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Effects of adalimumab on T-helper-17 lymphocyte- and neutrophil-related inflammatory serum markers in patients with moderate-to-severe hidradenitis suppurativa

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ABSTRACT

Background: T-helper (Th)-17 lymphocytes and neutrophils are the main sources of the proinflammatory cytokines involved in the pathogenesis of hidradenitis suppurativa (HS).
Objectives: This study aims to evaluate the improvement of the inflammatory serum markers (ISM) levels in patients with moderate-to-severe HS who receive adalimumab.
Methods: Nineteen moderate-to-severe HS patients were prospectively recruited. Each of the patients received 40 mg of adalimumab weekly. The ISM levels and modified Hidradenitis Suppurativa Score (mHSS) scores were assessed at baseline and at week 36. Nineteen healthy volunteers (HC) constituted the control group.
Results: Before adalimumab treatment, the HS patients showed significantly increased levels of interleukin (IL)-6, IL-8, IL-10, IL-17A, soluble TNF receptor II (sTNF-RII), and C-reactive protein (CRP) as well as an increased erythrocyte sedimentation rate (ESR) (all $P < .01$). At week 36, the circulating levels of IL-1β, IL-6, IL-8, IL-10, IL-17A, soluble TNF receptor I (sTNF-RI), sTNF-RII, and CRP, as well as the ESR (all $P < .05$), decreased significantly in the HS patients who received adalimumab. The decrease in levels of IL-6 ($r = 0.65$, $P = .003$), IL-8 ($r = 0.52$, $P = .024$), sTNF-RI ($r = 0.55$, $P = .015$), and CRP ($r = 0.47$, $P < .040$) and the ESR ($r = 0.60$, $P < .006$) were significantly well correlated with clinical improvements according to the mHSS.
Conclusions: Adalimumab improves the ISM-based systemic inflammatory burden in patients with moderate-to-severe HS. IL-6, IL-8, sTNF-RI and CRP and the ESR may serve as novel biomarkers for a therapeutic response.

1. Introduction

Hidradenitis suppurativa (HS) is a chronic, progressive, debilitating inflammatory skin disorder originating in the follicular infundibulum, with a prevalence of 1% [1,2]. Obesity, diabetes mellitus, dyslipidaemia, hypertension, and metabolic syndrome are the main comorbidities associated with HS. Tobacco use is also strongly associated with HS [3,4].

The interleukin (IL)-1β-IL-23/T-helper (Th)-17/IL-17 pathway and neutrophils are the main sources of proinflammatory cytokines in the pathogenesis of HS [5]. Circulating levels of IL-17, IL-6, and other serum markers such as C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR) and the white blood cell count are effective for evaluating the clinical inflammatory burden in HS patients [6–8]. Serum IL-6 and high-sensitivity C-reactive protein (hsCRP) have been investigated in HS to predict the response to infliximab [9]. However, studies evaluating changes in the inflammatory serum marker (ISM) levels in HS patients receiving systemic therapy are scarce. Only one study failed to demonstrate changes in the serum levels of IL-2R, tumour necrosis factor (TNF)-α, IL-17A and IL-17F in 12 HS patients who were treated with ustekinumab [10].

The treatment of HS remains challenging and unclear for dermatologists. Adalimumab, a TNF-α inhibitor, is the only approved drug for the treatment of moderate-to-severe HS by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) based on the results of PIONEER I and PIONEER II studies. Both

Abbreviations: Th, T-helper; HS, Hidradenitis suppurativa; ISM, Inflammatory serum markers; mHSS, modified Hidradenitis Suppurativa Score; IL, Interleukin; sTNF-RI, Soluble TNF receptor I; sTNF-RII, Soluble TNF receptor II; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; hsCRP, High-sensitivity C-reactive protein; TNF, Tumour necrosis factor; HiSCR, Hidradenitis suppurativa clinical response; AN, Abscess and inflammatory nodule count; HS-PGA, Hidradenitis Suppurativa - Physician global assessment

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studies were 36-week, phase III, randomized placebo-controlled trials. In the PIONEER I and II clinical trials, the percentages of patients with HS who achieved a hidradenitis suppurativa clinical response (HiSCR) with 40 mg of adalimumab weekly were 41.8% and 58.9%, respectively. A HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN) with no increase in the abscess count or the draining fistula count relative to the baseline values [11,12].

Otherwise, a recent study showed that the treatment of working age HS patients is associated with high healthcare costs [13]. Thus, it is important to select patients who may be failing to respond to biological therapies to minimize their potential side effects or high costs and prevent irreversible skin damage. Blood-based biomarkers may provide an estimation of the systemic inflammatory burden and response to HS therapy.

Our study aims to investigate the evolution of Th-17 lymphocyte- and neutrophil-related ISMs in patients with moderate-to-severe HS who were treated with adalimumab. Furthermore, we assessed the clinical therapeutic response according to the modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa - Physician global assessment (HS-PGA) score and HiSCR.

2. Materials and methods

2.1. Patients and controls

A prospective, single-centre case control study was performed on patients with moderate-to-severe HS (an HS-PGA score ≥ 3 and Hurley staging system ≥ II). In total, 19 HS patients (11 males and 8 females) with a mean ± standard deviation (SD) age of 35.7 ± 13.4 years (range: 21–62 years) were enrolled. Data, such as age, sex, smoking, body mass index and outcome variables were collected for HS patients (Table 1). HS was diagnosed according to well-established criteria [14].

Table 1
Demographics and outcomes variables of healthy controls and patients with hidradenitis suppurativa.

	Healthy controls	Patients with hidradenitis suppurativa
n	19 (9 males, 10 females)	19 (11 males, 8 females)
Age (years), mean ± SD	35.7 ± 13.4	45.6 ± 10.7
Smoking, current smoker, n (%)	3 (16)	14 (74)
BMI, kg/m^2	24.7 ± 3.1	31.9 ± 5.9
Normal weight: BMI ≤ 24.9, n (%)	Normal weight: 14 (21.1)	Normal weight: 4 (21.1)
Overweight: BMI ≥ 25, n (%)	Overweight: 4 (10.5)	Overweight: 2 (10.5)
Obesity: BMI ≥ 30, n (%)	Obesity: 1 (68.4)	Obesity: 13 (68.4)
Hurley staging system	Not applicable	Stage II: 9 (47.4) Stage III: 10 (52.6)
HS-PGA, Before TNF-α inhibitor treatment	Not applicable	Moderate: 9 (47.5) Severe: 4 (21.1) Very severe: 6 (31.6)
HS-PGA, After TNF-α inhibitor treatment (36 weeks)	Not applicable	Clear: 4 (21.1) Minimal: 4 (21.1) Mild: 4 (21.1) Moderate: 3 (15.8) Severe: 4 (21.1)
mHSS, Before TNF-α inhibitor treatment	Not applicable	82.79 ± 41.0
mHSS, After TNF-α inhibitor treatment (36 weeks)	Not applicable	34.5 ± 43.5
HiSCR (%), 36 weeks	Not applicable	68.42%

BMI, body mass index. HS-PGA, Hidradenitis Suppurativa - Physician global assessment. mHSS, modified Hidradenitis Suppurativa Score. HiSCR (at least a 50% reduction in total AN count, with no increase in abscess count, and no increase in draining fistula count relative to baseline).

The exclusion criteria were as follows: patients younger than 18 years of age and patients suffering from infectious, tumoural or autoimmune diseases. The washout period for systemic medication was > 5 half-lives. All patients received adalimumab 40 mg once a week. Assessments were performed by the same dermatologist at baseline (week 0) and at week 36. Various validated tools were used to evaluate the clinical severity of HS [15]. These included the Hurley staging system, HS-PGA score and mHSS. The Hurley staging system is a simple but static scale that does not measure the number of inflammatory lesions in each area. Outcome variables included pre-adalimumab and post-adalimumab HS-PGA and mHSS scores, and achievement of a HiSCR. The control cohort consisted of healthy volunteers (HC).

This study was conducted in accordance with the Helsinki Conference (64th World Medical Association General Assembly, Fortaleza, Brasil, October 2013). Approval was obtained from the Hospital Puerta del Mar Ethics Committee. Informed consent was obtained before screening.

2.2. Inflammatory serum marker assays

Fasting serum samples (5–10 mL) were prospectively collected from the HS patients and HC subjects. The serum samples were processed within 2 h of sampling (using centrifugation at 2500*g* for 15 min) and subsequently stored at −80 °C until analysis. All samples were processed and analysed in duplicate.

The levels of 8 cytokines, including IL-1β, IL-6, IL-8, IL-10, IL-17A, IL-23 and soluble TNF receptors I (sTNF-RI) and II (sTNF-RII), were measured in the serum at baseline and at week 36 using xMAP technology (Luminex Corporation, Austin, TX, USA). The Milliplex MAP multiplex assay was conducted in a 96-well microplate according to the manufacturer's instructions (Millipore, Billerica, MA, USA). The serum levels of sTNF-Rs were correlated with those of TNF-α [16].

CRP serum levels were measured using a turbidimetric assay with the Cobas 8000 (Roche Diagnostics, Mannheim, Germany). The Westergren method involving the collection of 2 mL of venous blood into a tube containing 0.5 mL of sodium citrate was used to measure the ESR (VES-MATIC 60, Menarini). A CRP level of greater than 6 mg/L and an ESR of greater than 20 mm/h were regarded as abnormal values.

2.3. Statistical analysis

The ISM data were analysed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA). All data are presented as the mean ± SD (median). We used the Mann-Whitney *U* test to evaluate differences between 2 groups: pretreatment HS patients vs. the HC subjects and post-treatment HS patients vs. the HC subjects. The Wilcoxon rank test was used to analyse two related samples at different points of the treatment: pre-treatment HS patients vs. post-treatment HS patients. The statistical significance was set at $P < .05$.

3. Results

3.1. Comparison of inflammatory serum marker levels between the healthy controls and hidradenitis suppurativa patients before adalimumab treatment

The levels of 8 cytokines, the CRP level and the ESR were analysed in 19 HS patients and 19 HC subjects. The serum levels of IL-6, IL-8, IL-10, IL-17A, sTNF-RII, and CRP and the ESR were significantly increased in HS patients before adalimumab treatment ($P < .05$) (Fig. 1). These findings indicate the systemic expression of Th-17 lymphocyte- and neutrophil-related ISMs in patients with moderate-to-severe HS.

3.2. Comparison of inflammatory serum markers among hidradenitis suppurativa patients before and after adalimumab therapy

We started adalimumab treatment at dosages of 40 mg weekly in HS