



Is Psoriasis Treatment a Risk Factor for Inflammatory Bowel Disease?

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Abstract

Inflammatory bowel diseases—ulcerative colitis and Crohn’s disease—are linked with several environmental and genetic risk factors. There are also known drugs able to induce de novo disease or to exacerbate its course. Several autoimmune disorders are more frequent in patients with inflammatory bowel diseases, including psoriasis. The aim of the presented review was to summarise current knowledge on the links between psoriasis therapy and inflammatory bowel diseases. The interleukin-17 inhibitors (secukinumab, brodalumab and ixekizumab) and tumour necrosis factor inhibitor (etanercept), have the potential to induce ulcerative colitis and Crohn’s disease de novo or exacerbate existing but silent diseases. There is no evidence that other biologic agents used in psoriasis are lined with such risk. The biologic drugs for psoriasis differ in their potential to induce or worsen inflammatory bowel diseases. Currently, there are no recommendations in European guidelines to screen patients with psoriasis for inflammatory bowel diseases. However, based on available evidence, inflammatory bowel diseases should not be forgotten on in-depth diagnostics in patients with psoriasis.

Key Points

The biologic drugs for psoriasis differ in their potential to induce or worsen inflammatory bowel diseases.

The interleukin-17 inhibitors and etanercept have the potential to induce ulcerative colitis and Crohn’s disease de novo or exacerbate existing but silent diseases.

1 Introduction

The European Crohn’s and Colitis Organisation (ECCO 2016) list the following environmental risk factors as being associated with ulcerative colitis (UC) and Crohn’s disease (CD): delivery by caesarean section (it is explained that caesarean section isolates foetus from maternal microbiota on delivery), small family size, being the older sibling, no breastfeeding, high animal fat and animal proteins

consumption, food additives, low fibre diet, smoking, dysbiosis, urban air pollution, white-collar and sedentary occupations, and moving to areas with a high incidence of inflammatory bowel diseases (IBD) [1]. Drugs that are associated with incidence of IBD are non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of aspirin, oral contraception and antibiotics. Exposure to antibiotics (metronidazole, fluoroquinolones, broad-spectrum penicillin, tetracyclines, cephalosporins, macrolides, sulphonamides) is claimed to be a risk factor of IBD, especially CD, and this association is stronger in paediatric-onset IBD [1, 2].

Up to 50% of patients with IBD experience at least one extra-intestinal manifestation (EIM) of the disease, particularly, spondyloarthritis, osteoporosis, eye disorders (e.g. episcleritis, uveitis and scleritis), erythema nodosum, pyoderma gangrenosum, Sweet’s syndrome, psoriasis, primary sclerosing cholangitis, non-alcoholic fatty liver disease, portal vein thrombosis and granulomatous hepatitis [3].

2 Inflammatory Bowel Diseases and Psoriasis

There are several pathophysiological links between psoriasis and IBD. Elevated concentrations of cytokines in serum and tissues (i.e. tumour necrosis factor [TNF], interleukin [IL]-12 and IL-23) are present both in psoriasis and IBD,

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and agents that inhibit their action often improve both conditions. Approximately 15% of patients with IBS are diagnosed with cutaneous EIM of IBD [4].

Psoriasis affects approximately 10% of general population and may be characterised by the involvement of several organs, leading to arthritis, cardiovascular diseases, chronic kidney disease, diabetes and metabolic syndrome, the so-called 'psoriatic march'.

The incidence of IBD is higher in populations with psoriasis, psoriatic arthritis and ankylosing spondylitis (AS) [5–7]. The risk of UC in psoriatic patients is 1.6-times higher than in the general population [8]. There are several hypothetic explanations for this phenomena including genetic predisposition or environmental factors with growing evidence for the deleterious role of T helper (Th) 17 cells in IBD and psoriasis [9]. Psoriasis is more frequent in patients with CD; in a study by Lee et al., psoriasis was present in 9.6% patients with CD compared to 2% controls, and patients with CD were more likely to have a first-degree relative with psoriasis (10% vs 3%, respectively) [10]. Systemic inflammation is responsible for the severity and chronicity of psoriasis, as well as for the development of concomitant diseases, e.g. cardiovascular diseases or metabolic syndrome.

First-line treatments for psoriasis comprise phototherapy, methotrexate, retinoids and cyclosporine A. Where conventional therapy is ineffective, second-line drugs are used, such as TNF inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol), anti-IL-12/IL-23 antibody (ustekinumab), anti-IL-17 antibodies (secukinumab and ixekizumab), anti-IL-17 receptor antibody (brodalumab) and the anti-IL-23/IL-39 antibodies (guselkumab and tildrakizumab).

3 Interleukin-17 Inhibitors

Compared to the general population, patients with CD have a 7-times higher risk of developing psoriasis [11]. On the other hand, patients with psoriasis have a 2.9-times higher risk of developing CD [12]. Th1, Th17 and regulatory T cells induce cytokine pathways mediated by TNF, IL-1, IL-12/23 and IL-6 that can affect the intestine, joints, metabolic pathways and the cardiovascular system [13]. IL-17 is a pro-inflammatory protein whose expression is induced by the differentiation of naïve CD4-positive T cells into Th17 [14]. IL-17A plays a role in the recruitment of neutrophils, host defence and pathology of autoimmunology and inflammation. Moreover, IL-17 plays a role in numerous immune-mediated disorders, such as rheumatoid arthritis, CD, multiple sclerosis and autoimmune encephalomyelitis [15]. Anti-IL-17 therapies (ustekinumab, ixekizumab and brodalumab) are used in moderate-to-severe psoriasis. It was observed that anti-IL-17 antibodies are linked with the risk

of IBD [16, 17]. Whitlock et al. from the Medical Board of the National Psoriasis Foundation performed a systematic review of 132 articles on psoriasis treatment and showed that secukinumab, brodalumab, and ixekizumab have demonstrated efficacy in psoriasis and psoriatic arthritis but may exacerbate or induce IBD [18].

Improper regulation of immunological response is one of the proposed backgrounds for IBD development. It has been stated that IL-17, as a cytokine, may play an important role in IBD pathogenesis [19]. IL-17A was found to be increased in the intestinal mucosa in patients with CD, therefore, was treated as a potential target of immunotherapy. However, it was found to be ineffective and resulted in high rates of adverse events [16].

The role of IL-17 in IBD is still controversial. Murine models suggest a protective role against IBD; however, human studies showed no efficacy of IL-17 antagonists in CD [20]. Some agents used in psoriasis treatment, e.g. brodalumab were proved to worsen the course of CD [21]. Other studies demonstrated the triggering potential of ixekizumab for UC [22]. Over 15 years ago, Ogawa et al. showed that a neutralising IL-17 monoclonal antibody exacerbated colitis in mice via increases in CD4-positive helper T cells and CD11b-positive granulocytes, monocytes infiltration and an increase in TNF- α , interferon-gamma and IL-6 [23]. However, several studies showed dichotomy of IL-17 inhibition in patients with psoriasis for IBD exacerbation and reduction [23–25]. Psoriasis is associated with CD and UC, therefore, incidence of this condition in psoriatic patients may be more frequent [26]. Skin and intestinal epithelium is affected by IL-17 in both enhancing antimicrobial defence and cellular strength, and interconnections. Blockade of IL-17 has positive effects in repairing tissue damage in psoriasis; however, may increase epithelium damage in IBD [27]. Several studies reported diarrhoea as a relatively common adverse event, and it is difficult to conclude if all these cases should be investigated for IBD; severe episodes are obvious and easier to follow. Clinicians should be watchful before prescribing IL-17 antagonists, especially in patients with IBD, and therefore patients with IBD receiving IL-17 antagonists should be monitored for symptoms of exacerbation.

3.1 Secukinumab

The fully human monoclonal antibody, secukinumab, is an IL-17A antagonist used in psoriasis and AS. Recently, observations of IBD onset have been reported after secukinumab infusion and evidence is evolving [28].

Schreiber et al. analysed pooled data from 21 clinical trials of 7355 patients with psoriasis, psoriatic arthritis and AS treated with secukinumab [29]. Of the 5181 analysed patients with psoriasis, there were 14 new cases of UC,

five cases of CD and 1 case of unclassified IBD (IBDU). Among 1380 patients with psoriatic arthritis, there were 7 patients with new-onset IBD, and among 794 patients with AS, there were nine cases of new-onset IBD. Using Good Vigilance Practice terminology, the authors concluded that the frequency of IBD event in this group was uncommon (<1%) and that exposure-adjusted incidence rates of IBD did not increase over time with secukinumab. A history of IBD was not an exclusion criterion in the secukinumab trials; however, patients were excluded from the ankylosis spondylitis studies if they had active IBD or from the psoriasis and psoriatic arthritis studies if they had active ongoing inflammatory diseases. Moreover, all IBD-related assessments were based on each physician's clinical judgement, and no specific diagnostic procedures or criteria were mandated. A similar conclusion was made by Yamada et al. after a meta-analysis of 38 randomised controlled trials (RCTs) including 16,690 patients treated with anti-IL-17 agents (brodalumab, ixekizumab and secukinumab); however, as the authors stated, interpretation of the results needs caution due to the presence of many zero-event studies [30]. Other Phase 2 or 3 RCTs also did not mention new onset of IBD or IBD exacerbation among the most common side effects [31, 32]. A review of three RCTs showed that secukinumab should be used with prudence in patients with active IBD; however, no new cases of CD and UC were reported in these trials [33]. A pooled analysis of 10 Phase 2 or 3 trials involving 3430 patients treated over 52 weeks showed that exposure-adjusted incidence rates were 0.11 and 0.15 per 100 patient-years for CD and UC, respectively, whereas for etanercept it was 0.34 per 100 patient-years [34]. In Fries et al. survey study of 434 patients treated with secukinumab for 48 months, approximately 1% developed new-onset IBD [35]. In 2020, Lee et al. reported a case of patient with UC treated with a maintenance dose of mesalazine who developed severe UC exacerbation after 3 months of therapy with secukinumab for psoriasis [36]. Moreover, Lee et al. reported a case of patient without IBD history, who developed CD after introduction of secukinumab for AS.

In 2018, the European Medicines Agency (EMA) changed the product information for secukinumab (variation) by adding a warning on IBD. In 2019, with growing evidence, the EMA added 'inflammatory bowel disease' to the adverse drug reactions (ADRs) of secukinumab, with a frequency of 'uncommon'.

3.2 Brodalumab

Brodalumab is a fully human anti-IL-17 receptor A monoclonal antibody. It was approved for the treatment of moderate-to-severe psoriasis if other biological therapies fail. In patients who had previously received ustekinumab, Puig et al. assessed exposure-adjusted treatment-emergent

adverse events over 120 weeks' treatment with brodalumab [37]. Puig et al. showed similar rates of serious adverse events and adverse events leading to discontinuation in patients who received brodalumab 210 mg every 2 weeks, continuous brodalumab 210 mg every 2 weeks or any dose of brodalumab. The authors did not mention new cases of IBD or the proportion with IBD in each group. The most frequently reported treatment-emergent adverse events related to brodalumab were arthralgia, headache, diarrhoea, oropharyngeal pain, and *Candida* infections. Similar results were observed in a previous Phase 2 trial by Umezawa et al. [38]. In other Phase 3 trials, there was one case of new-onset CD reported from 1567 patients [39, 40]. Whereas, no cases of IBD were reported in an open-label multicentre Phase 3 study by Yamasaki et al. where active IBD was not an exclusion criterion [41]. In 2020 EMA recommended variation of the product information of brodalumab in order to add information on IBD risk.

3.3 Ixekizumab

Ixekizumab is a selective monoclonal antibody targeting IL-17A, which is approved for the treatment of chronic plaque psoriasis. In a Phase 3 trial, ixekizumab showed potential for triggering new-onset IBD [22]. In 2018, there was also a report of a case of severe new-onset UC complicated with *Clostridioides difficile* and cytomegalovirus infections after ixekizumab administration [42]. In a meta-analysis of 7 RCTs, 19 patients of 4209 treated with ixekizumab were considered to have definite or probable IBD, and 12 were reported to have UC. In a Phase 3 trial of 91 patients with psoriasis, no cases of new-onset IBD were reported [43]. Another Phase 3 trial showed no new cases of IBD in patients taking ixekizumab in a 24-week observation period; however, one case of anal abscess was reported, which may be consistent with IBD [44]. In a Phase 3 trial comparing ixekizumab with etanercept or placebo for psoriasis, one patient developed exacerbation of previously diagnosed UC, and one had a new-onset CD [45]. Another case of Crohn's-like colitis was reported in a patient receiving ixekizumab for chronic plaque psoriasis [46]. After review of available data, recommendation to update product information for ixekizumab to inform patients and healthcare professionals about the IBD risk has been issued by EMA.

4 TNF Inhibitors

TNF inhibitors are drugs used in inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, IBD, AS and psoriasis. They reduce inflammation and can stop disease progression by targeting inflammation-causing TNF. In psoriasis, etanercept, infliximab,

adalimumab and certolizumab pegol are used, whereas in IBD, infliximab, adalimumab and golimumab are registered.

The anti-TNF antibodies, infliximab, adalimumab and certolizumab used to treat IBD are claimed to increase the risk induction or recurrence of psoriasis or psoriasiform skin lesions in children [47]. Bae et al. suggested that TNF inhibitors used in adult patients with IBD may increase the risk of psoriasis, especially palmoplantar pustulosis [48], meanwhile the opposite effect, i.e. increased risk of IBD in patients treated with etanercept for psoriasis is convincingly documented. According to Wendling et al. who proposed new-onset IBD as a possible adverse drug reaction to TNF inhibition, etanercept was reported most frequently; however, it is not indicated for IBD treatment [49]. Tolu et al. reported a case of a 29-year-old male with AS who developed CD taking etanercept; after treatment interruption and a switch to adalimumab, a prompt improvement of the gastrointestinal symptoms was achieved [50]. This case report indicated the immune dysregulation and proinflammatory effects of etanercept. O'Toole et al. analysed cases of IBD reported with etanercept between 2003 and 2014 in the Food and Drug Administration Adverse Event Reporting System and in a Research Patient Database Registry at the Brigham and Women's Hospital between 1998 and 2014. In total, 443 cases (297 CD, 146 UC) of new-onset IBD were identified that were associated with etanercept therapy [51]. From data pooled from 49 complete cases, etanercept was discontinued in 34 patients, 19 required a change to another anti-TNF agent, 8 improved on discontinuation of etanercept and, in three patients, etanercept was continued combined with 5-aminosalicylic acid therapy. However, data were inadequate to assess causality fully because a direct relationship between the initiation of etanercept and IBD diagnosis was not explicit.

Toussirot et al. investigated 16 cases of new-onset IBD in patients with inflammatory rheumatic disease receiving anti-TNF therapy: 14 patients received etanercept and 2 infliximab [52]. All patients improved after interruption of the etanercept treatment and after a switch to infliximab or adalimumab. In 2019, Korzenik et al. published data from a nationwide cohort study based on Danish health registries concerning patients who utilised TNF inhibitors for other indications than IBD [53]. Korzenik et al. included 17,018 individuals with autoimmune diseases who were exposed to TNF inhibitors and 63,308 controls. They showed that patients treated with etanercept had an increased risk of CD and UC, compared to those receiving infliximab and adalimumab [53].

Other TNF inhibitors used in psoriasis (adalimumab, infliximab, certolizumab pegol) showed no increases in IBD risk [18]. Adalimumab and infliximab are registered agents in IBD treatment. There is a biotechnological difference between etanercept and other TNF inhibitors. Etanercept is

an artificially engineered dimeric fusion protein – a combination of two naturally occurring soluble human TNF receptors linked to an Fc portion of an IgG1 acting as a trap for TNF (TNFR₂/IgG₁). Other TNF inhibitors (adalimumab, infliximab, golimumab) are monoclonal antibodies (combination of fragment antigen binding [Fab] linked to Fc portion of an IgG). Adalimumab and infliximab are in the form of naturally occurring antibodies and are capable of neutralising all forms of TNF (extracellular, transmembrane, and bound to the receptor). Etanercept as a receptor-construct fusion protein cannot neutralise receptor-bound TNF. Moreover, adalimumab and infliximab, but not etanercept, have the capability of lysing cells involved in the inflammatory process. It is not clearly stated whether this biotechnological dissimilarity of etanercept may result in a potential to exacerbate IBD.

In 2019, the EMA updated the product information of etanercept adding IBD to the ADRs list with a frequency of 'uncommon'.

5 Conclusions

Targeted anti-IL-17 drugs as well as the anti-TNF drug etanercept may increase the risk of IBD in patients with psoriasis. Currently, there is no evidence that other biological drugs used in psoriasis, the anti-IL-23/IL-39 antibodies (guselkumab, tildrakizumab, risankizumab) and anti-IL-12/IL-23 inhibitor (ustekinumab), induce or worsen IBD. There are no recommendations in European guidelines to screen patients with psoriasis for IBD. However, based on available evidence, IBD should not be forgotten on in-depth diagnostics in patients with psoriasis.

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Compliance with Ethical Standards

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