Approach to the Patient with Axial Spondyloarthritis and Suspected Inflammatory Bowel Disease

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KEYWORDS

• Axial spondyloarthritis • Inflammatory bowel disease • Digestive system
• Gastrointestinal diseases • Ankylosing spondylitis

KEY POINTS

- The evaluation of gastrointestinal symptoms in patients with axial spondyloarthritis requires careful evaluation, taking into account the increased risk of inflammatory bowel disease but not forgetting other causes, such as infections.
- Endoscopic studies remain fundamental in the diagnostic process.
- The available fecal and serologic markers do not allow, by themselves, a good distinction between the possible causes of intestinal inflammation.
- The treatment should be evaluated considering both the articular and intestinal manifestations and without forgetting the interactions and adverse effects of the different immunosuppressants available.

INTRODUCTION

Axial spondyloarthritis (axSpA) and inflammatory bowel diseases (IBD) share common genetic and pathogenic mechanisms, with an estimated prevalence of IBD in axSpA patients between 4.1% and 6.4%.[1]

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The incidence of IBD after the diagnosis of axSpA is estimated at 0.6% per year,[2] and the diagnosis is more frequent near the initial diagnosis of axSpA, in younger patients,[3] in women,[4] in those with a higher body mass index,[5] and in those with greater disease activity, worse functionality and worse evaluation of baseline well-being.[2] It might be more frequent in populations of higher socioeconomic status, but the evidence is not definitive in this regard.[6]

To adequately and efficiently evaluate patients with gastrointestinal symptoms in the context of axSpA can be difficult, considering that many of these patients suffer from chronic pain, present high inflammatory parameters, and use drugs with possible gastrointestinal adverse effects. In addition, the immunosuppressive treatments that these patients can receive make it necessary to always consider infections within the differential diagnoses of IBD.

In this article, we propose a practical approach to patients diagnosed with axSpA and suspected IBD (**Table 1**).

IN WHICH PATIENTS WITH AXIAL SPONDYLOARTHRITIS SHOULD WE SUSPECT THE PRESENCE OF INFLAMMATORY BOWEL DISEASE?

Recently, screening criteria have been postulated.[7] They suggest that a patient who presents with one of the following symptoms should be evaluated by the gastroenterologist: rectal bleeding without an evident cause: chronic diarrhea (>4 weeks) with

Table 1
Approach to the patient with axSpA and suspected IBD

Suspicion	Symptoms: rectal bleeding, chronic diarrhea, perianal disease, chronic abdominal pain, fever, weight loss, extraintestinal manifestations of IBD[a] Laboratory: Iron deficiency, leukocytosis, hypokalemia, hypoalbuminemia, high ESR or CRP, not explained by joint disease. Family history of IBD.
Evaluation	Endoscopic study if high clinical suspicion (always biopsy if possible). Fecal calprotectin >150 μg/g: consider additional tests (do not forget infections). Endoscopic capsule in selected cases (suspected IBD with normal colonoscopy). Extension study if IBD is confirmed (CT, MRI of small intestine; pelvic floor study).
Treatment	Stop smoking, lower body fat. NSAIDs and corticosteroids only if no better treatment available csDMARDs. No clear benefit for axial disease, consider if it is not possible to use biologicals. Biologics: adalimumab and infliximab useful for UC and CD, and joint involvement.
Colorectal cancer screening	From 8–10 y after onset of IBD symptoms, unless risk factors for early CRC are present. Surveillance frequency according to risk estimation (personal and family history, biopsy result). Biologicals: possible protective effect.

Abbreviations: CD, Crohn's disease; CRC, colorectal cancer; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying drugs; CT, computed tomography; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs; UC, ulcerative colitis.

[a] Erythema nodosum, pyoderma gangrenosum, oral thrush, and cholangitis.

characteristics that suggest organicity (watery, wakes up the patient at night, or with accompanying symptoms such as weight loss, fever, signs of malabsorption, or extraintestinal symptoms such as erythema nodosum, pyoderma gangrenosum, oral thrush, cholangitis), and perianal disease (fissures, fistulas, abscesses, skin tags, and maceration or ulceration).

If the patient does not present any of those symptoms but has 2 of the following, a referral is also needed: chronic abdominal pain (>4 weeks, persistent or recurrent), iron deficiency with or without anemia, extraintestinal manifestations (mentioned within the major criteria), fever without apparent origin of more than a week of evolution, not explainable weight loss, or a family history of IBD.

These screening criteria for referral have the advantage of being based on the patient's clinical presentation and not relying on laboratory tests, except for the presence of iron deficiency. Although these criteria need to be validated, and their specificity and sensitivity evaluated, they reflect in a good way the clinic of patients who may present IBD.

HOW SHOULD A PATIENT DIAGNOSED WITH AXIAL SPONDYLOARTHRITIS AND SUSPECTED INFLAMMATORY BOWEL DISEASE BE STUDIED?

For the diagnosis of IBD, there is no definitive diagnostic test; rather, a combination of elements, compatible history, and laboratory tests (deposition study, endoscopy, histology, and images) are required.

Within the laboratory, the presence of anemia, thrombocytosis, erythrocyte sedimentation rate elevation, leukocytosis, hypokalemia, hypoalbuminemia, and C-reactive protein elevation help us to diagnose and to evaluate the severity of the condition. The microbiological study in stool is mandatory to rule out infections.[8]

a. Fecal and serologic markers
   i. Fecal calprotectin is a cytosolic protein derived from neutrophils. There is a very good correlation between its values and inflammatory activity in the intestinal mucosa. Although a value of 50 μg/g or greater may be considered abnormal, an optimal cut-off for distinguishing IBD from other entities, like infections, has not been fully determined,[9] hence the importance of associating it with a microbiological study of feces.[10] Another factor that can raise the levels of fecal calprotectin is the use of nonsteroidal anti-inflammatory drugs (NSAIDs),[11] which is common in the treatment of axSpA. In contrast, higher levels of fecal calprotectin are associated with greater severity of axSpA, in patients without gastrointestinal symptoms.[12] Therefore, the current role of calprotectin in the diagnosis of IBD in patients with axSpA with high disease activity is not clear. Some experts recommend that invasive studies should not be performed in patients with gastrointestinal symptoms if the value is less than 100 μg/g, to repeat the fecal calprotectin if the value is between 100 and 150 μg/g, and consider additional tests if it is greater than 150 μg/g.[13] In patients with IBD, the elevation of calprotectin may precede clinical symptoms by up to 3 months, being a very good noninvasive follow-up parameter, because it has a good correlation with the endoscopic indexes of inflammation, and its progressive decrease is one of the best markers of response to treatment.[13] Serum calprotectin, less used in clinical practice, has been associated with subclinical microscopic colitis in patients with axSpA and elevated C-reactive protein.[14]
   ii. Lactoferrin, a protein found in neutrophil granules, acts inhibiting bacterial proliferation by binding iron. Like calprotectin, it is resistant to degradation and proteolysis, and has a sensitivity of 67% to 80% and a specificity of 65% to 82% to

identify patients with IBD. Fecal lactoferrin has been correlated with active inflammation seen in endoscopy, and with clinical symptoms, but its use is less standardized than that of fecal calprotectin.[10]

iii. Serologic markers such as antineutrophil cytoplasm and anti-*Saccharomyces cerevisiae* antibodies can be used to support the diagnosis, but they have low sensitivity and specificity, and do not allow distinguishing between ulcerative colitis (UC) and Crohn's disease (CD). The additional diagnostic value of anticarbohydrate antibodies like antimannobioside, antilaminaribioside, or antichitobioside antibodies, and of antimicrobials antibodies against the *Escherichia coli* outer membrane porin C, flagellin, and *Pseudomonas fluorescens*–associated sequence I-2, is minimal.[15]

b. Colonoscopy and endoscopic capsule

i. In the case of suspected IBD, a colonoscopy should be performed, always with ileal intubation, and biopsies should be taken of all segments, both healthy and those with an inflammatory appearance. Ileocolonoscopy can confirm the diagnostic suspicion, evaluate the extent and degree of involvement, and identify complications (fistulas, stenosis, and neoplasms). A frequent mistake is to biopsy only from macroscopic inflamed segments, being that there may be a microscopic intestinal compromise, and it will be the latter that determines the extent of the disease.[16] In UC the affectation is only colonic, always continuous from rectum to proximal, with a clear boundary between healthy and diseased mucosa. Depending on the severity, the findings could be edema and loss of the submucosal vascular pattern; friable, erythematous mucosa, with superficial erosions; and ulceration with exudate and spontaneous bleeding.[8] In CD the affectation can exist from mouth to anus, with a patched pattern. The degree of affectation can go from isolated scars to deep ulcers, with geographic or serpiginous aspect, with a cobblestone pattern, complicated with stenosis or fistulas, or with scars that retract the mucosa. It is possible to present only ileal involvement, so ileal evaluation is always necessary.[16] Colonoscopy is not recommended as a test for IBD screening in patients with axSpA without digestive complaints, but it should be noted that, in this group, ileocolonoscopy has revealed inflammatory lesions in up to one-third of patients.[17,18]

ii. The endoscopic capsule has been shown to be superior to colonoscopy in detecting inflammatory lesions compatible with CD in patients with axSpA, observing inflammation of the small intestine in 42.2% versus 10.7% of patients, respectively.[19] Interestingly, the positive results were not associated with gastrointestinal symptoms but with high levels of fecal calprotectin, which has also been observed in other studies.[20] Further studies are required to assess whether studying these asymptomatic patients modifies the long-term results of the disease. In patients with suspected IBD, mainly CD, with elevated C-reactive protein, unexplained iron deficiency anemia, high fecal calprotectin, and normal colonoscopy, the endoscopic capsule is a sensitive tool to detect abnormalities in the mucosa of the small intestine with a diagnostic performance comparable with other modalities (magnetic resonance enterography, MRI, ultrasound examination with contrast of the small intestine), and it seems to be superior in the evaluation of the proximal small intestine. The presence of at least 3 ulcers in the small intestine is considered as a diagnosis of CD, provided that the patient has not used NSAIDs for at least 1 month before. It should be kept in mind that its use is contraindicated in patients with swallowing disorders and in suspected stenosis and/or intestinal obstruction given the risk of impaction.[21,22]

c. Other studies
   i. Gastroduodenoscopy is only recommended when IBD is suspected in pediatric patients. In adults, it is only performed in CD when the symptoms justify its use, because there may be compromise of the upper digestive tract (part of the extension study).[23]
   ii. Images are fundamental for the extension study, being much more important in CD than in UC. At the time of diagnosis of CD, the small intestine should be evaluated with a noninvasive test to define the extent and phenotype of the disease. Computed tomography or MRI enterography can evaluate the small intestine with similar sensitivity and specificity.[24] Both techniques allow the determination of the extent of the disease, the presence of fistulas or stenosis, and the degree of inflammatory activity, based on the thickness of the wall and the increased intravenous contrast uptake.[25] MRI can reduce the radiation exposure, especially in young patients, and allows the differentiation between inflammation and residual fibrostenosis, relevant information for treatment.
   iii. A pelvic floor study (MRI, endosonography, evaluation under anesthesia) should also be carried out on suspicion of perianal disease involvement.

WHAT RESULTS SHOULD BE CONSIDERED DIAGNOSTIC IN THE BIOPSY?

a. *UC:* Histology in UC characteristically presents alterations of the histoarchitecture with branching and shortening of the crypts. The presence of cryptic microabscesses is related to the activity of the disease, although this alteration is also present in infectious conditions, so it is not diagnostic of UC by itself. In initial UC, the presence of diffuse or focal plasma cell clusters can be observed and may be the earliest feature.[8]
b. *CD:* In CD, the histology is more varied, the affectation is transmural, so the biopsy, being more superficial (mucosa), can be normal or with minimal alterations. The presence of granulomas is the pathognomonic lesion, found in about 10% of biopsies. Distortion of crypts, increase in plasma cells, and accumulation of eosinophils may be present. The presence of abnormalities between normal areas supports the diagnosis.[8]

WHAT IS THE ROLE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, CORTICOSTEROIDS AND CONVENTIONAL SYNTHETIC DISEASE-MODIFYING DRUGS IN TREATMENT?

a. *NSAIDs:* In clinical practice, the relationship between IBD reactivation and the use of NSAIDs is recognized, although a recent meta-analysis did not find a consistent association between its use and the risk of flair.[26] Causality is difficult to demonstrate because patients with active disease seem to use more NSAIDs.[27,28] Some experts suggest that, in nonactive IBD, using celecoxib or etoricoxib for short periods is acceptable,[29–32] but further research is still needed.
b. *Corticosteroids:* The usefulness of corticosteroids in axSpA is controversial,[33,34] but in patients with active IBD, in whom it is desired to avoid the use of NSAIDs, who present flares of their axSpA, corticosteroids may be an option, especially in patients without access to biologics.[35]
c. *Conventional synthetic disease-modifying drugs:* There is no clear benefit of sulfasalazine in the axial symptoms of axSpA,[36] and the evidence is worse for mesalazine, azathioprine,[37] and methotrexate.[38] In cases with active IBD and axSpA, with no possibility of biologic use, where it is decided to use any of these disease-modifying drugs, adverse effects, and possible drug interactions, should be carefully considered given the lack of proven efficacy.

WHICH BIOLOGICAL CAN BE USED?

Within the approved biologicals, with proven efficacy in axSpA, only some have usefulness in IBD. Infliximab and adalimumab are the best studied tumor necrosis factor-α blockers with approval for use in CD, UC, and axSpA.[39,40] Certolizumab has proven usefulness for CD,[41] and is being studied in UC,[42] with efficacy reports already published.[43] Golimumab is currently approved only for UC,[44] although there are usefulness reports in CD.[45,46] Etanercept has no proven usefulness in IBD.[47]

Secukinumab, a monoclonal antibody against IL-17, has proven usefulness in axSpA, but, despite the fact that, owing to its mechanism of action, a good response was expected, the results have been negative in IBD,[48] and there was a concern of increased incidence of IBD in patients starting treatment. In a retrospective analysis of 7355 patients, incident cases were uncommon[49]; however, some groups still recommend caution and monitoring of digestive symptoms.[50]

Although ustekinumab is useful in CD,[51] it failed to demonstrate efficacy in axSpA.[52] Vedolizumab has demonstrated efficacy in CD and UC,[53] but there is concern that it may be related to the appearance of arthritis,[54,55] although a recent post hoc analysis showed the opposite.[56]

IS THERE EVIDENCE FOR THE USE OF JANUS KINASE INHIBITORS?

Tofacitinib has no proven usefulness in CD,[57] but it has proven action in UC[58] and its usefulness in axSpA is being studied.[59,60] Filgotinib looks promising in CD[61] and in axSpA.[62]

WHAT IS THE ROLE OF SMOKING AND BODY COMPOSITION?

Smoking

Quitting smoking has a demonstrated benefit in patients with CD and should be established as an important treatment goal.[63] It has been reported that smoking is protective against UC, but its causality has not been clarified.[64] The rather modest benefits of transdermal nicotine replacement suggest that more research is required in this area.[63] A recent study showed that nonsmokers seem to have a lesser risk of developing IBD.[65] Similarly, smoking is associated with a worse disease profile in patients with axSpA.[66]

Body Composition

Body fat decreases with higher disease severity, and fat-free mass decreases with longer disease duration in CD, UC and axSpA.[67,68] Higher fat mass content has been associated with worse response to tumor necrosis factor-α blockers.[69]

WHAT IS THE RISK OF COLORECTAL CANCER?

a. *Start of monitoring:* Long-term UC and CD are associated with an increased risk of colorectal cancer (CRC), with different estimates between studies.[70,71] Current guidelines recommend monitoring for CRC from 8 to 10 years after the start of IBD symptoms. However, the incidence within 8 to 10 years from the onset of IBD varies from 12% to 42%, and the risk factors predictive of early CRC are onset of IBD at 28 years or older and active tobacco smoking.[72] These patients should be considered for earlier screening.
b. *Surveillance frequency:* Because the scientific data available for patients with CD are more limited,[73] the same surveillance schedules apply as for patients with UC,[8] for an early detection of dysplasia and prevention of the development of

CRC. Patients with low risk (active endoscopic or histologic inflammation, left colitis or affecting <50% colon) should be scoped every 5 years, those with intermediate risk (mild active endoscopic or histologic inflammation, postinflammatory polyps, first-degree family history of CRC after age 50) should have a colonoscopy every 2 to 3 years, and those with high risk (moderate or severe endoscopic or histologic active inflammation, first-degree relative with CRC before age 50, history of primary sclerosing cholangitis, stenosis in the last 5 years, biopsy with dysplasia in the last 5 years in a patient who refused surgery) should undergo annual colonoscopy.[70,74,75]

c. *Biologicals:* There is a lack of data and experience to estimate the impact of biologic therapy on the risk of CRC in patients with axSpA and IBD, but it seems that the risk does not increase and that there may be a chemopreventive effect in controlling the inflammation of the mucosa.[76]

ARE THERE CLINICAL SCALES FOR MONITORING THE ACTIVITY OF INFLAMMATORY BOWEL DISEASE IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS?

In the Netherlands, the use of the Dudley Inflammatory Bowel Symptom Questionnaire (DISQ) in patients with spondyloarthritis was validated. This consists of 15 questions that are scored from 0 to 4, and a higher score is related to worse gastrointestinal symptoms.[77] It must be validated in other populations but can be considered as a useful tool for monitoring the disease.

SUMMARY

IBD can be found frequently in axSpA. The diagnostic study should be performed carefully, considering the differential diagnoses and the limitations of the different diagnostic test. There are good therapeutic options, although biological therapies can be difficult to access in some parts of the world.

DISCLOSURE

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