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A Manifestation of Ulcerative Colitis During Treatment for Severe Plaque Psoriasis with Ixekizumab – A Report of Two Cases and Review of the Literature

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ABSTRACT IL-17 inhibitors belong to the group of the most effective and highly safe biological preparations intended for the treatment of psoriasis, and in the case of secukinumab and ixekizumab, also for the treatment of some immune-mediated inflammatory diseases of the joints. Despite initial expectations, they did not prove to be effective for the treatment of non-specific bowel inflammations (IBD). On the contrary, IBD worsening was reported in some cases where IL-17 inhibitors were used, and registration studies were terminated for this indication. In clinical studies, extensive meta-analyses of IL-17 inhibitor use for psoriasis and joint inflammation indications generally did not demonstrate any statistically significant increase in the risk of de-novo IBD with this type of treatment. Data from real-time practice are mostly similar. The literature describes individual cases with an obvious relation of *de novo* IBD development subsequent to treatment with IL-17 inhibitors in registered indications. The activation of latent, thus far clinically asymptomatic bowel inflammation is usually expected. Therefore, a careful review of medical history focused on bowel problems in personal and family history is necessary before starting therapy with IL-17 inhibitors. We present a similar experience with *de novo* onset of ulcerative colitis in two patients treated for psoriasis with ixekizumab, with associated psoriatic arthritis in one case.

KEY WORDS: psoriasis, ixekizumab, ulcerative colitis

INTRODUCTION

Interleukin 17 (IL-17) is one of the key anti-inflammatory effector cytokines in the pathogenesis of psoriasis. IL-17 consists of six subtypes, including proteins IL-17A-F. The role of proteins IL-17A, F, and E has been most extensively studied so far, while the biological importance of proteins B to D is less known (1). Outputs from clinical studies have shown that the inhibition of IL-17 is a highly effective therapeutic tool in the treatment of psoriasis (2-4). The optimistic conclusions of clinical studies have been subsequently confirmed in clinical practice. The group of IL-17 inhibitors, specifically secukinumab, ixekizumab, and brodalumab, has been classified among the highly effective biological preparations in psoriasis treatment that also have a very good safety profile.

As there is a wealth of information available about the close relationship betweem psoriasis and many other diseases, i.e. its so-called comorbidities, it is logical that therapies for such immunogenetically related diseases often interfere with each other (5-7).

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This is particularly apparent in the group of immune-mediated inflammatory diseases that include psoriatic arthritis (PsA), rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis or non-specific bowel inflammations (IBDs – Inflammatory Bowel Diseases) – Crohn's disease (CD) – and ulcerative colitis (UC). According to the literature, the most common comorbidity of psoriasis from this disease category is PsA, which occurs in different forms in up to 40% of patients with psoriasis (5,7). IBDs constitute a much less common comorbidity of psoriasis, with a most frequently reported prevalence of 1-2% vs 0.4% in the normal population (8).

Given the similar pathogenetic features of the diseases mentioned above, the excellent therapeutic results of IL-17 inhibitors in psoriasis were assumed to be present in the other immune-mediated comorbidities as well. While this assumption has proved true for inflammatory diseases of the joints, specifically for secukinumab and ixekizumab, this was not the case for IBDs (9,10). Studies on IL-17 inhibitor efficacy and safety in IBDs were usually prematurely terminated due to inefficacy or aggravation of Crohn's disease (11,12). For this reason, a history of IBD is a limiting factor for the use of IL-17 inhibitors for other cleared indications. Below we present our own observations concerning the onset of ulcerative colitis in two patients treated with ixekizumab primarily for a severe form of psoriasis, also with associated PsA in one case.

DESCRIPTION OF CASES

The first case was a young 37-year-old man who had been suffering from psoriasis since the age of 17. The patient was not treated for any other general disease and did not have a history of bowel problems, and the family history for IBD was negative. The gradual progression of psoriasis and the transition to a severe form of the disease necessitated the introduction of systemic treatment – the patient received repeated UVB 311-nm full-body phototherapy treatments as well as methotrexate (MTX) and ciclosporin A treatments. None of these systemic treatments

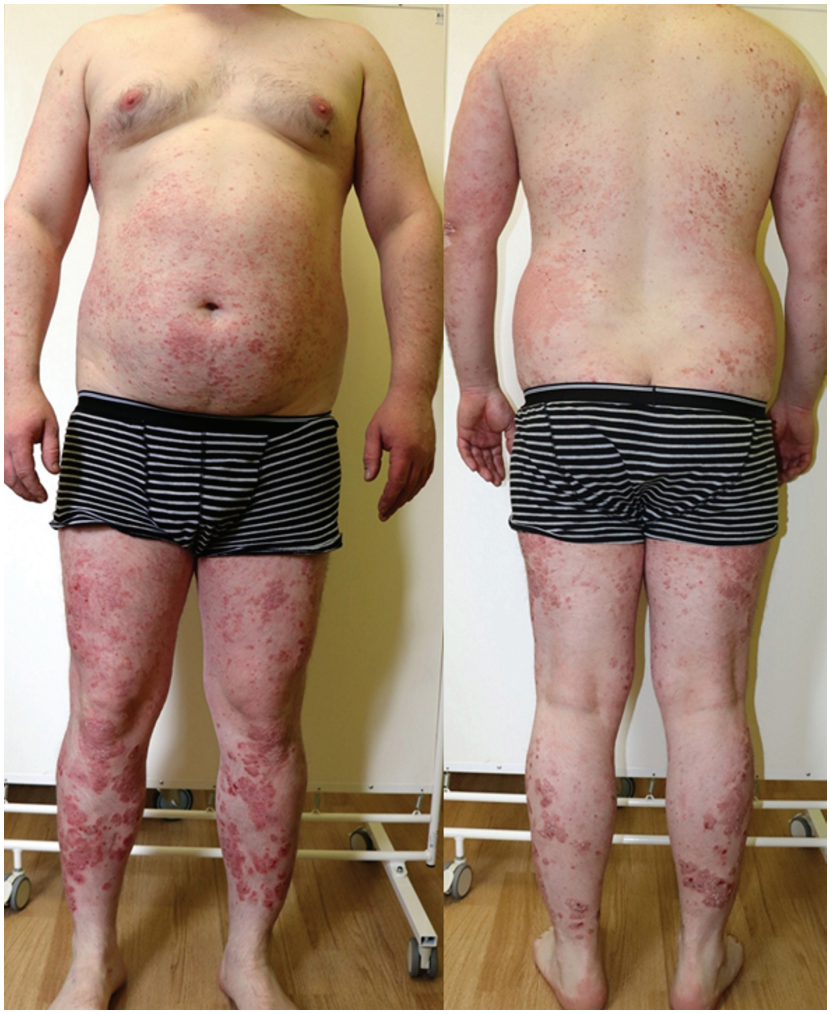

Figure 1. Severe plaque psoriasis before ixekizumab therapy.

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achieved a satisfactory and long-term remission. Consequently, certolizumab pegol treatment was started as a standard therapy in April 2019. However, the effect was insufficient, so the maintenance dose of certolizumab was elevated, accounting for the patient's weight (117 kg), to 400 mg s.c. once every 2 weeks. This treatment adjustment did not achieve sufficient improvement either, and the patient did not meet the criteria for continued therapy. Ixekizumab treatment was therefore started in October 2019, which induced complete disease remission and achieved a PASI 100 response (baseline PASI 24.6, Week 12 PASI 0) (Figure 1, Figure 2). In July 2020, after eight months of ixekizumab therapy, severe bouts of protracted watery diarrhea not responding to probiotic and antibiotic (rifaximin) treatment occurred; the patient lost 13 kg. Colonoscopy and subsequent bowel biopsy confirmed a diagnosis of ulcerative colitis (UC), and mesalazine therapy was started, leading to the remission of ulcerative colitis. Ihe ixekizumab therapy was discontinued immediately after diagnosis of UC. Two months after biological treatment with ixekizumab, psoriasis is still in complete remission. In the event of psoriasis exacerbation and depending on UC activity, the therapeutic plan includes infliximab or ustekinumab therapy in consultation with the gastroenterologist, or alternatively also IL-23 inhibitors guselkumab and risankizumab.

The second patient was a 56-year-old woman who developed the first signs of psoriasis 6 years ago with a predilection for the limbs, concurrently affecting the nails in the form of pits and oil spots. The problems gradually escalated, and external therapy ceased to be effective. Therefore, the patient received repeated UVB 311-nm full-body phototherapy treatments, with partial and short-term effect only. Subsequent acitretin therapy was not very effective either and was poorly tolerated. Three years ago, joint problems appeared in the form of synovitis and dactylitis of small hand joints, fitting into the clinical picture of PsA. MTX therapy was thus started in cooperation with the rheumatologist, with a mitigation of the laboratory activity of PsA and a partial regression of psoriasis. However, the effect of treatment was becoming

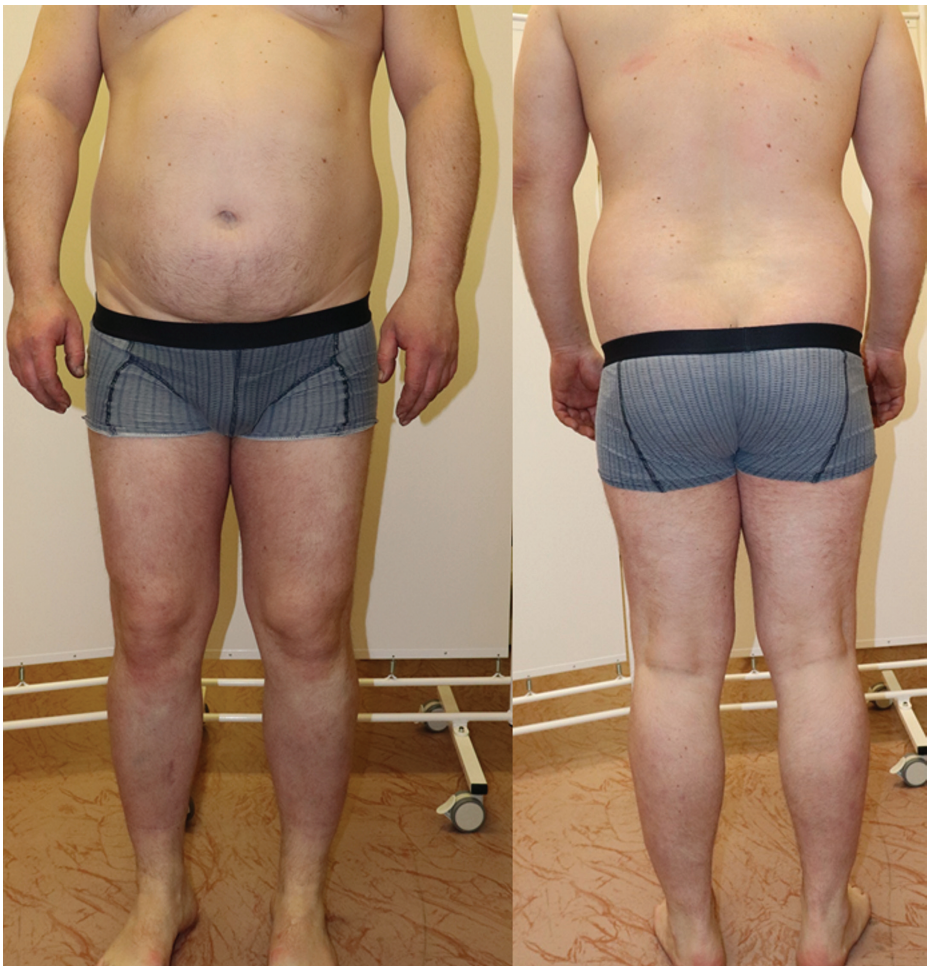

Figure 2. Week 12 of ixekizumab therapy – complete remission of psoriasis.

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weaker over time, with skin problems being in particularly prominent, and even MTX dose escalation to 20 mg once per week did not lead to a satisfactory remission of psoriasis. Therefore, biological treatment with adalimumab began in November 2018, which was discontinued after 12 weeks due to very little effect, and the patient was switched to ixekizumab. A complete remission of psoriasis in the form of PASI 100 (baseline PASI 13.6, Week 12 PASI 0) was induced in the 16th week of ixekizumab treatment; the joint condition was stabilized without manifestations of synovitis. The 20 mg MTX treatment once per week indicated by the rheumatologist was retained. In January 2020, severe bouts of diarrhea occurred at about week 72 of ixekizumab treatment, with blood also being temporarily present in the stool. Her general practitioner prescribed antibiotic (rifaximin) and probiotic treatment. After temporary mitigation of the bowel problems, the bouts of diarrhea became severe again and persisted regardless of the established treatment. Colonoscopy and biopsy were indicated and confirmed ulcerative colitis. The ixekizumab therapy was discontinued immediately after diagnosis of UC. The gastroenterologist started mesalazine therapy, which mitigated the bowel problems. 12 weeks after ixekizumab discontinuation, the patient is still in full remission of psoriasis and the PsA activity is also minimal, with 20 mg of MTX monotherapy once per week. In case of psoriasis or PsA, the therapeutic plan includes, as in the previous case, starting the biological treatment with infliximab or alternatively ustekinumab, guselkumab, or risankizumab depending on UC activity if the treatment fails.

DISCUSSION AND CONCLUSION

The benefit of IL-17 inhibitors in psoriasis therapy (secukinumab, ixekizumab, brodalumab), or PsA therapy (secukinumab, ixekizumab) in ankylosing spondylitis and axial spondyloarthritis (secukinumab) is beyond question. What is under discussion is the role of these preparations in relation to non-specific bowel inflammations. Clinical studies did not confirm the original assumption that IL-17 inhibition could have the same favorable therapeutic effect on IBD as it has on the diagnoses above. On the contrary, clinical trials were in most cases prematurely discontinued for inefficacy, and there were also cases of IBD aggravation (11,12). Subsequently, reports from clinical practice usually describing individual cases or small series of cases of IBD outbreaks, most commonly during secukinumab or ixekizumab treatment, started to be published in the literature. In their review article, Fieldhouse *et al.* (13) provide an overview and analysis of each report. The highest number of cases of IBD outbreak was described during secukinumab therapy, which logically corresponds to its longest use in clinical practice, widest spectrum of indications, and thus the highest number of patients treated. With regards to the mechanism of action, secukinumab seems to be the least risky from the group of IL-17 inhibitors because ixekizumab, with its humanised molecule structure, has a higher affinity to IL-17 and so the inhibition of IL-17 is apparently somewhat more intense (1,4). In the case of brodalumab, the inhibition of the IL-17 receptor results in a complete blockade of all subtypes of this cytokine (1,13). These nuances in the structure of each preparation are also reflected in dermatological practice, as ixekizumab or brodalumab therapy is very likely to be effective after secukinumab failure. Similarly, cases of successful brodalumab treatment have been reported after ixekizumab treatment (14). This is probably the reason why practically no cases of IBD outbreak during psoriasis treatment with brodalumab have been reported, as it has been in use for a much shorter time and in fewer patients, rather than brodalumab being a trouble-free option for IBD from amongst the IL-17 inhibitors.

There is a disagreement as to the contribution of IL-17 inhibitors to IBD outbreaks, which is documented by the analyses. It seems obvious that suppression of the protective action of IL-17 on the intestinal mucosa may induce a clinical manifestation of IBD in predisposed patients (15-18). Both cases described herein had a primary manifestation of ulcerative colitis with no prior history of bowel problems and no positive family history of IBD. On the other hand, these are the first two patients with this complication from a total of about 90 patients treated with IL-17 inhibitors at our site in the last 5 years. In addition, a *de novo* IBD flare-up was observed in one patient with Crohn's disease treated with etanercept for a severe form of psoriasis and in one patient with ulcerative colitis treated with ustekinumab (19).

Increased prevalence of IBD in patients with psoriasis as compared with the normal population should therefore be considered, as well as the fact that IBD manifestations may also occur during treatment with biological preparations from other groups. This may be caused by primary inefficacy of the biological drug in the IBD indication, different dosages for psoriasis and IBD, loss of preparation efficacy due to the formation of neutralizing antibodies, or also a paradoxical drug reaction (19,20). To date, documented cases of *de novo* IBD outbreaks in IL-17 inhibitor therapy from real-life practice are rare, and the conclusions of the analyses differ as to whether or not the risk of this complication is increased (13,21-23). Based on the

outputs of clinical studies, we are in favor of a certain level of potential risk in predisposed patients. Based on our experience, however, we can assess the real risk as relatively low and evaluate the safety profile of the entire group of IL-17 inhibitors as very good. As has been also suggested by other authors, we recommend carefully reviewing personal and family history focused on bowel problems before starting psoriasis therapy with IL-17 inhibitors, and we currently see this measure as sufficient. In case of suspected history, it is advisable to prefer a biological preparation from the group of TNF-alpha (adalimumab, infliximab), IL 12/23 (ustekinumab), and IL 23 (guselkumab, risankizumab) inhibitors in patients with psoriasis. Given the well-known good therapeutic results (adalimumab, infliximab, ustekinumab), or potential expectations (guselkumab, risankizumab), the risk of IBD outbreak with this category of preparations is minimal, but is not zero, as our experience shows.

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