

# Managing Inflammatory Bowel Disease in Spondyloarthritis

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**S**pondyloarthritis is a chronic inflammatory rheumatism associated with a variety of extra-articular manifestations, including chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis). Subclinical gastrointestinal manifestations in patients with spondyloarthritis are common, and clinical involvement exists in a number of patients. The pathophysiology remains poorly understood and involves genetic and immunological factors, as well as the gut microbiome. Screening for inflammatory bowel disease in patients with spondyloarthritis is important because its occurrence modifies the therapeutic management of these patients.

## Keywords

Spondyloarthritis, ankylosing spondylitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, biological therapy

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Spondyloarthritis are chronic rheumatic diseases associated with diverse extra-articular manifestations, such as psoriasis, uveitis and inflammatory bowel diseases (IBDs), namely Crohn's disease (CD) and ulcerative colitis (UC). Historically, spondyloarthritis (SpA) was divided into several subcategories, namely, ankylosing spondylitis (AS), psoriatic arthritis, enteropathic arthritis, reactive arthritis and undifferentiated spondyloarthropathy. Given the possible overlap between these different entities, it is now preferred to use a phenotypic classification, associating the distribution of joint involvement (axial, peripheral or both) with any associated extra-articular manifestations, including IBD.

## Epidemiology

Clinical SpA occurs in up to 13% of patients with IBD, and CD in particular.<sup>1</sup> However, in a Canadian cohort, subclinical sacroiliitis was found in 16% of cases, with no difference in prevalence between CD and UC.<sup>2</sup> On the contrary, up to 60% of patients with SpA have subclinical, histological, gastrointestinal inflammation.<sup>3</sup> IBD seems to be more associated with AS than with psoriatic arthritis.<sup>4</sup> In a large British AS cohort, the prevalence of IBD at diagnosis was 3.7%, which was lower than the rate of acute anterior uveitis or psoriasis.<sup>5</sup> The incidence rate was 2.4 per 1,000 person-years, giving a cumulative incidence at 20 years of 7.5%, with a higher risk in the first year after diagnosis. High Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Bath Ankylosing Spondylitis Disease Functional Index (BASFI) scores were associated with microscopic gut inflammation, without necessarily having a clinical impact.<sup>6</sup> Interestingly, a study of the British BSRBR-AS cohort revealed that, overall, exposure to anti-tumour necrosis factor (TNF) therapy was associated with an increased risk of developing IBD compared with unexposed patients; however, this finding was only replicated in the observational studies and not in the randomized controlled trials included in the meta-analysis, possibly due to unadjusted confounding factors.<sup>7</sup>

## Pathophysiology

The relationship between SpA and IBD is complex and not yet fully understood. It involves both genetic and immunological mechanisms. Moreover, in recent years, the role of the gut microbiome has been increasingly studied. Genetically, human leukocyte antigen B27 (HLA-B27) is the most studied risk factor. Different theories have been formulated regarding its involvement in the pathogenesis of SpA. However, large genetic studies have shown that it is not a risk factor for the occurrence of IBD,<sup>8</sup> which could suggest different pathophysiological pathways. A clinical study of Caucasian patients with AS showed that HLA-B27-negative patients had more extra-articular manifestations, besides uveitis, than HLA-B27-positive patients.<sup>9</sup> Conversely, HLA-B27 was also associated with gut dysbiosis in patients with SpA, and these effects were highly dependent on host genetic background and environment.<sup>9</sup> On the contrary, genome-wide association studies have shown common genetic factors between SpA and IBD. The largest genome-wide association study explains 27.8% of the heritability of SpA, which is mostly related to major histocompatibility complex loci.<sup>10</sup> Others, such as genes related to type 3 immunity and epithelial barrier integrity are shared risk factors for SpA and IBD. Some variants are associated with only one of the two diseases. Finally, some variants are a risk factor in one disease and protective in the other.<sup>3,10</sup>

Immunologically, type 3 immunity, which is involved in the integrity of the intestinal endothelial barrier, seems to play a major role in the development of both SpA and IBD.<sup>11</sup> Apart from TNF- $\alpha$ , the key cytokine in the pathophysiology of IBD is interleukin (IL)-23, whereas in SpA it is IL-17A. IL-23, produced by dendritic cells and macrophages, promotes differentiation and activation of several cell types, including T-helper lymphocytes type 17, which in turn produce TNF- $\alpha$  and IL-17A. There is, therefore, an IL-23/IL-17A axis of inflammation, but it is not inflexible: treatments directed against IL-23 work well in both IBD and SpA, whereas treatments directed against IL-17A are effective in SpA but not in IBD. This could be explained by different interaction networks and cytokine effects depending on the tissue studied.<sup>11</sup>

Serum IL-17A is also higher in patients with AS compared with both healthy controls and patients with IBD,<sup>12</sup> and small-intestine IL-23 concentrations are higher in patients with AS and CD than in healthy controls.<sup>13</sup>

The gut microbiome has been increasingly studied in SpA, but many questions remain unanswered. Several studies have shown variations in the diversity and composition of the gut microbiome in patients, with some bacteria even being associated with disease activity.<sup>14,15</sup> In particular, an imbalance in the ratio of Firmicutes/Bacteroidetes could cause AS.<sup>16</sup>

These three mechanisms – genetic, immunological and microbiome – are strongly linked, altering the epithelial barrier, causing subclinical inflammation, and leading to recruitment of pro-inflammatory cells and cytokines in the axial and peripheral skeleton. It is therefore a real 'gut–joint axis'.<sup>3</sup>

### Recognizing inflammatory bowel disease in the context of spondyloarthritis

It is important for clinicians, including rheumatologists, to have good knowledge of the clinical signs and diagnosis of IBD, to ensure it is promptly diagnosed and treated. An Italian team proposed a set of criteria for referral to a gastroenterologist: chronic diarrhoea, rectal bleeding, perianal abscess/fistula, chronic abdominal pain and nocturnal symptoms were major criteria (one is sufficient for referral), while oral aphthosis, fever, anaemia, a family history of IBD, and weight loss were minor criteria (at least two criteria are necessary for referral).<sup>17</sup> These signs should be assessed at each follow-up visit.

The diagnostic strategy for IBD in a patient with a history of SpA does not change from that for the general population. As mentioned in the European Crohn's and Colitis Organisation (ECCO)/European Society of Gastrointestinal and Abdominal Radiology recommendations,<sup>18</sup> no single test is diagnostic of IBD. Instead, diagnosis is based on a combination of clinical and paraclinical evidence. Faecal calprotectin is a sensitive marker of intestinal inflammation in IBD. However, its performance as a screening test in the context of SpA may be diminished due to the high prevalence of microscopic inflammation, which may not have a clinical impact.<sup>19</sup> This marker could also define patients at risk of developing IBD.<sup>20</sup> An ileocolonoscopy remains mandatory to diagnose IBD, with two biopsies in the inflamed zone and biopsies in each colonic segment, except in cases of acute severe colitis in which sigmoidoscopy may be sufficient.<sup>18</sup> There are only a few endoscopic studies in SpA. In a Korean series of 108 patients, lesions were found in 40 cases (37%).<sup>21</sup> Ulceration was the most frequently found lesion, and the terminal ileum was the most frequently affected site.<sup>21</sup> Small-bowel capsule endoscopy can also be used. Two studies have evaluated its use in SpA, in comparison with

ileocolonoscopy. Eliakim et al. showed in 2005 that, in 20 patients, small-bowel capsule endoscopy uncovered more lesions than ileocolonoscopy (30% versus 5%, respectively).<sup>22</sup> Similar results (42.2% versus 10.9%, respectively) were found in a prospective study of 64 patients in 2018.<sup>23</sup>

### Managing inflammatory bowel disease in the context of spondyloarthritis

Consideration of IBD is important for the therapeutic management of patients with SpA. Indeed, some treatments are not effective, or are even contraindicated, in the presence of this extra-articular manifestation. Disease activity at the articular and digestive levels is also an element to be taken into account.

Non-steroidal anti-inflammatory drugs (NSAIDs), the first-line treatment for SpA, are contraindicated in active IBD because of the risk of aggravating the digestive disease. However, some authors suggest that this relation is only the consequence of a residual bias,<sup>24</sup> and there are more and more studies questioning this effect. In cases of quiescent IBD, treatment with NSAIDs may be proposed for a short period of time and with the agreement of the patient's gastroenterologist. A selective cyclooxygenase-2 inhibitor may be preferred because of the absence of short-term exacerbation of IBD in two studies included in a Cochrane review.<sup>25</sup>

Systemic corticosteroids should not be used long term in pure axial involvement, and may be used with caution in psoriatic arthritis.<sup>26</sup> Studies are rare, and have small sample sizes and short follow-up periods.<sup>27,28</sup> ECCO guidelines suggest the use of systemic corticosteroids for inducing clinical response and remission in CD, but long-term use does not prevent relapse.<sup>29</sup>

Regarding conventional, synthetic, disease-modifying anti-rheumatic drugs, the latest European League Against Rheumatism (EULAR) recommendations suggest that they can be tried in cases of peripheral involvement, with preference given to sulfasalazine, which has demonstrated efficacy, unlike methotrexate.<sup>30</sup> The ECCO guidelines are against the use of aminosalicylic acid (5-ASA) compounds due to lack of efficacy in CD.<sup>29</sup> On the contrary, in UC, there is a strong recommendation to use 5-ASA orally and/or rectally for inducing remission, and a weak recommendation for maintaining remission.<sup>31</sup> No agreement was reached regarding methotrexate in CD, but the authors state that this treatment can be considered in cases of moderate-to-severe disease when alternative options cannot be used.<sup>29</sup> No study suggests its use in UC.

If disease activity persists despite conventional therapy, TNF inhibitors, IL-17 inhibitors and Janus kinase (JAK) inhibitors are indicated in axial disease, with the usual practice of starting with TNF inhibitors or IL-17 inhibitors. In peripheral SpA, IL-23 inhibitors can also be considered. The Assessment of SpondyloArthritis International Society (ASAS)-EULAR guidelines also state that, in active IBD, a monoclonal antibody to TNF should be preferred.<sup>30</sup> Indeed, various studies have shown the efficacy of anti-TNF antibodies in CD and UC, and the lack of efficacy of etanercept and secukinumab.<sup>32–35</sup>

Furthermore, the ASAS-EULAR guidelines do not suggest one anti-TNF antibody over another, but it should be noted that certolizumab is not approved for UC and golimumab is not approved for CD.<sup>30</sup> In addition, a network meta-analysis showed superiority of infliximab plus azathioprine and of adalimumab monotherapy over certolizumab in inducing remission in patients with CD.<sup>36</sup>

The ineffectiveness of IL-17 inhibitors in IBD, and their association with disease worsening, despite the IL-23/IL-17 pathway being involved in its occurrence and these treatments working in SpA, illustrates the complex links between type 3 immunity and the pathophysiology of IBD and SpA. Although no excess risk of developing *de novo* IBD has been definitively demonstrated, patients on anti-IL-17 therapy should be carefully monitored for the occurrence of digestive signs.<sup>37</sup>

Ustekinumab, an anti-IL-12/-23 monoclonal antibody, has demonstrated efficacy<sup>38,39</sup> and is recommended for the induction and maintenance of remission in both CD and UC.<sup>29,31</sup> It is also effective in peripheral spondyloarthritis<sup>40</sup> but not effective in axial involvement.<sup>41</sup>

Regarding JAK inhibitors, two are approved by the US Food and Drug Administration (FDA) for AS and psoriatic arthritis: tofacitinib (non-selective) and upadacitinib (JAK1-selective).<sup>42–45</sup> Tofacitinib is approved for UC and recommended by ECCO.<sup>31</sup> Upadacitinib is also approved for UC. However, evidence of an increased risk of major cardiovascular events in selected patients treated with JAK inhibitors versus TNF inhibitors for rheumatoid arthritis (age  $\geq 50$  years, and at least one additional cardiovascular risk factor)<sup>46</sup> prompted the FDA and European Medicines Agency to issue a warning about the use of this treatment for all approved indications. Additional data are needed to clarify the safety and place of this therapeutic class in the management of SpA and IBD.

Finally, some treatments are recommended in IBD but not in SpA.<sup>47,48</sup> In particular, vedolizumab, a monoclonal antibody directed against  $\alpha 4\beta 7$

integrin is effective in inducing and maintaining remission in CD and UC, thanks to gut-selective anti-inflammatory activity. The ECCO guidelines suggest the use of vedolizumab rather than adalimumab for inducing and maintaining remission in patients with moderately-to-severely active UC based on the results of a randomized controlled trial.<sup>31,49</sup> Several authors have reported the occurrence of severe *de novo* SpA<sup>50</sup> and isolated enthesitis<sup>51</sup> following vedolizumab treatment.

Thiopurines such as azathioprine are also recommended for maintaining remission in patients with steroid-dependent CD or UC.<sup>29,31</sup> However, they are not recommended in patients with newly diagnosed CD, as it has been speculated that early introduction of thiopurines may alter the course of the disease.

Thus, the clinical phenotype of SpA, the type of IBD and its activity, and previous treatments are all important to consider when making treatment decisions for patients with both SpA and IBD. In any case, clinical and biological evaluation before introducing immunosuppressive therapy, as well as regular monitoring of infection risk, should be performed, as in the case of SpA without associated IBD.

## Conclusions

In conclusion, recognizing IBD in a patient with SpA is important. Indeed, IBD with clinical manifestations is not rare in patients with SpA, and some treatments are not effective on one or other of these pathologies. Collaboration with the gastroenterologist remains important for optimal patient management.  $\square$

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