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**Single Case**

# Risankizumab and Certolizumab Pegol Dual-Targeted Therapy for Crohn's Disease and Axial Spondyloarthritis: A Case Report

Anouk Lehmann[a] Juerg Vosbeck[b] Diego Kyburz[c] Petr Hruz[a]
Jan Hendrik Niess[a, d]

[a]Department of Gastroenterology and Hepatology, University Digestive Healthcare Center, Clarunis, Basel, Switzerland; [b]Institute for Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland; [c]Department of Rheumatology, University Hospital Basel, Basel, Switzerland; [d]Department of Biomedicine, University of Basel, Basel, Switzerland

**Keywords**
Crohn's disease · Axial spondyloarthritis · Dual-targeted therapy · Risankizumab · Anti-TNF antibodies

**Abstract**
***Introduction:*** Treatment of Crohn's disease (CD) and axial spondyloarthritis (axSpA) is challenging, with CD refractory to anti-TNF antibodies. Here, we present for the first time a case treated with dual-targeted therapy (DTT) using the anti-IL-23 monoclonal risankizumab and the anti-TNF antibody certolizumab pegol. ***Case Presentation:*** Our patient initially presented with axSpA at the age of 27. Nine years later, CD was diagnosed by the age of 36. One year after the diagnosis of CD, a spontaneous ileal perforation occurred as part of a disease course refractory to multiple anti-TNF antibodies and intolerance to immunomodulators. However, the axSpA showed a response to the anti-TNF certolizumab pegol. After stopping certolizumab pegol, we enrolled the patient into the M15-991 induction trial (MOTIVATE) and the maintenance trial (FORTIFY) testing the anti-IL-23 antibody risankizumab versus placebo in CD with failure to prior biological therapy. As a result, risankizumab induced a CD response but failed to control the axSpA. Considering the CD refractory and the axSpA responding to anti-TNFs, we initiated a DTT with risankizumab and certolizumab pegol. Risankizumab and certolizumab pegol together improved both CD and axSpA. As adverse events, there were only two episodes of spontaneously resolving common colds during the 19-month reviewed period. ***Conclusion:*** DTT using risankizumab and certolizumab pegol is effective in CD

Correspondence to:
Jan Hendrik Niess, janhendrik.niess@unibas.ch

and axSpA without serious adverse events in our patient. Combining biologicals that target specific pathways in immune-mediated diseases promises excellent potential in CD associated with extraintestinal manifestations.



## Introduction

Extraintestinal manifestations (EIMs) in Crohn's disease (CD), including axial spondyloarthritis (axSpA), significantly impact morbidity and mortality with a prevalence of up to 47% (reviewed in [1]). The treatment of patients with EIMs in CD is challenging as this phenotype is associated with more treatment escalations, higher risk for surgery, and increased disease activity (reviewed in [1]). Combination therapies of two biologics offer an attractive possibility for treating CD and its EIM by targeting two specific pathways involved in their pathogenesis. However, reports successfully describing this mode of action in CD and axSpA are limited.

TNF blockers are approved for treating CD and axSpA. Approximately 40% of patients with CD achieve clinical remission and about 56% reach clinical response with TNF blockers (reviewed in [2]). The selective targeting of IL-23 with monoclonal antibodies has emerged as an essential treatment strategy with the recent approval of risankizumab for CD and mirikizumab for ulcerative colitis (UC). Risankizumab and mirikizumab bind the p19 subunit of IL-23. Conversely, ustekinumab binds to the p40 subunit, which IL-12 and IL-23 share. The ADVANCE (NCT03105128)/MOTIVATE (NCT03104413) induction and FORTIFY (NCT03105102) maintenance trial have demonstrated efficient induction and maintenance rates of risankizumab in biological-naïve and -experienced CD patients [3, 4]. Conversely, risankizumab did not meet the primary endpoints in axSpA [5].

Here, we report for the first time the case of a patient with CD and axSpA who received dual-targeted therapy (DTT) with risankizumab for CD and certolizumab pegol for axSpA, in which the CD was refractory to anti-TNF therapy. DTT with risankizumab and certolizumab improved both CD and axSpA. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542759).

## Case Presentation

We present a 45-year-old Caucasian male with a history of axSpA manifested in 2005 and a penetrating, non-stricturing CD with involvement of the terminal ileum and the colon (rectum and sigmoid) diagnosed in 2014, Montreal classification A2L3B1p. The patient had a negative family history of inflammatory bowel disease (IBD).

At the time of diagnosis of axSpA, our patient was less than 45 years of age. The diagnosis of axSpA in our patient with elevated C-reactive protein (CRP) was based on back pain for more than 3 months and an MRI showing active sacroiliitis. Treatments with the cyclooxygenase-2 inhibitor celecoxib and steroid injections into both sacroiliac joints did not improve axSpA. Furthermore, the anti-TNF antibodies etanercept, infliximab, adalimumab, and the anti-interleukin-6 receptor antibody tocilizumab failed to achieve remission.

Later, in 2014, the patient presented with hematochezia and abdominal pain and developed a perianal abscess requiring surgical abscess opening. Following abscess drainage,

the patient's inflammatory laboratory parameters, including CRP, further increased. Subsequent imaging with abdominal ultrasound and a CT scan showed findings compatible with Ileitis terminalis (shown in Fig. 1a, b). An ileocolonoscopy with biopsies confirmed CD.

Considering the axSpA's nonresponsiveness to etanercept, infliximab, and adalimumab, treatment with another anti-TNF antibody, golimumab, was initiated. One year later, the patient presented with an ileal perforation requiring ileocecal resection (shown in Fig. 1c). Therefore, postoperative therapy with golimumab was escalated to azathioprine and budesonide due to the persistence of inflammation in the neo-terminal ileum.

Golimumab and the additional immunomodulator improved CD, documented by fecal calprotectin normalization. However, the combination therapy with golimumab and azathioprine led to a flare of axSpA with severe back pain.

The treatment was switched again to certolizumab pegol and methotrexate. However, the latter had to be stopped because of rising liver enzymes.

We concluded that certolizumab pegol improved back pain caused by axSpA; however, CD showed a secondary loss of response. After a multidisciplinary discussion, we decided to stop the treatment and enrolled the patient in the M15-991 (MOTIVATE) trial. The MOTIVATE trial was a multicenter, double-masked, randomized, placebo-controlled induction trial testing the anti-IL-23 antibody risankizumab in patients with CD who had previously failed at least one biologic therapy [3].

The patient met the clinical response criteria of MOTIVATE (defined as ≥30% decrease in mean stool frequency of daily values reported for 7 days before the scheduled assessment visit or ≥30% decrease in mean daily abdominal pain score, both not worse than the baseline of the induction study) and could enter the FORTIFY maintenance trial at week 12. Although risankizumab achieved clinical response with CD, the axSpA further deteriorated, illustrated by an active sacroiliitis in a T2-weighted MRI scan (shown in Fig. 2) and requiring treatment with the cyclooxygenase-2 inhibitor Celecoxib. Despite its response to CD, the patient had to be excluded from the FORTIFY maintenance trial. Considering CD response to risankizumab and axSpA to certolizumab pegol, a DTT was initiated using risankizumab and certolizumab pegol simultaneously.

An ileocolonoscopy and histology illustrated improvement after starting the dual treatment with risankizumab/certolizumab pegol (shown in Fig. 3). Risankizumab/certolizumab pegol restored the ileal villous architecture with a persisting lightly active inflammation compared to the highly active and ulcerating inflammation of the terminal ileum before risankizumab treatment. The colonic mucosa had only slight and nonspecific crypt architectural changes before dual therapy with risankizumab that showed persisting focally slightly elevated mixed cellularity of the colonic lamina propria under risankizumab/certolizumab pegol (shown in Fig. 3b).

The Harvey-Bradshaw index (HBI) before risankizumab was 10 points calculated after assessing the following clinical parameters: general well-being, very poor (3 points); abdominal pain, moderate (2 points); the number of liquid stools 4, no abdominal mass (0 points) and presence of arthralgias (1 point), which as well as the axSpA disease activity indices decreased after starting DTT (shown in Table 1): Harvey-Bradshaw index for Crohn's disease (HBI; reduction by 8 points), simple endoscopic score (SES-CD; decreased by 6 points), bath ankylosing disease activity index (BASDAI decreased by 7.8 points), bath ankylosing spondylitis metrology index (BASMI decreased by 1.7 points), and the ankylosing spondylitis disease activity score with CRP (ASDAS-CRP decreased by 3.6 points) compared to monotherapy with risankizumab.

With DTT, the patient developed two adverse events, described as spontaneously resolving common colds during the reviewed 19-month period. DTT provides a promising perspective for optimizing treatment outcomes of patients with CD and axSpA who fail to achieve remission with monotherapy.

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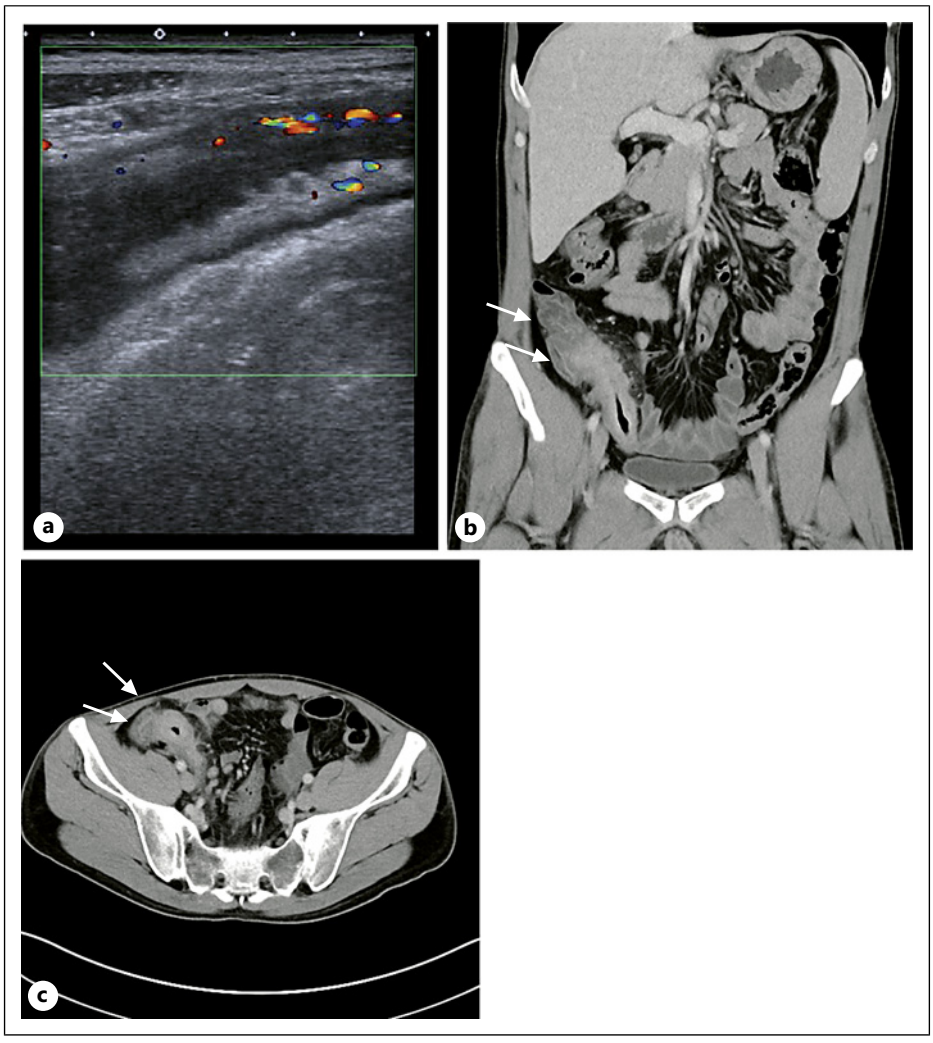


**Fig. 1.** Manifestation of CD in 2014 as terminal ileitis indicated by intestinal bowel ultrasound (**a**) and abdominal CT scan (**b**). **c** Contained ileal perforation 1 year after CD manifestation illustrated by a CT scan.

## Discussion

For the first time, we can illustrate that DTT using risankizumab and certolizumab pegol can be used to treat CD and axSpA. Only two common colds occurred during the 19 months reviewed, indicating that the combination of risankizumab and certolizumab pegol was safe in this patient. Clinical trials are currently testing combination therapies with anti-IL-23 and anti-TNF for induction and maintenance therapy for CD and UC, for example, the combination of guselkumab and golimumab in CD (NCT05242471) or UC (NCT05242484). To date, there are no clear guidelines about second-line treatment after failure of anti-TNF in CD (reviewed in [2]). At that time, when CD and axSpA flared in our patient, the selective Janus kinase (JAK) 1 inhibitor, upadacitinib, was not available. The anti-alpha 4 beta 7 integrin antibody vedolizumab was not considered in this patient, given the current flare of axSpa and vedolizumab known to inhibit the homing of lymphocytes to the gut tissue explicitly.

We considered the intricate mechanism in the pathogenesis of CD and axSpA in our decision to pursue DTT for this patient. The difference in the effectiveness of different

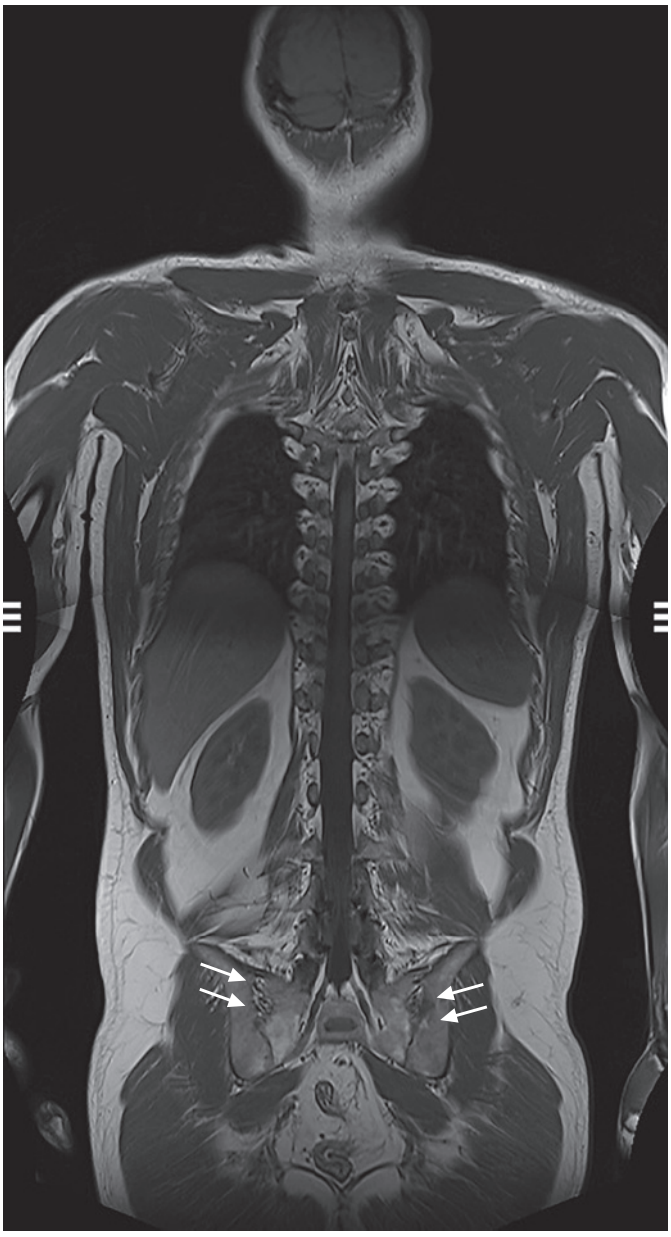

**Fig. 2.** Axial spondyloarthritis flares by risankizumab monotherapies indicated by a T2-weighted MRI scan.

cytokine blockades in treating IBD and axSpA stems from these cytokines' distinct roles in the involved immune pathways (shown in Table 2). For example, it has been reported that CD, not responding to anti-TNF therapy, has apoptosis-resistant T cells that express the IL-23 receptor, suggesting that IL-23 is an essential cytokine in anti-TNF refractor CD [6]. Clinical trials testing anti-IL-23 antibodies in CD show a remarkable efficacy in biologic (mainly anti-TNF) experienced patients [3, 4]. Our patient exhibited improved CD activity with risankizumab. Risankizumab, however, failed to control axSpA in our patient. This is consistent with findings from a phase 2, randomized, placebo-controlled trial, where risankizumab did not meet its primary endpoints in axSpA [5]. In line, ustekinumab, blocking both IL-23 and IL-12, is ineffective in axSpA, as shown in phase 3 randomized placebo-controlled trials [7]. Monoclonal antibodies, including secukinumab or ixekizumab, that inhibit IL-17 A downstream of

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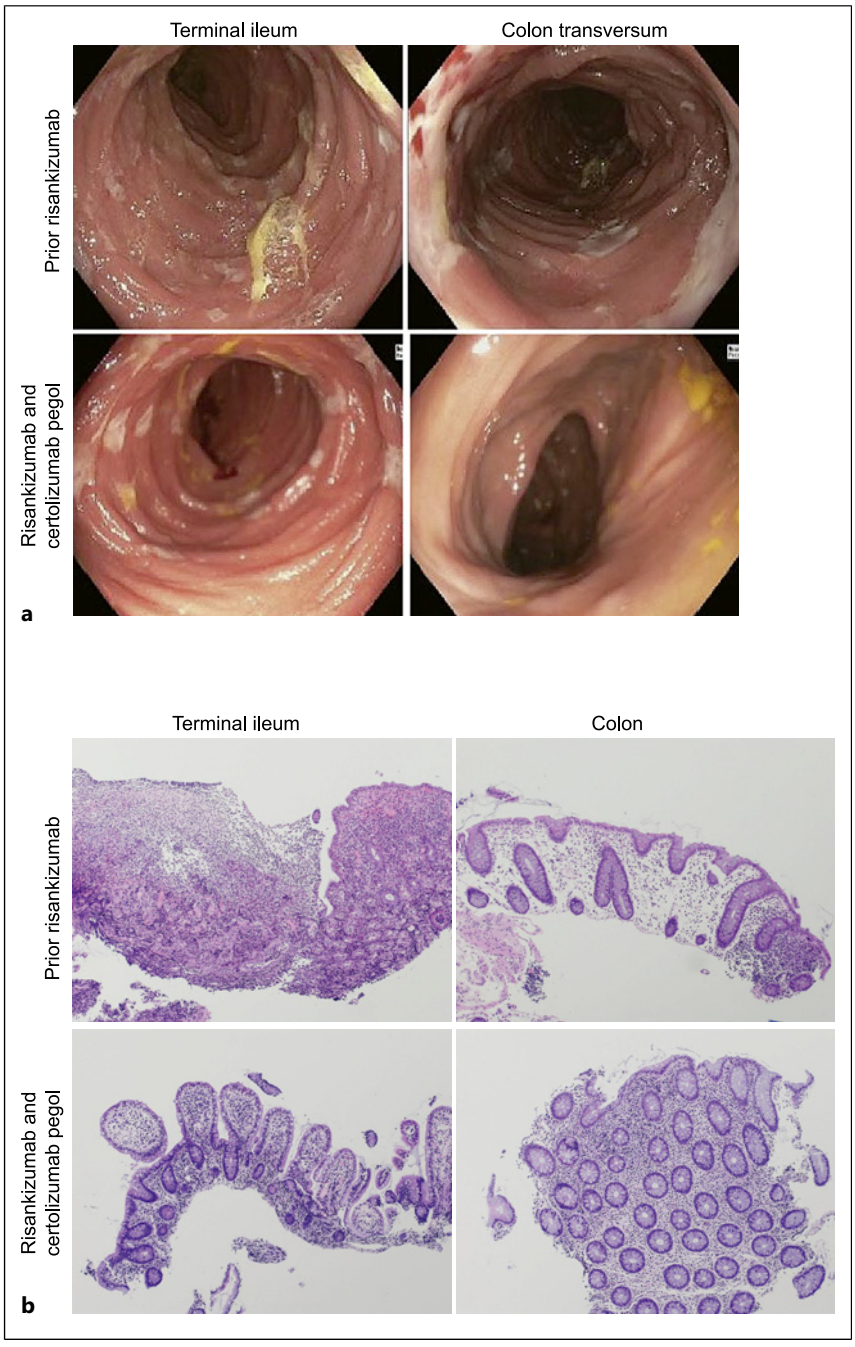


**Fig. 3.** Risankizumab and certolizumab pegol dual-target therapy improve CD, illustrated by endoscopic images (**a**) and hematoxylin-eosin-stained histology (**b**) (magnification, ×100) from the terminal ileum and colon before and under DTT.

IL-23 are, in axSpA, in contrast to CD, more effective than IL-23 inhibition. Possible reasons are that cytokines other than IL-23 induce IL-17. Experimental evidence suggests that mast cells and mucosal-associated invariant T cells can produce IL-17 in response to different signals, including the cytokine IL-7 [8]. In line, dual inhibition of IL-23 and IL-17 A was more effective in attenuating a mouse imiquimod-induced skin inflammation and experimental autoimmune encephalitis model [9].

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**Table 1.** Crohn's disease (CD) and axial spondyloarthritis (axSpA) scores before and under risankizumab and certolizumab pegol dual-target therapy

| | Prior risankizumab | Risankizumab | Risankizumab and certolizumab pegol |
|---|---|---|---|
| BASDAI | 5.6 | 10 | 2.2 |
| BASMI | 2.6 | 5.1 | 3.4 |
| ASDAS-CRP | N/A | 5 | 1.5 |
| HBI | 10 | 6 | 2 |
| SES-CD | 10 | 5 | 4 |

BASDAI, bath ankylosing spondylitis disease activity index; BASMI, bath ankylosing spondylitis metrology index; ASDAS-CRP, ankylosing spondylitis disease activity score with CRP; HBI, Harvey-Bradshaw index for Crohn's disease; SES-CD, simple endoscopic score; N/A, not assessed.

**Table 2.** Approved CD, UC, and axSpA advanced therapies

| Target | Class | Substance | CD | UC | axSpA |
|---|---|---|---|---|---|
| TNF | mAb | Infliximab<br>Adalimumab<br>Certolizumab<br>Golimumab | Effective (infliximab, adalimumab, certolizumab, approved) | Effective (infliximab, adalimumab, golimumab approved) | Effective |
| p40 subunit (IL-12/ IL-23) | mAb | Ustekinumab | Effective | Effective | Not effective |
| p19 subunit (IL-23) | mAb | Risankizumab<br>Mirikizumab<br>Guselkumab | Effective | Effective | Not effective |
| IL-17A | mAb | Secukinumab<br>Ixekizumab | Not effective | Not effective | Effective |
| JAK1 and JAK3 | Small molecule | Tofacitinib | Not effective | Effective | Effective |
| JAK1 | Small molecule | Upadacitinib | Effective | Effective | Effective |

mAb, monoclonal antibody.

Conversely, TNF remains the central cytokine in the pathogenesis of AxSpA, driving the chronic inflammation of the sacroiliac joints, entheses, and vertebrae, leading to structural damage. To date, anti-TNF agents remain the best option for treating both IBD and AxSpA due to the central role of TNF in both diseases, whereas IL-12/23 blockade has a more restricted effect, primarily benefiting IBD but not AxSpA. Patients may have different phenotypes characterized by distinct cytokine profiles and "immune escape mechanisms" to targeted therapies. Such phenotypes could benefit from future DTT, but a deeper understanding and broader application of combined treatments are needed.

One of the main concerns for DTT with combinations of two biologicals from different classes is the increased risk of (serious) infections. Combining the anti-TNF etanercept with

the interleukin 1 receptor antagonist protein anakinra was associated with an increased risk of severe infections while not showing sufficient improvements in patients with rheumatoid arthritis [10]. During the 19-month reviewed period, we only observed two episodes of common colds in our patient while on combination therapy. The risk of serious infections depends on the combinations used, and they need to be individually and carefully selected. The DTT using risankizumab and certolizumab pegol is well tolerated and safe for our patient.

Combination therapies of monoclonal antibodies for CD and its EIMs allow the specific inhibition of defined cytokines involved in the disease's progress and maintenance. The approach of a DTT offers the possibility of treating CD and its EIM in one individual, as exemplified in our patient. While CD and axSpA share fundamental principles of the underlying immunobiology, their manifestation in the respective organs has characteristic and tissue-specific immune pathologies, as in our patient, where CD and axSpA respond to different target therapies. We believe that advances in understanding immune pathways and the underlying manifestations of other organs will allow the specific blockade of defined pathways with monoclonal antibodies and provide personalized medicine/individual treatments. Dual-targeted treatments will offer increasing possibilities for complex patients to benefit.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The Ethical Committee of the northwestern part of Switzerland (EKNZ PB 2016-02242) has approved our research related to inflammatory bowel disease.

## Conflict of Interest Statement

J.H.N. is an advisor for AbbVie, Bristol Myers Squibb, Janssen, Falk, Roche, and Takeda. P.H. is an advisor for AbbVie, Bristol Myers Squibb, Falk, Janssen, Lilly, Pfizer, Sandoz, Sanofi, and Takeda. D.K. is an advisor for AbbVie, Bristol Myers Squibb, Janssen, MSD, Novartis, Pfizer, and Roche.

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## Author Contributions

Writing – original draft: A.L. and J.H.N. Data and image curation: A.L., J.V., D.K., and P.H. J.H.N. reviewed the manuscript, revised it, and approved the final version for publication.

## Data Availability Statement

The data supporting this case report are available on request from the corresponding author, J.H.N. The manuscript's data are not publicly available to protect the patient's privacy.

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