Indications for Lowering LDL Cholesterol in Rheumatoid Arthritis: An Unrecognized Problem

MARTIN SOUBRIER, DJAMILA ZERKAK, and MAXIME DOUGADOS

ABSTRACT. ***Objectives.*** To evaluate the prevalence of patients with rheumatoid arthritis (RA) in whom lowering low density lipoprotein cholesterol (LDL-C) should be considered in accord with the ATPIII guidelines. The treatment goals are based on the number of risk factors (RF) other than LDL-C. The goal for 0–1 RF is < 160 mg/l, for multiple RF < 130 mg/l, and < 100 mg/l for coronary heart disease (CHD) or CHD risk equivalent (other clinical atherosclerotic diseases and diabetes mellitus).

Methods. A cross-sectional study was conducted in 145 patients with RA. We recorded the patients' characteristics, the potential risk factors for CHD, and results of lipid profile tests [total cholesterol (TC), high density lipoprotein cholesterol, and LDL-C].

Results. Of the 145 patients recruited, 23 had LDL-C lowering therapy. Of the remaining 122 patients (mean age 54 ± 15 years), of whom 101 (83%) were women, 109 were taking a disease modifying antirheumatic drug. At the time of the study, disease duration was 12 ± 10 years. Twenty-seven (22%) of the 122 patients needed lowering of LDL-C. If RA was considered as an additional risk factor or a major risk factor, like diabetes mellitus, 35 patients (29%) and 86 (70%) patients, respectively, needed lowering therapy.

Conclusion. Our study shows the high percentage of patients with RA for whom LDL-C intervention should be considered. As cardiovascular morbidity and mortality is increased in patients with RA, it would be useful to determine whether RA should be considered as an independent cardiovascular risk factor or as a major risk factor like diabetes that warrants more aggressive cardiac prevention measures. (First release July 15 2006; J Rheumatol 2006;33:1766–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CARDIOVASCULAR DISEASE ATHEROSCLEROSIS STATINS

In patients with established rheumatoid arthritis (RA) mortality is higher than that in the general population and cardiovascular disease is the most common cause of death[1-3]. There is also documented evidence of increased incidence of nonfatal cardiovascular events in RA[4-8]. This increased cardiovascular risk could be caused by the increased prevalence of classical risk factors for cardiovascular disease in RA patients such as dyslipidemia, diabetes mellitus or insulin resistance, hypertension and smoking habits, by the underlying inflammatory process of RA itself, by the effects of disease modifying antirheumatic drugs (DMARD) or corticosteroids, or because of undertreatment of cardiovascular comorbidity[1]. In this study we focused on the management of hypercholesterolemia in RA patients.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) has issued recommendations on the optimal low density lipoprotein-cholesterol (LDL-C) value according to the patient's overall cardiovascular risk factor profile[9].

We conducted a cross-sectional analysis of a referral cohort of French patients with RA to determine the prevalence of patients for whom lowering of LDL-C should be considered in accord with the ATPIII recommendations.

MATERIALS AND METHODS

We conducted a prospective monocentric study in Cochin Hospital, Paris, a tertiary-care center with a large RA population, between January and April 2004. We asked consent from 220 consecutive patients fulfilling the American College of Rheumatology (ACR) criteria for RA to perform a lipid profile, and 145 agreed.

Treatment goals for LDL-C were set according to the number of risk factors. The positive risk factors are: age (male ≥ 45 yrs, female ≥ 55 yrs); family history of premature coronary heart disease (CHD; definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative); current cigarette smoking; hypertension (≥ 140/90 or antihypertensive medication); and low high-density lipoprotein cholesterol (HDL-C; < 40 mg/dl). A high HDL-C level (≥ 60 mg/dl) is a protective risk factor. The guidelines recommend that in patients without CHD the goal for 0–1 risk factors (RF) is < 160 mg/l, for multiple RF < 130 mg/l, and < 100mg/l for multiple RF with a CHD risk > 20% per 10 years. The goal in patients with CHD or CHD risk equivalent (other clinical atherosclerotic diseases, diabetes mellitus) is < 100 mg/dl.

Data collection

Cardiovascular disease. All patients were asked about any history of cardiovascular disease, cardiovascular risk factors (personal and family history of

From Service de Rhumatologie, Hôpital G. Montpied, Clermont-Ferrand; and Université René Descartes, AP-HP Hôpital Cochin, Paris, France.

M. Soubrier, MD, PhD, Service de Rhumatologie, Hôpital G. Montpied; D. Zerkak, MD; M. Dougados, MD, Université René Descartes, AP-HP Hôpital Cochin.

Address reprint requests to Dr. M. Soubrier, Service de rhumatologie, Hôpital G. Montpied, Place H. Dunant, B.P. 69, 63003 Clermont-Ferrand, France. E-mail: msoubrier@chu-clermontferrand.fr

Accepted for publication April 27, 2006.

cardiovascular events, current cigarette smoking, hypertension, and diabetes), and use of lipid-lowering drugs. Arterial blood pressure and body mass index were recorded.

Assessment of RA. A thorough survey of all patients' records from disease onset was performed including disease duration, actual and previous DMARD, and total and daily dose of corticosteroids. Disease activity was evaluated in each patient using the following indices: tender and swollen joint count (28 j), morning stiffness, visual analog scale (VAS) for pain (0-10), patient's and doctor's global assessment, Westergren erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). We used the Disease Activity Score (DAS28) based on ESR or CRP to assess disease activity (26). A DAS28 > 5.1 means high disease activity, < 3.2 low disease activity, and 3.2–5.1 moderate disease activity.

Total cholesterol (TC) and HDL-C determinations. Plasma lipids were determined after 12 h overnight fast. TC, HDL-C, and triglycerides were measured and LDL-C was calculated by the method of Friedewald, *et al*[10].

Statistics. All results were expressed as means (SD). Comparison between groups was done by chi-square test. A p value < 0.05 (two tailed) was considered significant.

RESULTS

Clinical and demographic characteristics of study population. One hundred forty-five patients (116 women, 29 men) were enrolled for the study. Twenty-three patients were receiving LDL-C lowering therapy (20 on statins) and 8 had had myocardial infarction. Of the 122 remaining patients, most had longstanding (mean disease duration 12 yrs) seropositive (74%) and erosive (88%) RA (Table 1). One hundred nine patients (89%) were taking a DMARD: 46 (38%) were taking anti-tumor necrosis factor (TNF), 19 methotrexate, 14 combination leflunomide-methotrexate, 8 leflunomide, 5 hydroxychloroquine, and the remaining 17 different DMARD combinations including 9 with hydroxychloroquine. Eighty-four percent were taking corticosteroids. The mean DAS28(ESR) was 3.95 and the mean DAS28(CRP) was 3.7. According to the DAS28(CRP) criteria, 47 patients had low disease activity, 54 moderate disease activity, and 21 high disease activity.

In the 122 patients, the mean cholesterol values were: TC, 220 ± 47 mg/dl; HDL-C 69 ± 22 mg/dl; LDL-C 129 ± 41 mg/dl. Atherogenic index (TC/HDL-C) was 3.55 ± 1.7.

Two patients had had previous myocardial infarction and 3 had diabetes mellitus. One patient had 3 risk factors, 25 had 2 risk factors, 53 one risk factor, and 38 no risk factors (Table 2). According to ATPIII guidelines, 27 patients (22%) needed LDL-C-lowering therapy. If RA is considered an additional risk factor, 35 patients (29%) should have been receiving primary prevention. If RA is considered a strong risk factor for cardiovascular disease, similar to diabetes mellitus, 86 patients (70%) should have been receiving primary prevention. On the basis of disease activity, 5 patients with high disease activity, 12 with moderate disease activity, and 11 with low disease activity (p = 0.98) should have been receiving primary prevention and 7, 17, and 12, respectively, if RA is considered an additional risk factor (p = 0.74).

Table 1. Characteristics of the 122 patients.

	No. (%) of Patients, mean ± SD
Demographics	
Age, yrs	54 ± 14
Female, no. (%)	101 (83)
Disease duration, yrs	12 ± 10
Positive RF, no. (%)	90 (74)
Bony erosions (%)	106 (87)
No. of previous DMARD	4.1 ± 2.1
Concomitant treatment	
Corticosteroids, no. (%)	103 (84)
Corticosteroid dose, mg/day	4.5 ± 3.7
TNF-α blockers	46 (38)
Disease characteristics	
Tender joint count	3.7 ± 4.7
Swollen joint count	5.5 ± 4.6
VAS for pain	3.8 ± 2.8
Patient's global assessment (0–10)	4 ± 2.8
Physician's global assessment (0–10)	3.6 ± 2.3
ESR, mm/lh	25 ± 20
CRP, mg/l	14 ± 18
DAS 28 (VS)	3.97 ± 1.43
DAS 28 (CRP)	3.69 ± 1.29

RF: risk factors; DMARD: disease modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

DISCUSSION

Despite an inordinately high risk of cardiovascular events in RA, assessment of cardiovascular risks was uncommon in our practice and cholesterol-lowering treatment was insufficiently prescribed. The precise reasons for the observed increase in cardiovascular disease-related morbidity and mortality in RA patients remain to be established. The prevalence of traditional cardiovascular disease risk factors (smoking, diabetes mellitus, hypertension, dyslipidemia, family history) has not been consistently documented in this population. Thus, traditional risk factors were examined in a cross-sectional study of women with and without RA who were enrolled in the Nurses' Health Study[11]. No significant differences between these groups were observed for current smoking status, body mass index, menopause status, diabetes, hypertension, and family history of early myocardial infarction. However, an unfavorable lipid profile, i.e., decreased HDL-C and/or increased atherogenic index, has been documented in active RA[12,13]. The lipid profile usually returns to normal when control of the joint disease is achieved[12,14], but DMARD may alter lipid levels. Antimalarials improve the lipid profiles by increasing

Table 2. Cardiovascular risk factors.

Risk Factor	No. (%) of Patients
Age (male > 45 yrs, female > 55 yrs)	64 (52)
Family history	9 (7)
Tobacco use	21 (17)
Hypertension or antihypertensive medication	28 (23)
HDL cholesterol < 40 mg/dl	9 (7)

HDL-C levels and decreasing those of LDL-C[15]. The effects of TNF-α antagonists on lipid profile are controversial[16-18].

RA itself is an independent risk factor for developing cardiovascular disease. Del Rincon, *et al* compared the incidence of fatal and nonfatal myocardial infarctions and ischemic strokes in 236 patients with RA and 4635 controls participating in an epidemiological study (age 25-65 yrs, mean followup 8 yrs and 33,881 patient-yrs)[6]. After adjustment for cardiovascular risk factors (age, sex, smoking history, diabetes, hypercholesterolemia, and systolic blood pressure), the relative risk for cardiovascular events was 3.17 (95% CI 1.33–6.36) in the patients with RA. In the prospective Nurses' Health Study, 114,342 women aged 30 to 55 years and free of cardiovascular disease and RA in 1976 were followed up until 1996[7]. After 2.4 million patient-years of followup, the relative risk for cardiovascular events in the 527 patients who experienced onset of RA was 2 (95% CI 1.23–3.29) after adjustment for cardiovascular risk factors. In patients with RA for longer than 10 years, the relative risk of myocardial infarction was 3.1 (95% CI 1.64–5.87). Accumulating evidence suggests that atherosclerosis and cardiovascular disease are truly inflammatory disorders[19]. Overlapping pathogenic features of the 2 diseases include T cell activation, the predominant role of proinflammatory cytokines (TNF-α, interleukin 6) with elevated serum levels of acute–phase reactant[19]. Epidemiological studies in general populations have established that higher CRP levels predict cardiovascular events[20-23]. Because CRP and LDL-C reflect different risk factors, determining both variables may improve cardiovascular risk detection[20]. Thus, the inflammatory syndrome that characterizes RA may lead to early atheroma.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors reduce cardiovascular morbidity and mortality and are widely used in primary and secondary prevention of vascular disease. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial was important because it showed that LDL-lowering statin therapy in persons with only borderline-high LDL-C levels and few other risk factors produces a large reduction in relative risk (–37% in major coronary events and –33% in revascularization procedures)[24]. While there is no evidence specifically in patients with RA that controlling dyslipemia according to current recommendations reduces cardiovascular disease, there is no reason to believe that benefits would not occur. The beneficial effect of statins as primary or secondary prevention is not entirely ascribable to a cholesterol-lowering effect. Statins exert antiinflammatory effects, decreasing CRP production by 15% to 25%[25]. Patients who experience decreases in both LDL-C and CRP during statin therapy have a lower risk of recurrent myocardial infarction[26] and greater decreases in plaque burden as measured by intracoronary ultrasound[27]. They are therefore potentially ideal drugs to target CHD risk in RA, which is associated with inflammation. Furthermore, atorvastatin has clinically apparent antiinflammatory effects in active RA[28].

The goals to aim for in LDL-C treatment depend on the number of cardiovascular risk factors. We have shown that if traditional cardiovascular risk factors alone are taken into account too many patients miss out on cholesterol-lowering treatment. Given the elevated risk of CHD in RA, we think RA itself should be considered as an extra risk factor. Were this the case, there would be wider prescription of cholesterol-lowering drugs. The decision to initiate treatment could also be taken by multiplying overall cardiovascular risk as assessed by existing charts by 1.7 or 2 to derive a more accurate level of risk in RA patients[29]. The question also arises whether RA should be considered a major risk factor, like diabetes mellitus, requiring more aggressive cardiac prevention.

Our conclusion is that cholesterol-lowering therapy is insufficiently prescribed in our patients with RA. As the lipid profile changes with disease activity, serial lipid determination should be performed. Our results highlight the need for all physicians to screen appropriately for cardiovascular risk factors and to treat all rheumatoid patients with abnormal lipid values.

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