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Subclinical atherosclerosis evolution during 5 years of anti-TNF-alpha treatment in psoriatic arthritis patients

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ABSTRACT

Objective. *Our aim was to evaluate subclinical atherosclerosis progression during 5 years of anti-tumour necrosis factor (TNF)-α treatment in psoriatic arthritis (PsA) patients.*

Methods. *Thirty-two consecutive PsA patients starting TNF-α inhibitors were enrolled and evaluated at baseline (T0), 2 years (FU1) and 5 years (FU2) of treatment. Arterial structural properties were evaluated by B-mode ultrasound of mean carotid intima-media thickness (mean-IMT) and maximum IMT (M-MAX) in each segment (common, bulb, internal), bilaterally. Endothelial function was assessed by post-occlusion flow-mediated dilation (FMD) of the brachial artery using high-sensitivity ultrasonography. Treatment response was studied through DAS28 (disease activity score) and inflammatory biomarkers (C-reactive protein, TNF-α, osteoprotegerin). Metrologic and metabolic data were collected.*

Results. *At T1, a significant decrease of DAS28 (4.2±0.7 vs. 2.3±0.8, p<0.001) and CRP (11.25±9.16 vs. 2.91±1.72, p<0.01) was observed. Efficacy was preserved at FU2 (DAS28 2.4±0.9, CRP 2.73±2.51; p=ns vs. FU1). Systolic blood pressure and BMI remained stable throughout the follow-up, while diastolic blood pressure decreased significantly from FU1 to FU2 (80±10 vs. 74±7 mmHg, p=0.001). From T0 to FU1 there was an increase of IMT-mean and M-MAX (0.7±0.1 vs. 0.9±0.4 and 0.9±0.2 vs. 1.1±0.4, p<0.01). At FU2, IMT-mean and M-max did not change significantly (0.9±0.3 and 1.1±0.3, p=ns vs. FU1). No significant variation in FMD values was observed during the study period.*

Conclusion. *A slight progression of subclinical atherosclerosis in PsA was observed in the first 2 years of anti-TNF-α treatment. This process seemed to decelerate in follow-up extension to 5 years.*

Introduction

Psoriatic arthritis (PsA) frequently presents with metabolic comorbidities and cardiovascular (CV) disease. The PsA inflammatory process is implied in subclinical atherosclerosis progression even in patients without overt CV risk factors (1). In fact, pro-inflammatory cytokines, highly increased in plasma and synovial fluid of PsA patients, are able to induce endothelial cell dysfunction. This allows the progression from fatty streaks to the development of atherosclerotic plaques (2).

International recommendations underline the need, in PsA, of an early and effective anti-rheumatic treatment, not only in order to control arthritis but also to lower inflammation level, and consequently CV risk (3). One of the most effective and well-established treatments for PsA is tumour necrosis factor (TNF)-α blocking therapy. In contrast with rheumatoid arthritis, where the evidence that anti-TNF-α therapy is able to reduce CV mortality is quite robust, results in PsA are more sparse. We previously demonstrated in a two-years prospective observational study that PsA patients without overt CV diseases who initiated a first line anti-TNF-α therapy were still prone to subclinical atherosclerosis progression, despite improvement in patients' clinical status (4). We then followed the same patients up for a total of 5 years to evaluate the effect of a long-term anti-TNF-α treatment on vascular remodelling, inflammation, and PsA disease activity.

Methods

In our initial study, 32 consecutive outpatients fulfilling ClASsification criteria for PsA (CASPAR) (5) and attending our Rheumatology Unit in the period September 2011 to June 2012 were enrolled and followed-up for 2 years (follow-up 1, FU1). Twenty-eight patients then completed a 5-year follow-up (follow-up 2, FU2). At baseline (T0), all patients had inadequate response/were intolerant to traditional disease-modifying anti-rheumatic drugs (DMARDs), therefore were treated with anti-TNF-α (patients were biotechnological drug-naïve). None of them used DMARDs as concomitant therapy. Use of sporadic NSAIDs or low-dose glucocorticoid was allowed for cyclic use (max 1 week per month).

Patients were excluded in case of: glomerular filtration rate <60 ml/min, dia-

Table I. Clinical, laboratory and ultrasound data in PsA patients treated with TNF-α agents.

	Baseline	Follow-up 1	Comparison with previous timepoint, *p*-value	Follow-up 2	Comparison with previous timepoint, *p*-value
TJ	8.1 ± 5.6	2.1 ± 2.3	0.01	3.8 ± 3.8	ns
SJ	3.8 ± 3.8	0.2 ± 0.7	0.01	0.5 ± 0.9	ns
DAS 28	4.2 ± 0.7	2.3 ± 0.8	<0.001	2.4 ± 0.9	ns
PASI	2.3 ± 2.1	1.1 ± 1.6	<0.001	1.2 ± 1.6	ns
BMI kg/m^2	26.3 ± 4.0	25.8 ± 2.4	ns	25.9 ± 3.4	ns
SBP mmHg	130 ± 15	133 ± 13	ns	132 ± 12	ns
DBP mmHg	79 ± 8	80 ± 10	ns	74 ± 7	0.001
Hearth rate bpm	67 ± 9	62 ± 10	<0.001	65 ± 5	ns
TC mmol/l	5.45 ± 1.08	5.10 ± 0.93	0.01	5.09 ± 0.89	ns
LDL-c mmol/l	3.42 ± 0.77	3.10 ± 0.87	0.02	3.02 ± 0.64	ns
HDL-c mmol/l	1.33 ± 0.37	1.34 ± 0.43	ns	1.31 ± 0.34	ns
Triglycerides mmol/L	1.47 ± 0.74	1.25 ± 0.15	<0.0001	1.72 ± 0.62	<0.0001
Glucose mmol/l	5.13 ± 0.97	5.34 ± 0.62	0.03	5.45 ± 1.40	ns
CRP mg/L	11.25 ± 9.16	2.91 ± 1.72	0.01	2.73 ± 2.51	ns
TNF-α pg/ml	74.8 (9-89)	109 (58-143)	0.01	113 (61-151)	ns
hs-CRP mg/l	2.85 ± 2.86	1.88 ± 2.27	0.001	2.18 ± 2.26	ns
OPG pg/ml	1430 ± 648	1297 ± 615	0.01	1393 ± 992	ns
IMT mean mm	0.7 ± 0.1	0.9 ± 0.4	<0.0001	0.9 ± 0.3	ns
IMT max mm	0.9 ± 0.2	1.1 ± 0.4	<0.0001	1.1 ± 0.3	ns
FMD %	5.4 ± 1.9	5.4 ± 1.7	ns	5.4 ± 1.9	ns

TJ: tender joints; SJ: swollen joints; DAS28: Disease Activity Score on 28 joints; PASI: Psoriasis Area and Severity Index; BMI: Body Mass Index, SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; CRP: C-reactive protein; TNF: tumour necrosis factor; hs-CRP: high sensitivity C-reactive protein; OPG: osteoproteogirin; IMT: intima-media thickness; FMD: flow-mediated dilation.

betes mellitus, pre-existing coronary artery disease, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease, treatment for metabolic syndrome (*e.g.* statins, antihypertensive or hypoglycaemic drugs), active smokers.

The study was approved by the local research ethics committee and carried out in accordance with the declaration of Helsinki (no. 52723, October 11, 2010). All participants gave informed written consent.

Full clinical examination entailing 66/68 tender/swollen joint count (TJ and SJ), Psoriasis Area and Severity Index (PASI), Disease Activity Score (DAS)-28, minimal disease activity (MDA) was performed. Systolic and diastolic blood pressure (SBP, DBP) were determined (average of three consecutive readings five minutes apart), as well as Body Mass Index (BMI).

Fasting serum samples were collected at T0, FU1 and FU2 and stored at 80°C until analysis. Total cholesterol (TC), low-density and high-density lipoproteins (LDL-C, HDL-C), triglycerides (TG), blood glucose, C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), TNF-α and osteoprotegerin (OPG) were assessed. TNF-α was measured by immunometric assays using an Immulite One Analyzer, Serum OPG by the Duo-Set ELISA Development System for human OPG (R&Dsystems, Minneapolis, MN, USA).

Subclinical atherosclerosis progression was assessed by ultrasound examination of the carotid arteries. An Aspen Advanced Ultrasound System Instrument (Acuson, USA) with a linear probe (7–10 MHz) was used. Intima-media thickness (IMT, the distance between the lumen-intima and the media-adventitia), 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. IMT measurements were expressed in mm as cumulative mean of mean-IMT (mean-IMT) and as cumulative mean of maximum-IMT (IMT-max) recorded for each vascular segment. Endothelial function was assessed by flow-mediated vasodilation (FMD, dilation of the brachial artery to increased flow, expressed as % by a B-mode scan of the right brachial artery in longitudinal section above the elbow). For further specification please refer to our previous work (4).

Statistical analysis

Data are presented as mean (±SD). Differences between T0-FU1 and FU1-FU2 were compared by *t*-test or Mann-Whitney test as appropriate. The SPSS Statistics 18 package was used.

Results

Thirty-two consecutive patients were enrolled (mean age 51±8 years, mean PsA duration 12±10 years). All patients started anti-TNF-α treatment at baseline: etanercept (n=21), adalimumab (n=6), infliximab (n=5). Twenty-eight patients participated to FU2 evaluation. All of them continued the same therapy at a standard dose for the whole 5-year period, except one patient who switched from infliximab to golimumab during the first year for inefficacy.

No major CV events were observed over the 5-year period in our low-risk population (see exclusion criteria). A good response to treatment was evident already at FU1, with a significant decrease of TJ, SJ, DAS 28, CRP and PASI; efficacy was preserved throughout FU2 (Table 1). Twenty-one patients at FU1 and 27 at FU2 reached MDA. Inflammatory biomarkers (CRP, TNF-α) decreased at FU1 and settled

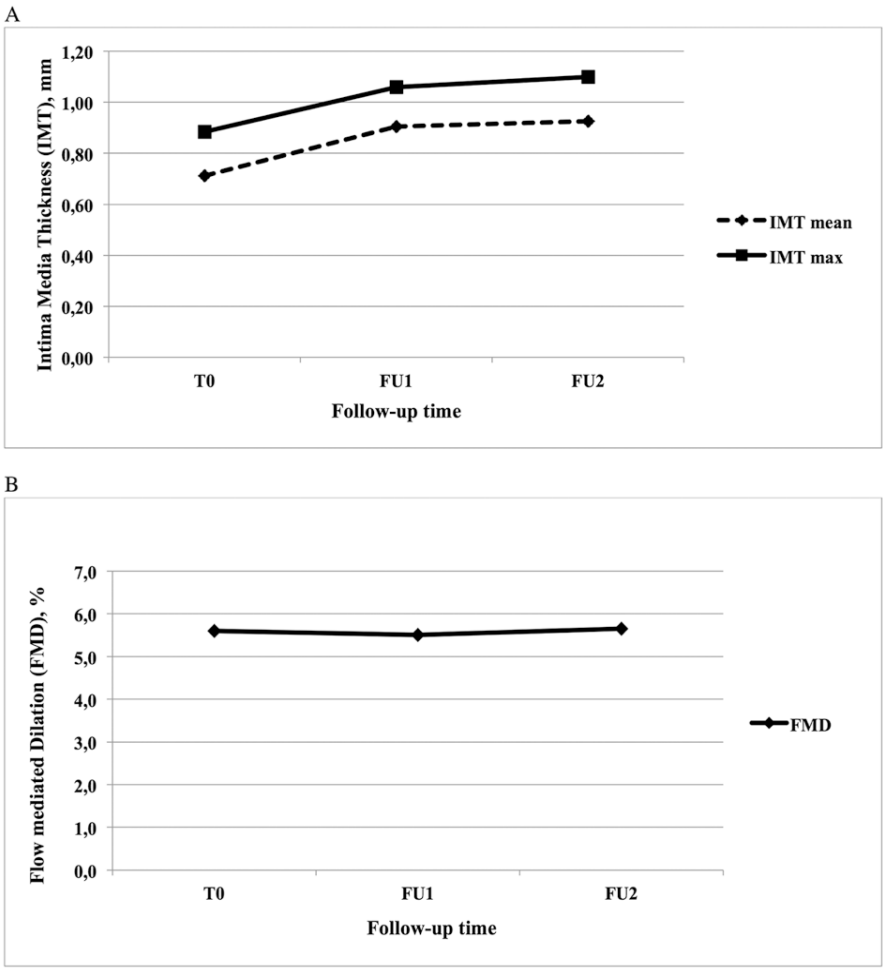

Fig. 1. Vascular remodelling during the study period.
A: From T0 to T1 there was a significant increment in both IMT-mean and M-MAX. At T2 IMT-mean and M-MAX did not change significantly.
B: No significant variation in FMD values was observed during the 5-year follow-up.

on low levels at FU2 (Table I). As for atherosclerosis biomarkers: a) hs-CRP, OPG, TC, LDL-C decreased at FU1, and remained stable at FU2 b) fasting glucose slightly increased at FU1 but then tended to stabilise at FU2 c) triglycerides decreased at FU1, and then increased back at FU2 d) no significant difference was observed in HDL-C levels throughout the study period. Noteworthy, SBP and BMI remained stable throughout follow-up, while DBP decreased significantly.

From T0 to FU1, already in our previous publication a significant increment in both IMT-mean and M-MAX was noted (both $p<0.0001$) (Fig. 1A). From FU1 to FU2, however, IMT-mean and M-MAX did not change significantly (p=ns FU1 *vs*. FU1, but $p<0.0001$ FU2 *vs*. baseline) (Table I, Fig. 1A). No significant variation in FMD values was observed during the 5-year follow-up (comparisons baseline *vs*. FU1/ FU1 *vs*. FU2/ baseline *vs*. FU2, all p=ns; Table I, Fig. 1B).

Discussion

The follow-up extension up to 5 years of our PsA patients' showed that, after an initial worsening of subclinical atherosclerosis ultrasound parameters during the first 2 years of TNF-inhibitors therapy, a stabilisation of IMT-mean and IMT-max was reached. At the same time, FMD did not vary significantly. Serum biomarkers of atherosclerosis, like TC, LDL-C and OPG tended instead to decrease from baseline to FU1, to remain then unchanged during further follow-up.

Subclinical atherosclerosis is more frequent in PsA than in the general population. Moreover, coronary plaque formation is associated with PsA disease activity independently of metabolic disease. In fact, even in PsA patients without classical atherosclerosis factors, IMD was found to be increased, and FMD impaired (6). The link between PsA and atherosclerosis is complex, as systemic inflammation contributes to various stages of atherosclerosis, from endothelium activation and inflammatory cells recruitment, to monocyte differentiation and foam cell formation, with subsequent plaque development (7). Adequate control of inflammation, through anti-TNF-α agents, might help reducing atherosclerosis progression (8). In a Canadian study on PsA, anti-TNF-α therapy was independently associated with reduced atherosclerosis progression in men; improvement in vascular inflammation was seen in both men and women (9). Moreover, reports on inflammatory arthritis in general observed IMT reduction in the anti-TNF-treated patients as opposed to controls (10). In contrast, in our previous study, a beneficial effect on subclinical atherosclerosis was not evident after 2 years of anti-TNF-α therapy (4). However, the results of follow-up extension suggest that the treatment effect might become evident over time, when a more stable control of the disease is achieved. This would be in accordance with data showing that, in PsA treated patients, stained MDA achievement –but not MDA at a single timepoint- is associated to less chance of plaque progression (11). Moreover, anti-TNF-α could have additional beneficial effects on blood pressure, independently from atherosclerosis. Some studies, in fact, showed how circulating TNF-α is associated to hypertension (12). Thus, its antagonists might be effective in regulate it, as our results seems to suggest, with a decrease in DBP observed at FU2.

Serum biomarkers displayed a more heterogeneous trend compared to ultrasound-based markers of atherosclerosis. TC, LDL-C and OPG initially tended to decrease, and then to stabilise during follow-up, while triglycerides initially decreased but then significantly increased back. HDL-C did not change over the study period. In literature, data about these biomarkers' behaviour during anti-TNF-α treatment are also

discordant. Some authors suggest that a tighter control of the disease (MDA achievement) might be associated to lower triglycerides and higher HDL-C levels (13). Other studies showed an increase in triglycerides and TC (14). Notwithstanding, it is recognised that the relationship between anti-TNF-α therapy and lipid profile might be more complex than merely quantitative: TNF-α-blockers could change qualitative lipid composition (15).

The limitations of the present study include the small study population and the lack of a control group. However, the focus was not to compare PsA patients to the general population, but rather to describe subclinical atherosclerosis progression in PsA patients over a longer period of time. The strengths are a long prospective follow-up and the evaluation of ultrasound parameters of subclinical atherosclerosis by experienced physicians.

In conclusion, our study indicated a slight albeit significant atherosclerosis progression in the first 2 years of anti-TNF-α therapy. However, in the subsequent follow-up, up to 5 years, the ultrasound-based atherosclerosis parameters as well as the majority of serum biomarkers become stable. This suggests that the effect of anti-TNF-α drugs on atherosclerosis progression might vary according to disease stage and length of follow-up.

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