



## Original article

# TNF-alpha inhibition could reduce biomarkers of endothelial dysfunction in patients with moderate to severe psoriasis: A 52-week echo-Doppler based quasi-experimental study<sup>☆</sup>

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## ABSTRACT

**Objectives:** Psoriasis is associated to endothelial dysfunction, which causes impaired vascular functioning. TNF- $\alpha$  blockers have shown the ability to improve vascular functioning in psoriasis. The nailfold vessel resistance index (NVRI) assesses microvascular functioning at nailfold. The objectives of the study are to assess the effect of the TNF- $\alpha$  inhibition with adalimumab on NVRI.

**Material and methods:** Quasi-experimental study. Fifteen patients with moderate-severe psoriasis received adalimumab 40 mg sc according to label information. Participants were assessed at baseline and at 12, 24 and 52 weeks after study intervention.

**Results:** A reduction of  $-0.09 \pm 0.02$  ( $p < .01$ ) in NVRI and a  $-11.2 \pm 2.41$  ng/ml ( $p < .001$ ) in E-selectin was observed at week 52.

**Conclusions:** Adalimumab could produce a progressive and sustained reduction of vessel resistance at nailfold and E-selectin in patients with psoriasis.

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## La inhibición del TNF- $\alpha$ puede disminuir los biomarcadores de disfunción endotelial en pacientes con psoriasis de moderada-grave: un estudio cuasiexperimental eco doppler a 52 semanas

## RESUMEN

**Objetivos:** La psoriasis se asocia a la disfunción endotelial, lo cual provoca un deterioro del funcionamiento vascular. Los inhibidores del TNF- $\alpha$  han mostrado la capacidad de mejorar el funcionamiento vascular en la psoriasis. El índice de resistencia de los vasos ungueales (IRVU) evalúa el funcionamiento microvascular en la uña. El objetivo del estudio fue evaluar el efecto de la inhibición del TNF- $\alpha$  con adalimumab en el IRVU.

**Material y métodos:** Estudio cuasiexperimental. Quince pacientes con psoriasis moderada-grave recibieron adalimumab 40 mg sc según ficha técnica. Se valoró a los participantes al inicio y a las 12, 24 y 52 semanas tras la intervención del estudio.

**Resultados:** En la semana 52 se observó una reducción del IRVU de  $-0,09 \pm 0,02$  ( $p < 0,01$ ) y de  $-11,2 \pm 2,41$  ng/ml ( $p < 0,001$ ) en la E-selectina.

**Conclusiones:** Adalimumab podría producir una reducción progresiva y sostenida de la resistencia de los vasos ungueales y marcadores de disfunción endotelial.

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## Palabras clave:

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## Introduction

New insights in psoriasis pathogenesis have evidenced that the dysfunction of the endothelial cell plays an important role in the development of the disease and its comorbidities.<sup>1,2</sup>

Different studies in psoriasis have shown changes in the functioning of large, medium and small blood vessels as a consequence of the endothelial dysfunction.<sup>1–3</sup> In a previous study, we explored the nailfold microvascular functioning of moderate to severe patients with psoriasis and disease-free patients assessing the nailfold vessel resistance (NVRI) by echo Doppler.<sup>4</sup> We observed that patients had a higher NVRI compared to controls. The increased vascular smooth muscle tone exhibited in endothelial dysfunction would increase vessel resistance to blood flow due to reduced vessel diameter.<sup>1–3</sup>

We hypothesize that TNF $\alpha$  inhibition would improve endothelial dysfunction and consequently reduce the NVRI.

The aim of our study is to assess the NVRI in response to the administration of a TNF $\alpha$  blocker, adalimumab.

## Methods

### Design

Between 05/30/2013 and 05/30/2015, we conducted a quasi-experimental study in the psoriasis unit of Complejo Hospitalario de Granada. Participants were assessed at baseline and at 12, 24 and 52 week after the study intervention. The Ethics Committee of Complejo Hospitalario de Granada approved the study.

### Participants

Study sample was recruited from among patients with moderate to severe plaque psoriasis attending to their scheduled follow-up visits at the psoriasis unit. The first fifteen consecutive patients who fulfilled inclusion/exclusion criteria were enrolled in the study. All participants gave written informed consent to participate in the study.

Inclusion criteria were: age >18 years and a moderate to severe psoriasis defined by a body surface area affected by psoriasis (BSA) >10 or Psoriasis Area and Severity Index (PASI) >10. Exclusion criteria were: high blood pressure, diabetes mellitus, cardiac disease, vascular peripheral disease or any other organic disease different from psoriasis, smoking, alcoholism, psoriasis arthritis or suggestive symptoms of it, prior treatment with methotrexate, acitretin, cyclosporine or phototherapy the 12 weeks before the beginning of the study, prior treatment with psoriasis biologic drugs, use of vasoactive drugs.

### Study intervention

Adalimumab 40 mg subcutaneous was administered according to label information.<sup>5</sup>

### Main outcome measures

#### Nailfold Vessel Resistance Index (NVRI)

The NVRI was the main variable of the study. Echo Doppler was used to determine the maximum speeds of flow in systole (Qs) and in diastole (Qd) on the proximal nailfold of the fourth finger of the non-dominant hand by NVRI was calculated as: (Qs – Qd)/Qs. Three measurements were performed, and the arithmetic mean was considered as the definitive NVRI. The NVRI ratio ranges from 0 (no resistance to blood flow at all) to 1 (maximum resistance to blood flow).<sup>7</sup>

### Clinical and laboratory measures

Medical and psoriasis history was collected by means of clinical interview. A trained dermatologist assessed psoriasis severity and nail psoriasis involvement calculating the BSA, PASI and Nail Psoriasis Area and Severity Index (NAPSI). Clinical response to treatment was evaluated calculating PASI75 response. Biometric parameters and blood pressure were assessed through physical examination. A peripheral venous blood sample was collected in each visit to evaluate E-selectin, C-reactive protein (Crp), and other analytical parameters.

### Data analysis

Descriptive statistics were used to explore characteristics of the sample. Kolmogorov–Smirnov test was used to check the normality of the variables. Continuous data are expressed as the mean  $\pm$  standard deviation or the median and 25th/75th percentile. NVRI, E-selectin and NAPSI were normally distributed; the ANOVA test for repeated measures and the post hoc Dunnett's test were used for the analyses. PASI and Crp were non-normally distributed and the Friedman test and the post hoc Dunn's multiple comparisons test were used for the analyses. Significance was set for all tests at two tails,  $p < .05$ . Statistical analyses were performed using SPSS version 11 (SPSS, Chicago, IL, USA).

## Results

Characteristics of the study participants are summarized in Table 1. All the participants completed the study protocol without any adverse reactions. Blood pressure, glycaemia, glycosylated hemoglobin and hematocrit of all participants were within normal range during the study period.

### Nailfold Vessel Resistance Index

NVRI experienced an intense reduction of  $-0.05 \pm 0.02$ ,  $p = .03$ , in the first 12 weeks (Fig. 1a). At week 52, the total reduction from baseline was  $-0.08 \pm 0.02$ ,  $p < .01$ .

There was no correlation between the severity of nail involvement of the fourth finger of the non-dominant hand or NAPSI and NVRI (Fig. 1a).

### E-selectin and C-reactive protein

At week 52, the cumulative reduction of E-selectin was  $-11.2 \text{ ng/ml} \pm 2.41$ ,  $p < .001$ , but Crp showed no statistical significant differences from baseline  $0.12 \text{ mg/L}$  ( $-1.66/2.10$ ),  $p = .39$ , because of a mild increase between weeks 12–24 (Fig. 1b and c). There were no differences on E-selectin or Crp based on nail involvement.

**Table 1**

Baseline characteristics of participants.

Variable	No. = 15
Age <sup>a</sup>	49.8 $\pm$ 11.61
Females	2 (13%)
BMI	29.64 $\pm$ 5.69
Waist circumference	108.0 $\pm$ 15.71
Nail psoriasis	7 (46.67%)
Psoriasis duration <sup>a</sup>	23.17 $\pm$ 31

Continuous data is expressed as mean standard deviation or as median and 25th/75th percentile. Nominal data is expressed as absolute and relative frequencies. BMI: Body Mass Index.

<sup>a</sup> Measured in years.

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