Four-year follow-up of atherogenicity in rheumatoid arthritis patients: from the nationwide Korean College of Rheumatology Biologics Registry

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Abstract
Objective This study aimed to evaluate the impact of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) on lipid profile and atherogenic index of plasma (AIP) in rheumatoid arthritis (RA) patients and to compare the occurrence of dyslipidemia between patients using bDMARDs, tsDMARDs, or conventional DMARDs (cDMARDs).

Methods Data on lipid profile, AIP, and occurrence of dyslipidemia were collected from the Korean College of Rheumatology BIOlogics registry. A comparison was conducted between patients using bDMARDs (tumor necrosis factor (TNF)-α inhibitor, tocilizumab, abatacept), Janus kinase inhibitors (JAKis), and cDMARDs. The Kaplan-Meier method was used to compare the occurrence of dyslipidemia between groups, and hazard ratios (HR) were calculated using the cox proportional hazard method.

Results The data of 917, 826, 789, 691, and 520 RA patients were eligible for analysis at the baseline, 1-year, 2-year, 3-year, and 4-year follow-ups, respectively. Baseline total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) were higher in the cDMARDs group, whereas AIP was comparable. During the 4-year follow-up, AIP was comparable between the groups. The occurrence of dyslipidemia did not show a significant difference when comparing the bDMARDs/tsDMARDs and cDMARDs groups (P=0.06) or the TNF-α inhibitor, tocilizumab, abatacept, JAKi, and cDMARD user groups (P=0.3). In the multivariate cox proportional hazard model, older age (HR=1.03, P=0.005) and concomitant hypertension (HR=2.21, P=0.013) were significantly associated with dyslipidemia occurrence.

Conclusion Long-term use of bDMARDs and tsDMARDs is relatively safe with regard to lipid profile, AIP, and the occurrence of dyslipidemia in RA patients.

Key Points
- The use of bDMARDs and tsDMARDs did not increase the risk of dyslipidemia than cDMARDs use in patients with RA.
- AIP was comparable between bDMARDs user, tsDMARDs user, and cDMARDs user group in 4-year follow-up data.
- Based on the present study, the long-term use of bDMARDs or tsDMARDs did not significantly deteriorate atherogenic lipid profile nor an increased risk of dyslipidemia in patients with RA.

Keywords Atherogenic index of plasma · Biologic disease-modifying antirheumatic drugs · Janus kinase inhibitor · Lipid profile · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune-mediated systemic arthritis, which impacts about 0.3–1% of the population worldwide [1, 2]. The leading cause of death in these patients is cardiovascular disease (CVD) [3]. The risk of developing CVD is 1.5 to 2 times higher for RA patients than for a healthy population [4]. The European League Against Rheumatism (EULAR) task force recommends to estimate the risk of CVD in RA patients and to properly manage CVD-related comorbidities, such as hypertension and dyslipidemia [5].

Several biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been applied in RA therapy and showed excellent therapeutic effects [6, 7]. However, aggravation of the lipid profile has been identified as a side effect of these drugs. Soutu et al. showed that tocilizumab increased the odds ratio (OR) for hyperlipidaemia and the levels of both high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), whereas TNF-α inhibitor did not [8]. Janus kinase inhibitors (JAKi)—tofacitinib and upadacitinib—caused dose-dependent increases of LDL-C and HDL-C [8, 9]. Also, conventional DMARDs could alter lipid profiles. Methotrexate monotherapy and triple therapy (methotrexate, sulfasalazine, hydroxychloroquine) increased total cholesterol (TC), LDL-c, and HDL-c in patients with RA [10]. Another study demonstrated that hydroxychloroquine therapy lowered TC, LDL-c, and triglyceride than methotrexate therapy [11]. These imply that bDMARDs, tsDMARDs, and cDMARDs could affect on lipid profile of RA patients.

Recently, we demonstrated in a prospective cohort study that TNF-α inhibitor usage in spondyloarthritis patients did not result in a significant exacerbation of the atherogenic lipid profile or atherogenic index of plasma (AIP) [12]. Many CVD risk estimators exist, such as ASCVD plus, SCORE, Framingham score, Reynold score, and QRISK3. These measures are applied to predict the 10-year risk for CVD; however, they often over- or underestimate the real CVD risk in RA patients [13]. Such risk calculators include a lipid profile of total cholesterol, HDL-C, and LDL-C. While plasma levels of LDL-C have been targeted in the treatment of dyslipidemia, small particle size LDL-C is particularly implicated for atherosclerosis [14]. Therefore, an estimation of the atherogenic lipid profile can provide more precise information for CVD risk.

The AIP is calculated using the logarithm of the ratio of plasma triglyceride (TG) and HDL-C and has shown potential to predict CVD [15]. Patients with angiographically proven coronary artery disease exhibited a higher AIP than the control group, and AIP correlated with lipoprotein particle size and fractional esterification rate in apoB-lipoprotein-depleted plasma (FER_{HDL}) [15–17]. Both FER_{HDL} and lipoprotein particle size are biomarkers for atherogenicity [17]. Furthermore, in various autoimmune diseases, AIP showed significant association with atherosclerosis [18–20].

Here, we aim to evaluate the real-world influence of bDMARDs/tsDMARDs on the atherogenic lipid profile of RA patients by comparing the lipid profiles and AIP of those treated with bDMARDs/tsDMARDs and those undergoing cDMARD treatments. In addition, the occurrence of dyslipidemia was also compared between the two groups and further assessed according to the subgroup of bDMARDs/tsDMARDs.

Methods

Data sources

The Korean College of Rheumatology BIOlogics (KOBIO) registry is a nationwide resource for inflammatory arthritis conducted by the Korean College of Rheumatology. This registry collected information on the clinical manifestation, treatment response, safety profiles, and laboratory data of RA patients, using various treatments, from 58 tertiary care hospitals in the Republic of Korea. Between December 2012 and December 2019, subjects undergoing bDMARD or tsDMARD treatment and, as a control group, RA patients who were not exposed to bDMARDs or tsDMARDs were enrolled. Baseline and annual follow-up data were collected. This study was conducted in accordance with the Declaration of Helsinki (1964). Written informed consent for enrolment in the KOBIO registry was obtained from all participants. This study was approved by the Institutional Review Board of Konkuk University Medical Center (approval number: 2020-05-003).

Collected data

Baseline demographic characteristics, comorbidities, disease activity score-28 (DAS28), smoking status, laboratory data including lipid profile, and medication information were collected from the KOBIO registry. The annually obtained lipid profile data were also extracted. Patients lacking information for lipid profile or taking lipid-lowering agents at baseline were excluded. In the bDMARD/tsDMARD user group, when a change or cessation of bDMARD/tsDMARD treatment occurred, the lipid profile before any alteration was used and data after change or cessation were excluded from the analysis. The patients’ AIPs were calculated and categorized into low-risk (AIP < 0.11), intermediate-risk (0.11 ≤ AIP ≤ 0.21), and high-risk groups (AIP > 0.21) [12].

The safety profile of drugs used in patients with new-onset dyslipidemia, defined as those requiring lipid-lowering agents according to the American Heart Association treatment guideline, was recorded in the KOBIO registry [21]. The lipid
profiles of enrolled patients after the prescription of lipid-lowering agents were excluded from the analysis of follow-up data.

**Study design**

To evaluate the differences in lipid profile and AIP between the bDMARDs/tsDMARDs group and the cDMARDs group, we compared their respective baseline and 1-year to 4-year follow-up data. The comparison was also performed after subgrouping the bDMARD/tsDMARD users into TNF-α inhibitor, tocilizumab, abatacept, and JAKi (tofacitinib, baricitinib) groups. The bDMARD or tsDMARD treatment group was allowed to use cDMARDs. The occurrence of dyslipidemia was compared between the bDMARDs/tsDMARDs and cDMARDs groups and between the TNF-α inhibitor, tocilizumab, abatacept, and JAKi, and cDMARDs groups.

**Statistical analysis and data management**

The data’s normality was tested using the Kolmogorov-Smirnov test, and continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR). A Student’s t test, one-way analysis of variance (ANOVA), or Wilcoxon signed rank test was properly selected for the analysis of continuous variables. Post hoc analysis was performed by Turkey method. Categorical variables were compared using a Chi-square test or Fisher’s exact test. The Kaplan-Meier method and log rank test were used to compare the occurrence of dyslipidemia between groups. Hazard ratio (HR) was calculated using cox regression analysis. Factors with a P value under 0.1 following univariate cox regression analysis were included in the multivariate cox regression analysis. Values of P < 0.05 were considered statistically significant. All tests were performed using the R software (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Comparison of baseline characteristics between the bDMARDs/tsDMARDs group and cDMARDs group**

The data of a total of 2949 patients for baseline, 2565 for 1-year follow-up, 2073 for 2-year follow-up, 1612 for 3-year follow-up, and 1197 for 4-year follow-up were collected in the KOBIO registry. After excluding non-eligible data, 917 (baseline), 826 (1-year follow-up), 789 (2-year follow-up), 691 (3-year follow-up), and 520 (4-year follow-up) patients were included in the analysis (Fig. 1). RA patients using bDMARDs/tsDMARDs experienced a longer disease duration and showed a higher DAS28 score. The most commonly used bDMARD/tsDMARD was TNF-α inhibitors (48.7%). For laboratory findings, the inflammatory markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were significantly higher in the bDMARDs/tsDMARDs group than the cDMARDs group, whereas TC, LDL-C, and TG levels were higher in the cDMARDs group. When analyzing AIP, the bDMARDs/tsDMARDs and cDMARDs groups were comparable (Table 1). In subgroup analysis, TC was higher in the cDMARDs group than the TNF-α inhibitor group, and LDL-C was higher in the cDMARDs group than in the tocilizumab group (Supplementary Table 1).

**Comparison of lipid profile and AIP over 1-year to 4-year follow-up between bDMARDs/tsDMARDs and cDMARDs groups and subgroup analysis**

For the 1-year follow-up data, LDL-C was significantly higher in the bDMARDs/tsDMARDs than in the cDMARDs group; however, other lipid profiles and AIP were comparable between the groups (Table 2). In subgroup analysis, TC of the tocilizumab group was significantly higher than the TNF-α inhibitor and cDMARDs groups, and HDL-C was higher in the JAKi group than the abatacept group (Table 3).

When analyzing the 2-year follow-up data, the lipid profile and AIP of the bDMARDs/tsDMARDs and cDMARDs groups showed no significant differences (Supplementary Table 2-1). In subgroup analysis, HDL-C was higher in the JAKi group (median HDL-C 73.5 mg/dL) than the TNF-α inhibitor, tocilizumab, abatacept, and cDMARDs groups (median HDL-C 57.0, 59.0, 57.0, 61.0 mg/dL, respectively; Supplementary Table 2-2).

For the 3- and 4-year follow-up data, lipid profile and AIP did not show significant differences when comparing the bDMARDs/tsDMARDs and cDMARDs groups (Supplementary Table 3-1, 4-1) or in subgroup analysis (Supplementary Table 3-2, Table 4-2).

**Associated factors of dyslipidemia and comparison of new-onset dyslipidemia between bDMARDs/tsDMARDs and cDMARDs groups and subgroup analysis**

The mean follow-up duration for the bDMARDs/tsDMARDs group and the cDMARDs group was 30.1 ± 17.4 and 34.4 ± 16.7 months, respectively. During the observation period, dyslipidemia was observed in 59 patients (8.5%) of the bDMARDs/tsDMARDs group and 15 patients (6.8%) of the cDMARDs group, with the difference being non-significant (P=0.508). A cumulative hazard proportion curve of dyslipidemia occurrence did not show a significant difference between the bDMARDs/tsDMARDs group and cDMARDs groups (Fig. 2a, P=0.06). The occurrence of dyslipidemia was similar after dividing bDMARDs/tsDMARDs into each medication.
Table 1 Baseline characteristics of RA patients with bDMARDs/tsDMARDs and cDMARDs

|                               | RA patients with bDMARDs or tsDMARDs (N=696) | RA patients with cDMARDs (N=221) | P     |
|-------------------------------|---------------------------------------------|----------------------------------|-------|
| Female, N (%)                 | 590 (84.8%)                                 | 188 (85.1%)                      | 1.000 |
| Age (years)                   | 55.1 ± 12.8                                 | 55.4 ± 11.9                      | 0.717 |
| Disease duration (years)      | 8.2 ± 7.7                                    | 6.7 ± 7.6                        | 0.016 |
| BMI (kg/m²)                   | 22.5 ± 3.3                                   | 22.9 ± 3.2                       | 0.063 |
| Smoking                       |                                             |                                  | 0.826 |
| Never                         | 594 (85.3%)                                  | 184 (83.6%)                      |       |
| Ex-smoker                     | 51 (7.3%)                                    | 18 (8.2%)                        |       |
| Current smoker                | 51 (7.3%)                                    | 18 (8.2%)                        |       |
| Hypertension, N (%)           | 197 (28.3%)                                  | 64 (29.0%)                       | 0.918 |
| Ischemic heart disease, N (%) | 16 (2.3%)                                    | 2 (0.9%)                         | 0.306 |
| Congestive heart failure, N (%)| 11 (1.6%)                                    | 0 (0.0%)                         | 0.127 |
| DM without complication, N (%)| 70 (10.1%)                                   | 16 (7.2%)                        | 0.623 |
| DM with complication, N (%)   | 8 (1.1%)                                     | 2 (0.9%)                         | 1.000 |
| Stroke, N (%)                 | 6 (0.9%)                                     | 1 (0.5%)                         | 0.868 |
| Obesity, N (%)                | 14 (2.0%)                                    | 5 (2.3%)                         | 1.000 |
| ESR (mm/hr)                   | 47.9 ± 26.3                                  | 31.9 ± 26.5                      | <0.001|
| CRP (mg/dL)                   | 2.3 ± 3.0                                    | 0.7 ± 1.6                        | <0.001|
| DAS28-ESR                     | 5.7 ± 1.0                                    | 3.5 ± 1.3                        | <0.001|
| DAS28-CRP                     | 5.0 ± 1.0                                    | 2.8 ± 1.2                        | <0.001|
| bDMARDs or tsDMARDs           |                                             |                                  |       |
| TNF-α inhibitor               | 339 (48.7%)                                  |                                  |       |
| Tocilizumab                   | 200 (28.7%)                                  |                                  |       |
| Abatacept                      | 94 (13.5%)                                   |                                  |       |
| JAKi (tofacitinib or baricitinib) | 63 (9.1%)                             |                                  |       |
| cDMARDs                       |                                             |                                  |       |
| Methotrexate, N (%)           | 591 (84.9%)                                  | 195 (88.2%)                      | 0.263 |
| Hydroxychloroquine, N (%)     | 143 (20.5%)                                  | 92 (41.6%)                       | <0.001|
| Sulfasalazine, N (%)          | 59 (8.5%)                                    | 28 (12.7%)                       | 0.085 |
| Leflunomide, N (%)            | 160 (23.0%)                                  | 65 (29.4%)                       | 0.065 |
| Tacrolimus, N (%)             | 101 (14.5%)                                  | 20 (9.0%)                        | 0.048 |
| Corticosteroid, N (%)         | 584 (83.9%)                                  | 163 (73.8%)                      | 0.011 |
| Dose of corticosteroid (equivocal to prednisolone, mg/day) | 5.5 ± 3.8                                    | 4.5 ± 3.6                        | 0.003 |
| Rheumatoid factor positivity, N (%) | 594 (87.0%)                           | 182 (83.9%)                      | 0.298 |
| ACPA positivity, N (%)        | 515 (86.3%)                                  | 162 (85.3%)                      | 0.821 |
| Total cholesterol (mg/dL)     | 175.3 ± 37.0                                 | 182.5 ± 34.0                     | 0.011 |
| HDL-C (mg/dL)                 | 58.3 ± 23.0                                  | 58.6 ± 16.4                      | 0.812 |
| LDL-C (mg/dL)                 | 76.2 ± 49.0                                  | 84.1 ± 46.9                      | 0.034 |
| Triglyceride (mg/dL)          | 102.6 ± 51.2                                 | 116.4 ± 74.6                     | 0.011 |
| AIP                           | −0.142 ± 0.249                               | −0.108 ± 0.292                   | 0.129 |
| AIP category                  |                                             |                                  | 0.089 |
| Low risk (AIP<0.11)           | 582 (83.6%)                                  | 174 (78.7%)                      |       |
| Intermediate risk (0.11≤AIP≤0.21) | 57 (8.2%)                             | 18 (8.1%)                        |       |
| High risk (AIP>0.21)          | 57 (8.2%)                                    | 29 (13.1%)                       |       |

ACPA, anti-citrullinate protein antibody; AIP, atherogenic index of plasma; bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; cDMARDs, conventional disease-modifying antirheumatic drugs; CRP, C-reactive protein; DAS28, disease activity score-28; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; JAKi, janus kinase inhibitor; TNF-α, tumor necrosis factor α
subgroup (Fig. 2b, \( P=0.3 \)). In univariate Cox proportional analysis, older age (HR=1.03, \( P=0.004 \)), TNF-\( \alpha \) inhibitor use (HR=3.461, \( P=0.018 \)), tocilizumab use (HR=3.654, \( P=0.014 \)), abatacept use (HR=3.724, \( P=0.032 \)), and JAKi use (HR=5.761, \( P=0.044 \)) were associated with dyslipidemia occurrence (Table 4). Following multivariate analysis, older age (HR=1.029, \( P=0.005 \)) and combined hypertension (HR=2.206, \( P=0.013 \)) showed significant association, whereas bDMARDs/tsDMARDs use did not (Table 4).

Discussion

The present study demonstrated some important points on the safety profile of bDMARDs and tsDMARDs, focusing on dyslipidemia and atherogenic lipid profile. First, the level of individual lipid profile components was influenced by the use of bDMARDs/tsDMARDs. However, atherogenicity, represented by AIP, did not deteriorate in the bDMARDs/tsDMARDs group. Second, the occurrence of dyslipidemia, which required lipid-lowering agents, was not higher in the bDMARDs/tsDMARDs group. These results suggest that bDMARDs and tsDMARDs would not negatively affect atherogenicity in RA patients when starting treatment with these drugs.

Since TNF-\( \alpha \) inhibitors were first introduced in RA treatment, various bDMARDs and tsDMARDs have shown excellent therapeutic effects in RA patients who do not respond to cDMARDs. However, the deterioration of the patient’s lipid profile, especially for LDL-C and TG, has been identified as a potential issue. A cohort study conducted in Israel analyzed the 24-month follow-up data of patients using TNF-\( \alpha \) inhibitors for inflammatory arthritis (including RA, ankylosing spondylitis (AS), and psoriatic arthritis). A significant increase in TC and TG levels was seen, with changes being more prominent in the first 6 months after beginning treatment.

Table 2  Comparison between RA patients with bDMARDs/JAKi and cDMARDs of 1-year follow up lipid profile and AIP

| Lipid Profile Component | RA patients with bDMARDs or JAKi (N=652) | RA patients with cDMARDs (N=174) | \( P \) |
|-------------------------|--------------------------------------------|---------------------------------|------|
| Total cholesterol (mg/dL) | 184.0 [161.0;209.0] | 181.0 [159.0;203.0] | 0.212 |
| HDL-C (mg/dL) | 59.0 [49.0;69.0] | 59.0 [49.0;68.0] | 0.652 |
| LDL-C (mg/dL) | 95.0 [66.8;120.0] | 85.5 [44.0;112.0] | 0.005 |
| Triglyceride (mg/dL) | 109.0 [76.0;152.0] | 97.5 [72.0;137.0] | 0.164 |
| AIP | \(-0.090 \pm 0.286\) | \(-0.116 \pm 0.269\) | 0.275 |

*The Mantel–Haenszel \( \chi^2 \) test was used.

AIP, atherogenic index of plasma; bDMARDs, biologic disease-modifying antirheumatic drugs; cDMARDs, conventional disease-modifying antirheumatic drugs; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; JAKi, janus kinase inhibitor.
Table 3  Comparison of lipid profile and AIP between RA patients with cDMARDs, TNF-α inhibitor, tocilizumab, abatacept, and JAKi (1-year follow up data)

|                      | RA patients with cDMARDs (N=174) | RA patients with TNF-α inhibitor (N=319) | RA patients with tocilizumab (N=209) | RA patients with Abatacept (N=87) | RA patients with JAKi (N=37) |
|----------------------|-----------------------------------|------------------------------------------|-------------------------------------|----------------------------------|-----------------------------|
| **Total cholesterol (mg/dL)** | 181.0 [159.0;203.0]†             | 181.0 [160.0;206.0]‡                     | 192.0 [165.0;219.0]†‡               | 183.0 [156.0;204.0]             | 183.0 [164.0;212.0]         |
| HDL-C (mg/dL)        | 59.0 [49.0;68.0]                  | 59.0 [48.0;68.0]                         | 94.0 [68.0;117.5]                   | 99.0 [56.0;122.0]               | 68.0 [54.0;76.0]‡           |
| LDL-C (mg/dL)        | 85.5 [44.0;112.0]                 | 94.0 [68.0;117.5]                        | 99.0 [56.0;122.0]                   | 94.0 [72.0;121.7]               | 97.0 [75.0;118.0]           |
| Triglyceride (mg/dL) | 97.5 [72.0;137.0]                 | 107.0 [76.0;142.0]                       | 112.0 [77.0;165.0]                  | 111.0 [80.5;152.5]              | 110.0 [71.0;147.0]          |
| AIP                  | −0.116 ± 0.269                    | −0.095 ± 0.280                          | −0.086 ± 0.291                      | −0.066 ± 0.242                  | −0.121 ± 0.388              |

AIP, atherogenic index of plasma; cDMARDs, conventional disease-modifying antirheumatic drugs; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; JAKi, janus kinase inhibitor; TNF-α, tumor necrosis factor α

Table 4  Univariable and multivariable cox regression analysis of predicting new onset dyslipidemia

|                      | Univariable HR | 95% CI | P       | Multivariate HR | 95% CI | P   |
|----------------------|----------------|--------|---------|-----------------|--------|-----|
| Age (year)           | 1.033          | 1.010, 1.055 | 0.004  | 1.029           | 1.009, 1.050 | 0.005 |
| Female               | 1.106          | 0.539, 2.270 | 0.783  |                 |        |     |
| Disease duration (year) | 0.972     | 0.938, 1.008 | 0.126  |                 |        |     |
| BMI (kg/m²)          | 1.006          | 0.927, 1.093 | 0.881  |                 |        |     |
| Hypertension         | 1.835          | 0.944, 3.568 | 0.073  | 2.206           | 1.183, 4.116 | 0.013 |
| Diabetes mellitus    | 1.023          | 0.443, 2.362 | 0.958  |                 |        |     |
| DAS28-ESR            | 0.901          | 0.507, 1.600 | 0.722  |                 |        |     |
| DAS28-CRP            | 0.907          | 0.523, 1.572 | 0.728  |                 |        |     |
| Rheumatoid factor positivity | 1.259      | 0.608, 2.609 | 0.535  |                 |        |     |
| ACPA positivity      | 0.984          | 0.476, 2.032 | 0.965  |                 |        |     |
| TNF-α inhibitor      | 3.461          | 1.237, 9.688 | 0.018  | 1.787           | 0.931, 3.429 | 0.081 |
| Tocilizumab          | 3.654          | 1.301, 10.267 | 0.014  | 1.918           | 0.925, 3.980 | 0.080 |
| Abatacept            | 3.724          | 1.118, 12.399 | 0.032  | 2.099           | 0.861, 5.121 | 0.103 |
| JAKi                 | 5.761          | 1.050, 31.620 | 0.044  | 3.070           | 0.675, 13.972 | 0.147 |
| Methotrexate         | 0.947          | 0.446, 2.012 | 0.888  |                 |        |     |
| Hydroxychloroquine   | 0.921          | 0.479, 1.769 | 0.804  |                 |        |     |
| Sulfasalazine        | 0.260          | 0.035, 1.904 | 0.185  |                 |        |     |
| Leflunomide          | 0.940          | 0.520, 1.700 | 0.838  |                 |        |     |
| Tacrolimus           | 0.750          | 0.336, 1.677 | 0.484  |                 |        |     |

ACPA, anti-citrullinate protein antibody; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28, disease activity score-28; ESR, erythrocyte sedimentation rate; HR, hazard ratio; JAKi, janus kinase inhibitor; TNF-α, tumor necrosis factor α

The Mantel–Haenszel χ² test was used
†Significant difference in total cholesterol between cDMARDs group and tocilizumab group demonstrated by post hoc analysis via Tukey method
‡Significant difference in total cholesterol between TNF-α inhibitor group and tocilizumab group demonstrated by post hoc analysis via Tukey method
§Significant difference in HDL-C between abatacept group and JAKi group demonstrated by post hoc analysis via Tukey method
and then reaching a plateau before the 24-month follow-up [22]. Furthermore, spondyloarthritis patients who used TNF-α inhibitors for 2 years displayed a slight increase in TC, but their AIP did not change significantly [12]. Souto et al. showed that tocilizumab increased the OR for hyperlipidaemia and LDL-C/HDL-C increment, and tofacitinib increased the OR for LDL-C/HDL-C increment dose-dependently [8]. Another meta-analysis revealed that TNF-α inhibitor usage increased TC significantly, but neither LDL-C nor atherogenic index (TC to HDL-C ratio) was affected [23].

In the present study, we included bDMARDs other than just TNF-α inhibitors and JAKi, including baricitinib, in the analysis. Here, LDL-C was lower in the bDMARDs/tsDMARDs group than the cDMARDs group (LDL-C 76.2 vs 84.1 mg/dL, \( P=0.005 \)) at baseline. However, after a short time (1-year follow-up data), LDL-C became higher in the bDMARDs/tsDMARDs than in the cDMARDs group (LDL-C 95.0 vs 85.5 mg/dL, \( P=0.005 \)). Other lipid profile components, which showed significant differences at baseline, TC, and TG, did not display differences in the 1- to 4-year follow-up data. This may imply that the use of bDMARDs/tsDMARDs definitely increases LDL-C, but this increment occurred only within the first year of using these medications.

Moreover, estimating the atherogenic lipid profile is more useful for predicting the risk of CVD than simply using TC, LDL-C, HDL-C, or TG. Small dense LDL-C plays a key role in the progression of atherosclerosis and can more precisely represent a patient’s atherogenicity [24]. However, measuring these particles via electrophoresis is not feasible in clinical practice. An alternative biomarker for atherogenicity is \( \text{FER}_{\text{HDL}} \), which appears to correlate with angiographically confirmed atherosclerosis [25]. The AIP has been shown to correlate with both lipoprotein particle size and \( \text{FER}_{\text{HDL}} \) [17]. In the EULAR guidelines for CVD risk management, intima-media thickness (IMT) measured by carotid ultrasound is recommended as an adjuvant CVD risk estimator [5]. Carotid IMT also correlated positively with AIP in several autoimmune diseases (Behcet’s disease, AS, and systemic lupus erythematosus) [18–20]. Since AIP can be calculated when the level of plasma HDL-C and TG is available, it is a feasible biomarker for measuring atherogenicity in clinical practice. In the current study, AIP levels were not significantly different between the bDMARDs/tsDMARDs group and the cDMARDs group through a 4-year follow-up, which indicates that bDMARDs/tsDMARDs are relatively safe with respect to atherogenic lipid profile when used in RA patients.

In the present study, the occurrence of dyslipidemia did not differ between the bDMARDs/tsDMARDs and cDMARDs groups, and this was also observed in subgroup analysis. In multivariate cox proportional regression analysis, the use of bDMARDs/tsDMARDs did not influence the occurrence of dyslipidemia, whereas older age and combined hypertension significantly increased the risk of new-onset dyslipidemia. The results of the regression analysis support the safety of bDMARDs/tsDMARDs regarding new-onset dyslipidemia.

While notable results were obtained, several limitations exist in the present study. First, we excluded non-eligible data from analysis due to missing information. For some RA
patients enrolled in the KOBIO registry, all data from baseline to the 4-year follow-up was present, whereas several had missing data. Therefore, it was impossible to compare the paired lipid profile and AIP measurements for the same patients, as it reduced the eligible data set. Second, the sample size of tsDMARDs users was relatively small. The use of tsDMARDs was approved in the Republic of Korea in 2014 for tofacitinib and 2017 for baricitinib. Therefore, at first, these drugs could only be used as third-line therapy after the failure of one kind of bDMARD. The KOBIO registry is an on-going prospective cohort study; therefore, the inclusion of tsDMARDs users will continue to increase, and further evaluation is possible in future.

In conclusion, AIP, a feasible atherogenic biomarker did not significantly deteriorate in RA patients using bDMARDs or tsDMARDs when compared with those undergoing cDMARD treatments. Furthermore, the occurrence of dyslipidemia, requiring lipid-lowering agents, was comparable between the bDMARDs/tsDMARDs group and the cDMARDs group. While an increase in certain lipid profile components was observed in the bDMARDs/tsDMARDs group, this increase did not progress further after the first year of administration. Therefore, using bDMARDs or tsDMARDs to treat RA patients would be relatively safe with regard to their atherogenic lipid profile.

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Declarations

Ethics approval and consent to participate This study was conducted in accordance with the Declaration of Helsinki (1964 Declaration of Helsinki and its later amendments). Written informed consent was obtained from each patient. This study was approved by the Institutional Review Board of Konkuk University Medical Center (approval number: 2019-05-003). Informed consent was obtained from all participants.

Consent for publication All authors agreed to publish the present article.

Competing interests The authors declare no competing interests.

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