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Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis

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ABSTRACT

Background and aims: In patients with psoriasis, the chronic exposure to systemic inflammation can result in coronary microvascular dysfunction (CMD). In this self-controlled, prospective pilot study, we investigated whether a long-term treatment with TNF-α inhibitors effective against skin symptoms also improves coronary flow reserve in psoriasis patients (CFR).

Methods: We prospectively studied 37 consecutive psoriasis patients (31 male; age, 37.7 ± 8.5 years) without cardiovascular disease, before and after anti-TNF-α treatment. CFR in the left anterior descending coronary artery was detected by transthoracic Doppler echocardiography, at rest and during adenosine infusion. CFR was the ratio of hyperemic to resting diastolic flow velocity. A CFR ≤ 2.5 was considered a marker of CMD. Psoriasis was assessed by Psoriasis Area and Severity Index (PASI). High sensitive C-reactive protein (hs-CRP) and serum TNF-α were assessed.

Results: Overall, CFR increased from 2.2 ± 0.7 to 3.02 ± 0.8 ($p < 0.0001$) after TNF-α inhibitors therapy. In patients with CMD, CFR increased from 1.88 ± 0.3 to 2.74 ± 0.5 ($p < 0.0001$). In patients with normal CFR, CFR increased from 3.0 ± 0.5 to 3.7 ± 0.9 ($p = 0.08$). CFR improvement after TNF-α inhibitors treatment was correlated with hs-CRP and TNF-α reduction ($p = 0.004$ and $p = 0.02$, respectively), but not with change in PASI ($p = 0.5$).

Conclusions: The present study demonstrates that TNF-α inhibitors treatment ameliorates CMD in patients with established psoriasis not responding to long-term conventional therapy. These findings suggest that a therapy specifically targeted against inflammation is able to positively affect coronary microvascular function.

1. Introduction

Psoriasis is a chronic, inflammatory skin disease affecting more than 2% of the world's population [1]. This disease is characterized by T helper (Th)1/17/22-driven inflammation which culminates in the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interferon-gamma, interleukin (IL)-17 and IL-22 [2,3].

Psoriasis is believed, although not by all authors, to be an independent risk factor for cardiovascular diseases [4–6,8–16]. The increased cardiovascular risk associated with psoriasis could be partially explained by the presence of chronic inflammation [17]. Psoriasis shares similar pathophysiological mechanisms with the inflammatory process in atherosclerosis [17], with an overproduction of TNF-α that overlaps with the inflammatory profile of psoriasis [18,19].

TNF-α inhibitors are highly effective in the treatment of psoriasis and other inflammatory diseases and can also have a positive impact on cardiovascular risk [20,21]. In patients with psoriasis, even in absence of traditional cardiovascular risk factors or angiographic evidence for coronary artery disease (CAD), the chronic exposure to systemic inflammation results in coronary microvascular dysfunction (CMD), which is an early marker of coronary atherosclerosis [22,23]. Coronary flow reserve (CFR) by

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transthoracic Doppler echocardiography (TDE) can provide important information about CMD [23,24]. Data regarding whether and how anti-TNF-α therapies influence cardiovascular comorbidity in psoriasis are limited and conflicting [25–27].

In this self-controlled, prospective pilot study, we investigated whether a long-term treatment with TNF-α inhibitors improves CFR in patients with severe psoriasis and without evidence for epicardial coronary artery disease, as assessed by multi-slice computed tomography (MSCT) coronary angiography.

2. Materials and methods

2.1. Study population

We prospectively studied 37 consecutive patients (31 male, aged 37.7 ± 8.5 years) referred to the Center for Psoriasis of the University of Padova. The study design is experimental, non-randomized and non-blinded to treatment. Patients served as their own controls. All patients had a diagnosis of severe psoriasis since at least 12 months, stable plaque psoriasis since at least 2 months before screening and the clinical indication for TNF-α inhibitor therapy. Exclusion criteria were age <18 years, presence of psoriatic arthritis, high blood pressure at CFR evaluation, diabetes mellitus, hyperlipidemia, history or clinical evidence of cardiopulmonary, renal (serum creatinine >133 μmol/L in men and >120 μmol/L in women), or hepatic disease and malignant or infectious disease. For risk factor definition see Supplementary Material online. The study was approved by the Institutional Ethics Committee, and a written informed consent was obtained from all participants.

2.2. Clinical characteristics and dermatologic evaluation

We evaluated gender and age, BMI, years elapsed since the first diagnosis of psoriasis, previous dermatological treatment and Psoriasis Area Severity Index (PASI). PASI grades psoriatic plaques based on three criteria: redness, thickness, and scaliness. Severity is rated for each feature on a 0–4 scale (0 for skin integrity up to 4 for severe involvement). Currently, PASI is considered the gold standard method used to assess psoriasis severity and is widely accepted as an outcome measure in clinical research and by health authorities [28]. A 75% improvement in the PASI score (PASI 75) is considered as clinically meaningful and therefore used to document the effectiveness of therapies in patients with psoriasis. Moreover, remission or almost remission has been defined as an improvement of PASI = 100% (PASI 100) and PASI>90% (PASI 90), respectively. Twenty-two patients were treated with etanercept, 8 patients with adalimumab and 7 with infliximab. For detailed PASI evaluation and psoriasis treatment see Supplementary Material online.

2.3. CFR assessment

TDE was performed before and after an average 6.3 months (range 5.5–7.1 months) of anti-TNF-α treatment, with a commercially available ultrasound system (Vivid 7, GE Medical System, Inc., Hortem, Norway). Coronary images were obtained in the distal part of the left anterior descending artery (LAD) with 7-MHz transducer. Coronary blood flow was obtained by Color Doppler flow-mapping guidance, and sample volume was positioned within the color signal in the LAD by pulse wave Doppler. After baseline recordings of coronary diastolic flow velocity (DFV), adenosine was intravenously infused (140 $\mu g/kg^{-1}$/min) for 3 min, obtaining hyperemic Doppler flow profiles. CFR was estimated as the ratio of hyperemic to baseline peak DFV. A CFR ≤ 2.5 was considered abnormal [22]. Echocardiographic methods are detailed in the Supplementary Material online.

2.4. MSCT coronary angiography protocol

Patients with abnormal CFR underwent MSCT coronary angiography to exclude significant epicardial CAD and we assessed calcium score. For MSCT protocol see Supplementary Material online.

2.5. Laboratory methods

Fasting serum samples were collected at baseline and at the end of the study and stored at −80 °C until they were analyzed. For laboratory methods see Supplementary Material online.

2.6. Statistical analysis

A single stage (fixed sample size) design was chosen. For specified $\alpha = 0.05$, effect $\mu_2 - \mu_1 = 1$ and standard deviation $\sigma = 2$, the power $(1-\beta)$ is 80.0% if the test has sample size of 33.4 patients. Assuming a 10% drop out rate, the final sample size is of 37 patients. Continuous variables are reported as mean ± SD or median and interquartile range (IQR) if not normally distributed. Matched pairs were compared with the paired Student's *t*-test for normally distributed data or Wilcoxon signed rank sum test if highly skewed. In preplanned multiple endpoint analysis 9 outcomes has been performed using simple Bonferroni correction leading the *p* value threshold to be 0.005 to keep the nominal overall p value at 0.05. Categorical variables are reported as percentages and compared with χ^2-test or Fisher exact test as appropriate. The distribution of the data was analyzed with a 1-sample Shapiro-Wilk test. Comparisons between more groups were examined with nonparametric Kruskal–Wallis test. Bivariate correlations were assessed by the Pearson coefficient (r). Time and other confounding variables were tested using univariable and multivariable linear mixed models to take into account the intrasubject correlation of measures. In the mixed model, with CFR improvement as dependent variable, we used each patient as a random factor and the time (duration of TNF-α inhibitors therapy), decrease in PASI score, TNF-α decrease, hsCRP decrease, age and gender as fixed factors. Intraobserver and interobserver reproducibilities of CFR were evaluated by linear regression analysis and expressed as correlation of coefficients (r) and standard error of estimates (SEE), by the Bland-Altman method and the intraclass correlation coefficient (ICC). Reproducibility is considered satisfactory if the intraclass correlation coefficient is between 0.81 and 1.0. Intraobserver and interobserver reproducibility measurements were calculated in all 37 patients. Statistical significance was assumed if the null hypothesis could be rejected at $p = 0.05$. Data were analyzed with SPSS software version 20.0 (Chicago, SPSS, Inc., Chicago, IL). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

3. Results

3.1. Baseline clinical features and CFR evaluation

Baseline clinical features are presented in the Supplementary Table. In the whole patient population CFR was 2.2 ± 0.7. CFR was ≤2.5 in 26 patients (70.3%). A severe CFR impairment (CFR ≤ 2) was found in 14 patients (37.8%).

CFR studies were always well tolerated. There were no significant electrocardiographic changes or LV wall motion abnormalities during adenosine infusion in any patients. Calcium score was <10 in all patients with CFR ≤ 2.5. A nonsignificant epicardial stenosis