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Disease Modifying Antirheumatic Medications and the Effect on Cardiovascular System: A Narrative Review

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ABSTRACT

Background: Rheumatoid arthritis is an independent risk factor for cardiovascular disease (CVD) owing to the higher prevalence of traditional risk factors in conjunction with chronic systemic inflammation.

Objective: This review aims to elucidate the effect of various types of disease-modifying antirheumatic drugs on cardiovascular diseases.

Method: A review of existing literature through PubMed, PubMed Central, MEDLINE, Science Direct, Google scholar was done. Keywords like; Rheumatoid arthritis, Disease modifying antirheumatic medications, cardiovascular diseases, tumor necrosis factor inhibitors (TNFi), Janus Kinase inhibitors (JAKi), Methotrexate were used in the search. Articles included in the study were full text, free articles, review articles, randomized clinical trials that were published in English language carried in humans. The articles excluded were articles not published in English language, paid articles, animal studies.

Results: It was revealed that Methotrexate, TNF inhibitors, and IL-6 inhibitors reduce the risk of cardiovascular diseases. Although not demonstrated consistently across studies, JAK inhibitors have been associated with an increased risk of cardiovascular adverse events. This appears to agree with current guidelines in restricting the use of JAK inhibitors only in the absence of safer alternatives in those with enhanced cardiovascular risk factors.

Conclusion: Rheumatoid arthritis, being an inflammatory disorder predisposes an individual to CVD risk while managing RA patients it becomes important to use medications that decrease the risk of CVD. JAK inhibitors have been linked with increasing the CVD risk, while TNFi and IL-6 inhibitors have shown no statistically significant data till now. However, there is a lack of data on JAK inhibitors as well as TNFi on their effects on CVD and more research is needed.

Keywords: Rheumatoid arthritis; Disease modifying antirheumatic medications; Cardiovascular diseases; Tumor necrosis factor inhibitors; Janus kinase inhibitors; Methotrexate

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder of the immune system which predominantly affects the joints. However, it also affects other body systems either directly or indirectly. RA pathogenesis involves complex interactions among dendritic cells, macrophages, T cells, B cells, neutrophils, fibroblasts, and osteoclasts[1]. The prevalence of RA in adults varies widely, depending on the study and country, from 0.00% to 2.70%[2]. Cardiovascular disease (CVD) is the most common comorbidity of RA, along with atherosclerotic heart disease and heart failure, and hence, CVD is the leading cause of death in patients with RA[3]. This is due to an increase in the prevalence of traditional cardiovascular (CV) risk factors such as smoking, abnormal lipid profiles, high body fat: muscle mass ratio, shared genetic risk factors, and the effect of systemic inflammation on the vasculature[4-6]. The European League Against Rheumatism (EULAR) has recently highlighted six key comorbidities for systematic screening in routine care: infections, CVD, malignancy, gastrointestinal disease, osteoporosis, and depression[7].

The management of RA comprises nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (biological, conventional, and targeted synthesis)[8], as illustrated in (Figure 1).

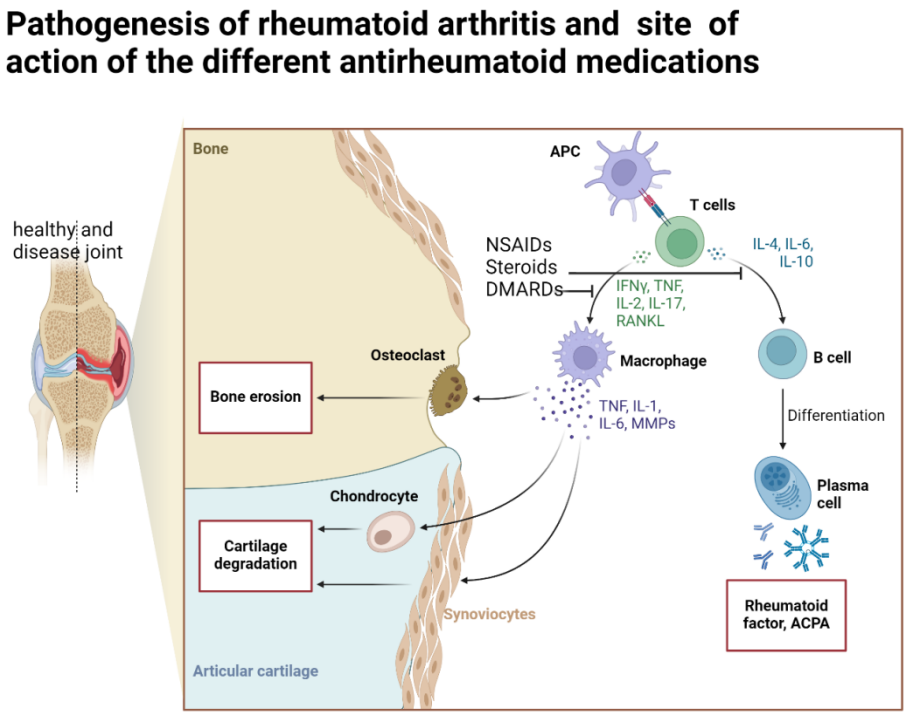

Figure 1. Image showing rheumatoid arthritis pathogenesis and antirheumatic medications sites of action.

There are many studies demonstrating that some antirheumatic medications have beneficial effects on the cardiovascular systems thereby reducing the occurrence of CAD[9]. The association between inflammation and atherosclerosis suggests CAD risk may be particularly responsive to anti-rheumatoid medications[10].

One of the major causes of death and increased healthcare utilization among Rheumatoid arthritis (RA) patients is the occurrence of cardiovascular diseases (CVD) compared to the general population[11]. While systemic inflammation may be the primary reason for having an increased predisposition for CVD risk in RA patients, it is also important to know how the biological DMARD (bDMARD) and targeted synthetic DMARD (tsDAMRD) affect the risk of CVD[12,13].

In this review, we focus on the use of disease-modifying antirheumatic drugs and their effect on cardiovascular diseases, given that there is less data about these adverse events. The study will add more to the existing literature and raise awareness in the healthcare community to look for these cardiovascular events when patients are taking these medications.

METHODOLOGY

A review of existing literature through PubMed, PubMed Central, MEDLINE, Science Direct, Google scholar was done. Keywords like; Rheumatoid arthritis, Disease modifying antirheumatic medications, cardiovascular diseases, tumor necrosis factor inhibitors, Janus Kinase inhibitors, Methotrexate were used in the search. Articles included in the study were full text, free articles, review articles, randomized clinical trials that were published in English language carried in humans. The articles excluded were articles not published in English language, paid articles, animal studies.

REVIEW

Role of Methotrexate

With the recent use of newer therapeutic agents, there is limited data on the effect of newer bDMARD or tsDMARD on CVD risk in patients with RA. Although there have been some promising studies that have examined the potential CVD benefits of these newer agents in RA patients[14-17], Methotrexate has been reported to be associated with reduced risk of CVD events, and some show no CVD benefit of the same[18,19]. One of the systematic reviews and meta-analysis done by Roubille et al. showed an RR of 28% (RR 0.72, 95% CI 0.57-0.91) with MTX in RA patients for the risk of CVD[18]. It was also seen that a 15 mg/week dose of MTX was associated with a lower risk of CVD compared to other doses[20]. Such a high dose of MTX may have a better and well-controlled effect on disease activity and direct vascular effects[20]. Having an optimal use of MTX may reduce CVD risk along with its ability to control the disease activity in RA patients.

Role of Tumor Necrosis Factor Inhibitors (TNFi)

The use of TNF inhibitors (TNFi) such as etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab in the management of RA has been also linked with CVD risk. A study done by Ozen et al. showed that TNFi and Abatacept (ABA) were significantly associated with reduced risk of CVD with HR of 0.81, 95% CI 0.71-0.93; and HR of 0.50, 95% CI 0.30-0.83, respectively compared with CsDMARD[20]. They also showed that a higher exposure to glucocorticoid steroids was associated with a higher risk of CVD events (HR 1.15, 95% CI 1.11-1.19)[20]. Several studies did report a significant reduction in CVD risk with the use of TNFi compared with csDMARD without MTX with an HR of 0.39-0.45[21,22]. It is interesting to know that this risk reduction is observed for both MI and TIA/stroke among TNFi. TNF alpha receptors have been found in endothelium, smooth muscle cells as well as macrophages that are associated with the buildup of plaques[23]. This might be one of the mechanisms by which inhibiting these receptors may reduce the CVD risk, however, there are several inflammatory pathways also inhibited by TNFi which leads to reduced inflammation and damage to endothelium[24-26]. Based on this available data, TNFi can serve to stabilize atheromatous plaques and prevent rupture[26,27]. It is also seen that TNFi also shows an improvement in flow-mediated vasodilation and endothelial function[9,28]. (Table 1) shows various studies that compared TNFi with other medications used in RA patients.

Table 1. TNF inhibitors (eg, etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab)

S no	Drug studied	Results	Reference
1.	TNF inhibitors vs DMARD	Cardiovascular disease risk reduction with TNFi (HR 0.81, 95% CI 0.71-0.93) and ABA (HR 0.50, 95% CI 0.30-0.83) compared to conventional synthetic DMARD	[20]

2.	TNF inhibitors	Infliximab and adalimumab (monoclonal antibodies to tumor necrosis factor α) may help decrease the cardiovascular risk; however, they are associated with worsening of moderate to severe heart failure with these medications	[29]
3.	DMARD	A positive effect of biologics and targeted synthetic therapies on vascular dysfunction associated with RA.	[30]
4.	TNF inhibitors	TNF inhibitors may reduce the cardiovascular risk associated with RA.	[31]
5.	TNF inhibitors	TNF inhibitor agents likely reduce cardiac event risk in patients with RA.	[32]
6.	Biologics	Significant effect of abatacept, anakinra, and rituximab in improving endothelial dysfunction associated with RA	[33]
7.	TNF inhibitors	Cardiac event risk was significantly elevated among TNF inhibitors overall (adjusted HR (aHR) 1.3; 95% CI 1.0 to 1.6)	[17]
8.	JAK inhibitors vs TNF inhibitors	Increased risk of cardiac events with tofacitinib (combined doses) versus TNFi (HRs 1.41-5.19)	[34]

9.	TNF inhibitors	Cardiac events were observed in the etanercept group (P<0.001, r=0.758), in the adalimumab group (P<0.001, r=0.761), and in the infliximab group (P<0.001, r=0.829).	[35]
10.	TNF inhibitors	Incidence rates of (0.16%) of coronary artery disease were reported with the use of TNF inhibitors in patients with RA	[36]

Role of IL-6 inhibitors

IL-6 inhibitors were similar to TNFi in reducing the CVD risk in RA patients. When tocilizumab was compared with TNFi the combined HR was 0.84 at a 95% confidence interval of 0.56-1.26 which was not significant suggesting the similar effect of IL-6 inhibitors on CVD risk compared to TNFi[15]. Similarly, another study by Giles et al. comparing tocilizumab with etanercept showed an HR of 1.05 with a 95% confidence interval of 0.77-1.43[37].

IL-6 inhibitors such as tocilizumab have been associated with elevated lipid levels, however, such an increase does not appear to affect the increased risk of CVD[38,39]. Several other studies also have demonstrated the intriguing relationship between cholesterol levels, systemic inflammation, and CVD risk in RA patients and have failed to show any association between LDL levels and CVD risk[40-42]. In systemic inflammatory states such as sepsis or RA, LDL levels remain low[5]. Hence, when an anti-inflammatory biologic drug is used such as IL-6 inhibitors, one can observe an elevation in the total cholesterol or LDL. (Table 2) shows a summary of studies that show the association of IL-6 with CVD risk in RA patients.

Table 2. IL-6 inhibitors (eg, tocilizumab and sarilumab)

S no	Drug studied	Results	Reference

1.	Tocilizumab vs TNF inhibitors	The risk of cardiovascular events associated with tocilizumab use versus TNFi use was similar with a combined HR of 0.84 (95% confidence interval 0.56-1.26).	[15]
2.	Tocilizumab vs etanercept	The estimated hazard ratio for the occurrence of cardiac events in the tocilizumab group vs etanercept group was 1.05 (95% confidence interval 0.77-1.43)	[37]
3.	Tocilizumab vs etanercept	No statistically significant differences in the risk of CVD between tocilizumab and any other biologics, however, Tocilizumab was associated with a CVD risk comparable to that for etanercept with an adjusted hazard ratio of 1.10 (95% CI 0.80-1.51) for etanercept	[16]
4.	Tocilizumab vs DMARD	Found no difference between Tocilizumab and other treatments for cardiac events (0.66 [0.42;1.03] with abatacept, 1.04 [0.60;1.81] with RTX, 0.78[0.53;1.16] and 0.91 [0.54;1.51] with DMARD), but the risk of cardiac events was lower with Tocilizumab compared to Abatacept (0.67 [0.47;0.97])	[43]
5.	Tocilizumab vs TNF inhibitors	Tocilizumab has a significantly lower risk than rituximab in myocardial infarction (hazard ratio [HR] 0.12, 95% confidence interval [CI] 0.02-0.56; P = 0.008), and other cardiac events(HR 0.41, 95% CI 0.23-0.72; P = 0.002).	[44]

6.	IL6 inhibitors	Impaired flow-mediated dilatation increased from 3.3 ± 0.8 to 4.4 ± 1.2 to 5.2 ± 1.9% ($p = 0.003$), and aortic stiffness by pulse wave velocity decreased from 8.2 ± 1.2 to 7.7 ± 1.3 to 7.0 ± 1.0m/s ($p < 0.001$).	[45]
7.	Tocilizumab	Tocilizumab did not increase the overall risk of acute cardiovascular events (hazard ratio HR 0.95, 95% confidence interval 95%CI 0.54-1.66), specifically of acute myocardial infarction (HR 0.39, 95%CI 0.15-1.06), stroke (HR 1.44, 95%CI 0.24-8.68) or other cardiovascular event (1.07, 95%CI 0.59-1.92).	[46]
8.	Tocilizumab	An adverse event of myocardial infarction (0.25/100 patient-years) was reported in the use of tocilizumab	[47]
9.	Tocilizumab	Atherosclerotic plaques were revealed after treatment with tocilizumab in 17 (41.4%) patients from 41, in 5 (12.2%) patients the plaques arose after 6 months of treatment, and in 5 (12.2%) patients the number of plaques increased.	[48]
10.	TNF inhibitors	Intravascular administration of TNF inhibitors antibody ameliorates endothelial function in patients with RA	[49]

Role of JAK inhibitors

Compared with TNFi, JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib have been associated with an increased risk of CVD. Among patients with a history of Atherosclerotic cardiovascular disorder, the occurrence of cardiac events was higher with the use of tofacitinib 5 mg BDS (8.3%) and 10 mg BDS (7.7%) compared to TNFi (4.2%). However, the HR was not significant (p-value 0.196)[50]. There have been studies that also demonstrated no statistically significant association of JAK inhibitors with increasing CVD risk[51,52]. Even though there have been concerns with the use of tofacitinib, a JAK inhibitor associated with increased CVD risk, most of the results were not significant when observed in IBD patients or any other CID patients with a higher dose[53]. After 8.5 years of follow-up data among RA patients, the role of JAK inhibitors in association with CVD was not significantly associated (p>0.0.5)[54]. Although JAK inhibitors have been associated with some alteration in lipid profile causing hyperlipidemia, the exact mechanism by which a higher dose of 10 mg BDS causes lipid abnormality is not well understood[55]. However, the lipid profile seems to normalize with a dose de-escalation suggesting an unknown mechanism for its effect[55]. In one meta-analysis also focused on a population of RA patients, when exposed to JAK inhibitors (upadacitinib, filgotinib, tofacitinib, and baricitinib), JAK inhibitors were statistically insignificant in increasing the risk for CVD (RR = 1.02, 95% CI, 0.45–2.34)[56]. (Table 3) shows a comparison of JAK inhibitors with other medications used in RA patients and their association with the risk of CVD.

Table 3. JAK inhibitors tofacitinib, baricitinib, and upadacitinib

S no	Drug studied	Results	Reference
1.	JAK inhibitor vs TNF inhibitor	No increased rate of cardiac event with JAK inhibitors (HR=0.71, 95% CI 0.51 to 0.99) compared to TNF inhibitors.	[57]
2.	JAK inhibitors vs DMARDs	The risk of the cardiac event was not significantly different between the JAK inhibitor and DMARD with an adjusted HR of 1.28 (95% CI of 0.53-3.11).	[58]
3.	JAK inhibitors	No association was found between baricitinib treatment and the incidence of cardiac events such as chronic heart failure, and thromboembolic events (1.23 per 100 patient-years for 4 mg baricitinib)	[52]

4.	JAK inhibitors vs TNF inhibitors between two groups	No adverse events showed a significantly higher incidence rate ratio in the JAKi groups than in the TNFi groups of sets 1 and 2. The Hazard ratio(HRs) for cardiac events in the JAKi groups of sets 1 and 2 were 0.59 (95% confidence [CI], 0.35 to 0.99) and 0.80 (95% CI, 0.67 to 0.97), respectively. The JAKi group of set 2 showed a significantly higher risk of all-cause mortality (HR, 1.71; 95% CI, 1.32 to 2.20),	[59]
5.	JAK inhibitors	Potential adverse events such as myocardial infarction and thromboembolic events were identified based on a disproportionality analysis using the proportional reporting ratio (PRR), reporting odds ratio (ROR), and the information component (IC).	[60]
6.	Tofacitinib	Carotid intima media thickness did not significantly change from baseline to 54 weeks (1.09 ± 0.69 and 1.08 ± 0.78 mm, p = 0.82) and those who previously had atherosclerosis at baseline (carotid intima-media thickness > 1.10 mm), there was a significant decrease in Carotid intima media thickness (0.05± 0.026 mm; p < 0.05).	[61]
7.	Tofacitinib	Cardiac events occurred in the usage of tofacitinib within use of first 24 months (incidence rate 0.4 patients with events per 100 patient-years)	[62]
8.	JAK inhibitors	Janus kinase inhibitors, such as tofacitinib, have been associated with thromboembolism events.	[29]
9.	JAK inhibitors vs TNF inhibitors	In patients with a history of Atherosclerotic cardiovascular disease (14.7%; 640/4362), cardiac events incidence was higher with tofacitinib 5 mg two times per day (8.3%) and 10 mg two times per day (7.7%) vs TNFi (4.2%). HR (combined tofacitinib doses vs TNFi) was 1.98 (95% confidence interval (CI) 0.95 to 4.14; interaction p values: 0.196)	[50]

10.	Tofacitinib	No evidence was found for an increased risk of cardiovascular outcomes with tofacitinib in patients with RA treated in the real-world setting	[51]

CONCLUSION

Rheumatoid arthritis, being an inflammatory disorder predisposes an individual to CVD risk while managing RA patients it becomes important to use medications that decrease the risk of CVD. JAK inhibitors have been linked with increasing the CVD risk, while TNFi and IL-6 inhibitors have shown no statistically significant data till now. However, there is a lack of data on JAK inhibitors as well as TNFi on their effects on CVD and more research is needed.

DECLARATION

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Consent to Participate: Not applicable.

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Availability of Data: Our data and materials will be available for research and learning purposes. The Data used to support the findings of this study are included within the manuscript.

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