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Efficacy of the anti-IL 17 secukinumab in refractory Behçet's syndrome: A preliminary study

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ABSTRACT

Objective: To evaluate the efficacy and safety of secukinumab in Behçet's patients with active mucocutaneous and articular manifestations refractory to previous treatments.

Methods: We retrospectively evaluated 5 patients treated with the IL17-inhibitor secukinumab and diagnosed with Behçet according to ISG/ICBD criteria. All patients had active mucocutaneous and articular manifestations refractory to colchicine, conventional DMARDs and at least one anti-TNFα agent. Four patients received secukinumab in the dose of 150 mg/monthly since also fulfilling the criteria for ankylosing spondylitis, while the fifth patient received secukinumab 300 mg/monthly because she met psoriatic arthritis criteria. Achievement of response was based on the number of oral ulcers, BASDAI and ASDAS for articular involvement, and BDCAF for Behçet activity. Complete response was defined as: i) decrease ≥50% in the number of oral ulcers; ii) BASDAI index < 4; iii) ASDAS index < 1.4; iv) decrease of 50% or more in BDCAF index.

Results: The patient starting secukinumab 300 mg/month successfully achieved complete response within 3 months. Complete response was maintained during all 9-months follow-up. Among the 4 subjects starting secukinumab 150 mg/month, two achieved complete response at month 6, but one relapsed. This patient and the two who not achieved complete response at month 6 were switched to secukinumab 300 mg/month. Within 3 months from the dosage increase, all three subjects successfully (re)achieved complete response.

Conclusion: Our study suggested for the first time that secukinumab (either 150 mg and 300 mg/month) improved active mucocutaneous manifestations refractory to previous treatments, while secukinumab 300 mg/monthly resulted superior in inducing articular and complete response in Behçet's patients.

1. Introduction

Behçet's syndrome (BS) is a systemic vasculitis characterised by different organ involvement as mucocutaneous, articular, ocular, vascular, gastrointestinal and of the central nervous system [1]. However, the hallmark of BS is the muco-cutaneous lesions [2]. In particular, recurrent ulcers, either oral and genital, can be very painful and disabling, with a great worsening of the quality of life [3]. Common therapies for oral ulcers include topical preparations with corticosteroids and anesthetic gel, or systemic drugs. Colchicine is usually the first line treatment, even if its efficacy it is not definitely proved. Second line therapy for resistant mucocutaneous manifestations consists of thalidomide, azathioprine, interferon (IFN)-α and tumor necrosis factor (TNF)-α [4]. More recently, the oral phosphodiesterase-4 inhibitor apremilast proved effective for the treatment of recurrent oral ulcers [5].

Articular manifestations occur in about 30–50% of patients with BS with a prevalence ranging from 11.6% in Turkey to 93% in UK. Common localisations are either large or small joints, such as knees, ankles, wrists and up to 10% of patients with articular involvement complain also inflammatory back pain [6]. Indeed, sacroiliitis and enthesopathy are not rare among BS patients with low back pain [7] and in the past BS was classified among spondyloarthritis [8]. Colchicine is also the first line-treatment for the articular involvement of BS. In refractory patients, azathioprine or biologic treatments (either IFN-α or anti-TNF-α) can be used according to the latest EULAR recommendations [4].

Recently, the IL17 blocking agent secukinumab, has been approved

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for the treatment of psoriatic arthritis (PsA) [9,10] and ankylosing spondylitis (AS) [11]. Interestingly, several clues suggest that BS shares with seronegative spondyloarthritides not only clinical features [7,8], but also a strong pathogenetic background [12]. Moreover, the pivotal role of the IL-17 axis has also been recently demonstrated in BS [13–15].

Furthermore, ustekinumab, a biologic treatment for PsA able to interfere with the IL-23/IL-17 pathway, recently showed to also be effective for treatment of refractory oral ulcers in BS patients [16,17].

Given this pathogenetic and clinical background, this retrospective study aims at evaluating the efficacy and safety of secukinumab on Behçet's patients with active mucocutaneous and articular manifestations refractory to other immunosuppressive treatments.

2. Material and methods

2.1. Study design

From January 2017 to March 2018, a cohort of BS patients that met ISG/ICBD criteria [18] and failed or did not tolerate colchicine, a second line DMARDs and at least one anti TNF-α agent, was treated at our institution with the anti-IL17 secukinumab. Dosage of secukinumab was based on the label dosages approved for AS or PsA, and all the patients underwent a weekly induction regimen [9,11]. Co-administration of methotrexate was permitted.

2.2. Study population

Five female BS patients received secukinumab. Four patients who also met criteria for AS were treated with secukinumab 150 mg/monthly, whereas one patient who met criteria for PsA was treated with 300 mg/monthly.

2.3. Outcome assessment

Patients were followed-up at 3 month' intervals for systemic assessment, according to our routine clinical practice. Achievement of response was assessed based on 1) the decrease in number of oral ulcers, 2) BASDAI and ASDAS scores for the articular involvement, and 3) the BDCAF score for overall BS activity.

Complete response was defined as: i) decrease of 50% or more in the number of oral ulcers; ii) BASDAI index < 4; iii) ASDAS index < 1.4; iv) decrease of 50% or more in the BDCAF index. Partial response was defined as the fulfilment of at least 2 of these criteria, including the decrease in number of oral ulcers. No response was defined as the fulfilment of less than 2 response criteria.

In patients initially treated with secukinumab 150 mg/monthly, increase of the dosage to 300 mg/monthly was considered in case of non-achievement of complete response within 6 months from treatment beginning, or in case of relapse, following the achievement of complete response. Relapse was defined as the change from complete to partial response or to no response, or from partial response to no response.

All adverse events experienced by patients during secukinumab treatment were reported.

3. Results

Baseline demographic and clinical characteristics of patients included in the study are reported in Table 1.

All 5 subjects were women aged between 30 and 62. Three of them were positive for HLA B-51. All patients failed or did not tolerate colchicine, a second line DMARDs treatment, and adalimumab (plus other biologic treatments in two cases).

All subjects had history of recurrent disabling oral ulcers and arthralgia and/or arthritis. One patient (case 1) also had a previous history of scalp psoriasis, thus meeting criteria for psoriatic arthritis and

Table 1
Baseline characteristics of the five Behçet's patients.

ID	Age (years)	Sex	Disease manifestations	ISGB/ICBD criteria	HLA B51	Colchicine (cause for switch)	Second-line DMARD (cause for switch)	Anti TNF-α (cause for switch)	Active mucosal and articular manifestations at baseline	PsA Criteria	AS Criteria	Available Follow-up
1	59	F	Oral aphthosis, pustolosis, monolateral anterior uveitis; gastrointestinal involvement; arthritis of wrists and knees; low back pain and sacroiliitis	Yes	Yes	Yes (failure)	Azathioprine (intolerance)	Adalimumab, Golimumab (+Methotrexate) (loss of efficacy)	Oral aphthosis and arthritis (polyarticular involvement)	Yes	No	9 months
2	62	F	Bipolar aphthosis, pathergy phenomenon, arthritis of hands, wrists, knees, ankles and sacroiliac joint	Yes	Yes	Yes (intolerance)	Methotrexate (intolerance), Salazopyrin (loss of efficacy), Cyclosporine (intolerance)	Adalimumab (loss of efficacy)	Oral ulcers; active arthritis of both ankles and knees with pain and swelling of the joints	No	Yes	12 months
3	48	F	Bipolar aphtosis, recurrent erythema nodosum, pustolosis, recurrent dactylitis of both feet and low back pain with active sacroiliitis	Yes	No	Yes (failure)	Methotrexate, Salazopyrin, and Azathioprine (failure to all 3)	Adalimumab (failure)	Oral ulcers, recurrent dactylitis of feet and low back pain with active sacroiliitis	No	Yes	15 months
4	49	F	Bipolar aphtosis, pseudofolliculitis, erythema nodosum, vascular involvement (two previous deep vein thrombosis episodes), low back pain with sacroiliitis	Yes	No	Yes (loss of efficacy)	Methotrexate (intolerance), Cyclosporine (loss of efficacy)	Adalimumab (loss of efficacy), Etanercept (inefficacy), Golimumab (intolerance)	Sever painful oral ulcers and inflammatory low back pain	No	Yes	6 months
5	30	F	Bipolar aphthosis, pseudofolliculitis and gastrointestinal involvement;	Yes	Yes	Yes (failure)	Azathioprine (intolerance)	Adalimumab (recurrent upper airway infections)	Recurrent oral ulcers, persistent inflammatory	No	Yes	6 months

(continued on next page)

Table 1 (*continued*)

ID	Age (years)	Sex	Disease manifestations	ISGB/ ICBD criteria	HLA B51	Colchicine (cause for switch)	Second-line DMARD (cause for switch)	Anti TNF-α (cause for switch)	Active mucosal and articular manifestations at baseline	PsA Criteria	AS Criteria	Available Follow-up
			inflammatory arthralgias and low back pain with sacroiliitis						arthralgias and low back pain			

was started on secukinumab 300 mg/month. All other subjects met criteria for AS, and were therefore treated with secukinumab 150 mg/month.

Available follow-up period ranged from 6 to 15 months.

Fig. 1 reports therapeutic starting dosage and treatments' adjustment, achievement of response, and score evaluations during secukinumab treatment.

After 3 months of treatment, the patient who started secukinumab 300 mg/month (case 1) discontinued co-treatment with methotrexate due to achievement of complete response. In particular, the number of oral ulcers decreased from 2/month to 0/month, BASDAI score normalised from 4.55 to 3.05, ASDAS normalised from 3.43 to 1.29 and BDCAF score decreased from 7 to 0. Complete response was stably maintained during all 9 months' follow-up.

On the other hand, after 3 months of treatment, none of the 4 patients who started secukinumab 150 mg/month, achieved complete response.

Two patients (case 3 and 5) achieved complete response at the 6th month of follow-up. However, case 3 lost response after 3 months from complete response achievement. This patient was switched to secukinumab 300 mg/month. Within 3 months from the increase in dosage, case 3 successfully re-achieved complete response, with BASDAI score decreasing to 2, ASDAS to 0.94 and BDCAF to 3. Complete response was maintained during all available follow-up.

The other 2 patients (case 2 and 4) switched to secukinumab 300 mg/month because they did not achieve complete response within the first 6 months of secukinumab therapy. In particular, case 2 only reached partial response at the 6th month, whereas case 4 had no response to treatment.

Within 3 months from the increase in dosage, case 2 achieved complete response. Complete response was maintained during all available follow-up period.

In case 4, the follow-up period after the increase of secukinumab dosage was too short to draw a result.

The treatment was generally well tolerated, without any significant drug reaction. Only mild infections of the urinary tract were recorded in two patients, with no fungal infections during the whole observation period.

4. Discussion

Based on our preliminary small data, our study suggests that secukinumab is effective in controlling mucocutaneous and articular manifestations refractory to other immunosuppressant treatments in BS patients. In particular, considering the overall response, as defined in the method section, patients treated with 300 mg/month reached a complete response within 3 months, at any stage of treatment. Conversely, the 150 mg dosage, was able to induce a complete response only within 6 month in one case, and no response in another one.

BS is not a unique entity, and there are several different phenotypes of the disease. Skin, mucosal and joint involvement are frequently associated with a typical relapsing/remitting course [19].

Recently, a small prospective open labelled study has been published on the use of ustekinumab in patients with BS with refractory mucocutaneous manifestations, showing the efficacy of interfering with the IL17 pathway, blocking the IL12/23 axys [17]. Moreover, several studies demonstrated a role of IL-17 in Behçet's pathogenesis [13–15]. Interestingly, IL-17 has been also involved in the pathogenesis of recurrent oral ulcers [20]. This data might partly explain the ability of secukinumab to induce a rapid and sustained resolution of the oral ulcers in our case series. Indeed, in all the patients reported, the number of oral ulcers (independent from the starting dosage), significantly reduced during the treatment with secukinumab.

BS, together with spondyloarthritis, belongs to the so-called MHC-I opathy [12]. Moreover, the IL-17 pathway plays a central role in the pathogenesis of both psoriatic arthritis and ankylosing spondylitis [21]

	Baseline	3 months	6 months	9 months	12 months	15 months
Treatment; achievement of response						
Subject 1	Start Secukinumab 300mg / month + MTX.	Discontinuation of MTX for achievement of complete response	Maintain complete response	Maintain complete response		
Subject 2	Start Secukinumab 150 mg/ month.	No response	Achievement of partial response Switch to Secukinumab 300 mg/ month	Achievement of complete response	Maintain complete response	
Subject 3	Start Secukinumab 150 mg/ month.	No response	Achievement of complete response	Loss of complete response Switch to Secukinumab 300 mg/ month	Re-achievement of complete response	Maintain complete response
Subject 4	Start Secukinumab 150 mg/months	No response	No response Switch to Secukinumab 300 mg/ month			
Subject 5	Start Secukinumab 150 mg/ month + MTX.	Achievement of partial response	**Achievement of complete response** Discontinuation of MTX for achievement of complete response			
Scores						
Subject 1						
Oral ulcers*	2	0	0	0		
BASDAI	4,55	3,05	1,6	1,45		
ASDAS	3,43	1,29	0,79	0,61		
BDCAF	7	0	0	0		
Subject 2						
Oral ulcers*	4	1	1	0	0	
BASDAI	6,2	4,75	4,5	2,35	2,15	
ASDAS	2,52	1,54	1,29	0,86	0,75	
BDCAF	9	7	7	3	3	
Subject 3						
Oral ulcers*	2	1	1	1	0	0
BASDAI	6,4	4.2	2,05	5,3	2	2,2
ASDAS	2,61	2	0,91	3,64	0,94	0,84
BDCAF	8	5	3	7	3	0
Subject 4						
Oral ulcers*	6	1	1			
BASDAI	7	5,25	4,95			
ASDAS	2,6	1,85	1,54			
BDCAF	8	5	5			
Subject 5						
Oral ulcers*	1	0	0			
BASDAI	4,7	2,95	2,75			
ASDAS	2,14	1,45	1,19			
BDCAF	9	6	3			

Fig. 1. Treatment and achievement of responses. *: number of oral ulcers in the last 30 days; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS**: Ankylosing Spondylitis Disease Activity Score; **BDCAF**: Behçet's Disease Current Activity Form. **Light green**: achievement of complete response on Secukinumab 300 mg/month; **Dark green**: achievement of complete response on Secukinumab 150 mg/month; **Yellow**: achievement of partial response; **Red**: No response. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

as well as in BS [13–15]. The 300 mg/month dosage appeared to be superior than 150 mg/month to control both axial and peripheral articular manifestations, since the 3 patients on 300 mg achieved within 3 months the articular remission and maintained it at the following 3–6 month follow up visit, while the 2 patients on 150/month did not. Recently a randomised, double-blind phase 3 clinical trial (MEASURE 3) comparing the efficacy of endovenous secukinumab 300 mg/month vs 150 mg/month in ankylosing spondylitis has been published [22]. Intriguingly, despite an overall response to both regimens, some difference on efficacy emerged, also suggesting that a higher dosage could be more effective for AS. However, since all the patients reported also met the criteria for PsA or AS, the generalisation of these results to BS patients with other articular manifestations, should be further assessed.

Notably, BDCAF significantly improved within 3 months from start of secukinumab 300 mg/month, and stably maintained. Of note, also in 2 out of 4 patients treated with secukinumab 150 mg/month, BDCAF significantly improved within 6 months of treatment. However, given that in our patients no other BS manifestations except mucocutaneous and articular ones were active at time of secukinumab beginning, BDCAF variation is strictly related to the improvement of mucocutaneous and articular involvements.

The main limitations of our study are correlated to its retrospective nature and to the small number of patients observed. However, BS is a rare disease, and despite the great number of available treatments, discontinuation of such therapies for adverse reaction and/or loss of efficacy/inefficacy is not infrequent [23]. Since mucocutaneous and articular involvement are the more frequent manifestations of BS, often with a relapsing/remitting course [24], to have new and safe therapies could be of importance.

Moreover, given the short length of follow-up available for these patients, our preliminary findings on the efficacy and safety of secukinumab in BS need to be revaluated over a longer period, in order to assess both the maintenance of achieved responses and the long-term safety profile.

In addition, our results have some issues that need to be addressed. In particular, some concerns about the efficacy and safety of secukinumab in patients with uveitis [11] and intestinal bowel disease (IBD) [25] have been raised. This could be important in BS, in which ocular and intestinal involvement are frequent and with a great impact in terms of morbidity and mortality [6].

Notably, in our study, only one patient had a previous history of monolateral anterior uveitis. Secukinumab at the dosage of 300 and 150 mg/month did not result effective in BS non-infectious uveitis [26]. However, only intermediate, posterior or panuveitis were treated, while data on anterior uveitis are lacking. More recently, a multicenter, randomised, phase 2 clinical trial demonstrated that endovenous high dose secukinumab was significantly more effective than subcutaneous secukinumab 300 mg, suggesting that the endovenous route could be necessary to reach therapeutic concentrations at ocular level [27]. Notably, in our patient no reactivation of the ocular involvement occurred during the follow-up period.

One of the more important concerns in the use of secukinumab, is the potential exacerbation of intestinal manifestations in patients with IBD [25]. One of our patients also had gastrointestinal involvement, with diarrhoea and abdominal pain, with increase in fecal calprotectin. Intriguingly, fecal calprotectin significantly reduced during treatment with secukinumab 150 mg. Accordingly, our prior study showed that the intestinal mucosa of BS patients is infiltrated by Th17 cells with cytotoxic ability, suggesting a potential benefit of their blockade [13]. However, since safety concerns in IBD for the use of secukinumab are strong, and specific studies on Behçet's patients with intestinal involvement are lacking, some attention must be paid in this setting.

Lastly, despite being generally well tolerated in our BS population, infections, and in particular, upper respiratory tract and *Candida* infections, are commonly reported adverse events during secukinumab therapy [28,29]. Thus, major attention should be paid by clinicians for the prompt treatment of such events."

5. Conclusions

To our knowledge, this is the first report on the efficacy and safety of the anti-IL17 secukinumb for the treatment of mucocutaneous and articular BS manifestations.

Our study suggests that secukinumab (either 150 mg and 300 mg/month) improved active Behçet mucocutaneous manifestations in patients refractory to previous treatments, and secukinumab 300 mg/monthly resulted superior in inducing both articular and complete response.

This preliminary data adds some further evidence on the effectiveness of agents targeting the IL-17 pathway, for the control of mucocutaneous and articular manifestations in BS. However, larger studies specifically addressing the role of secukinumab in Behçet's syndrome are needed to draw solid conclusions.

Informed consent

Informed consent of all patients was obtained.

Declarations of interest

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