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Review

The management of patients with inflammatory bowel disease-associated spondyloarthritis: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and Italian Society of Rheumatology (SIR) recommendations based on a pseudo-Delphi consensus

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Abbreviations: 5-ASA, 5-aminosalicylates; AS, Ankylosing spondylitis; CD, Crohn's disease; GRADE, Grading of recommendation assessment, development, and evaluation; IBD, Inflammatory bowel diseases; IG-IBD, Italian Group for the Study of Inflammatory Bowel Disease; JAK-i, JAK-inhibitors; MTX, Methotrexate; PsA, Psoriatic arthritis; RCT, Randomized controlled trials; SIR, Italian Society of Rheumatology; SpA, Spondyloarthritis; SSZ, Sulphasalazine; TNF, Tumor necrosis factor; UC, Ulcerative colitis; UST, Ustekinumab; VDZ, Vedolizumab.

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ABSTRACT

Spondyloarthritis (SpA) is the most frequent extraintestinal manifestation in patients with inflammatory bowel diseases (IBD). When IBD and spondyloarthritis coexist, musculoskeletal and intestinal disease features should be considered when planning a therapeutic strategy. Treatment options for IBD and SpA have expanded enormously over the last few years, but randomized controlled trials with specific endpoints focused on SpA are not available in the IBD setting. To address this important clinical topic, the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and the Italian Society of Rheumatology (SIR) jointly planned to draw updated therapeutic recommendations for IBD-associated SpA using a pseudo-Delphi method. This document presents the official recommendations of IG-IBD and SIR on the management of IBD-associated SpA in the form of 34 statements and 4 therapeutic algorithms. It is intended to be a reference guide for gastroenterologists and rheumatologists dealing with IBD-associated SpA.

1. Introduction

Inflammatory bowel diseases (IBD) – a term encompassing Crohn's disease (CD), ulcerative colitis (UC) and unclassified IBD – are chronic inflammatory conditions characterized by relapsing and remitting inflammation [1]. Disability and poor quality of life reported by patients with IBD are mainly due to disease symptoms and to the effect of the progressive inflammation-related intestinal damage. This scenario can be complicated by the presence of immune-mediated and non-immune-mediated extraintestinal manifestations [2]. Their frequent occurrence justifies the assumption that these diseases are not restricted to the gut and that they should be regarded as systemic conditions. Spondyloarthritis (SpA) is the most frequent extraintestinal manifestation in IBD patients, with a prevalence of approximately 15% [3]. The term SpA refers to a group of several diseases with similar clinical, radiologic and genetic (association with HLA—B27) features, including the following: radiographic ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, non-radiographic axial SpA, undifferentiated SpA and SpA associated with IBD [4]. In IBD-associated SpA, the onset of rheumatic symptoms precedes IBD diagnosis in about 25% of patients [5,6]. When IBD and SpA coexist, musculoskeletal and intestinal disease features should be considered when planning a therapeutic strategy. Between 2014 and 2017, expert panels including Italian gastroenterologists and rheumatologists focused on the management of patients with IBD-associated SpA, producing excellent therapeutic algorithms [7,8]. Since then, the therapeutic scenario of IBD and SpA has expanded enormously [9], demanding an update of management recommendations. The Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) has recently published clinical practice guidelines on the use of biologics and small molecule drugs in UC and CD [10–13]. These guidelines were formulated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology - the current reference method for developing high-quality, evidence-based recommendations for clinical practice [14]. The GRADE methodology requires a preliminary choice of the outcomes that will be evaluated and systematically reviewed to subsequently formulate clinical recommendations. IG-IBD guidelines considered only outcomes related to the intestinal features of IBD, as these were the only endpoints assessed across all randomized controlled trials (RCTs) in the IBD field. Therapeutic options in case of coexistence of SpA and IBD were not assessed. To fill this important gap, IG-IBD and the Italian Society of Rheumatology (SIR) jointly planned to draw new therapeutic recommendations for IBD-associated SpA with the aim of updating the aforementioned consensus papers [7,8]. As GRADE was not applicable in this setting, a different approach was used: the pseudo-Delphi method.

This document presents the official recommendations of IG-IBD and SIR on the management of IBD-associated SpA. The consensus does not provide indications for treating PsA. Although IBD and PsA can occur simultaneously [15], the contemporary presence of psoriasis introduces a more complex scenario that needs to be addressed separately.

2. Methods

2.1. Focus on pseudo-Delphi method

A pseudo-Delphi study was conducted. The pseudo-Delphi method emerged as a contemporary and refined alternative to the traditional Delphi, which has long been employed to gather expert opinions anonymously and iteratively. This method harnesses real-time communication to streamline the consensus-building process, by facilitating interactive discussions and immediate feedback, offering a more dynamic and efficient approach to achieve convergence among experts in clinical studies [16]. The pseudo-Delphi study retains the core principles of the traditional Delphi method, including anonymity, iterative feedback and expert aggregation.

In the present study, the facilitator presented a series of questions or statements related to the clinical topic under consideration. Participants provided their responses instantaneously and the facilitator summarised the input to be shared with the group. This dynamic process allowed experts to revise and refine their opinions based on real-time feedback, eliminating the delay associated with traditional Delphi rounds [17–19]. The recommended methodologic criteria for reporting methods and results from Delphi studies [20,21] were followed. The essential requirements of a high-quality Delphi study - i.e., anonymity, iteration, controlled feedback and statistical stability of consensus [22] - were taken into account from the beginning and during each phase of the study. Real-time communication platforms were used, enabling more rapid feedback and interaction among participants.

2.2. Steps for statements formulation

The Steering Committee was composed of five members of IG-IBD (FSM, AA, AO, DP, FC), four members of SIR (RG, RC, FC, SDA) and three methodologists (LB, PM, MZ) acting as Delphi masters. In addition, other 12 experts from both IG-IBD and SIR completed the entire panel. Participants were selected based on their expertise and qualifications, ensuring a diverse and knowledgeable panel. The panel was composed of 22 expert clinicians: 12 members of IG-IBD and 10 members of SIR. Supplementary Fig. 1 illustrates the flowchart of the whole methodological process of this study. Supplementary Fig. 2 provides information about the timeline of the project.

A narrative literature review was conducted to update the previous consensus [7,8] and define the main areas of investigation for the Delphi survey. Subsequently, a first version of the statements was prepared by the Steering Committee during a preliminary virtual meeting and five main areas of investigation were identified, each one including a range of statements on specific topics: i) Classification, Diagnosis, Assessment of activity; ii) Active axial SpA and active IBD; iii) Active axial SpA and IBD in remission; iv) Active peripheral SpA and active IBD; v) Active peripheral SpA and IBD in remission.

2.2.1. Exploration (Q0)

A kick-off meeting was organised to explain the methodology to all project participants and outline the steps. For organisational reasons, two sessions were necessary and were held on 15th February 2023 and 14th March 2023. During these meetings (face-to-face but virtual), the first version of the statements, extracted from the literature and grouped in five sections corresponding to the five previously identified areas of investigation, was proposed and discussed by the entire panel of experts. In addition to these areas, two overarching principles were introduced at the beginning of the questionnaire. The response scale and the convergence criterion were also chosen.

For the response scale, a 4-point Likert scale was used (*"Completely disagree"*, *"Disagree"*, *"Agree"*, *"Completely agree"*). This choice was motivated by the need to make the respondents take a clear position avoiding a neutral point. The group decided to insert a specific question asking the reasons underlying the disagreement *("Only if you disagree, please explain why"*). In this way, all the statements that had not reached the consensus of the experts could be reformulated from one iteration to the next, reflecting on why they were not considered suitable. The group examined all the statements one-by-one, evaluating them in detail and proposing modifications if deemed appropriate. At the end of the meeting, it was possible to define the first questionnaire.

The convergence criterion was set as a percentage of agreement among the experts equal to two thirds of the respondents, i.e., 67% of agreement.

2.2.2. First round (Q1)

All the panellists received an invitation to participate and a link to complete the survey through a web platform (SurveyMonkey®). The online survey was active from 4th April to 18th April 2023. The survey presented a first section about the overarching principles. Two statements were included and an additional open question was inserted to collect any comments or suggestions. The second part of the questionnaire was divided into the five previously identified areas of investigation. For each statement, the panellists had to express their level of agreement or disagreement through the above mentioned 4-item Likert scale. Consensus was measured using the percentage of agreement.

For each statement, the answers "fully agree" or "partially agree" were counted together as agreement, as well as "fully disagree" or "partially disagree" were considered together as disagreement. Consensus was defined as reached when at least two-thirds of experts agreed on a specific statement. From a methodological point of view, it was considered appropriate to divide some statements concerning more than one therapeutic decision that had been initially proposed together. This was decided to evaluate whether there was consensus on all therapeutic possibilities or if critical issues emerged with respect to any indication in particular. For all items, the threshold of 67% of agreement was exceeded. Nonetheless the clinical steering committee decided that those statements should be merged. As a result, a lean Q2 was created to gauge consensus on these inclusive statements.

2.2.3. Second round (Q2)

The second online survey was conducted from 16th to 20th June 2023. Similarly to the first round, all panellists received the invitation and the link to participate and were asked to express their level of agreement or disagreement through the 4-item Likert scale. Consensus was measured using a percentage above 67% of agreement.

The consistency of answers between subsequent iterations indicated an overall correctness in the definition of the statements, which led to the consensus of the panellists to all the statements, therefore putting an end to the iterations.

2.2.4. Consensus

The final results were discussed with the Steering Committee and were presented to the panellists on 4th July 2023. Since consensus was reached on each statement, the pseudo-Delphi process terminated after two rounds. Finally, during the draft of the manuscript, the statements 4.7 and 4.8, as well as the statements 5.4 and 5.5, were merged (final statements: 4.7 and 5.4, respectively) to improve the clarity of the clinical messages. As they were previously voted as distinct statements, their respective agreement rates were presented singularly.

3. Results

Among the 22 panellists, 21 (92% IG-IBD, 100% SIR) and 17 (67% IG-IBD, 90% SIR) participated in the kick-off meetings held on 15th February and 14th March 2023, respectively. All the experts answered Q1, while 21 of them (100% IG-IBD, 90% SIR) answered Q2.

Table 1 provides information about the number of statements for each area of investigation, distinguishing between the first and the second questionnaire and reporting the final number of approved statements. Tables 2 and 3 show the percentage of agreement for each statement in Q1 and Q2, respectively.

3.1. Overarching principles

> *Statement 0.1:* Patients with IBD-associated SpA should be preferentially managed with an integrated rheumatological and gastroenterological approach (*Agreement rate: 95%*).

Patients with IBD-associated SpA should be treated with an evidence-based and tailored approach. An integrated management involving rheumatologists and gastroenterologists should be regarded as the best modality to guarantee the proper care for these difficult-to-treat patients.

> *Statement 0.2*: The dosage of a drug must always be evaluated on a case-by-case basis, based on the patient's clinical history (*Agreement rate: 86%*).

The drugs used for IBD-associated SpA are indicated for both rheumatological and gastroenterological diseases, but sometimes with different doses (dosages are generally lower in rheumatological indications). For a patient with inactive IBD and active SpA, two possible dosages could be chosen. The panel believes that the patient's history should guide this choice: a history of moderate or severe IBD should suggest the use of gastroenterological dosages even in patients with inactive IBD at the time of the therapeutic choice.

> *Statement 0.3*: The treatment of patients with IBD-associated SpA should be based on a decision shared by the patient and the physician (*Agreement rate: 95%)*.

The engagement of the patient in the decision for a specific treatment plan improves the long-term adherence and should be encouraged [23]. The decision on the best care should arise from an informative dialogue between the patient and the physician.

Table 1
Overview of the statements for each round.*

	Q1	Q2	Final
Overarching Principles	2	1	3
Section 1. Classification, Diagnosis, Assessment of activity	7	0	7
Section 2. Active axial SpA and active IBD	5	1	4
Section 3. Active axial SpA and IBD in remission	7	1	6
Section 4. Active peripheral SpA and active IBD	12	1	9
Section 5. Active peripheral SpA and IBD in remission	7	1	5
	40	5	34

* During the draft of the manuscript, the statements 4.7 and 4.8, as well as the statements 5.4 and 5.5, were merged into the final statements 4.7 and 5.4, respectively.

3.2. Section 1. Classification, diagnosis, assessment of activity

Statement 1.1: IBD-associated SpA should be classified according to the Assessment of SpondyloArthritis international Society (ASAS) criteria in axial or peripheral SpA (*Agreement rate: 95%*).

No validated criteria are available for the classification of IBD-associated SpA and the diagnosis is usually made following the Assessment in SpondyloArthritis (ASAS) criteria [24,25]. The same criteria strictly describe the two main patterns of IBD-associated SpA: peripheral arthritis and axial manifestations related to sacroiliitis with or without concomitant spondylitis. These subsets may coexist in the same patient. The distinction of the peripheral involvement into type I (pauci-articular) and type II (polyarticular) – the so-called Orchard classification [26] - should be discouraged.

Statement 1.2: In cases of SpA, the diagnosis of IBD and the distinction between Crohn's disease, ulcerative colitis and unclassified IBD should rely on commonly accepted criteria as defined by the European Crohn's and Colitis Organization (ECCO) (Agreement rate: 100%).

Sometimes, the occurrence of SpA may precede the IBD diagnosis by as much as several years. In the case of clinical suspicion of IBD, the lack of a single diagnostic gold standard test should be kept in mind. The diagnosis should be established based on the combination of medical history, clinical evaluation and typical endoscopic, radiologic and histological findings. The diagnosis modality is extensively described in the 2017 European Crohn's and Colitis Organization (ECCO) guidelines [27,28].

Statement 1.3: In the case of specific "red flags", an appropriate referral of patients with suspected IBD and SpA to the gastroenterologist or the rheumatologist should be promptly performed (*Agreement rate: 100%*).

The occurrence of IBD and SpA in a patient may not be simultaneous. Several signs and symptoms should be monitored to identify those patients with association of IBD and SpA. A prompt diagnosis of these disorders may prevent the complications related to progressive and irreversible intestinal and/or articular tissue damage. Gastroenterologists and rheumatologists may benefit from the identification of disease-specific signs and symptoms ("red flags") for a more appropriate patient referral. In 2018, a consensus among expert gastroenterologists and rheumatologists performed a systematic review of the literature using the GRADE method and identified several 'major' (one sufficient for patient referral) or 'minor' (at least three needed for patient referral) red flag criteria for specialist referral (Table 4) [29]. Even if not included among the "red flags", faecal calprotectin has emerged as a widely used tool for diagnosis and monitoring of IBD over the last years [30]. It has also been assessed in the setting of rheumatologic diseases [31]. However, this test should be interpreted with caution: a minimum of two elevations of the faecal calprotectin (carried out at least 15–20 days apart) is needed to be considered clinically relevant, after the exclusion of other factors that may cause a false positive test (for example: enteric infections, use of proton pump inhibitors, use of NSAIDs). When interpreting the results of the test, one should also keep in mind the well-known possibility of a non-IBD subclinical inflammation in patients with ankylosing spondylitis [32].

Statement 1.4: In cases of axial SpA, evaluation of disease activity on joints should be assessed at baseline and during therapy using the Ankylosing Disease Activity Score (ASDAS)-CRP (*Agreement rate: 100%*).

The Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP is a widely accepted composite index to assess disease activity in AS [33]. The cut-offs selected to distinguish between the different degrees of disease activity are as follows: $\leq$1.3 for inactive disease, >1.3 and $\leq$ 2.1 for low disease activity, >2.1 and $\leq$ 3.5 for high disease activity and > 3.5 for very high disease activity. The cut-offs used to define improvement of disease are a reduction of $\geq$1.1 units and $\geq$ 2.0 units for "clinically important improvement" and "major improvement", respectively [34].

Statement 1.5: In the case of peripheral SpA, evaluation of disease activity on joints should be assessed at baseline and during therapy using Disease Activity Index for Psoriatic Arthritis (DAPSA) *(Agreement rate: 91%).*

Table 2
Percentages of agreement for each statement in Q1 ($N = 22$).

Section	Statement	% *Agreement*
Overarching Principles	0.1	100%
Overarching Principles	0.2	86%
Section 1. Classification, Diagnosis, Assessment of activity	1.1	95%
Section 1. Classification, Diagnosis, Assessment of activity	1.2	100%
Section 1. Classification, Diagnosis, Assessment of activity	1.3	100%
Section 1. Classification, Diagnosis, Assessment of activity	1.4	100%
Section 1. Classification, Diagnosis, Assessment of activity	1.5	91%
Section 1. Classification, Diagnosis, Assessment of activity	1.6	95%
Section 1. Classification, Diagnosis, Assessment of activity	1.7	91%
Section 2. Active axial SpA and active IBD	2.1	100%
Section 2. Active axial SpA and active IBD	2.2	91%
Section 2. Active axial SpA and active IBD	2.3	91%*
Section 2. Active axial SpA and active IBD	2.4	73%*
Section 2. Active axial SpA and active IBD	2.5	91%
Section 3. Active axial SpA and IBD in remission	3.1	91%
Section 3. Active axial SpA and IBD in remission	3.2	95%
Section 3. Active axial SpA and IBD in remission	3.3	91%
Section 3. Active axial SpA and IBD in remission	3.4	91%*
Section 3. Active axial SpA and IBD in remission	3.5	73%*
Section 3. Active axial SpA and IBD in remission	3.6	68%
Section 3. Active axial SpA and IBD in remission	3.7	82%
Section 4. Active peripheral SpA and active IBD	4.1	95%
Section 4. Active peripheral SpA and active IBD	4.2	95%
Section 4. Active peripheral SpA and active IBD	4.3	95%
Section 4. Active peripheral SpA and active IBD	4.4	91%
Section 4. Active peripheral SpA and active IBD	4.5	91%
Section 4. Active peripheral SpA and active IBD	4.6	86%
Section 4. Active peripheral SpA and active IBD	4.7	77%
Section 4. Active peripheral SpA and active IBD	4.8	82%
Section 4. Active peripheral SpA and active IBD	4.9	95%*
Section 4. Active peripheral SpA and active IBD	4.10	77%*
Section 4. Active peripheral SpA and active IBD	4.11	86%*
Section 4. Active peripheral SpA and active IBD	4.12	82%
Section 5. Active peripheral SpA and IBD in remission	5.1	91%
Section 5. Active peripheral SpA and IBD in remission	5.2	95%
Section 5. Active peripheral SpA and IBD in remission	5.3	91%
Section 5. Active peripheral SpA and IBD in remission	5.4	86%
Section 5. Active peripheral SpA and IBD in remission	5.5	86%
Section 5. Active peripheral SpA and IBD in remission	5.6	95%*
Section 5. Active peripheral SpA and IBD in remission	5.7	86%*

* These statements were merged in Q2

Table 3
Percentages of agreement for each statement in Q2 ($N = 21$).

Section	Statement information	% *Agreement*
Overarching Principles	New	95%
Section 2. Active axial SpA and active IBD	2.3 and 2.4 merged	95%
Section 3. Active axial SpA and IBD in remission	3.4 and 3.5 merged	100%
Section 4. Active peripheral SpA and active IBD	4.9, 4.10 and 4.11 merged	100%
Section 5. Active peripheral SpA and IBD in remission	5.6 and 5.7 merged	95%

Table 4
"Red flags" for specialist referral. Modified from Felice et al. [29].

Red Flags for IBD	Major/ Minor	Red Flags for SpA	Major/ Minor
Chronic diarrhoea	Major	Chronic low back pain	Major
Rectal bleeding	Major	Dactylitis	Major
Perianal fistula/ abscess	Major	Enthesitis	Major
Chronic abdominal pain	Major	Peripheral joint pain/ swelling	Major
Nocturnal symptoms	Major	Family history of SpA	Minor
Oral aphtosis	Minor	Psoriasis	Minor
Fever	Minor	Anterior uveitis	Minor
Anaemia	Minor	Chest pain	Minor
Family history of IBD	Minor		
Weight loss	Minor		

The panel defined the Disease Activity Index for Psoriatic Arthritis (DAPSA) as the most suitable evaluation method for patients with IBD-associated SpA. This index has shown reliability and validity for PsA and employs a 66/68 joint count [35]. Its performance in peripheral SpA (including not only PsA) was found to be overall acceptable [36]. Cut-off values of $\leq$4 for remission, >4 and $\leq$ 14 for low disease activity, >14 and $\leq$ 28 for moderate disease activity and > 28 for high disease activity have been proposed. DAPSA reductions of 50%, 75% and 85% compared to baseline values reflected minor, moderate and major improvements, respectively [37].

Statement 1.6: In the case of Crohn's disease, evaluation of disease activity on gut should be assessed at baseline and during therapy using the Harvey-Bradshaw Index (HBI) *(Agreement rate: 95%)*.

Even if most RCTs used the Crohn's Disease Activity Index (CDAI), the panel defined the Harvey-Bradshaw Index as the most useful and simple tool to be used in clinical practice to define CD activity [38]. Cut-off values of $\leq$4 for remission, >4 and $\leq$ 7 for low disease activity, >7 and $\leq$ 16 for moderate disease activity and > 16 for severe disease activity are widely accepted. The Harvey-Bradshaw Index has an excellent correlation with CDAI [39].

Statement 1.7: In the case of ulcerative colitis, evaluation of disease activity on gut should be assessed at baseline and during therapy using the partial Mayo score (PMS) *(Agreement rate: 95%)*.

The partial Mayo Score is easy to calculate and should be employed in clinical practice to define the degree of activity of UC [40]. Commonly accepted cut-off values are: $\leq$1 for remission, >1 and $\leq$ 4 for low disease activity, >4 and $\leq$ 7 for moderate disease activity and > 7 for severe activity.

3.3. Section 2. Active axial SpA and active IBD

The therapeutic algorithm for this clinical scenario is shown in Fig. 1.

Statement 2.1: In patients with active axial SpA and active IBD, TNF inhibitors (infliximab and adalimumab in CD and UC, or golimumab in UC) are recommended as first-line treatment *(Agreement rate: 100%)*.

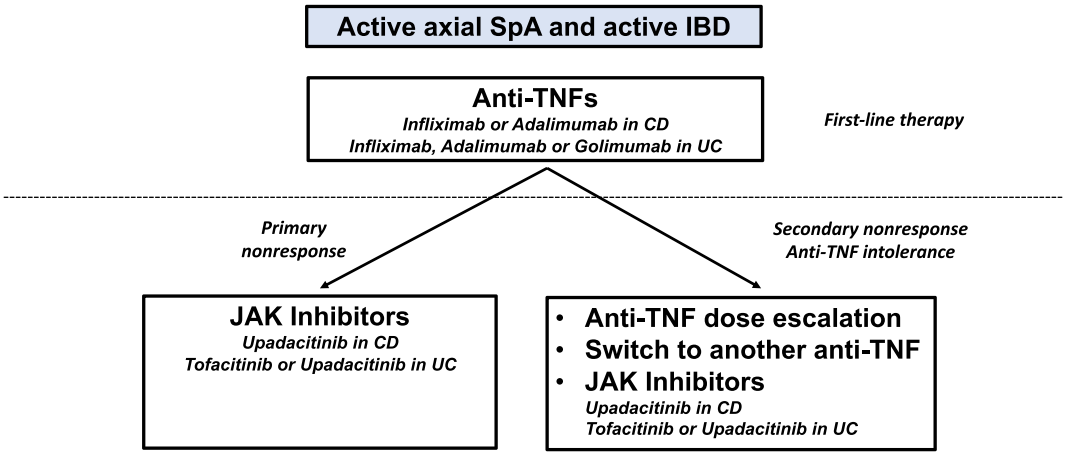


Fig. 1. Active axial SpA and active IBD: therapeutic algorithm.

In the case of active CD or UC associated with axial SpA, the use of anti-TNF agents is recommended as first-line treatment. Anti-TNFs' efficacy in both axial SpA and IBD has been widely proven in the literature [11,13,41]. The recommendation to use these drugs as first-line agents is reinforced by the availability of biosimilars of infliximab and adalimumab, that have equivalent effectiveness and safety to the originator products with reduced costs [42–44]. Etanercept, another anti-TNF agent, is ineffective in active CD [45] and is a possible trigger for new onset of CD [46]. Certolizumab pegol is approved by the Food and Drug Administration for the treatment of CD and is an effective option for axial SpA [41].

Statement 2.2: In case of primary non-response to one anti-TNF, swapping to JAK inhibitors is recommended *(Agreement rate: 91%).*

Robust evidence on the choice between "switching in-class" or "swapping out-of-class" in case of failure to one anti-TNF is lacking. Most experts emphasize how current availability of several biologics with different mechanisms of action makes it reasonable to change the mechanism of action in case of primary non-response to an anti-TNF. In active axial SpA, JAK inhibitors (JAKi) are options to be considered in case of failure to anti-TNFs, particularly in case of primary failure.

At the time of manuscript drafting three JAKi were available for the treatment of UC (tofacitinib, filgotinib and upadacitinib), while upadacitinib has been recently approved by the European Medicine Agency (EMA) for the treatment of CD. In the choice between different JAKi, it should be considered that tofacitinib [47] and upadacitinib [48] have been proven to be effective and that they are indicated for AS treatment, while filgotinib does not have this indication.

Statement 2.3: In patients with active axial SpA and active IBD, in case of secondary non-response or intolerance to one anti-TNF, consider dose escalation or switching to another anti-TNF. JAK inhibitors can also be considered *(Agreement rate: 95%).*

In case of secondary non-response or intolerance to one anti-TNF, multiple options can be considered. A switch from one anti-TNF agent to another should be considered when an effective anti-TNF agent has been withdrawn due to intolerance [49]. Dose escalation is an option able to recapture response in the case of secondary non-response [50], while a change in mechanism of action – and thus swapping to a JAKi – may also be considered.

Statement 2.4: There is no evidence of efficacy of sulphasalazine or methotrexate for the treatment of IBD-associated axial SpA *(Agreement rate: 91%).*

Sulfasalazine (SSZ) and methotrexate (MTX) are not recommended for purely axial disease due to their lack of efficacy [41], as largely demonstrated by data from the literature [51,52].

3.4. Section 3. Active axial SpA and IBD in remission

The therapeutic algorithm for this clinical scenario is shown in Fig. 2.

Statement 3.1: In patients with active axial SpA and IBD in remission, symptomatic therapy with a short (2–4 weeks) cycle of COXIBs is an acceptable option *(Agreement rate: 91%).*

In the case of active axial SpA and IBD in remission, treatment should be focused on the rheumatological disease. Symptoms of the axial diseases may be severe. Even if the use of NSAIDs should be generally avoided in patients with IBD, the panel deemed that administration of a short cycle (2–4 weeks) of selective COXIBs is acceptable in patients with quiescent IBD. Data from the literature are reassuring, given that no differences were reported in IBD flares between patients treated with celecoxib for 2 weeks [53] and etoricoxib for 3 months [54] and their respective control groups.

Statement 3.2: In patients with active axial SpA and IBD in remission, TNF inhibitors (infliximab and adalimumab in CD and UC, or golimumab in UC) are recommended *(Agreement rate: 95%).*

Statement 3.3: In patients with active axial SpA and IBD in remission, in case of primary non-response to one anti-TNF, swapping to JAK inhibitors is recommended *(Agreement rate: 91%)*.

Statement 3.4: In patients with active axial SpA and IBD in remission, in case of secondary non-response or intolerance to one anti-TNF, consider dose escalation or switching to another anti-TNF. JAK inhibitors can also be considered *(Agreement rate: 100%)*.

In the case of active axial SpA, the main therapeutic options regarding biologics or small molecules are the same regardless of IBD activity. For the choice of the appropriate dosage of the various drugs, one should refer to statement 0.2 of the overarching principles.

Statement 3.5: In patients with active axial SpA and stable long-term remission of IBD, who are unresponsive to all other treatments, anti-IL-17 agents may be considered, with close monitoring of any recurrence of intestinal activity *(Agreement rate: 67%)*.

This statement was deeply debated and the opinions were sometimes discordant; however, the minimum agreement rate was finally reached. Anti-IL-17 agents are effective for the treatment of axial SpA [55], but some cases of newly-onset IBD or exacerbations of IBD were reported with the use of these biologics [56–60]. The absence of response to all treatments should prompt re-evaluation of the axial SpA diagnosis and exclusion of other causes of back pain [41]. In patients with "real" axial SpA that is unresponsive to all other treatments and long-term remission of IBD, anti-IL-17 agents are an option, but caution and strict monitoring of IBD is warranted.

Statement 3.6: In patients with active axial SpA and IBD in remission who achieve stable long-term remission of axial disease, long-term advanced therapy should be continued because of a high probability of recurrence of axial SpA *(Agreement rate: 82%)*.

Axial SpA is a potentially severe disease with a high impact on health-related quality of life [61]. Inflammation control has a key role in its management, given the consequences of a continuous disease activity on the structural axial damage [62]. The panel deemed the use of long-term therapies as useful to avoid inflammation recurrence in these patients, even in cases with stable remission of axial disease.

3.5. Section 4. Active peripheral SpA and active IBD

The therapeutic algorithm for this clinical scenario is shown in Fig. 3.

Statement 4.1: In patients with active peripheral SpA associated with active UC, sulphasalazine can be considered in cases of mild disease and as an additional therapy only for the control of peripheral SpA in CD *(Agreement rate: 96%)*.

Mesalazine compounds are still a milestone in the treatment of a large proportion of patients with UC, particularly in cases with mild disease [63]. Sulphasalazine (SSZ) could be the treatment of choice in cases with mild UC associated with peripheral, mild-to-moderate musculoskeletal manifestations, at a dose range of 2–3 g/day [64]. Conversely, all 5-aminosalicylates (5-ASA), including SSZ, are not indicated in the treatment of the intestinal side of CD, as they have no therapeutic effect [65]. SSZ can be considered as an additional therapy, in conjunction with other drugs which are effective in the treatment of luminal CD, to reach a therapeutic control of the articular manifestations in case of concomitant peripheral SpA.

Statement 4.2: Local therapy with glucocorticoid injections is useful for the control of inflammation of peripheral SpA *(Agreement rate: 96%)*.

Statement 4.3: Short-term systemic glucocorticoid treatment can be considered for a rapid induction of remission in case of moderate to severe symptoms and as a bridge for steroid-free maintenance therapies *(Agreement rate: 95%)*.

In cases of peripheral oligoarthritis (≤4 joints), peripheral enthesitis and dactylitis, local therapy with steroid infiltration is an effective option [64]. Local steroidal injections may be useful in patients treated with advanced therapies and incomplete control of musculoskeletal manifestations. In cases with moderate-to-severe UC and/or moderate-to-severe manifestations of SpA, systemic steroids should be considered to give a fast symptomatic relief. Long-term therapies with systemic steroids should always be avoided and steroids should be considered only as a bridge for steroid-free maintenance therapies [66].

Statement 4.4: Methotrexate can be considered for the control of both mild-to-moderate luminal and peripheral SpA in CD *(Agreement rate: 91%)*.

Statement 4.5: Methotrexate can be considered as an additional therapy only for the control of peripheral SpA in UC (*Agreement rate: 91%*).

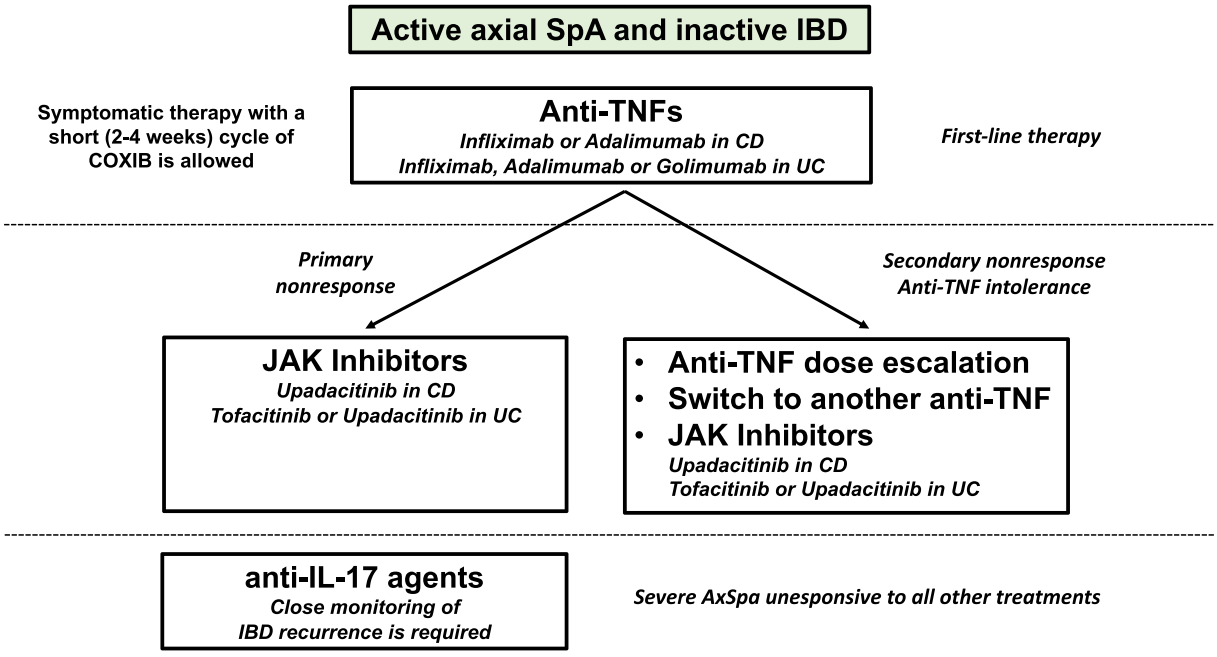


Fig. 2. Active axial SpA and IBD in remission: therapeutic algorithm.

MTX is an option as a steroid-sparing agent in steroid-dependent CD [67,68] and a well-known therapeutic agent for the management of peripheral arthritis [69]. MTX is not useful for the treatment of luminal UC [70] and should be considered only as an additional therapy for the control of peripheral musculoskeletal symptoms in patients treated with drugs which are known to be effective for luminal UC.

Statement 4.6: In patients with active peripheral SpA associated with moderate-to-severe active IBD, or in case of failure to sulphasalazine or methotrexate, TNF inhibitors (infliximab and adalimumab in CD and UC, or golimumab in UC) are recommended as first-line treatment. JAK inhibitors and ustekinumab may also be considered (*Agreement rate: 86%).*

Almost all advanced therapies available for the treatment of IBD are also able to control the peripheral musculoskeletal manifestations which can be associated with IBD [71]. The indication of TNF inhibitors as first-line treatment is based on the vast amount of data demonstrating their effectiveness in IBD-associated SpA [72], as well as on the availability of low-cost, effective and safe biosimilars of infliximab and adalimumab. JAKi and Ustekinumab (UST) may be considered, even though no head-to-head comparisons between the various drugs are available in IBD-associated SpA. Regarding JAKi, Tofacitinib was shown to be effective in patients with rheumatoid arthritis (RA) and incomplete response to conventional DMARDs [73–75] and in patients with PsA [76,77]. Filgotinib was effective as monotherapy or in combination with MTX in several RCTs on patients with RA [78–80] and PsA [81]. Recently, efficacy of Upadacitinib on PsA has also been reported [82,83]. UST was primarily approved for psoriasis and PsA [84] and it was also shown to be effective in improving joint pain in IBD patients in a real-world setting [85].

Efficacy of Vedolizumab (VDZ) for the treatment of the musculoskeletal manifestations in IBD is controversial. The panel ultimately decided to exclude this biologic from the treatment options. On the one hand, the gut-specificity of VDZ should make it ineffective for musculoskeletal manifestations. On the other hand, the well-known relationship between the gut and the joints may explain the improvement of arthralgias in some IBD patients who achieved remission of intestinal symptoms when treated with VDZ [86–88]. Following failure of all other lines of therapy, an attempt with vedolizumab in the case of SpA and active intestinal disease can be considered. This scenario is further complicated by case series reporting VDZ causing new onset arthralgias/arthritis or worsening of pre-existing arthralgias [89–91]. However, it is difficult to discriminate whether such detrimental manifestations can be attributed to corticosteroid or TNF inhibitors withdrawal instead of a real paradoxical mechanism of action of VDZ [92].

Statement 4.7: In patients with active peripheral SpA associated with moderate-to-severe active IBD, in case of primary non-response to one anti-TNF, consider swapping to ustekinumab *(Agreement rate: 77%)* or JAK inhibitors (*Agreement rate: 82%).*

Statement 4.8: In patients with active peripheral SpA and active IBD, in case of secondary non-response or intolerance to one anti-TNF, consider dose escalation or switching to another anti-TNF. JAK inhibitors or ustekinumab can also be considered *(Agreement rate: 100%).*

After a primary anti-TNF failure, the current availability of several biologics with different mechanisms of action calls for swapping to a biologic with a different mechanism of action, as previously stated. In

case of secondary non-response or intolerance to one anti-TNF, several options are available: switching from one anti-TNF agent to another (particularly when an effective anti-TNF agent has been withdrawn due to intolerance), anti-TNF dose escalation, or swapping to a JAKi or to UST.

Statement 4.9: In patients who achieve stable remission of both musculoskeletal and intestinal symptoms, discontinuation of the advanced therapy can be considered on a case-by-case basis. In UC, 5-ASA compounds should be continued. Thiopurines (in CD and UC) or methotrexate (in CD) can be considered for maintenance treatment *(Agreement rate: 82%)*.

In cases of stable remission of IBD and associated SpA, the possibility of de-escalating or withdrawing the advanced therapy should be assessed on a case-by-case basis and discussed with the patient. Factors that need to be considered include the risk of relapse in case of discontinuation [93] and the need for an alternative therapy to maintain remission. While de-escalation to 5-ASA compounds may offer an adequate therapeutic coverage in UC, the same is not applicable in CD, where the only alternatives are represented by thiopurines or methotrexate, which are currently seldom employed as maintenance therapy.

3.6. Section 5. Active peripheral SpA and IBD in remission

The therapeutic algorithm for this clinical scenario is shown in Fig. 4.

Statement 5.1: In patients with active, oligoarticular peripheral SpA and IBD in remission, the first-line therapeutic approach is the administration of local steroid injections or, in case of failure, of sulphasalazine *(Agreement rate: 81%)*.

Statement 5.2: In patients with active, polyarticular peripheral SpA associated with IBD in remission, short cycles of systemic glucocorticoids or short (2–4 weeks) cycles of COXIBs may be considered, together with sulphasalazine or methotrexate treatment *(Agreement rate: 95%)*.

In cases of active peripheral SpA and IBD remission, the rheumatological disease should drive the treatment choice. The distinction between oligoarticular and polyarticular peripheral SpA marks the border for the opportunity of local steroid injections, while systemic therapies including DMARDs should be considered in the case of mild-to-moderate disease. A fast symptomatic relief may be reached with short cycles of systemic glucocorticoids or short (2–4 weeks) cycles of COXIBs, particularly in the case of polyarticular disease.

Statement 5.3: In patients with active peripheral SpA and IBD in remission, unresponsive to sulphasalazine or methotrexate, TNF inhibitors (infliximab and adalimumab in CD and UC, or golimumab in UC) are recommended as first-line treatment. JAK inhibitors and ustekinumab may also be considered *(Agreement rate: 91%)*.

Statement 5.4: In case of primary non-response to one anti-TNF, consider swapping to ustekinumab *(Agreement rate: 86%)* or JAK inhibitors *(Agreement rate: 86%)*.

Statement 5.5: In patients with active peripheral SpA and IBD in remission, in case of secondary non-response or intolerance to one anti-TNF, consider dose escalation or switching to another anti-TNF. JAK inhibitors or ustekinumab can also be considered *(Agreement rate: 95%)*.

Regarding advanced therapies, the therapeutic possibilities to be considered in case of failure to DMARDs and active peripheral SpA are overall the same for active and inactive IBD. For the choice of the dosage of the various drugs, refer to statement 0.2 of the overarching principles.

4. Conclusions and research agenda

The 34 statements jointly formulated by IG-IBD and SIR are intended to be a minimal reference guide for clinicians dealing with IBD and associated SpA, including gastroenterologists and rheumatologists. The European Crohn's and Colitis Organization (ECCO) has recently published clinical practice guidelines on the management of extraintestinal manifestations of IBD which were mainly driven by gastroenterologists [2]. These guidelines took a broad view on all extraintestinal manifestations, and they were not limited to SpA, which is the focus of the present consensus. Furthermore, some of the drugs covered in our consensus (e.g. JAK inhibitors) were not included in the ECCO guidelines. Therefore, we believe that our document presents the most updated and detailed recommendation in the field of IBD-associated SpA.

The final indication in clinical practice should not arise solely from the statement itself, but the statement should be integrated with the experience of each physician, as well as with the safety and the cost of the intervention. RCTs with specific endpoints focused on SpA are not available in IBD patients. The panel is aware of the frailty of the current evidence for IBD-associated SpA, as it is mainly driven by real-world evidence, or it is simply translated from “pure” rheumatological settings. Given all the existing gaps in the literature, the first point on the research agenda should be the design and conduction of head-to-head comparisons between different treatment options for IBD-associated SpA. Future studies should focus specifically on analysing the efficacy of switching in class versus swapping between different drug classes. Another important research point lies in the availability of selective IL-23 inhibitors, a novel class of biologics with proven efficacy for the treatment of PsA [94]. Risankizumab was recently approved by EMA for CD, while mirikizumab was approved for UC and guselkumab is currently under study. It is unclear whether selective IL-23 inhibitors will have a different efficacy compared to UST and whether their field of indication in IBD (and IBD-associated SpA) will differ from that of UST. This last issue will arise in the future for all new drugs under development for IBD. A continuous update of these statements for IBD-associated SpA will be inevitable.

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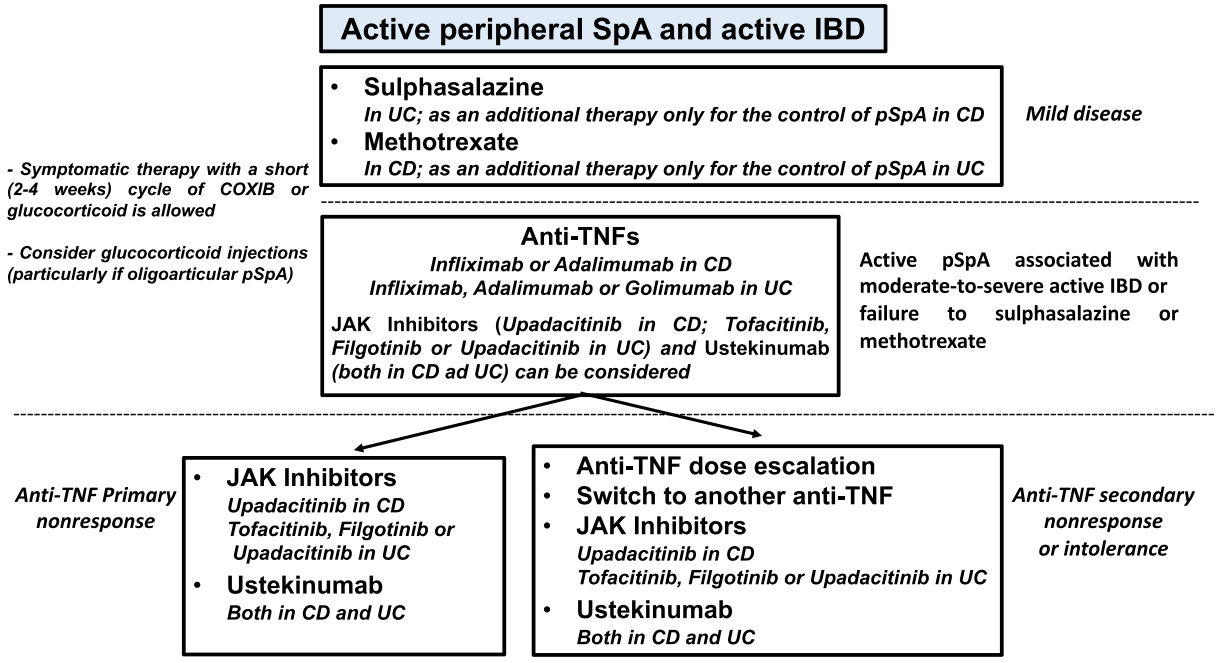


Fig. 3. Active peripheral SpA and active IBD: therapeutic algorithm.

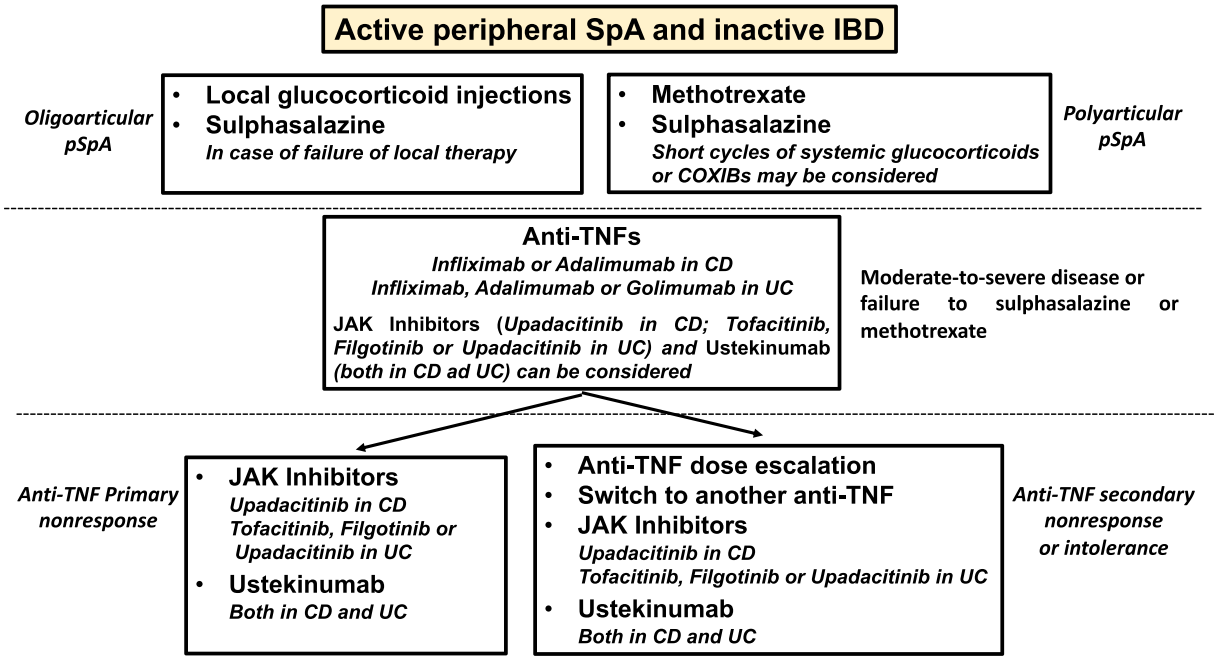


Fig. 4. Active peripheral SpA and IBD in remission: therapeutic algorithm.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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