A case of new onset ulcerative colitis following secukinumab treatment

Introduction

A 27-year-old man presented to the emergency department with rectal bleeding 4 months after starting secukinumab for ankylosing spondylitis. He was diagnosed with ulcerative colitis. He was started on intravenous hydrocortisone, secukinumab was stopped, and infliximab was started. He improved clinically and was discharged from hospital, but went on to have further flare-ups.

Secukinumab is a recombinant human monoclonal antibody that selectively binds to the cytokine interleukin-17A (IL-17A); it was associated with exacerbations and new onset cases of inflammatory bowel disease in trials for ankylosing spondylitis. There has been debate in the literature as to whether this simply reflects the increased prevalence of inflammatory bowel disease in patients with spondyloarthropathies.

Discussion

Secukinumab is a recombinant human monoclonal antibody that selectively binds to the cytokine IL-17A, inhibiting the release of inflammatory cytokines. It is indicated for use in psoriatic arthritis, ankylosing spondylitis and plaque psoriasis (Joint Formulary Committee, 2018). IL-17A, part of the IL-17 family, is a pro-inflammatory cytokine produced by T-helper 17 (Th17) cells (Blair and Dhillon, 2016).

Secukinumab was associated with exacerbations and new onset cases of inflammatory bowel disease in trials for ankylosing spondylitis (Novartis Pharmaceuticals Corporation, 2018). There has been discussion in the literature around whether secukinumab truly increases the risk of developing inflammatory bowel disease, or whether the development of inflammatory bowel disease reflects the increased prevalence of the disease in patients with spondyloarthropathies. Bergman et al (2018) reported that the incidence of ulcerative colitis in patients with ankylosing spondylitis is 0.8% per year. However, Schreiber et al (2019) reported that cases of inflammatory bowel disease were uncommon in patients with spondyloarthropathies treated with secukinumab. Reporting such cases is therefore important.

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CASE REPORT

A 22-year-old man was referred to the rheumatology clinic in 2013. He had a 4-year history of symmetrical polyarthritis involving the knees, elbows and wrists, and had also developed spinal stiffness, especially in the neck and lower back. He was experiencing early morning stiffness. He had no history of psoriasis, colitis or iritis. He had loss of the normal lumbar lordosis, an accentuation of the cervical lordosis and mild bilateral knee effusions.

He was diagnosed with severe ankylosing spondylitis with peripheral arthritis. The intention was to start biologic therapy, but the patient initially did not engage with follow up, and therefore remained reliant on steroids.

Three years later, the patient re-presented and had markedly deteriorated. Biologic therapy with etanercept was commenced. The patient initially had a good response to this, but then developed secondary loss of efficacy. Biologic therapy was changed to adalimumab, but this showed lack of effect. Secukinumab was therefore commenced.

In 2018, at the age of 27 years, 4 months after starting secukinumab, the patient presented to the emergency department with rectal bleeding. This had been ongoing for 1 month, but was increasing in frequency, and he was currently having six episodes per day. There was some associated mucus per rectum, and occasional lower abdominal pain. There was no family history of inflammatory bowel disease. The patient smoked 15 cigarettes per day. The patient was tachycardic (heart rate 123 beats/minute) and pyrexic (39.2ºC). His abdomen was soft and non-tender. Digital rectal examination showed an empty rectum, no masses and bright red blood. His white cell count was 15.4 x10^9/litre, and his C-reactive protein level was 111 mg/litre. Cytomegalovirus polymerase chain reaction and stool microbiology tests were negative.

A computed tomography scan of the abdomen and pelvis with contrast showed appearances consistent with proctitis and distal sigmoid colitis. Flexible sigmoidoscopy showed inflamed and ulcerated mucosa. Histological examination of biopsies showed a marked acute colitis with ulceration and crypt abscess formation, in keeping with ulcerative colitis.

The patient was started on intravenous fluids, piperacillin/tazobactam, oral mesalazine, steroid enemas and intravenous hydrocortisone.

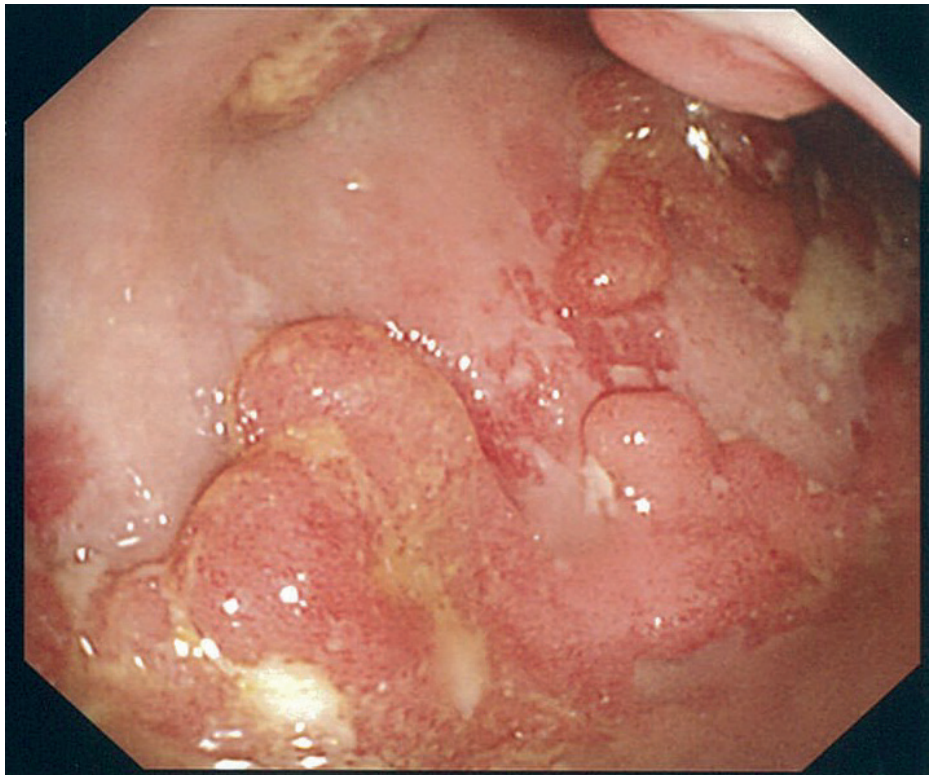
The patient's inflammatory markers remained elevated. Repeat computed tomography showed deterioration in the appearance of the distal large bowel, with further bowel wall thickening involving the descending colon, proximal sigmoid colon and rectum.

Following discussion with the rheumatology team, secukinumab was stopped and the patient was started on infliximab. The frequency of rectal bleeding reduced and inflammatory markers settled. The patient was changed from intravenous hydrocortisone to oral prednisolone and discharged.

A repeat colonoscopy was carried out 2 months after his initial hospital admission. The mucosa was granular, congested and erythematous with mucopurulent exudate, with confluent ulceration, in keeping with severe colitis (*Figure 1*).

The patient went on to have further hospital admissions with flare-ups of his ulcerative colitis requiring intravenous hydrocortisone. His dose of infliximab was increased, and he was subsequently also started on azathioprine.

Figure 1. Photograph of sigmoid colon from colonoscopy, showing multiple ulcers and moderate inflammation, in keeping with ulcerative colitis.



LEARNING POINTS

- The published literature contains only a very small number of case reports of possible new onset or exacerbation of inflammatory bowel disease in patients treated with secukinumab. This case report provides valuable further evidence of a potential association.
- Patients commenced on secukinumab should be monitored carefully for the development or worsening of inflammatory bowel disease.
- The potential risks and benefits of treatment with secukinumab should be carefully considered before it is started.
- Potential adverse effects of medication which are disputed in the literature should be reported to add to the published knowledge base.
- Interleukin-17 (IL-17) may exert a protective effect in the intestine, potentially by its effect on the fungal microbiome or by promoting epithelial integrity.

As IL-17A has a pro-inflammatory role in ankylosing spondylitis, there has been debate about why secukinumab may increase the risk of developing inflammatory bowel disease.

Hueber et al (2012) showed that secukinumab was ineffective in the treatment of Crohn's disease and was associated with a greater incidence of adverse effects than placebo. Brodalumab, a human anti-IL-17 receptor monoclonal antibody, caused worsening of Crohn's disease (Targan et al, 2016).

Marwaha et al (2012) suggest that Th17 cells can exert protective or pro-inflammatory effects, depending on their environment. O'Connor et al (2009) suggest an environment-specific protective function for IL-17 in the intestine.

Targan et al (2016) report that regulatory Th17 cells, a subset of Th17 cells, have anti-inflammatory properties, and that anti-IL-17 treatment may prevent their migration and development.

IL-17 may therefore exert a protective effect in the intestine. Wang et al (2018) suggest that inhibiting IL-17 could alter the intestinal fungal microbiome, predisposing certain individuals to developing inflammatory bowel disease. Furthermore, anti-IL-17 treatment may reduce intestinal epithelial integrity, causing leakage of micro-organisms and inflammation (Targan et al, 2016). **BJHM**

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