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Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist

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ABSTRACT

Cardiovascular (CV) morbidity and mortality are increased in patients with active, untreated rheumatoid arthritis (RA), despite lower levels of total and low-density lipoprotein cholesterol reported in individuals with active RA compared with those without RA. Alterations in non-traditional lipid assessments, such as high-density lipoprotein (HDL) function and HDL-associated proteins, have been described in patients with active RA, including elevated HDL-associated serum amyloid A and decreased paraoxonase-1 activity. We review changes in both traditional lipoprotein concentrations and non-traditional lipoprotein assessments in multiple studies of treatment with disease-modifying antirheumatic drugs (DMARDs), including non-biologic and biologic DMARDs and tofacitinib. In addition, data from a recently published clinical trial with tofacitinib that describe a potential mechanism for suppression of cholesterol levels in active RA patients are reviewed. Finally, CV event data from various studies of DMARDs are presented, and the current management of RA patients with regard to the CV risk is reviewed.

Introduction

It is well known that cardiovascular (CV) morbidity and mortality are increased in patients with active, untreated rheumatoid arthritis (RA). A recent meta-analysis [1] indicated that the risk of CV events and mortality is approximately 50% higher in RA patients compared with the general population. However, the pathophysiological mechanisms linking CV disease (CVD) and RA are not completely understood. Traditional risk factors including smoking, hypertension, dyslipidemia, and diabetes mellitus do not alone explain the higher CV risk in patients with RA [2]. A genetic component has been associated with the increased risk of CVD in RA [3]. Inflammation, a key link between RA and CVD, which plays an important role in all stages of atherosclerosis, also accentuates some traditional CV risk factors, such as dyslipidemia [4]. It has previously been observed that lipid levels change significantly during acute and chronic inflammatory illnesses, with an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP) [5].

In the general population, serum low-density lipoprotein cholesterol (LDL-C) levels are strongly associated with an increased risk of CVD [6,7]. HMG-CoA reductase inhibitors, or “statins”, which lower LDL-C levels and have anti-inflammatory properties [8,9], reduce the risks for coronary outcomes in both primary and secondary prevention [10]. Low levels of HDL-C have also been associated with increased CV risk in epidemiological studies [11]; however, emerging data, such as the poor performance of recent clinical trials targeting elevation of HDL-C levels [12], suggest that other factors are also involved. Increasingly, research is now

Abbreviations: Apo, apolipoprotein; BID, twice daily; CV, cardiovascular; CVD, cardiovascular disease; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CRP, C-reactive protein; DAS28, Disease Activity Score with 28 joint-count; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; FC, free cholesterol; FCR, fractional catabolic rate; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; JAK, Janus kinase; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; MACE, major adverse cardiovascular event; MPO, myeloperoxidase; MTX, methotrexate; PON-1, paraoxonase-1; RA, rheumatoid arthritis; SAA, serum amyloid A; TC, total cholesterol; TCZ, tocilizumab; TG, triglyceride; TNF, tumor necrosis factor.

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focusing on the function and structure of HDL particles, rather than the levels of HDL-C alone [13].

In patients with RA, the relationship of LDL-C and HDL-C to CV risk is even more complex, and our understanding of cholesterol levels in the setting of active inflammation from RA has continued to evolve. Myasoedova et al. [14] initially reported that, in the 5 years prior to diagnosis, patients with RA had significant decreases in total cholesterol (TC) and LDL-C levels over time compared with a control population, despite lower rates of statin use. These findings were consistent with studies showing lower cholesterol levels in the setting of active inflammation from other causes, including the post-surgical state, critical illness, and sepsis [15–17]. Follow-up work in the same RA cohort of over 600 patients described a "lipid paradox", in which lower TC and LDL-C levels were not only associated with active inflammation in RA patients, but also with higher rather than lower risk of CVD [18]. This work further suggests significant interactions between systemic inflammation and cholesterol levels in the development of CVD in RA.

Here we explore current thinking on the role of dyslipidemia as a risk factor in RA. We also examine the impact of disease-modifying antirheumatic drugs (DMARDs), including non-biologic and biologic DMARDs and the oral Janus kinase (JAK) inhibitor tofacitinib, on both traditional and non-traditional lipid profiles in patients with RA. In particular, we will discuss recent evidence for a potential mechanism of cholesterol kinetics, which may in part explain the cholesterol changes associated with inflammation in RA patients, and which is impacted by treatment with DMARDs. In addition, we will present data on CV events in patients with RA treated with DMARDs, including a number of observational studies that have reported decreased CVD risk in RA patients associated with treatment with various DMARDs [19–22].

Methods

For data on the effects of DMARDs on lipid levels, PubMed was searched using the name of the agent in question in combination with terms such as "lipid," "lipoprotein," "cholesterol," "cardiovascular," "paraoxonase," and "rheumatoid arthritis". Further relevant information was identified from the reference lists of articles returned using these search terms and from authors' own experience and knowledge of the literature.

Results

Effects of DMARDs on traditional lipid profiles

Non-biologic DMARDs

A relationship between changes in lipid levels and disease activity was first observed with non-biologic DMARDs. In the Dutch Combinatietherapie Bij Reumatoide Artritis (Combination Therapy in Early RA; COBRA) study, in which 134 newly diagnosed RA patients received either sulphasalazine as monotherapy or in combination with MTX and prednisolone, both groups showed significant increases in cholesterol levels from baseline, with significantly greater increases in TC and HDL-C at Week 16 in the combination group, which also had greater improvement in disease activity [23].

In another study by Georgiadis et al. [24], lipid profiles were evaluated in 58 DMARD-naïve, early-RA patients who were treated with MTX and prednisolone. Significant increases from baseline in TC and HDL-C levels, and significant decreases in the TC/HDL-C ratio, occurred after 1 year of therapy. The increases in TC and HDL-C were inversely correlated with the reduction in both ESR and CRP values [24].

Finally, the use of hydroxychloroquine (HCQ) in RA has been associated with improvement in lipid profiles in RA patients. Specifically, in an observational study of 706 RA patients, HCQ use was independently associated with a significant decrease in TC, LDL-C, and the TC/HDL-C ratio [25].

Biologic DMARDs

Tocilizumab. Interest in the impact of DMARDs on lipids and CV risk has largely been driven by the lipid changes observed in clinical trials of tocilizumab (TCZ), a humanized monoclonal antibody against the interleukin-6 receptor.

In a study of active controlled RA monotherapy (SAMURAI study), 306 patients with active RA of <5 years duration were randomized to receive TCZ monotherapy at 8 mg/kg intravenously every 4 weeks or non-biologic DMARDs for 52 weeks [26]. No change in the TC/HDL-C ratio was observed during the study, although increases in TC, LDL-C, and triglycerides (TG) were observed in 38%, 26%, and 17% of patients, respectively. HDL-C levels were elevated above the normal range with TCZ treatment in 24% of patients [26]. Smolen et al. [27] have described a double-blind, randomized, placebo-controlled Phase 3 trial of TCZ (OPTION study) involving 623 patients with moderate-to-severe active RA despite MTX treatment. In this study, increases $>30\%$ above baseline in TC/HDL-C ratios occurred in 8% and 17% of patients administered 4 mg/kg and 8 mg/kg TCZ, respectively. A similar level of effects on lipid profiles has been noted in other studies of TCZ [28–34].

In light of these observations, a further double-blind, placebo-controlled Phase 3 trial (MEASURE) was conducted to assess the impact of TCZ on lipid and lipoprotein levels, as well as markers of coagulation, thrombosis, and vascular function [35]. In this study, median TC and LDL-C increased in TCZ versus placebo recipients by Week 12.

TNF inhibitors. A meta-analysis of 15 studies in over 700 patients found increases in TC (to a maximum of 10% above baseline) and HDL-C (to a maximum of 7% above baseline) within 6 months of starting TNFi treatment [36]. In another meta-analysis that included 13 prospective studies, 6–12 months of TNFi treatment in 338 patients was associated with increased levels of HDL-C, whereas LDL-C levels and the atherogenic index did not change significantly after treatment [37].

Effects of the newer TNFi treatment golimumab on lipids in two randomized controlled trials in patients with RA — GO-BEFORE ($n = 637$, MTX-naïve) and GO-FORWARD ($n = 444$, MTX-inadequate responders) — have been reported [38]. Patients were randomized to receive placebo + MTX, golimumab 100 mg + placebo, golimumab 50 mg + MTX, or golimumab 100 mg + MTX. In GO-FORWARD, TC, LDL-C, and HDL-C levels were increased in all treatment groups at Week 14 and were greater in the golimumab + MTX groups than in the placebo + MTX group. In GO-BEFORE, TC and LDL-C levels increased from baseline to Week 24 in all treatment groups, without any significant differences between the placebo + MTX and the golimumab + MTX groups [38].

The relationship between cholesterol changes and treatment response has also been studied in RA patients receiving TNFi treatment. In the Etanercept Treatment in RA (ETRA) observational cohort study, which followed 292 patients with RA treated with etanercept over 1 year, significant changes in apolipoprotein A-I (apoA-I; increased from baseline by 3.5% [$p = 0.002$] at 4 months and 3.1% [$p = 0.005$] at 1 year) and apolipoprotein B (apoB)/apoA-I ratio (decreased from baseline by 6.2% [$p < 0.001$] at 4 months and 3.6% [$p = 0.025$] at 1 year) were observed in patients who achieved European League Against Rheumatism (EULAR) response

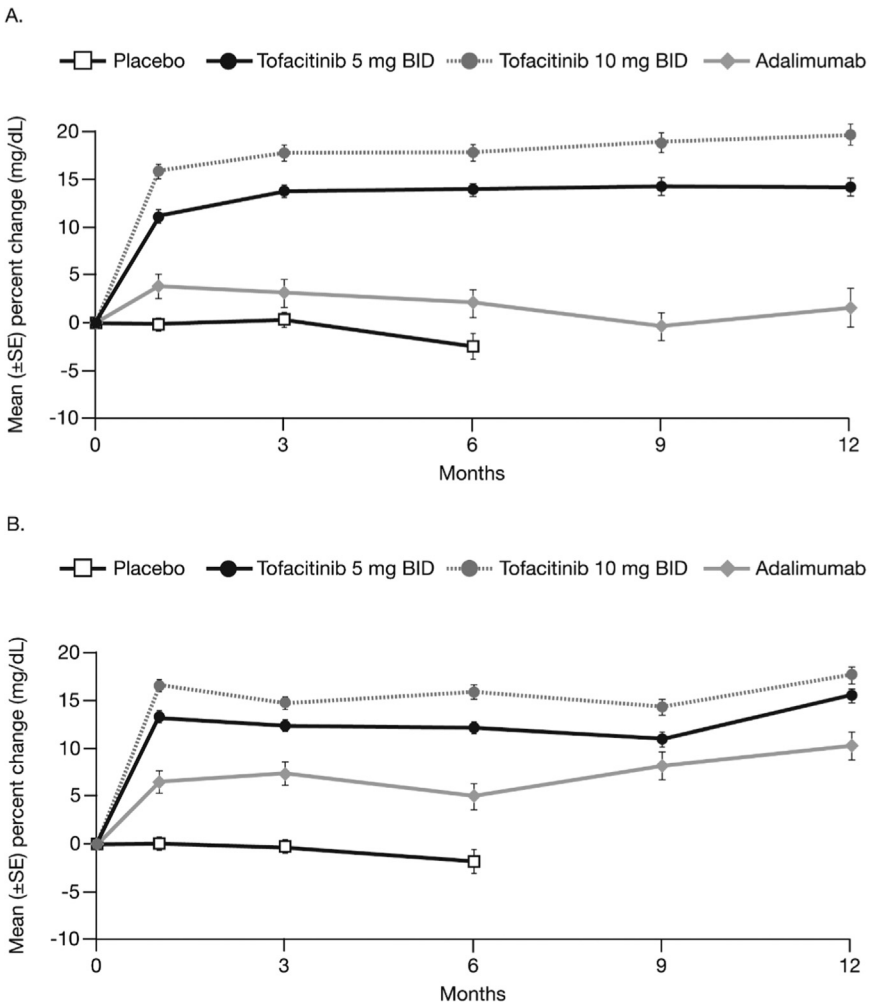
criteria; no significant differences were observed at any time point in patients who did not achieve the EULAR response criteria [39].

Tofacitinib

In Phases 2 and 3 studies of tofacitinib 5 mg or 10 mg twice daily (BID) administered either as monotherapy or with background non-biologic DMARDs, mean increases in LDL-C and HDL-C were generally between 10% and 20%, with most increases occurring during the first 4 weeks of treatment and stabilizing after 3 months of treatment [40–48]. These increases were similar in the monotherapy and background DMARD studies.

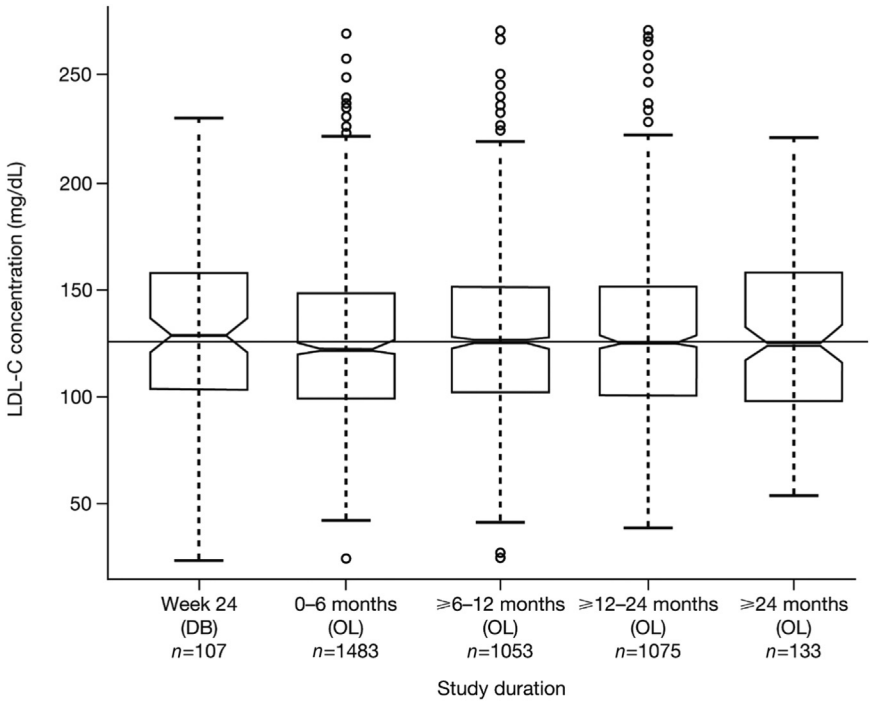
A pooled analysis was conducted using data from five Phase 3 trials of tofacitinib in patients with an inadequate response to DMARDs, one trial as monotherapy (NCT00814307) [47], and four with background non-biologic DMARDs (NCT00847613; NCT00960440; NCT00856544; and NCT00853385) [43–46]. This analysis corroborated the individual trial results, demonstrating dose-dependent increases in serum TC, LDL-C (Fig. 1a), and HDL-C (Fig. 1b), with changes observed within 1–3 months of the start of tofacitinib therapy and showing stable levels thereafter [49]. In the tofacitinib 10 mg BID group, LDL-C increased by approximately 20% and HDL-C increased by approximately 15–20% from baseline. In the tofacitinib 5 mg BID group, both LDL-C and HDL-C increased by approximately 15% from baseline. These increases were similar irrespective of whether patients received tofacitinib as monotherapy or together with non-biologic DMARDs. Importantly, given evidence suggesting that both TC/HDL-C and LDL-C/HDL-C ratios are predictors of CV risk [50,51], little change was seen in the LDL-C/HDL-C ratio in either dose group [49].

Additional analyses have been performed to better characterize the impact of tofacitinib on lipid profiles. LDL-C data from 1474 patients participating in five double-blind, Phase 2 trials, and two open-label long-term extension (LTE) studies, were pooled and analyzed using a longitudinal, non-linear mixed-effects model [52]. Patients achieving an American College of Rheumatology 50% response (ACR50) showed a modestly greater maximal LDL-C increase compared with non-responders [52]. Consistent with trial results, mean maximal LDL-C increases were predicted to be reached by 5 weeks. There was no evidence of a progressive increase for treatment durations of up to 3 years in LTE studies (Fig. 2). An additional analysis of pooled Phase 3 tofacitinib data [43–47] investigated the relationship between laboratory parameters, including LDL-C and HDL-C, and CRP, and showed that the greatest mean changes from baseline in LDL-C and HDL-C were observed in those patients with the greatest reductions in CRP [53]. The relationship between the increases in LDL-C and HDL-C and the reduction in CRP were approximately linear [53].



BID, twice daily; DMARD, disease-modifying antirheumatic drug; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

Fig. 1. Mean (± SE) percentage change from baseline in (A) LDL-C and (B) HDL-C in five Phase 3 studies of tofacitinib over 0–12 months of treatment (data shown include patients on tofacitinib monotherapy as well as those receiving concomitant background DMARDs).



BID, twice daily; DB, double-blind; LDL-C, low-density lipoprotein cholesterol; OL, open-label.

Fig. 2. Comparison of LDL-C levels in Phase 2 and long-term extension studies of tofacitinib 5 mg BID at different time points.

Another study investigated the effect of atorvastatin on tofacitinib-associated elevations in TC, LDL-C, TG, and apoB. In this study, patients with RA receiving open-label treatment with tofacitinib 10 mg BID were randomized (after 6 weeks of tofacitinib treatment) to receive, in addition, double-blind atorvastatin 10 mg once daily ($n=50$) or placebo ($n = 48$) for a further 6 weeks [54]. The addition of atorvastatin significantly reduced tofacitinib-associated increases in TC, LDL-C, TG, and apoB to below baseline levels (Fig. 3) [54].

Comparison of lipid changes between DMARDs

A recent meta-analysis of randomized controlled trials found that tofacitinib, TCZ, and TNFi treatment were all associated with moderate changes in lipids (including higher levels of LDL-C and HDL-C) in patients with RA [55]. Additional studies have also shown, however, that lipid levels vary significantly depending on the RA patient population and response to therapy, as well as the specific treatment received.

In the Treatment of Early Rheumatoid Arthritis (TEAR) trial, DMARD-naïve patients with early RA were randomized to receive treatment with MTX monotherapy, MTX and etanercept combination therapy, or triple oral therapy (MTX + sulphasalazine + HCQ). After 6 months, lipid levels were assessed in 459 patients and significant increases from baseline in mean TC (53–57.3 mg/dL), LDL-C (28.7–31.4 mg/dL), and HDL-C (19.3–22.3 mg/dL) were noted, with no differences between treatment arms. TC/HDL-C ratios decreased slightly in all treatment arms and CRP levels were significantly and negatively associated with TC and LDL-C levels [56].

Potential mechanism for changes in traditional lipid profiles in patients with active RA and following treatment with tofacitinib

Cholesterol flux through the HDL/reverse cholesterol transport pathway involves the transport of free cholesterol (FC) from peripheral tissues via transporter-dependent and -independent mechanisms to the HDL particle. Once part of the HDL particle, FC can be esterified to cholesterol ester (CE) by lecithin–cholesterol acyltransferase (LCAT). CEs may then be transferred from HDL to LDL via CE transfer proteins (CETP). CEs are delivered to the liver for secretion in bile and ultimately excretion in the stool (Fig. 4) [57].

In order to better understand the mechanisms behind suppression of cholesterol levels in patients with active systemic inflammation as well as the changes in lipids observed during RA treatment, a novel *in vivo* model of cholesterol and lipoprotein kinetics was used [58]. In a small Phase 1 mechanism-of-action trial, 36 patients with RA and 33 matched healthy volunteers received [^{13}C] cholesterol and [^{13}C] leucine infusions. A multicompartment model was used to determine the CE fractional catabolic rate (CE FCR), CE production rate, and total cholesterol efflux rate.

The CE FCR was greater in patients with active RA compared with healthy volunteers; however, no differences in CE production rate, CETP, or HDL-apoA-I and LDL-apoB FCR were observed (Table 1). Following tofacitinib treatment in patients with RA, the CE FCR decreased ($p = 0.0014$ versus baseline) and cholesterol levels increased (Table 1). A significant inverse correlation was noted between the change in CE catabolism and the change in HDL-C. Greater decreases in CE catabolism with tofacitinib treatment were associated with greater increases in HDL-C. These data suggest that lower cholesterol levels in patients with active RA may be driven in part by increases in CE catabolism, which are reversed by tofacitinib [57]. Results of this study are discussed in detail elsewhere [57].

Changes in non-traditional lipid parameters and the effects of DMARDs in RA patients: lipoprotein function and structure

Changes in non-traditional lipid parameters in RA patients

Accumulating data in both the general population as well as RA patients suggest that alterations in the composition and function of lipoproteins may be particularly important additional determinants of CV risk [1]. RA patients with active disease and high levels

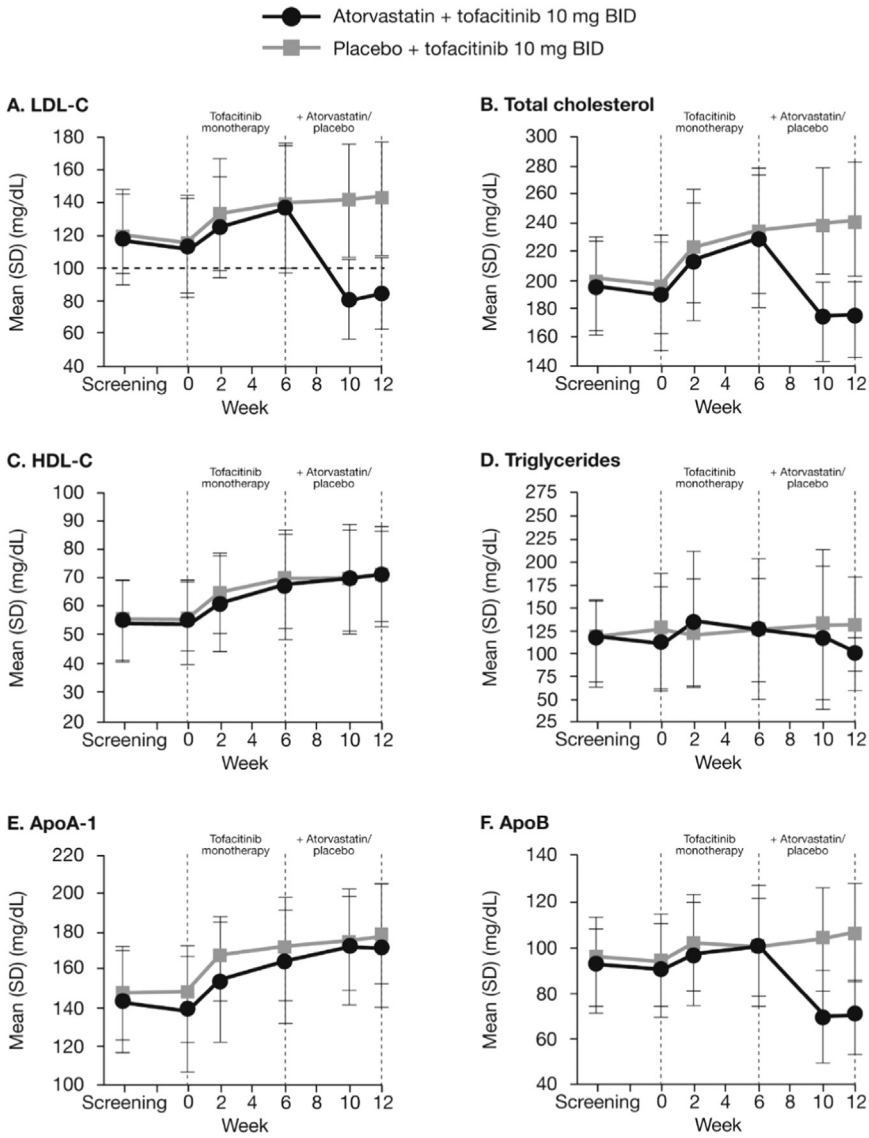


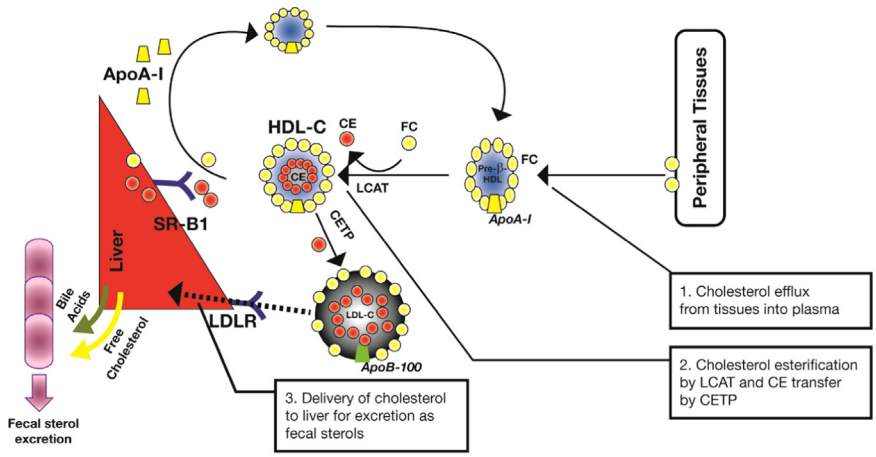
Fig. 3. Mean LDL-C, total cholesterol, triglyceride, apoA-I, and apoB levels over time with atorvastatin + tofacitinib and placebo + tofacitinib [54]. Reproduced from McInnes et al. [54] with permission from BMJ Publishing Group Ltd.

of systemic inflammation over time are at highest risk of CV-related morbidity and mortality [3]. These patients have circulating HDL that is impaired in its ability to prevent oxidation of LDL, and may even promote rather than prevent LDL oxidation (pro-inflammatory HDL) [59]. Previous proteomic analysis of HDL from RA patients with active disease and pro-inflammatory HDL has demonstrated significant differences in multiple HDL-associated proteins — including acute-phase proteins such as serum amyloid A (SAA) and haptoglobin, as well as several other proteins such as those involved in the complement cascade — when compared with HDL from patients with quiescent RA and anti-inflammatory HDL [60].

Active RA has also been associated with impairment in the ability of HDL to promote cholesterol efflux from peripheral cells. Initial work in a small number of RA patients showed that HDL from RA patients with high disease activity, measured by a Disease Activity Score (DAS) with 28 joint-count (DAS28) > 5.1, had significantly decreased ability to promote cholesterol efflux compared with HDL from patients with very low disease activity (DAS28 < 2.6). Correlations were noted between the cholesterol efflux capacity of HDL (the capacity of HDL to accept cholesterol from macrophages) and the DAS28 score ($r = -0.39$, $p = 0.01$), as well as inflammation measured by the erythrocyte sedimentation rate ($r = -0.41$, $p = 0.0009$) [61].

Vivekanandan-Giri et al. [62] also studied the cholesterol efflux capacity of HDL and showed that HDL derived from RA patients had diminished efflux capacity compared with HDL derived from healthy volunteers. Levels of myeloperoxidase (MPO), a heme peroxidase abundant in activated neutrophils that can oxidatively modify HDL, were higher in the RA patients compared with healthy subjects. There was also a marked increase in MPO-specific 3-chlorotyrosine and 3-nitrotyrosine content in HDL in the RA subjects, which was consistent with specific oxidative modification of HDL by MPO. The efflux capacity of HDL correlated inversely with the 3-chlorotyrosine content [62].

Serum paraoxonase-1 (PON-1) is an HDL-associated enzyme, which is synthesized and secreted by the liver. PON-1 reduces the oxidizing potency of lipids in atherosclerotic lesions, providing



Reverse cholesterol transport starts with the transfer of FC and phospholipid to a lipid-poor pre-β HDL particle. Esterification of FC to CE by LCAT then generates a mature HDL particle. From this mature HDL particle, CE may be transferred to LDL via CETP, and then delivered to the liver via the LDL receptor.
Alternatively, selective CE uptake via the SR-B1 receptor can deliver CE directly to the liver from HDL, regenerating a lipid-poor ApoA-1-containing particle. Once delivered to the liver, cholesterol can leave the body via biliary secretion.

Apo, apolipoprotein; CE, cholesterol ester; CETP, cholesterol ester transfer protein; FC, free cholesterol; HDL-C, high-density lipoprotein cholesterol; LCAT, lecithin-cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL-C receptor; SR-B1, scavenger receptor Class B Type 1.

Fig. 4. Reverse cholesterol transport [57]. Reproduced from Charles-Schoeman et al. [57] with permission from John Wiley & Sons Inc.

protection against oxidation, and low PON-1 activity has been shown to be associated with an increased risk of CV events [63,64]. Relationships between PON-1 activity, PON-1 genotype (for the functional polymorphism at position 192), and carotid plaque presence were determined in 168 RA patients [65]. Patients with the RR genotype (higher PON-1 activity) demonstrated decreased risk of carotid plaque on multivariate analysis, controlling for traditional CV risk factors, high-sensitivity CRP levels, and use of prednisone and cholesterol-lowering medication ($p < 0.05$). Lower plasma PON-1 activity was associated with increased risk of carotid plaque. A recent study in a cohort of 585 Spanish patients with RA did not support the association of subclinical atherosclerosis with the PON-1 rs662 polymorphism [66], suggesting that further CV outcome studies are warranted.

Table 1
Summary of lipid parameters and kinetics in patients with RA before and after treatment with tofacitinib, and in healthy volunteers [57].

Mean (standard deviation)	RA patients		Baseline healthy volunteers
	Baseline	Tofacitinib-treated[†]	
Lipid and lipoprotein concentrations	**(*n* = 36)**	**(*n* = 36)**	**(*n* = 31)**
Total cholesterol (mmol/L)	5.02 (0.84)**	5.69 (1.07)*	5.74 (1.09)
LDL-cholesterol (mmol/L)	3.23 (0.74)**	3.70 (1.01)*	3.75 (0.94)
HDL-cholesterol (mmol/L)	1.41 (0.32)**	1.61 (0.39)*	1.64 (0.44)
ApoB (g/L)	0.81 (0.42)	0.93 (0.42)*	0.82 (0.48)
ApoA-1 (g/L)	1.17 (0.56)**	1.35 (0.58)*	1.28 (0.68)
Cholesterol and lipoprotein kinetics	**(*n* = 32)**	**(*n* = 32)**	**(*n* = 30)**
LDL-ApoB FCR (%/h)	1.61 (0.37)	1.57 (0.41)	1.50 (0.35)
LDL-ApoB production rate (mg/kg/h)	0.49 (0.12)	0.52 (0.12)	0.50 (0.13)
HDL-ApoA-1 FCR (%/h)	1.08 (0.22)	1.11 (0.28)	1.02 (0.22)
HDL-ApoA-1 production rate (mg/kg/h)	0.57 (0.11)	0.65 (0.15)*	0.59 (0.16)
HDL dysfunction	**(*n* = 36)**	**(*n* = 36)**	**(*n* = 31)**
HDL-SAA (mg/L)	34.76 (62.83)**	17.79 (34.45)	2.98 (2.33)
SAA (mg/L)	51.93 (95.61)**	24.97 (48.96)	3.47 (2.71)
Myeloperoxidase (pmol/L)	1092.00 (1017.05)**	942.86 (942.64)	736.39 (344.79)
LCAT mass (μg/L)	8200 (2020)**	8980 (2320)*	9810 (1540)
LCAT activity (nmol/mL/h)	596.03 (138.58)**	642.47 (133.57)*	687.81 (120.52)
CETP activity (pmol/mL/min)	60.41 (8.87)	58.87 (7.25)	58.25 (6.58)
CETP mass (μg/L)	1960 (520)	1970 (450)	1920 (570)
Particle size	**(*n* = 36)**	**(*n* = 36)**	**(*n* = 31)**
Total HDL particles (μmol/L)	30.66 (4.80)**	33.85 (5.51)*	35.00 (5.92)
HDL size (nm)	9.10 (0.40)	9.09 (0.51)	9.20 (0.39)
Total LDL particles (nmol/L)	1276.19 (391.50)	1352.67 (498.79)	1357.87 (540.11)
LDL size (nm)	21.01 (0.85)	21.20 (0.97)*	21.36 (0.89)

Apo, apoliprotein; BID, twice daily; CETP, CE transfer protein; FCR, fractional catabolic rate; HDL, high-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; RA, rheumatoid arthritis; SAA, serum amyloid A.

* $p < 0.05$ versus baseline for patients with RA.
** $p < 0.05$ paired difference versus healthy volunteers.
† Tofacitinib 10 mg BID for 6 weeks.

Effects of DMARDs on non-traditional lipid parameters

Biologic DMARDs. In a study by Popa et al. [67], investigating the impact of 6 months of infliximab therapy on plasma lipids and PON-1 activity in 45 patients with RA, plasma HDL-C levels did not exhibit any significant changes, but stable increases in PON-1 activity were observed ($p < 0.03$) and the total antioxidative capacity of HDL-C significantly improved ($p = 0.015$) [67].

Tocilizumab. In the Phase 3 MEASURE trial of 132 patients who received treatment with TCZ 8 mg/kg + MTX or placebo + MTX, HDL-SAA was significantly reduced (by 78%) versus baseline in the TCZ + MTX arm at Week 12 [35]. In contrast, PON-1 was significantly increased (by 16%) in TCZ-treated patients. These observations suggest a remodeling of HDL-C particles from a pro-inflammatory to an anti-inflammatory phenotype in response to TCZ treatment [35].

TNF inhibitors. In the GO-FORWARD trial in MTX-inadequate responders, atherogenic ratios, including TC/HDL-C and apoB/apoA-I, were generally stable in all treatment groups, but patients treated with golimumab + MTX had significantly greater median decreases in serum SAA concentrations compared with patients receiving placebo + MTX at Week 14. In the GO-BEFORE trial in an MTX-naïve population, total small, very small, and medium small LDL-C levels decreased in all treatment groups, without any significant differences between groups. At Week 24, decreases in SAA were significantly greater in the combined golimumab + MTX groups than in the placebo + MTX group [38].

In the double-blind TEAR study comparing lipid changes between DMARDs, levels of HDL-SAA were lower by an average of 66 ranks following treatment with MTX plus etanercept compared with triple oral therapy [68].

Tofacitinib. Exploratory analyses of protein biomarkers related to HDL-C function were performed in the Phase 1 study of tofacitinib described above and in Table 1, and patients with RA were found to have higher levels of HDL-associated SAA (HDL-SAA), SAA, and MPO, and lower activity and mass of LCAT — an HDL-associated enzyme integral to efflux capacity compared with healthy volunteers at baseline (Table 1) [57]. Higher MPO activity and HDL-SAA have previously been associated with dysfunctional HDL in both RA and non-RA patients [59]. After tofacitinib treatment, LCAT mass and activity were significantly increased, and total and HDL-SAA were decreased (Table 1). In additional exploratory analyses, small but potentially favorable effects on lipoprotein particle size and number were observed with tofacitinib treatment. Specifically, the total HDL-C particle number was decreased in patients with RA compared with healthy volunteers at baseline, and increased in RA patients after treatment with tofacitinib. LDL-C particle size also increased slightly following treatment with tofacitinib (Table 1) [57].

An additional exploration of biomarkers relevant to lipid biochemistry and CV risk has been performed on pooled data from two Phase 2 and one Phase 3 study of tofacitinib versus placebo in patients with RA [69]. Compared with placebo, tofacitinib 5 mg BID or 10 mg BID significantly increased activity of LCAT and PON-1 at Month 3 versus baseline (Table 2). Decreases in total and HDL-SAA were observed with tofacitinib versus placebo, but no significant changes in CETP activity, or levels of lipoprotein(a) or lipoprotein-PLA2, occurred (Table 2) [69].

Correlations are starting to emerge between reductions in RA inflammation and increases in lipid levels and changes in lipoprotein composition with some DMARDs such as tofacitinib, but further work is needed to fully understand the mechanisms behind these relationships. It remains unclear if or how tofacitinib inhibition of the JAK pathway and signaling by pro-inflammatory cytokines can influence lipid structure and function. The similarities in the changes in lipid profiles observed in association with tofacitinib and TCZ treatment [70] suggest that interleukin-6 or its inhibition may affect lipid levels, but this remains speculative.

CV events and the impact of DMARDs

The apparently paradoxical reduction in cholesterol levels and elevated CV risk in patients with active RA highlights our current lack of knowledge about the role of lipids in CV risk in RA patients. It is becoming increasingly clear that traditional scoring systems for CV risk in the general population do not accurately predict CV risk for patients with RA [71,72]. Non-invasive surrogate markers of atherosclerosis, such as carotid ultrasound, can improve CV risk stratification in patients with RA [73–75], enabling patients who were previously wrongly categorized as immediate risk with classic chart scores to be identified as high or very high risk, and be treated appropriately to minimize risk.

A number of studies have reported a reduction in CV risk associated with both biologic and non-biologic DMARDs, despite

Table 2
Summary of mean change from baseline at Month 3 in lipid biomarkers in patients treated with tofacitinib or placebo in a pooled analysis from two Phase 2 and one Phase 3 trial [69]. Reproduced from McInnes et al. [69] with permission from BMJ Publishing Group Ltd.

	Pooled Phase 2/Phase 3 studies			
Mean (standard error)	**Tofacitinib (5 mg BID)**	**Tofacitinib (10 mg BID)**	**Placebo**	**Interpretation**
Total SAA (mg/L)	−54.99 (8.03)* [$n = 94$]	−42.69 (7.81)* [n = 95]	13.40 (9.31) [$n = 66$]	⇩ with tofacitinib 5 and 10 mg BID Decrease suggests improved function of HDL
HDL-associated SAA (mg/L)	−30.79 (6.36)* [$n = 85$]	−34.44 (6.33)* [$n = 83$]	9.46 (7.32) [$n = 62$]	
LCAT (nmol/mL/h)	40.29 (12.27)* [$n = 99$]	27.43 (12.70)* [$n = 89$]	−24.32 (15.57) [$n = 59$]	⇧ with tofacitinib 5 and 10 mg BID Increased activity would promote reverse cholesterol transport
Lp(a) (mg/dL)	−1.51 (0.85) [$n = 101$]	−1.58 (0.90) [$n = 89$]	0.97 (1.02) [$n = 68$]	No significant change with tofacitinib 5 and 10 mg BID Increases associated with CV risk
PON-1 (U/L)	3.34 (0.76)* [$n = 166$]	3.62 (0.77)* [$n = 157$]	0.29 (0.92) [$n = 97$]	⇧ with tofacitinib 5 and 10 mg BID Increase may indicate improved function of the HDL particle
CETP (pmol/mL/min)	−1.98 (0.64) [$n = 62$]	−0.38 (0.64) [$n = 63$]	−0.37 (0.77) [$n = 45$]	No significant change with tofacitinib 5 and 10 mg BID Reductions associated with CV benefit
Lp-PLA2	17.90 (12.50) [$n = 101$]	−27.83 (12.85) [$n = 92$]	−1.76 (14.65) [$n = 70$]	No change with tofacitinib 5 and 10 mg BID Reduced levels associated with reduced inflammation and atherosclerotic progression

BID, twice daily; CETP, cholesteryl ester transfer protein; CV, cardiovascular; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; Lp(a), lipoprotein (a); Lp-PLA2, lipoprotein-associated phospholipase A2; PON-1, paraoxonase-1; SAA, serum amyloid A.

* $p < 0.05$ versus placebo.

the evidence for increases in lipid levels with treatment described above. In a 10-year observational cohort study of 741 patients with RA, decreased CVD risk was associated with use of any biologic or non-biologic DMARD and MTX during the first year following diagnosis, or regular use of MTX after the first year [19]. A significantly lower overall rate of serious cardiac events was seen in etanercept-treated patients (1.0 per 100 person-years) compared with those receiving non-biologic DMARDs (1.8 per 100 person-years) in a UK observational study of 3529 RA patients [20]. A recent meta-analysis that included 28 studies in RA has shown TNFi treatment to be significantly associated with a reduction in the risk of all CV events [21]. Analysis of data from 14,878 RA patients in Finland showed that patients with recent-onset RA who receive consistent RA medication had no increased risk for CV mortality compared with the general population over the duration of the study, and that treatment with MTX was associated with reduced CV mortality [76].

Accumulating evidence indicates that treatment with a TNFi may lower CV risk. Data from 10,156 patients enrolled in the large Consortium of Rheumatology Researchers of North America (CORRONA) RA registry showed that, after adjusting for age, gender, CV risk factors and RA disease characteristics, patients using a TNFi experienced a reduced risk of CV events (hazard ratio = 0.39, 95% CI: 0.19–0.82) compared with users of non-biologic DMARDs [22].

A prospective cohort study in Canada found that RA patients receiving biologic DMARDs (adalimumab, abatacept, TCZ, and etanercept or rituximab) experienced a 12% reduction in risk of cardiac events over 2 years, with TCZ ($p = 0.002$) and abatacept ($p = 0.042$) associated with the greatest reduction in CV risk [77].

Analysis of pooled data from TCZ-treated RA patients found that changes in lipid parameters were not statistically significantly associated with risk for on-treatment major adverse CV events (MACE; CV death, non-fatal myocardial infarction, and non-fatal cerebrovascular events) [78], despite increases in TC, LDL-C, and TC/HDL-C ratio observed with TCZ treatment. A postmarketing surveillance study of TCZ-treated RA patients in Japan showed no increase in serious cardiac dysfunction in 4527 patients completing 3 years of follow-up [79]. However, more data are needed to fully characterize the CV risk presented by TCZ. The ENTRACTE trial (NCT01331837) is currently ongoing and compares the effects of TCZ and etanercept on CV outcomes in patients with RA and at least one CV risk factor.

To date, studies conducted with tofacitinib show no increase in MACE despite elevated lipid levels, although more data from ongoing long-term studies are needed to further assess any possible link between CV events and treatment with tofacitinib. In a pooled analysis of data from five Phase 3 trials [43–47], the incidence rate for MACE was similar for tofacitinib and placebo [0.57 (95% CI: 0.33–1.01) versus 0.99 [95% CI: 0.25–3.95] events per 100 patient-years, including 3030 patients exposed for 2098 patient-years] [80]. The incidence rates for MACE in the tofacitinib and placebo groups in the Phase 3 populations corresponded to a 10-year Framingham CV risk of 6–10%, which is categorized as low in the general population [49].

A lower incidence rate for MACE compared with the Phase 3 pooled analysis was seen in a pooled analysis of two open-label LTE tofacitinib studies [0.19 (95% CI: 0.09–0.46) events per 100 patient-years; including 3227 patients with 2622 patient-years of exposure, data cut-off date March 2011] [80]. In a later pooled analysis from these two LTE trials (data cut-off date April 2013), the incidence rate for MACE with tofacitinib was still below that reported in the Phase 3 trials [0.37 (95% CI: 0.26–0.52) events per 100 patient-years, including 4827 patients with 8699 patient-years of exposure] [81]. However, the characterization of the risk/benefit profile of tofacitinib in LTE studies is potentially limited due to the selection of patients who completed preceding index studies, remained enrolled in the LTE studies, and in whom tofacitinib was efficacious and well tolerated. As such, no definitive conclusions can currently be reached on the potential CV risk presented by tofacitinib for RA and larger, longer-term studies are required. An ongoing Phase 3b/4 study (NCT02092467) will compare the safety of tofacitinib versus TNFi, particularly with respect to MACE and malignancies.

Conclusions and future directions

RA is associated with a high CV morbidity and mortality, and as our knowledge of the relationship between lipid levels, lipoprotein function, and CV risk continues to evolve, it is important to follow currently available guidelines and monitor traditional lipid profiles. Previous data suggest there may be underdiagnosis and undertreatment of dyslipidemia in patients with RA. In a recent population-based cohort study, rates of lipid testing were lower in patients with RA than in the general population and only around a quarter of RA and non-RA subjects who met National Cholesterol Education Program Adult Treatment Panel III criteria for lipid-lowering therapy received it within 2 years of meeting the guidelines for initiation [82]. Further to such findings described in this paper, it is recommended that assessment of lipid parameters should be performed approximately 4–8 weeks after initiation of tofacitinib therapy [83].

There are currently no definitive guidelines for statin use in RA patients, and the Trial of Atorvastatin for the primary prevention of Cardiovascular Events in patients with Rheumatoid Arthritis (TRACE RA) (controlled-trials.com; ISRCTN41829447) was terminated early with low numbers of CV events. However, these agents continue to be widely used in the RA population. A population-based longitudinal study of RA patients with incident statin use followed from 1996 to 2006 showed that statin discontinuation in patients with RA is associated with an increased risk of death from CVD and all causes, supporting the importance of compliance in RA patients who are prescribed statins [84].

Additional CV outcome studies with RA therapies are necessary to further evaluate non-traditional lipid measurements such as lipoprotein function, particle size, and number in relation to CV risk in RA. Future studies should also explore the correlation of treatment-related resolution of inflammation, changes in lipid levels and other risk factors with CVD outcomes in RA [70]. We anticipate that in the future, the CV risk profile of RA therapies may be a key component of treatment selection with ongoing monitoring of lipid levels and lipoprotein function and structure becoming the standard of care.

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