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EXTENDED REPORT

Effects of golimumab, an anti-tumour necrosis factor- α human monoclonal antibody, on lipids and markers of inflammation

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ABSTRACT

Objectives To assess the effect of golimumab, with or without methotrexate (MTX), on serum lipids and inflammatory markers of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) in two phase 3, randomised, placebo-controlled trials (GO-BEFORE and GO-FORWARD).

Methods Patients in GO-BEFORE (n=637, MTX-naïve) and GO-FORWARD (n=444, MTX-inadequate response) were randomised to placebo+MTX, golimumab 100 mg +placebo, golimumab 50 mg+MTX, or golimumab 100 mg+MTX. Subcutaneous injections (placebo and golimumab) were given every 4 weeks. Patients with an insufficient response entered early escape at week 16 (GO-FORWARD) or 28 (GO-BEFORE). All placebo+MTX patients in GO-FORWARD crossed over to golimumab 50 mg+MTX at week 24. Changes from baseline to weeks 14 (GO-FORWARD) or 24 (GO-BEFORE), and 52 in serum lipid levels and inflammatory markers were assessed.

Results At week 14 in the GO-FORWARD trial, total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) increased in golimumab+MTX patients versus MTX-only patients (16.00 vs 2.00 (p<0.001); 3.00 vs 0.00 (p<0.05); 8.00 vs 4.00 (p<0.001); respectively); favourable changes in LDL subfractions were only observed in golimumab-treated patients. At week 24 in GO-BEFORE, TC and LDL increased, and LDL subfractions improved in the MTX-only and golimumab+MTX groups. Inflammatory markers of CVD risk improved significantly with golimumab+MTX versus placebo+MTX in both studies and were generally maintained through week 52. Atherogenic indices were generally stable.

Conclusions While TC and LDL levels increased mildly in RA patients receiving golimumab+MTX, atherogenic indices generally remained stable, favourable changes in LDL subfractions were observed, and inflammatory markers improved.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic immune-mediated inflammatory disorder that affects approximately 1% of the population in the USA. An increased risk for cardiovascular disease (CVD) in patients with RA is well established. Specifically, patients with RA have been shown to be 30–60% more likely to suffer from a cardiovascular event than age- and gender-matched arthritis-free patients.¹ The chronic inflammation that is characteristic of RA is

believed to play a key role, as some of the increased cardiovascular morbidity and mortality that are observed in RA patients is independent of the traditional risk factors for CVD.² Microvascular endothelial dysfunction that occurs early in the development of CVD is worsened by inflammation,³ and proinflammatory cytokines, including tumour necrosis factor- α (TNF- α), have been shown to have proatherosclerotic effects.^{4–5} Short-term anti-TNF treatment has been shown to have a positive effect on endothelial function, and also has been associated with a decrease in inflammation, improved lipid levels, and an improvement in the atherogenic index in patients with RA, indicating a potential role of TNF blockade in ameliorating cardiovascular risk.^{6–7}

Active inflammation is associated with decreased high-density lipoprotein (HDL) levels and total cholesterol (TC) levels,⁸ and although levels of low-density lipoprotein (LDL) are decreased, this is accompanied by increases in small, dense LDL.⁹ These small LDL particles have been shown to be an independent risk factor for CVD¹⁰; however, the utility of LDL subfractions as a surrogate marker for CVD is not clear as this is a relatively new area of investigation.

Golimumab is a human monoclonal antibody specific for human TNF- α and is approved for the treatment of moderately-to-severely active RA.¹¹ The safety and efficacy of golimumab were evaluated in two large, phase 3, multicentre, randomised, double-blind, placebo-controlled trials of patients with RA. The GO-BEFORE study enrolled methotrexate (MTX)-naïve RA patients,¹² and the GO-FORWARD study enrolled patients with active RA despite MTX therapy.¹³ In both studies, golimumab (50 or 100 mg) plus MTX every 4 weeks significantly improved the signs and symptoms of RA and was well tolerated.^{12–13}

The effects of the anti-TNF therapies adalimumab, etanercept and infliximab on lipid profiles have been evaluated in small studies of patients with RA, with discordant results.^{7–14–16} Given the increased risk of CVD in patients with RA, the role of dyslipidaemia in atherogenesis, and the growing use of anti-TNF therapies for the treatment of RA, the relationship between use of these agents and changes in lipid profiles in patients with RA is of particular interest. We prospectively evaluated the effect of golimumab on serum lipid levels, including a novel marker of LDL subfractions, and inflammatory markers which may be associated with CVD among patients with RA in

the two phase 3, randomised, placebo-controlled trials, GO-BEFORE and GO-FORWARD.

PATIENTS AND METHODS

Patients

Patient inclusion and exclusion criteria for the GO-BEFORE¹² and GO-FORWARD¹³ studies have been previously described. Briefly, for inclusion in either trial, eligible adults had to have active RA, with diagnosis having occurred at least 3 months before the initial study agent administration. For the MTX-naïve patients in the GO-BEFORE study, patients could not have received more than three weekly doses of oral MTX. In the GO-FORWARD study, patients must have received MTX for at least 3 months with a stable dose (≥ 15 but ≤ 25 mg/week) for 4 weeks prior to screening.

Study designs

GO-BEFORE and GO-FORWARD were randomised, double-blind, placebo-controlled trials; details of the study designs have been previously published.^{12 13} In both trials, golimumab was administered as a subcutaneous injection at baseline and every 4 weeks thereafter. Patients in the GO-BEFORE (n=637) and GO-FORWARD (n=444) studies were randomly assigned to receive placebo plus MTX, golimumab 100 mg plus placebo, golimumab 50 mg plus MTX, or golimumab 100 mg plus MTX. In the GO-BEFORE trial, treatment with placebo plus MTX in the control group continued through week 52 if the patient had a clinical response. In the GO-FORWARD trial, patients randomised to receive placebo plus MTX crossed over to receive golimumab 50 mg plus MTX at week 24. Concurrent use of non-steroidal anti-inflammatory drugs, other analgesics for RA, and oral corticosteroids (≤ 10 mg of prednisone/day or equivalent) was allowed if doses were stable for at least 2 weeks prior to study agent start and remained stable during the study.

Patients who had an insufficient response, as defined by pre-specified criteria,^{12 13} entered double-blinded early escape at either week 16 (GO-FORWARD) or week 28 (GO-BEFORE) according to the study protocol. During early escape, patients who initially received placebo plus MTX switched to golimumab 50 mg plus MTX, and those receiving golimumab 50 mg had their golimumab dose increased to 100 mg. Patients who initially received golimumab 100 mg plus placebo switched from placebo capsules to MTX, while those who initially received golimumab 100 mg plus MTX had no change in treatment, regardless of early escape status.

The studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation good clinical practices. The protocols were reviewed and approved by each site's institutional review board or ethics committee. All patients provided written informed consent before undergoing study-related procedures.

Serum lipids

Fasting serum samples were collected at weeks 0, 24 and 52 in GO-BEFORE and at weeks 0, 14 and 52 in GO-FORWARD for determination of lipid concentrations (triglycerides, TC, HDL, LDL, LDL subfractions, LDL particle size, apolipoprotein A1 and apolipoprotein B). LDL subfractions including mean particle sizes were determined by nuclear magnetic resonance spectroscopy.^{17 18}

Serum inflammatory markers of CVD

Serum samples were collected at weeks 0, 24 and 52 in GO-BEFORE and at weeks 0, 14 and 52 in GO-FORWARD to

determine serum concentrations of the following inflammatory markers: serum amyloid A, high sensitivity C-reactive protein (hsCRP), fibrinogen, interleukin (IL)-6, IL-8, intracellular adhesion molecule (ICAM)-1, matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF).

Statistical methodology

In both trials, summaries of median change and median percentage change from baseline include all treated patients with available data and are categorised by actual treatment group. Baseline concentrations of serum inflammatory markers below the lower limit of quantification (LLOQ) were set to half the LLOQ value for that assay. For both the serum lipid markers and serum inflammatory markers, median percentage changes from baseline to week 14 (GO-FORWARD) or week 24 (GO-BEFORE), and week 52 (both studies) are reported.

All statistical tests were conducted at the 0.05 level of significance. No adjustment for multiple tests was made.

RESULTS

Patient disposition and baseline characteristics

A total of 1081 patients participated in these trials (GO-BEFORE, n=637; GO-FORWARD, n=444) (table 1). Within each trial, randomised treatment groups were generally well balanced with regard to baseline demographic and disease characteristics, as well as for concentrations of serum lipids and inflammatory markers of CVD. Previous MTX therapy was mandated by the GO-FORWARD inclusion/exclusion criteria but was precluded by those of GO-BEFORE (table 1).

Lipid markers of CVD

At week 14 in the GO-FORWARD trial of RA patients with an inadequate response to MTX, those who received golimumab plus MTX had significant median increases in TC (16.00 vs 2.00 mg/dl; $p < 0.001$), HDL (3.00 vs 0.00 mg/dl; $p = 0.008$) and LDL (8.00 vs 4.00 mg/dl; $p < 0.001$) levels compared with patients who received placebo plus MTX. However, atherogenic ratios that included TC/HDL, LDL/HDL and apolipoprotein B/A1 were generally stable in golimumab-treated patients relative to patients treated with MTX only (table 2). Also at week 14, significant changes in LDL subfractions were observed in the combined golimumab plus MTX group when compared with patients treated with placebo plus MTX, including increases in large LDL (median: 90.50 vs 21.00 nmol/l; $p = 0.004$) and mean LDL particle size (median: 0.20 vs 0.00 nM; $p < 0.001$) and decreases in total small LDL (median: -56.50 vs 30.00 nmol/l; $p < 0.001$), medium small LDL (median: -12.50 vs 6.00 nmol/l; $p = 0.001$) and very small LDL (median: -50.50 vs 19.00 nmol/l; $p = 0.003$) (table 2).

All patients in the placebo plus MTX group in the GO-FORWARD study crossed over to active treatment at week 24; therefore, all patients had been receiving treatment with golimumab with or without MTX for several months by week 52. All treatment groups exhibited similar significant increases in LDL and TC levels from baseline to week 52. Statistically significant percentage increases from baseline to week 52 in LDL/HDL and TC/HDL ratios were also observed in all treatment groups; however, the absolute increases were small. The golimumab plus MTX groups had significant changes in LDL subfractions, including increases in large LDL and mean LDL particle size and decreases in total small LDL, medium small LDL, and very small LDL (table 3).

At week 24 in the GO-BEFORE trial of MTX-naïve RA patients, TC and LDL levels increased, and changes in LDL subfractions (decreases in very small and medium small LDL and

Table 1 Baseline patient and disease characteristics for patients in GO-FORWARD and GO-BEFORE

	GO-FORWARD: RA patients with an inadequate response to MTX					GO-BEFORE: MTX-naïve RA patients				
	Placebo+MTX	Golimumab+MTX				Placebo+MTX	Golimumab+MTX			
Golimumab 100 mg + Placebo		50 mg	100 mg	Combined	Golimumab 100 mg + Placebo		50 mg	100 mg	Combined	
Patients randomised, n	133	133	89	89	178	160	159	159	159	318
Female	109 (82.0)	105 (78.9)	72 (80.9)	72 (80.9)	144 (80.9)	134 (83.8)	134 (84.3)	135 (84.9)	125 (78.6)	260 (81.8)
Age, years	52.0	51.0	52.0	50.0	51.0	50.0	49.0	51.0	50.0	51.0
Body mass index	25.6	26.3	26.3	25.6	25.9	26.4	25.7	27.1	25.9	26.4
Duration of RA, years	6.5	5.9	4.5	6.7	5.3	1.2	1.8	1.0	1.3	1.1
Extra-articular manifestations	37 (28.2)	48 (36.4)	35 (39.3)	23 (25.8)	58 (32.6)	45 (28.1)	42/156 (26.9)	35 (22.0)	30 (18.9)	65 (20.4)
Anti-CCP antibodies	107 (80.5)	106 (79.7)	72 (80.9)	68 (76.4)	140 (78.7)	121 (75.6)	125 (78.6)	106 (66.7)	116 (73.0)	222 (69.8)
Rheumatoid factor	108 (81.2)	111 (83.5)	77 (86.5)	75 (84.3)	152 (85.4)	130/159 (81.8)	129 (81.1)	121 (76.1)	127 (79.9)	248 (78.0)
Concomitant use of HMG-CoA reductase inhibitor	9 (6.8)	9 (6.8)	4 (4.5)	8 (9.0)	12 (6.7)	7 (4.4)	10 (6.3)	8 (5.0)	12 (7.5)	20 (6.3)
Patients with a history of:										
Hyperlipidaemia	17 (12.8)	19 (14.3)	10 (11.2)	16 (18.0)	26 (14.6)	19 (11.9)	18 (11.4)	29 (18.2)	23 (14.5)	52 (16.4)
Required therapy	10 (7.5)	13 (9.8)	5 (5.6)	8 (9.0)	13 (7.3)	11 (6.9)	10 (6.3)	12 (7.5)	12 (7.5)	24 (7.5)
Systemic corticosteroid use	120 (90.2)	113 (85.0)	79 (88.8)	79 (88.8)	158 (88.8)	109 (68.1)	101 (63.5)	111 (69.8)	104 (65.4)	215 (67.6)
Serum lipid markers										
Triglycerides (mg/dl)	103.5	116.5	102.5	117.0	108.0	114.0	105.0	114.0	104.0	107.0
Total cholesterol (mg/dl)	194.0	192.0	190.5	206.0	198.5	193.0	190.0	195.5	190.0	191.0
LDL (mg/dl)	107.5	108.0	107.0	117.0	112.0	109.0	106.0	108.5	108.0	108.0
HDL (mg/dl)	61.0	58.0	61.0	60.0	60.5	58.0	58.0	56.5	57.0	57.0
Total cholesterol/HDL	3.2	3.3	3.3	3.4	3.3	3.3	3.3	3.5	3.3	3.4
LDL/HDL	1.8	1.8	1.8	2.0	1.9	1.9	1.9	2.0	1.9	2.0
Apolipoprotein B (mg/dl)	78.0	79.0	83.0	88.5	85.0	79.0	80.5	84.0	81.0	82.0
Apolipoprotein A1 (mg/dl)	147.0	146.0	148.0	147.0	148.0	140.0	144.0	143.0	139.0	142.0
Apolipoprotein B/A1	0.5	0.6	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Apolipoprotein A1 (mg/dl)										
LDL subfractions										
Total LDL particles (nmol/l)	1089.0	1136.0	1074.0	1192.5	1133.0	1188.0	1131.0	1157.0	1120.5	1149.0
Total small LDL (nmol/l)	543.0	600.0	578.0	660.5	648.0	679.0	623.0	681.0	612.5	644.5
Very small LDL (nmol/l)	433.0	488.0	456.0	531.0	509.0	537.0	493.0	544.5	488.0	513.5
Medium small LDL (nmol/l)	114.0	124.0	119.5	141.0	130.5	140.0	136.0	136.5	127.0	130.0
Large LDL (nmol/l)	465.5	451.0	434.5	485.5	457.0	406.0	420.0	464.5	461.0	464.5
Mean LDL size (nM)	21.3	21.3	21.2	21.2	21.2	21.2	21.1	21.1	21.2	21.2
Inflammatory markers										
Serum amyloid A (µg/ml)	14.1	15.6	17.0	19.4	18.3	30.0	19.5	22.3	19.5	21.8
hsCRP (mg/dl)	7.0	9.1	9.7	10.1	9.7	13.3	13.4	12.4	13.0	12.5
Fibrinogen (mg/dl)	420.0	413.0	419.0	420.0	419.0	433.0	416.0	439.5	439.0	439.0
ICAM-1 (ng/ml)	340.0	344.0	324.0	344.0	340.0	338.0	354.0	348.0	343.0	345.0

Continued

Table 1 Continued

	GO-FORWARD: RA patients with an inadequate response to MTX				GO-BEFORE: MTX-naïve RA patients			
	Golimumab+MTX		Golimumab+MTX		Golimumab+MTX		Golimumab+MTX	
	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg
IL-6 (pg/ml)	7.3	6.0	6.9	6.6	10.7	10.1	10.5	11.8
IL-8 (pg/ml)	19.1	19.2	19.7	17.3	17.6	16.7	16.6	17.4
MMP-3 (ng/ml)	39.4	35.2	43.9	46.4	51.1	44.8	45.4	42.8
VEGF (pg/ml)	84.0	94.9	85.4	89.6	104.9	100.1	99.1	101.5
					Combined	Combined	Combined	Combined
					6.9	6.9	10.5	11.2
					18.9	16.7	16.6	16.7
					44.7	44.8	45.4	43.7
					86.3	100.1	99.1	99.9

Data shown are median value or number (%) of patients unless otherwise noted. Anti-CCP, anti-cyclic citrullinated peptide; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; LDL, low-density lipoprotein; MMP-3, matrix metalloproteinase; MTX, methotrexate; RA, rheumatoid arthritis; VEGF, vascular endothelial growth factor.

increases in large LDL) occurred in all treatment groups without any significant differences between the combined golimumab plus MTX group and the placebo plus MTX group. Although HDL levels in patients who received golimumab plus MTX increased significantly from baseline (1.00 mg/dl or 2.50%), these increases were not statistically significant when compared with the placebo plus MTX group (0.50 mg/dl or 0.63%). A similar pattern was observed for decreases in the apolipoprotein B/A1 ratio (table 2). At week 52, changes from baseline in these lipid parameters were not significantly different between the placebo plus MTX group and the combined golimumab plus MTX group (table 3).

Inflammatory markers of CVD

At week 14 in the GO-FORWARD study, patients who received golimumab plus MTX had significantly greater median decreases in serum concentrations of serum amyloid A (-10.65 vs -1.60 µg/ml; p<0.001), fibrinogen (-80.00 vs -2.00 mg/dl; p<0.001), hsCRP (-5.01 vs -0.63 mg/dl; p<0.001), ICAM-1 (-40.00 vs 0.00 ng/dl; p<0.001), IL-6 (-3.60 vs -1.20 pg/ml; p<0.001), IL-8 (-5.30 vs -1.75 pg/ml; p=0.001), MMP-3 (-9.71 vs -4.27 ng/ml; p<0.001) and VEGF (-19.80 vs 0.90 pg/ml; p<0.001) than did patients who received placebo plus MTX (table 2).

Median changes from baseline to week 52 in these inflammatory markers of CVD were generally similar across the golimumab monotherapy and golimumab plus MTX therapy groups in the GO-FORWARD study (table 3). A notable exception included a significant percentage increase in IL-6 from baseline in the golimumab 100 mg plus placebo group (16.92%; p<0.001 vs baseline) that contrasted with a significant median decrease in the combined golimumab plus MTX group (-0.80 pg/ml; p<0.001 vs baseline). In addition, significant decreases in hsCRP from baseline to week 52 were observed in patients treated with golimumab plus MTX (-3.74 mg/dl or -56.73% for 50 mg and -5.20 mg/dl or -64.78% for 100 mg; p<0.001 for both dose groups), while a non-significant decrease was observed with golimumab monotherapy (-0.64 mg/dl or -18.60%) (table 3).

At week 24 in the GO-BEFORE study, patients who received golimumab plus MTX had significantly greater median decreases from baseline in hsCRP (-6.05 vs -5.40 mg/dl; p=0.001), ICAM-1 (-40.00 vs -2.00 mg/dl; p<0.001), IL-6 (-7.30 vs -4.85 pg/ml; p<0.001), IL-8 (-5.10 vs -2.80 pg/ml; p=0.001), MMP-3 (-19.21 vs -14.70 ng/ml; p=0.049) and VEGF (-29.15 vs -21.85 pg/ml; p=0.001) concentrations when compared with patients receiving MTX alone (table 2). At week 52, significant decreases from baseline in hsCRP, ICAM-1 and IL-6 levels were observed in all treatment groups (table 3). Additionally, changes from baseline to week 52 in these putative inflammatory markers of CVD were generally similar across the treatment groups. Greater median decreases in ICAM-1 (-81.00 ng/ml or -25.81%) and IL-6 (-4.00 or -50.35%) were observed in the combined golimumab plus MTX group versus the placebo plus MTX group (-59.50 ng/ml or -17.48%; p=0.001 and -4.55 or -49.82%; p=0.005).

DISCUSSION

Lipid markers of CVD and inflammatory markers were evaluated in patients with RA in the GO-FORWARD and GO-BEFORE trials. In the GO-FORWARD trial, TC, HDL and LDL levels increased in all treatment groups at week 14 and were greater in the golimumab plus MTX groups than in the placebo plus MTX group; however, atherogenic ratios, including TC/HDL and apolipoprotein B/A1, were generally stable

Table 2 Median and median percentage change from baseline to week 14 (GO-FORWARD) or week 24 (GO-BEFORE) in serum lipid and inflammatory markers of cardiovascular disease in patients with RA

	GO-FORWARD: RA patients with an inadequate response to MTX (week 14)					GO-BEFORE: MTX-naïve RA patients (week 24)				
	Golimumab+MTX					Golimumab+MTX				
	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined
Patients randomised,† n	133	133	89	89	178	160	159	159	159	318
Serum lipid markers										
Triglycerides (mg/dl)	2.00 1.89%	1.00 0.65%	4.00* 5.31%*	0.00 0.16%	3.00 3.68%*	-3.00 -2.04%	-3.00 -2.34%	7.00 4.88%*	-3.00 -2.61%	4.00 4.09%*
Total cholesterol (mg/dl)	2.00 1.01%	8.00*** 3.79%***	16.00*** 8.51%***	15.50*** 8.04%***	16.00###/*** 8.44%***	6.50** 4.00%***	9.00*** 4.74%***	10.50** 4.54%***	8.00** 3.94%**	8.00*** 4.12%***
LDL (mg/dl)	4.00 3.25%	8.00** 7.27%***	8.00*** 11.67%***	9.00*** 10.09%***	8.00###/*** 11.64%***	7.50** 6.27%***	8.00*** 7.89%***	3.00 2.92%	3.00* 2.67%**	3.00*** 2.68%***
HDL (mg/dl)	0.00 0.00%	3.00* 5.08%**	3.00** 5.88%**	3.50** 5.05%**	3.00###/*** 5.41%***	0.50 0.63%	3.00** 4.26%**	1.00 1.33%	2.00* 3.53%**	1.00* 2.50%***
Total cholesterol/HDL	0.07 1.90%	0.03 0.99%	0.11* 3.26%*	0.04 1.22%	0.09* 2.78%*	0.16* 4.77%**	0.03 1.42%	0.05 1.50%	-0.01 -0.52%	0.03 0.79%
LDL/HDL	0.07 4.00%*	0.04 2.66%	0.09* 4.81%*	0.05 3.07%*	0.07* 3.41%***	0.16** 6.79%***	0.03 1.49%	0.03 1.80%	0.01 1.28%	0.03 1.29%
Apolipoprotein B (mg/dl)	0.00 0.00%	5.00*** 6.10%***	4.50* 4.68%*	3.00* 3.75%**	3.50*** 4.14%***	1.00 0.93%	1.00 1.61%	0.00 0.00%	1.00 1.25%	0.00 0.00%
Apolipoprotein A1 (mg/dl)	4.50 2.68%	10.00*** 7.37%***	8.00*** 5.77%***	10.00** 6.71%**	9.50*** 6.16%***	6.50** 5.14%**	6.00** 4.41%***	10.50*** 6.72%***	10.00*** 6.32%***	10.00*** 6.67%***
Apolipoprotein B/ Apolipoprotein A1 (mg/dl)	-0.01 -1.08%	-0.01 -1.20%	-0.02 -3.34%	-0.02 -4.37%	-0.02 -3.78%	-0.01 -2.00%	-0.02 -3.76%	-0.02* -3.54%	-0.03 -4.00%	-0.02*** -3.84%*
LDL subfractions										
Total LDL particles (nmol/l)	47.00** 4.79%**	25.50 1.51%*	33.00 2.94%	36.00 2.39%	33.00 2.62%*	-7.00 -0.72%	-51.00 -4.67%	-20.50 -1.89%	-67.00 -6.15%	-47.00 -5.51%
Total small LDL (nmol/l)	30.00 4.25%	-36.00 -5.96%	-53.00 -9.90%*	-67.00 -10.52%*	-56.50###/*** -10.52%***	-71.00 -10.41%	-62.00 -10.94%	-79.50* -16.84%	-53.00** -16.90%	-72.00*** -16.87%*
Very small LDL (nmol/l)	19.00 1.93%	-29.50 -5.25%	-44.00 -9.65%*	-64.00 -12.59%*	-50.50###/*** -11.20%***	-41.00 -9.73%	-43.00 -12.18%	-70.00* -18.36%	-49.00* -11.73%	-63.00*** -16.26%*
Medium small LDL (nmol/l)	6.00 4.88%	-9.50 -8.59%	-11.50 -11.21%	-13.00 -12.82%*	-12.50###/*** -12.82%*	-11.00* -8.35%	-14.00* -9.23%	-15.50* -14.35%	-16.00** -16.67%*	-16.00*** -15.03%*
Large LDL(nmol/l)	21.00 3.41%	54.50** 11.95%***	106.50*** 27.73%***	69.00** 18.58%***	90.50###/*** 21.45%***	43.00** 11.82%**	32.00 7.05%*	27.50 4.21%*	54.00** 13.16%***	38.00*** 7.98%***
Mean LDL size (nM)	0.00 0.00%	0.10 0.46%	0.25*** 1.16%***	0.20** 0.97%**	0.20###/*** 0.98%***	0.10** 0.48%**	0.10* 0.46%*	0.10 0.47%*	0.20*** 0.95%***	0.20*** 0.91%***
Inflammatory markers										
Serum amyloid A (µg/ml)	-1.60** -20.07%	-2.00** -28.90%	-11.80*** -72.07%***	-8.70*** -57.95%***	-10.65###/*** -65.59%***	-15.95*** -66.39%***	-4.40*** -41.84%***	-14.55*** -68.65%***	-7.60*** -72.37%***	-10.10###/*** -70.90%***
hsCRP (mg/dl)	-0.63 -10.42%	-2.74** -50.11%	-5.36*** -71.83%***	-3.40*** -69.54%***	-5.01###/*** -70.68%***	-5.40*** -49.58%**	-4.00*** -57.20%***	-4.79*** -70.38%***	-7.21*** -72.66%***	-6.05###/*** -71.74%***
Fibrinogen (mg/dl)	-2.00 -0.58%	-38.50** -9.02%*	-88.50*** -18.45%***	-79.00*** -18.63%***	-80.00###/*** -18.63%***	-38.50*** -10.03%**	-40.00*** -10.17%**	-83.00*** -18.75%***	-68.00*** -15.02%***	-74.00*** -17.29%***
ICAM-1 (ng/ml)	0.00	-20.00**	-40.00***	-36.00***	-40.00###/***	-2.00	-40.00***	-36.00***	-40.00***	-40.00###/***

Continued

Table 2 Continued

	GO-FORWARD: RA patients with an inadequate response to MTX (week 14)				GO-BEFORE: MTX-naïve RA patients (week 24)				
	Golimumab+MTX				Golimumab+MTX				
	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined
IL-6 (pg/ml)	0.00%	-5.26%**	-12.50%***	-9.09%***	-0.65%	-12.50%***	-10.33%***	-13.33%***	Combined -12.50%***
	-1.20*	-1.40**	-4.10***	-1.50***	-4.85***	-2.90***	-6.70***	-8.20***	-7.30###/****
	-20.47%	-42.86%*	-70.37%***	-44.44%**	-60.97%***	-57.14%***	-76.09%***	-77.78%***	-76.92%***
IL-8 (pg/ml)	-1.75**	-4.20***	-6.30***	-4.70***	-2.80***	-6.00***	-5.15***	-5.00***	-5.10###/****
	-9.08%*	-22.60%***	-33.82%***	-35.26%***	-18.07%***	-33.33%***	-33.62%***	-33.32%***	-33.62%***
MMP-3 (ng/ml)	-4.27***	-2.50**	-13.40***	-4.31***	-14.70***	-4.30***	-18.90***	-21.00***	-19.21###/****
	-13.20%***	-9.88%*	-32.45%***	-24.23%***	-38.61%***	-22.71%***	-47.95%***	-45.49%***	-46.70%***
VEGF (pg/ml)	0.90	-8.90***	-20.40***	-18.70***	-21.85***	-23.10***	-27.60***	-30.30***	-29.15###/****
	1.50%	-10.67%***	-22.99%***	-29.33%***	-25.11%***	-21.24%***	-35.75%***	-32.18%***	-33.25%***

†Not all randomised patients had week 14/24 biomarker data.
 *, **, *** indicate p≤0.05, 0.01, 0.001, respectively, for change from baseline within group.
 #, ##, ### indicate p≤0.05, 0.01, 0.001, respectively, for the comparison of the combined golimumab+MTX and placebo+MTX groups.
 HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; LDL, low-density lipoprotein; MMP-3, matrix metalloproteinase; MTX, methotrexate; RA, rheumatoid arthritis; VEGF, vascular endothelial growth factor.

among all groups. At week 52, following placebo-crossover at week 24, all treatment groups had significant increases from baseline in TC and LDL concentrations. Of note, decreases in total small, very small and medium small LDL were observed in the golimumab plus MTX groups at weeks 14 and 52, while these levels generally increased in the placebo plus MTX group at week 14. In the GO-BEFORE trial, TC, HDL and LDL levels increased from baseline to week 24, and total small, very small and medium small LDL levels decreased in all treatment groups. As observed in the GO-FORWARD trial, atherogenic ratios were also stable among the treatment groups in GO-BEFORE. No significant differences were observed between the combined golimumab plus MTX group and the placebo plus MTX group in the changes from baseline to week 52 in the evaluated lipid markers. No consistent changes in triglycerides were observed through week 52 in either study.

The increases in HDL and TC following golimumab treatment are consistent with other studies of anti-TNF agents in patients with RA.¹⁹ Although changes in lipid levels were generally more pronounced in the golimumab treatment groups compared with the placebo plus MTX group, overall, changes were generally mild across all groups. Differences between the golimumab groups and the placebo plus MTX group in GO-FORWARD were more pronounced when evaluating the LDL subfractions. Although total LDL levels increased from baseline, those of small LDL particles, which have been associated with an increased risk for CVD and atherosclerosis, decreased following treatment with golimumab (monotherapy or with concomitant MTX). While the functional implications are still unknown, overall, there appeared to be a favourable change in LDL particle distribution associated with golimumab treatment, with increases in large LDL particles, decreases in small LDL particles and increases in mean LDL particle size. LDL subfractions are relatively new markers for evaluating CVD with limited commercial availability; currently, studies have not clearly shown if LDL particle size is an accurate surrogate marker for CVD outcomes across various populations.²⁰

In both GO-FORWARD (week 14) and GO-BEFORE (week 24), serum levels of all inflammatory markers evaluated decreased significantly from baseline in all golimumab treatment groups, and decreases in serum amyloid A, hsCRP, ICAM-1, IL-6, IL-8, MMP-3 and VEGF were significantly greater in the combined golimumab plus MTX groups than in the placebo plus MTX group. At week 52, levels of all of the inflammatory markers tested were decreased from baseline in all treatment groups, with the exception of IL-6 in the golimumab 100 mg plus placebo group in GO-FORWARD. Most of these decreases were statistically significant, including those in the placebo plus MTX group in GO-BEFORE. These decreases in inflammatory markers are not surprising given the clinical improvements seen with golimumab. Any effective therapy for RA is expected to decrease inflammatory markers; however, the magnitude of the decrease may differ between treatments in relation to their efficacy. Although a reduction in inflammatory markers was seen in the placebo plus MTX group, the reductions were greater in the golimumab plus MTX group. Similarly, greater improvements in disease activity parameters were also seen in the golimumab plus MTX treatment group compared with the placebo plus MTX group.^{12 13} It has been postulated that the reduction in inflammation afforded by both MTX and anti-TNF therapies can lead to the reduction in cardiovascular events as shown in other studies.²¹

In general, previous studies of lipid profiles following anti-TNF therapy in patients with RA were not randomised and

Table 3 Median and median percentage change from baseline to week 52 in serum lipid and inflammatory markers of cardiovascular disease in patients with RA

	GO-FORWARD: RA patients with an inadequate response to MTX				GO-BEFORE: MTX-naïve RA patients				
	Golimumab+MTX				Golimumab+MTX				
	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined
Patients randomised,† n	133	89	89	178	160	159	159	159	318
Serum lipid markers									
Triglycerides (mg/dl)	-1.00 -0.96%	2.00 1.81%	3.50 4.00%	3.00 3.37%*	-4.00 -3.41%	2.00* 2.41%*	6.00 8.01%**	0.00 0.00%	3.00* 3.82%***
Total cholesterol (mg/dl)	8.00** 4.55%**	7.00** 4.02%***	11.50*** 5.45%***	9.00*** 4.58%***	5.00 1.90%*	3.00** 1.80%**	12.00** 6.41%***	8.00*** 3.56%***	10.00*** 4.91%***
LDL (mg/dl)	8.50*** 8.48%***	7.00*** 6.19%***	11.50*** 9.50%***	8.00*** 7.09%***	6.00* 6.08%**	7.00** 5.93%**	8.00*** 7.80%***	6.00*** 6.04%***	7.00*** 6.56%***
HDL (mg/dl)	-1.00 -2.49%	0.00 0.00%	1.50 1.78%	0.00 0.00%	-1.00 -1.28%	0.00 0.00%	-0.50 -0.85%	0.00 0.00%	0.00 0.00%
Total cholesterol/HDL	0.20*** 6.37%***	0.10** 3.31%**	0.04 1.03%*	0.06*** 1.87%***	0.12* 2.91%*	0.13** 4.43%**	0.23*** 7.51%***	0.09* 2.76%**	0.14*** 4.16%***
LDL/HDL	0.22*** 9.46%***	0.09** 5.09%**	0.09* 4.65%**	0.09*** 5.03%**	0.09* 4.52%**	0.12** 5.25%**	0.16*** 8.64%***	0.15** 7.98%**	0.15*** 8.19%**
Apolipoprotein B (mg/dl)	5.00** 5.43%***	2.00* 2.35%**	1.00 1.57%	1.00* 2.17%***	0.00 0.00%	3.00** 3.33%	3.00** 4.41%**	3.00* 3.85%**	3.00*** 3.95%***
Apolipoprotein A1 (mg/dl)	5.00* 3.16%**	10.00*** 6.88%***	12.00*** 8.30%***	11.00*** 7.51%***	6.00** 4.55%***	6.00** 4.55%***	7.00** 5.08%***	8.00*** 5.59%***	8.00*** 5.26%***
Apolipoprotein B/ Apolipoprotein A1 (mg/dl)	0.02 3.99%	-0.02 -4.44%	-0.03* -5.48%	-0.02*** -4.68%*	-0.01 -3.14%	-0.01 -1.82%	0.00 -1.10%	0.00 -0.69%	0.00 -0.69%
LDL subfractions									
Total LDL particles (nmol/l)	66.50* 4.92%*	-28.00 -2.33%	-43.00 -3.82%	-31.00 -3.25%	-19.00 -1.58%	-49.00 -3.88%	-5.50 -0.42%	-3.50 -0.34%	-4.50 -0.42%
Total small LDL (nmol/l)	-1.00 -0.39%	-98.00*** -17.87%**	-105.00* -19.09%*	-105.00*** -18.93%***	-53.00* -7.41%	-104.00* -17.43%	-28.50* -6.72%	-72.50** -14.80%	-46.50*** -10.60%*
Very small LDL (nmol/l)	7.50 0.62%	-78.00*** -19.17%**	-85.00* -21.00%**	-78.00*** -19.81%***	-37.00* -8.29%	-76.00* -18.06%	-19.00 -6.50%	-58.50* -14.22%	-42.50*** -11.90%*
Medium small LDL (nmol/l)	2.50 1.16%	-18.00*** -21.84%**	-17.00* -19.51%*	-17.00*** -19.75%***	-11.50* -9.30%	-16.00* -13.26%	-10.50* -14.68%	-17.50* -17.11%	-16.00*** -15.38%*
Large LDL(nmol/l)	16.50 4.18%	62.50*** 12.28%***	71.00*** 14.12%***	63.00*** 13.30%***	38.50** 14.56%**	17.00 4.28%	74.00*** 14.33%***	54.00*** 14.40%***	60.00*** 14.40%***
Mean LDL size (nM)	0.00 0.00%	0.30*** 1.42%***	0.20** 0.96%**	0.20*** 1.02%***	0.20** 0.95%**	0.20 0.93%	0.10** 0.48%**	0.20*** 0.93%***	0.20*** 0.91%***
Inflammatory markers									
Serum amyloid A (µg/ml)	-1.70* -32.14%*	-8.80*** -59.75%***	-5.60*** -57.76%***	-8.00*** -58.82%***	-21.30*** -76.57%***	-7.30*** -51.39%***	-15.80*** -72.58%***	-11.90*** -70.87%***	-12.50*** -72.50%***
hsCRP (mg/dl)	-0.64 -18.60%	-3.74*** -56.73%***	-5.20*** -64.78%***	-4.30*** -56.93%***	-8.35*** -75.29%***	-8.00*** -61.54%***	-4.14*** -66.60%***	-9.01*** -71.73%***	-6.27*** -69.59%***
Fibrinogen (mg/dl)	-46.00* -11.75%	-40.50*** -10.73%***	-71.00*** -15.63%***	-57.00*** -12.00%***	-41.00** -9.33%*	-44.00** -11.55%*	-59.00*** -13.90%**	-61.00*** -12.00%***	-60.50*** -13.18%***
ICAM-1 (ng/ml)	-69.50*** -22.59%***	-80.00*** -25.00%***	-96.50*** -25.53%***	-84.00*** -25.17%***	-59.50*** -17.48%***	-87.00*** -26.32%***	-86.00*** -27.78%***	-81.00*** -24.23%***	-81.00###/*** -25.81%***

Continued

Table 3 Continued

	GO-FORWARD: RA patients with an inadequate response to MTX				GO-BEFORE: MTX-naïve RA patients			
	Golimumab+MTX		Combined		Placebo+MTX		Golimumab+MTX	
	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Placebo+MTX	Golimumab 100 mg + Placebo	50 mg	100 mg
IL-6 (pg/ml)	0.95	-1.25**	-0.60**	-0.80***	-4.55***	-1.00*	-3.80***	-5.30***
	16.92%***	-24.76%	-10.71%	-22.92%	-49.82%	-10.38%	-50.70%	-50.00%*
IL-8 (pg/ml)	-1.60	-2.80***	-1.15**	-2.30***	-1.80	-0.20	-3.10***	-3.00***
	-9.61%	-16.21%	-10.74%	-13.30%*	-10.43%	-1.74%	-22.12%*	-18.63%*
MMP-3 (ng/ml)	-10.54***	-15.73***	-16.82***	-16.20***	-24.43***	-13.53***	-25.76***	-18.71***
	-32.72%***	-41.05%***	-44.74%***	-42.56%***	-56.46%***	-37.53%***	-61.74%***	-49.52%***
VEGF (pg/ml)	-17.80***	-23.50***	-28.80***	-26.70***	-37.45***	-20.10***	-23.70***	-29.90***
	-22.47%***	-27.60%***	-34.20%***	-31.78%***	-40.17%***	-25.74%***	-33.56%***	-35.11%***

†Not all randomised patients had week 52 biomarker data.
 *, **, *** indicate p<0.05, 0.01, 0.001, respectively, for change from baseline within group.
 # indicates p<0.01, for the comparison of the combined golimumab+MTX and placebo+MTX groups.
 HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; LDL, low-density lipoprotein; MMP-3, matrix metalloproteinase; MTX, methotrexate; RA, rheumatoid arthritis; VEGF, vascular endothelial growth factor.

were uncontrolled, particularly for changes in concomitant medications that could change lipid profiles (eg, glucocorticoids), with small population sizes and various time points of testing, yielding inconsistent results.²² A systematic review by Pollono *et al*²² found a slight trend of increases in TC and HDL after anti-TNF therapy. In two short-term studies, significant increases in TC were noted following anti-TNF therapy for 2⁷ and 14 weeks²³; however, other studies with longer follow-up did not find any significant differences after 16¹⁴ or 52 weeks.¹⁶ While some studies have reported significant increases in HDL levels after 2–24 weeks of anti-TNF therapy,^{7 23 24} others of varying duration have found only a transient increase in HDL,¹⁶ an initial increase followed by a significant decrease in HDL,²⁵ or no change.^{14 26} In addition, statistically significant increases in LDL levels at weeks 14²³ and 30²⁷ have also been observed, although most report no significant change in LDL levels following anti-TNF therapy.^{7 14 16}

The current analysis of 1081 patients in the GO-FORWARD and GO-BEFORE trials is the largest prospective study of the effects of anti-TNF treatment on levels of lipids and inflammatory markers in patients with RA. Unlike many of the previous studies on anti-TNF agents and CVD, these data were obtained from two large randomised placebo-controlled trials with 1-year data. We found that patients treated with golimumab plus MTX generally had improvements in LDL subfractions and markers of inflammation through week 52. Patients in the GO-BEFORE trial were MTX-naïve, and many responded well to MTX, which may explain why patients in this trial who received MTX monotherapy also had favourable changes in many of these markers. Others have shown that TC and LDL levels decrease during the 5 years prior to an RA diagnosis, suggesting a possible relationship to inflammation.²⁸ This may partially account for the increase in lipid levels among patients responding to treatment (MTX alone, golimumab alone or combination therapy). Increases in lipid levels have also been seen in RA patients treated with therapies other than anti-TNF agents, such as tocilizumab,²⁹ tofacitinib³⁰ and rituximab.^{31 32} However, the mechanism of such an effect may differ among the various therapies, as increases in lipid levels are more pronounced with some therapies than with others.

It is well documented that the increase in cardiovascular adverse outcomes in patients with RA is greater than that attributed to conventional cardiovascular risk factors,² raising the possibility that the importance of lipids as a risk factor for increased cardiovascular morbidity and mortality in these patients has not been fully elucidated. Risk factors, including other lipid subsets or inflammatory markers of vascular activation, warrant further investigation. The short length of the follow-up period and number of patients involved in this study limit the scope of our conclusions about the effect of golimumab on clinical cardiovascular outcomes. Although the results of the GO-FORWARD and GO-BEFORE trials reported here indicate that treating the inflammation of RA may improve CVD markers, long-term studies with larger populations are needed to evaluate if treatment with golimumab affects cardiovascular outcomes in patients with RA.

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Contributors BWK, MCW, ECH, RMF, MCG, ELM and MUR designed the study. ECH, HL and MUR analyzed the data. All authors interpreted the data, critically revised the manuscript, and approved the final draft for submission.

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Competing interests BK conducts clinical trials and sits on speaker panels for Abbott, Janssen Research & Development, LLC, Merck, Bristol-Myers-Squibb, and Amgen. MCW has received consulting fees and is an investigator for Janssen Research & Development, LLC. MCG has received grant support from, and served as a consultant to, Janssen Research & Development, LLC, Spring House, PA. RF has received consulting fees and/or research grants from Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb, Janssen, F Hoffmann-LaRoche Ltd, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Pharmaceuticals, UCB, Genentech, Lexicon, Lilly and Wyeth Pharmaceuticals. ELM has been a paid consultant and advisory board member and is an investigator for Johnson & Johnson/Janssen Research & Development, LLC. ECH and HL are employees of Janssen Research & Development, LLC, and own stock in Johnson & Johnson. MUR was an employee of Janssen Research & Development, LLC, at the time this study was conducted and is currently employed by Pfizer and owns Pfizer stock.

Ethics approval The studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation good clinical practices. The protocols were reviewed and approved by each site's institutional review board or ethics committee. All patients provided written informed consent before undergoing study-related procedures.

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REFERENCES

- 1 Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. *J Rheumatol* 2003;30:1196–202.
- 2 del Rincon ID, Williams K, Stern MP, *et al*. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737–45.
- 3 Galaraga B, Belch JJ, Pullar T, *et al*. Clinical improvement in rheumatoid arthritis is associated with healthier microvascular function in patients who respond to antirheumatic therapy. *J Rheumatol* 2010;37:521–8.
- 4 Bacon PA, Townend JN. Nails in the coffin: increasing evidence for the role of rheumatic disease in the cardiovascular mortality of rheumatoid arthritis. *Arthritis Rheum* 2001;44:2707–10.
- 5 Skoog T, Dichtl W, Boquist S, *et al*. Plasma tumour necrosis factor- α and early carotid atherosclerosis in healthy middle-aged men. *Eur Heart J* 2002;23:376–83.
- 6 Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, *et al*. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006;24:309–12.
- 7 Popa C, Netea MG, Radstake T, *et al*. Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005;64:303–5.
- 8 Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. *Ann Rheum Dis* 2009;68:460–9.
- 9 Hurt-Camejo E, Paredes S, Masana L, *et al*. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. *Arthritis Rheum* 2001;44:2761–7.
- 10 Lamarche B, Tchernof A, Moorjani S, *et al*. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation* 1997;95:69–75.
- 11 Janssen Biotech, Inc. Simponi: Package insert. Horsham, PA: Janssen Biotech, Inc, 2011.
- 12 Emery P, Fleischmann RM, Moreland LW, *et al*. Golimumab, a human anti-tumour necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60:2272–83.
- 13 Keystone EC, Genovese MC, Klareskog L, *et al*. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789–96.
- 14 Soubrier M, Jouanel P, Mathieu S, *et al*. Effects of anti-tumour necrosis factor therapy on lipid profile in patients with rheumatoid arthritis. *Joint Bone Spine* 2008;75:22–4.
- 15 Spanakis E, Sidiropoulos P, Papadakis J, *et al*. Modest but sustained increase of serum high density lipoprotein cholesterol levels in patients with inflammatory arthritides treated with infliximab. *J Rheumatol* 2006;33:2440–6.
- 16 Wijbrandts CA, van Leuven SJ, Boom HD, *et al*. Sustained changes in lipid profile and macrophage migration inhibitory factor levels after anti-tumour necrosis factor therapy in rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1316–21.
- 17 Freedman DS, Otvos JD, Jeyarajah EJ, *et al*. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. *Clin Chem* 2004;50:1189–200.
- 18 Otvos JD. Measurement of lipoprotein subclass profiles by nuclear magnetic resonance spectroscopy. *Clin Lab* 2002;48:171–80.
- 19 Atzeni F, Turiel M, Caporali R, *et al*. The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases. *Autoimmun Rev* 2010;9:835–9.
- 20 Brunzell JD, Davidson M, Furberg CD, *et al*. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care* 2008;31:811–22.
- 21 Avouac J, Allanore Y. Cardiovascular risk in rheumatoid arthritis: effects of anti-TNF drugs. *Expert Opin Pharmacother* 2008;9:1121–8.
- 22 Pollono EN, Lopez-Olivo MA, Lopez JA, *et al*. A systematic review of the effect of TNF- α antagonists on lipid profiles in patients with rheumatoid arthritis. *Clin Rheumatol* 2010;29:947–55.
- 23 Tam LS, Tomlinson B, Chu TT, *et al*. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. *Clin Rheumatol* 2007;26:1495–8.
- 24 Serio B, Paolino S, Sulli A, *et al*. Effects of anti-TNF- α treatment on lipid profile in patients with active rheumatoid arthritis. *Ann N Y Acad Sci* 2006;1069:414–19.
- 25 Dahlqvist SR, Engstrand S, Berglin E, *et al*. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. *Scand J Rheumatol* 2006;35:107–11.
- 26 Del Porto F, Lagana B, Nofroni I, *et al*. Effects of tumour necrosis factor alpha blockade on lipid profile in active rheumatoid arthritis. *Rheumatology (Oxford)* 2007;46:1626–7.
- 27 Mathieu S, Kahan A, Sellam J, *et al*. Effects of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. *Clin Chim Acta* 2006;365:143–8.
- 28 Myasoedova E, Crowson CS, Kremers HM, *et al*. Total cholesterol and LDL levels decrease before rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1310–14.
- 29 Kawashiri SY, Kawakami A, Yamasaki S, *et al*. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. *Rheumatol Int* 2011;31:451–6.
- 30 Kremer JM, Bloom BJ, Breedveld FC, *et al*. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009;60:1895–905.
- 31 Mathieu S, Pereira B, Dubost JJ, *et al*. No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. *Rheumatology (Oxford)* 2013;52:204–9.
- 32 Kerekes G, Soltesz P, Der H, *et al*. Effects of rituximab treatment on endothelial dysfunction, carotid atherosclerosis, and lipid profile in rheumatoid arthritis. *Clin Rheumatol* 2009;28:705–10.