Four-year Follow up of Atherogenicity in Rheumatoid Arthritis Patients: From Nationwide Korean College of Rheumatology Biologics Registry

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Abstract

Background: 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 dyslipidaemia between patients using bDMARDs, tsDMARDs, or conventional DMARDs (cDMARDs).

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

Results: Data of a total 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. Occurrence of dyslipidaemia 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 dyslipidaemia occurrence.

Conclusion: Long term use of bDMARDs and tsDMARDs is relatively safe with regards to lipid profile, AIP, and the occurrence of dyslipidaemia in RA patients.

Background

Rheumatoid arthritis (RA) is an autoimmune-mediated systemic arthritis, which impacts about 0.3–1% of the population worldwide [1, 2]. Uncontrolled inflammation induces arthralgia, systemic symptoms such as fatigue, and chronically destroys articular structures [3]. These harmful results reduce the quality of life and range of motion in RA patients, and changes to the articular structure are irreversible. Therefore, the primary treatment goals for RA are to control inflammation, reduce arthralgia, and eventually, to prevent the structural damage of joints [4]. However, the causes of death in RA patients are not related to these symptoms or structural changes. The leading cause of death in these patients is cardiovascular disease (CVD) [5].

The risk of developing CVD is 1.5 to 2 times higher for RA patients than for a healthy population [6]. Inflammatory mediators, such as tumour necrosis factor-α (TNF-α) and the interleukin 1 family, are critically implicated in the pathogenesis of RA. These cytokines are also known to promote destabilisation of the atherosclerotic plaque, the formation of vulnerable plaques, platelet aggregation, and to create an environment that is susceptible to acute myocardial infarction [7]. The European League Against Rheumatism (EULAR) taskforce recommends to estimate the risk of CVD in RA patients, and to properly manage CVD related comorbidities, such as hypertension and dyslipidaemia [8].

Several biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been applied in RA therapy and showed excellent therapeutic effects [3, 9]. 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 [10]. Janus kinase inhibitors (JAKi), tofacitinib and upadacitinib, caused dose dependent increases of LDL-C and HDL-C [10, 11]. 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. Whilst plasma levels of LDL-C have been targeted in the treatment of dyslipidaemia, 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 conventional DMARD (cDMARD) treatment. In addition, the occurrence of dyslipidaemia was also compared between the two groups, further assessed according to the subgroup of bDMARDs/tsDMARDs.

Methods

Data sources

The Korean College of Rheumatology BIOlogics (KOBIO) registry is a nation-wide 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), intermediated 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 of dyslipidaemia, 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 bDMARDSs/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 occurrence of dyslipidaemia was compared between the bDMARDs/tsDMARDs and cDMARDs groups, and between the TNF-α inhibitor, tocilizumab, abatacept, JAKi, and cDMARDs groups.

Statistical analysis and data management

The data's normality was tested by the Kolmogorov-Smirnov test, and continuous variables were 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 were properly selected for the analysis of continuous variables. Categorical variables were compared using a Chi-square test or Fisher's exact test. The Kaplan-Meir method and Log rank test were used to compare the occurrence of dyslipidaemia between groups. Hazard ratio (HR) was calculated via 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 patients (baseline), 826 patients (1-year follow up), 789 patients (2-year follow up), 691 patients (3-year follow up), and 520 patients (4-year follow up) were included in the analysis (Figure 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 total cholesterol (TC), LDL-C, and TG levels were higher in the cDMARDs group. When analysing 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 the tocilizumab group (Supplementary Table 1).

Table 1. Baseline characteristics of RA patients with bDMARDs/tsDMARDs and cDMARDs

	RA patients with bDMARDs or tsDMARDs	RA patients with cDMARDs	*P*
	(N=696)	(N=221)	
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/m^2)	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%)	0.263
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

	RA patients with bDMARDs or tsDMARDs	RA patients with cDMARDs	*P*
	(N=696)	(N=221)	
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
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

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).

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

	RA patients with bDMARDs or JAKi	RA patients with cDMARDs	*P*
	(N=652)	(N=174)	
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 ± 0.286	-0.116 ± 0.269	0.275
AIP category			0.704*
Low risk (AIP<0.11)	498 (76.4%)	138 (79.3%)	
Intermediate risk (0.11≤AIP≤0.21)	54 (8.3%)	12 (6.9%)	
High risk (AIP>0.21)	100 (15.3%)	24 (13.8%)	

* The Mantel–Haenszel χ2 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	RA patients with TNF-α inhibitor	RA patients with tocilizumab	RA patients with Abatacept	RA patients with JAKi	*P*
	(N=174)	(N=319)	(N=209)	(N=87)	(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]	0.040
HDL-C (mg/dL)	59.0 [49.0;68.0]	59.0 [48.0;68.0]	60.0 [50.0;70.0]	56.0 [46.0;67.0] □	68.0 [54.0;76.0] □	0.037
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]	0.050
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]	0.398
AIP	-0.116 ± 0.269	-0.095 ± 0.280	-0.086 ± 0.291	-0.066 ± 0.242	-0.121 ± 0.388	0.362
AIP category						0.451*
Low risk (AIP<0.11)	138 (79.3%)	251 (78.7%)	153 (73.2%)	66 (75.9%)	28 (75.7%)	
Intermediate risk (0.11≤AIP≤0.21)	12 (6.9%)	21 (6.6%)	22 (10.5%)	10 (11.5%)	1 (2.7%)	
High risk (AIP>0.21)	24 (13.8%)	47 (14.7%)	34 (16.3%)	11 (12.6%)	8 (21.6%)	

* 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.

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

When analysing 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 dyslipidaemia and comparison of new onset dyslipidaemia 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, dyslipidaemia 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 dyslipidaemia occurrence did not show a significant difference between the bDMARDs/tsDMARDs group and cDMARDs groups (Figure 2A, *P*=0.06). The occurrence of dyslipidaemia was similar after dividing bDMARDs/tsDMARDs into each medication subgroup (Figure 2B, *P*=0.3). In univariate cox proportional analysis, older age (HR=1.033, *P*=0.004), TNF-α 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 dyslipidaemia 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).

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

	Univariable			Multivariate		
	HR	95% CI	*P*	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/m^2)	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

Discussion

The present study demonstrated some remarkable points on the safety profile of bDMARDs and tsDMARDs, focusing on dyslipidaemia and atherogenic lipid profile. First, the level of individual lipid profile components were influenced by the use of bDMARDs/tsDMARDs. However, atherogenicity, represented by AIP, did not deteriorate in the bDMARDs/tsDMARDs group. Second, the occurrence of dyslipidaemia, which required lipid lowering agents, was not higher in the bDMARDs/tsDMARDs group. These results may reassure physicians that bDMARDs and tsDMARDs would not have a negative effect on atherogenicity in RA patients when starting treatment with these drugs.

Since TNF-α 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 analysed the 24-month follow up data of patients using TNF-α inhibitors for inflammatory arthritis (including RA, ankylosing spondylitis (AS), and psoriatic arthritis). A significant increase in TC and TG levels were seen, with changes being more prominent in the first 6 months after beginning treatment 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 [10]. Another meta-analysis revealed that TNF-α inhibitor usage increased TC significantly, but neither LDL-C nor atherogenic index (TC to HDL-C ratio) were effected [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 FER_{HDL}, which appears to correlate with angiographically confirmed atherosclerosis [25]. The AIP has been shown to correlate with both lipoprotein particle size and FER_{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 [8]. Carotid IMT increased the predictive power by 4.9% over simply using a conventional CVD risk estimator [26]. Carotid IMT also correlated positively with AIP in several autoimmune diseases (Behcet's disease, AS, and systemic lupus erythematosus) [18-20]. In post-menopausal women, AIP showed the most powerful predictive value for coronary artery disease when compared to other lipid profiles [27]. Since AIP can be calculated when the level of plasma HDL-C and TG are 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.

However, the management of dyslipidaemia depends not only on lipid profile but also on comorbidity status, family history of early CVD (age under 60), 10-year risk of CVD, and coronary calcium score [21]. In the present study, the occurrence of dyslipidaemia 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 had no influence on the occurrence of dyslipidaemia, whereas older age and combined hypertension significantly increased the risk of new onset dyslipidaemia. The results of the regression analysis support the safety of bDMARDs/tsDMARDs regarding new onset dyslipidaemia.

Whilst 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 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 on-going prospective cohort study, therefore, the inclusion of tsDMARDs users will continue to increase and further evaluation could be possible in future.

Conclusions

In conclusion, AIP, a feasible atherogenic biomarker, did not significantly deteriorate in RA patients using bDMARDs or tsDMARDs when compared with those undergoing cDMARD treatment. Furthermore, the occurrence of dyslipidaemia, requiring lipid lowering agents, was comparable between the bDMARDs/tsDMARDs group and the cDMARDs group. Whilst 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 regards to their atherogenic lipid profile.

Abbreviations

AIP: atherogenic index of plasma; ANOVA: analysis of variance; AS: ankylosing spondylitis; bDMARDs: biologic disease-modifying antirheumatic drugs; cDMARDs: conventional DMARDs; CRP: C-reactive protein; CVD: cardiovascular disease; DAS28: disease activity score-28; EULAR: European League Against Rheumatism; FER_{HDL}: fractional esterification rate in apoB-lipoprotein-depleted plasma; HDL-C: high-density lipoprotein cholesterol; HR: hazard ratio; IMT: intima-media thickness; KOBIO: Korean College of Rheumatology BIOlogics; LDL-C: low-density lipoprotein cholesterol; JAKi: Janus kinase inhibitors; OR: odds ratio; RA: Rheumatoid arthritis; SD: standard deviation; TC: total cholesterol; TG: triglyceride; TNF-α: tumour necrosis factor-α; tsDMARDs: targeted synthetic DMARDs

Declaration

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional file.

Authors' contributions

HKM and SKK designed the study. HKM, HRK, SHL, KCS, HAK, and SHP collected the data. HKM performed the statistical analyses and prepared the figures. HKM and SKK reviewed the results and wrote the manuscript. All authors have made an intellectual contribution to the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided written informed consent according to the Declaration of Helsinki, and the present study was approved by the Institutional Review Board of Konkuk University Medical Center (approval number: 2020-05-003).

Consent for publication

Informed consent was obtained from all participants for publication.

Competing interests

The authors declare that they have no competing interests

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Figures

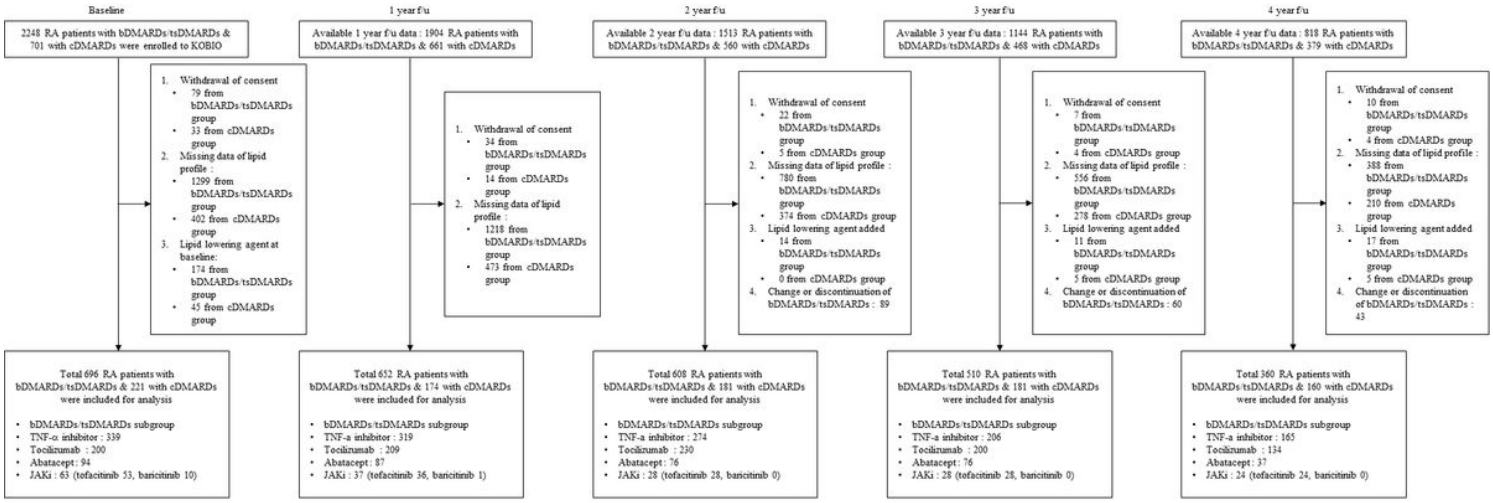

Figure 1

Flow chart of patients enrolled in analysis based on inclusion and exclusion criteria.

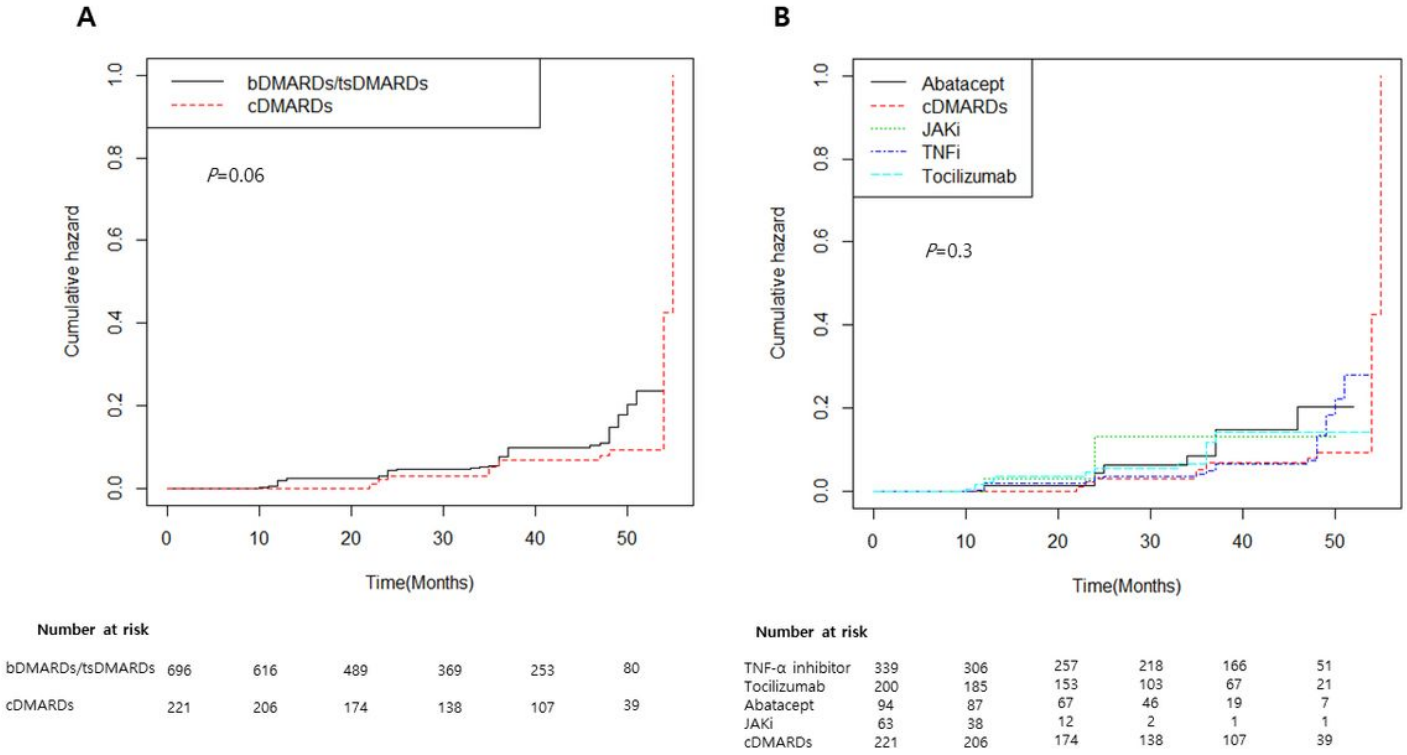

Figure 2

Cumulative hazard curve for the occurrence of dyslipidaemia. (A) Comparison between the bDMARDs/tsDMARDs group and cDMARDs group. (B) Comparison between TNF-α inhibitor, tocilizumab, abatacept, JAKi, and cDMARDs groups.

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