Risk Factors Associated with Different Stages of Atherosclerosis in Colombian Patients with Rheumatoid Arthritis

Adriana Rojas-Villarraga, MD,* Oscar-Danilo Ortega-Hernandez, MD,†
Luis F. Gomez, MD,‡ Aryce L. Pardo, BSc,§ Silvia López-Guzmán, MD,¶
Camila Arango-Ferreira,‖ Maria-Eugenia Hincapie, RN, MSc,†
Juan F. Betancur,‖ Ricardo Pineda-Tamayo, MD,**
Francisco J. Diaz, PhD,†† and Juan-Manuel Anaya, MD‡‡

Objectives: Rheumatoid arthritis (RA) is associated with an increased prevalence of cardiovascular disease (CVD). Since atherosclerosis development is a gradual process of damage inside the artery wall, and the phenotype–genotype correlation of complex diseases may vary depending on ethnicity, we sought to investigate the influence of clinical features, routine inflammatory markers, and the genetic component of RA on different stages of atherosclerosis in northwestern Colombian patients with RA.

Methods: A group of 140 patients with RA were enrolled in this study. All patients underwent a noninvasive evaluation of endothelial function by flow-mediated vasodilation (FMV) and an assessment of carotid intima-media thickness (IMT) by high-resolution B-mode ultrasonography. The patients were classified into 3 categories: endothelial dysfunction (FMV <5%), increased IMT (0.91-1.29 mm), and plaque (IMT >1.30 mm). The risk of being in each category was assessed by investigating traditional and nontraditional cardiovascular risk factors. For each stage of atherosclerosis development, we searched for nontraditional risk factors that were significantly associated with the stage after adjusting for traditional risk factors and current age.

Results: Rheumatoid factor seropositivity was significantly associated with endothelial dysfunction (adjusted odds ratio, AOR = 3.0). A duration of RA >10 years (AOR = 29.0) and being a carrier of an HLA-DRB1 shared epitope allele (AOR = 4.8) were associated with atherosclerotic plaque. No association of extra-articular manifestations, anticyclic citrullinated peptide (anti-CCP3) antibodies, and tumor necrosis factor −308 polymorphism with CVD was found.

Conclusions: Our results reveal the presence of RA-related risk factors for CVD which act independently of traditional risk factors. These factors can be used by clinicians to predict CVD in RA patients, and this data should assist in the development of public health policies in our population for the improvement of patient outcomes.

 Semin Arthritis Rheum 38:71-82

*Assistant Researcher, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia; School of Medicine, Universidad del Rosario (UR), Bogotá, Colombia; and School of Medicine, Universidad Pontificia Bolivariana (UPB), Medellín, Colombia.

†Assistant Researcher, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia.

‡Chief, Vascular Laboratory-Vasculab, Clinica Medellín, Medellín, Colombia.

§Assistant Researcher, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia; and Department of Statistics, Universidad Nacional de Colombia (UNALM), Medellín, Colombia.

¶Assistant Researcher, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia; and School of Medicine, Universidad del Rosario (UR), Bogotá, Colombia.

‖Medical student, School of Medicine, Universidad Pontificia Bolivariana (UPB), Medellín, Colombia.

**Assistant Researcher, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia ; and School of Medicine, Universidad Pontificia Bolivariana (UPB), Medellín, Colombia.

††Associate Professor, Department of Statistics, Universidad Nacional de Colombia (UNALM), Medellín, Colombia.

‡‡Professor of Medicine and Chief, Cellular Biology and Immunogenetics Unit (CBIGU), Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia; and School of Medicine, Universidad del Rosario (UR), Bogotá, Colombia.

Address reprint requests to: Juan-Manuel Anaya, MD, Corporación para Investigaciones Biológicas, Cra. 72A-78B-141, Medellín, Colombia. E-mail: anayajm@gmail.com.

0049-0172/08/$-see front matter

doi:10.1016/j.semarthrit.2008.01.019

Keywords: *rheumatoid arthritis, cardiovascular disease, endothelial dysfunction, intima-media thickness, atherosclerotic plaque, HLA, TNF, rheumatoid factor, anti-CCP antibodies, extra-articular manifestations*

Ischemic heart disease secondary to atherosclerosis is the most prevalent cause of death associated with cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) (1-3). Traditional risk factors such as dyslipidemia, smoking, increased waist circumference, and old age (4-6), and nontraditional risk factors such as extra-articular manifestations, swollen joint count, autoantibody levels, C-reactive protein (CRP), and other inflammatory markers have been implicated in accelerated atherosclerosis in these patients (7-10). Atherosclerosis is a process of gradual inflammation inside the artery wall. It begins with a change in the endothelium phenotype, followed by artery wall thickening, and finally, by the appearance of atherosclerotic plaque (11-13). Carotid intima-media thickness (IMT) is a measurement that is used to detect changes in the thickness of the artery wall secondary to the development of atherosclerosis (14). There is strong evidence supporting an increased carotid IMT in patients with RA (15-17). Increased carotid artery IMT has also been reported in long-term treated RA patients without clinically evident CVD or cardiovascular risk factors (18). Therefore, it is important to investigate the risk factors associated with different stages of atherosclerosis development since knowledge of these factors may help to improve prevention and treatment of CVD in RA patients. In addition, since RA patients may have impaired endothelial function before entering an early stage of atherosclerosis (19,20), the evaluation of endothelial function through flow-mediated vasodilation (FMV) in the brachial artery may be helpful in detecting initial pathological changes in the artery wall and, therefore, in assessing early cardiovascular risk in these patients (21-23).

The mechanisms and risk factors influencing atherosclerotic plaque formation in patients with autoimmune diseases, such as RA, are not fully understood (24-26). A genetic feature that has been consistently associated with RA is the presence of *HLA-DRB1* alleles, which also have been implicated in RA disease severity and atherosclerosis development (27-30). Some tumor necrosis factor-α (*TNF*) gene polymorphisms have been associated with susceptibility to RA (31,32). However, it is not clear whether these polymorphisms are also associated with vascular damage in RA patients. The *TNF* gene influences body weight homeostasis as well as insulin resistance, diabetes mellitus, lipid levels, hypertension, coagulation, endothelial damage, and inflammation (33-36).

Controversy exists as to whether *HLA-DRB1* polymorphisms affect susceptibility to RA, or affect disease severity and progression (30,37,38). Moreover, the fact that more than 1 autoimmune disease may coexist in a single patient or in the same family supports the hypothesis of additional susceptibility genes (39,40). Interestingly, 1 specific autoimmune disease (ie, RA) may be present in various members of a nuclear family, the so-called familial autoimmune disease, and different autoimmune diseases may occur in the relatives of a patient with RA (ie, familial autoimmunity) (41). These facts reinforce the polygenic character of RA (42).

Since the phenotype and genotype of complex diseases may vary depending on ethnicity, we sought to investigate the potential contribution of clinical RA features, routine inflammatory markers, and the genetic component to the development of atherosclerosis in northwestern Colombian patients with RA, controlling for potential confounders such traditional CVD risk factors (43,44). Special attention was given to the different stages of atherosclerosis development. Since in practice the clinician may prefer to assess only 1 or a few inflammatory markers and/or genetic factors to predict CVD risk, we searched for those variables that may, by themselves and independently of traditional CVD risk factors, be predictors of increased atherosclerosis risk. This may be a more sensible approach than searching for predictors that can be used only when the clinician has access to a large number of other nontraditional predictors. An attempt was also made to answer the question of whether or not the presence of familial autoimmunity confers additional susceptibility to atherosclerosis in RA patients.

METHODS

Study Population

Consecutive RA patients attending the Clinical Immunology and Rheumatology Unit at the "Clínica Universitaria Bolivariana-Corporación para Investigaciones Biológicas" at Medellín, and fulfilling the American College of Rheumatology classification criteria were included (45). This study was undertaken between 2006 and 2007 and conducted in compliance with the 1993 Act 008430 by the Ministry of Health of the Republic of Colombia. The institutional review board of the "Corporación para Investigaciones Biológicas" approved the study design.

Age at RA onset was defined as the age at which patients began to suffer from pain, morning stiffness, and inflammation of hand and/or foot joints in a symmetrical fashion. Familial autoimmunity was defined as the presence of any diagnosed autoimmune disease in another member of the patient's nuclear family (46). Autoimmune hypothyroidism was diagnosed when there was a thyroid-stimulating hormone level >5.0 IU, or evidence of thyroid hormone replacement because of primary hypothyroidism together with the presence of antithyroid peroxidase