Impact of Biologic and Janus Kinase Inhibitor Therapy on Lipid Profile Parameters in Malaysian Rheumatoid Arthritis Patients: A Retrospective Cohort Study

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Abstract

Objectives: Evaluate the influence of biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) on lipid profile and atherogenic index (AI) in patients with rheumatoid arthritis (RA)

Methods: This retrospective study was conducted at five major tertiary rheumatology centers across Malaysia. All patients had received b/tsDMARDs for at least one year. Baseline lipid profiles were recorded before treatment initiation, followed by two additional lipid tests at six and twelve months.

Results: Total of 203 RA patients were recruited: 66 received TNF inhibitors (TNFi), 46 tocilizumab, and 91 Janus kinase inhibitors (JAKi). Among patients not on statins, JAKi treatment led to significant increases in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and non high density lipoprotein cholesterol (HDL-C) after six months, while no significant lipid changes were seen with TNFi or IL-6 inhibitors .No significant changes in AI across all treatment groups at both 6 and 12 months. Multivariable analysis showed baseline LDL-C was predictor for TC elevation. Compared to TNFi, neither tocilizumab or JAKi were linked to a higher risk of TC increase.

Conclusions: Treatment with Janus kinase inhibitors in RA patients not receiving statins was associated with significant elevations in TC, LDL-C, and non-HDL-C, whereas TNFi and tocilizumab showed no significant impact on lipid levels. However, atherogenic index remained stable across all treatment groups. Baseline LDL-C was predictors of total cholesterol elevation. These findings highlight the need for routine lipid monitoring, particularly in patients on JAKi, to manage potential cardiovascular risks.

Keywords: rheumatoid arthritis ;cholesterol ;tumor necrosis factor inhibitor ; tocilizumab ;janus kinase inhibitor

Introduction

Rheumatoid arthritis (RA) is chronic inflammatory disease which increases the risk of cardiovascular morbidity and mortality compared to the general population.[1,2] The higher inflammatory burden and prevalent cardiovascular risk factors such as such as dyslipidemia, diabetes mellitus and systemic hypertension play a role in cardiovascular risk in these rheumatic diseases.[3] Inflammation may have an impact on the circulating lipid levels. Patients with untreated severely active RA may have lower cholesterol levels which is paradoxical, as these same patients have an increased risk of cardiovascular disease.[4] The lipid paradox in RA refers to the observation that patients with active inflammation may have lower lipid levels despite a higher cardiovascular risk. Persistent systemic inflammation can suppress circulating cholesterol concentrations while at the same time promoting endothelial dysfunction and atherosclerosis. Therefore, reduced lipid levels in RA do not necessarily indicate a lower cardiovascular risk, but may instead reflect a greater inflammatory burden.[5]

Treatment with tumor necrosis factor inhibitors (TNFi), IL-6 inhibitors (IL6i), and janus kinase inhibitor inhibitors (JAKi) has been associated with increases in circulating lipid levels, often within the first few months of therapy.[4] However, this should be interpreted in the context of the lipid paradox in rheumatoid arthritis, where suppression of systemic inflammation may normalize lipid levels despite persistent cardiovascular risk. The cardiovascular impact may differ between drug classes, with greater concern reported for JAK inhibitors in patients with underlying cardiovascular risk factors.[6-8]

Our objective was to evaluate the influence of biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) on lipid profile and atherogenic index (AI) in Malaysian patients with RA.

Methods

This retrospective study was conducted at five major tertiary rheumatology centers across Malaysia, recruiting a total of 203 patients. This retrospective study was based on the review of patients' medical records from the participating rheumatology centres. Patients with incomplete medical records, particularly those lacking key clinical or laboratory data required for the study, were excluded from the analysis. This study was approved by the Malaysia Medical Research and Ethics Local Committee (NMRR ID-24-03347-LE1). All RA patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria and had received b/tsDMARDs for at least one year.[9] Baseline lipid profiles were recorded before treatment initiation, followed by two additional lipid tests at six and twelve months.

Data on conventional synthetic DMARDs (csDMARDs) comedication, as well as glucocorticoids were collected from the medical records .Conventional synthetic DMARDs (csDMARDs), including methotrexate, sulfasalazine, and leflunomide, were permitted throughout the study. Nonsteroidal Anti-Inflammatory Drug (nsaids) include celecoxib, etoricoxib and naproxen. However, patients who started statin therapy after initiating b/ts DMARDs were excluded.The b/tsDMARDs administered included four TNFi(adalimumab or its biosimilar, infliximab or its biosimilar, etanercept, and golimumab), an IL6i (tocilizumab), and three JAKi(tofacitinib, baricitinib, and upadacitinib).

Baseline demographics, including age, ethnicity, gender, diagnosis, comorbidities, and comedications, were recorded. Standard lipid profiles, including TC, LDL-C, HDL-C, and TG were collected at baseline, 6 months, and 12 months during follow-up. The atherogenic index (AI) was calculated using the formula AI = log (TG/HDL-C) , while non-HDL cholesterol was determined using the formula non-HDL-C = TC - HDL-C .[10,11]

Standard lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), were retrieved from patients' medical records at baseline, 6 months, and 12 months of follow-up. All lipid measurements were performed according to the laboratory's standard operating procedures and accredited quality control processes.The laboratory reference ranges were <5.2 mmol/L for TC, <3 mmol/L for LDL-C, >0.9mmol/L for HDL-C, and <1.8 mmol/L for TG. In this study, dyslipidemia was defined as the presence of any abnormal lipid parameter based on the laboratory reference range and/or a prior documented diagnosis of dyslipidemia.

Continuous variables were summarised as median and interquartile range (IQR), while categorical variables were presented as frequencies and percentages. The Kruskal–Wallis test was used to compare lipid parameters across the three treatment groups , while categorical variables were compared using the chi-square test, as appropriate.Longitudinal changes in lipid parameters, including TC, TG, HDL-C, LDL-C, non-HDL-C and the AI were assessed at baseline, 6 months and 12 months using the Friedman test within each treatment and statin-use subgroup. For lipid parameters with significant Friedman test results, post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test, comparing baseline with 6 months, baseline with 12 months, and 6 with 12 months, with Holm adjustment for multiple comparisons.

The primary outcome was the change in total cholesterol at 6 months from baseline (ΔTC), calculated as the 6-month TC level minus the baseline TC level. Univariable and multivariable linear regression analyses were performed to identify factors associated with ΔTC. Treatment class was included as a categorical predictor, with TNFi as the reference group. The multivariable model included the prespecified clinical and treatment-related covariates. AI was not included alongside its component lipid measures in the same regression model because of their mathematical relationship. Multicollinearity was assessed using variance inflation factors.All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 203 patients were recruited for this study, including 66 (32.5%) RA patients treated with TNFi , 46 (22.7%) with tocilizumab and 91 (44.8%) with JAKi. Complete lipid profile data were available for all patients at baseline, 6 months, and 12 months. No patients were lost to follow-up and no missing data required imputation.

The mean age of RA patients was 58.1±11.4, which was with majority of RA patients were female (Female: male ,ratio 10:1). In terms of ethnicity, malay had the highest number (43.8%) follow by indian (30.5%) and chinese (24.1%).There were no significant between-group differences in diabetes mellitus, hypertension, ischaemic heart disease, obesity or smoking history. Comedication with methotrexate was more common in the TNFi group compare to the other 2 groups (p=0.004).The baseline lipid profiles were well balanced among the 3 groups (Table 1).

Table 1: Baseline characteristics rheumatoid arthritis patients.

	Total (n=203)	**TNF (n=66)**	**Tocilizumab (n=46)**	**JAKi (n=91)**	***p*-value**
Age (years)(Mean, SD)	58.1±11.4	57.6±12.2	59.2±10.8	58.0±11.3	0.758[a]
Gender, n(%)					
Male	18 (8.9)	7 (10.6)	4 (8.7)	7 (7.7)	0.817[b]
Female	185 (91.1)	59 (89.4)	42 (91.3)	84 (92.3)	
Ethnicity					
Malay	89 (43.8)	27 (40.9)	26 (56.5)	36 (39.6)	0.302[b]
Chinese	49 (24.1)	17 (25.8)	6 (13.0)	26 (28.6)	
Indian	62 (30.5)	20 (30.3)	14 (30.4)	28 (30.8)	
Others	3 (1.5)	2 (3.0)	0 (0)	1 (1.1)	
Comorbids					
Diabetes Mellitus	33 (16.3)	9 (13.6)	7 (15.2)	17 (18.7)	0.683[b]
Hypertension	71 (35.0)	19 (28.8)	22 (47.8)	30 (33.0)	0.100[b]
Ischaemic heart disease	12 (5.9)	3 (4.5)	6 (13.0)	3 (4.5)	0.268[b]
Obesity	2 (1.0)	0 (0)	0 (0)	2 (2.2)	0.289[b]
Smoking History					
Ever Smoke	5 (2.5)	2 (3.0)	2 (4.3)	1 (1.1)	0.479[b]
Never Smoke	198 (97.5)	64 (97.0)	44 (95.7)	90 (98.9)	
Comedication					
Methotrexate	124 (61.1)	50 (75.8)	21 (45.7)	53 (58.2)	**0.004[b]**
Leflunomide	62 (30.5)	26 (39.4)	13 (28.3)	23 (25.3)	0.154[b]
Sulphasalazine	45 (22.2)	16 (24.2)	11 (23.9)	18 (19.8)	0.761[b]
Hydroxychloroquine	48 (23.6)	17 (25.8)	12 (26.1)	19 (20.9)	0.704[b]
NSAIDs	59 (29.1)	19 (28.8)	17 (37.0)	23 (25.3)	0.363[b]
Glucocorticoids	65 (32.0)	25 (37.9)	13 (28.3)	27 (29.7)	0.456[b]
Statin	74 (36.5)	17 (25.8)	19 (41.3)	38 (41.8)	0.089[b]
Baseline Lipid Parameters					
TC (median, IQR)	4.8 (1.3)	4.8 (1.1)	4.6 (1.4)	4.9 (1.3)	0.825[c]
TG (median, IQR)	0.9 (0.5)	0.9 (0.4)	0.9 (0.6)	1.0 (0.6)	0.411[c]
HDL-C (median, IQR)	1.5 (0.5)	1.6 (0.6)	1.6 (0.6)	1.4 (0.5)	0.106[c]
LDL-C (median, IQR)	2.7 (1.1)	2.8 (0.8)	2.6 (1.3)	2.8 (1.2)	0.714[c]
Non HDL-C(median, IQR)	3.2 (1.3)	3.1 (0.9)	3.1 (1.1)	3.4 (1.4)	0.247[c]
AI (Median, IQR)	-0.2 (0.3)	-0.3 (0.3)	-0.2 (0.3)	-0.2 (0.4)	0.151[c]

NSAIDs, Nonsteroidal anti-inflammatory drugs; TNFi , Tumor necrosis factor inhibitor ;JAKi, Janus Kinase inhibitor ; TC, total cholesterol ,TG,Triglycerides ;LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; AI , Artherogenic index
[a] One-way ANOVA [b] Chi-square test [c] Kruskal-Wallis test

Longitudinal lipid profiles remained generally stable across treatment groups and statin-use subgroups over 12 months. Among patients not receiving statins, the JAKi group showed significant increases in total cholesterol, LDL-C and non-HDL-C over time, with post-hoc comparisons indicating increases from baseline at 6 and/or 12 months. Among patients receiving statins, non-HDL-C increased significantly over time in the tocilizumab group. No significant longitudinal changes were observed in the TNFi groups or the remaining lipid parameters (Table 2).

Table 2: Changes in lipid profiles during 1 year of b/tsDMARDs therapy In RA.

Treatment	**Lipid**	**0 month**	**6 months**	**12 months**	**Friedman P**	**Significant time point comparison***
With Statin						
TNFi	TC	4.85 (1.16)	4.95 (1.38)	4.92 (1.29)	0.481	

	TG	1.07 (0.49)	1.12 (0.55)	1.20 (0.53)	0.816	
	HDL-C	1.61 (0.45)	1.54 (0.47)	1.49 (0.50)	0.898	
	LDL-C	2.78 (1.01)	2.89 (1.18)	2.96 (1.21)	0.654	
	Non-HDL-C	3.24 (1.00)	3.42 (1.23)	3.43 (1.25)	0.874	
	AI	3.12 (0.68)	3.35 (0.80)	3.62 (1.38)	0.662	
IL-6i	TC	4.78 (1.08)	5.50 (1.37)	5.34 (1.40)	0.134	
	TG	1.16 (0.62)	1.59 (0.93)	1.26 (0.53)	0.216	
	HDL-C	1.54 (0.44)	1.61 (0.47)	1.52 (0.44)	0.959	
	LDL-C	2.70 (0.97)	3.17 (1.19)	3.22 (1.26)	0.128	
	Non-HDL-C	3.24 (1.21)	3.89 (1.40)	3.81 (1.44)	0.016	0 vs (6,12)
	AI	3.38 (1.34)	3.63 (1.18)	3.73 (1.38)	0.128	
JAKi	TC	5.13 (1.26)	5.11 (1.09)	5.26 (1.12)	0.974	
	TG	1.34 (1.00)	1.28 (0.75)	1.41 (1.19)	0.953	
	HDL-C	1.54 (0.41)	1.72 (0.49)	1.69 (0.36)	0.118	
	LDL-C	3.03 (1.15)	2.82 (0.98)	2.95 (0.98)	0.771	
	Non-HDL-C	3.58 (1.16)	3.39 (0.94)	3.57 (1.01)	0.721	
	AI	3.45 (0.88)	3.10 (0.75)	3.19 (0.73)	0.191	
Without Statin						
TNFi	TC	4.76 (0.79)	4.92 (0.83)	4.88 (0.88)	0.935	
	TG	1.09 (0.75)	1.01 (0.36)	1.07 (0.47)	0.623	
	HDL-C	1.68 (0.62)	1.52 (0.53)	1.55 (0.51)	0.239	
	LDL-C	2.89 (0.65)	2.89 (0.68)	2.90 (0.82)	0.964	
	Non-HDL-C	3.08 (0.84)	3.40 (0.74)	3.33 (0.79)	0.054	
	AI	3.11(0.91)	3.53 (1.14)	3.39 (1.00)	0.062	
IL-6i	TC	4.99 (1.09)	5.32 (1.21)	5.37 (1.26)	0.122	
	TG	1.21 (0.75)	1.46 (0.83)	1.22 (0.56)	0.131	
	HDL-C	1.62(0.33)	1.67 (0.48)	1.71 (0.47)	0.618	
	LDL-C	2.89 (1.05)	3.07 (0.95)	3.04 (1.20)	0.584	
	Non-HDL-C	3.37 (1.07)	3.65 (1.15)	3.66 (1.14)	0.289	
	AI	3.18 (0.91)	3.36 (1.08)	3.29(0.92)	0.895	
JAKi	TC	4.74 (0.88)	5.32 (0.95)	5.25 (1.07)	<**0.001**	0 vs(6,12)
	TG	1.16 (0.68)	1.43 (1.15)	1.40(0.93)	0.195	
	HDL-C	1.45 (0.35)	1.54 (0.37)	1.52 (0.37)	0.053	
	LDL-C	2.73 (0.72)	3.18 (0.83)	3.09 (0.94)	**0.002**	0 vs(6,12)
	Non-HDL-C	3.31 (0.87)	3.80 (0.94)	3.75 (1.03)	**<0.001**	0 vs (12)
	AI	3.46 (1.00)	3.68 (1.15)	3.63 (0.97)	0.298	

Results are presented as Median (IQR)
TNFi , Tumor necrosis factor inhibitor ;JAKi, Janus Kinase inhibitor ;IL6i, Interleukin 6 inhibitor ;TC, total cholesterol ,TG,Triglycerides ;LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol;AI , Artherogenic index; RA, Rheumatoid arthritis. Bold values are significant at p<0.05
** For parameters with significant Friedman test results, post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test, with Holm adjustment for multiple comparison.*

In multivariable analysis, higher baseline LDL-C was independently associated with a smaller increase in TC at 6 months (β = −0.429, 95% CI −0.586 to −0.273, p < 0.001). Neither tocilizumab nor JAKi was significantly associated with change in TC compared with TNFi. Ever-smoking was associated with greater TC change, although this finding should be interpreted cautiously given the small number of smokers (Table 3).

Table 3: Univariable and Multivariable analysis of predictors for increased TC after 6 months treatment with b/ts DMARDs.

	Univariable			**Multivariable**		
	β	**95% CI**	***p*-value**	**β**	**95% CI**	***p*-value**
Male (ref: female)	0.116	−0.415 to 0.647	0.668	−0.357	−0.949 to 0.236	0.237
Smoking (ever vs	1.043	0.105 to 1.982	0.029	1.400	0.334 to 2.467	0.010

never)						
Obesity	0.128	−0.219 to 0.474	0.468	0.137	−0.193 to 0.468	0.413
Baseline LDL-C, mmol/L	−0.417	−0.572 to −0.262	<0.001	−0.429	−0.586 to −0.273	<0.001
Baseline HDL-C, mmol/L	−0.204	−0.527 to 0.119	0.215	−0.129	−0.452 to 0.193	0.429
Baseline TG, mmol/L	−0.007	−0.203 to 0.189	0.943	−0.001	−0.192 to 0.189	0.989
Methotrexate	−0.036	−0.339 to 0.267	0.815	0.063	−0.248 to 0.374	0.689
Leflunomide	−0.243	−0.561 to 0.075	0.134	−0.152	−0.478 to 0.174	0.359
Sulphasalazine	0.210	−0.147 to 0.566	0.247	0.254	−0.100 to 0.608	0.158
Hydroxychloroquine	−0.092	−0.438 to 0.255	0.602	−0.261	−0.606 to 0.084	0.137
NSAIDs	0.072	−0.252 to 0.396	0.662	−0.038	−0.361 to 0.285	0.816
Glucocorticoids	−0.202	−0.517 to 0.112	0.206	−0.125	−0.429 to 0.179	0.418
Statin	−0.162	−0.468 to 0.144	0.296	−0.205	−0.497 to 0.087	0.167
b/tsDMARD class						
TNFi (ref)	—	—	—	—	—	—
Tocilizumab	0.245	−0.105 to 0.595	0.170	0.318	−0.072 to 0.709	0.110
JAKi	0.039	−0.258 to 0.336	0.796	0.200	−0.133 to 0.532	0.238

β, regression coefficient; CI, confidence interval ;NSAIDs, Nonsteroidal anti-inflammatory drugs; b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs ;TNFi , Tumor necrosis factor inhibitor ;JAKi, Janus Kinase inhibitor ; TC, total cholesterol ,TG,Triglycerides ;LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol;
ΔTC was calculated as TC at 6 months minus baseline TC. Univariable and multivariable linear regression analyses were performed. TNFi was used as the reference treatment group. β represents the estimated change in TC (mmol/L) associated with each predictor. AI was not included in the multivariable model because of its mathematical relationship with TC and HDL-C. Multicollinearity was assessed using variance inflation factors; all VIFs were <2.

Discussion

In this study, lipid parameters demonstrated differential longitudinal changes according to b/tsDMARD treatment and concomitant statin use. Among patients not receiving statins, treatment with JAKi was associated with significant increases in total cholesterol and, at selected time points, LDL-C and non-HDL-C compared with baseline. In contrast, no significant longitudinal changes in lipid parameters or atherogenic index were observed among patients receiving TNFi or IL-6i without statin therapy. Among patients receiving concomitant statin therapy, no significant changes in lipid parameters or atherogenic index were observed from baseline to 6 or 12 months across the three b/tsDMARD groups. However, these within-group findings should be interpreted cautiously, as the adjusted between treatment analysis did not demonstrate a statistically significant difference in the change in TC between JAKi and TNFi. Overall, our findings suggest that lipid changes during b/tsDMARD treatment may vary according to treatment class and concomitant statin use. However, the observational nature of our study limits our ability to draw causal conclusions.The demographics of our cohort align with those reported in previous studies with predominantly female.[12]

A higher proportion of RA patients in the TNFi group were prescribed MTX compared to those in the tocilizumab and JAKi groups. MTX has been shown to reduce the formation of anti-drug antibodies, thereby lowering the risk of treatment failure and enhancing the long-term efficacy of TNFi therapy.[13]This may explain the more frequent use of combination therapy with TNFi and MTX in clinical practice. In contrast, the ADACTA study demonstrated that tocilizumab monotherapy was superior to adalimumab monotherapy, highlighting its effectiveness without the need for concomitant MTX.[14] Furthermore, the efficacy of JAKi as monotherapy in RA has been well established through multiple randomized controlled trials.[15,16] These findings support the observed prescribing patterns in our study, where TNFi was typically combined with MTX to optimize therapeutic outcomes.

The concept of the "lipid paradox" in RA suggests that patients with high disease activity and lower LDL-C levels have a higher cardiovascular risk than those with moderate LDL-C levels.[17] However, effective disease control with treatments such as TNFi ,IL6i, JAKi has been shown to elevate TC and LDL-C levels while paradoxically lowering cardiovascular risk.[17-19] The underlying mechanism remains unclear but may be linked to alterations in lipid metabolism and the reverse cholesterol transport pathway.[20] Studies have shown that the lipid paradox, driven by inflammation, leads to increased cholesterol catabolism, as demonstrated by research measuring the fractional catabolic rate (FCR) of cholesterol ester.[21] Without a corresponding increase in cholesterol ester production, this results in lower circulating LDL-C and HDL-C levels.

In our study, RA patients did not exhibit any significant increase in lipid parameters following treatment with TNF inhibitors (TNFi) in patients without statin comedication. This finding is consistent with previous

studies that assessed lipid profiles over a similar duration of at least six months.[22] In contrast, earlier studies with shorter follow-up periods typically less than three months reported transient increases in TC shortly after TNFi initiation.[23] However, unlike previous reports, we observed a reduction in HDL-C levels numerically after TNFi therapy. A meta-analysis involving 766 RA patients reported increases of up to 10% in TC and 7% in HDL-C within six months of initiating TNFi therapy [19]. This discrepancy may be attributed to the timing of lipid measurement and the dynamics of HDL-C changes over time. Rantapaa Dahlqvist S et al demonstrated a transient rise in HDL-C at 3 months post TNFi initiation, followed by a progressive decline at 6 and 12 months,findings that align with the temporal pattern observed in our study, which assessed lipid parameters at the 6 and 12 month marks. Mechanistically, evidence from animal models has shown that HDL-C can exert anti-inflammatory effects by downregulating TNF expression and binding circulating TNF for removal.[24,25] Therefore, the observed decrease in HDL-C levels after TNFi treatment may reflect the clearance of TNF-rich HDL particles, offering a potential explanation for our findings.

In the present study, we didn't observe significant increases in TC, LDL and TG in patients receiving IL6i therapy without statin comedication at both 6 and 12 months. This was in contrary to a study by Pierini FS et al. reported a 7% increase in TC after three months of tocilizumab treatment.[26] This hypercholesterolemic effect of tocilizumab has led to recommendations for careful lipid monitoring, particularly in patients with underlying cardiovascular risk factors.[27]However, emerging evidence suggests that the quality of circulating lipids, rather than their quantity, may be more relevant in determining cardiovascular risk in RA patients.[28] For instance, Florencia SP et al. demonstrated that tocilizumab treatment was associated with a reduction in oxidized LD,a key contributor to atherosclerotic plaque formation.[29] These findings highlight the complexity of lipid metabolism in inflammatory conditions and underscore the need for a more nuanced approach to cardiovascular risk assessment in patients receiving IL6i therapy.

Our study demonstrated that RA patients receiving JAKi experienced increases in both TC , LDL-C and non HDL-C levels. This finding is consistent with a pooled analysis by Fleischmann R et al., which reported approximately a 15% rise in LDL-C levels following treatment with tofacitinib.[30] Charles Schoeman et al. further explored this phenomenon and found that the elevation in cholesterol levels associated with tofacitinib use may be attributed to a reduction in cholesterol ester catabolism, along with improvements in markers of anti-atherogenic HDL function.[31]Additionally, tofacitinib has been shown to shift lipid particle size distribution from small, dense LDL particles to larger, less atherogenic forms, potentially lowering the risk of atherosclerosis.[32] Despite these potentially protective lipid quality changes, concerns about cardiovascular safety arose from the ORAL Surveillance trial, which compared tofacitinib with TNF inhibitors and reported a higher incidence of major adverse cardiovascular events in the tofacitinib group.[33] These findings led to a black box warning issued by the U.S. Food and Drug Administration (FDA) regarding the cardiovascular risks associated with JAKi.[34] However, subsequent real world studies and analyses of other selective JAKi have not consistently replicated these findings, suggesting variability in cardiovascular risk across different JAKi agents and patient populations.[35]

The significant longitudinal increase in LDL-C among patients receiving JAKi without statin therapy is clinically relevant because LDL-C is an established marker used in cardiovascular risk assessment and lipid-lowering treatment decisions. Although this study did not evaluate cardiovascular events or determine whether patients met criteria for statin initiation, these findings support the importance of regular lipid assessment during treatment, alongside an individualised evaluation of overall cardiovascular risk.

In our cohort, concomitant statin therapy was not associated with a reduction in LDL-C among RA patients receiving IL6i or TNFi, while only a modest numerical improvement was observed in those treated with JAKi. These findings should be interpreted in the context of our study design, which excluded patients who commenced statin therapy after initiating JAK inhibitor treatment. In contrast, McInnes et al specifically evaluated the lipid-lowering effect of adding atorvastatin after initiation of tofacitinib and demonstrated a reduction in LDL-C levels after six weeks of treatment.[36] Therefore, our findings reflect lipid profile changes in patients receiving concurrent statin therapy during routine clinical care, rather than the specific effect of statin initiation following JAKi exposure.

Several limitations should be acknowledged in our study. First, it was a retrospective observational study without a control group. Second, disease activity measures were not incorporated into our analysis, despite evidence that higher disease activity in RA, AS, and PsA may influence lipid profiles.[37] Therefore, we could not determine whether the observed lipid changes were related to changes in underlying inflammatory activity or to the effects of b/tsDMARD therapy.

Excluding patients who initiated statins after b/tsDMARD treatment may have introduced selection bias and potentially underestimated the lipid changes associated with b/tsDMARD therapy, while limiting the generalisability of our findings to routine clinical practice.Finally, we did not include any cardiovascular risk

scoring systems in our analysis, which could have provided important insights into the estimated risk of coronary heart disease, particularly in patients with elevated total cholesterol levels.

A key strength of this study is its multicentre design, which included patients from five tertiary rheumatology referral centres and therefore provides a broader representation of Malaysian patients with RA encountered in routine clinical practice. This enhances the generalisability of the findings within the local setting. In addition, to our knowledge, this is the first study in Malaysia to examine changes in lipid profile parameters among RA patients receiving advanced therapies, including TNFi, IL6 i, and JAKi, with consideration of concomitant statin use. As such, our study contributes novel local data to an area where evidence from Southeast Asian populations remains limited.

Conclusion

Treatment with JAKi in RA patients not receiving statins was associated with significant elevations in total cholesterol, LDL-C, and non-HDL-C, whereas TNFI and tocilizumab showed no significant impact on lipid levels. However, atherogenic index remained stable across all treatment groups. Baseline LDL-C was predictors of total cholesterol elevation. These findings highlight the need for routine lipid monitoring, particularly in patients on JAKi, to manage potential cardiovascular risks.

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Disclosure

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