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Case Report

CASE REPORT

Secukinumab induced Behçet's syndrome: a report of two cases

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Abstract

Secukinumab is a human monoclonal antibody against IL-17A that has been shown to be effective in psoriasis, psoriatic arthritis and ankylosing spondylitis (AS). On the other hand, in randomized controlled trials among patients with Crohn's disease (CD) and uveitis due to Behçet's syndrome (BS) treated with secukinumab, primary end points were not met and the drug caused more exacerbations compared to placebo. The drug fact sheet states that secukinumab should be used with caution in patients with CD; however, there are no warnings for those with BS. Here, we present two patients with AS treated with secukinumab; we observed exacerbation of BS in one and emergence of *de novo* BS in another. Although IL-17A is thought to contribute to the pathogenesis of BS, our observations suggest that it might have a protective role. Finally, we suggest caution is required with the inhibition of IL-17 in BS.

INTRODUCTION

Secukinumab, a fully human monoclonal antibody against IL-17A, has been shown to be effective in psoriasis, psoriatic arthritis and ankylosing spondylitis (AS) [1–3]. On the other hand, in a randomized controlled trial (RCT) among patients with moderate to severe Crohn's disease (CD), primary end points were not met and secukinumab caused more exacerbations compared to placebo [4]. Emergence of inflammatory bowel disease in one patient with psoriasis and another with AS treated with secukinumab have also been reported [5]. Moreover, secukinumab was reported to be ineffective in controlling non-infectious uveitis as stated in a comprehensive review of three RCTs (ENDURE, INSURE and SHIELD) [6]. Of the three RCTs, only one enrolled patients with Behçet's syndrome (BS) with posterior uveitis or panuveitis (SHIELD study), while non-BS patients with active (INSURE study) or inactive noninfectious uveitis (ENDURE study) were included in two. Secukinumab was ineffective to prevent ocular attacks and also BS-associated clinical manifestations have been observed in SHIELD [6]. After completion of the SHIELD trial, the INSURE trial was terminated early. The ENDURE trial also was terminated early because the primary efficacy end points were not met as shown in prespecified interim data analysis [6]. The licensed product specification states that secukinumab should be used with caution in patients with CD; however, there are no warnings for those with BS. We report here exacerbation of BS in one and emergence of *de novo* BS in another patient treated with secukinumab for AS.

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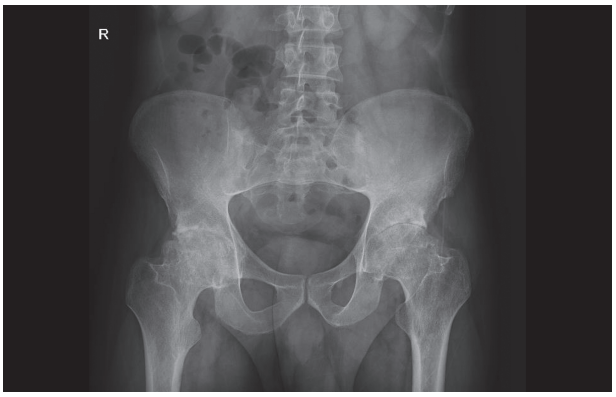

Figure 1: Plain radiography of pelvis in patient 1 disclosing bilateral grade 4 sacroiliitis.

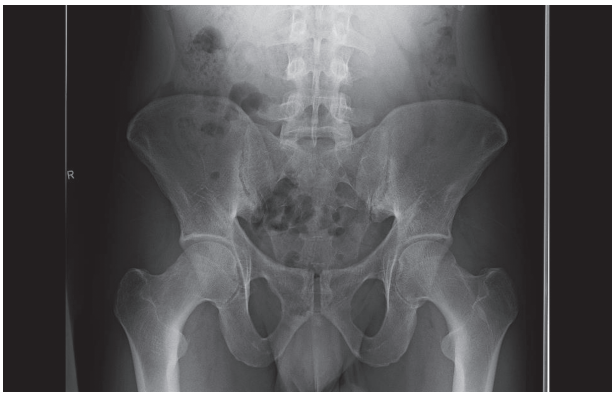

Figure 2: Plain radiography of pelvis in patient 2 showing bilateral grade 3 sacroiliitis.

CASE REPORTS

Patient 1, a 34-year-old man, was diagnosed with AS in 2008 with bilateral grade 4 sacroiliitis on plain radiograph (Fig. 1) and peripheral inflammatory arthritis. He also had BS diagnosed in 2010 with oral and scarring genital ulcers, pathergy positivity, papulopustular lesions and two episodes of deep vein thrombosis in the right and left femoral and popliteal veins. He was positive for both HLA-B27 and HLA-B51. As monoclonal TNFi drugs are reported to be effective also in BS, the patient was initially treated with infliximab for 3 months (BASDAI: 6.3), adalimumab for 6 months that were partially effective for his inflammatory back pain. Then he received etanercept for 4 years, during which time he had no symptoms of AS and BS. He then began to have knee and low back pains with CRP: 70 mg/dl (normal range:0–5) (BASDAI: 5.5). He was switched to secukinumab with loading doses of 150 mg/week. After the fourth dose, he developed multiple oral and genital ulcers, arthritis of the knee with fever (38°C), CRP: 95 mg/dl and ESR: 44 mm/hr. Fecal occult blood test was positive in addition to the presence of fecal leucocytes. Due to the evidence of inflammation in the stool, we decided to do a colonoscopy. It has to be noted that he was asymptomatic for gastrointestinal disease; therefore, he did not have a colonoscopy before. His colonoscopy revealed three ileal deep ulcers of 1 cm diameter, multiple aphthous ulcers from descending colon to rectum. Ileal and colonic biopsies revealed edema with preserved villi (no granuloma) and focal active colitis with lymphoid follicles, increased pericryptal connective tissue, respectively. Secukinumab was stopped; 10 mg/day prednisolone and certolizumab were started. After 1 week of treatment, his symptoms disappeared; the acute phase regressed while back pain continued. He refused to have control colonoscopy as he was clinically well. After 5 months of treatment with certolizumab, he had no symptoms of active AS or BS.

Patient 2, a 29-year-old male, was diagnosed with AS in 2010 with bilateral grade 3 sacroiliitis on plain radiograph (Fig. 2) and peripheral inflammatory arthritis (BASDAI: 6.8). He was positive for HLA-B27 and negative for HLA-B51. He received adalimumab with a partial remission for 2 years, etanercept for 1 year and certolizumab for 6 months, which was stopped due to attacks of anterior uveitis. After partial response of three different TNFi drugs, secukinumab was started with loading doses of 150 mg/week. After the third dose, he began to have fever (38–39°C), high acute phase response (CRP: 96 mg/dl, ESR: 45 mm/hr), multiple oral and genital ulcers, bilateral lower extremity superficial thrombophlebitis and bilateral panuveitis. He was diagnosed with BS. Secukinumab was stopped; three pulses of methylprednisolone and infliximab 5 mg/kg were started. After 1 week of this treatment, he felt better and the acute phase response regressed (CRP: 5 mg/dl, ESR: 37 mm/hr). He is asymptomatic with normal acute phase reactants at fifth month of infliximab.

DISCUSSION

IL-17A is a proinflammatory cytokine mainly produced by Th17 cells [1]. Besides proinflammatory properties, it plays important role in the protection against bacterial and fungal infections at the mucosa [1]. Higher levels of IL-17A have been also found in the peripheral blood of patients with Behçet uveitis and as such it has been considered important in disease mechanisms. However, in the SHIELD study, not only secukinumab was ineffective in controlling uveitis, but the most frequently reported serious adverse events were non-ocular BS exacerbations, uveitis and papulopustular lesions in the secukinumab arm [6].

We observed—to the best of our knowledge for the first time—full blown BS in two patients with AS who were treated with secukinumab. There was exacerbation of BS in one and emergence of *de novo* BS in another patient. Only patient 1 was positive for HLA-B51, which suggested that the exacerbation with secukinumab was not associated with HLA-B51. Both patients presented with fever and high acute phase response, which were highly suggestive for gastrointestinal involvement. In patient 1, evidence for gastrointestinal involvement after secukinumab use was present. Unfortunately, although planned we failed to do a control colonoscopy in the second patient in whom acute phase response decreased immediately after steroids.

For decades, there has been a lumper's attempt to cluster BS with seronegative spondyloarthritides [7]. More recently, the IL-17A pathway was also considered important to tie BS with this group of diseases [8]. Our observation of two patients, the unfruitful experience with secukinumab use in CD [4, 5], a condition with which BS has many shared features, and the findings from the SHIELD study [6] indicate that we should be more cautious in our conclusions about the role of IL-17A in the disease mechanisms of BS. After all, we might even consider it is somewhat protective in BS. BS has a very involved morbid entity, and we maintain splitting rather lumping should be the way forward in deciphering it [7].

CONFLICT OF INTEREST STATEMENT

None of the authors had any financial interest or any conflict of interest with regard to this work.

FUNDING

There was no financial support for this work.

ETHICAL APPROVAL

Ethical approval was not required because of the nature of data collection.

CONSENT

Informed patient consent was obtained from both patients and the documents are available from the authors.

GUARANTOR

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