Vascular Pharmacology 81 (2016) 22–30

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Effects of synthetic and biological disease modifying antirheumatic drugs on lipid and lipoprotein parameters in patients with rheumatoid arthritis

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ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form 24 December 2015
Accepted 23 January 2016
Available online 21 February 2016

Keywords:
Rheumatoid arthritis
Lipids
Lipoproteins
Disease modifying antirheumatic drugs
Biologicals

ABSTRACT

Background: Dyslipidemia in rheumatoid arthritis (RA) patients is frequently observed, and treatment with anti-rheumatic drugs has an impact on lipid profiles. Pathophysiologically, inflammation leads to decreased blood lipids and lipoproteins; RA treatment reduces inflammation and therefore may increase lipids and lipoproteins. Whether the lipid changes with RA treatment confer an increased risk of cardiovascular disease or just reflect their potentially atheroprotective anti-inflammatory effect is currently unclear due to limited and conflicting data.
Objective: The aim of this review is to summarize the current knowledge on the effects of synthetic and biological disease modifying antirheumatic drugs for the treatment of RA on lipid and lipoprotein parameters.
Results: Recent studies on methotrexate emphasize its anti-atherogenic effect. Golimumab combined with methotrexate revealed a trend towards an anti-atherogenic potential. The known pro-atherogenic lipid-spectrum alterations caused by tofacitinib can be effectively treated with atorvastatin. Tocilizumab signals a favorable impact on the extent of lipid modifications when combined with methotrexate. Abatacept indicated a trend towards an anti-atherogenic lipid profile demonstrated by favorable effects on HDL-C and on the TC/HDL-C ratio. Rituximab has beneficial effects on HDL-C and ApoA1, as well as on the ApoB/ApoA1 ratio.
Clinical implications: Anti-rheumatic drugs have various effects on lipid parameters, which in part appear pro-atherogenic. However, because many of these lipid changes may well reflect their potentially atheroprotective anti-inflammatory action the cardiovascular impact of these changes remains unclear. Whatsoever, cardiovascular safety trials for antirheumatic drugs would be valuable.

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http://dx.doi.org/10.1016/j.vph.2016.01.006
1537-1891/

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune-mediated inflammatory joint disorder, affecting 0.5–1% of the world population [1]. While RA primarily involves the synovial membrane, it has been associated with a significantly increased risk of coronary heart disease (CHD) [2]. Compared to the general population, evidence indicates increased mortality ratio in RA going along with a loss of life expectancy. This increased mortality in RA is largely due to cardiovascular disease (CVD) [3,4].

The reasons behind this are diverse: RA is associated with risk factors that are conventional (e.g. family history of CVD, smoking, obesity, type 2 diabetes mellitus, dyslipidemia,) and non-conventional (disease associated inflammation and systemic medication, disease activity, physical inactivity due to joint destruction) [5–10]. One of the most important mechanisms in this context is the disease related chronic inflammation which in turn contributes to the development of a pro-atherogenic lipid profile [11].

Numerous studies have cross-sectionally investigated data on lipid profiles in patients with RA. Myasoedova and coworkers have demonstrated that as a consequence of systemic inflammation, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels decrease significantly already during a 5 year period before the actual diagnosis of RA in patients with RA compared to controls [12]. However, despite lowering TC, the underlying inflammatory processes may be pro-atherogenic [13]. Compared with a healthy population, patients with RA at the time of diagnosis typically have lower TC, lower LDL-C, lower HDL-C and a smaller LDL particle size, which reflects more atherogenic LDL particles [14–16]. In general, the severity of dyslipidemia is positively associated with disease activity in RA [17,18].

Inflammation appears to play an important role in accelerating atherosclerosis [19–21]. This gives a rationale for an aggressive approach in the treatment of inflammatory arthritis [22]. Different conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs) and biological disease modifying antirheumatic drugs (bDMARDs) are available. In contrast to the well investigated effects of these drugs on controlling joint inflammation, inhibiting radiographic progression and maintaining physical function, their effects on lipid and lipoprotein levels and the potential anti-atherosclerotic benefits of specific therapies still give rise to debate.

This work therefore aims at reviewing the current knowledge on serial changes of lipids and lipoproteins in RA patients on therapy with the csDMARD methotrexate as well as the tsDMARD tofacitinib and bDMARDs.

2. Methods

Pubmed and Medline were searched from 1966 to April 2015 for full-text articles in English, French, Italian, Spanish and German. No restriction was posed on study designs. Letters, editorials, and commentaries were excluded. The following search terms (MESH and free textword) were used in combinations with boolean operators (i.e. arthritis/RA terms were combined with OR which in turn were combined with AND and lipidparameters which were linked with each other with OR. Finally all those were linked with AND and medication terms which were linked with each other with OR): "rheumatoid arthritis(tw)", "Arthritis, Rheumatoid(MESH)", "Cholesterol(Mesh)", "Cholesterol, HDL(Mesh)", "Cholesterol, LDL(Mesh)", "Cholesterol, VLDL(Mesh)", "Lipid Metabolism Disorders(Mesh)", "Dyslipidemias (Mesh)", "Lipids(Mesh)", "Lipoproteins(Mesh)", "Hypercholesterolemia (Mesh)", "Hypertriglyceridemia(Mesh)", "Triglycerides (Mesh)", "anti-TNF therapy(tw)", "anti-TNF agents(tw)", "anti-TNF alpha(tw)", "TNF blocker*(tw)", "tumor necrosis factor antagonist*(tw)", "tumor necrosis factor blocker*(tw)","tumor necrosis factor inhibitor*(tw)", "anti-tumor necrosis factor alpha therapy(tw)", "golimumab(tw)", "tocilizumab(tw)", "abatacept(tw)", "rituximab(tw)", "tofacitinib(tw)", "methotrexate(tw)".

The identification of articles was initially carried out by screening titles and abstracts. The final decision to include or exclude potential articles was made after evaluation of the fulltext of these articles. Additionally the bibliographies of the selected articles were manually screened for related literature.

3. Results

A key summary of reviewed studies addressing the effects of csDMARDs, tsDMARDs and bDMARDS on lipid profiles in patients with RA is shown in Table 1. Additionally, more detailed information is provided in an online appendix (Table S1).

3.1. Studies assessing the effects of the conventional synthetic disease modifying antirheumatic drug (csDMARD) Methotrexate on lipid and lipoprotein parameters

Methotrexate (MTX) is the anchor drug for the treatment of RA, primarily due to its efficacy and acceptable toxicity profile [38]. Despite its extensive use either as monotherapy or in combination, data on the effects of MTX on lipid and lipoprotein levels are scarce.

A recent 24 week substudy ($n = 495$) [23] of the TEAR Trial investigating therapy naïve very early RA patients (mean disease duration 3.8 months) showed that therapy with either a biological plus MTX, or MTX alone or a triple therapy of MTX plus sulphasalazine (SSZ) plus hydroxychloroquine (HCQ) entailed significant increases in mean total cholesterol (TC), LDL-C and high-density lipoprotein cholesterol (HDL-C) compared to baseline ($p < 0.001$ for all three groups, respectively). In spite of these elevations, there was a slight but significant decrease in the TC/HDL-C-ratio for all treatment arms. A negative correlation with changes in C-reactive protein (CRP) was seen for changes in LDL-C ($p = 0.03$), TC ($p = 0.01$) and, non-significantly, for HDL-C ($p = 0.09$).

In contrast, data from a pilot study ($n = 30$) by Filippatos et al. [24] found that early RA patients showed no significant changes in the levels of TC, LDL-C and triglycerides (TG) after therapy with MTX and prednisone. However, HDL-C significantly increased in patients who responded to MTX ($p = 0.001$), which was attributed to an increase in the HDL-2-C subclass. These early RA patients exhibited significantly higher baseline small dense low density lipoprotein cholesterol (sdLDL-C) and decreased HDL-C levels compared to healthy controls ($p < 0.05$). This was accounted for by a significant decrease in the small HDL-C (HDL-3-C) subclass levels.

In 34 RA patients on MTX [25] a significant reduction of Lp(a) after 6 weeks and 6 months of treatment ($p = 0.001$ for both) versus baseline was shown. LDL-C and apolipoprotein A1 (ApoA-1) serum levels did not change significantly whereas HDL-C increased significantly during treatment with MTX ($p = 0.001$ for both timepoints). There was no significant difference in the TG level but a significant elevation in the TC level after 6 months. The researchers also examined the relationship between Lp(a) and markers of endothelial function by measuring the serum levels of adhesion molecules (inter cellular molecule-1 = ICAM, vascular cell adhesion molecule-1 = VCAM-1, E-selectin) and the reactive hyperaemic index (RHI). Interestingly, when investigating the relationship between Lp(a) and markers of endothelial function