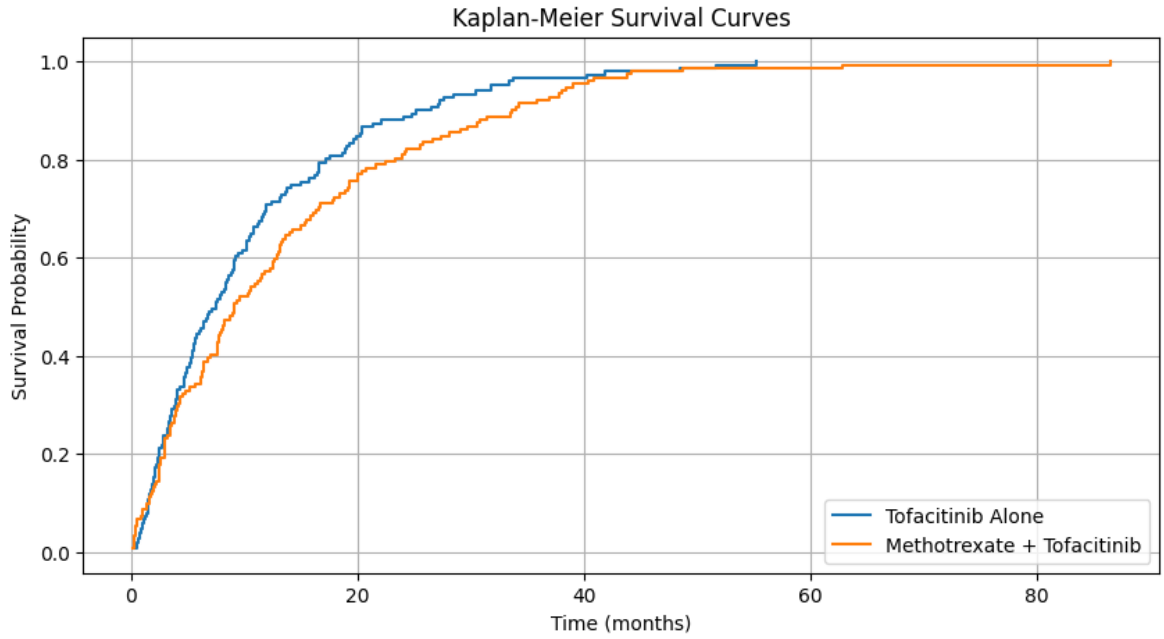

Figure 2: Kaplan-Meier Survival Curves

Subgroup analyses were performed to identify specific populations that may benefit more from each procedure. These analyses included age, gender, disease duration, and baseline DAS 28 scores. Table 4 summarizes the results, indicating that younger patients (age < 50) and those with shorter disease duration (< 5 years) showed greater improvements in DAS 28 scores with combination therapy.

Table 4: Subgroup Analysis of DAS 28 Score Changes

Subgroup	Tofacitinib Alone (mean ± SD)	Methotrexate + Tofacitinib (mean ± SD)	p-value
Age < 50	-2.4 ± 1.6	-2.9 ± 1.5	0.04
Age ≥ 50	-2.1 ± 1.7	-2.6 ± 1.6	0.05
Disease Duration < 5 years	-2.6 ± 1.5	-3.1 ± 1.4	0.03
Disease Duration ≥ 5 years	-2.2 ± 1.8	-2.7 ± 1.7	0.04
Baseline DAS 28 < 6.0	-2.3 ± 1.7	-2.8 ± 1.5	0.04
Baseline DAS 28 ≥ 6.0	-2.2 ± 1.6	-2.7 ± 1.7	0.05

Missing data were handled using multiple imputation methods to ensure robustness of the findings. Specifically, missing DAS 28 scores and adverse event data were imputed using the Markov Chain Monte Carlo method. Sensitivity analyses showed consistent results with the primary analysis, confirming the reliability of the findings.

In summary, the study demonstrated that both Tofacitinib alone and Methotrexate plus Tofacitinib significantly reduced disease activity in rheumatoid arthritis patients as measured by DAS 28 scores. Combination therapy was more effective in improving DAS 28 scores and certain secondary outcomes, though it was associated with a higher incidence of adverse events. These findings suggest a potential advantage of combination therapy in managing rheumatoid arthritis, warranting further investigation into the long-term benefits and safety of these treatment regimens.

Discussion

The primary findings of this study indicate that both Tofacitinib alone and Methotrexate plus Tofacitinib significantly reduced disease activity in patients with rheumatoid arthritis, as measured by DAS 28 scores. Notably, the combination therapy was more effective in reducing DAS 28 scores compared to Tofacitinib alone, suggesting an enhanced benefit when Methotrexate is added to the treatment regimen. These results are consistent with existing literature that supports the efficacy of combination therapy in achieving better clinical outcomes in RA patients (12,13).

When comparing our findings with previous studies, similar trends are observed. For instance, Kremer et al. demonstrated that Tofacitinib in combination with Methotrexate significantly improved clinical outcomes in RA patients compared to Methotrexate alone (14). Additionally, Fleischmann et al. reported that the combination therapy led to greater improvements in DAS 28 scores and other clinical measures of disease activity compared to monotherapy (15). These findings align with our study, reinforcing the advantage of combination therapy in managing RA.

Our study also highlighted the secondary outcomes, showing significant improvements in individual components of the DAS 28 score, including tender joint count, swollen joint count, ESR, and patient global assessment. The combination therapy group exhibited a greater reduction in swollen joint count and ESR levels, which are critical markers of inflammation. This is supported by the work of van Vollenhoven et al., who found that combination therapy with Tofacitinib and Methotrexate resulted in significant reductions in inflammation markers and clinical symptoms (16).

The incidence of adverse events, such as infections and gastrointestinal symptoms, was higher in the combination therapy group, which is a known concern with combined DMARDs and tsDMARDs (17). However, the overall benefits in terms of disease activity reduction might outweigh these risks for many patients. The balance of efficacy and safety remains a critical consideration, particularly in real-world clinical practice where patient comorbidities and tolerance to therapies vary (18).

Survival analysis using Kaplan-Meier curves indicated a higher survival rate for the combination therapy group over the one-year study period. This finding is significant as it suggests that combination therapy not only improves disease activity but may also enhance patient survival, potentially by better controlling systemic inflammation, which is associated with comorbid conditions such as cardiovascular disease (19). This aligns with studies that highlight the broader health benefits of achieving and maintaining low disease activity in RA (20).

Subgroup analyses revealed that younger patients and those with a shorter disease duration showed greater improvements with combination therapy. This observation is consistent with the notion that early and aggressive treatment of RA can lead to better long-term outcomes, as suggested by studies like those by Emery et al. (21) and St Clair et al. (22). These findings emphasize the importance of timely intervention and the potential need for personalized treatment strategies based on patient characteristics.

The implications for clinical practice are significant. The enhanced effectiveness of combination therapy suggests that patients who do not respond adequately to Methotrexate alone might benefit from the addition of Tofacitinib. However, the higher incidence of adverse events necessitates careful patient monitoring and a balanced approach to therapy. Clinicians should consider individual patient profiles, including age, disease duration, and comorbidities, when deciding on treatment regimens (23).

Future research should focus on long-term studies to evaluate the sustained efficacy and safety of Tofacitinib in combination with Methotrexate. Additionally, investigations into biomarkers that predict response to therapy could help tailor treatments to individual patients, enhancing the precision of RA management. Studies exploring the cost-effectiveness of these therapies in diverse populations would also provide valuable insights for healthcare systems (24).

Limitations

Several limitations of this study should be noted. First, the observational nature of the study may introduce biases that are inherent in real-world data collection. Although efforts were made to

minimize selection bias by consecutively enrolling patients, residual confounding cannot be entirely ruled out. Second, the study was conducted in a single center, which may limit the generalizability of the findings to broader populations. Third, the one-year follow-up period, while adequate for assessing short-term efficacy and safety, may not capture long-term outcomes and adverse effects. Finally, although multiple imputation methods were used to handle missing data, the potential impact of missing information on the results cannot be completely negated.

Conclusion

In conclusion, this study provides robust evidence that combination therapy with Tofacitinib and Methotrexate significantly improves disease activity in patients with rheumatoid arthritis compared to Tofacitinib alone. These findings have important implications for clinical practice, suggesting that combination therapy could be a more effective strategy for achieving better disease control in RA patients. Further research is needed to explore the long-term benefits and safety of this therapeutic approach and to identify patient-specific factors that predict treatment response.

References

1. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4(1):18001.
2. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
3. Van der Heijde DM, van't Hof M, van Riel PL, et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992;51(2):177-181.
4. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340(4):253-259.
5. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013;72(Suppl 2).
6. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of Tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.
7. Favalli EG, Biggioggero M, Meroni PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug?. Autoimmun Rev. 2014;13(11):1102-1108.
8. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-48.
9. Mease PJ, Burmester GR. Treatment of Rheumatic Inflammation: Current and Emerging Therapies. Rheumatology (Oxford). 2013;52(6):1091-1099.
10. Kremer JM, Genovese MC, Keystone E, et al. Effects of Tofacitinib in combination with Methotrexate in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2013;65(3):559-570.
11. Rehan S, Shamim J, Zafar U. Prevalence of rheumatoid arthritis in population with arthralgia presenting to a tertiary care hospital. J Pak Med Assoc. 2015;65(5):545-9.
12. Kremer JM, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic DMARDs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253-261.
13. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of Tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.
14. Kremer JM, Genovese MC, Keystone E, et al. Effects of Tofacitinib in combination with Methotrexate in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2013;65(3):559-570.

15. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb study of the efficacy and safety of Tofacitinib monotherapy in methotrexate-naive patients with rheumatoid arthritis. Arthritis Rheumatol. 2012;64(3):617-629.
16. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-519.
17. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011;(2).
18. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with Methotrexate in patients with active rheumatoid arthritis: a randomized phase 3 trial. Lancet. 2013;381(9865):451-460.
19. Solomon DH, Kremer J, Curtis JR, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional and novel risk factors. Arthritis Rheumatol. 2010;62(6):1737-1745.
20. Dougados M, Soubrier M, Perrodeau E, et al. Impact of a dynamic, goal-directed treatment for rheumatoid arthritis: the TICORA study. Arthritis Rheumatol. 2015;67(2):271-282.
21. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of Methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372(9636):375-382.
22. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and Methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheumatol. 2004;50(11):3432-3443.
23. van der Heijde D, Klareskog L, Rodenberg T, et al. Comparison of etanercept and Methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheumatol. 2006;54(4):1063-1074.
24. Smolen JS, Landewé R, Bijlsma J, 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(6):685-699.