Cardiovascular Risk Evaluation through Heart Rate Variability (HRV) Analysis in Patients with Psoriasis before and after 12 Weeks of Etanercept Therapy: A Preliminary Prospective Study

Concetta Potenza[1#], Gianfranco Raimondi[2#], Riccardo Pampena[1], Nicoletta Bernardini[1], Giorgio La Viola[1], Ersilia Tolino[1], Sara Zuber[1], Beatrice Scordamaglia[2], Nevena Skroza[1]

[1]Department of Medical and Surgical Sciences and Biotechnologies, Division of Dermatology "Daniele Innocenzi", Sapienza University of Rome, Polo Pontino, Italy; [2]Department of Medical and Surgical Sciences and Biotechnologies, Faculty of Pharmacy and Medicine, Sapienza University of Rome, Italy
# These authors contributed equally to this work.

Corresponding Author:
Riccardo Pampena, MD
Dermatology Unit "Daniele Innocenzi",
"Sapienza" University of Rome
A. Fiorini Hospital, via Firenze, snc
04019, Terracina (LT)
Italy
riccardopampena@gmail.com

Received: July 7, 2015
Accepted: May 30, 2016

ABSTRACT The association between psoriasis and cardiovascular diseases has been indicated by epidemiological studies. The sub-inflammatory systemic state that characterizes both psoriasis and atherosclerosis has been proposed as the link between these conditions; it cannot, however, explain the increased incidence of sudden cardiac death reported in young patients with severe psoriasis without common cardiovascular risk factors. In a previous study, we reported higher levels of autonomic dysregulation in patients with psoriasis, concluding that the prevalence of the sympathetic arm over the parasympathetic could increase cardiovascular risk. Objective of this study was to assess the influence of etanercept on autonomic cardiovascular regulation in young patients with moderate-to-severe psoriasis without cardiovascular risk factors. Five-minute ECG recordings were collected at rest before and after 12 weeks of therapy with etanercept in 19 young patients with psoriasis without cardiovascular risk factors. The Cardiolab CE pocket PC ECG system was used for linear methods of heart rate variability (HRV) analysis. No significant change in HRV analysis parameters was apparent after 12 weeks of etanercept therapy. Our data suggest that treatment with etanercept in patients with moderate-to-severe psoriasis does not affect cardiovascular autonomic regulation and cardiovascular risk.

KEY WORDS: etanercept; cardiovascular risk; heart rate variability analysis; psoriasis

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease affecting 3% of the Caucasian population (1) and is associated with systemic manifestations such as arthritis, hypertension, dyslipidemia, and metabolic syndrome (2). In particular, of emerging significance is the relationship between cardiovascular diseases (CVDs) and psoriasis (3), as increased mortality, mainly related to myocardial infarction and ventricular arrhythmias, has been reported in patients with severe psoriasis (Psoriasis Area Severity Index (PASI) score ≥10) (4,5).

Acta Dermatovenerol Croat
2016;24(3):181-186

Recently, a meta-analysis indicated a higher risk of cardiovascular (CV) events in patients with psoriasis when compared to non-psoriatic controls (odds ratio (OR) 1.28, 95% confidence interval (CI) 1.18-1.38) (6); nevertheless it is still debated if the increase in CV morbidity and mortality can be attributable solely to psoriasis (7). Common pathogenic mechanisms have been proposed for psoriasis and CVDs. Griffiths *et al*. suggested that the increased inflammatory burden of the patient with psoriasis can cause a state of insulin resistance, resulting in endothelial cell dysfunction and atherosclerosis; when coronary, carotid, or cerebral arteries are involved, this cascade will result in myocardial infarction or stroke (8). As supporting proof, the increase of intima-media thickness and coronary calcifications has been documented in patients with psoriasis (9). These are perhaps only a part of the pathogenic mechanisms shared by CVDs and psoriasis.

Heart rate variability (HRV) analysis is a non-invasive and easy-to-perform method to evaluate the autonomic control of the sinus node (10). A higher prevalence of the sympathetic arm, assessed by HRV, has been associated with an increased CV risk in the general population (11,12). However, no published studies have used HRV analysis to assess the effects of biologic drugs on the CV system in patients with psoriasis. The association between these drugs and CVDs (myocardial infarction and/or heart failure) is still controversial (13,14). Nevertheless, the label of etanercept (a soluble tumor necrosis factor (TNF)-alpha receptor inhibitor) reports the following disease-related warning: "Use with caution in patients with heart failure or decreased left ventricular function". Given the evidence to date, Sinagra *et al*. suggest that treatment strategies other than TNF-alpha inhibitors should be employed in patients with symptomatic heart failure. A drug-induced cause should be suspected in patients who develop heart failure while receiving a TNF-alpha inhibitor, and use of the medication should be suspended (15).

An open-label study was performed to assess whether etanercept treatment influences the autonomic CV regulation (evaluated with HRV analysis) and CV risk in a population of young patients with moderate-to-severe psoriasis, in the absence of CV comorbidities.

MATERIAL AND METHODS

Study population

We enrolled consecutive patients with psoriasis who attended our outpatient clinic from October 2013 to February 2014. The inclusion criteria were: age between 18 and 35 years, diagnosis of moderate-to-severe cutaneous psoriasis (PASI >10), and absence of psoriatic arthritis or other forms of psoriasis; no assumption of both long-term (psycho-drugs) and short-term modifiers of the autonomic function; no previous treatment with biologic agents for psoriasis, and a period of at least 12 weeks of wash-out from traditional drugs for psoriasis (cyclosporine, acitretin, methotrexate); absence of the common CV risk factors, including smoking habit, metabolic syndrome, hypertension, family history of CVDs, and being overweight, defined as body mass index (BMI) >25.

Metabolic syndrome was defined as the presence of at least 3 of 5 criteria according to the 2009 Joint Scientific Statement: waist circumference ≥102 cm (88 for women), triglycerides ≥150 mg/dL, blood pressure (BP) ≥130/85 mmHg, high-density lipoprotein (HDL) cholesterol <40 mg/dL (50 mg/dL for women) and fasting plasma glucose ≥100 mg/dL (16).

Finally, any intoxicating agent (caffeine, theine) was forbidden within the three hours preceding the electrocardiogram (ECG) recording.

Each enrolled patient gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki (17).

Procedure

First, an accurate clinical (CV and dermatological) history was collected. Information about gender, age, waist circumference, HDL cholesterol, triglycerides, and fasting blood glucose was recorded and BMI and PASI were calculated.

Heart rate, BP, and a 5-minute digital ECG in rest conditions (supine position for 3 minutes before recording) were then obtained from all the subjects included in the study at baseline (t_0) and 12 weeks after first etanercept administration (t_1). Linear methods, consisting of a time-domain analysis (traditional statistical analysis) and a frequency-domain analysis (spectral analysis), were used to analyze HRV. The Cardiolab CE pocket PC ECG system (XAI-Medica, Kharkov, Ukraine) was used for ECG recording and data analysis.

Time-domain analysis included SDNN (Standard Deviation of all normal-to-normal (NN) intervals) and RMSSD (Root Mean Square Successive Difference between adjacent NNs).

Frequency-domain analysis of HRV provides information on the frequency of periodic oscillations of the heart rate signal. Two principal bands can be identified: the low frequency band (LF) and the high frequency band (HF). The HF component is considered

Table 1. Registry data

	Patients (*N*=19)
Men, *n* (%)	11 (57.9)
Women, *n* (%)	8 (42.1)
Age (years)	28.5±4.9
BMI	23.0±2.0
FPG (mg/dL)	80.6±3.5
SAP (mmHg)	116.8±10.7
DAP (mmHg)	76.1±7.2
WC (cm)	82.5±7.4
HDL-c (mg/dL)	60.6±7.4
TG (mg/dL)	88.9±17.7
HR (b/min) t_0	66.1±12.2
HR (b/min) t_1	67.9±10.9*
PASI t_0	12.6±3.1
PASI t_1	5.7±09†

Data are expressed as mean ± SD.

FPG, fasting plasma glucose; WC, waist circumference; TG, triglycerides; HDL-c, high density lipoprotein-cholesterol; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; BMI, body mass index; PASI, Psoriasis Area Severity Index.

*P=0.135 vs. t_0.

†P<0.001 vs. t_0.

to be a reliable index of vagal modulation, whereas both the sympathetic and the parasympathetic nervous systems appear to be involved in modulating the LF component. The LF/HF ratio represents an index of sympatho-vagal balance (18).

Etanercept administration

Each patient enrolled in the study auto-administered etanercept according to the classical dosing schedule of 50 mg × 2 per week for the first 12 weeks (induction period) and subsequently 50 mg per week.

Statistical analysis

Data are expressed as mean ± standard deviation. Paired T-test for quantitative variables was used to compare baseline and week 12 data. Statistical analysis was performed with SigmaStat 3.5 software for Windows. Statistical significance was fixed at P<0.05.

RESULTS

Nineteen consecutive psoriatic patients were enrolled in the study (11 male patients and 8 women, median age 28.5±4.9). Each of the enrolled patients completed the treatment. No side effects were recorded in the observation period.

Table 1 summarizes the clinical findings in the whole group of patients at baseline and after 12 weeks of treatment. Data showed a non-significant reduction of the mean heart rate at t_1 compared to baseline (66.1±12.2 at t_0 vs. 67.9±10.9 at t_1; P=0.135). In contrast, a statistically significant improvement in PASI score was reported after 12 weeks (P<0.001; mean PASI at baseline: 12.6±3.1; mean PASI at week 12: 5.7±0.9).

Neither time-domain nor frequency-domain analysis showed a significant difference between t_0 and t_1 (Table 2). There was a non-significant decrease in both SDNN and RMSSD parameters with time-domain analysis, whereas frequency-domain analysis showed a non-significant decrease in total power and HF%, and a non-significant increase in LF% and LF/HF ratio.

DISCUSSION

Psoriasis is now considered a systemic inflammatory disorder, rather than a disease affecting only the skin or joints (19). An increased CV risk in patients with

Table 2. Linear analysis: Time-domain analysis (traditional statistical analysis) and frequency-domain analysis (spectral analysis)

		T_0	T_1	*p* Value
Time Domain	**SDNN (ms)**	48.7±21.7	45.8±22.9	0.613
	RMSSD (ms)	41.6±22.7	34.5±22.6	0.267
	TOTAL ms²	2700.5±2429.0	2493.4±2455.1	0.757
Frequency Domain	**LF%**	53.6±17.2	60.5±13.9	0.121
	HF%	46.4±17.2	39.5±13.9	0.121
	LF/HF	1.5±1.1	1.9±1.3	0.142

Data are expresed as mean ± SD.

SDNN, standard deviation of all normal-to-normal (NN) intervals; RMSSD, root mean square successive difference between adjacent NNs; LF, low frequencies; HF, high frequencies.

psoriasis has been reported (20,21); however, no randomized trials have been conducted to demonstrate the causal nature of this association. Several hypothesis have been proposed to explain the link between psoriasis and CVDs that have so far all focused on the common inflammatory subset of these disorders.

There is growing evidence that different subsets of T-helper (Th) cells are implicated in the pathogenesis of psoriasis; in particular Th-1, Th-17, and Th-22 have been reported (22). Cardiovascular diseases are mainly related to atherosclerosis. Innate as well as adaptive immune responses have been identified during the course of atherosclerosis, also involving the Th-1 and Th-17 pathways (23). Inflammatory markers, such as white blood cell count, fibrinogen, ferritin, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), haptoglobin, ceruloplasmin, and α1-antitrypsin have been demonstrated to be related to both psoriasis severity and CV risk (19). The reduction of these parameters (in particular hs-CRP, fibrinogen and ESR) has been shown to occur during therapy with etanercept, an anti-TNF-alpha agent (24).

In 2010, the European League against Rheumatism (EULAR) recommended annual CV risk assessment, as well as aggressive suppression of inflammatory processes, in order to lower the risk for CV events in patients with arthritis, including psoriatic arthritis (25). Even if the evidence appears to definitively indicate inflammation as the bridge between psoriasis and CVDs pathogenesis, it is not yet completely clear how inflammation can actually act. No studies in the literature have considered the role of the autonomic cardiac regulation. The heart is innervated by the sympathetic and the parasympathetic nervous system. Parasympathetic fibers are carried in the vagus nerve and their discharge results in a decreased heart rate and, to a lesser extent, reduced contractility. The sympathetic nervous system acts on the heart via direct neuronal control and also via the release of adrenaline and noradrenaline, mediated by beta receptors. This results in an increased heart rate and increased myocardial contractility. Information on blood pressure is fed to the brain from baroreceptors in the ventricles, aortic arch, and carotid bodies (26).

In a previous study, we evaluated the effect of psoriasis on the autonomic nervous system using HRV analysis (27). We concluded that moderate psoriasis, in young naïve patients without CV comorbidities, might represent a possible independent CV risk factor, because a balanced reduction of the parasympathetic heart modulation associated with an increased sympathetic modulation of the sinus node was detected when comparing the study population with a homogenous control group. HRV analysis was performed with both the classical linear methods and with non-linear methods such as Poincaré plot, Detrended Fluctuation Analysis, and entropy analysis (28).

In the present study, we first used HRV analysis to assess the effects of biologic drugs on the CV regulation. In particular, we showed that etanercept treatment does not modify the autonomic CV regulation, and consequently the CV risk, in a population of young patients with moderate-to-severe psoriasis in absence of metabolic syndrome and other CV comorbidities. Both time-domain and frequency-domain linear HRV analysis failed to demonstrate a statistically significant difference between t_0 and t_1, even if both reported an unbalance toward the sympathetic arm. In particular, linear time-domain analysis (traditional statistical analysis) showed a reduction of the RMSSD values, considered as an index of parasympathetic modulation, even if the effect did not reach statistical significance. Linear frequency-domain analysis (spectral analysis) showed a non-significant increase in oscillatory components attributable to sympathetic activity (LF%) and a simultaneous decrease of the oscillatory components attributable to parasympathetic modulation (HF%). Consequently, an increase in the LF/HF ratio was observed, which is considered an index of sympatho-vagal balance.

The principal limitation of our study is the low number of subjects enrolled, which was mainly related to the strict inclusion criteria. As a pilot study, the evaluation of HRV during treatment was performed after 12 weeks of therapy; new data will come from further studies.

CONCLUSION

Our data suggest that etanercept therapy in patients with moderate-to-severe psoriasis does not modify CV regulation. Thus etanercept does not seem to influence the CV risk associated with psoriasis. This preliminary data needs to be validated by further studies. Finally, emerging evidence from the medical literature indicates that psoriasis and CVDs seem to be closely related, so we believe that CV screening should be mandatory in patients with psoriasis, especially when CV risk factors are present.

References

1. Skroza N, Proietti I, Pampena R, La Viola G, Bernardini N, Nicolucci F, *et al*. Correlations between psoriasis and inflammatory bowel diseases. Biomed Res Int 2013;2013:983902. Epub 2013 Jul 21.

2. Potenza C, Annetta A, Bernardini N, Ciccone V, Grossi B, La Viola G, *et al*. Plaque psoriasis: anatomical, clinical and immunohistochemical correlations during anti-TNFa treatment. J Medical Books Edizioni Srl;2010; ISBN 978-88-904609-1-3.
3. Armstrong AW, Gelfand JM, Boehncke WH, Armstrong EJ. Cardiovascular comorbidities of psoriasis and psoriatic arthritis: a report from the GRAPPA 2012 annual meeting. J Rheumatol 2013;40:1434-7.
4. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, *et al*. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143:1493-9.
5. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010;31:1000-6.
6. Pietrzak A, Bartosinska J, Chodorowska G, Szepietowski JC, Paluszkiewicz P, Schwartz RA. Cardiovascular aspects of psoriasis: an updated review. Int J Dermatol 2013;52:153-62.
7. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, *et al*. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 2013;27 Suppl 3:12-29.
8 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370:263-71.
9. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190:1-9.
10. Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate variability? IEEE Trans Biomed Eng 2001;48:1342-7.
11. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2004;25:363-70.
12. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-65.
13. Behnam SM, Behnam SE, Koo JY. TNF-alpha inhibitors and congestive heart failure. Skinmed 2005;4:363-8.
14. Pariser DM, Leonardi CL, Gordon K, Gottlieb AB, Tyring S, Papp KA, *et al*. Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. J Am Acad Dermatol 2012;67:245-56.
15. Sinagra E, Perricone G, Romano C, Cottone M. Heart failure and anti tumor necrosis factor-alpha in systemic chronic inflammatory diseases. Eur J Intern Med 2013;24:385-92.
16. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
17. 41st World Medical Assembly. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925-6.
18. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, *et al*. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178-93.
19. Montaudié H, Albert-Sabonnadière C, Acquacalda E, Fontas E, Danré A, Roux C, Ortonne JP, *et al*. Impact of systemic treatment of psoriasis on inflammatory parameters and markers of comorbidities and cardiovascular risk: results of a prospective longitudinal observational study. J Eur Acad Dermatol Venereol 2014;28:1186-91.
20. Vena GA, Vestita M, Cassano N. Psoriasis and cardiovascular disease. Dermatol Ther 2010;23:144-51.
21. Xu T, Zhang YH. Association of psoriasis with stroke and myocardial infarction: meta-analysis of cohort studies. Br J Dermatol 2012;167:1345-50.
22. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol 2010;130:1373-83.
23. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006;6:508-19.
24. Kanelleas A, Liapi C, Katoulis A, Stavropoulos P, Avgerinou G, Georgala S, *et al*. The role of inflammatory markers in assessing disease severity and response to treatment in patients with psoriasis treated with etanercept. Clin Exp Dermatol 2011;36:845-50.

25. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.
26. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014;114:1004-21.
27. Proietti I, Raimondi G, Skroza N, Pampena R, Bernardini N, La Viola G, *et al*. Cardiovascular risk in psoriatic patients detected by heart rate variability (HRV) analysis. Drug Dev Res 2014;75:S81-4.
28. Balocchi R, Cantini F, Varanini M, Raimondi G, Legramante JM, Macerata A. Revisiting the potential of time-domain indexes in short-term HRV analysis. Biomed Tech (Berl) 2006;51:190-3.