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## Inflammatory bowel diseases and spondyloarthropathies: From pathogenesis to treatment

George E Fragoulis, Christina Liava, Dimitrios Daoussis, Euangelos Akriviadis, Alexandros Garyfallos, Theodoros Dimitroulas

**ORCID number:** George E Fragoulis (0000-0003-4932-7023); Christina Liava (orcid.org/0000-0001-9523-5694); Dimitrios Daoussis (0000-0001-8027-3655); Evangelos Akriviadis (0000-0002-7906-6445); Alexandros Garyfallos (0000-0001-7289-1293); Theodoros Dimitroulas (0000-0002-0364-1642).

**Author contributions:** Fragoulis GE reviewed the literature, drafted the manuscript, designed the structure of the manuscript; Liava C reviewed the literature, drafted the manuscript; Daoussis D drafted the manuscript, critically revised the manuscript; Akriviadis E drafted the manuscript, critically revised the manuscript; Garyfallos A drafted the manuscript, critically revised the manuscript; Dimitroulas T drafted the manuscript, reviewed the literature, critically revised the manuscript, designed the structure of the manuscript.

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**George E Fragoulis**, First Department of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, “Laiko” General Hospital, Athens 11527, Greece

**George E Fragoulis**, Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow G128TA, United Kingdom

**Christina Liava, Euangelos Akriviadis, Alexandros Garyfallos, Theodoros Dimitroulas**, 4<sup>th</sup> Department of Internal Medicine, Hippokraton Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

**Dimitrios Daoussis**, Department of Internal Medicine, Division of Rheumatology, Patras University Hospital, Patras 26504, Greece

**Corresponding author:** Theodoros Dimitroulas, MD, PhD, Assistant Professor, 4<sup>th</sup> Department of Internal Medicine, Hippokraton Hospital, School of Medicine, Aristotle University of Thessaloniki, 49 Konstantinoupoleos Str, Thessaloniki 54642, Greece. [dimitroul@hotmail.com](mailto:dimitroul@hotmail.com)  
**Telephone:** +30-231-0892169  
**Fax:** +30-231-0818254

### Abstract

Spondyloarthropathies (SpA) include many different forms of inflammatory arthritis and can affect the spine (axial SpA) and/or peripheral joints (peripheral SpA) with Ankylosing spondylitis (AS) being the prototype of the former. Extra-articular manifestations, like uveitis, psoriasis and inflammatory bowel disease (IBD) are frequently observed in the setting of SpA and are, in fact, part of the SpA classification criteria. Bowel involvement seems to be the most common of these manifestations. Clinically evident IBD is observed in 6%-14% of AS patients, which is significantly more frequent compared to the general population. Besides, it seems that silent microscopic gut inflammation, is evident in around 60% in AS patients. Interestingly, occurrence of IBD has been associated with AS disease activity. For peripheral SpA, two different forms have been proposed with diverse characteristics. Of note, SpA (axial or peripheral) is more commonly observed in Crohn's disease than in ulcerative colitis. The common pathogenetic mechanisms that explain the link between IBD and SpA are still ill-defined. The role of dysregulated microbiome along with migration of T lymphocytes and other cells from gut to the joint (“gut-joint” axis) has been recognized, in the context of a genetic background including associations with alleles inside or outside the human leukocyte antigen system. Various therapeutic modalities are available with monoclonal antibodies against tumour necrosis

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factor, interleukin-23 and interleukin-17, being the most effective. Both gastroenterologists and rheumatologists should be alert to identify the co-existence of these conditions and ideally follow-up these patients in combined clinics.

**Key words:** Spondyloarthropathies; Axial spondyloarthropathies; Peripheral spondyloarthropathies; Ankylosing spondylitis; Inflammatory bowel disease

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**Core tip:** Spondyloarthropathies (SpA) are subdivided to axial and peripheral SpA with ankylosing spondylitis (AS) being the prototype disease of the former. They have many extra-articular manifestations the most common of which is bowel involvement. Inflammatory bowel disease (IBD) (silent or clinically evident) occurs much more frequently in AS compared to the general population and associates with AS disease activity. Both axial and peripheral SpA occur more frequently in Crohn's disease than ulcerative colitis. Pathogenetic mechanisms that have been proposed to explain the link between SpA and IBD include dysregulated microbiome and migration of T lymphocytes and other cells from gut to the joint.

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## INTRODUCTION

Under the term spondyloarthropathy (SpA) are classified many inflammatory arthropathies with similar clinical and imaging features. However, diagnostic laboratory or pathological findings with high specificity are lacking. SpA affects mainly the spine, but symptomatology from the peripheral joints as well as from entheses and other tissues might occur. SpA include: psoriatic arthritis (PsA), peripheral SpA, enteropathic [also known as inflammatory bowel disease (IBD)-related] arthritis, reactive arthritis, undifferentiated spondyloarthropathy and axial spondyloarthropathy (axSpA) which includes non-radiographic axial spondyloarthropathy (nraxSpA), and Ankylosing spondylitis (AS)<sup>[1]</sup>. The latter is considered the prototype of these diseases<sup>[2]</sup>. Enthesitis (inflammation of the entheses which are the insertions of the ligaments and tendons into the bone) is thought to be one of the key manifestations in SpA, helping to distinguish from other inflammatory arthropathies<sup>[1]</sup>. Apart from the skeletal disease, extra-articular manifestations like uveitis, psoriasis and inflammatory bowel disease often occur<sup>[2]</sup>, offering significant help in the diagnosis of these diseases and being part of their classification criteria<sup>[3,4]</sup>. Of note, IBD contributes to the diagnosis of axSpA, as it has a positive likelihood ratio of 4.3 for axSpA diagnosis in patients with chronic low back pain<sup>[5,6]</sup>.

According to the latest Assessment of SpondyloArthritis Society (ASAS) criteria, SpA can be classified to axSpA or peripheral SpA. The former pertains to patients with low back pain for  $\geq 3$  mo and age of onset  $< 45$  years old and requires either sacroiliitis on imaging and at least one other SpA feature (*e.g.*, dactylitis, enthesitis) or positivity for HLA-B27 and at least two other SpA features (Table 1)<sup>[4]</sup>. Difference between nraxSpA and axSpA is the lack of radiographically confirmed sacroiliitis in the former. Under the term "peripheral SpA" are classified patients without current low back pain, with peripheral arthritis, or enthesitis or dactylitis plus at least one or two of the following SpA features: (uveitis, psoriasis, crohn's disease/ulcerative colitis, preceding infection, positive HLA-B27, sacroiliitis on imaging) or (arthritis, enthesitis, dactylitis, inflammatory back pain in the past, family history of SpA), respectively<sup>[3]</sup>.

It is well known that there is a close association between IBD and SpA<sup>[7]</sup>. Purpose of our review was to present in detail the existing epidemiological data and treatment approaches to these patients and to delineate the current diagnostic challenges. Also, we aimed to describe the underlying pathogenetic mechanisms that have been

**Table 1 Assessment of Spondyloarthritis International Society Classification criteria for axial spondyloarthropathy and peripheral spondyloarthropathy**

Axial Spondyloarthropathy		
Patients with back pain $\geq$ 3 months and age at onset $<$ 45 years		
<i>Sacroiliitis on imaging</i> <sup>1</sup> plus $\geq$ 1	OR	<i>HLA-B27 plus <math>\geq</math> 2 other</i>
<b>Spondyloarthropahty feature</b> (Imaging arm)		<b>Spondyloarthropahty features</b> (Clinical arm)
<b>Spondyloarthropahty features</b>		
Inflammatory back pain		
Arthritis		
Enthesitis (heel)		
Uveitis		
Dactylitis		
Psoriasis		
Crohn's Disease/Ulcerative colitis		
Good response to NSAIDs		
Family history of spondyloarthropahty		
HLA-B27		
Elevated CRP		
Peripheral Spondyloarthropathy		
Arthritis OR Dactylitis OR Enthesitis <sup>2</sup>		
PLUS		
$\geq$ 1		$\geq$ 2
Uveitis		Arthritis
Psoriasis		Enthesitis
Inflammatory bowel disease	OR	Dactylitis
Preceding infection		IBP (past)
HLA-B27		Family history of Spondyloarthropahty
Sacroiliitis on imaging		

ASAS (ASAS, Assessment of Spondyloarthritis international Society) classification criteria for axial Spondyloarthropathy (axSpA) and peripheral Spondyloarthropathy (peripheral SpA).

<sup>1</sup>Definite radiographic sacroiliitis according to the modified New York criteria or positive sacroiliac magnetic resonance imaging.

<sup>2</sup>Without current back pain. NSAIDs: Non-steroidal anti-inflammatories; HLA: Human leukocyte antigen; CRP: C-reactive protein; IBP: Inflammatory back pain (3,4).

suggested to link these two entities.

## IBD AND SPA: EPIDEMIOLOGY, AND ASSOCIATION WITH DISEASE CHARACTERISTICS

### IBD in the context of SPA

IBD [including Crohn's disease (CD) and ulcerative colitis (UC)] is not rare in AS, with its prevalence ranging from 6%-14%<sup>[2,6,8,9]</sup>. In detail, in a large population, control-matched study, including 4101 patients with AS, Stolwijk *et al*<sup>[6]</sup> found that at the time of AS diagnosis, the cumulative incidence was 4%. Additionally, in a French large, prospective study for early inflammatory back pain, IBD occurred in 7.2% of patients with newly diagnosed AS<sup>[10]</sup>. Furthermore, in an early axSpA cohort frequency of IBD was calculated to be 2.6% (1.7% for AS and 0.9% for nraxSpA, difference was not significant)<sup>[11]</sup>. In fact, it has been suggested that the risk for IBD is more pronounced in the first years of AS diagnosis and falls at baseline levels approximately 10 years after<sup>[6]</sup>. However, this has not been confirmed by a SLR and meta-analysis<sup>[2]</sup>. In that, Stolwijk *et al*<sup>[6]</sup> found that prevalence of IBD in AS was 6.8% (95%CI: 6.1%-7.7%), which is much higher than the percentages observed in the general population (0.01% to 0.5%). Likewise, in a large population study was shown that the incidence rate of IBD was 5.3-fold increased to the AS patients compared to healthy controls. For nraxSpA the results seem to be largely similar. In a meta-analysis addressing the

prevalence of extra-articular disease in nraxSpA versus AS, it was found that IBD was almost equally frequent (pooled prevalence difference of 1.4% in favour of AS) between these two entities<sup>[8]</sup>.

The question remains open whether we can predict which SpA patients suffer from or will develop IBD. Stolwijk *et al*<sup>[6]</sup> 2014 found that IBD was in general more common in males and that its frequency decreases with age, in AS. In a multi-centre AS study with a long follow-up, no differences were recorded between patients who had a history of IBD at baseline and those who did not<sup>[9]</sup>. On the other hand, development of IBD was associated with disease activity and spinal pain scores at baseline and worse physical function and patient well-being, at the time of IBD diagnosis<sup>[9]</sup>. Additionally, in a case control study<sup>[12]</sup> it was found that anterior uveitis was less frequent in patients with IBD-related spondyloarthropathy compared to those with SpA without bowel involvement<sup>[12]</sup>. Interestingly, in a sub-analysis of the GIANT cohort, it was shown that in patients with axSpA, there is a link between bone marrow edema of the sacroiliac joints and the gut inflammation. For this, SPARCC (Spondyloarthritis Research Consortium of Canada) scores which is a tool to measure MRI-defined sacroiliitis and ileocolonoscopy were used, respectively. It was found that SPARCC scores were higher in patients with chronic gut inflammation, compared to those without gut lesions<sup>[13]</sup>.

### **Clinically silent IBD in SPA**

Despite clinically evident IBD in the context of AS is observed in less than 15%, it has been suggested that clinically silent macroscopic and microscopic gut inflammation occurs in about 60% of AS patients<sup>[14-16]</sup>. From them, 5%-20% will develop CD within 5 years<sup>[17,18]</sup>. Microscopic gut inflammation, in axSpA, has been associated with younger age, male gender, progressive disease, early disease onset, radiologic sacroiliitis, high disease activity as assessed by the BASDAI and restricted spinal mobility measured by the Bath Ankylosing Spondylitis Metrology Index<sup>[9,16]</sup>. No association was identified with other extra-articular features or with the status of HLA-B27. Results were comparable between nraxSpA and AS<sup>[16]</sup>.

### **SPA occurring in patients with IBD**

Seeing the opposite flip of the coin, SpA is encountered in about 10-39% of patients with IBD, being the most frequent extra-intestinal manifestation in these individuals<sup>[16,19-25]</sup>. SpA is more commonly observed in patients with CD compared to those with UC<sup>[26-28]</sup>. Axial/arthritis symptomatology usually follows IBD diagnosis, but in about 20% the opposite is the case<sup>[19,23]</sup> especially for axial disease<sup>[20]</sup>. In general, AS and sacroiliitis (symptomatic or not) is estimated to occur in about 2%-16% and 12%-46% of IBD patients, respectively<sup>[19,20,22,23,27,29]</sup>, both being more common in CD than in UC<sup>[19,30]</sup>. In a recent meta-analysis, it was shown that prevalence of AS and sacroiliitis in IBD were 3% (95%CI: 2%-4%) and 10% (95%CI: 8%-12%), respectively.

Comparing CD patients with and without AS, in a small single centre study, Liu *et al* did not observe any differences between these two groups<sup>[31]</sup>. Of note, they demonstrated that there was a significant correlation between disease activities of these two entities. These were measured by CD activity index for CD and with BASDAI for AS. They also showed that activity of CD significantly correlated with functional disability in AS, as assessed by Bath AS functional index - BASFI. All these possibly imply that there is a tight connection in the pathogenetic mechanisms of these conditions.

On the other hand, in a study examining possible associations between clinical and other characteristics with the occurrence of AS or SI in patients with CD, it was found that there was an association between SI and peripheral arthritis as well as between AS and uveitis, in these patients<sup>[32]</sup>. Besides, it has been suggested that in CD patients, colitis is more commonly associated with arthritic involvement compared with patients suffering from ileitis, while regarding UC, it seems that isolated proctitis is rarely combined with rheumatic manifestations<sup>[20,23]</sup>.

Finally, patients with IBD-related ankylosing spondylitis and IBD-related isolated sacroiliitis are HLA-B27 positive in about 25%-78% and 7%-15%, respectively<sup>[20,22,32,33]</sup>, possibly suggesting that isolated sacroiliitis is of different nature compared to AS in the setting of IBD<sup>[23]</sup>. These percentages are also lower compared to the prevalence of HLA-B27 observed in patients with AS which range from 80%-90%<sup>[1,20,34-36]</sup>.

Peripheral SpA is also common in IBD with its prevalence ranging from 0.4% to 34.6%<sup>[19,28,37]</sup>. A recent systematic review and meta-analysis found that the pooled prevalence of peripheral arthritis, in the context of IBD was 13% (95%CI: 12%-15%) with its prevalence being much higher in the younger ages: 25% (95%CI: 19%-32%) and 2% (95%CI: 1%-5%) for age groups between 20-30 and 50-60 years old, respectively<sup>[30]</sup>. As observed for axial disease, peripheral SpA is more common in CD compared to UC<sup>[28,30,38]</sup>. A large retrospective study in the IBD Oxford clinics, had

shown that peripheral arthritis occurred in 10% and 6% of patients with CD and UC, respectively<sup>[38,39]</sup>. This study, led to identification of two major groups of peripheral arthritis in the context of IBD, namely: oligoarticular (< 5 joints are affected) and polyarticular (≥ 5 joints are affected)<sup>[20]</sup>. Some authors suggest that in the first group, which is more frequent than the second<sup>[39]</sup>, arthritis is usually asymmetrical, non-erosive, affects lower limbs<sup>[20]</sup> and is associated with IBD activity and positivity for HLA-B27<sup>[23,39]</sup>. Patients belonging in the second group tend to have a more chronic course and be destructive and unrelated with IBD activity and HLA-B27 status<sup>[38]</sup>. Furthermore, Yüksel *et al*<sup>[26]</sup>, examining the characteristics of peripheral arthritis in patients with IBD, they found that erythema nodosum and pyoderma gangrenosum were more commonly observed in IBD patients who also had peripheral arthritis, compared to those without. Various risk factors have been reported for peripheral arthritis in the context of IBD including: family history of IBD, appendectomy, smoking and presence of other extra-intestinal manifestations<sup>[19,40,41]</sup>.

Finally, some IBD patients might exhibit clinical features of SpA (*e.g.*, dactylitis) without fulfilling diagnostic criteria for SpA<sup>[20,42]</sup>. The frequency of dactylitis in patients with SpA in the context of IBD varies from 0% to 15.5%, but it seems to be around 5%<sup>[12,30]</sup> and therefore less common than in patients with SpA without IBD<sup>[12]</sup>. Incidence of enthesitis also varies largely, among different studies, in these patients<sup>[12,30]</sup>. A case control study<sup>[12]</sup> found that enthesitis was also less frequent in IBD-SpA patients compared to SpA individuals without IBD. For both dactylitis and enthesitis, no differences in their frequency were detected between CD and UC patients, while they occurred more frequently in patients with IBD and psoriasis compared to the IBD patients without skin disease<sup>[12]</sup>.

## PATHOPHYSIOLOGY

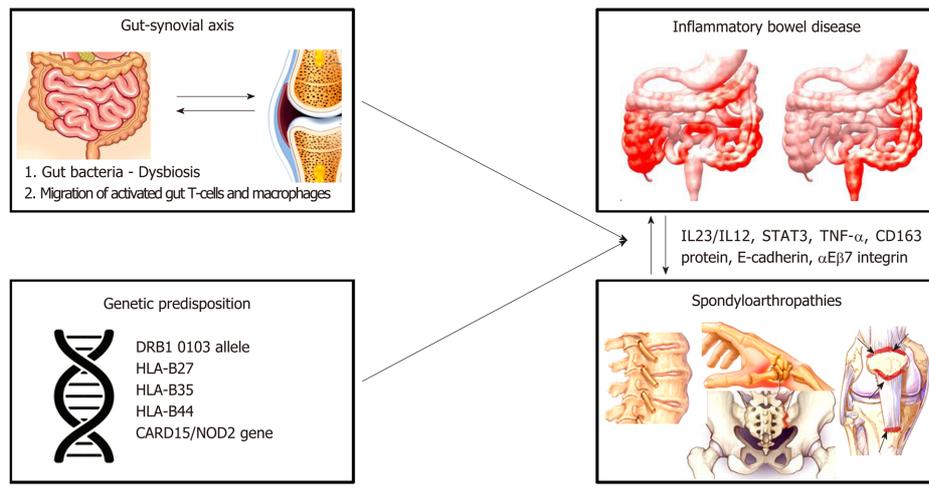
The pathophysiology of spondylarthropathies associated with IBD involves the so-called “gut-synovial axis” hypothesis, which implicates environmental and host factors. Many of them act as triggers leading to initiation of inflammation in genetically predisposed individuals (Figure 1). Several studies have confirmed the link between joint and gut inflammation. It seems likely that both bacterial antigens and reactive T-cell clones, activated into the gut home the joint. However, the exact immunological mechanisms linking gut and joint inflammation are not fully understood<sup>[43,44]</sup>.

### Genetic predisposition

Genetic predisposition seems to carry a significant role in linking these conditions. In a large genotyping study, investigating risk variants for AS, it was shown that many of these were also linked with CD and UC<sup>[45]</sup>. Additionally, in a genealogic study in Iceland it was shown that first and second-degree relatives of patients with AS had increased risk (3.0 and 2.1, respectively) for IBD and vice versa<sup>[46]</sup>.

Genetic factors play an important role, through alterations in both the adaptive and innate immune pathways<sup>[43,44]</sup>. Certain human leukocyte antigen (HLA) alleles have been recognized in patients with IBD who are at higher risk for having SpA. As mentioned, 25%-78% of patients with AS and IBD are positive for HLA class I molecule B27 (HLA-B27)<sup>[23,43,44]</sup>. Furthermore, MHC class II allele DRB1 0103 along with HLA-B35 and HLA-B27 are frequently associated with type I peripheral arthritis<sup>[23,47,48]</sup>, while approximately 38% of patients with active UC or CD have been identified as carrying the allele DRB1 0103. On the other hand, type II peripheral arthritis is associated with HLA-B44<sup>[44,49]</sup>.

Genetic factors outside the HLA system, have also been described. Variations of CARD15 gene (which encodes the protein product NOD2) increase the risk of CD about 4-40 times and has been linked to the development of sacroiliitis in IBD patients<sup>[50-52]</sup>. In addition, patients with AS and CARD15 mutations are at higher risk for subclinical intestinal inflammation<sup>[44,51,53]</sup>. NOD2 is an intracellular receptor for bacterial molecules and is expressed in the surface of macrophages, lymphocytes, paneth cells and intestinal epithelial cells. This receptor plays a role in the innate immune response by activating nuclear factor-κB (NFκB) which is a transcriptional regulator of a large variety of genes encoding pro-inflammatory cytokines, adhesion molecules, cytokines, growth factors and enzymes<sup>[43,44,48,51,54]</sup>. As a result, NOD2 protein is responsible for positive regulation of immune defense in the gut and induction of a pro-inflammatory state<sup>[54]</sup>. However, though NOD2 gene mutations are associated with the clinical expression of CD in 20%-30% of patients there is no established association between presence of NOD2 mutations and development of SpA in IBD patients<sup>[44,51,55]</sup>.



**Figure 1 Pathogenic mechanisms linking gut and joint inflammation.** The pathogenic link between spondyloarthropathies (SpAs) and inflammatory bowel disease (IBD) involves the so-called “gut-synovial axis” hypothesis. Various environmental (gut bacteria-dysbiosis) and host factors (migration of activated gut-T cells and macrophages) leading to initiation of inflammation in genetically predisposed individuals may act as triggers of inflammatory responses against gut and joints components. IBD patients carrying specific human leukocyte antigens (HLA) alleles (such as DRB1 0103 allele, HLA-B27, HLA-B35, HLA-B44) and mutations of the CARD15/NOD2 gene are at higher risk of developing SpAs. Recently, up-regulation of adhesion molecules (E-cadherin,  $\alpha$ E $\beta$ 7 integrin), increased levels of pro-inflammatory cytokines (tumor necrosis factor- $\alpha$ ), macrophages expressing CD163 protein, interleukin (IL)-12/IL-23 signaling pathway and signal transducer and activator of transcription 3 protein have also been implicated in the pathophysiology of SpAs in IBD patients. IL: Interleukin; STAT: Signal transducer and activator of transcription; TNF: Tumor necrosis factor; HLA: Human leukocyte antigen; CARD15: Caspase recruitment domain-containing protein 15; NOD: Nucleotide-binding oligomerization domain-containing protein 2.

Furthermore, CD, AS and PsA have been associated with polymorphisms in some common genes like IL-23R, IL-12B, STAT3, and CARD9, all of them implicated in the anti-IL-23/IL-17 axis<sup>[56-60]</sup>.

Having said that, IL-23/-17 axis seems to play an important role in both axSpA and IBD (regarding the latter, the evidence mainly pertains to CD rather than UC)<sup>[61-63]</sup>. This axis is mainly regulated by IL-23, resulting in the production of IL-17, IL-22 and to a lesser extent of tumor necrosis factor (TNF)<sup>[1]</sup> by the so-called Th17 cells, which are a subgroup of T-helper cells. These cytokines are also produced from other cells like innate lymphoid cells<sup>[64]</sup>. In the gut of patients with CD or patients with SpA, it has been observed increased expression of IL-23<sup>[65]</sup>. Similarly, in the peripheral blood of AS patients there is increased number of T $\gamma$  $\delta$  cells expressing IL-23R and producing IL-17; additionally, increased expression of IL-23 is noticed in patients' facets. Interestingly, it seems that there are some cells able to produce IL-17 irrespective of the presence of IL-23. This, as discussed below, might have some implications in the therapeutic approach of these patients<sup>[66]</sup>.

### Links between the gut and the joints

Several other findings also highlight the common underlying pathogenetic mechanisms between IBD and SpA.  $\alpha$ E $\beta$ 7 integrin which is expressed by intraepithelial T cells in the intestinal mucosa and binds to the glycoprotein E-cadherin expressed by gut epithelial cells, has been found to be upregulated on colonic T cells from AS patients and also from lymphocytes obtained from synovial tissue of SpA patients<sup>[67,68]</sup>. The E-cadherin molecules have been also observed to be up-regulated in the gut of patients with IBD and SpA individuals with subclinical gut inflammation<sup>[51,67-69]</sup>.

In another study increased levels of macrophages expressing the protein CD163 have been reported in both gut mucosa of IBD patients with and without SpA and in the synovial tissue and gut from SpA patients<sup>[51,70,71]</sup>. Finally, animal models have shown that prolonged exposure to the pro-inflammatory cytokine TNF- $\alpha$  might lead to a phenotype resembling IBD-SpA<sup>[72]</sup>. In the last decade, it was recognized that a common target of this cytokine could be the synovial fibroblasts and the intestinal myofibroblasts<sup>[68,73]</sup>.

### The Gut-synovial axis

Two - probably complementary- theories have been formulated to explain the development of SpA in patients with IBD. These theories include both alterations in gut bacteria and migration of gut lymphocytes to the joint<sup>[43,44]</sup>. Changes in the gut

microbiome, which is also known as dysbiosis, have been associated with SpA. In detail, *Faecalibacterium prausnitzii* has been found to be in reduced numbers, in stools of SpA patients<sup>[18,74,75]</sup>. Also, in AS patients, increased numbers of *Dialister* microbes in ileal and colon biopsies have been correlated with Ankylosing Spondylitis Disease Activity Score (ASDAS)<sup>[18,75]</sup> and of *Ruminococcus gnavus* in the stools with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)<sup>[18,76,77]</sup>. Furthermore, other studies have detected in the inflamed joints of these patients certain bacteria like *Yersinia enterocolitica*, *Salmonella enteritidis* and *typhimurium*, or antigens related to them<sup>[26,78,79]</sup>. Role of microbiome in the pathogenesis of SpA is also supported by data from animal models. For example, the arthritis and inflammatory colitis features developed in HLA-B27 transgenic rats are ameliorated when they are raised in germ-free conditions<sup>[18,80]</sup>. These observations suggest that gut and joint inflammation process depends on the presence of bacteria into the gastrointestinal tract, which emphasizes the role of autoimmunity and antigen mimicry<sup>[26,44]</sup>.

The second hypothesis is based on experimental studies which showed that gut T-cells activated by antigens migrate to the joints and induce inflammation<sup>[43,44,51]</sup>. In state of inflammation alterations occur in the mucosal vasculature, such as vasodilation, hyperemia and increased vascular permeability which are induced by various inflammatory cytokines, resulting in enhanced extravasation of leukocytes. Furthermore, the migration pathways of lymphocytes are altered by aberrant expression patterns of adhesion molecules, inflammatory cytokines and receptors<sup>[51]</sup>. It is known that integrins  $\alpha4\beta7$  and  $\alpha E\beta7$  and MadCAM-1 mucosal vascular receptor play an important role in the lymphocytes' gut homing. It has been shown that leukocytes populations from inflamed gut can bind to synovial vessels and home into the joint, using multiple adhesion molecules<sup>[81]</sup>, such as  $\alpha E\beta7$  integrins, vascular adhesion protein-1 (VAP-1) and intracellular adhesion molecule-1 (ICAM-1/CD54)<sup>[26]</sup>. The increased number of T cells expressing  $\alpha E\beta7$  integrins in the synovial membrane is in favor of the mucosal origin of these cells, however this hypothesis remains to be proven<sup>[68]</sup>.

Additionally, It has been shown that macrophages from the gut of IBD patients are able to adhere in endothelial cells of synovial tissue<sup>[81]</sup>, further enhancing the activation of T cells locally<sup>[26]</sup>. Collectively, one could argue that gut T-cells are activated in the Peyer's patches and mesenteric lymph nodes, express a pattern of adhesion molecules that under specific conditions leads to migration of these activated T-cells into the joint causing inflammation<sup>[43,44,51,82]</sup>. Further studies are needed to fully understand the pathogenic pathways linking IBD and SpA.

## TREATMENT

Given the common pathogenetic mechanisms underlying SpA and IBD, therapeutic approach to these entities is largely similar. However, there are some differences in the safety and efficacy of the various treatment modalities used.

Non-steroidal anti-inflammatory drugs (NSAIDs) although commonly used in SpA, should be generally avoided in IBD especially in the active ones, but short courses (*e.g.*, 2 wk) do not seem to cause exacerbations<sup>[20]</sup>. On the other hand, short courses of systemic steroids, although demonstrate some efficacy for CD or UC are not effective for axSpA<sup>[20,83]</sup>. Local steroids injections and low doses of systemic steroids have been used for peripheral SpA<sup>[20]</sup>.

The most common conventional Disease modifying antirheumatic drugs (DMARDs) used for treatment of SpA are methotrexate and sulfasalazine, both demonstrating some efficacy for peripheral but not for axial SpA<sup>[84,85]</sup>. Furthermore, methotrexate has proved to be helpful in inducing and maintaining remission in CD patients<sup>[86,87]</sup> but is not recommended as first line treatment of UC. Similarly, sulfasalazine has some efficacy in CD (but not for ileal CD)<sup>[20]</sup> and UC<sup>[88,89]</sup>.

Anti-TNF regimes are the gold-standard treatment for the patients with co-existing IBD with SpA who are not controlled with conventional DMARDs. All of them are approved for the treatment of axSpA<sup>[90]</sup> while infliximab and adalimumab are the most well studied for patients with IBD, both having indication for CD and UC<sup>[87]</sup>. Etanercept, was not effective for IBD<sup>[91]</sup>. Many hypotheses have been made to explain its lack of efficacy, including that this might be related to its insufficiency to induce apoptosis in the T cells of the lamina propria<sup>[92]</sup>. Also, etanercept blocks both TNF $\alpha$  and TNF $\beta$ . The latter seems to regulate, in the lamina propria, T-cell dependent IgA production, which in turn controls the intestinal microbiota composition<sup>[93,94]</sup>.

Interestingly, new onset IBD in the context of AS, has been observed in patients who started treatment with anti-TNF reagents<sup>[95,96]</sup>. These cases were more frequently resembling CD rather than UC and have been associated with commencement of

etanercept<sup>[97-99]</sup>. Of note, a large multicentre AS study examining the presence and development of extra-articular manifestations did not find any correlation between biologics use and development of IBD<sup>[9]</sup>. Whether there is a true association between treatment with anti-TNF drugs in AS patients and new-onset of IBD, remains to be defined.

The role of the IL-23/-IL-17 axis in the pathogenesis of SpA and IBD is supported by many studies of basic and clinical research<sup>[61]</sup>. Despite, monoclonal antibodies targeting the key cytokines of the axis (*i.e.*, IL-23 and IL-17) were thought to be very effective, data from clinical trials did not fully support this notion. Ustekinumab, a monoclonal antibody against the common p40 subunit of IL-12 and IL-23, has proved to be effective for CD but does not appear to work for AS. Although data derived from post hoc analyses of phase 3 trials in patients with psoriatic spondylitis were promising, ustekinumab did not achieve the primary endpoint in phase 3 trials for AS and non-radiographic axSpA<sup>[100]</sup>. Similarly, risankizumab, which is an antibody specifically targeting the p19 subunit of IL-23 failed to show clinical and radiological efficacy in a phase 2 trial for AS<sup>[101]</sup>. Data from clinical trial about other antibodies against p19 subunit of IL-23 are eagerly awaited. To explain the differences observed in the efficacy of anti-IL-23 between psoriatic spondylitis and AS, it is not irrational to speculate that the pathogenetic mechanisms underlying AS are somewhat different to those of spondylitis in the context of PsA.

Secukinumab, which is a monoclonal antibody against IL-17 recently received approval for AS and therefore is another therapeutic option in patients with axSpA. Phase 3 trials are now underway for secukinumab in nraxSpA. One could expect, based on the underlying pathogenetic mechanisms that secukinumab would have good results in CD. However, results in phase 2 trials were negative with the drug being numerically worse than placebo. Many hypotheses have been formed to explain the failure of secukinumab in CD. *Candida albicans* proliferation has been proposed as a plausible explanation for the CD exacerbation given the role of IL-17 in fighting fungal infections<sup>[61,102]</sup>. Although new cases of IBD in axSpA patients treated with secukinumab have been described<sup>[103]</sup>, a recently published study analysing data from 21 clinical trials from patients with psoriasis, psoriatic arthritis and ankylosing spondylitis, has shown that exposure adjusted incidence rates for IBD did not increase over time with secukinumab treatment<sup>[104]</sup>. Interestingly, a recent study provided some evidence supporting that suppression of IL-17F but not IL-17A was indeed protective for colitis by inducing T regulatory cells via modifications in colonic microbiota<sup>[105]</sup>.

An obvious question is how ustekinumab, which blocks IL-23 and subsequently IL-17 works for CD but secukinumab does not? There is accumulated evidence that IL-17 can be produced also -to a lesser extent possibly- in an IL-23 independent manner from innate lymphoid, T  $\gamma\delta$  or other types of cells<sup>[64,106]</sup>. Therefore, blocking IL-23 leaves some "basal" levels of IL-17. Lee *et al*<sup>[107]</sup> have shown, that T  $\gamma\delta$  cells in the lamina propria are the producers of gut-protective IL-17, in an IL-23 independent way. Its effect is possibly mediated through regulation of the tight-junction protein "occludin" which maintain barriers integrity.

Vedolizumab, a gut selective  $\alpha 4\beta 7$  integrin antagonist, has shown to be effective in patients with CD<sup>[108,109]</sup> and for inducing or maintaining therapy in UC patients<sup>[110]</sup>. Results of this drug in articular symptoms are somewhat conflicting. Whether this drug is linked with exacerbation or new-onset arthralgias or inflammatory arthritis remains to be answered<sup>[87,111-113]</sup>. Of note, a recent post hoc analysis of the "Gemini" trials showed that vedolizumab was associated with decreased likelihood of new or worsening arthritis/arthralgia in CD patients while in UC the incidence was similar between patients treated with the active drug or with placebo<sup>[114]</sup>.

JAK inhibitors are a new drug class category with promising results in various immune mediated diseases. Genome wide association studies have shown that there is association between CD and single nucleotide polymorphisms in the JAK-STAT pathway<sup>[115]</sup>. Results in a phase 2 trial for CD has shown that tofacitinib was not effective<sup>[116]</sup>. However, newer and more selective JAK-inhibitors, like filgotinib and upadacitinib have favorable results in achieving clinical remission in phase 2 trials for CD<sup>[117,118]</sup>. For UC, tofacitinib after the promising results with patients achieving higher rates of clinical remission and clinical response compared to placebo<sup>[119]</sup> received Food and Drug Administration (FDA) approval for patients with moderate to severely active UC.

As regards to the efficacy of JAK-inhibitors in SpA, tofacitinib has shown favorable results in phase 2 trials of AS with 80.8% of the patients treated with tofacitinib achieving ASAS20 improvement at week 8, compared to 41.2% of placebo-treated patients<sup>[120]</sup>. Recently published results from a phase 2 clinical trials showed also that filgotinib was effective for AS with patients experiencing significant clinical improvement, compared to placebo, at week 12. A phase 2b/3a clinical trial assessing

the efficacy and safety of upadacitinib in patients with AS is currently underway (NCT03178487). Whether JAK-inhibitors could be another potential therapeutic option in patients with IBD and SpA remains to be defined from future studies.

## DIAGNOSIS - THE ROLE OF CALPROTECTIN

Although colonoscopy is being considered as the gold-standard for IBD diagnosis, a recent study has shown that capsule endoscopy was superior to classical colonoscopy in diagnosing CD in the context of SpA. It was shown that small bowel inflammation was present in 42.2% and 10.9% of the patients who underwent capsule endoscopy and classical colonoscopy, respectively. Interestingly, positive findings were not associated with symptomatology from the gastrointestinal system but with elevated faecal calprotectin levels, confirming that many SpA patients have “silent” IBD<sup>[121]</sup>. Calprotectin measured in the serum or in the stools has been used to identify subclinical bowel inflammation in patients with SpA. Cypers *et al*<sup>[14]</sup> have found that elevated serum calprotectin levels have been associated with subclinical microscopic colitis in SpA patients. In detail, individuals who had both CRP and calprotectin elevated had a frequency of bowel inflammation of 64% compared to 25% in patients who had low levels of these proteins. Additionally, in patients who had high levels of either serum calprotectin or CRP, frequency of bowel inflammation was significantly higher in SpA patients with high faecal calprotectin compared to those with low<sup>[14]</sup>. In a recent study, Ostgard *et al*<sup>[122]</sup> confirmed that faecal calprotectin could serve as a biomarker to identify patients with subclinical bowel inflammation. It has to be noted however that faecal calprotectin levels can be influenced by NSAIDs use, which is quite common in SpA patients<sup>[123]</sup>. Interestingly, patients with elevated faecal calprotectin levels had more inflammation in the sacroiliac joints compared to those with low levels. Also, the former had better response to adalimumab as assessed by ASDAS. It has to be said however, that these patients received an extra loading dose of 80 mg adalimumab, at baseline<sup>[122]</sup>. The concept of calprotectin as biomarker of treatment response has been suggested also previously: In proof of concept trials for SpA, serum calprotectin has been found to be decreased after treatment of axSpA and peripheral SpA with infliximab and etanercept, respectively<sup>[124]</sup>.

## DISCUSSION - POINTS TO CONSIDER

It is increasingly being recognized that there is a very close link between IBD and SpA. As outlined in this review, there are several hints for that: epidemiological, clinical, laboratory (*i.e.*, positivity for HLA-B27) histopathologic and pathogenetic. Regarding the latter, it is very intriguing to define to which extent these are common between these entities and identify the diversities that lead to different clinical expressions. However, many limitations impede this venture. Firstly, over the last years, many different criteria have been used for the classification of SpA, which comprise a group of relatively heterogenous diseases. Besides, classification criteria in SpA do not mean necessarily a certain diagnosis and *vice versa*<sup>[125]</sup>. Secondly, these patients, depending on the cardinal manifestation, are followed up by a gastroenterologist or a rheumatologist that might overlook the articular or bowel manifestations of the disease, respectively. To that end, the effective communication between different professions and the interdisciplinary approach, through combined clinics for example, is imperative.

Treatment of these entities has progressed significantly over the last years. To the successful anti-TNF reagents, drugs targeting IL-23 and IL-17 as well as the JAK-inhibitors have been added to the clinician’s arsenal. However, treating patients with co-existing SpA and IBD, should not only include these manifestations but also considerate other extra-articular and extra-intestinal manifestations like skin disease or uveitis. Comprehensive algorithms, designed by clinicians of many disciplines are urgently needed, in light of the numerous emerging therapeutic modalities.

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