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**Review**

**Management of patients with inflammatory bowel disease and spondyloarthritis**

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### **Abstract**

**Introduction:** More than half of the patients with inflammatory bowel disease (IBD) experience at least one extra-intestinal manifestation (EIM). The most common EIM in patients with IBD is spondyloarthritis (SpA). Microscopic intestinal inflammation is documented in almost 50% of the patients with SpA.

**Areas covered:** We give an overview of the classification, the epidemiology and the diagnosis of IBD and SpA. The treatment goals, the pharmacologic management options and the available treatment guidelines in IBD patients with SpA are discussed.

**Expert Commentary:** The coexistence of IBD and SpA generates challenges and opportunities for both the gastroenterologist and the rheumatologist. The potential of drugs with a gut-specific mode of action in the treatment of IBD-related arthritis warrants further exploration.

### **Keywords**

Crohn's disease, Inflammatory bowel disease, Spondyloarthritis, Treat-to-target, Ulcerative colitis

## Abbreviations

AS: ankylosing spondylitis; ASAS: Assessment in SpondyloArthritis international Society; CI: confidence interval; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; DAS: disease activity score; ECCO: European Crohn's and Colitis Organisation; EIM: extra-intestinal manifestation; HLA-B27: human leukocyte antigen B27; IBD: inflammatory bowel disease; JAK: janus kinase; MDA: minimal disease activity; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; NSAID: non-steroidal anti-inflammatory drug; SpA: spondyloarthritis; TNF: tumor necrosis factor; RA: rheumatoid arthritis; r-axSpA: radiographic axial spondyloarthritis; UC: ulcerative colitis; US: ultrasound; uSpA: undifferentiated spondyloarthritis

## 1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic disabling conditions <sup>1,2</sup>. More than half of the patients with IBD experience at least one extra-intestinal manifestation (EIM) <sup>3</sup>. The most common EIM in patients with IBD is spondyloarthritis (SpA) <sup>4</sup>. SpA is a group of diseases with similar clinical, radiological and serological features. It includes ankylosing spondylitis (AS), also defined as radiographic axial SpA (r-axSpA), non-radiographic axial SpA (nr-axSpA), psoriatic arthritis, reactive arthritis, IBD-associated SpA and undifferentiated SpA (uSpA) <sup>5</sup>. SpA causes a significant burden to the patient and to the society <sup>6-9</sup>. Microscopic intestinal inflammation is documented in approximately 50% of patients with SpA <sup>10</sup>, and 7% of these patients develop IBD <sup>11</sup>. An integrated management of

patients with coexisting IBD and SpA, with cooperation between the gastroenterologist and the rheumatologist, is necessary to provide the best possible care. Most anti-tumor necrosis factor (anti-TNF) agents work for both diseases<sup>12,13</sup>. Only etanercept, an anti-TNF agent licensed for the use in patients with AS, is not a treatment option in patients with IBD.

Ustekinumab, a monoclonal antibody that binds to the p40 subunit of interleukin-12 and interleukin-23, proved efficacy in patients with CD<sup>14</sup> and in patients with psoriatic arthritis<sup>15</sup>, but its value in patients with (non-)radiographic axial SpA remains unclear. Whether drugs with a gut-specific mode of action, such as vedolizumab, work for IBD-related arthritis is debated.

Herein, we give an overview of the classification, the epidemiology and the diagnosis of IBD and SpA. The treatment goals, the pharmacologic management options and the available treatment guidelines in IBD patients with SpA are discussed. Finally, an expert opinion about the treatment of patients with coexisting IBD and SpA is provided.

## 1. Methodology

We searched for relevant manuscripts in PubMed/MEDLINE, EMBASE (Excerpta Medica Database) and Cochrane CENTRAL from their inception until June 1<sup>st</sup>, 2017. The following keywords were included alone or in combination: ‘Crohn’s disease’, ‘ulcerative colitis’, ‘inflammatory bowel disease’, ‘spondyloarthritis’, ‘ankylosing spondylitis’, ‘epidemiology’, ‘diagnosis’, ‘management’, ‘treatment goals’, ‘treat-to-target’, ‘corticosteroids’, ‘aminosalicylates’, ‘immunomodulators’, ‘anti-tumor necrosis factor therapy’, ‘vedolizumab’, ‘ustekinumab’, ‘janus kinase inhibitors’. Bibliographies of included articles were searched and experts in IBD and rheumatology were consulted to identify additional studies. Relevant articles published in English were critically reviewed. Priority was given to randomized

controlled trials and meta-analyses published in the last 5 years. Relevant abstracts presented at major meetings were also considered.

## 2. Epidemiology

A recent meta-analysis assessed the prevalence and incidence of peripheral and axial SpA in IBD patients<sup>16</sup>. The authors included 71 studies reporting on the prevalence of sacroiliitis, AS, arthritis, enthesitis and dactylitis in 27524 patients. SpA occurred in up to 13% of patients with IBD. A detailed description about the criteria used for diagnosing SpA is lacking, but the authors state that in 56.3% of the studies ‘objective standard criteria for the measurement of SpA’ were used and that ‘SpA was measured reliable’ in 46.5% of patients. The pooled prevalence of sacroiliitis was 10% (95% confidence interval (CI) 8-12%), the pooled prevalence of AS was 3% (95% CI 2-4%) and the pooled prevalence of peripheral arthritis was 13% (95% CI 12-15%). The prevalence of sacroiliitis, AS and peripheral arthritis was higher in CD patients compared to UC patients<sup>16</sup>. Earlier data report evidence of radiologic sacroiliitis in 20% to 50% of IBD patients<sup>17-19</sup>. In a cohort study with a duration of almost 2 years in a combined gastroenterology-rheumatology clinic, 269/1495 (18%) IBD patients reported musculoskeletal pain. Enteropathic SpA was diagnosed in 136/269 (50.5%) of these patients<sup>20</sup>. To establish the diagnosis of enteropathic SpA, clinical and biochemical data were collected and joint imaging, including ultrasound (US) and traditional radiography for the assessment of peripheral involvement (arthritis, enthesitis, dactylitis) and traditional radiography and magnetic resonance imaging (MRI) for the assessment of axial involvement, was requested when appropriate<sup>20</sup>. In a multicenter study evaluating the subclinical affected joint and enthesal involvement by US in 76 patients with IBD, 20 patients with SpA and 45 healthy controls, 84.1 % of IBD patients had at least one enthesal abnormality. The



prevalence was higher in the IBD patients than in the healthy controls, but there was no difference between the IBD and the SpA patients <sup>21</sup>.

### 3. Diagnosis

#### 4.1 Diagnosing SpA in IBD patients

SpA is classified according to the Assessment in SpondyloArthritis international Society criteria, distinguishing peripheral from axial SpA (table 1) <sup>22,23</sup>. The positive predictive value of these sets of criteria is 89.5% for peripheral SpA and 93.3% for axial SpA <sup>24</sup>. European Crohn's and Colitis Organisation (ECCO) consensus describes a diagnostic approach for arthritis in IBD patients (table 2) <sup>3</sup>. Given the non-erosive character of peripheral arthritis, especially oligoarthritis, conventional radiography is usually normal and the recognition of IBD-related peripheral SpA remains mainly clinical (eg. joint swelling and tenderness) <sup>25</sup>. When clinical exam alone is doubtful, US examination or MRI may be used to confirm peripheral enthesitis or to detect peripheral arthritis, tenosynovitis and bursitis <sup>26</sup>. The diagnosis of axial SpA in IBD patients is based on the combination of inflammatory low back pain associated with conventional radiographic or MRI features of sacroiliitis <sup>3</sup>. Inflammatory back pain must be suspected in the presence of 2 or more of the following features, and the presence of 4 or more of these features are considered diagnostic: onset before 45 years, insidious onset, duration of more than 3 months, morning stiffness more than 30 minutes, improvement with exercise, no improvement with rest, awaking from pain and alternating buttock pain <sup>27</sup>. Added to clinical and biological data, MRI analysis contributes to an earlier diagnosis of axial SpA in patients with IBD <sup>28</sup>, especially in the subgroup of patients with nr-axSpA (ie. axial SpA but without abnormalities of the sacroiliacal joint on conventional radiography). Evidence of bone marrow inflammation, as defined by the ASAS-MRI working group, is required for the definition of active sacroiliitis on MRI <sup>29</sup>. Human leukocyte antigen

B27 (HLA-B27) positivity is seen in 78% of patients with IBD and AS<sup>17,30</sup> and possession of HLA-B27 conveys a very high risk of developing axial inflammation in CD<sup>31</sup>. Nevertheless, the lower overall prevalence of HLA-B27 positivity in IBD-related SpA as compared to idiopathic SpA, makes HLA-B27 unreliable to be used as a diagnostic test for SpA in IBD patients<sup>3,32</sup>.

SpA symptoms are not always recognized in patients with IBD. A diagnostic delay of SpA in IBD patients of 5.2 years is reported<sup>20</sup>. A Canadian study showed that 129 out of 350 (36.9%) unselected IBD patients had musculoskeletal SpA features meeting the ASAS criteria.

Nevertheless, only 51% of those patients was seen by a rheumatologist. In that group of patients, SpA was diagnosed in 58% of the cases, while another rheumatic disorder was found in 21%<sup>33</sup>. Subsequently, patients with symptoms of SpA may be underdiagnosed and effective treatment may be delayed, which can lead to a chronic debilitating disease course and a decreased quality of life<sup>34</sup>. The use of a SpA self-reported questionnaire in IBD patients led to an increased recognition of SpA<sup>35</sup>. Diagnostic clues that should trigger the gastroenterologist to refer the patient for further rheumatologic evaluation are summarized in table 3, part A<sup>4,5</sup>.

#### 4.2 Diagnosing IBD in SpA patients

The diagnosis of IBD is made by clinical evaluation and a combination of biochemical, endoscopic, histological and/or radiological data<sup>36,37</sup>. Importantly, IBD can still be asymptomatic at the time that patients present with musculoskeletal symptoms<sup>38</sup>. In a cohort of 65 SpA patients, 46.2% had microscopic evidence of gut inflammation<sup>10</sup>. Risk factors associated with the presence of microscopic gut inflammation in axial SpA are younger age, progressive disease, male sex and a high disease activity<sup>10</sup>. 7% of SpA patients with microscopic gut inflammation develop IBD<sup>11</sup>. Occurrence of EIMs should therefore prompt

physicians to look for underlying IBD. This is especially important for the detection of CD, where the concept of early intervention is emerging<sup>39</sup>. Diagnostic clues that should trigger the rheumatologist to refer the patient for further gastroenterological evaluation are summarized in table 3, part B<sup>4,5</sup>. In addition, Cyfers et al. demonstrated an association between elevated serum calprotectin and C-reactive protein (CRP) and microscopic bowel inflammation in a cohort of 125 patients with SpA<sup>40</sup>. Also fecal calprotectin was significantly higher in patients with microscopic bowel inflammation. Calprotectin measurements in stool and serum, in addition to CRP, therefore provide an extra tool to identify SpA patients at risk of IBD<sup>40</sup>.

#### **4. Treatment goals**

##### **5.1 Treatment goals in IBD**

The STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) consensus defined mucosal healing in combination with resolution of symptoms as one of the major treatment goals for patients with IBD<sup>41</sup>. Mucosal healing is associated with sustained clinical remission, steroid-free remission, and reduced rates of hospitalization and surgery in CD<sup>42,43</sup>. In UC, studies demonstrated the association of mucosal healing with improved long-term clinical outcomes and a reduced risk of colectomy<sup>44-47</sup>. However, all data available on the value of mucosal healing as a target in IBD are mainly retrospective or circumstantial, and disease-modifying studies in IBD are scarce<sup>48</sup>. Also, the definition of mucosal healing is debated in both CD and UC, and the current definitions, based on cut-offs of endoscopic activity indices, are less favorable to be used as an instrument for disease remission<sup>49,50</sup>. The STRIDE consensus did not retain biomarkers as a treatment target<sup>41</sup>. In the recent CALM study, a treat-to-target strategy based on a composite target of tight control of biomarkers (fecal calprotectin and CRP) and clinical symptoms (Crohn's disease activity index or CDAI) was superior to standard care based on symptom control alone. Significantly more patients

achieved mucosal healing with absence of deep ulcers after 1 year<sup>51</sup>. In UC, Osterman et al. showed that a calprotectin-guided approach in aminosalicylates treated patients reduced relapse rates<sup>52</sup>. In 52 patients with UC in remission but with fecal calprotectin >50 µg/g taking multimatrix mesalamine 2.4g/day, mesalamine was either continued at the same dose or increased by 2.4 g/day for 6 weeks. The primary outcome of continued remission with fecal calprotectin <50 µg/g was achieved by 3.8% of controls and 26.9% of the dose escalation group (p=0.05). More patients in the dose escalation group reduced fecal calprotectin to below 100 µg/g (p=0.04) and 200 µg/g (p=0.005). Clinical relapse occurred sooner in patients with fecal calprotectin >200 µg/g compared to those with fecal caproctectin <200 µg/g (p=0.01)<sup>52</sup>. Nevertheless, whether treat-to-target strategies in IBD patients will prevent negative long-term outcomes, such as disability and bowel damage in CD, is yet to be established, whereas in another inflammatory disease such as rheumatoid arthritis (RA), evidence has accumulated over the last decade<sup>48,53,54</sup>.

## 5.2 Treatment goals in SpA

Similar to RA and CD, the treatment goals in SpA are maintenance of physical function, control of disease activity and prevention of organ damage<sup>55</sup>. The primary treatment goal of axial SpA is, according to the updated ASAS-EULAR management recommendations, to maximise long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation or normalisation of function and social participation<sup>56</sup>. A predefined target when initiating therapy is recommended to achieve this goal<sup>56</sup>. Recently, the association between disease activity and progression of tissue damage was established in patients with early axial SpA<sup>57</sup>. Nevertheless potent inflammatory drugs like anti-TNF agents do not prevent disease progression<sup>58</sup>. Treat-

to-target recommendations in SpA were formulated in 2014 by an international task force, but the investigators admitted evidence base was not strong<sup>59</sup>.

## 5. Treatment options

Current pharmacologic treatment options in patients with IBD are aminosalicylates, corticosteroids, immunomodulators, anti-TNF therapy, vedolizumab, ustekinumab and JAK inhibitors. A schematic overview of the pharmacologic treatment options in patients with IBD and SpA is shown in figure 1. Non-steroidal anti-inflammatory drugs (NSAIDs) are considered a first-line therapy in patients with SpA<sup>22,23</sup> and secukinumab, an anti-interleukin-17A monoclonal antibody, is a well-established treatment option for AS<sup>60</sup>. Nevertheless, both have no place in the specific treatment of IBD and will therefore not be discussed separately in this section.

### 6.1 Aminosalicylates

There is a lack of evidence for the use of 5-aminosalicylates (olsalazine and mesalamine) in CD<sup>61,62</sup>. Sulfasalazine shows low efficacy for the treatment of active CD<sup>62</sup>, but its incidental side effects should be taken into account when initiated<sup>36</sup>. Oral 5-aminosalicylates are highly effective for inducing and maintaining remission in mild to moderate UC<sup>63-65</sup>. Also sulfasalazine is effective in the treatment of UC<sup>66</sup>.

Sulfasalazine treatment was not more effective than placebo in a 24-week trial in patients with axial SpA<sup>67</sup>. A Cochrane review confirmed that there is not enough evidence to support any benefit of sulfasalazine in reducing pain, disease activity, radiographic progression, or improving physical function and spinal mobility in the treatment of AS<sup>68</sup>. Nevertheless, sulfasalazine can be used for peripheral SpA since it has demonstrated its efficacy in these patients<sup>56,69,70</sup>.

## 6.2 Corticosteroids

Two historical trials established corticosteroids as an effective therapy in inducing remission in CD<sup>71,72</sup>. Both topically (oral budesonide) and systemically acting corticosteroids can be used, depending on the disease distribution and severity. Although good at inducing remission, steroids are ineffective for maintaining remission in CD<sup>36</sup>. In UC, systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to mesalamine. Topical acting oral steroids (beclomethasone dipropionate) can also be used in patients with mild to moderately active disease<sup>66</sup>.

Furthermore, budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and proctosigmoiditis<sup>73</sup>. In acute severe UC, intravenously administration of methylprednisolone 60 mg each 24 hours or hydrocortisone 100 mg four times daily is promptly warranted<sup>66,74</sup>.

Systemic corticosteroid therapy is not recommended in the current treatment guidelines for axial SpA<sup>56,69</sup>. Only high dose (50 mg daily) of oral prednisone was effective in patients with AS<sup>75</sup>, and this approach might be considered as a short bridging therapy<sup>76</sup>. Local steroid injections are a valuable treatment option only in patients with peripheral SpA with oligoarthritis ( $\leq 4$  joints involved)<sup>76</sup>. Systemic corticosteroids can also be given in case of peripheral flare, but rapid tapering is required<sup>69</sup>.

## 6.3 Immunomodulators

Thiopurine therapy (azathioprine and 6-mercaptopurine) offers no advantage over placebo for induction of remission or clinical improvement in active CD, although it allows patient to reduce steroid consumption<sup>77</sup>. In UC, thiopurines are efficacious in patients who flare when steroids are withdrawn<sup>78,79</sup>. Furthermore, thiopurine therapy appears to be more effective than

placebo for maintenance of remission in both CD<sup>80</sup> and UC<sup>81</sup>. Also, the combination treatment of infliximab with azathioprine is more effective than infliximab monotherapy in CD<sup>82</sup> and UC<sup>83</sup>. There is evidence, coming from a single large randomized trial, that intramuscular methotrexate provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory CD<sup>84</sup>. Also, intramuscular methotrexate is superior to placebo for maintenance of remission in CD<sup>85</sup>. Addition of methotrexate to infliximab therapy does not appear to provide an additional benefit over infliximab monotherapy in CD<sup>86</sup>. In UC, parenteral methotrexate is not superior to placebo for induction of steroid-free remission, however it induces clinical remission without steroids in a significantly larger percentage of patients<sup>87</sup>. According to the ECCO guidelines, methotrexate can be considered in patients with steroid-dependent disease<sup>66</sup>. There is currently insufficient evidence to recommend methotrexate for the maintenance of remission in UC<sup>88</sup>. Treatment guidelines do not support the use of thiopurine therapy nor methotrexate in axial SpA<sup>56,69</sup>. Methotrexate did not show any benefit for axial manifestations in patients with active AS beyond the expected placebo response in a 16-week open-label trial<sup>89</sup>. Also, the combination of methotrexate with a TNF blocker for the treatment of axial SpA is not recommended given the lack of clear data<sup>76</sup>. Nevertheless, methotrexate is a well-proven therapeutic strategy in patients with psoriatic arthritis<sup>90</sup> and RA<sup>91</sup>, and may therefore be considered in patients with peripheral SpA<sup>32,56,69,70</sup>.

#### 6.4 Anti-TNF therapy

Numerous randomized controlled trials support the use of anti-TNF therapy in the treatment of CD and UC<sup>92-95</sup>. Anti-TNF therapy remains the cornerstone in the treatment of IBD<sup>13</sup>. Infliximab and adalimumab are indicated in case of failure of corticosteroids and/or immunosuppressants in both CD and UC. Certoluzimab pegol is only labelled for the use in

CD, and golimumab is only labelled for the use in UC <sup>36,66</sup>. Both infliximab and adalimumab can be used in the case of complex fistulising perianal disease, in conjunction with surgical drainage, but the level of evidence is lower for adalimumab compared to infliximab <sup>96-99</sup>.

Infliximab, adalimumab, golimumab and certolizumab pegol have approval, both in the EU and in the USA, for the use in patients with AS (r-axSpA), as multiple treatment trials showed improvement in clinical symptoms, CRP levels and MRI-detectable inflammation in the sacroiliac joints and spine in these patients <sup>27,76</sup>. Adalimumab, golimumab and certolizumab pegol, but not infliximab, seem to be equally effective in patients with nr-axSpA as in patients with r-axSpA <sup>100</sup>. All 3 agents already have additional approval for the use in nr-axSpA in the EU, but not yet in the USA. TNF blockers should be initiated in patients with active axial SpA who are refractory to NSAIDs and with at least one of the following: sacroiliitis on x-ray for r-axSpA, and inflammatory sacroiliitis on MRI and/or elevated CRP levels for nr -axSpA <sup>56,69,76</sup>. Etanercept, another anti-TNF agent, has proven efficacy in the treatment of axial SpA <sup>100</sup>, but not in IBD. Concerning peripheral arthritis, anti-TNF agents have demonstrated efficacy in psoriatic arthritis (adalimumab, certolizumab, etanercept) <sup>101</sup> and adalimumab also showed promising results in two placebo-controlled trials in patients with peripheral SpA <sup>102,103</sup>. Furthermore, the CARE study, a large European open-label trial, showed resolution of EIMs exceeding 50% in CD patients treated with adalimumab, including peripheral arthritis and r-axSpA <sup>104</sup>.

### 6.5 Vedolizumab

Vedolizumab is a gut-selective  $\alpha 4\beta 7$  integrin antagonist, modulating gut lymphocyte trafficking. Vedoluzimab is more effective than placebo as induction and maintenance therapy for CD <sup>105</sup> and UC <sup>106</sup>.



Although an exclusively local effect of vedolizumab could be expected based on the restricted presence of the  $\alpha4\beta7$  ligand, namely mucosal vascular addressin cell adhesion molecule 1 (madcam-1), in vascular and lymphatic vessels of the gut <sup>107,108</sup>, previous demonstration of  $\alpha4\beta7$  integrin in the joint <sup>109</sup> led to the expectation of a therapeutic efficacy in SpA. In contrast, vedolizumab induced arthritis flare and/or sacroiliitis in a recent small case-series of 5 IBD patients treated with the drug <sup>110</sup>. Nevertheless, arthritis is often driven by intestinal inflammation and in a recent study in IBD patients who were initiated with vedolizumab a complete remission of pre-existing arthropathies was noticed in 24/46 (52.2%) patients <sup>111</sup>. Also, in a post-hoc analysis of the GEMINI-2 cohort, there was a trend for reduced incidence of new or worsening arthralgia and arthritis and increased rates of sustained resolution of arthralgia and arthritis in patients receiving vedolizumab <sup>112</sup>. Orlando et al initiated vedolizumab in 22 IBD patients with associated SpA. No patient experienced a flare-up of the rheumatic disease and in 6 out of 14 patients (46.2%) with active SpA at the time of induction with vedolizumab, a sharp clinical benefit of the SpA was noticed <sup>113</sup>. Altogether, there is a need for large cohort studies exploring the potential benefit of vedolizumab on IBD-associated SpA.

## 6.6 Ustekinumab

Ustekinumab is a monoclonal antibody that binds to the p40 subunit common to interleukin-12 and interleukin-23 and prevents their binding to IL-12R $\beta$ 1 expressed on the surface of immune cells. Patients with moderately to severely active CD that received intravenous ustekinumab had a significantly higher rate of response than those receiving placebo. Subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy <sup>14</sup>. A study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in moderately to severely active UC is ongoing <sup>114</sup>.

Ustekinumab has demonstrated its efficacy in psoriatic arthritis <sup>15</sup> and induced a reduction of signs and symptoms in a prospective, open-label, proof-of-concept clinical trial in patients with active AS <sup>115</sup>. Nevertheless, the use of ustekinumab in axial SpA is not yet firmly demonstrated and final results of phase 3 trials in r-axSpA <sup>116</sup> and nr-axSpA <sup>117</sup> need to be awaited.

### 6.7 Janus kinase (JAK) inhibitors

Tofacitinib is an orally active small chemical molecule, targeting all JAKs (JAK1/JAK2/JAK3/TYK2), but preferentially JAK1 and JAK3 <sup>118,119</sup>. Tofacitinib is not effective in CD <sup>120,121</sup>, but results from the phase 3 OCTAVE trials showed superiority of tofacitinib over placebo as induction and maintenance therapy in patients with moderately-to-severe active UC <sup>122</sup>. Filgotinib is a selective JAK1 inhibitor that induces clinical remission in significantly more patients with active CD compared to placebo <sup>123</sup>, but these promising results need to be confirmed in phase 3 trials. Also upadacitinib, another selective JAK1 inhibitor, demonstrated endoscopic improvement and clinical benefit as induction therapy in a recent dose-ranging study in 220 patients with moderate to severe refractory CD <sup>124</sup>. Further clinical data are necessary to assess the potential of selective JAK 1 inhibition in UC <sup>125</sup>. In a recent phase 2 study in patients with active AS, tofacitinib 5 mg and 10 mg twice daily demonstrated greater clinical efficacy versus placebo in reducing signs, symptoms and objective endpoints after 12 weeks of treatment <sup>126</sup>. There are no data available on the use of selective JAK1 inhibitors in SpA.

## 6. Treatment guidelines in patients with IBD and SpA

An Italian expert panel developed therapeutic algorithms in patients with IBD and SpA depending on the disease activity of both entities <sup>5</sup>. Based on these principles, also a very

recent a Delphi consensus summarizes strategies for the best management of patients with coexisting IBD and SpA<sup>127</sup>. The first ECCO consensus on EIMs in IBD provides a limited set of statements concerning the treatment of peripheral and axial SpA in IBD patients<sup>3</sup>. The current available treatment guidelines in IBD patients with SpA are summarized in table 4. The jointly management of IBD patients with SpA by the gastroenterologist and the rheumatologist is generally supported. The choice of a pharmacologic treatment depends on the dominant disease. Steroids and 5-aminosalicylates should only be used when indicated for IBD, but not for SpA. Sulfasalazine and methotrexate may have a role in the treatment of concomitant (mainly peripheral) SpA. Anti-TNF blockers have to be started according to the treatment guideline of the dominant disease. NSAIDs for SpA can only be considered in patients without active IBD and should be limited to short periods in time.

## 7. Summary

SpA is the most common EIM in IBD and occurs in up to 13% of patients. On the other hand, microscopic intestinal inflammation is documented in approximately 50% of patients with SpA. SpA is classified according to the ASAS criteria, distinguishing peripheral from axial involvement. Timely diagnosis of both SpA in IBD patients and IBD in SpA patients is important. Cooperation between the gastroenterologist and the rheumatologist is necessary to guarantee an integrated management that provides the best possible care to IBD patients with SpA. Whether treat-to-target strategies will prevent long-term outcomes such as disability and organ damage is yet to be established in both IBD and SpA. Current treatment guidelines in patients with IBD and SpA are developed by an Italian expert panel (2014) and by ECCO (2016). Given its well-documented efficacy in both diseases, anti-TNF therapy remains the cornerstone in the treatment when IBD and SpA coexist. Whether drugs with a gut-specific

mode of action, such as vedolizumab, work for IBD-related arthritis is still debated. NSAIDs use for SpA can only be considered in patients without active IBD and should be limited to short periods in time.

## **8. Expert commentary**

The coexistence of IBD and SpA generates challenges as well as opportunities for both the gastroenterologist and the rheumatologist.

Although concomitant IBD and SpA is frequent, awareness in health care practitioners remains low and too often a well-structured multidisciplinary management is not offered to the patient. Therefore, regular deliberation between the gastroenterologist and the rheumatologist, for example in a monthly multidisciplinary team meeting, can optimise care by giving the opportunity to discuss complex cases and make jointly treatment decisions. Joint complaints in IBD patients are often difficult to deal with and a broad differential diagnosis exists. Mainly arthralgia (joint pain without inflammation) and arthritis (joint pain with objective signs of inflammation) need to be distinguished. Arthralgia in IBD patients can be caused by the introduction of thiopurines<sup>128,129</sup> or by the withdrawal of corticosteroids<sup>130</sup>. It is also a common side effect in patients treated with anti-TNF therapy<sup>131,132</sup>. Furthermore, corticosteroid-related osteonecrosis and infliximab-related lupus-like syndrome can mimic SpA in IBD patients<sup>133,134</sup>. Given the important repercussions of a correct diagnosis for the treatment strategy, IBD patients who develop joint pain deserve a thoroughly assessment by a rheumatologist. On the other hand, gastrointestinal complaints in SpA patients are not always caused by IBD. Other entities such as irritable bowel syndrome, coeliac disease, lactose ingestion, gastrointestinal infection, bacterial overgrowth, bile salt diarrhea, ischemia or

vasculitis are part of the differential diagnosis. An expert advice by a gastroenterologist to choose the most appropriate diagnostic strategy is warranted.

Practitioners need to be aware that management options for SpA can influence the IBD disease course in a negative way. NSAIDs are a first-line treatment option for SpA but increase the risk of IBD relapse<sup>135,136</sup>. Some data suggest that the use of COX-2 inhibitors may be safer than conventional NSAIDs<sup>137,138</sup>, but this needs to be confirmed. We support the general idea that the use of NSAIDs in IBD patients should be avoided when possible, although short-term use is acceptable when necessary<sup>139</sup>. Etanercept, an anti-TNF agent with proved efficacy in the treatment of axial SpA<sup>100</sup> can induce IBD<sup>140,141</sup>. Its use should not be recommended in first line of treatment of SpA in patients with concomitant IBD.

Nevertheless, it may be considered in patients with active SpA who fail all other TNF agents and have no flare of their IBD.

Treatment targets in IBD and SpA are similar and include the early intervention in the disease course by tight control of the inflammation to prevent structural damage. To further optimise these goals, new prospective disease-modifying trials are eagerly needed in both diseases.

The well-established advantage of anti-TNF therapy in patients with EIMs<sup>142</sup> illustrates the possibility to treat two diseases with one management option. In this regard, the potential of drugs with a gut-specific mode of action in the treatment of IBD-related arthritis warrants further exploration, since arthritis is often driven by intestinal inflammation. The efficacy of ustekinumab in CD<sup>14</sup> and tofacitinib in UC<sup>122</sup> is recently confirmed, but their potential to simultaneously treat SpA needs further evaluation.

## 9. Five-year view

To develop better treatment strategies for patients with concomitant IBD and SpA, we need a more profound understanding of the underlying disease mechanisms that play in these patients. Research will focus around two major topics in the upcoming years: the role of drugs with a gut-specific mode of action in the treatment of concomitant rheumatic disease and the role of gut microbiota in the pathogenesis of IBD and SpA.

Real-life experience of the use of vedolizumab and more prospectively collected data in large cohort studies will clarify the effect of the drug in the treatment of IBD-related arthritis. We believe that vedolizumab will more likely have a beneficial, rather than a paradoxical, effect in patients with concomitant IBD and SpA. Several recent clinical data support this expectation<sup>111–113</sup>. The upregulation of mucosal vascular cell adhesion molecule 1 in the high endothelial venules of bone marrow in patients with active axial SpA<sup>143</sup> could (partially) explain this effect.

Growing insight into the composition and functionality of the mucosal microbiota has revealed its involvement in mucosal barrier integrity and immune function. The association between compositional and metabolic changes in the intestinal microbiota (dysbiosis) and IBD is now widely accepted. Gut microbiota also shapes local and systemic immune responses, and therefore can potentially affect the development and progression of rheumatic diseases<sup>144</sup>. Further basic and translational research will elaborate the exact mechanisms that play a part in this interaction, and this can hopefully lead to new therapeutic strategies for patients with concomitant IBD and SpA.

## 10. Key issues

1. The most common extra-intestinal manifestation in patients with inflammatory bowel disease (IBD) is spondyloarthritis (SpA). Microscopic intestinal inflammation is documented in almost 50% of the patients with SpA.  
- An integrated management of patients with coexisting IBD and SpA is necessary to guarantee the timely diagnosis of both entities, and to provide the best possible care to patients.
2. Current treatment guidelines in patients with IBD and SpA are developed by an Italian expert panel (2014). Also the European Crohn's and Colitis Organisation (ECCO) (2016) consensus describes a diagnostic approach for arthritis in IBD patients.
3. Anti-TNF therapy remains the cornerstone in the treatment of patients with coexisting IBD and SpA.
4. NSAIDs for SpA can only be considered in patients without active IBD and should be limited to short periods in time.
5. The potential of drugs with a gut-specific mode of action in the treatment of IBD-related arthritis warrants further exploration.

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Figure 1: Pharmacologic treatment options in patients with IBD and SpA.

Legend: CD: Crohn's disease; JAK: janus kinase; NSAIDs: non-steroidal anti-inflammatory drugs; SpA: spondyloarthritis; UC: ulcerative colitis.

Treatment option	CD	UC	SpA
Aminosalicylates	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Efficacy not proven/use generally not supported (1)
Corticosteroids	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Use can be considered in specific situations (2)
Thiopurines	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Efficacy not proven/use generally not supported
Methotrexate	Well-proven efficacy and use generally recommended/accepted	Use can be considered in specific situations (3)	Use can be considered in specific situations (4)
Infliximab	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted
Adalimumab	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted
Certolizumab pegol	Well-proven efficacy and use generally recommended/accepted	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted
Golimumab	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted
Etanercept	Efficacy not proven/use generally not supported	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted
Vedolizumab	Well-proven efficacy and use generally recommended/accepted	Well-proven efficacy and use generally recommended/accepted	Efficacy not proven/use generally not supported (5)
Ustekinumab	Well-proven efficacy and use generally recommended/accepted	Insufficient data or efficacy needs to be confirmed in larger trials	Insufficient data or efficacy needs to be confirmed in larger trials
Tofacitinib	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted	Insufficient data or efficacy needs to be confirmed in larger trials
Selective JAK1 inhibitors	Insufficient data or efficacy needs to be confirmed in larger trials	Insufficient data or efficacy needs to be confirmed in larger trials	Insufficient data or efficacy needs to be confirmed in larger trials
Secukinumab	Efficacy not proven/use generally not supported	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted
NSAIDs	Efficacy not proven/use generally not supported	Efficacy not proven/use generally not supported	Well-proven efficacy and use generally recommended/accepted

Well-proven efficacy and use generally recommended/accepted  
 Efficacy not proven/use generally not supported  
 Use can be considered in specific situations  
 Insufficient data or efficacy needs to be confirmed in larger trials

- (1) Sulfasalazine can be considered in patients with peripheral SpA, but not in axial SpA.
- (2) Local corticosteroid injection is a valuable option in peripheral SpA; systemic corticosteroids can only be considered as a short bridge to other therapies.
- (3) Methotrexate can be considered in UC patients with steroid-dependent disease.
- (4) Methotrexate can be considered in patients with peripheral SpA, but not in axial SpA.
- (5) Vedolizumab is not a specific treatment option for SpA, but might improve IBD-related arthritis.

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Table 1: ASAS classification criteria for peripheral and axial SpA<sup>22,23</sup>.

<b>Peripheral SpA</b>	
Arthritis or Enthesitis or Dactylitis	
PLUS	
<u>≥ 1 of:</u> o Psoriasis o IBD o Preceding infection o HLA-B27 o Uveitis o Sacroiliitis on imaging*	<b>OR</b>
	<u>≥ 2 of the remaining:</u> o Arthritis o Enthesitis o Dactylitis o Inflammatory back pain in the past o Positive family history for SpA
<b>Axial SpA (in patients with back pain ≥ 3 months and age of onset &lt; 45 years)</b>	
Sacroiliitis on imaging*	HLA B-27
PLUS	<b>OR</b> PLUS
≥ 1 SpA feature**	≥ 2 other SpA features**

\* Sacroiliitis on imaging:

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- OR
- Definite radiographic sacroiliitis according to modified New York criteria

\*\* SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- CD/UC
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

Table 2: Classification of IBD-related arthritis according to ECCO consensus (2016) <sup>3</sup>.

Localisation	Disease characteristics	Subtypes
<b>Peripheral</b>	<ul style="list-style-type: none"> <li>- Signs of inflammation</li> <li>and</li> <li>- Exclusion of other specific forms of arthritis</li> </ul>	<p><u>Type 1</u></p> <ul style="list-style-type: none"> <li>- Affecting <math>\leq</math> 5 joints</li> <li>- Predominantly lower limbs</li> <li>- Mostly acute and self-limiting</li> <li>- Parallels IBD activity</li> </ul> <p><u>Type 2</u></p> <ul style="list-style-type: none"> <li>- Affecting <math>&gt;</math> 5 joints</li> <li>- Predominantly upper limbs</li> <li>- Can persist months/years</li> <li>- Independently from IBD activity</li> </ul>
<b>Axial</b>	<ul style="list-style-type: none"> <li>- Inflammatory back pain</li> <li>and</li> <li>- Magnetic resonance imaging or radiographic features of sacroiliitis</li> </ul>	Sacroiliitis +/- spondylitis

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Table 3: Diagnostic clues for referral of the IBD patient to the rheumatologist and for referral of the SpA patient to the gastroenterologist <sup>4,5</sup>.

**Part A: Diagnostic clues that should trigger the gastroenterologist to refer the IBD patient for further rheumatologic evaluation**

- Chronic (>3 months) back pain
- Peripheral joint pain/swelling
- Presence of signs of enthesitis
- History or evidence of dactylitis

**Part B: Diagnostic clues that should trigger the rheumatologist to refer the SpA patient for further gastroenterological evaluation**

- Family history of IBD
- Clinical symptoms:
  - Chronic diarrhea
  - Chronic abdominal pain
  - Rectal bleeding
  - Weight loss
  - Persistent fever
- History or evidence of perianal fistula/abscess
- Anemia

Table 4: Key components of the current available treatment guidelines in IBD patients with coexisting SpA.

<b>Olivieri et al. (2014)</b> <sup>5</sup>
<b>Peripheral SpA (≤ 4 joints, enthesitis, dactylitis) and active IBD</b>
<ul style="list-style-type: none"> <li>o Systemic steroids and/or sulfasalazine according to IBD indications.</li> <li>o Anti-TNF according to IBD guidelines.</li> <li>o Consider stopping anti-TNF only after complete IBD remission.</li> </ul>
<b>Peripheral SpA (&gt; 4 joints) and active IBD</b>
<ul style="list-style-type: none"> <li>o Systemic steroids and/or sulfasalazine according to IBD indications.</li> <li>o NSAIDs should be avoided.</li> <li>o Anti-TNF according to IBD guidelines.</li> <li>o Consider stopping anti-TNF only after complete IBD remission.</li> </ul>
<b>Peripheral SpA and IBD in remission</b>
<ul style="list-style-type: none"> <li>o Local steroid injections, short- term (≤ 15 days) NSAIDs and oral sulfasalazine are appropriate options in peripheral oligoarthritis (≤ 4 joints, enthesitis, dactylitis).</li> <li>o Short-term (≤ 15 days) NSAIDs/systemic steroids may be considered as a bridge to oral sulfasalazine in peripheral polyarthritis (&gt; 4 joints).</li> <li>o Anti-TNF according to rheumatological indications.</li> <li>o Anti-TNF can be gradually suspended according to rheumatologist's opinion in case of prolonged remission.</li> </ul>
<b>Axial SpA and active IBD</b>
<ul style="list-style-type: none"> <li>o Rehabilitation therapy according to ASAS recommendations.</li> <li>o Anti-TNF according to IBD guidelines.</li> <li>o Anti-TNF long-term treatment according to axial SpA treatment recommendations only after complete IBD remission.</li> </ul>
<b>Axial SpA and IBD in remission</b>
<ul style="list-style-type: none"> <li>o Rehabilitation therapy according to ASAS recommendations.</li> <li>o NSAIDs can be used only short-term (≤ 15 days).</li> <li>o Anti-TNF according to ASAS guidelines.</li> <li>o Anti-TNF long-term treatment according to ASAS ° guidelines.</li> </ul>
<b>ECCO consensus (2016)</b> <sup>3</sup>
<b>Peripheral SpA</b>
<ul style="list-style-type: none"> <li>o Treatment of underlying gut inflammation is often sufficient to treat peripheral arthritis.</li> <li>o Short-term NSAID or local steroid injection can be used to provide symptomatic relief.</li> <li>o Short-term oral corticosteroids are effective but should be discontinued as soon as practicable.</li> <li>o Sulfasalazine and methotrexate may have a role the treatment.</li> <li>o Anti-TNF therapy is appropriate and effective in resistant cases.</li> </ul>
<b>Axial SpA</b>
<ul style="list-style-type: none"> <li>o Intensive physiotherapy is effective.</li> <li>o Short-term NSAIDs is effective but long-term treatment with NSAIDs is not recommended.</li> <li>o Sulfasalazine and methotrexate are of limited efficacy.</li> <li>o Anti-TNF is the preferred treatment for those intolerant or refractory to NSAIDs.</li> </ul>