THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Impact of obesity on clinical outcomes and treatment continuation in rheumatoid arthritis patients receiving non-TNF-targeted therapies

Ther Adv Musculoskelet Dis

2024, Vol. 16: 1–13

DOI: 10.1177/1759720X241308027

Dong-Jin Park*, **Hyemin Jeong***, **Sung-Eun Choi**, **Ji-Hyoun Kang** and **Shin-Seok Lee**

Abstract

Background: Recent studies have shown the impact of obesity on achieving low disease activity or remission in rheumatoid arthritis (RA) patients treated with tumor necrosis factor inhibitors. However, there is limited research on the effects of obesity on clinical responses to non-TNF-targeted treatments.

Objectives: This study investigated the influence of body mass index (BMI) on clinical response to non-TNF-targeted treatments in RA patients.

Design: We used data from the KOrean nationwide BIOlogics & targeted therapy (KOBIO) registry, a multicenter, prospective, observational cohort that included RA patients in South Korea.

Methods: Patients who received at least one prescription for non-TNF-targeted treatments, including abatacept, tocilizumab, and Janus kinase inhibitors, were included. They were categorized into three BMI groups: under 25 kg/m^2 (434 patients), between 25 and 30 kg/m^2 (146 patients), and over 30 kg/m^2 (22 patients). After 1 year of treatment, treatment continuation rates and clinical responses among these BMI groups were compared. Time on treatment for each category was analyzed using Kaplan–Meier curves and Cox regression, adjusting for confounders.

Results: The 1-year continuation rate of the targeted treatment was significantly lower in the obese group (81.8%) compared to the normal BMI (93.8%) and overweight (89.0%) groups ($p = 0.033$). Disease Activity Score of 28 joints-erythrocyte sedimentation rate score improvement was less in the obese group (2.06 ± 2.14) than in the normal BMI group (2.76 ± 1.55) ($p = 0.045$). Multivariable Cox proportional hazard analysis showed a higher discontinuation rate in the obese group (hazard ratio: 3.407, 95% confidence interval: 1.157–10.211; $p = 0.029$).

Conclusion: Higher BMI in RA patients was associated with poorer clinical response and higher discontinuation rates for non-TNF-targeted treatments.

Plain language summary

How obesity affects treatment success in rheumatoid arthritis patients using non-TNF therapies

This study looked at how body mass index (BMI) affects the success of certain rheumatoid arthritis (RA) treatments that don't target Tumor Necrosis Factor (TNF). It included patients taking abatacept, tocilizumab, and JAK kinase inhibitors. Patients were divided into three BMI groups: normal (under 25 kg/m²), overweight (25-30 kg/m²), and obese (over

Correspondence to:
Shin-Seok Lee
Division of Rheumatology, Department of Internal Medicine, Chonnam National University Medical School and Hospital, 42 Jebong-ro, Dong-gu, Gwangju 61469, Republic of Korea
shinseok@chonnam.ac.kr

Dong-Jin Park
Hyemin Jeong
Sung-Eun Choi
Ji-Hyoun Kang
Division of Rheumatology, Department of Internal Medicine, Chonnam National University Medical School and Hospital, Gwangju, Republic of Korea

*These authors contributed equally

30 kg/m²). We compared how well patients in these groups continued their treatment and responded clinically after one year. Our findings showed that obese patients were less likely to continue their treatment after one year (81.8%) compared to normal BMI (93.8%) and overweight (89.0%) patients. Additionally, obese patients had less improvement in their disease activity score (DAS28-ESR) compared to those with normal BMI. Further analysis indicated that obese patients were more likely to stop their treatment sooner, with a hazard ratio of 3.407, meaning they had over three times the risk of discontinuation compared to patients with normal BMI. In summary, RA patients with higher BMI had worse clinical responses and higher rates of stopping their non-TNF-targeted treatments. This suggests that obesity negatively impacts the effectiveness and continuation of these RA therapies.

Keywords: body mass index, non-TNF targeted treatment, obesity, rheumatoid arthritis, treatment continuation

Received: 17 July 2024; revised manuscript accepted: 3 December 2024.

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune inflammatory diseases, characterized by synovial hypertrophy, joint inflammation, and significant structural damage.[1] RA affects up to 1% of the global population, leading to considerable functional impairment and a marked decline in health-related quality of life compared to the general population.[2,3] Although methotrexate (MTX) and other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) remain the first-line therapy for RA, the development of targeted treatments, such as biologic DMARDs (bDMARDs) including tumor necrosis factor inhibitors (TNFi), anti-CD20 antibody (rituximab), T-cell costimulatory inhibitor (abatacept), and interleukin (IL)-6 receptor inhibitors (tocilizumab and sarilumab), as well as targeted synthetic DMARDs (tsDMARDs) like Janus kinase inhibitors (JAKi), has led to substantial progress in the treatment of RA.[4–6] These targeted treatments effectively control inflammation and decrease bone destruction, but the overall remission rates of RA still remain unsatisfactory.[7]

In parallel to RA, obesity represents a major public health crisis due to its prevalence and association with significant adverse health outcomes. Obesity is characterized as a chronic low-grade inflammatory state associated with elevated levels of inflammatory cytokines, including TNF-α, IL-6, IL-18, and C-reactive protein (CRP).[8] Consequently, there has been a longstanding concern that obesity is not only associated with an increased risk of developing RA but also impacts clinical outcomes and the response to therapy. In fact, a recent systematic review found that individuals with a higher body mass index (BMI) have an increased risk of developing RA.[9] Moreover, reduced response rates have been observed for certain medications in RA patients who are obese. Patients with a higher BMI at baseline exhibited diminished efficacy when treated with TNFi.[10] Several observational studies have shown that RA patients who are obese experience a negative impact on achieving treatment goals, such as changes in the Disease Activity Score of 28 joints (DAS28), Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI), or maintaining remission or low-disease-activity (LDA).[11,12] In addition, the retention rate of TNFi therapy is significantly reduced in obese patients compared to normal-weight patients.[13]

Evidence that obesity negatively affects the response to treatment is primarily found with TNFi, while the impact of weight/BMI on the efficacy of non-TNF-targeted treatments is lacking. Therefore, further studies are needed to better understand the treatment outcomes and to offer more individualized therapy for patients with a higher BMI. Using data from the KOrean

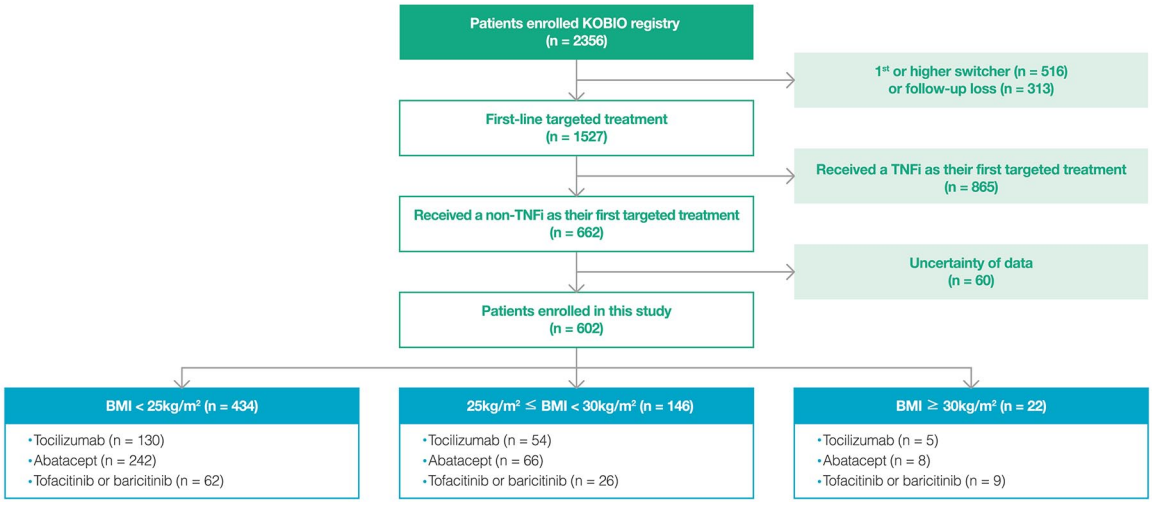


Figure 1. Flow diagram for study enrollment.

nationwide BIOlogics & targeted therapy (KOBIO) registry, a nationwide real-world prospective cohort assessing outcomes of RA patients treated with any targeted treatment, the present study was performed to evaluate the association between BMI and the effectiveness of non-TNF-targeted treatment, in terms of clinical response and drug discontinuation rate 1 year, in RA patients.

Patients and methods

Study design and population

The present study used cohort data from the KOBIO registry, a nationwide multicenter, hospital-based observational registry managed by the Korean College of Rheumatology (KCR). This real-world registry aimed to prospectively evaluate the clinical manifestations and outcomes, including adverse events, of RA patients who had received any targeted treatment, such as bDMARDs or tsDMARDs.[14] All patients eligible for the study were classified as having RA by their treating rheumatologists and fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA.[15] The KOBIO registry enrolls RA patients upon initiating targeted treatment or switching to another targeted therapy. These patients were recruited from 47 tertiary academic and community rheumatologic centers across South Korea and underwent follow-up assessments at approximately 12-month intervals. For this investigation, subjects were identified from baseline and follow-up data within the KOBIO registry.

A total of 2356 RA patients receiving either bDMARDs or tsDMARDs were enrolled in the KOBIO registry between December 2013 and November 2020. Among these, 829 patients who switched their targeted treatment for the first time or more and those who were lost to follow-up were excluded. Furthermore, among patients receiving their initial targeted therapy, those receiving TNFi as their first targeted therapy ($n = 865$), along with those with missing follow-up data or data uncertainty ($n = 60$), were excluded. Finally, a total of 602 patients were included in this study. Patients were stratified into three BMI categories: $<25\,kg/m^2$ (lower or normal BMI, 434 patients), 25–30 kg/m^2 (overweight BMI, 146 patients), and $\geqslant 30\,kg/m^2$ (obese BMI, 22 patients), as per the National Institutes of Health classification (Figure 1).[16] Obese patients (BMI $\geqslant 30\,kg/m^2$) constituted the cohort of interest. Patients were followed up at least once from initiating non-TNF-targeted treatment until discontinuation. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed.[16]

Data collection

All data were transferred to the KOBIO web server (http://www.rheum.or.kr/kobio/) by individual investigators. Medical records for each patient were obtained via interviews or from

patient medical charts upon enrollment. RA patients were interviewed using a structured questionnaire to gather sociodemographic data and details on concomitant medications. The collected data included age, sex, education level, smoking status, blood pressure, BMI, and presence of hypertension and diabetes mellitus. Laboratory findings, such as erythrocyte sedimentation rate (ESR), CRP, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (CCP) antibody levels, were also recorded. In addition, radiographs of the hands and feet were obtained to assess joint erosion and joint space narrowing at enrollment. BMI was calculated by dividing weight (kg) by the square of height (m).

Disease activity assessments were based on physical examinations conducted by trained investigators at each institution, which involved assessing tender and swollen joints. Disease activity was evaluated using validated composite measures, and physical examinations recorded the presence of tender and swollen joints (44 joints). Results of 10-cm visual analog scales for patient global assessment (PGA) and physician global assessment (PhGA) were also documented. Quantitative assessments of RA disease activity, including DAS28, SDAI, and CDAI, were performed at the initiation of non-TNF-targeted treatment. In addition, achievement of remission or LDA was assessed after 1 year of treatment. Concomitant csDMARD use was recorded after initiation of the non-TNF-targeted treatment. The use of csDMARDs was determined based on any use of oral or subcutaneous MTX, sulfasalazine, hydroxychloroquine, leflunomide, tacrolimus, or cyclosporine.

Outcomes

The primary outcome was to define whether obesity influences the discontinuation rate of non-TNF-targeted bDMARDs/tsDMARDs. In addition, to evaluate the efficacy of targeted therapies, several parameters were assessed: the proportion of patients continuing targeted treatment at 1 year, disease activity (tender/swollen joint counts, DAS28-ESR/CRP, CDAI, and SDAI) at 1 year, change in DAS28-ESR/CRP score from baseline to 1 year, and proportion of patients achieving DAS28-ESR remission at 1 year.

Statistical analysis

Descriptive statistical analyses were conducted, presenting values as means ± standard deviation (SD) or numbers and percentages. Categorical variables were analyzed using the Chi-square test, while continuous variables were analyzed using the Mann–Whitney *U* test or one-way analysis of variance. The cutoff value for LDA was defined as DAS28 $\leqslant 3.2$, and clinical remission as DAS28 $\leqslant 2.6$.[17] Kaplan–Meier curves were used to examine the duration of treatment, and the log-rank test was used to compare drug continuation among the three BMI groups. Univariable or Multivariable Cox proportional hazard model was performed to evaluate potential predictors of drug discontinuation. Variables significant at $p < 0.5$ in univariable analysis, along with age and sex, were included in multivariable analysis to assess predictors of discontinuation of non-TNF-targeted treatment. Hazard ratios (HRs), 95% confidence intervals (CIs), and *p*-values were used for interpretation. Statistical analyses were performed using SPSS for Windows software (ver. 21.0; SPSS Inc., Chicago, IL, USA), with significance set at $p < 0.05$.

Results

The baseline characteristics of the patients at enrollment are shown in Table 1. The mean age was 49.7 ± 14.0 years, with most patients being women (80.9%), and 3.65% had a BMI $\geqslant 30\,kg/m^2$. In addition, 84.3% were RF positive, 85.9% were anti-CCP positive, and the mean ± SD of DAS28-ESR was 5.55 ± 1.01. Among all patients, tocilizumab (52.5%) was the most prescribed non-TNF-targeted treatment, followed by abatacept (31.4%) and JAKi (16.1%). In the obese group, JAKi (40.9%) was the most common non-TNF targeted drug, while tocilizumab was the most prescribed drug in the lower or normal BMI group (55.8%) and the overweight BMI group (45.2%); these differences were statistically significant ($p = 0.004$). In the obese group, the patients were younger, and the prevalence of diabetes mellitus was higher compared to the other groups (both $p = 0.001$). The use of concomitant corticosteroids of more than 5 mg/day and the presence of joint space narrowing on hand or foot X-ray were more likely to be higher in the obese group than in the other groups ($p = 0.077$ and $p = 0.094$, respectively). Regarding disease activity at the time of enrollment, there were no significant differences between the groups in the 44 tender joint counts, 44 swollen joint counts, levels of ESR and CRP, PGA, PhGA, DAS28-ESR/CRP, SDAI, or CDAI.

Table 1. Baseline characteristics of rheumatoid arthritis patients receiving non-TNF-targeted treatments.

	All patients ($n=602$)	BMI <25 kg/m^2 ($n=434$)	25 kg/m$^2 \leq$ BMI <30 kg/m^2 ($n=146$)	BMI ≥ 30 kg/m^2 ($n=22$)	*p* Value
Age at start, years	49.7 ± 14.0	48.6 ± 14.6	53.5 ± 11.1	46.8 ± 13.9	0.001
Disease duration, months	83.7 ± 86.0	88.3 ± 69.9	71.4 ± 71.5	75.3 ± 91.2	0.110
Men	115 (19.1)	77 (17.7)	35 (24.0)	3 (13.6)	0.203
Height, cm	158.3 ± 7.44	158.4 ± 7.13	158.3 ± 8.03	151.5 ± 30.7	0.906
Weight	58.0 ± 10.4	53.7 ± 7.57	67.0 ± 8.00	81.4 ± 13.4	<0.001
BMI, kg/m^2	23.0 ± 3.57	21.4 ± 2.23	26.7 ± 1.22	35.6 ± 2.83	<0.001
Current smoker	40 (6.6)	23 (5.3)	15 (10.7)	2 (9.1)	0.071
Diabetes mellitus[a]	59/502 (11.8)	35/358 (9.8)	16/126 (13.5)	7 (38.9)	0.001
Hypertension[a]	56/543 (10.3)	34/384 (8.8)	18/135 (13.3)	4 (18.2)	0.153
Targeted treatment					0.004
Abatacept	189 (31.4)	130 (30.4)	54 (37.0)	5 (22.7)	
Tocilizumab	316 (52.5)	242 (55.8)	66 (45.2)	8 (36.4)	
JAKi	97 (16.1)	62 (14.3)	26 (17.8)	9 (40.9)	
Drug administration					0.004
Subcutaneous	99 (16.4)	80 (18.4)	16 (11.1)	3 (13.6)	
Intravenous	406 (67.4)	292 (67.3)	104 (71.2)	10 (45.5)	
Oral	97 (16.1)	62 (14.3)	26 (17.8)	9 (40.9)	
Use of concomitant csDMARDs	511 (84.9)	372 (85.7)	123 (84.2)	16 (72.7)	0.245
Concomitant corticosteroids, 5 mg/day[a]	154/601 (25.6)	118/433 (27.3)	28 (19.2)	8 (36.4)	0.077
Erosion on X-ray[a]	145/347 (41.8)	109/251 (43.7)	29/84 (34.5)	7/12 (58.3)	0.178
Joint space narrowing on X-ray[a]	156/379 (44.4)	110/255 (43.1)	37/84 (44.0)	9/12 (75.0)	0.094
RF positivity[a]	458/543 (84.3)	330/297 (83.1)	110/124 (88.7)	18 (81.8)	0.310
Anti-CCP positivity[a]	372/433 (85.9)	270/315 (85.7)	88/100 (88.0)	14/18 (77.8)	0.508
Swollen joint count (44 joints)	6.24 ± 4.78	6.38 ± 4.93	5.79 ± 4.19	6.45 ± 5.80	0.433
Tender joint count (44 joints)	8.00 ± 5.73	8.21 ± 5.87	7.56 ± 5.11	6.86 ± 6.59	0.317
PGA	7.02 ± 1.96	7.10 ± 1.81	6.88 ± 2.16	6.45 ± 3.05	0.198
PhGA	6.48 ± 1.78	6.47 ± 1.70	6.54 ± 1.93	6.36 ± 2.31	0.868
ESR	47.6 ± 27.2	47.4 ± 27.7	48.2 ± 25.8	47.6 ± 28.3	0.958
CRP	2.32 ± 3.37	2.22 ± 2.92	2.71 ± 4.56	1.88 ± 2.09	0.258
DAS28-ESR[a]	5.55 ± 1.01	5.58 ± 1.00	5.23 ± 1.01	5.23 ± 1.01	0.242
DAS28-CRP[a]	4.80 ± 1.01	4.92 ± 0.99	4.82 ± 1.03	4.52 ± 1.25	0.144
SDAI	28.8 ± 10.4	29.2 ± 10.3	28.2 ± 10.3	25.9 ± 11.4	0.257
CDAI	26.5 ± 9.68	27.0 ± 9.72	25.5 ± 9.10	24.0 ± 11.5	0.140

Data are shown as mean ± standard deviation or number (%).
[a]Missing data were excluded from the analyses.
Anti-CCP, anti-cyclic citrullinated peptide; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, Disease Activity Score-28 joints; ESR, erythrocyte sedimentation rate; JAKi, Janus kinase inhibitor; PGA, patient global assessment; PhGA, physician global assessment RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; TNF, tumor necrosis factor inhibitor.

Table 2. Comparison of treatment response at 1 year among three different BMI groups.

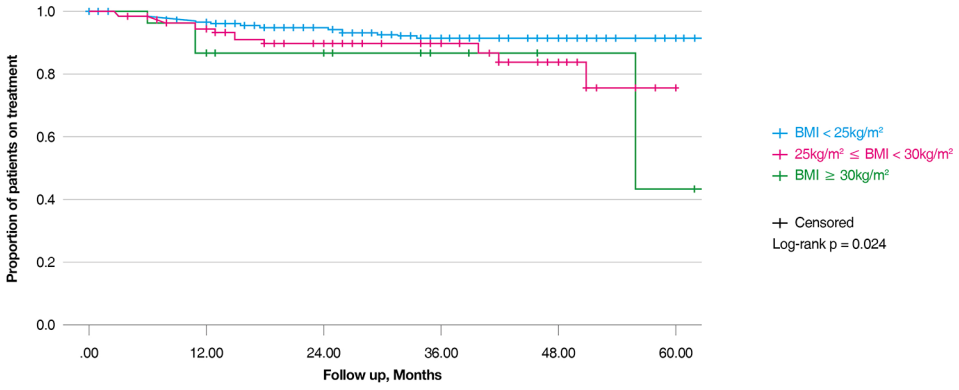
	All patients ($n=602$)	BMI <25 kg/m^2 ($n=434$)	25 kg/m^2 $\leq$ BMI <30 kg/m^2 ($n=146$)	BMI ≥ 30 kg/m^2 ($n=22$)	p Value[a]
Continuation of treatment at 1 year	555 (92.2)	407 (93.8)	130 (89.0)	18 (81.8)	0.033
Remission or LDA at 1 year[b]	394 (65.4)	284 (65.4)	96 (65.8)	14 (63.6)	0.981
Swollen joint count (44 joints)	1.39 ± 2.98	1.30 ± 2.72	1.42 ± 2.80	3.09 ± 6.61	0.022
Tender joint count (44 joints)	2.21 ± 4.25	2.11 ± 3.98	2.47 ± 4.73	2.59 ± 5.82	0.614
PGA	3.61 ± 2.30	3.66 ± 2.29	3.49 ± 2.25	3.45 ± 2.81	0.721
PhGA	3.24 ± 2.11	3.22 ± 2.08	3.21 ± 2.08	3.91 ± 2.82	0.321
ESR	21.4 ± 22.6	20.9 ± 22.5	21.7 ± 21.2	30.5 ± 22.6	0.148
CRP	0.64 ± 2.06	0.68 ± 2.27	0.52 ± 1.44	0.58 ± 0.75	0.707
DAS28-ESR at 1 year	2.86 ± 1.41	2.82 ± 1.38	2.91 ± 1.40	3.17 ± 1.95	0.458
Delta DAS28-ESR[c]	2.69 ± 1.60	2.76 ± 1.55	2.59 ± 1.63	2.06 ± 2.14[d]	0.096
DAS28-CRP at 1 year	2.51 ± 1.17	2.50 ± 1.17	2.51 ± 1.14	2.66 ± 1.59	0.809
Delta DAS28-CRP[c]	2.37 ± 1.43	2.42 ± 1.38	2.30 ± 1.45	1.85 ± 2.06	0.162

Data are shown as mean ± standard deviation or number (%).
[a]Values were determined using the χ^2 test or Mann–Whitney U test.
[b]The cutoff value of LDA was defined as DAS28-ESR ≤ 3.2 and that of clinical remission was defined as DAS28-ESR < 2.6.
[c]Delta DAS28-ESR/CRP was defined as the change in DAS28-ESR/CRP scores between baseline and 1-year follow-up.
[d]p Value was 0.045, determined using the Mann–Whitney U test comparing the obese group with the normal or lower BMI group.
BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score-28 joints; ESR, erythrocyte sedimentation rate; LDA, low disease activity; PGA, patient global assessment; PhGA, physician global assessment.

Table 2 shows the response to treatment after 1 year among three different BMI groups. At the 1-year follow-up, the continuation rate of the targeted treatment was significantly lower in the obese BMI group (81.8%) compared to the normal or lower BMI group (93.8%) and the overweight BMI group (89.0%) ($p=0.033$). In addition, the swollen joint count was significantly higher in the obese BMI group (3.09 ± 6.61) than in the normal or lower BMI group (1.30 ± 2.72) and the overweight BMI group (1.42 ± 2.80) ($p=0.022$). Moreover, the change in the DAS28-ESR score from baseline to 1 year was significantly lower in the obese BMI group (2.06 ± 2.14) compared to the normal or lower BMI group (2.76 ± 1.55) ($p=0.045$). However, clinical parameters measured at 1 year, such as tender joint counts, ESR, CRP, DAS28-CRP, and the proportion of patients achieving remission or LDA, did not differ among the three BMI groups (all $p>0.05$).

The mean duration of follow-up after initiating non-TNF targeted treatment was 25.2 months (range: 0–73 months). Kaplan–Meier analysis revealed that the treatment duration was significantly shorter in the obese BMI group compared to both the normal or lower BMI group and the overweight BMI group ($p=0.024$) (Figure 2). Although not shown as a table, regarding the reason for treatment discontinuation (e.g., inefficacy, adverse events, other causes), it is not statistically different among the three groups.

Table 3 presents the results of univariable and multivariable Cox proportional hazards analyses for predictors of discontinuation of non-TNF-targeted treatments. In the multivariable Cox proportional hazards analysis, the obese BMI group had a higher risk of discontinuation compared to the normal or lower BMI group after adjustment for baseline demographic and clinical variables (HR = 3.402, 95% CI: 1.157–10.211,



No. of patients						
BMI < 25kg/m²	434	425	413	401	390	377
25kg/m² ≤ BMI < 30kg/m²	146	133	121	109	97	85
BMI ≥ 30kg/m²	22	10	6	3	2	1

Figure 2. Kaplan–Meier curve of the duration of treatment.

$p = 0.029$). Even when using BMI as a continuous variable instead of a categorical one, the multivariable model showed that a higher BMI was significantly associated with an increased risk of discontinuation after adjustment (HR = 1.111, 95% CI: 1.031–1.197, $p = 0.006$).

Discussion

In this real-world analysis of the KOBIO registry, obese patients with RA initiating non-TNF-targeted treatment exhibited a poorer treatment response at 1 year compared to non-obese patients. Specifically, a higher BMI was associated with an increased risk of treatment discontinuation. These findings highlight the reduced efficacy and continuity of non-TNF-targeted treatments among obese patients, underscoring the need for customized therapeutic strategies for this population.

In recent years, interest in adipose tissue has surged due to the rapid rise in global obesity rates. Adipose tissue predominantly expands through fat cell hypertrophy, with increased adipocyte size strongly correlating with BMI.[8] Beyond their role in lipid storage, adipose tissue actively influences the immune system by releasing adipokines (leptin, resistin, adiponectin, and visfatin) and increasing the expression of inflammatory cytokines such as TNFα, IL-1, and IL-6. These molecules can affect immune functions, leading to local and generalized inflammation, potentially contributing to disease activity and therapy resistance in RA.[8] Recent research indicates that obesity is not only associated with RA activity but also affects response to targeted therapy. A previous meta-analysis revealed that DAS28 was significantly higher in obese RA patients (BMI ⩾30 kg/m²) compared to non-obese RA patients (BMI <30 kg/m²), with a mean difference of 0.14 (95% CI: 0.01–0.27).[12] Another meta-analysis showed that the odds of achieving remission were lower in obese patients (BMI ⩾30 kg/m²) compared to non-obese patients (BMI <30 kg/m²) treated with TNFi (odds ratio (OR): 0.34, 95% CI: 0.18–0.64).[18] Moreover, a recent study associated obesity with higher disease activity in ACPA-positive RA, obese RA patients had a 0.32 higher DAS44-CRP compared to normal weight patients over a 5-year follow-up.[19]

Most studies investigating the relationship between higher BMI and therapeutic response have focused on TNFi treatment. Elalouf et al.[13] found that a higher BMI reduces the retention rate of various TNFis. In addition, Gremese et al.[11] evaluated the correlation between BMI and response to TNFi treatment in long-standing RA, finding that obesity is a risk factor for a lower remission rate after 12 months of treatment. However, given that adipose tissue's overproduction of pro-inflammatory cytokines extends beyond TNF, it is crucial to explore the influence of weight/BMI on the efficacy of other targeted treatments to provide personalized care for obese patients with RA. Despite this necessity, the relationship between obesity and the response to non-TNF-targeted treatment remains insufficiently explored.

Table 3. Univariable and multivariable Cox proportional hazard models using baseline variables to predict factors associated with discontinuation of non-TNF-targeted treatments.[a]

	Univariate analysis	*p* Value	Multivariate analysis[b]	*p* Value
Age at start, years	1.000 (0.980–1.022)	0.979	0.998 (0.963–1.014)	0.358
Disease duration, months	0.997 (0.993–1.001)	0.175	0.996 (0.991–1.001)	0.083
Men	1.479 (0.751–2.914)	0.257	0.920 (0.397–2.132)	0.845
BMI, kg/m^2 [c]	1.097 (1.022–1.178)	0.011	1.108 (1.028–1.193)	0.007
BMI category				
BMI $\leqslant$ 24.9 kg/m^2	Reference group		Reference group	
BMI between 25.0 and 29.9 kg/m^2	1.815 (0.978–3.370)	0.059	1.846 (0.894–3.831)	0.098
BMI $\geqslant$ 30 kg/m^2	3.206 (1.119–9.182)	0.030	3.533 (1.147–10.879)	0.028
Current smoker	1.496 (0.536–4.173)	0.442		
Diabetes mellitus[a]	0.926 (0.328–2.616)	0.885		
Hypertension[a]	2.328 (1.019–5.317)	0.045	2.097 (0.909–4.836)	0.083
Targeted treatment				
Abatacept	Reference group		Reference group	
Tocilizumab	0.461 (0.251–0.846)	0.012	0.397 (0.196–0.808)	0.011
JAK inhibitors	0.667 (0.248–1.793)	0.422	0.521 (0.179–1.521)	0.233
Drug administration				
Subcutaneous	Reference group			
Intravenous	0.801 (0.241–2.655)	0.714		
Oral	1.032 (0.395–2.700)	0.948		
Use of concomitant csDMARDs	1.267 (0.500–3.212)	0.617		
Concomitant corticosteroid $\geqslant$5 mg/day	2.436 (1.368–4.340)	0.002	2.429 (1.218–4.842)	0.012
Erosion on X-ray[a]	1.029 (0.466–2.271)	0.943		
Joint space narrowing on X-ray[a]	1.624 (0.737–3.578)	0.229		
RF positivity[a]	0.998 (0.419–2.377)	0.996		
Anti-CCP positivity[a]	0.861 (0.297–2.495)	0.782		
Swollen joint counts (44 joints)	1.007 (0.950–1.067)	0.808		
Tender joint counts (44 joints)	0.951 (0.896–1.010)	0.102		
PGA	0.926 (0.805–1.066)	0.283		
PhGA	1.012 (0.8464–1.185)	0.882		
ESR	1.006 (0.996–1.016)	0.261		
CRP	1.025 (0.956–1.099)	0.485		

(Continued)

Table 3. (Continued)

	Univariate analysis	*p* Value	Multivariate analysis[b]	*p* Value
DAS28-ESR	0.909 (0.682–1.211)	0.391		
DAS28-CRP	0.825 (0.621–1.095)	0.182		
SDAI	0.987 (0.959–1.017)	0.389		
CDAI	0.982 (0.951–1.013)	0.247		

[a]Patients with missing data were excluded from the analyses.
[b]Multivariable Cox regression analysis was performed with adjustment for potential confounders (age, sex, disease duration, hypertension, targeted treatments, and use of concomitant corticosteroids were included).
[c]Instead of a categorical variable (normal or lower BMI vs overweight BMI vs obese BMI), a continuous variable (BMI, kg/m^2) was used in the multivariable model.
Anti-CCP, anti-cyclic citrullinated peptide; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, Disease Activity Score-28 joints; ESR, erythrocyte sedimentation rate; JAK, Janus kinase; PGA, patient global assessment; PhGA, physician global assessment; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; TNFi, tumor necrosis factor inhibitor.

In this study, we have demonstrated the negative impact of a high BMI on the efficacy and drug retention rate in RA patients treated with non-TNF-targeted therapies. To date, the impact of BMI on the efficacy of non-TNF-targeted treatments has been inconsistent. In a meta-analysis investigating the influence of obesity on the effect of non-TNF biologic agents, including abatacept and tocilizumab, no significant difference in the odds of achieving remission between obese and non-obese RA patients was found for abatacept (OR: 0.84, 95% CI: 0.65–1.09) and tocilizumab (OR: 0.91, 95% CI: 0.50–1.66).[18] Another systematic review found no significant influence of increased BMI in RA patients treated with tocilizumab and abatacept.[20] In an observational cohort study from the SCQM registry assessing the comparative effectiveness of abatacept versus adalimumab, no differences in DAS28-remission were found between abatacept and adalimumab in RA patients, regardless of BMI.[21] For JAKi, data on the impact of BMI on drug efficacy are scarce. Post hoc analyses of pooled data from phase III RCTs assessing the effect of BMI on tofacitinib or filgotinib suggested that BMI did not appear to affect the efficacy of tofacitinib or filgotinib in RA patients.[22,23] On the other hand, in a recent study using a large observational cohort, Schafer et al. suggested that obesity negatively impacts the effectiveness of cytokine-targeted therapies but not cell-targeted therapies. In that study, obesity negatively impacted the improvement in DAS28-ESR by −0.22 units (95% CI: −0.42 to −0.03) for women receiving tocilizumab and −0.41 units (95% CI: −0.74 to −0.07) for men receiving tocilizumab, while no effect of obesity was found for rituximab and abatacept.[24] They explained this difference by noting that white adipose tissue produces pro-inflammatory cytokines such as TNF and IL-6; the higher fat mass in adipose tissue in RA patients might lead to higher concentrations of these cytokines, affecting the therapeutic response.[25] In addition, a pooled analysis reported that patients with obese BMI receiving tocilizumab were less likely to achieve remission compared to those with normal BMI (adjusted HR: SDAI 0.80 (0.70–0.92), CDAI 0.77 (0.68–0.87)).[26] Another study assessed the impact of BMI on clinical outcomes in RA patients starting a second-line non-TNF-targeted treatment after the failure of a first TNFi. In that study, obese RA patients showed poor persistence and remission rates in second-line non-TNF-targeted treatment (abatacept, rituximab, or tocilizumab) compared to patients with normal BMI.[27] For baricitinib, in a post hoc analysis of the RA-BEACON trial, although not statistically different, the proportion of patients achieving CDAI $\leq$ 10 at week 12 was numerically lower in patients weighing over the median weight (20% vs 35%, $p = 0.130$).[28] Therefore, it is possible that physiological and pharmacokinetic factors in obese individuals could alter drug distribution, metabolism, and clearance, thereby impacting therapeutic efficacy.[29] Although more research is required regarding the impact of

obesity/BMI on non-TNF-targeted therapies, our study suggests the potential influence of BMI on the effectiveness of these treatments.

In our cohort, there was a notable difference in the swollen joint count after 1 year, particularly in the obese BMI group, compared to the normal or lower BMI group. Those patients with a BMI $\geq 30\,kg/m^2$ had significantly higher swollen joint counts after 1 year compared to the patients with a BMI $< 25\,kg/m^2$ ($p = 0.022$). This elevated swollen joint count likely contributed to the lesser improvement observed in the DAS28-ESR score in the obese BMI group ($p = 0.045$ when compared to the normal or lower BMI group). The persistence of a higher swollen joint count at baseline and after 1-year could indicate more severe or refractory inflammation in obese RA patients, which, in turn, may have contributed to lower drug continuation rates. In fact, a recent study showed that RA patients with obesity had a significantly higher swollen joint count during the disease course compared to normal-weight patients.[19] Therefore, while the differences in other clinical parameters were not statistically significant, the swollen joint count could be a key driver behind the lesser DAS28-ESR improvement and lower treatment retention in the obese BMI group.

In the current study, the analysis was conducted on KOBIO data collected up to 2021, which included newer classes of biologic agents as well as JAKi. Notably, most research exploring the relationship between BMI and the efficacy of b/tsDMARDs has not included analyses involving JAKi. Furthermore, the KOBIO registry enrolled RA patients during routine clinical practice, with data collected prospectively from both academic and community centers. Therefore, our data reflect the prescribing patterns of targeted treatments in real-world settings.

However, this investigation also had several limitations. In the KOBIO cohort, the prevalence of obesity among RA patients was approximately 4%, markedly lower than the 10%–30% reported in other studies.[11,13,30] This rate, however, aligns with the overall prevalence of obesity reported in the Korean population. While the prevalence of obesity among Korean adults has steadily increased over the decades, it was 5.4% in 2019 (6.3% for men and 4.4% for women), considerably lower than in other developed countries. Therefore, caution is needed when interpreting our findings. Second, along with regional differences in obesity prevalence, there is debate about the interpretation of recommended BMI cutoff points for determining overweight and obesity in Asian populations. Obesity could be defined as BMI $\geq 25\,kg/m^2$ according to the Asia-Pacific criteria of the World Health Organization guidelines.[31] In our study, we did not find a difference in treatment response between patients with a BMI $< 25\,kg/m^2$ and those with a $25\,kg/m^2 \leq$ BMI $< 30\,kg/m^2$. In general, Koreans with a BMI $\geq 30\,kg/m^2$ are classified as severely obese, and there were few patients with a BMI of 30 or higher in the KOBIO cohort. Therefore, caution should be needed when comparing these findings with Western RA patients. Third, our study did not include RA patients treated with TNFi. TNFi is still one of the most commonly prescribed targeted agents. However, as time progressed, there was an increase in the use of non-TNF-targeted treatment, including a recent rise in the use of JAKi. Actually, in Korea, non-TNF-targeted treatments were frequently prescribed as first-line treatment. Our earlier study found that more than 30% of RA patients with inadequate response to csDMARDs prescribed non-TNF-targeted treatments as a first-line targeted treatment. Moreover, although TNF inhibition was the first-choice mechanism of action among the various targeted drugs in the first targeted agent, tocilizumab was the most commonly used targeted agent (26.6%) among individual agents.[32] Therefore, our study aimed to specifically investigate the impact of BMI on the efficacy of non-TNF-targeted treatments in RA patients, an area that is less explored compared to the effects of obesity on TNFi. While it would have been beneficial to compare the effects of obesity on clinical outcomes between patients receiving TNFi and those receiving non-TNF-targeted treatments, the scope of our data access did not permit such a comparison. We acknowledge this as a limitation of our study and suggest future research should explore this comparison to provide a clearer understanding. Fourth, stratifying by BMI could reduce the sample size for obesity in our cohort, thereby diminishing study power. To address this limitation and ensure robustness in our findings, we performed additional analyses using BMI as a continuous variable rather than solely as a categorical variable (normal or lower BMI vs overweight BMI vs obese BMI). This approach allowed us to maximize the available data and explore the direction of the effect of BMI on treatment persistence across the full spectrum of BMI values. Fifth,

JAKi was the most commonly prescribed targeted treatment in the obese BMI group. In fact, all targeted treatment agents in RA are generally effective and considered to be comparable to one another. Both abatacept and tocilizumab are available for treatment in both subcutaneous and intravenous forms in Korea. However, unlike the intravenous formulation, the subcutaneous formulation does not allow for flexible dosing, which could result in reduced efficacy in especially obese patients with RA. For this reason, in obese RA patients where reduced efficacy due to dosing limitations is expected, an oral agent like JAKi may have been preferred over the intravenous or subcutaneous formulation. In addition, recent evidence showing the comparable efficacy of JAKi in monotherapy to combination therapy may be related to the lower rate of concomitant csDMARD in obese RA patients.[33] Lastly, discrepancies could exist in the use of targeted drugs due to differences in healthcare systems and the accessibility of RA treatment among countries. There could be a potential selection bias due to the dissimilar availability of targeted drugs with different mechanisms of action on the market. In Korea, the targeted treatments included in our study, with their approval date in Korea, are as follows: abatacept in 2010, tocilizumab in 2012, and JAKi, tofacitinib, and baricitinib in 2014 and 2019, respectively. Therefore, during the study period, except baricitinib, there may have been differences in the availability of the drugs over time, but they were likely not substantial. Moreover, economic accessibility to the drugs did not differ significantly based on the drug with different mechanisms of action. Under the Korean National Health Insurance reimbursement system, the medical costs among the originator, biosimilar TNFi, and non-TNF-targeted treatments are generally similar due to government-regulated pricing policies. Therefore, similar to other research derived from observational studies, more data are needed to improve the generalizability of our results.

Conclusion

In conclusion, our study found that obesity was associated with a lower clinical response and a higher rate of drug discontinuation for non-TNF-targeted treatments in patients with RA. Although various targeted treatments have revolutionized the management of RA, treatment failure with these drugs may still occur in actual practice. Therefore, understanding factors that influence the choice of b/tsDMARDs, at least in terms of clinical efficacy, is important to establish evidence-based guidelines for RA treatment. This study underscores the significance of considering patient-specific factors, such as BMI, in the treatment strategy for RA, highlighting the necessity for a more personalized approach to treatment in this population.

Declarations

Ethics approval and consent to participate

This analysis was conducted according to the principles of the Declaration of Helsinki. The study protocol and data collection forms were approved by the institutional review board or local ethics committee of all participating institutions, including that of Chonnam National University Hospital (approval no. CNUH-2012-239). All participants provided written informed consent for enrollment in the KOBIO registry.

Consent for publication

Not applicable.

Author contributions

Dong-Jin Park: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft.

Hyemin Jeong: Data curation; Formal analysis; Investigation; Project administration; Resources.

Sung-Eun Choi: Data curation; Formal analysis; Investigation; Project administration; Resources.

Ji-Hyoun Kang: Data curation; Formal analysis; Investigation; Project administration; Resources.

Shin-Seok Lee: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Acknowledgements

The authors are grateful to all of the rheumatologists and nurses who provided the data. In addition, the authors acknowledge support from the KCR board members and the members of the KCR Clinical Trials Committee for establishing the national registry. The authors also thank the patients and their families for their participation.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by a grant from the Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant numbers: HI19C0481, HC19C0052). The KCR commissioned the KOBIO as a Korean nationwide project to investigate the safety of biological agents in routine medical practice. KCR receives restricted grants from Korean pharmaceutical companies, presently AbbVie, BMS, Celltrion, Janssen, JW Pharmaceutical, and Pfizer. The investigators and their team have full academic freedom and can work independently of pharmaceutical industry influence. All decisions concerning analyses, interpretation, and publication are made autonomously of any industrial contribution.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Data are available upon reasonable request.

ORCID iDs
Dong-Jin Park https://orcid.org/0000-0002-8709-987X

Shin-Seok Lee https://orcid.org/0000-0001-6810-7355

References

1. Di Matteo A, Bathon JM and Emery P. Rheumatoid arthritis. *Lancet* 2023; 402: 2019–2033.
2. Salaffi F, Carotti M, Gasparini S, et al. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. *Health Qual Life Outcomes* 2009; 7: 25.
3. Finckh A, Gilbert B, Hodkinson B, et al. Global epidemiology of rheumatoid arthritis. *Nat Rev Rheumatol* 2022; 18: 591–602.
4. Pope J, Sawant R, Tundia N, et al. Comparative efficacy of JAK inhibitors for moderate-to-severe rheumatoid arthritis: a network meta-analysis. *Adv Ther* 2020; 37: 2356–2372.
5. Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2021; 73: 1108–1123.
6. Smolen JS, Landewe RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023; 82: 3–18.
7. Nagy G, Roodenrijs NMT, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021; 80: 31–35.
8. Li Q, Hagberg CE, Silva Cascales H, et al. Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce. *Nat Med* 2021; 27: 1941–1953.
9. Ohno T, Aune D and Heath AK. Adiposity and the risk of rheumatoid arthritis: a systematic review and meta-analysis of cohort studies. *Sci Rep* 2020; 10: 16006.
10. Singh S, Facciorusso A, Singh AG, et al. Obesity and response to anti-tumor necrosis factor-alpha agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One* 2018; 13: e0195123.
11. Gremese E, Carletto A, Padovan M, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor alpha in rheumatoid arthritis: an approach to a personalized medicine. *Arthritis Care Res (Hoboken)* 2013; 65: 94–100.
12. Vidal C, Barnetche T, Morel J, et al. Association of body mass index categories with disease activity and radiographic joint damage in rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol* 2015; 42: 2261–2269.
13. Elalouf O, Lidar M, Reitblat T, et al. High body mass index is associated with shorter retention of tumor necrosis factor-alpha blocker treatment in rheumatoid arthritis. *Biologics* 2021; 15: 279–287.
14. Kim J, Koh JH, Choi SJ, et al. KOBIO, the first web-based Korean biologics registry operated with a unified platform among distinct disease entities. *J Rheum Dis* 2021; 28: 176–182.
15. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Ann Rheum Dis* 2010; 69: 1580–1588.
16. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement:

guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

17. Van Gestel AM, Haagsma CJ and Van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998; 41: 1845–1850.
18. Shan J and Zhang J. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine* 2019; 86: 173–183.
19. Hollander NKD, Boeren AMP, Van Der Helm-Van Mil AHM, et al. Patients with obesity have more inflamed joints and higher CRP levels during the disease course in ACPA-positive RA but not in ACPA-negative RA. *Arthritis Res Ther* 2024; 26: 42.
20. Gialouri CG, Pappa M, Evangelatos G, et al. Effect of body mass index on treatment response of biologic/targeted-synthetic DMARDS in patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis. A systematic review. *Autoimmun Rev* 2023; 22: 103357.
21. Vallejo-Yague E, Burkard T, Finckh A, et al. Comparative effectiveness of biologics in patients with rheumatoid arthritis stratified by body mass index: a cohort study in a Swiss registry. *BMJ Open* 2024; 14: e074864.
22. 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: e00210.
23. 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: 1555–1574.
24. Schafer M, Meissner Y, Kekow J, et al. Obesity reduces the real-world effectiveness of cytokine-targeted but not cell-targeted disease-modifying agents in rheumatoid arthritis. *Rheumatology (Oxford)* 2020; 59: 1916–1926.
25. Francisco V, Pino J, Gonzalez-Gay MA, et al. Adipokines and inflammation: is it a question of weight? *Br J Pharmacol* 2018; 175: 1569–1579.
26. Abuhelwa AY, Hopkins AM, Sorich MJ, et al. Association between obesity and remission in rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs. *Sci Rep* 2020; 10: 18634.
27. Iannone F, Fanizzi R, Notarnicola A, et al. Obesity reduces the drug survival of second line biological drugs following a first TNF-α inhibitor in rheumatoid arthritis patients. *Joint Bone Spine* 2015; 82: 187–191.
28. Genovese MC, Kremer JM, Kartman CE, et al. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology (Oxford)* 2018; 57: 900–908.
29. Gouju J and Legeay S. Pharmacokinetics of obese adults: not only an increase in weight. *Biomed Pharmacother* 2023; 166: 115281.
30. Baker JF, Reed G, Poudel DR, et al. Obesity and response to advanced therapies in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2022; 74: 1909–1916.
31. Kim BY, Kang SM, Kang JH, et al. 2020 Korean society for the study of obesity guidelines for the management of obesity in Korea. *J Obes Metab Syndr* 2021; 30: 81–92.
32. Park DJ, Choi SJ, Shin K, et al. Switching profiles in a population-based cohort of rheumatoid arthritis receiving biologic therapy: results from the KOBIO registry. *Clin Rheumatol* 2017; 36: 1013–1022.
33. Pope J, Finckh A, Silva-Fernandez L, et al. Tofacitinib monotherapy in rheumatoid arthritis: clinical trials and real-world data contextualization of patients, efficacy, and treatment retention. *Open Access Rheumatol* 2024; 16: 115–126.