

Increased lipid levels but unchanged atherogenic index in rheumatoid arthritis patients treated with biologic disease modifying antirheumatic drugs: published experience

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Abstract

Background

Cardiovascular disease (CVD) is a major cause of increased mortality in rheumatoid arthritis (RA) patients, and it is recommended to treat risk factors for CVD in RA patients aggressively, including increased lipid levels. However, the effect of biological disease modifying antirheumatic drugs (DMARD) on the lipid profile of RA patients remains under-researched, and what data exist are often contradictory.

Objectives

To review available data published to date on lipid profile changes in RA patients treated with biologic DMARDs.

Methods

We searched the PubMed database without time limits until January 31, 2008 for original clinical trials regarding the effect of biological DMARDs on the lipid profiles of RA patients, tabulating total cholesterol, LDL, HDL and atherogenic index (ratio of total cholesterol to HDL) data for RA patients treated with biologic DMARDs. Percent change values from baseline to end of study were calculated.

Results

Eighteen studies fulfilled our inclusion criteria. The total cholesterol levels of patients treated with biological DMARDs was reported to increase in eleven studies (mean change 14.8%). One study reported a decrease (change 4.07%), and six reported no significant change. In HDL levels, nine studies reported increases (mean change 13.1%), two reported decreases (mean change 8.69%) and six reported no significant changes. Five studies reported an increase in LDL levels (mean change 11.2%), no studies reported a decrease, and six studies reported no significant change. The atherogenic index was reported to increase in two studies (mean change 4.27%), decrease in two studies (mean change 7.26%), and not significantly change in nine studies. Only a third of the reviewed articles reported on the LDL/HDL ratio, but of those that did, two reported an increase (mean change 4.55%), one reported a decrease (change 8.03%), and three reported no significant changes.

Discussion

Our data suggest increases in lipid levels between baseline and end of study in clinical trials of RA patients treated with biologic DMARDs. However, the clinical implications of this finding with regard to cardiovascular outcomes are not clear in part due to the fact that in most of the studies the atherogenic index was not significantly changed from baseline to end of study. Those studies that do provide data on effects on cholesterol rarely provide information on the complete lipid profile.

Key words

Lipids, cholesterol, biologic therapy, rheumatoid arthritis.

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Introduction

Cardiovascular disease (CVD) is a major cause of increased mortality in rheumatoid arthritis (RA) patients (1, 2). Though the mechanisms involved in this increased comorbidity are various and not completely understood, one factor may be the association between active RA and dyslipidemia. This includes decreased total cholesterol and relatively more depressed high density lipoprotein (HDL) cholesterol as compared to RA patients in remission (3). In addition, raised levels of low-density lipoprotein (LDL) were demonstrated in patients with RA compared to controls (4). The fact that HDL is decreased to a greater extent than the total cholesterol results in an increased atherogenic index (ratio of total cholesterol to HDL), which is a leading predictor of cardiovascular risk (5, 6). This altered lipid profile associated with RA inflammation is thought to lead to an increased risk of atherosclerosis (7). An increased prevalence of subclinical atherosclerosis as assessed by increased carotid intima-media thickness in RA patients with or without traditional cardiovascular risk factors compared to healthy controls has been reported (8-10).

Biological disease modifying anti-rheumatic drugs (DMARD) include tumor necrosis factor-alpha antagonists (anti-TNF), interleukin (IL)-1 antagonists, IL-6 inhibitors, and T-cell and B-cell modulators. These drugs have been shown to slow and frequently stop disease progression, reduce structural damage, and increase the quality of life for RA patients (11). However, some studies have raised concerns about the adverse effects of such drugs particularly in relation to the lipid levels of patients and the corresponding CVD risk. Data directly examining the affect of these biologic agents on the lipid profile of RA patients is scarce and the results often vary between studies. Because of the preeminence of CVD comorbidity and the uncertainty of the affects on CVD risk factors of such important RA treatments, we undertook a systematic review of the available data on lipid profile changes in RA patients treated with biologic DMARDs.

Methods

We searched the PubMed database with our search terms and no time limits up until January 31st 2008. The earliest article reviewed was from 2000. We combined the term "rheumatoid arthritis" with the names of biological DMARDs and terms relating to a lipid profile and recorded the number of articles that each combination of search terms yielded (see Table I). We did not include anakinra in our search as it is currently not widely used in RA treatment and, additionally, has been left out of the latest American College of Rheumatology RA treatment guidelines (12).

Only those articles from a search combining "rheumatoid arthritis," a lipid term, and a biologic agent term were further reviewed. After repeat articles were eliminated, 158 articles remained. All review articles and non-English articles were excluded with the exception of one article whose English abstract included nearly all of the information we sought (13). The remaining articles were reviewed in full-text in order to ascertain if they were original human clinical trials directly relating to the affect of biologic agents on total cholesterol, HDL, LDL, atherogenic index (total/HDL) or the LDL/HDL ratio of RA patients. If a study only mentioned an effect on lipid levels, but failed to provide any data supporting the effect, it was excluded. However, some studies gave specific data for only a few lipid measures but alluded to changes in other measures for which no data was supplied. Those reported changes that did not include data were factored into the results of overall trends in change (14-16).

Two studies that provided lipid data only in graphs were included (14, 17); the reviewer (EKS) approximated the value based on the graph to two significant digits. Four articles could not be retrieved in full-text and were excluded. The average duration of all the included studies was calculated. The percent change values for each lipid measurement were calculated.

Results

Eighteen studies fulfilled our inclusion criteria. The mean duration of

Conflict of interest: Dr Y. Yazici is a consultant and is a member of speakers' bureau for Bristol-Myers Squibb, Centocor, Celgene, Genentech, Roche and UCB; Dr E. Schimmel has declared no competing interests.

Table I. PubMed searches on 1/31/08. All searches included the term “rheumatoid arthritis” as listed in top left corner of chart along with the number of articles that were yielded by that search. Lipid terms paired with that term appear to the left of the rows along with the number of studies yielded. Biologic agents searched appear at the top of columns with their number of articles. The number of articles yielded when “rheumatoid arthritis” was paired with a lipid term and a biologic agent are given in the intersecting box.

Rheumatoid arthritis (91266)	Infliximab (1437)	Etanercept (1180)	Adalimumab (457)	TNF inhibitors (1150)	Abatacept (146)	Rituximab (249)	Tocilizumab (38)	IL-6 (1493)
Lipid (3061)	27	12	5	84	1	5	2	167
Cholesterol (365)	15	3	3	11	0	1	1	10
HDL (105)	14	2	3	12	0	0	0	4
LDL (134)	9	1	2	6	0	0	0	6
Atherogenic (42)	9	2	3	4	0	0	0	0

the studies was 23.9 weeks. In eleven studies, infliximab was the only biologic agent tested (13-16, 18-24). Two reports studied the effect of infliximab, etanercept, and adalimumab together (25, 26); one report studied only infliximab and etanercept (27); and two reports studied only adalimumab (28, 29). Two studies were trials of tocilizumab (17, 30). Twelve studies allowed patients to continue using methotrexate in combination with the biologic agent tested (15, 16, 18-25, 27, 29). All of the studies allowed patients to continue corticosteroid therapy though in most studies only at stable doses that did not exceed 10 mg per day.

Three studies included non-RA patients with either ankylosing spondylitis or psoriatic arthritis (13, 15, 22). Four studies included a control group of RA patients under stable, unchanged treatment regimens (14, 18, 27, 29). Two studies included a RA placebo group (28, 30). Four studies included a group of healthy controls (16, 18, 19, 21).

The total cholesterol levels of patients treated with biological DMARDs was reported to significantly increase in eleven studies (mean change 14.8%) (15-18, 21, 23-25, 27, 28, 30). One

study reported a decrease (change 4.07%) (19), and six reported no significant change (13, 14, 20, 22, 26, 29). Nine studies reported increases (mean change 13.1%) in HDL levels (18, 22-25, 27-30), two reported a decrease (mean change 8.69%) (13, 14), and six reported no significant change (15, 16, 19, 20, 26, 28). Five studies reported an increase in LDL levels (mean change 11.2%) (14, 17, 18, 21, 23), no studies reported a decrease, and six studies reported no significant change (13, 15, 16, 22, 26, 28).

The atherogenic index was reported to increase in two studies (mean change 4.27%) (14, 21), decrease in two studies (mean change 7.26%) (28, 29), and not significantly change in nine studies (15, 18, 20, 22-27). Only a third of the articles reported on the LDL/HDL ratio, but of those that did two reported an increase (mean change 4.55%) (14, 21), one reported a decrease (change 8.03%) (28), and three reported no significant change (18, 22, 23).

Discussion

Our review suggests increases in lipid levels between baseline and end of study in RA patients treated with

biologic DMARDs. This trend appears independent of the specific biologic DMARD studied. However, the clinical implications of this finding with regard to cardiovascular outcomes are not clear in part due to the fact that in most of the studies the atherogenic index, an important prognostic marker for future CVD, was not significantly changed from baseline to end of study. In some studies, lipid measures were increased initially but eventually stabilized or returned to baseline values after 3 to 6 months (14, 20, 22). This may cast doubt on how informative the short-term results of many studies are to comorbidity considerations for long-term treatment of RA with these medications.

All but two of the reviewed studies looked at the affect of TNF inhibitors on lipid profile (13-16, 18-29). Infliximab was the TNF inhibitor most reported on with regard to lipid profiles. The exact role of TNF and TNF inhibition on lipid profiles is not clear at this time. Treatment of RA with TNF blockers may lower the risk of developing CVD due to different mechanisms (31). In this regard, the use of anti-TNF-alpha monoclonal antibodies has been associated with improvement of endothelial function (32) that is an early step in the atherogenesis process. Also, following TNF-alpha blockade, improvement of insulin resistance and decrease in some adhesion molecules that are biomarkers of endothelial dysfunction has been observed (33, 34). Moreover, a rapid decrease of the proinflammatory adipokine resistin, an important molecule in NF-κB activation and cytokine production but no change in adiponectin concentration was observed following

Total articles identified in searches	(n=158)
Review article	(n=46)
Non-English	(n=2)
Letter to editor about another study	(n=1)
No data on lipids	(n=14)
Animal studies	(n=20)
No biologic agents tested	(n=22)
No RA patients	(n=5)
Laboratory (non-clinical, non-human) studies	(n=26)
Abstract only with no lipid data	(n=4)
Total excluded	(n=140)
Total reviewed	(n=18)

Fig. 1. Literature search; list of reasons for exclusion of articles.

Table II. Chart of basic information regarding each study, the patients included in the study, and if certain lipid data were provided within the article (+). TC is total cholesterol and AI is atherogenic index. For full citation see end of article.

First Author	Publication Year	Duration (weeks)	No. RA patients	Male: Female	Mean Disease Duration (years)	Mean age (years)	TC	HDL	LDL	AI	LDL/HDL
Cauza, E (13)	2002	6	7	5:10		56.7	+	+	+		
Nishimoto, N (17)	2003	24	16	4:11	7	55	+		+		
Irace, C (19)	2004	6	10	4:6	7	46	+	+			
Nishimoto, N (30)	2004	12	109	37:125			+	+			
Popa, C (28)	2005	2	33				+	+	+	+	+
Vis, M (24)	2005	6	69	12:55	12	55	+	+		+	
Gonzalez-Juanatey (29)	2006	12	8	1:7	20	51	+	+		+	
Allanore, Y (18)	2006	30	56	8:51	13	52	+	+	+	+	+
Seriolo, B (25)	2006	24	34	0:34	14	51.6	+	+		+	
Kiortsis, D (15)	2006	24	50	12:38	10.9	52.8	+	+	+	+	
Dahlqvist, S (14)	2006	104	52	11:41			+	+	+	+	+
Spanakis, E (22)	2006	24	24	7:17	1.2	62.7	+	+	+	+	+
Tam, K (23)	2007	14	19	0:19	11	49	+	+	+	+	+
Seriolo, B (27)	2007	24	32				+	+		+	
Popa, C (20)	2007	52	67	16:40	9	56	+	+	+	+	+
Saiki, O (16)	2007	24	32	5:27	9.5	57	+		+		
Soubrier, M (26)	2007	14	29	3:26		57.45	+	+	+	+	
Peters, M (20)	2007	48	80	18:62	10	56	+	+		+	

Percentages of Reported Effects

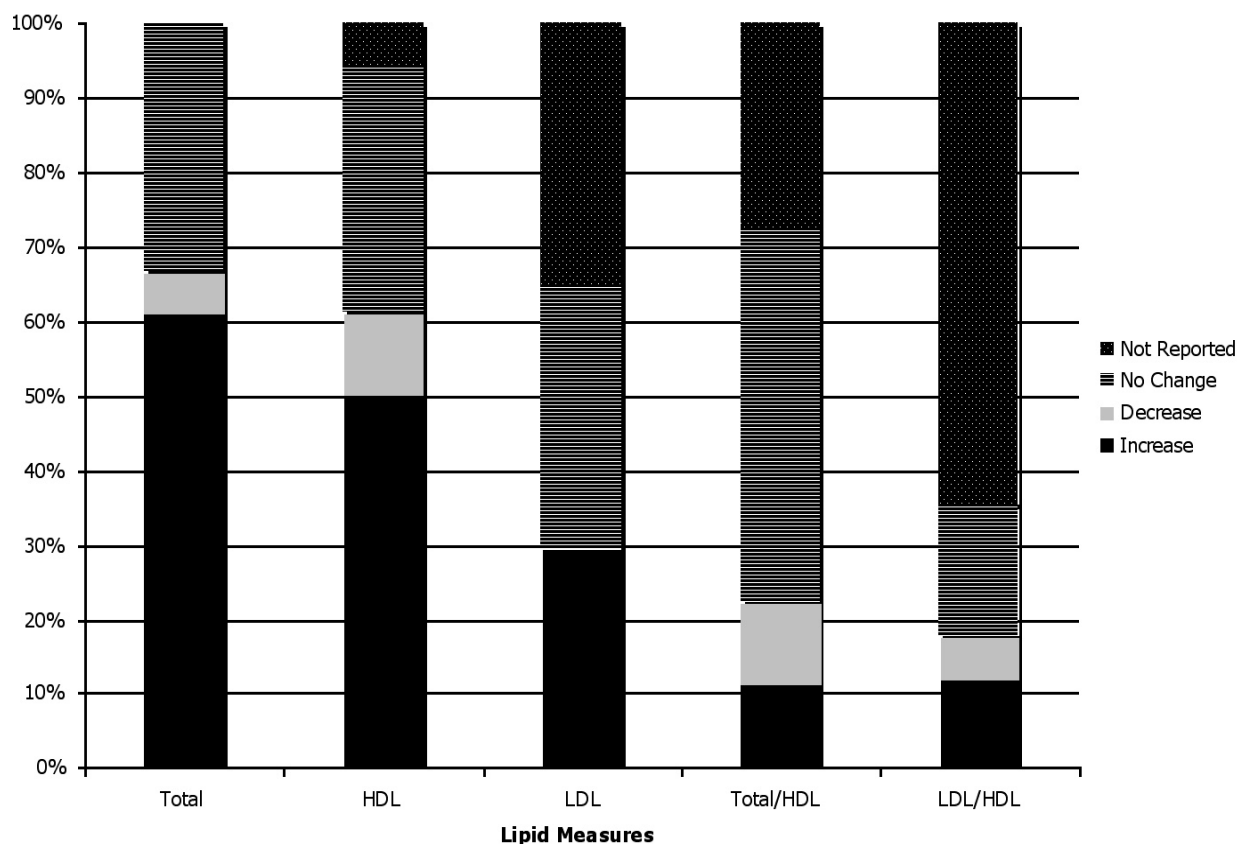


Fig. 2. Percentages of reviewed articles that reported increases, decreases, no change, or did not report for different lipid measures.

the infusion of the chimeric anti-TNF-alpha monoclonal antibody infliximab (35, 36). In addition, a recent report disclosed an increase in ghrelin concentration, a peptide playing a role in the appetite regulation that possesses anti-inflammatory properties, upon TNF-alpha blockade that was also associated with reductions in P-selectin, a biomarker of endothelial activation that predicts cardiovascular event rates (37). Yet the relative contributions of inflammation and raised lipid profiles in RA patients to the overall risk for CVD are not known. Current conventional wisdom seems to suggest that benefit towards decreased CVD due to the therapeutic effectiveness of biologic agents in reducing inflammation outweighs any potential negative effect these drugs may cause to the lipid profile.

Only two studies investigated tocilizumab, both labeled safety and efficacy trials (17, 30). Both found increases in total cholesterol values, but neither reported on the atherogenic index. One study (excluded from this review because it failed to provide any data on the changes in the lipid profile) tested tocilizumab and found moderate but reversible increases in total cholesterol and HDL (38). The mean atherogenic index in this study remained unchanged except in patients treated with high doses, in which case it was reduced to below baseline levels by the end of the study.

Some limitations to this review are related to the difficulties of comparing heterogeneous studies. Units of measurement were not consistent; therefore, the studies could only be compared by calculating percent change values from the available data. These changes account for different time periods of treatment because the studies were not of uniform duration. The objectives of each study were different, resulting in different amounts of data provided within each paper. Most studies did not perform a complete lipid work-up on the patients or did not include the data for each lipid measurement taken. Not all of the studies included control groups. Those that did often did not provide corresponding data for the controls, thus complicating our ability

to state significance. In some studies data from RA patients were not reported separately from non-RA patients in the trial, so the information on lipid changes was not as specific to RA as we would like. Data from two studies had to be approximated from figures, thus yielding less precise results. It is also noted that, to date, few studies have reported the effects of biologic DMARDs on lipid levels in patients with RA, thus the pool of data available for review is limited. We were unable to find data on lipid changes for some of the biologic agents in use, such as rituximab and abatacept.

Further studies analyzing longitudinal databases and clinical trials are needed to enhance our understanding of the effect of biologic agents on the lipid profile of patients with RA, which would be useful to clinicians who must be vigilant against the increased prevalence of cardiovascular disease with RA. Full reporting of lipid profile elements would also be useful in accumulating enough good quality data to be able to draw firmer conclusions.

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