**ACR Open Rheumatology**
Vol. 7, No. 5, May 2025, e70040
DOI 10.1002/acr2.70040


American College of Rheumatology
Empowering Rheumatology Professionals

# Analysis of the Impact of Tofacitinib Treatment on Weight and Body Mass Index in Patients With Rheumatoid Arthritis

Jürgen Wollenhaupt,[1] Jacques Morel,[2] Claire Daien,[2] Adeline Ruyssen-Witrand,[3] Cédric Lukas,[4] Christophe Richez,[5] Andrea Shapiro,[6] Douglass S. Chapman,[7] Magali Cros,[8] Jose L. Rivas,[9] and Gustavo Citera[10]

**Objectives.** This post hoc analysis evaluated change from baseline (△) in weight/body mass index (BMI) and association with disease activity or lipid changes in tofacitinib-treated patients with rheumatoid arthritis (RA).

**Methods.** Data up to month 12 were pooled from eight phase 3 and 3b/4 studies of patients with RA receiving tofacitinib 5 or 10 mg twice daily or tofacitinib 11 mg modified-release once daily (alone or combined with conventional synthetic disease-modifying antirheumatic drugs), or placebo. Assessments included △weight/BMI and the proportion of patients with weight gain ≥5%, at months 3, 6, and 12. Correlations between △weight/△BMI and baseline/△Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR]), baseline C-reactive protein (CRP), and △lipids were assessed. Statistical analysis included a longitudinal linear mixed model for repeated measures.

**Results.** The analysis included 5,335 patients (tofacitinib 5 mg twice daily [n = 2,349], 10 mg twice daily [n = 1,611], 11 mg once daily [n = 694], and placebo [n = 681]). Increases in least squares mean △weight and △BMI were significantly greater ($P < 0.05$) at months 3 and 6 with all tofacitinib doses versus placebo; increases continued to month 12. Significantly greater (at least $P < 0.05$) proportions of tofacitinib-treated patients (all doses) had weight gain ≥5% at months 3 and 6 versus placebo. There were weak correlations between weight/BMI changes with tofacitinib and DAS28-4(ESR), baseline CRP, or lipid changes.

**Conclusion.** Patients receiving tofacitinib experienced weight and BMI changes (primarily increases) over time, with weak correlations with disease activity or lipids.

## INTRODUCTION

Biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs have been shown to influence body weight and body composition in rheumatoid arthritis (RA).[1–4] Moreover, the impact of higher body mass index (BMI) on treatment outcomes has been reported for conventional synthetic (cs)DMARDs,[5] tumor necrosis factor inhibitors (TNFi),[6] and the Janus kinase (JAK) inhibitor, baricitinib.[7]

A prior post hoc analysis of clinical trial data in patients receiving the JAK inhibitor tofacitinib reported improvements in RA outcomes (including Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)]) versus placebo through month 6, regardless of baseline BMI.[8] Generally, there were no clinically relevant differences in outcomes among patients in different baseline BMI categories who were treated with tofacitinib. In addition, a retrospective study reported that among 377 patients with RA who were prescribed tofacitinib,

ClinicalTrials.gov identifiers: NCT01039688; NCT00960440; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT02187055; NCT02831855.

This study was sponsored by Pfizer.

[1]Jürgen Wollenhaupt, MD: Struenseehaus Centre for Rheumatology and Clinical Immunology, Hamburg, Germany; [2]Jacques Morel, MD, PhD, Claire Daien, MD, PhD: Department of Rheumatology, Montpellier University Hospital and INSERM U1046, CNRS UMR 9214, PhyMedExp, Montpellier, France; [3]Adeline Ruyssen-Witrand, MD, PhD: Rheumatology Department, Toulouse University Hospital, CIC 1436, INSERM, Paul Sabatier University Toulouse III, Toulouse, France; [4]Cédric Lukas, MD, PhD: Department of Rheumatology, Montpellier University Hospital and University of Montpellier and INSERM UA11 (IDESP), Montpellier, France; [5]Christophe Richez, MD, PhD: Rheumatology Department, Groupe Hospitalier Pellegrin-CHU de Bordeaux and University of Bordeaux, CNRS, Immuno ConcEpT, UMR 5164, Bordeaux, France; [6]Andrea Shapiro, MD, MS: Pfizer Inc, Pearl River, New York; [7]Douglass S. Chapman, MS: Pfizer Inc, New York, New York; [8]Magali Cros, PhD: Pfizer Inc, Paris, France; [9]Jose L. Rivas, MD: Pfizer SLU, Madrid, Spain; [10]Gustavo Citera, MD: Department of Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr2.70040).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr2.70040.

Address correspondence via email to Jose L. Rivas, MD, at JoseLuis.Rivas@pfizer.com.

Submitted for publication September 29, 2023; accepted in revised form March 24, 2025.

68% had weight gain, 25% had weight loss, and 7% had no change in weight over a ≥6-month period.[9] An observational, open-label, prospective study of 31 patients with RA showed that after 1 year of tofacitinib treatment, 32% of patients moved to a higher BMI category; however, a statistically significant ($P$ = 0.030) decrease in the visceral adiposity index was noted, indicating a potential reduction in overall cardiometabolic risk despite the increase in BMI.[4]

This post hoc analysis assessed change from baseline (Δ) in weight and BMI in patients with moderate to severe RA receiving tofacitinib through month 12. Additionally, correlations between baseline/changes in disease activity, baseline C-reactive protein (CRP), and changes in lipids with Δweight and ΔBMI were evaluated.

## PATIENTS AND METHODS

**Study design and patients.** Data were pooled from phase 3 and 3b/4 studies of tofacitinib in patients who were methotrexate-naïve (ORAL Start [NCT01039688][10]) or inadequate responders to csDMARDs or bDMARDs (ORAL Step [NCT00960440][11]; ORAL Scan [NCT00847613][12]; ORAL Solo [NCT00814307][13]; ORAL Sync [NCT00856544][14]; ORAL Standard [NCT00853385][15]; ORAL Strategy [NCT02187055][16]; and ORAL Shift [NCT02831855][17]). Patient eligibility criteria for each study have been published previously. Patients included in this post hoc analysis had received ≥1 dose of tofacitinib 5 or 10 mg twice daily, or tofacitinib 11 mg modified-release once daily, alone or with background csDMARDs, or placebo. Patients who advanced from placebo to tofacitinib were excluded from the analysis post-advancement visits.

All studies were conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines, and were approved by the Institutional Review Boards and/or Independent Ethics Committees at each investigational center participating in the studies. All patients provided written informed consent.

**Assessments.** Least squares (LS) mean Δweight (kg) and ΔBMI (kg/m$^2$) at months 3, 6, and 12 (months 3 and 6 only for tofacitinib 11 mg once daily and placebo), by treatment group (including whether tofacitinib was received as monotherapy vs combination therapy), were assessed in this post hoc analysis. Mean Δweight and ΔBMI were stratified by baseline concomitant glucocorticoid or antidepressant use, and whether tofacitinib was received as monotherapy or combination therapy. Mean Δweight was also presented by treatment group (including monotherapy vs combination therapy) and stratified by baseline weight category (<60 kg; 60–<90 kg; ≥90 kg). Proportions of patients with Δweight by treatment group and visit were presented by category: weight loss ≥0–<5%; weight loss ≥5%; weight gain >0–<5%; and weight gain ≥5%. Analysis of the proportion of patients with weight gain ≥5% (yes vs no) was performed by treatment group (including by monotherapy vs combination therapy) and visit. The correlations between Δweight or ΔBMI and ΔDAS28-4 (ESR), baseline DAS28-4(ESR), baseline CRP, and Δlipids (total cholesterol, high-density lipoprotein-cholesterol [HDL-c], low-density lipoprotein-cholesterol [LDL-c], total cholesterol/HDL-c ratio, and triglycerides) were assessed by treatment and visit. Change from baseline in lipids was also summarized descriptively by baseline weight category (<60 kg; 60–<90 kg; ≥90 kg), baseline BMI category (<18.5 kg/m$^2$; 18.5–<25 kg/m$^2$; 25–<30 kg/m$^2$; ≥30 kg/m$^2$), and Δweight category (weight loss ≥0–<5%; weight loss ≥5%; weight gain >0–<5%; weight gain ≥5%).

**Statistical analysis.** Continuous demographic and baseline characteristics were summarized using mean (standard deviation), and categorical variables were summarized using frequency and proportion, including when stratified by baseline BMI categories (<25 kg/m$^2$; 25–<30 kg/m$^2$; ≥30 kg/m$^2$). Longitudinal linear mixed model for repeated measures was used to calculate LS mean Δweight and ΔBMI (using observed data) under the missing at random (MAR) assumption. Terms for treatment, visit, treatment × visit interaction, baseline weight (or baseline BMI), age, sex, race, and RA duration were included in the models. In the studies, race was self-reported (White; Black; Asian; Other), captured via case report forms completed at the baseline visit. Some patients who selected the "Other" category on the case report form used a free-text option to specify their race/ethnicity. Mean (95% confidence interval [CI]) Δweight and mean (95% CI) ΔBMI were also reported. Analysis of the proportion of patients with weight gain of ≥5% (yes vs no) was performed using generalized estimating equations methodology with terms for treatment, visit, sex, race, baseline weight, age, and disease duration.

Correlations between Δweight or ΔBMI and ΔDAS28-4 (ESR) were analyzed in each case using a general linear model, with age, race, sex, and RA disease duration included as covariates in the model. Similarly, correlations between Δweight or ΔBMI and baseline DAS28-4(ESR), baseline CRP, or Δlipids were adjusted for the baseline variables age, race, sex, and RA disease duration. An additional sensitivity analysis was conducted, which investigated the correlation between Δweight or ΔBMI and ΔDAS28-4(ESR) or ΔCRP, by treatment group and visit, with the additional covariates of baseline weight or BMI (as appropriate) and baseline DAS28-4(ESR) or CRP (as appropriate) added into the statistical model. No adjustments to $P$ values were made for multiplicity. No imputations were made for missing data.

## RESULTS

**Patients.** In total, 5,335 patients were included in this analysis: 2,349, 1,611, 694, and 681 patients received tofacitinib

5 mg twice daily, 10 mg twice daily, 11 mg once daily, or placebo, respectively. Demographics and baseline characteristics were generally similar across treatment groups, except in patients receiving tofacitinib 11 mg once daily, where some numerical differences were observed. Notably, smaller proportions of patients in the tofacitinib 11 mg once daily group were female, Asian, and had concomitant glucocorticoid use; a larger proportion of patients were White, with higher age, baseline weight, and slightly higher BMI than the other groups (Table 1). Patient demographic and baseline characteristics were generally similar between patients treated with tofacitinib monotherapy or combination therapy, except for a slightly greater proportion of Asian patients, a longer duration of RA, and a notably higher proportion of patients with a history of prior methotrexate and TNFi use among patients treated with tofacitinib combination therapy versus monotherapy (Supplementary Table 1). The proportion of Asian patients with BMI <25 kg/m$^2$ was nearly twice as high as the proportion of Asian patients in the overall population for each group, indicating that Asian patients were more likely to have BMI <25 kg/m$^2$ compared with patients of other races (Table 1; Supplementary Table 2). Across all treatment groups, the prevalence of cardiovascular-related conditions at baseline generally increased (ie, diabetes, myocardial infarction, hypertension) as baseline BMI increased (Supplementary Table 2).

**Change in weight and BMI over time.** Significantly greater increases in LS mean Δweight at months 3 and 6 were observed with tofacitinib (all doses) versus placebo (month 3: $P < 0.001$ for both tofacitinib 5 and 10 mg twice daily, $P < 0.01$ for tofacitinib 11 mg once daily; month 6: $P < 0.001$ for both tofacitinib 5 and 10 mg twice daily, $P < 0.05$ for tofacitinib 11 mg once daily), with weight continuing to increase to month 12 in the tofacitinib 5 and 10 mg twice daily groups (Figure 1A). A similar trend was observed for LS mean ΔBMI (Supplementary Figure 1A). Based on the difference between the LS mean weight gain at months 3 and 12, almost 50% of weight gain occurred during the first 3 months of tofacitinib treatment (Figure 1). LS mean Δweight was numerically greater in patients receiving tofacitinib 10 versus 5 mg twice daily (Figure 1A) and in those receiving tofacitinib as monotherapy versus combination therapy (Figure 1B). Similarly, LS mean ΔBMI was greater in patients receiving tofacitinib as monotherapy versus combination therapy at each time point (Supplementary Figure 1B).

**Table 1.** Patient demographics and baseline characteristics

| | Tofacitinib 5 mg twice daily (n = 2,349) | Tofacitinib 10 mg twice daily (n = 1,611) | Tofacitinib 11 mg once daily (n = 694) | Placebo (n = 681) |
|---|---|---|---|---|
| Female, n (%) | 1,943 (82.7) | 1,357 (84.2) | 532 (76.7) | 553 (81.2) |
| Age, mean ± SD, y | 51.6 ± 12.2 | 51.7 ± 12.0 | 56.8 ± 11.8 | 52.5 ± 12.0 |
| Race, n (%) | | | | |
| White | 1,558 (66.3) | 1,007 (62.5) | 594 (85.6) | 439 (64.5) |
| Asian | 474 (20.2) | 377 (23.4) | 37 (5.3) | 166 (24.4) |
| Black | 88 (3.7) | 47 (2.9) | 33 (4.8) | 24 (3.5) |
| Other | 229 (9.7) | 180 (11.2) | 30 (4.3) | 52 (7.6) |
| Weight, mean ± SD, kg | 71.9 ± 19.0 | 71.2 ± 19.0 | 77.2 ± 19.0 | 72.3 ± 21.2 |
| BMI, mean ± SD [N1] | 27.3 ± 6.5 [2,346] | 27.0 ± 6.3 [1,611] | 28.2 ± 6.2 [691] | 27.2 ± 6.8 [680] |
| Smoking status, n (%)[a] | | | | |
| Smoker | 336 (14.3) | 282 (17.5) | 129 (18.6) | 130 (19.1) |
| Ex-smoker | 389 (16.6) | 238 (14.8) | 163 (23.5) | 124 (18.2) |
| Never smoked | 1,624 (69.1) | 1,091 (67.7) | 402 (57.9) | 425 (62.4) |
| Duration of RA, mean ± SD, y | 7.6 ± 7.7 | 7.7 ± 8.1 | 8.8 ± 8.8 | 9.3 ± 8.5 |
| DAS28-4(ESR), mean ± SD [N1] | 6.5 ± 1.0 [2,301] | 6.5 ± 1.0 [1,569] | 6.0 ± 1.0 [694] | 6.4 ± 1.0 [658] |
| Treatment history, n (%) | | | | |
| Prior methotrexate use | 1,946 (82.8) | 1,183 (73.4) | 690 (99.4) | 649 (95.3) |
| Prior nonmethotrexate csDMARD use | 1,122 (47.8) | 908 (56.4) | 100 (14.4) | 398 (58.4) |
| Prior TNFi use | 338 (14.4) | 287 (17.8) | 95 (13.7) | 201 (29.5) |
| Prior non-TNFi bDMARD use | 109 (4.6) | 72 (4.5) | 55 (7.9) | 46 (6.8) |
| Concomitant glucocorticoid use, n (%) | 1,348 (57.4) | 864 (53.6) | 174 (25.1) | 396 (58.1) |
| Concomitant antidepressant use, n (%) | 194 (8.3) | 125 (7.8) | 37 (5.3) | 46 (6.8) |
| Comorbidities at baseline, n (%) | | | | |
| Diabetes | 204 (8.7) | 127 (7.9) | 74 (10.7) | 48 (7.0) |
| Coronary heart disease | 14 (0.6) | 5 (0.3) | 2 (0.3) | 4 (0.6) |
| Myocardial infarction | 25 (1.1) | 20 (1.2) | 14 (2.0) | 7 (1.0) |
| Hypertension | 820 (34.9) | 579 (35.9) | 299 (43.1) | 243 (35.7) |

Percentages may not sum to 100% due to rounding. bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; N1, number of patients with nonmissing data in the specified category and treatment group; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.
[a]Two patients receiving placebo had an unknown smoking status.

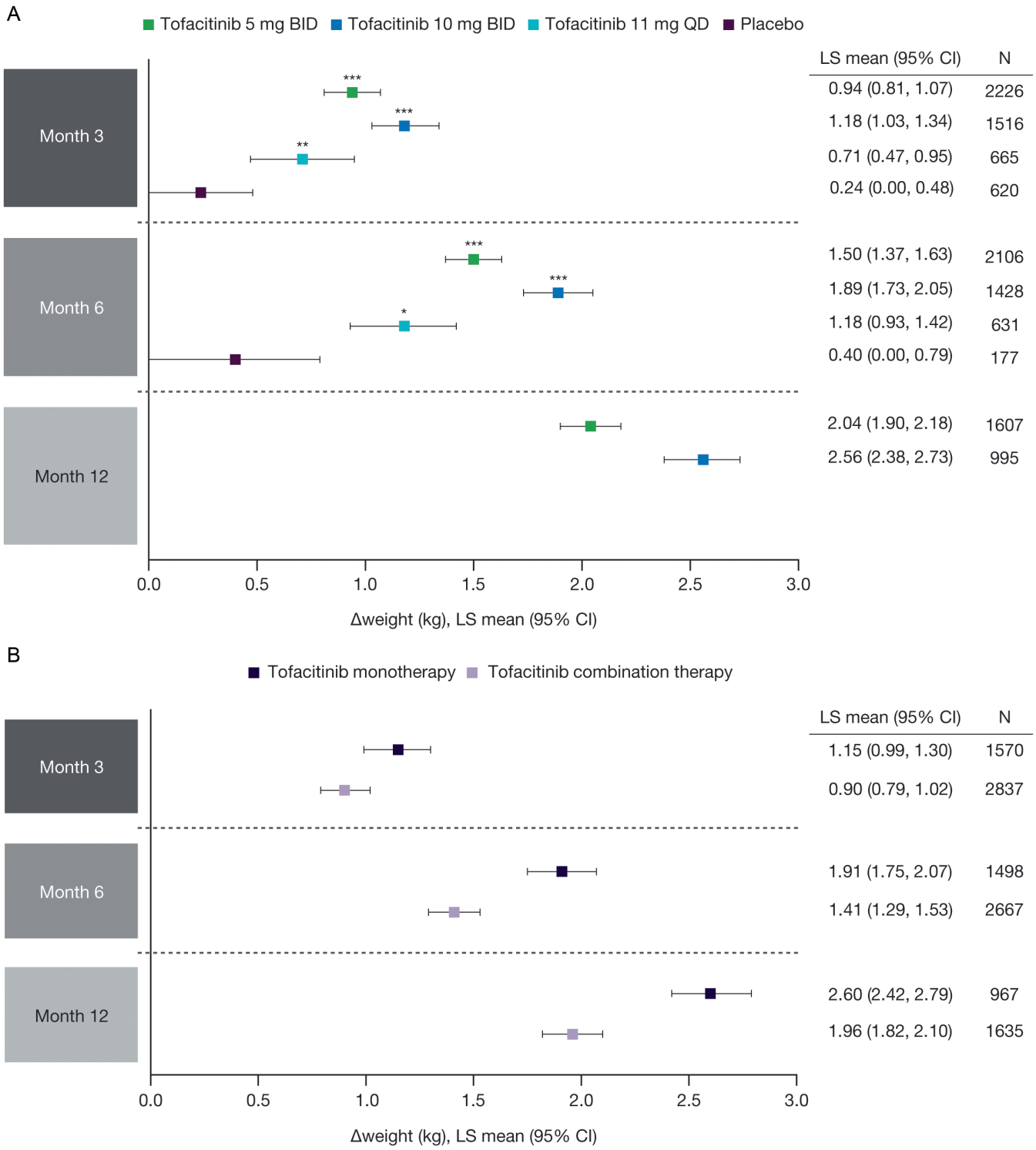


**Figure 1.** LS mean change from baseline in weight through month 12 in patients with RA receiving (A) tofacitinib 5 or 10 mg BID, tofacitinib 11 mg QD, or placebo[a] and (B) tofacitinib monotherapy or tofacitinib in combination with csDMARDs[b]. [a]Statistical analyses were performed for comparisons of LS mean Δweight in patients receiving tofacitinib versus placebo up to month 6 only. [b]Descriptive statistics only. LS means for Δweight were calculated using a longitudinal linear mixed model for repeated measures (observed data), with terms for treatment, visit, treatment × visit interaction, baseline weight, age, sex, race, and RA duration included in the model. For patients receiving tofacitinib 11 mg QD in ORAL Shift, only data up to month 6 were included. Patients who advanced from placebo to tofacitinib were excluded from the analysis post-advancement visits. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo. Δ, change from baseline; BID, twice daily; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LS, least squares; QD, once daily; RA, rheumatoid arthritis.

Mean (95% CI) Δweight stratified by tofacitinib monotherapy versus combination therapy and by glucocorticoid and antidepressant use at baseline is reported in Supplementary Figure 2. An impact of glucocorticoid or antidepressant drug use at baseline on mean Δweight in patients receiving tofacitinib was not observed (Supplementary Figure 2). The same was true for mean ΔBMI (Supplementary Figure 3).

Mean Δweight were numerically greater in patients who weighed <60 kg at baseline compared with those in categories 60–<90 kg and ≥90 kg, regardless of tofacitinib treatment group or monotherapy versus combination therapy (Supplementary Figure 4). Similarly, mean ΔBMI was numerically greater in patients with baseline BMI <25 kg/m$^2$ compared with the other BMI categories, with the same trend seen for the different tofacitinib dosages and for monotherapy versus combination therapy (data not shown).

In general, most patients experienced minor weight changes (<5%) compared with baseline, regardless of treatment group. However, a small proportion typically experienced large weight loss (≥5%), and varying proportions of patients (5.6–36.8%) experienced large weight gain (Figure 2). The proportion of patients with ≥5% weight gain or loss generally increased over time. Weight gain ≥5% was reported by numerically higher proportions of patients receiving tofacitinib 5 or 10 mg twice daily than those receiving tofacitinib 11 mg once daily or placebo.

**Analysis of patients with weight gain ≥5% from baseline.** After adjusting for treatment, sex, race, baseline weight, age, and disease duration, the proportion of patients with weight gain ≥5% from baseline was significantly higher for patients receiving all doses of tofacitinib compared with placebo at months 3 and 6 ($P < 0.001$ for both tofacitinib 5 and 10 mg twice daily, $P < 0.05$ for tofacitinib 11 mg once daily; Supplementary Figure 5A). This proportion continued to increase at month 12. Numerical differences in the proportion of patients with weight gain ≥5% from baseline at months 3 and 6 were greatest for tofacitinib 10 mg twice daily, followed by tofacitinib 5 mg twice daily, tofacitinib 11 mg once daily, and then placebo.

The proportion of patients with weight gain ≥5% from baseline increased over time regardless of whether they were receiving tofacitinib as monotherapy or combination therapy (Supplementary Figure 5B). However, a numerically higher proportion of patients receiving tofacitinib monotherapy had weight gain ≥5% compared with those receiving combination therapy, at all time points.

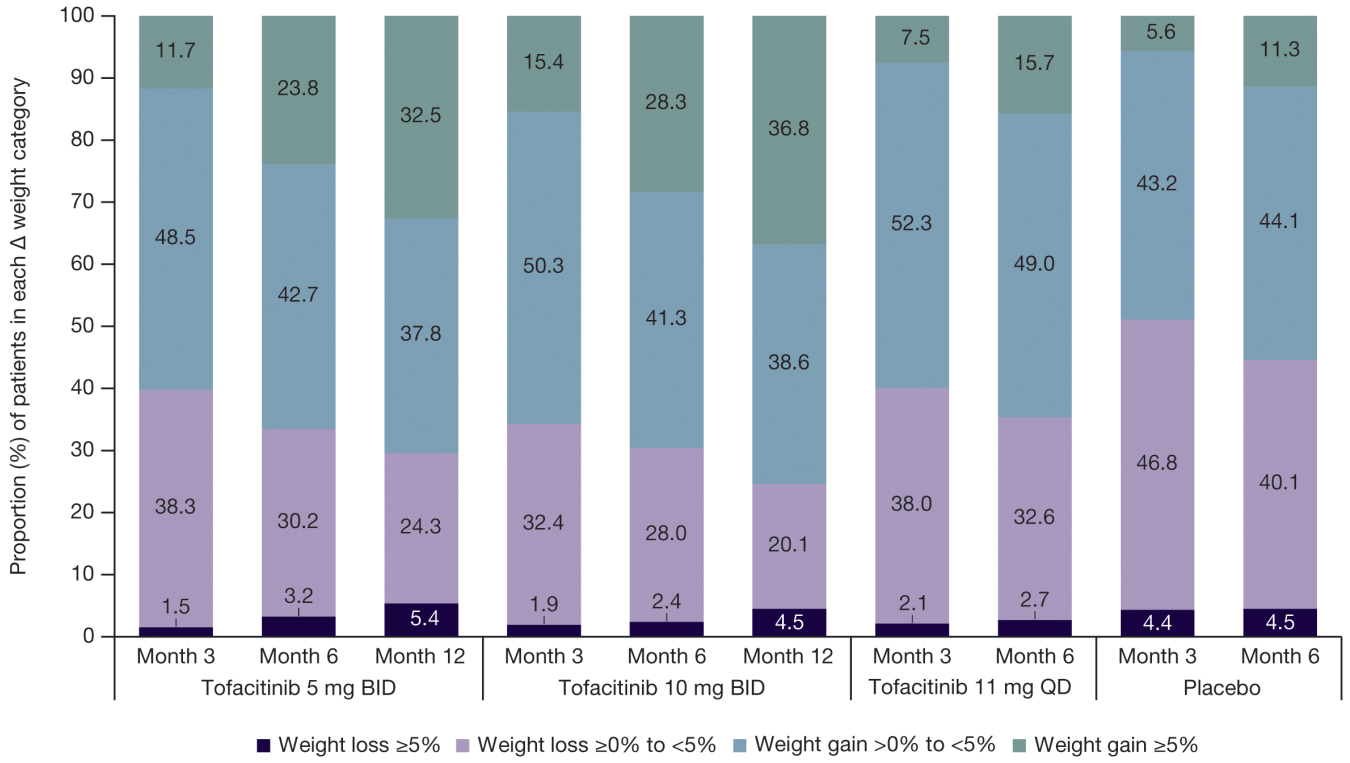


**Figure 2.** Proportion of patients with RA receiving tofacitinib 5 or 10 mg BID, tofacitinib 11 mg QD, or placebo in change from baseline in weight categories (descriptive statistics only) through month 12. Note that percentages may not sum to 100% due to rounding. For patients receiving tofacitinib 11 mg QD in ORAL Shift, only data up to month 6 were included. Patients who advanced from placebo to tofacitinib were excluded from the analysis post-advancement visits. Δ, change from baseline; BID, twice daily; QD, once daily; RA, rheumatoid arthritis.

**Table 2.** Correlations between ΔDAS28-4(ESR) and Δweight through month 12

| | Tofacitinib 5 mg twice daily | | | Tofacitinib 10 mg twice daily | | | Tofacitinib 11 mg once daily | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value |
| Month 3 | 2,034 | 0.119 | 0.0005 | 1,353 | 0.129 | 0.0036 | 644 | 0.089 | 0.3299 | 556 | 0.080 | 0.9262 |
| Month 6 | 1,935 | 0.130 | 0.0002 | 1,275 | 0.129 | 0.0001 | 614 | 0.039 | 0.8048 | 151 | 0.142 | 0.2995 |
| Month 12 | 1,468 | 0.134 | 0.0219 | 885 | 0.165 | <0.0001 | – | – | – | – | – | – |

Correlations between ΔDAS28-4(ESR) and Δweight were analyzed by a general linear model method, with age, race, sex, and RA duration included in the model. For patients receiving tofacitinib 11 mg once daily in ORAL Shift, only data up to month 6 were included. Patients who advanced from placebo to tofacitinib were excluded from the analysis post-advancement visits. Δ, change from baseline; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; RA, rheumatoid arthritis.

**Correlations between change in weight and BMI with disease activity and baseline CRP.** Across treatment groups, there were statistically significant correlations between ΔDAS28-4(ESR) scores and both Δweight and ΔBMI through month 12 for tofacitinib 5 and 10 mg twice daily (Tables 2 and 3, respectively). Although the correlations were statistically significant, the weak correlation coefficients (<0.2) raise questions about the clinical significance and suggest limited practical implications of the correlation.

In the sensitivity analysis, results for ΔDAS28-4(ESR) were generally consistent with those in Tables 2 and 3 (data not shown). In the sensitivity analysis for ΔCRP, results were also generally consistent with those in Tables 2 and 3 (Supplementary Tables 3 and 4). Weak correlation coefficients (all <0.25) were shown for all comparisons in the sensitivity analyses for ΔDAS28-4 (ESR) (data not shown) and ΔCRP (Supplementary Tables 3 and 4).

There were some statistically significant correlations between Δweight and ΔBMI and baseline DAS28-4(ESR) scores and baseline CRP, mainly for tofacitinib 5 and 10 mg twice daily. However, all were weak correlations (<0.25) (Supplementary Tables 5 and 6).

**Correlations between change in weight and BMI with change in lipids.** Correlations between Δweight and ΔBMI and changes from baseline in total cholesterol, HDL-c, LDL-c, total cholesterol/HDL-c ratio, and triglycerides were assessed. Some statistically significant correlations were observed between Δweight and ΔBMI and changes in some lipids; however, these were weak correlations (Supplementary Tables 7 and 8) (data not shown for total cholesterol/HDL-c ratio and triglycerides).

**Change in lipids by baseline weight, baseline BMI, and change in weight categories.** Generally, total cholesterol increased with tofacitinib 5 mg or 10 mg twice daily from baseline to 3 months, and then remained stable regardless of weight and BMI categories at baseline (Supplementary Figures 6 and 7). Similar trends were generally observed for HDL-c, LDL-c, and triglycerides (data not shown). Total cholesterol/HDL-c ratio was generally stable over time in all baseline weight and BMI categories (data not shown). Increases in total cholesterol were generally highest in patients weighing <60 kg, and lowest in those weighing ≥90 kg or with a BMI of ≥30 kg/m$^2$, receiving either dose of tofacitinib (Supplementary Figures 6 and 7).

Observed increases in total cholesterol were similar regardless of weight loss/gain, but were generally slightly higher for tofacitinib 10 mg twice daily versus 5 mg twice daily (Supplementary Figure 8). Similar trends were generally observed for HDL-c, LDL-c, and total cholesterol/HDL-c ratio (data not shown).

## DISCUSSION

In this post hoc analysis of pooled phase 3 and 3b/4 studies of tofacitinib in patients with RA, mean weight and BMI increased over time and were greater with tofacitinib (all doses) versus placebo at months 3 and 6, and with tofacitinib monotherapy versus combination therapy, at months 3, 6, and 12. Around 50% of

**Table 3.** Correlations between ΔDAS28-4(ESR) and ΔBMI through month 12

| | Tofacitinib 5 mg twice daily | | | Tofacitinib 10 mg twice daily | | | Tofacitinib 11 mg once daily | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value | n | Correlation coefficient | *P* value |
| Month 3 | 1,315 | 0.098 | 0.0039 | 1,348 | 0.124 | 0.0077 | 641 | 0.091 | 0.3268 | 554 | 0.078 | 0.9197 |
| Month 6 | 1,230 | 0.116 | 0.0023 | 1,270 | 0.140 | <0.0001 | 611 | 0.044 | 0.8211 | 150 | 0.156 | 0.1825 |
| Month 12 | 845 | 0.102 | 0.0283 | 874 | 0.183 | <0.0001 | – | – | – | – | – | – |

Correlations between ΔDAS28-4(ESR) and ΔBMI were analyzed by a general linear model method, with age, race, sex, and RA duration included in the model. For patients receiving tofacitinib 11 mg once daily in ORAL Shift, only data up to month 6 were included. Patients who advanced from placebo to tofacitinib were excluded from the analysis post-advancement visits. Δ, change from baseline; BMI, body mass index; DAS28-4 (ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; RA, rheumatoid arthritis.

weight gain occurred during the first 3 months of tofacitinib treatment. Weight and BMI changes were numerically larger in patients who were lighter (weight <60 kg, BMI <25 kg/m$^2$) at baseline. After adjustment, the proportion of patients with weight change ≥5% was significantly higher for patients receiving all doses of tofacitinib compared with those receiving placebo at months 3 and 6. There was no impact of concomitant glucocorticoid or antidepressant use on ΔweightorΔBMI. Correlations between changes in weight and BMI with tofacitinib, and DAS28-4(ESR), were weak (correlation coefficients <0.2, raising questions about the clinical significance and suggesting limited practical implications of the correlation).

A prospective study of patients with RA reported a median weight gain of 3 kg (4.2%) following one year of treatment with tofacitinib 5 or 10 mg twice daily, combined with either methotrexate or leflunomide, and with or without low-dose glucocorticoids.[4] A retrospective study also reported a significant mean weight gain of 1.52 kg in patients with RA who were prescribed tofacitinib for a mean duration of 8.6 months.[9] These findings are in line with the reported weight gain with 12 months of tofacitinib treatment in the present study (LS mean: tofacitinib 5 mg twice daily, 2.0 kg; tofacitinib 10 mg twice daily, 2.6 kg). The prospective study also found that patients with a lower baseline BMI had a greater chance of experiencing a BMI increase >5% after 12 months of treatment.[4] This is in agreement with observations from the present study, which demonstrated a tendency for a greater weight gain and BMI increase with tofacitinib in patients who were a lower weight at baseline (<60 kg). With respect to the effects of weight gain in patients with tofacitinib, we acknowledge that there may be additional health implications or comorbidities, although these were beyond the scope of this analysis. Being overweight or obese has been reported to be protective against cardiovascular and all-cause mortality in patients with RA, while being underweight (BMI <18.5 kg/m$^2$) appeared to confer an increased risk for both compared with patients with normal weight.[18] However, odds ratios for diabetes, hypertension, and myocardial infarction were greater in the overweight and obese groups versus normal weight.[18]

Increases in body weight and BMI in patients with RA receiving treatment with bDMARDs have also been documented, although the data are not entirely consistent across studies. A systematic review reported that, of 13 studies evaluating changes in body weight (including 633 patients receiving bDMARDs), 8 (including 558 patients) reported significant weight gain from baseline (mean: 1.63 kg); 2 (including 24 patients) reported a non-significant trend toward weight gain with treatment, and 3 (including 51 patients) showed no change in body weight. Furthermore, 14 studies comprising 451 patients receiving bDMARDs evaluated BMI. Six of those studies (representing 191 patients) reported a significant increase in BMI (0.94 kg/m$^2$), and the remaining 8 studies (representing 260 patients) reported no change in BMI.[19] Compared with methotrexate therapy, patients with RA treated with TNFi were 6 times more likely to gain weight over 24 months of treatment.[3] Together, these findings suggest that weight gain may occur with bDMARD and tofacitinib treatment, but not with csDMARD treatment. Interestingly, we found that patients treated with tofacitinib monotherapy tended to have greater weight gain than those treated with tofacitinib in combination with csDMARDs, although the reason behind this is unknown. As with tofacitinib treatment, a study of TNFi treatment in patients with RA showed that those with a lower baseline BMI tend to be more likely to gain weight.[20] Interestingly, another JAK inhibitor, filgotinib, did not lead to substantial changes in BMI in phase 3 RA studies, although most patients did experience a 1–2 kg/m$^2$ increase in BMI after 24 weeks of treatment.[21]

We found that correlations between ΔDAS28-4(ESR) scores and ΔweightandΔBMI were all weak. To our knowledge, this is the first report to evaluate these associations in patients with RA treated with tofacitinib. However, such associations have been assessed for the bDMARD, tocilizumab. A retrospective cohort study of patients with RA who were treated with tocilizumab plus methotrexate reported no association between weight change and treatment response after 24 weeks of treatment.[22] Similarly, all correlations between Δweight and ΔBMI and baseline DAS28-4(ESR) scores or baseline CRP in this analysis were weak.

Although it has been reported that treatment with tofacitinib can result in dose-dependent increases of serum total cholesterol, LDL-c, and HDL-c in patients with RA,[23] it is interesting to note that we found weak correlations between Δweight or ΔBMI and changes in total cholesterol, LDL-c, HDL-c, total cholesterol/HDL-c ratio, or triglycerides (data not shown for total cholesterol/HDL-c ratio and triglycerides). Of note, lipids did tend to increase between baseline and month 3, across all baseline weight/BMI categories, and regardless of weight loss/gain in this analysis. When high lipid levels are recorded, clinicians may advise their patients to change their diet or correct with statins. Furthermore, inflammation is associated with lower circulating lipid levels (total cholesterol, LDL-c, and HDL-c).[24] Therefore, correcting inflammation with tofacitinib could have a dissociated effect leading to an increase in lipid levels. Interestingly, a recent publication has shown that an increased risk of dyslipidemia in patients receiving tofacitinib did not induce higher major adverse cardiac events.[25] In the current analysis, change in weight/BMI did not necessarily correlate with an increase in lipids in patients receiving tofacitinib but, as previously mentioned, could potentially be associated with cardiovascular risk factors including hypertension, and diabetes mellitus.[18] Therefore, there is a need for the evaluation and monitoring of these long-term cardiovascular risk factors.

This study had several limitations. First, it was a post hoc analysis of data from pooled clinical studies with different study designs and inclusion criteria. As such, there were some differences in patient demographic and background characteristics, particularly between patients in the tofacitinib 11 mg once daily

group versus the other groups. The proportion of Asian patients was higher in those with lower BMI at baseline (<25 kg/$m^2$). Some groups had low patient numbers at some time points, making it difficult to interpret the study findings at those time points. Furthermore, data on patient energy expenditure, body composition (fat vs muscle), and insulin resistance were not collected; therefore, further investigations in these areas are required in a clinical study.

Weight and BMI continued to increase through 12 months of observation in the studies, so a new equilibrium had not yet been reached. Longer term observations are warranted to establish whether there is sustained weight gain, if this varies by tofacitinib dose, and if there are any health implications of continued weight gain.

In conclusion, this post hoc analysis of phase 3 and 3b/4 studies showed that patients with RA treated with tofacitinib experienced weight and BMI changes over time. The correlation and sensitivity analyses have shown weak correlations between ΔWeight or ΔBMI and ΔDAS28-4(ESR) or ΔCRP. Further research is warranted on the relationship between disease activity and changes in weight and BMI with tofacitinib in RA, and whether these changes are associated with increased risk of other comorbidities with known associations with weight.

## ACKNOWLEDGMENTS

Medical writing support, under the direction of the authors, was provided by Sarah Bubeck, PhD, on behalf of CMC Connect, and Kimberley Haines, MSc, of CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer, New York, New York, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med 2022;175:1298–304).

## AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Rivas confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

## ROLE OF THE STUDY SPONSOR

This study was sponsored by Pfizer. Authors were responsible for the study design, the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

## DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

## REFERENCES

1. Toussirot E. The interrelations between biological and targeted synthetic agents used in inflammatory joint diseases, and obesity or body composition. Metabolites 2020;10(3):107.
2. Chen CY, Tsai CY, Lee PC, et al. Long-term etanercept therapy favors weight gain and ameliorates cachexia in rheumatoid arthritis patients: roles of gut hormones and leptin. Curr Pharm Des 2013;19(10):1956–1964.
3. Sfriso P, Caso F, Filardo GS, et al. Impact of 24 months of anti-TNF therapy versus methotrexate on body weight in patients with rheumatoid arthritis: a prospective observational study. Clin Rheumatol 2016;35(6):1615–1618.
4. Novikova DS, Udachkina HV, Markelova EI, et al. Dynamics of body mass index and visceral adiposity index in patients with rheumatoid arthritis treated with tofacitinib. Rheumatol Int 2019;39(7):1181–1189.
5. Sandberg MEC, Bengtsson C, Källberg H, et al. Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. Ann Rheum Dis 2014;73(11):2029–2033.
6. Singh S, Facciorusso A, Singh AG, et al. Obesity and response to anti-tumor necrosis factor-α agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. PLoS One 2018;13(5):e0195123.
7. Zerbini CAF, Muram D, Arora VK, et al. Effect of BMI on baricitinib efficacy: pooled analysis from two phase 3 rheumatoid arthritis clinical trials. Arthritis Rheumatol 2016;68(suppl 10):1640.
8. Dikranian AH, Gonzalez-Gay MA, Wellborne F, et al. Efficacy of tofacitinib in patients with rheumatoid arthritis stratified by baseline body mass index: an analysis of pooled data from phase 3 studies. RMD Open 2022;8(1):e002103.
9. Prabu N, Petchaippan V, Anand G, et al. Tofacitinib leads to significant weight gain – a real life experience of 429 patients. Arthritis Rheumatol 2022;74(Suppl 9):0291.
10. Lee EB, Fleischmann R, Hall S, et al; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370(25):2377–2386.
11. Burmester GR, Blanco R, Charles-Schoeman C, et al; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381(9865):451–460.
12. van der Heijde D, Tanaka Y, Fleischmann R, et al; ORAL Scan Investigators. 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.
13. Fleischmann R, Kremer J, Cush J, et al; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367(6):495–507.
14. Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active

rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159(4): 253–261.

15. van Vollenhoven RF, Fleischmann R, Cohen S, et al; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367(6):508–519.
16. Fleischmann R, Mysler E, Hall S, et al; ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390(10093): 457–468.
17. Cohen SB, Pope J, Haraoui B, et al. Methotrexate withdrawal in patients with rheumatoid arthritis who achieve low disease activity with tofacitinib modified-release 11 mg once daily plus methotrexate (ORAL Shift): a randomised, phase 3b/4, non-inferiority trial. Lancet Rheumatol 2019;1(1):e23–e34.
18. Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012; 64(10):1471–1479.
19. de Souza MPGUES, Guimarães NS, de Resende Guimarães MFB, et al. Effect of biological disease-modifying antirheumatic drugs on body composition in patients with rheumatoid arthritis: a systematic review and meta-analysis. Adv Rheumatol 2022;62(1):16.
20. Brown RA, Spina D, Butt S, et al. Long-term effects of anti-tumour necrosis factor therapy on weight in patients with rheumatoid arthritis. Clin Rheumatol 2012;31(3):455–461.
21. Balsa A, Wassenberg S, Tanaka Y, et al. Effect of filgotinib on body mass index (BMI) and effect of baseline BMI on the efficacy and safety of filgotinib in rheumatoid arthritis. Rheumatol Ther 2023;10(6):1555–1574.
22. Choi IA, Sagawa A, Lee EY, et al. Tocilizumab increases body weight and serum adipokine levels in patients with rheumatoid arthritis independently of their treatment response: a retrospective cohort study. J Korean Med Sci 2020;35(22):e155.
23. Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, et al. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. Semin Arthritis Rheum 2016; 46(1):71–80.
24. Robertson J, Peters MJ, McInnes IB, et al. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat Rev Rheumatol 2013;9(9):513–523.
25. Ma XN, Shi MF, Wang SI, et al. Risk of dyslipidemia and major adverse cardiac events with tofacitinib *versus* adalimumab in rheumatoid arthritis: a real-world cohort study from 7580 patients. Front Pharmacol 2024;15:1370661.