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Cardiovascular risk evaluation through heart rate variability analysis in psoriatic patients before and after 24 weeks of etanercept therapy: Prospective study

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Abstract

Objective: To assess the influence of etanercept, an anti-tumour necrosis factor (TNF)-α agent, on autonomic cardiovascular regulation in young patients with moderate-to-severe psoriasis without cardiovascular risk factors.

Methods: Patients with psoriasis underwent 5-min electrocardiogram (ECG) recordings before and after 24 weeks of etanercept therapy. Linear heart rate variability (HRV) analysis was performed.

Results: The study recruited 19 patients. Frequency-domain analysis showed a significant decrease in oscillatory components attributable to sympathetic activity (LF%) and a significant decrease in low frequency/high frequency (LF/HF) ratio following etanercept therapy.

Conclusion: Treatment with etanercept in patients with moderate-to-severe psoriasis could affect cardiovascular autonomic regulation, and subsequently reduce cardiovascular risk.

Keywords

Autonomic nervous system, cardiovascular, etanercept, heart rate variability, psoriasis

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Introduction

There is increasing awareness that psoriasis, a chronic inflammatory skin disease, has systemic manifestations.[1,2] The relationship between cardiovascular disease (CVD) and severe psoriasis (Psoriasis Area Severity Index[3] [PASI] $\geq$ 10) is of increasing interest,[4] as this may explain the increased mortality related to acute myocardial infarction and ventricular arrhythmias in patients with psoriasis.[5–8]

Psoriasis and CVD may have common pathogenic mechanisms.[9,10] Heart rate variability (HRV) analysis evaluates autonomic control of the sinus node[11] and has been used to investigate the cardiac sympatho–vagal balance in patients with a subclinical inflammatory state.[12,13] There are no studies regarding the use of HRV analysis to assess the effects of biological drugs on the cardiovascular system, and the association between these drugs and CVD remains unclear.[14,15] In particular, although cases of worsening and new-onset heart failure have been reported during etanercept therapy,[16,17] an increased risk of myocardial infarction and/or heart failure has not yet been demonstrated.[18,19]

The aim of the present open-label study was to determine whether etanercept influences autonomic cardiovascular regulation, therefore affecting CVD risk, in young patients with moderate-to-severe psoriasis, in the absence of metabolic syndrome and other cardiovascular comorbidities.

Patients and methods

Study population

The study enrolled consecutive patients with psoriasis who attended the outpatient clinic of the Dermatology Unit "Daniele Innocenzi", University of Rome "La Sapienza", Fiorini Hospital, Terracina, Italy, between October 2013 and April 2014. Inclusion criteria were: aged 18–35 years; cutaneous moderate-to-severe plaque psoriasis (PASI $\geq$ 10); absence of treatment with long-term psychoactive drugs and short-term modifiers of autonomic function; absence of common cardiovascular risk factors; no previous treatment with traditional or biological psoriasis drugs. All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.[20] The requirement for ethics committee approval was waived.®

Data collection

Data regarding clinical, cardiovascular and dermatological history, sex, age and waist circumference were collected from each patient. Laboratory parameters including blood lipids and glucose were recorded, and body mass index and PASI calculated. Heart rate, blood pressure and a 5-min digital electrocardiogram were obtained from all patients at baseline (1–7 days before initiation of treatment) and at 24 weeks after etanercept initiation. Etanercept was self-administered at a dosage of 50 mg twice weekly for the first 12 weeks (induction period) and weekly thereafter.

HRV analyses

Data generated from the 5-min digital electrocardiogram were analysed with Cardiolab® CE pocket PC ECG software (Xai-Medica, Kharkov, Ukraine). Linear methods including time-domain and frequency-domain analyses were used for direct estimation of HRV. For time-domain analyses, statistical characteristics of dynamic row of cardiointervals included standard deviation of all normal-to-normal [NN] intervals (SDNN) and root mean square successive difference between adjacent NNs (RMSSD). Frequency-domain analysis of HRV describes the periodic oscillations of the heart rate signal at different frequencies and amplitudes. The power spectrum can be classified into two principal

bands: low frequency (LF) and high frequency (HF). The HF component is generally defined as a marker of vagal modulation. The LF component is modulated by both the sympathetic and the parasympathetic nervous systems. The LF/HF ratio is considered as an index of sympatho–vagal balance.[21]

Statistical analyses

Data were expressed as mean ± SD or *n* (%). Between-timepoint differences in quantitative variables were analysed using paired *t*-test. Statistical analyses were performed using SigmaStat® version 3.5 (Systat Software, Point Richmond, CA, USA) for Windows®. *P*-values < 0.05 were considered statistically significant.

Results

The study enrolled 19 patients (11 male/eight females, mean age 28.5 ± 4.9 years; age range 18–32 years), all of whom completed the 24-week treatment period. No side-effects were recorded during the observation period. Baseline demographic data and clinical data at baseline and 24 weeks are given in Table 1. Mean PASI was significantly lower than baseline at 24 weeks ($P < 0.001$). In particular, the entire study population reached at least PASI 50 (≥50% reduction in initial PASI) at 24 weeks, and two male patients reached PASI 75 (≥75% reduction in initial PASI). After the scheduled period of therapy, all patients continued on 50 mg/week etanercept according to international guidelines. At the time of writing, no adverse events were observed in the study population.

Data from HRV analyses are given in Table 2. Frequency-domain analysis showed a significant decrease in LF% ($P = 0.040$) and LF/HF ratio ($P = 0.026$) after 24 weeks, compared with baseline. There were no

Table 1. Demographic and clinical characteristics of patients with moderate-to-severe psoriasis, before (baseline) and after 24 weeks' etanercept treatment ($n = 19$).

Characteristic	Baseline	24 weeks
Sex, male/female	11/8 (57.9/42.1)	–
Age, years	28.5 ± 4.9	–
BMI, kg/m^2	23.0 ± 2.0	–
FPG, mg/dl	80.6 ± 3.5	–
Systolic BP, mmHg	116.8 ± 10.7	–
Diastolic BP, mmHg	76.1 ± 7.2	–
Waist circumference, cm	82.5 ± 7.4	–
HDL-C, mg/dl	60.6 ± 7.4	–
Triglycerides, mg/dl	88.9 ± 17.7	–
Heart rate, bpm	66.1 ± 12.2	68.7 ± 11.4
PASI	12.6 ± 3.1	4.5 ± 1.2***

Data presented as *n* (%) or mean ± SD.
***$P < 0.001$ vs baseline; paired *t*-test.
BMI, body mass index; FPG, fasting plasma glucose; BP; blood pressure; HDL-C, high density lipoprotein-cholesterol; PASI, Psoriasis Area Severity Index.[3]

Table 2. Heart rate variability analysis in patients with moderate-to-severe psoriasis, before (baseline) and after 24 weeks' etanercept treatment ($n = 19$).

Parameter	Baseline	24 weeks
Time domain analysis		
SDNN, ms	48.7 ± 21.7	62.4 ± 35.4
RMSSD, ms	41.6 ± 22.7	51.2 ± 34.1
Frequency domain analysis		
Total, ms^2	2700.5 ± 2429.0	3794.0 ± 4447.2
LF%	53.6 ± 17.2	43.7 ± 13.4*
HF%	46.4 ± 17.2	54.9 ± 13.2
LF/HF	1.5 ± 1.1	0.9 ± 0.6*

Data presented as mean ± SD.
*$P < 0.05$ vs baseline; paired *t*-test.
SDNN, standard deviation of all normal-to-normal (NN) intervals; RMSSD, root mean square successive difference between adjacent NNs; LF, low frequency; HF, high frequency.

other statistically significant differences in HRV parameters.

Discussion

Observational studies have found an increased risk of cardiovascular events in patients with psoriasis.[22–26] Explanations of this phenomenon have focused on the common inflammatory subset of these disorders.[27] Cardiovascular diseases are mainly caused by atherosclerosis, which is a chronic inflammatory disease of blood vessels,[28] and inflammatory markers are related to both psoriasis severity and cardiovascular risk.[22] Reductions in these parameters occur during etanercept therapy.[29,30] Despite evidence indicating inflammation acts as a bridge between psoriasis and CVD pathogenesis, uncertainty remains as to its mechanism of action. To the best of our knowledge, there have been no studies considering the role of the autonomic cardiac regulation in this scenario.

We used HRV analyses to assess the effects of biological drugs on the cardiovascular system, and found that etanercept modified autonomic cardiovascular regulation, and consequently CVD risk, in our patient population. Frequency-domain analysis showed a significant decrease in oscillatory components attributable to sympathetic activity (LF%) and a significant decrease in the LF/HF ratio, universally considered an index of sympatho–vagal balance.[21]

In conclusion, our preliminary data suggest that etanercept therapy could modify autonomic cardiovascular regulation in patients with moderate-to-severe psoriasis. It is possible that etanercept may influence the cardiovascular risk associated with psoriasis. The close relationship between psoriasis and CVD emphasises the importance of cardiovascular screening in patients with psoriasis, especially in the presence of risk factors.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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