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Original article

# Atherosclerosis progression in psoriatic arthritis patients despite the treatment with tumor necrosis factor-alpha blockers: A two-year prospective observational study

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ABSTRACT

*Objective:* To evaluate the progression of subclinical atherosclerosis in Psoriatic Arthritis (PsA) patients treated with anti-tumor necrosis factor (TNF)-α agents.
*Methods:* Thirty-two PsA patients classified according to the CASPAR criteria and attending the Rheumatology Unit of the University of Padua Medical Center were enrolled in a two-year prospective, observational study. In accordance with the ASAS/EULAR recommendations on the management of these patients, those studied were prescribed biological agents [etanercept ($n = 21$), adalimumab ($n = 6$), infliximab ($n = 5$)]. Plasma lipids, inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), vessel endothelium growth factor (VEGF), osteoprotegerin (OPG), and TNF-α, as well as Disease Activity Score 28 calculated with CRP (DAS 28-CRP) were evaluated at baseline and after two years of treatment. Bilateral carotid B-mode ultrasound measurements [the mean-intima media thickness (mean-IMT), the mean maximum-IMT (M-Max)] of each carotid artery segment (common, bulb, and internal carotid artery) and the post-occlusion flow-mediated dilation (FMD) of the brachial artery were also assessed at baseline and after two years.
*Results:* Despite an improvement in the DAS 28-CRP score ($P < 0.0005$) and lower low-density lipoprotein cholesterol ($P < 0.013$) and triglyceride ($P < 0.036$) values, there was a significant progression in both the mean-IMT ($P < 0.0005$) and M-Max ($P < 0.0005$). Moreover, no recovery in FMD ($P =$ ns) was observed after two years of anti TNF-α treatment. Serum TNF-α levels were increased ($P = 0.003$) and OPG values were decreased ($P = 0.011$) at the end of follow- up with respect to baseline values.
*Conclusions:* Despite improvement in clinical status, arterial remodelling was observed in the PsA patients who were treated with anti TNF-α agents for two years.
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## 1. Introduction

Psoriatic arthritis (PsA) is defined as an axial and/or peripheral inflammatory arthritis associated with psoriasis. As the term "psoriatic disease" implies, the clinical spectrum of disease manifestations in these patients is rather wide and frequently includes comorbidities. According to a study by Salaffi et al., more than half of the patients studied reported at least one comorbidity, [1]. Among these, hypertension (28.5%), hyperlipidemia (27.8%), type 2 diabetes (11.8%), ischemic heart disease (7.3%), cerebrovascular disease (3.1%), and peripheral vascular disease (2.9%) areknown to have a higher prevalence in PsA patients compared to controls [2]. Just as noted in other rheumatic diseases [3,4], recent reports suggest that PsA patients have higher cardiovascular (CV) risk [5], which is mainly attributed to atherosclerosis.

Atherosclerosis can be considered a chronic inflammatory condition of the vessel wall: inflammatory process plays in fact a pivotal role in the pathogenesis of each of the stages of atherosclerosis, including atheroma formation, endothelial dysfunction and end-stage atherothrombotic events. Enthesitis/synovitis and atherosclerosis in PsA are probably mediated by common pathways involving imbalanced secretions of pro-vs anti-inflammatory cytokines. Pro-inflammatory cytokines, especially

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tumor necrosis factor-(TNF)-α and interleukin (IL)-1β, may activate the macrophages which, in turn, can exert cytotoxic activity on endothelial cells [6]. Endothelial dysfunction, an early feature in atherogenesis [7], may be particularly relevant to atherosclerotic progression in PsA. In fact, pro-inflammatory cytokines have been shown to induce endothelial cell dysfunction [8] as well as to activate the immune pathways leading to PsA inflammatory manifestations [9]. Gonzalez-Juanatey et al. found that flow-mediated dilation (FMD), a marker of endothelial dysfunction [10], was significantly impaired in 50 PsA patients without CV risk factors or clinically evident CV disease compared to healthy controls [11]. PsA inflammatory process can act independently and/or synergistically with conventional CV risk factors, including waist circumference, smoking and obesity in accelerating atherosclerosis [12,13]. Just as TNF-α seems to play a major role in the pathogenesis of PsA [10], TNF-α blocking therapy has emerged as a highly effective treatment [14]. Indeed, according to recent European League Against Rheumatism (EULAR) recommendations, TNF-α antagonists should be used in PsA patients who do not respond or are intolerant to conventional drugs [15,16]. Among TNF-α blockers currently approved for the treatment of PsA patients, adalimumab, etanercept, and infliximab are the most widely prescribed. PsA treatment aims to arrest or delay disease progression and/or to achieve clinical remission while preventing comorbidities including CV diseases. Until now, no conclusive findings have been published about the influence of anti TNF-αagents on CV risk and atherosclerosis. The aim of this study was to evaluate the effect of a two-year treatment program with TNF-α antagonists on vascular remodelling, inflammation, and disease activity in PsA patients without overt CV diseases.

## 2. Methods

### 2.1. Study groups and inclusion/exclusion criteria

Thirty-two consecutive PsA outpatients (17 males) attending the Rheumatology Unit of the University of Padua Medical Center and fulfilling the Classification for Psoriatic Arthritiscriteria (CASPAR) [17] that established that antiTNF-α treatment should be prescribed to patients who are intolerant to or have an inadequate response to traditional disease-modifying antirheumatic drugs (DMARDs), were enrolled in the study. Twenty-one of the patients received etanercept (25 mg s.c. twice a week), 6 adalimumab (40 mg adalimumabs.c. fortnightly) and 5 infliximab (5 mg/kg i.v. infused once a month for 2 years). During follow-up, none of the patients received non-steroidal anti-inflammatory drugs (NSAIDs), because of possible side effect on blood pressure (BP). Patients were excluded from the study if they were diagnosed with renal failure characterized by glomerular filtration rate < 60 ml/min, diabetes mellitus (fasting overnight venous plasma glucose concentration in all individuals included in this study had to be < 110 mg/dl), pre-existing clinical coronary artery disease with history of angina pectoris or myocardial infarction, or had a history of cerebrovascular accident, transient ischemic attack or peripheral vascular disease. Patients affected with methabolic syndrome or methabolic disorders (e.g. isolated dyslipidemia or increased fasting glucose, without fulfilling all methabolic syndrome criteria) and smokers were also excluded from the study.

The study was approved by the local research ethics committee and carried out in accordance with the declaration of Helsinki. All of the participants who were recruited gave informed written consent.

The patients being studied were monitored for signs of disease activity and of atherosclerosis progression during the two-year treatment program. The tender joint (TJ) and swollen joint (SJ) scores, the disease activity score calculated with C-reactive protein (DAS 28-CRP) score, and CRP values were analyzed at 0, 6, 12, 18 and 24 months. The Psoriatic Arthritis Response Criteria (PsARC) index was not utilized as one of our parameters as our study was begun before that measure was validated.

The extent of subclinical atherosclerosis progression was assessed by ultrasound examination of the carotid arteries coupled with endothelial function assessment by FMD at baseline (before starting anti TNF-α therapy) and after two years of treatment. Carotid ultrasound and FMD are non-invasive methods that analyze the structural and functional properties of the arterial wall, parameters that can be used as markers of early atherosclerosis and as predictors of future myocardial infarction and stroke. FMD is, in particular, one of the most widely used tests of endothelial function, which measures the endothelial vasomotor response during reactive hyperemia [18,19]. All traditional risk factors for atherosclerosis were also assessed [12]. Systolic and diastolic BP levels (SBP and DBP) were determined and the average of three consecutive readings taken five minutes apart was recorded.

### 2.2. Biomarkers

Fasting serum samples were collected at baseline and at the end of the study and stored at 80 °C until they were analysed. Serum lipid profile [total cholesterol (TC), low-density lipoproteins (LDL-C), high-density lipoproteins (HDL-C), triglycerides (TG)], fasting blood glucose, and circulating biomarkers including CRP, interleukin (IL)-6, TNF-α, and vascular endothelial growth factor (VEGF), osteoprotegerin (OPG) were assessed. IL-6 and TNF-α were measured by immunometric assays using an Immulite One Analyzer. The analytical sensitivity was 1.7 and 2 pg/ml for TNF-α and IL-6, respectively. VEGF was determined by enzyme-linked immunosorbent assay (IBL International) with analytical sensitivity of 7.9 pg/ml. Serum OPG concentrations were determined by the DuoSet ELISA Development System for human OPG (R&Dsystems, Minneapolis, MN, USA). Monoclonal mouse anti-human OPG antibody was used as a capture reagent and a biotinylated polyclonal goat anti-human OPG antibody was used for detection. In our laboratory, the coefficient of variation, as evidenced from duplicate measurements, was 7.9%.

### 2.3. Ultrasound studies

#### 2.3.1. Ultrasound examination of carotid arteries

Carotid ultrasound examinations were performed using an Aspen Advanced Ultrasound System Instrument (Acuson, USA) equipped with a linear probe (7–10 MHz). The procedure was carried out in accordance with the Mannheim Intima-Media Thickness (IMT) Consensus Criteria [18]. All the examinations including assessment of both carotid arteries were performed by the same operator (MZ) and were carried out in a dimly lit room, with patients lying comfortably in a supine position. Once an optimal longitudinal image was obtained, it was stored on 1/2-inch super VHS videotape. Images were analysed using a high resolution video recorder together with a mouse-driven image analysis system. IMT, defined as the distance between the lumen-intima and the media-adventitia interfaces, was measured at end-diastole in the far wall of the right and left sides of the common carotid artery, in the bulb and in the internal carotid artery [20]. IMT measurements were expressed as cumulative mean of mean-IMT and as cumulative mean of maximum-IMT (M-Max) recorded for each vascular segment. To rule out the potential interference of arterial enlargement in IMT measurements, the intraluminal diameter of the common carotid artery 1 cm proximal to the dilation of the bulb was measured at end-diastole in lateral projection. The reproducibility of IMT measurements in our laboratory during different examinations resulted in a coefficient of variation of 4.4% and 9.6%, for mean-IMT

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