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Ustekinumab for Behçet's disease

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ABSTRACT

Objective: To evaluate the efficacy and safety of ustekinumab in the treatment of oral ulcers (OU) in patients with Behçet's disease (BD).
Patients and methods: Prospective study including 14 patients [median age of 39 (34; 41) years, with 71% of men] fulfilling criteria of the International Study Group for BD and with active OU resistant to colchicine. Patients received ustekinumab 90 mg (n = 11) or 45 mg (n = 3) subcutaneously at inclusion, at week 4, and every 12 weeks. The primary efficacy endpoint was the proportion of patients with complete response (CR), defined as no oral ulcer, at week 12.
Results: At week 12, 64% were in CR, 21% in partial response and 14% non-responders. The median number of OU decreased from 2 [2; 4] to 1 [0; 1.25] (p = 0.0005) at week 12. Mean change from baseline to week 12 of Behçet's syndrome activity score (BSAS) was 22.8 ± 0.3 (p = 0.01). The median daily corticosteroids dose decreased from 12.5 (10; 16.3) to 5 [5; 10] mg/day (p = 0.02). Three patients reported headaches, leading to discontinuation of ustekinumab in one case. After a median follow-up of 7 [3; 12] months, 10 (71%) patients were still receiving ustekinumab and four (28%) experienced a relapse. Decreased levels of circulating IL-17 and IL-12 [median [IQR]; 3.9 [1.6; 10.6] vs. 29.2 [25.2; 42.7] pg/ml, and 29.4 [23.1; 33.3] vs. 56.1 [51.1; 64.4] pg/ml, p = 0.008 for both] were observed under ustekinumab, respectively.
Conclusion: Ustekinumab seems to be efficient and safe for patient with BD and refractory OU although relapses are frequent.

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1. Introduction

Behçet's disease (BD) is a vasculitis of unknown aetiology characterized by muco-cutaneous, ocular, articular, vascular and central nervous system manifestations [1,2]. Muco-cutaneous lesions of BD include oral ulcers, genital ulcers, and papulopustular and nodular lesions.

Recurrent oral ulcers can be disabling and have a substantial effect on quality of life. First line therapy includes topical measures such as steroid preparations and lidocaine gel. Colchicine is widely used without solid proof of its efficacy [3,4]. Patients with resistant

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muco-cutaneous manifestations can be treated with azathioprine, thalidomide, TNFα antagonists and more recently apremilast [5–8]. However, most of these treatments have limited efficacy and carry potential serious adverse events, including teratogenicity, peripheral neuropathy, and/or bacterial infections [8]. There remains a need for a safe and effective treatment. A new drug effective against oral ulcers (the hallmark lesion of Behcet's syndrome) may be a good candidate for the treatment of other aspects of the disease.

Ustekinumab is a humanized monoclonal antibody against interleukin (IL) 12 and IL-23 [9]. Our group and others have demonstrated the critical role of Th1 and Th17 in the pathogenesis of BD and the correlation of these cytokines with the disease activity [10]. Previous study has shown higher IL-23 in sera of BD patients [11,12]. In patients with BD, peripheral blood Th17/Th1 ratio is significantly higher compared to control [13]. Recently, genome-wide association studies from Japan and Turkey identified an association at IL23R and IL12RB2 loci [14,15]. Taken together, these data provide a strong rationale for the use of ustekinumab in BD [16].

This study aims at assessing the efficacy of ustekinumab in refractory oral ulcers in Behçet's disease.

2. Patients and methods

We conducted an open pilot prospective study in the department of internal medicine and clinical immunology of La Pitié-Salpêtrière university hospital and in the departments of dermatology of La Pitié-Salpêtrière and Tenon university hospital in Paris, France, between 2014 and 2017. All adult patients met the criteria of the International Study Group for Behçet's Disease [17] and had at least one oral ulcer within 28 days before inclusion and at least two oral ulcers at the time of inclusion despite colchicine treatment. Steroids, colchicine and other immunosuppressive therapies were allowed if given at a stable dose over the month prior inclusion. The study was performed according to the Helsinki declaration and all patients gave their informed consent. Demographic features and past medical history of BD were recorded. Number of oral ulcer and other BD manifestations including genital ulcers, skin manifestations, vasculitis, uveitis, joints, vascular and central nervous system manifestations were collected. Disease activity was assessed by Behçet's Syndrome Activity Score (BSAS), a scale on which scores range from 0 to 100, with higher scores indicating more active disease. Clinical parameters, safety assessment, corticosteroids daily dose and laboratory findings were collected at inclusion, at week 4, at week 12 and then every 12 weeks until treatment discontinuation or end of follow-up.

2.1. Design

Patients included were treated with 90 mg of ustekinumab subcutaneously at week 0, week 4, and then every 12 weeks as it is recommended in France for maintenance therapy in Crohn's disease (French Ministry of Health approval, november 2015). Patients #2, #9, and #11 received 45 mg of ustekinumab subcutaneously at week 0, week 4, and then every 12 weeks because of lighter weight (≤55 kg). Colchicine treatment was stopped at the inclusion except for one patient (#11).

2.2. Endpoints

The primary efficacy endpoint was the proportion of patients with complete response at week 12, defined as patients who had no oral ulcer. Secondary endpoints at week 12 included (i) the proportion of patients with a partial response (defined as patients who had a reduction of 50% or more in the number of oral ulcers); (ii) proportion of non-responder (defined as all other patients); (iii) efficacy on other BD manifestations i.e. genital ulcers, pyoderma gangrenosum, pseudo-folliculitis, and articular, ocular, vascular, neurological or gastrointestinal tract involvements; (iv) BSAS score between day 0 and week 12; (v) relapse rate under ustekinumab; (vi) steroids sparing effect of ustekinumab, and (vii) safety, as all adverse events were collected prospectively during the follow-up.

2.3. Immunological analysis

IL-17 and IL-12 levels were measured in BD patients by using Luminex (Invitrogen, Cergy-Pontoise, France) at inclusion (day 0) and at week 12.

2.4. Statistical analysis

Data are presented as a mean (SD) or median [IQR] for continuous variables and as a percentage for qualitative variables. The nonparametric Mann Withney test was used to compare continuous variables. A p value of <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, San Diego, Calif).

3. Results

3.1. Characteristics of BD patients

During the study period, 14 patients (10 men) with a median age of 39 years [34; 41] were included. Main clinical features and outcome are summarized in Tables 1–3, and Fig. 1. All patients had a BD diagnosis with oral ulcers resistant or refractory to colchicine treatment. Some patients have also previously received

Table 1
Main characteristics for the 14 BD patients treated with ustekinumab.

Characteristics	BD patients treated with ustekinumab (n = 14)
Gender, male, n (%)	10 (71.4%)
Age, years, median [IQR]	39 [34; 41]
Previous BD manifestations	
Oral ulcerations, n (%)	14 (100%)
Number of oral ulcerations at baseline, median [IQR]	2 [2; 4]
Genital ulcerations, n (%)	14 (100%)
Pseudo-folliculitis, n (%)	11 (79%)
Pyoderma gangrenosum, n (%)	2 (14%)
Articular manifestations, n (%)	4 (29%)
Central nervous system, n (%)	3 (21%)
Uveitis, n (%)	2 (14%)
Venous thrombosis, n (%)	1 (7%)
BSAS score at inclusion, median [IQR]	39 [30; 65]
Number of previous treatment line, median [IQR]	2 [1.3; 3.8]
Previous BD treatment, n (%)	
Colchicine	14 (100%)
Methotrexate	3 (21%)
Thalidomide	3 (21%)
TNF inhibitor	2 (14%)
Apremilast	2 (14%)
Tocilizumab	2 (14%)
Anakinra	2 (14%)
Others[a]	5 (36%)
Steroids	
Steroids at inclusion, yes, n (%)	8 (57%)
Steroids dose at inclusion, mg/day, median [IQR]	12.5 [10; 16.3]
Follow-up, months, median [IQR]	7 [3; 12]

Definitions of abbreviations: BD: Behçet's disease; BSAS: Behçet's Syndrome Activity Score.
[a] **Others**: azathioprine, mycophenolate mofetil, cyclophosphamide, tacrolimus.

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