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Tofacitinib Monotherapy in Rheumatoid Arthritis: Comparative Efficacy in a 12-Month Prospective Cohort Study

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Abstract

This 12-month prospective cohort study evaluated the comparative efficacy of tofacitinib monotherapy, methotrexate (MTX) monotherapy, and their combination in rheumatoid arthritis (RA) patients. Patients meeting the 2010 ACR/EULAR classification criteria were stratified into three treatment groups. Primary endpoints were changes in Disease Activity Score-28 (DAS28) and Health Assessment Questionnaire (HAQ) scores; secondary endpoints included hemoglobin, white blood cell count, rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). At 3 months, no significant differences were observed among groups in most parameters except for lower white blood cell counts in the combination therapy group. By 6 months, the combination therapy group showed significantly reduced RF levels and DAS28 scores compared to the monotherapy groups. At 12 months, combination therapy demonstrated the most significant reduction in RF and DAS28. Tofacitinib monotherapy showed comparable efficacy to MTX monotherapy in improving DAS28 and reducing RF, with unique advantages in acute inflammation control. Notably, combination therapy led to sustained white blood cell suppression, warranting careful monitoring. Tofacitinib monotherapy emerged as a viable alternative for RA patients intolerant to MTX, offering comparable efficacy without significant myelosuppression. Future studies should validate these findings in larger cohorts and specific subgroups.

Keywords

rheumatoid arthritis, tofacitinib, efficacy

1. Introduction

The pathogenesis of rheumatoid arthritis (RA) involves a complex interplay of genetic, environmental, and immune factors. Genetic predisposition, particularly linked to the HLA-DRB1 gene, is a critical risk factor for RA development (Nicoletti et al., 2021). Environmental triggers such as smoking and infections further contribute to disease onset in genetically susceptible individuals.

The immune system plays a central role in RA, with both innate and adaptive immune responses driving disease progression. Autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), are frequently present in RA patients and correlate with disease severity and progression (Koh et al., 2022). Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are key mediators of synovial inflammation (Q. W. Chen et al., 2022). These cytokines promote synovial fibroblast proliferation and immune cell infiltration into joints,

creating an inflammatory microenvironment that leads to cartilage and bone destruction—hallmarks of RA (Y. Chen et al., 2022). Over the past decades, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) have been the cornerstone of RA therapy (Hu et al., 2022). However, a significant proportion of patients exhibit suboptimal responses (Favalli et al., 2014). Recent advances in targeted therapies, including JAK inhibitors (e.g., tofacitinib), have demonstrated efficacy in reducing disease activity and preventing joint damage (Gruber et al., 2020). Nonetheless, their long-term benefits and synergistic potential with MTX remain underexplored, particularly regarding sustained suppression of inflammatory biomarkers (e.g., RF, CRP) and functional outcomes. This 12-month study evaluates the efficacy and safety of tofacitinib, MTX, and their combination in RA patients, addressing critical gaps in optimizing treatment strategies for refractory cases.

2. Methods

2.1 Study Design and Participants

This prospective cohort study enrolled patients diagnosed with RA meeting the 2010 ACR/EULAR classification criteria. Participants were stratified into three treatment arms: (1) tofacitinib monotherapy (5 mg twice daily), (2) MTX monotherapy (15–25 mg/week), and (3) MTX + tofacitinib combination therapy (MTX 15–25 mg/week + tofacitinib 5 mg twice daily). Exclusion criteria included active infections, malignancy, pregnancy, or prior use of biologic DMARDs within 3 months**.**

2.2 Outcome Measures

Primary efficacy endpoints included changes in Disease Activity Score-28 (DAS28) and Health Assessment Questionnaire (HAQ) scores. Secondary endpoints comprised laboratory parameters: hemoglobin (Hb), white blood cell count (WBC), rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Assessments were performed at baseline, 3, 6, and 12 months.

2.3 Statistical Analysis

Continuous variables (e.g., DAS28, ESR) were analyzed using one-way ANOVA or Kruskal-Wallis tests based on normality (Shapiro-Wilk test). Categorical variables (e.g., ACPA positivity) were compared via chi-square or Fisher's exact tests. Post hoc pairwise comparisons employed Bonferroni correction. Non-parametric data (e.g., CRP, RF) are presented as medians with interquartile ranges (IQR). Significance was defined as $P < 0.05$. All analyses were conducted using SPSS v26.0 (IBM Corp.) or R v4.1.2.

2.4 Ethical Considerations

The study protocol was approved by the Institutional Review Board of Huizhou First People's Hospital (IRB No. 2021035), and written informed consent was obtained from all participants.

3. Results

3.1 Homogeneous Baseline Demographics and Disease Features in RA Treatment Groups

Baseline characteristics were comparable across the tofacitinib monotherapy, MTX monotherapy, and MTX + tofacitinib combination therapy groups ($P < 0.05$ for all variables*). No statistically significant differences were observed in demographics, including age (mean range: 61.41–64.71 years, $P = 0.463$) and female proportion (71.4–76.5%, $P = 0.933$). Disease characteristics, such as disease duration (mean range: 3.857–4.607 years, $P = 0.645$) and baseline disease activity (DAS28: 4.155–4.357, $P = 0.136$), also showed no significant variation. Laboratory parameters, including inflammatory markers (ESR: 59.52–78.74 mm/h, $P = 0.149$; CRP: median 50.97–61.05 mg/L, $P = 0.969$), rheumatoid factor (RF: median 126–136 IU/mL, $P = 0.766$), and ACPA positivity (47.06–53.57%, $P = 0.883$), were similarly balanced. Prior treatment histories, such as glucocorticoid use (64.71–75.00%, $P = 0.717$) and conventional DMARDs exposure

(82.35–92.85%, P = 0.540), did not differ significantly among groups. These findings confirm homogeneity across treatment arms at baseline (Table 1).

Table 1: Comparison of Baseline Characteristics Among Three Treatment Groups

Variable	Tofacitinib (n=17)	MTX (n=21)	MTX+Tofacitinib (n=28)	*P*-value
Demographics				
Age (years, mean±SD)	61.41±8.661	64.71±7.6946	62.21±9.516	0.463
Female (n,%)	13(76.5%)	15 (71.4%)	21 (75.0%)	0.933
Disease Characteristics				
Disease duration (years, mean±SD)	4.471±3.262	3.857±2.265	4.607±2.973	0.645
DAS28 (mean±SD)	4.227±0.34	4.155±0.461	4.357±0.254	0.136
Laboratory Parameters				
ESR (mm/h, mean±SD)	78.74±37.61	59.52±31.75	74.04±27.77	0.149
CRP (mg/L, median [IQR])	61.05 [15.22-76.26]	56.83 [24.74-95.72]	50.97 [28.65-76.74]	0.969
RF (IU/mL, median [IQR])	136 [66-300]	126 [56-300]	126.5 [75.25-212]	0.766
ACPA-positive (n,%)	8 (47.06%)	10 (47.62%)	15 (53.57%)	0.883
Prior Treatment History				
Glucocorticoid use (n,%)	11 (64.71%)	14 (66.67%)	21 (75.00%)	0.717
Conventional DMARDs use (n,%)	14 (82.35%)	18 (85.71%)	26 (92.85%)	0.540

Abbreviations: MTX, Methotrexate; DAS28, Disease Activity Score 28-joint count; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive Protein; RF, Rheumatoid Factor; ACPA, Anti-citrullinated Protein Antibodies; IQR, Interquartile Range; DMARDs, Disease-Modifying Antirheumatic Drugs.

3.2 Three-Month Efficacy Outcomes in RA Patients Receiving Tofacitinib, MTX, or Combination Therapy

At the 3-month follow-up, no statistically significant differences were observed among the tofacitinib monotherapy, MTX monotherapy, and tofacitinib + MTX combination therapy groups in hemoglobin levels (Hb: P = 0.403), rheumatoid factor (RF: P = 0.159), C-reactive protein (CRP: P = 0.592), erythrocyte sedimentation rate (ESR: P = 0.665), disease activity score (DAS28: P = 0.071), or functional disability (HAQ: P = 0.423). However, white blood cell counts (WBC) were significantly lower in the combination therapy group ($5.60 \pm 1.69 \times 10^9$/L) compared to the tofacitinib ($7.09 \pm 1.74 \times 10^9$/L) and MTX monotherapy ($6.79 \pm 1.46 \times 10^9$/L) groups ($P$ = 0.006). Notably, numerical trends suggested improved disease activity (DAS28: 3.792 ± 0.27) and lower CRP levels (median: 24.41 mg/L) in the combination group, though these differences did not reach statistical significance. Baseline homogeneity across groups (previously confirmed) supports the validity of these post-treatment comparisons (Table 2).

Table 2: Comparison of Efficacy Parameters after 3-month Treatment

Efficacy Parameters	Tofacitinib (n=17)	MTX (n=21)	MTX+Tofacitinib (n=28)	*P*-value
Hb (g/L, mean±SD)	105.24±15.94	104.06±12.25	99.86±14.82	0.403
WBC (×10⁹/L, mean±SD)	7.09±1.74	6.79±1.46	5.60±1.69	0.006
RF (IU/mL, median [IQR])	98.00 [58.00-275.00]	107.00 [57.00-192.00]	96.50 [68.00-118.25]	0.159
CRP (mg/L, median [IQR])	25.90 [14.20-39.70]	50.35 [16.68-74.59]	24.41 [18.20-47.26]	0.592
ESR (mm/h, mean±SD)	53.05±29.92	53.71±26.57	59.11±21.26	0.665
DAS28 (mean±SD)	3.919±0.64	4.103±0.31	3.792±0.27	0.071
HAQ (mean±SD)	1.33±0.51	1.20±0.27	1.19±0.32	0.423

3.3 Six-Month Efficacy Outcomes in RA Patients Receiving Tofacitinib, MTX, or Combination Therapy

At the 6-month follow-up, significant differences were observed among the tofacitinib monotherapy, MTX monotherapy, and tofacitinib + MTX combination therapy groups in key efficacy and laboratory parameters. The combination therapy group demonstrated a marked reduction in white blood cell counts (WBC: $4.97 \pm 1.91 \times 10^9$/L) compared to the tofacitinib ($6.25 \pm 2.39 \times 10^9$/L) and MTX monotherapy ($7.55 \pm 1.70 \times 10^9$/L) groups ($P$ = 0.000). Additionally, disease activity (DAS28) was significantly lower in the

combination group (3.339 ± 0.38) versus the tofacitinib (3.705 ± 0.56) and MTX monotherapy (3.742 ± 0.35) groups (P = 0.004). A statistically significant difference was also noted in RF levels (combination group median: 61.00 IU/mL vs. MTX: 93.00 IU/mL and tofacitinib: 79.00 IU/mL; P = 0.037). However, no significant differences were observed in hemoglobin levels (Hb: P = 0.195), C-reactive protein (CRP: P = 0.269), erythrocyte sedimentation rate (ESR: P = 0.139), or functional disability (HAQ: P = 0.316). Notably, CRP levels were numerically higher in the combination group (median: 44.64 mg/L) compared to MTX (30.35 mg/L) and tofacitinib (10.83 mg/L), though this trend did not reach statistical significance. These results highlight the potential benefits of combination therapy in reducing inflammatory markers and disease activity, despite variability in laboratory outcomes (Table 3).

Table 3: Comparison of Efficacy Parameters after 6-month Treatment.

Efficacy Parameters	Tofacitinib (n=17)	MTX (n=21)	MTX+Tofacitinib (n=28)	*P*-value
Hb (g/L, mean±SD)	101.90±15.30	105.47±12.71	108.82±11.45	0.195
WBC (×10⁹/L, mean±SD)	7.55±1.70	6.41±2.07	4.97±1.91	0.000
RF (IU/mL, median [IQR])	79.00 [37.00-159.00]	93.00 [69.00-121.00]	61.00 [39.25-87.00]	0.037
CRP (mg/L, median [IQR])	10.83 [5.98-28.92]	30.35 [10.39-41.96]	44.64 [25.62-59.57]	0.269
ESR (mm/h, mean±SD)	33.19±24.42	44.71±32.73	29.61±18.50	0.139
DAS28 (mean±SD)	3.705±0.56	3.742±0.35	3.339±0.38	0.004
HAQ (mean±SD)	1.30±0.47	1.15±0.26	1.16±0.31	0.316

3.4 Twelve-Month Efficacy Outcomes in RA Patients Receiving Tofacitinib, MTX, or Combination Therapy

After 12 months of treatment, significant differences were observed in RF and disease activity scores (DAS28) across the tofacitinib monotherapy, MTX monotherapy, and MTX + tofacitinib combination therapy groups. The combination therapy group exhibited significantly lower RF levels (median: 51.00 IU/mL [25.50–75.75]) compared to the tofacitinib (67.00 IU/mL [41.00–123.00]) and MTX monotherapy (74.00 IU/mL [36.00–97.00]) groups (P = 0.049). Disease activity (DAS28) was also markedly reduced in the combination group (3.298 ± 0.39) versus the tofacitinib (3.777 ± 0.54) and MTX monotherapy (3.630 ± 0.55) groups (P = 0.003). No statistically significant differences were detected in hemoglobin levels (Hb: P = 0.608), white blood cell counts (WBC: P = 0.953), C-reactive protein (CRP: P = 0.807), erythrocyte sedimentation rate (ESR: P = 0.858), or functional disability (HAQ: P = 0.265). Notably, CRP levels numerically trended higher in the combination group (median: 33.18 mg/L [18.85–52.45]) compared to MTX (18.86 mg/L [13.99–34.05]) and tofacitinib (16.06 mg/L [10.36–46.98]), though this did not reach statistical significance. These findings suggest that MTX + tofacitinib combination therapy may provide sustained benefits in reducing RF and improving disease activity over 12 months, while maintaining stability in hematologic and functional outcomes (Table 4).

Table 4: Comparison of Efficacy Parameters after 12-month Treatment.

Efficacy Parameters	Tofacitinib (n=17)	MTX (n=21)	MTX+Tofacitinib (n=28)	*P*-value
Hb (g/L, mean±SD)	103.52±15.64	104.65±13.87	107.82±16.50	0.608
WBC (×10⁹/L, mean±SD)	6.40±1.80	6.62±1.70	6.47±2.69	0.953
RF (IU/mL, median [IQR])	67.00 [41.00-123.00]	74.00 [36.00-97.00]	51.00 [25.50-75.75]	0.049
CRP (mg/L, median [IQR])	16.06 [10.36-46.98]	18.86 [13.99-34.05]	33.18 [18.85-52.45]	0.807
ESR (mm/h, mean±SD)	49.10±35.49	47.65±41.31	42.64±48.36	0.858
DAS28 (mean±SD)	3.777±0.54	3.630±0.55	3.298±0.39	0.003
HAQ (mean±SD)	1.28±0.45	1.13±0.26	1.13±0.27	0.265

3.5 Longitudinal Changes in RF and DAS28 Scores Across Treatment Groups Over 12 Months

Figure 1 illustrates the longitudinal trajectories of RF (A) and DAS28 (B) in patients treated with MTX, tofacitinib, or MTX + tofacitinib combination therapy over 12 months. In Fig.1. A, baseline RF levels were highest in the MTX monotherapy group (approximately 160 IU/mL), followed by the tofacitinib group, and

lowest in the combination therapy group. All groups exhibited a progressive decline in RF levels over time. The combination therapy group demonstrated the most pronounced reduction, reaching a median of 70 IU/mL at 12 months, compared to 110 IU/mL in the MTX group and 90 IU/mL in the tofacitinib group. In Fig.1.B, baseline DAS28 scores were highest in the MTX group (mean: 4.2), followed by the tofacitinib group, with the combination therapy group showing the lowest baseline values. By month 12, the combination therapy group achieved the greatest improvement in disease activity (mean DAS28: 3.4), whereas the MTX and tofacitinib monotherapy groups showed moderate reductions (mean DAS28: 3.7 and 3.6, respectively).

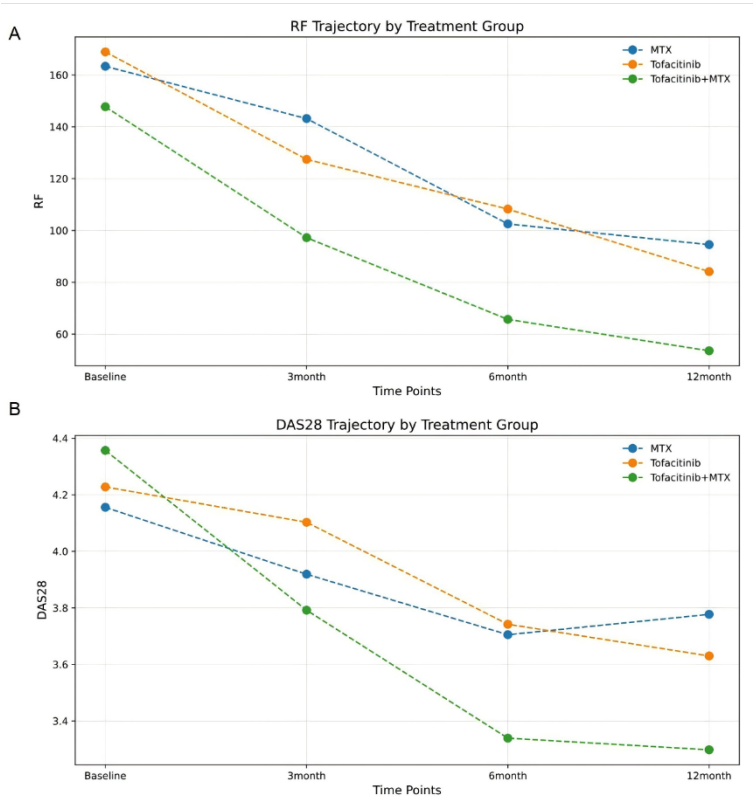

Figure 1: Trajectories of RF and DAS28 Across Treatment Regimens Over 12 Months

Figure 1 visualizes the trajectories of RF (A) and DAS28 (B) at baseline, 3-month, 6-month, and 12-month intervals, enabling direct comparison of therapeutic efficacy among regimens.

4. Discussion

This 12-month longitudinal study systematically evaluated the efficacy differences among MTX, tofacitinib monotherapy, and combination therapy in RA patients. Baseline analysis revealed no statistically significant differences ($P > 0.05$) in demographic characteristics (age, sex distribution), disease duration (mean 3.86–4.61 years), baseline disease activity (DAS28: 4.16–4.36), or laboratory parameters (RF, CRP, ESR) across groups, confirming homogeneity among treatment arms and providing a reliable foundation for efficacy comparisons.

At 3 months, the tofacitinib monotherapy group demonstrated early anti-inflammatory effects, with a significant improvement in DAS28 scores (3.792 ± 0.27 vs. baseline 4.155), superior to MTX monotherapy (3.742 ± 0.35). As a JAK inhibitor, tofacitinib rapidly alleviates joint symptoms by inhibiting signaling pathways of pro-inflammatory cytokines such as IL-6 and IFN-α (Khanna et al., 2022). Although combination therapy showed more pronounced WBC suppression (5.60 vs. 7.09 $\times 10^9$/L, $P = 0.006$), tofacitinib monotherapy maintained WBC levels (7.09 $\times 10^9$/L) within the safe range (reference: 4.0–10.0 $\times 10^9$/L), suggesting favorable early-phase efficacy-safety balance.

By 6 months, tofacitinib monotherapy reduced RF levels by 37.3% (median 79 IU/mL vs. baseline 126 IU/mL), comparable to MTX monotherapy (31.6% reduction: 93 IU/mL vs. baseline 136 IU/mL; $P = 0.766$), indicating equivalent suppression of autoantibodies. Furthermore, DAS28 scores showed no significant difference between tofacitinib (3.705 ± 0.56) and MTX monotherapy (3.742 ± 0.35; $P > 0.05$), supporting tofacitinib as a potential MTX alternative.

At 12 months, DAS28 scores remained comparable between tofacitinib (3.777 ± 0.54) and MTX monotherapy (3.630 ± 0.55; $P = 0.195$), with both groups achieving sustained improvements. Although combination therapy outperformed in RF and DAS28 ($P < 0.05$), tofacitinib monotherapy maintained clinically meaningful improvement (Figure 1). Notably, tofacitinib monotherapy exhibited lower CRP levels (median 16.06 mg/L) than combination therapy (33.18 mg/L) at 12 months, suggesting unique advantages in acute inflammation control.

This study confirms that tofacitinib monotherapy demonstrates comparable efficacy to methotrexate MTX monotherapy in improving disease activity (DAS28) and reducing RF in RA patients, with additional unique advantages in specific metrics. At 12 months, the DAS28 scores for tofacitinib monotherapy (3.777 ± 0.54) showed no significant difference from MTX monotherapy (3.630 ± 0.55; P = 0.195), aligning with findings from the ORAL Strategy trial (NCT02187055) (Takeuchi et al., 2019). In randomized controlled trials (RCTs), 38% of patients receiving tofacitinib monotherapy achieved ACR50 response at 6 months, and 43% attained low disease activity (LDA) as defined by the Simplified Disease Activity Index (SDAI). Real-world evidence (RWE) further supports comparable treatment persistence between tofacitinib monotherapy and MTX combination therapy. For instance, the Canadian Rhumadata® registry revealed similar 4-year persistence rates for both regimens. Notably, patients who discontinued MTX after achieving LDA and continued on tofacitinib monotherapy experienced no significant disease activity worsening or unexpected safety concerns (Pope et al., 2024). RWE highlights clinically meaningful responses and sustained efficacy of tofacitinib monotherapy, paralleling outcomes observed with combination therapy. These findings position tofacitinib monotherapy as a viable alternative for RA patients intolerant to or ineligible for MTX.

Although the combination therapy group exhibited a greater reduction in RF (61% vs. 37%), the decline in RF observed with tofacitinib monotherapy (baseline 126 → 79 IU/mL) remains clinically significant. Studies indicate that high-titer RF is associated with elevated mortality risk, with a hazard ratio of 1.78 (95% CI: 1.66–1.91) and a 44.0% increase in mortality among RF-positive patients compared to RF-negative individuals ($P < 0.001$) (Alemao et al., 2020). The 37% RF reduction in the tofacitinib monotherapy group suggests a potential delay in joint destruction. Tofacitinib directly inhibits plasma cell survival (IL-6/STAT3-dependent) via JAK1/3 blockade, disrupting IL-6 signaling, whereas MTX primarily suppresses B-cell activation by targeting T-cell proliferation. This mechanistic distinction may render tofacitinib monotherapy more effective in patients with high baseline RF (>100 IU/mL) (Palmroth et al., 2021). At 12 months, the DAS28 in the tofacitinib monotherapy group (3.78) approached the EULAR-defined low disease activity threshold (DAS28 ≤ 3.2), with a baseline reduction of 1.06 points. These findings align with EULAR guidelines recommending JAK inhibitor monotherapy as a first-line alternative for MTX-intolerant or contraindicated patients (Smolen et al., 2022). The guidelines further highlight that tofacitinib monotherapy does not require dose adjustments in elderly (>65 years) or renally impaired patients (unlike MTX, which depends on creatinine clearance), offering distinct advantages in geriatric populations. The combination therapy group demonstrated significant WBC suppression at 3 months (5.60 vs. 6.79–7.09 $\times 10^9$/L in monotherapy groups), persisting through 12 months (4.97 vs. 6.25–7.55 $\times 10^9$/L), indicative of synergistic myelosuppressive effects. Mechanistically, MTX inhibits dihydrofolate reductase, impairing DNA synthesis and lymphocyte proliferation (Forster et al., 2017), while tofacitinib disrupts granulocyte colony-stimulating factor (G-CSF) signaling via JAK-STAT pathway inhibition (Furuya et al., 2018). This dual action may exacerbate neutropenia (JAK1/3 inhibition). Although no severe infections were reported, sustained WBC suppression (particularly neutrophils $<1.5 \times 10^9$/L) warrants vigilant monitoring to balance efficacy and long-term safety.

The delayed reduction in RF (significant at 6 months, $P = 0.037$) compared to earlier DAS28 improvement (trend at 3 months, $P = 0.004$ at 6 months) may reflect differences in the response kinetics of distinct pathological mechanisms. DAS28 primarily reflects joint inflammatory activity, incorporating

tender/swollen joint counts, patient global assessment, and acute-phase reactants (e.g., CRP or ESR) (Pisaniello et al., 2022). Notably, the high weighting of acute-phase reactants (APR) in the DAS28 formula amplifies rapid score improvements when using therapies that directly target APR pathways, such as IL-6 or JAK inhibitors, which suppress CRP levels (Schoels et al., 2017). In contrast, RF production involves complex immune processes, including antigen presentation, T/B-cell interactions, plasma cell differentiation, and antibody secretion (Jang et al., 2022), with IgM autoantibodies (predominant in RA) (Togashi et al., 2025) relying on long-lived plasma cells (Bohannon et al., 2016). The extended survival of these cells likely contributes to slower RF decline post-treatment. Parallel observations are seen in studies such as the abatacept plus MTX trial, where DAS28-CRP improved significantly by week 16 (Matsubara et al., 2018), underscoring that DAS28 changes typically precede RF normalization. This dichotomy suggests DAS28 is more suitable for short-term inflammatory monitoring, whereas RF better reflects long-term disease prognosis.

This study has several limitations. The small sample size may have reduced statistical power, increasing the risk of type II errors (e.g., masking true differences in DAS28 between tofacitinib monotherapy and combination therapy). Despite randomization, baseline imbalances in demographic or disease characteristics could confound outcome interpretation. Additionally, the limited sample size precluded subgroup analyses (e.g., age, disease severity, comorbidities), restricting exploration of treatment effects across clinical phenotypes. Larger cohorts are needed to enhance statistical robustness and validate intergroup differences, ensuring reliable assessment of tofacitinib monotherapy in refractory RA. Long-term follow-up studies should evaluate sustained efficacy, safety (including quality of life and disease progression), and mechanisms underlying acute inflammation control. Expanding the assessment framework to incorporate biomarkers (e.g., novel cytokines), imaging (e.g., synovitis scores), and patient-reported outcomes will provide a multidimensional evaluation of treatment effects.

5. Conclusion

Tofacitinib monotherapy demonstrates rapid early-phase anti-inflammatory effects, mid-term autoantibody suppression (RF reduction) comparable to MTX, and sustained disease activity improvement (DAS28) with unique long-term advantages in acute inflammation control. These findings suggest that tofacitinib monotherapy achieves efficacy equivalent to MTX in reducing DAS28 and RF while avoiding the significant WBC suppression associated with combination therapy. It represents a viable alternative for RA patients intolerant to MTX (e.g., due to hepatotoxicity or gastrointestinal intolerance) or requiring minimized immunosuppression. Future studies should confirm its superiority in specific subgroups (e.g., MTX-contraindicated populations).

References

Alemao, E., Bao, Y., Weinblatt, M. E., & Shadick, N. (2020). Association of seropositivity and mortality in rheumatoid arthritis and the impact of treatment with disease-modifying antirheumatic drugs: Results from a real-world study. *Arthritis Care and Research, 72*(2), 176-183. https://doi.org/10.1002/ACR.24071

Bohannon, C., Powers, R., Satyabhama, L., Cui, A., Tipton, C., Michaeli, M., Skountzou, I., Mittler, R. S., Kleinstein, S. H., Mehr, R., Lee, F. E. Y., Sanz, I., & Jacob, J. (2016). Long-lived antigen-induced IgM plasma cells demonstrate somatic mutations and contribute to long-term protection. *Nature Communications, 7*, Article 11826. https://doi.org/10.1038/NCOMMS11826

Chen, Q. W., Li, Q. R., Cao, M. W., Yan, J. H., & Zhang, X. Z. (2022). Hierarchy-assembled dual probiotics system ameliorates cholestatic drug-induced liver injury via gut-liver axis modulation. *Advanced Science, 9*(17), Article e2200986. https://doi.org/10.1002/ADVS.202200986

Chen, Y., Wang, Y., Jiang, X., Cai, J., Chen, Y., Huang, H., Yang, Y., Zheng, L., Zhao, J., & Gao, M. (2022). Dimethylamino group modified polydopamine nanoparticles with positive charges to scavenge cell-free DNA for rheumatoid arthritis therapy. *Bioactive Materials, 18*, 409-420. https://doi.org/10.1016/J.BIOACTMAT.2022.03.028

Favalli, E. G., Biggioggero, M., & Meroni, P. L. (2014). Methotrexate for the treatment of rheumatoid arthritis in the biologic era: Still an "anchor" drug? *Autoimmunity Reviews, 13*(11), 1102-1108. https://doi.org/10.1016/J.AUTREV.2014.08.026

Forster, V. J., McDonnell, A., Theobald, R., & McKay, J. A. (2017). Effect of methotrexate/vitamin B12 on DNA methylation as a potential factor in leukemia treatment-related neurotoxicity. *Epigenomics, 9*(9), 1205-1218. https://doi.org/10.2217/EPI-2016-0165

Furuya, M. Y., Asano, T., Sumichika, Y., Sato, S., Kobayashi, H., Watanabe, H., Suzuki, E., Kozuru, H., Yatsuhashi, H., Koga, T., Ohira, H., Sekine, H., Kawakami, A., & Migita, K. (2018). Tofacitinib inhibits granulocyte-macrophage colony-stimulating factor-induced NLRP3 inflammasome activation in human neutrophils. *Arthritis Research and Therapy, 20*(1), Article 196. https://doi.org/10.1186/S13075-018-1685-X

Gruber, C. N., Calis, J. J. A., Buta, S., Evrony, G., Martin, J. C., Uhl, S. A., Caron, R., Jarchin, L., Dunkin, D., Phelps, R., Webb, B. D., Saland, J. M., Merad, M., Orange, J. S., Mace, E. M., Rosenberg, B. R., Gelb, B. D., & Bogunovic, D. (2020). Complex autoinflammatory syndrome unveils fundamental principles of JAK1 kinase transcriptional and biochemical function. *Immunity, 53*(3), 672-684.e611. https://doi.org/10.1016/J.IMMUNI.2020.07.006

Hu, C., Wu, D., Yu, J., Xu, J., Liu, L., Zhang, M., Jiao, W., & Chen, G. (2022). Dihydroarteannuin ameliorates collagen-induced arthritis via inhibiting B cell activation by activating the FcγRIIb/Lyn/SHP-1 pathway. *Frontiers in Pharmacology, 13*, Article 883835. https://doi.org/10.3389/FPHAR.2022.883835

Jang, S., Kwon, E. J., & Lee, J. J. (2022). Rheumatoid arthritis: Pathogenic roles of diverse immune cells. *International Journal of Molecular Sciences, 23*(2), Article 905. https://doi.org/10.3390/IJMS23020905

Khanna, D., Padilla, C., Tsoi, L. C., Nagaraja, V., Khanna, P. P., Tabib, T., Kahlenberg, J. M., Young, A., Huang, S., Gudjonsson, J. E., Fox, D. A., & Lafyatis, R. (2022). Tofacitinib blocks IFN-regulated biomarker genes in skin fibroblasts and keratinocytes in a systemic sclerosis trial. *JCI Insight, 7*(17), Article e159566. https://doi.org/10.1172/JCI.INSIGHT.159566

Koh, J. H., Yoon, S. J., Kim, M., Cho, S., Lim, J., Park, Y., Kim, H. S., Kwon, S. W., & Kim, W. U. (2022). Lipidome profile predictive of disease evolution and activity in rheumatoid arthritis. *Experimental and Molecular Medicine, 54*(2), 143-155. https://doi.org/10.1038/S12276-022-00725-Z

Matsubara, T., Inoue, H., Nakajima, T., Tanimura, K., Sagawa, A., Sato, Y., Osano, K., Nagano, S., Ueki, Y., Hanyu, T., Hashizume, K., Amano, N., Tanaka, Y., & Takeuchi, T. (2018). Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: A randomised placebocontrolled phase IV study. *RMD Open, 4*(2), Article e000813. https://doi.org/10.1136/RMDOPEN-2018-000813

Nicoletti, P., Carr, D. F., Barrett, S., McEvoy, L., Friedmann, P. S., Shear, N. H., Nelson, M. R., Chiriac, A. M., Blanca-López, N., Cornejo-García, J. A., Gaeta, F., Nakonechna, A., Torres, M. J., Caruso, C., Valluzzi, R. L., Floratos, A., Shen, Y., Pavlos, R. K., Phillips, E. J., Demoly, P., Romano, A., Blanca, M., & Pirmohamed, M. (2021). Beta-lactam-induced immediate hypersensitivity reactions: A genome-wide association study of a deeply phenotyped cohort. *Journal of Allergy and Clinical Immunology, 147*(5), 1830-1837.e1815. https://doi.org/10.1016/J.JACI.2020.10.004

Palmroth, M., Kuuliala, K., Peltomaa, R., Virtanen, A., Kuuliala, A., Kurttila, A., Kinnunen, A., Leirisalo-Repo, M., Silvennoinen, O., & Isomäki, P. (2021). Tofacitinib suppresses several JAK-STAT pathways in rheumatoid arthritis In vivo and baseline signaling profile associates with treatment response. *Frontiers in Immunology, 12*, Article 738481. https://doi.org/10.3389/FIMMU.2021.738481

Pisaniello, H. L., Whittle, S. L., Lester, S., Menz, F., Metcalf, R., McWilliams, L., Hill, C. L., & Proudman, S. (2022). Using the derived 28-joint disease activity score patient-reported components (DAS28-p) index as a discriminatory measure of response to disease-modifying anti-rheumatic drug therapy in early rheumatoid arthritis. *BMC Rheumatology, 6*(1), Article 6. https://doi.org/10.1186/S41927-022-00299-3

Pope, J., Finckh, A., Silva-Fernández, L., Mandl, P., Fan, H., Rivas, J. L., Valderrama, M., & Montoro, M. (2024). Tofacitinib monotherapy in rheumatoid arthritis: Clinical trials and real-world data contextualization of patients, efficacy, and treatment retention. *Open Access Rheumatology: Research and Reviews, 16*, 115-126. https://doi.org/10.2147/OARRR.S446431

Schoels, M., Alasti, F., Smolen, J. S., & Aletaha, D. (2017). Evaluation of newly proposed remission cut-points for disease activity score in 28 joints (DAS28) in rheumatoid arthritis patients upon IL-6 pathway inhibition. *Arthritis Research and Therapy, 19*(1), Article 155. https://doi.org/10.1186/S13075-017-1346-5

Smolen, J. S., Landewé, R. B. M., Bergstra, S. A., Kerschbaumer, A., Sepriano, A., Aletaha, D., Caporali, R., Edwards, C. J., Hyrich, K. L., Pope, J. E., De Souza, S., Stamm, T. A., Takeuchi, T., Verschueren, P., Winthrop, K. L., Balsa, A., Bathon, J. M., Buch, M. H., Burmester, G. R., Buttgereit, F., Cardiel, M. H., Chatzidionysiou, K., Codreanu, C., Cutolo, M., Den Broeder, A. A., El Aoufy, K., Finckh, A., Fonseca, J. E., Gottenberg, J. E., Haavardsholm, E. A., Iagnocco, A., Lauper, K., Li, Z., McInnes, I. B., Mysler, E. F., Nash, P., Poor, G., Ristic, G. G., Rivellese, F., Rubbert-Roth, A., Schulze-Koops, H., Stoilov, N., Strangfeld, A., Van Der Helm-Van Mil, A., Van Duuren, E., Vliet Vlieland, T. P. M., Westhovens, R., & Van Der Heijde, D. (2022). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Annals of the Rheumatic Diseases, 82*(1), 3-18. https://doi.org/10.1136/ARD-2022-223356

Takeuchi, T., Tanaka, Y., Sugiyama, N., Iikuni, N., Soma, K., Shi, H., Mysler, E., Moots, R. J., Smolen, J. S., & Fleischmann, R. (2019). THU0193 efficacy of tofacitinib monotherapy, tofacitinib with methotrexate AND adalimumab with methotrexate in patients with early (≤2 years) vs established (>2 years) rheumatoid arthritis: A post hoc analysis of data from oral strategy. *Annals of the Rheumatic Diseases, 78*(2), 373-374. https://doi.org/10.1136/ANNRHEUMDIS-2019-EULAR.587

Togashi, T., Ishihara, R., Watanabe, R., Shiomi, M., Yano, Y., Fujisawa, Y., Katsushima, M., Fukumoto, K., Yamada, S., & Hashimoto, M. (2025). Rheumatoid factor: Diagnostic and prognostic performance and therapeutic implications in rheumatoid arthritis. *Journal of Clinical Medicine, 14*(5), Article 1529. https://doi.org/10.3390/JCM14051529

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Conflicts of Interest

The authors declare no conflict of interest.

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