Management of Arthritis Associated with Inflammatory Bowel Disease (IBD): A Systematic Review of Conventional and Targeted Therapies

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Abstract.
Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract associated with significant extraintestinal manifestations. Arthritis is the most frequent extraintestinal manifestation, with an overall prevalence of 17–39%, and is classified as a subtype of spondyloarthritis involving axial and/or peripheral joints. Peripheral arthritis is generally non-erosive, with the oligoarticular variant correlating with intestinal disease activity, whereas axial arthritis—including sacroiliitis and ankylosing spondylitis—tends to progress independently of bowel disease activity. This narrative review aims to provide a comprehensive overview of IBD-associated arthritis, covering its definition, epidemiology, pathogenesis, clinical manifestations, diagnosis, and management. Pathogenesis involves three interconnected mechanisms: extension of intestinal immune responses, gut microbiota dysregulation through Th17 pathway activation, and genetic predisposition mediated by HLA-B27 and NOD2/CARD15. Diagnosis relies on ASAS clinical criteria, with MRI as the preferred modality for early detection of axial involvement. Management requires an integrated approach; TNF-α inhibitors serve as first-line therapy in active disease, while JAK inhibitors, ustekinumab, and vedolizumab represent promising novel therapeutic options. Multidisciplinary collaboration between gastroenterologists and rheumatologists is essential to optimize long-term clinical outcomes.
Keywords: *Arthritis, IBD, Axial Arthritis and Peripheral Arthritis.*

I. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory condition of the gastrointestinal tract comprising two primary entities: Crohn's disease and ulcerative colitis. Crohn's disease is characterized by discontinuous, transmural inflammation that can affect any segment of the gastrointestinal tract, whereas ulcerative colitis causes mucosal inflammation restricted to the colon (Arvikar & Fisher, 2011). IBD presents a significant global prevalence: nearly 4 million individuals worldwide suffer from the disease, with approximately 1.4 million cases reported in the United States alone. The prevalence of Crohn's disease and ulcerative colitis among US adults is 201 and 238 per 100,000 population, respectively (Arvikar & Fisher, 2011). In Asia, the incidence of IBD has increased over the past few decades, with a predominance of ulcerative colitis over Crohn's disease (Perkumpulan Gastroenterologi Indonesia, 2022).

IBD affects not only the gastrointestinal tract but also presents with various extraintestinal manifestations (EIMs), including arthritis, ocular involvement, dermatological manifestations, pulmonary manifestations, biliary tract complications, anemia, and thromboembolism (Arvikar & Fisher, 2011; Meisinger & Freuer, 2022). Among these EIMs, arthritis is the most frequently observed in IBD, with an overall reported prevalence ranging from 17% to 39% (Arvikar & Fisher, 2011). Arthralgia is reported in 40–50% of IBD patients, while active arthritis occurs in approximately 15–20% of patients with Crohn's disease and about 10% of those with ulcerative colitis at various stages of the disease course (Orchard, 2012). IBD-associated arthritis is classified as a subtype of spondyloarthritis (SpA), with manifestations that may involve axial joints, peripheral joints, or a combination of both. It has been shown to significantly impact patient morbidity and quality of life (Arvikar & Fisher, 2011; Faggiani et al., 2024).

Within the broader epidemiological context of spondyloarthritis, ankylosing spondylitis constitutes the largest SpA subgroup—reaching a prevalence of 0.24% in Europe, 0.31% in North America, and 0.35% in the Arctic region. Psoriatic arthritis ranks second, with a prevalence of 0.19% in Europe and 0.01% in the Middle East. IBD-associated spondyloarthritis itself has a relatively lower prevalence, ranging from 0.0% to

0.1%, and 0.0% to 0.7% in cases of undifferentiated spondyloarthritis. In patients with ankylosing spondylitis, the prevalence of IBD is reported to be 4–14%, with the risk of developing IBD being three to five times higher compared to the healthy population (Perhimpunan Reumatologi Indonesia, 2021).

Although IBD-associated arthritis has been clinically recognized for over a century—with early descriptions by Bargen, Hench, and later Zvaifler, who accurately delineated the relationship between the gut, spine, and peripheral joints—the condition remains incompletely understood and characterized to this day. A clear distinction between IBD-associated arthritis, rheumatoid arthritis, and ankylosing spondylitis only became possible following advancements in diagnostic detection systems in the mid-twentieth century, such as the discovery of rheumatoid factor and HLA-B27 (Ashrafi et al., 2021).

Several persistent gaps continue to pose clinical and research challenges in the management of IBD-associated arthritis. First, regarding diagnosis, there is no single gold standard for establishing a diagnosis of enteropathic arthritis, and evidence concerning standardized diagnostic strategies remains limited. A recent systematic review confirmed that evidence-based disease definitions and standardized diagnostic criteria for IBD-associated peripheral arthritis are not yet available (Falloon et al., 2025). Furthermore, a systematic review by Schwartzman et al. (2022) identified substantial heterogeneity in the design of studies evaluating SpA phenotypes in IBD patients, which directly limits the ability to draw comparative conclusions across studies. Second, concerning management, the underlying mechanisms driving the development of IBD-associated arthritis are not fully elucidated, precluding the determination of an optimal therapeutic approach. Treatment of the underlying IBD is not universally effective in controlling arthritis, and large-scale randomized controlled trials with specific endpoints focused on IBD-associated SpA remain highly limited (Arvikar & Fisher, 2011; Macaluso et al., 2024). Third, from a clinical management perspective, IBD-associated arthritis is often managed in silos by gastroenterologists and rheumatologists without optimal coordination. A structured, multidisciplinary approach is required but has not been widely institutionalized; failure in cross-specialty coordination can lead to delayed diagnosis, suboptimal management, and irreversible joint damage (Ashton et al., 2024).

Given the extensive disease burden, the complexity of its pathogenesis, and the various existing gaps in diagnosis and management, a comprehensive review integrating the latest advancements from scientific literature is warranted. Therefore, this narrative literature review aims to provide a contemporary understanding of inflammatory bowel disease (IBD)-associated arthritis, encompassing definitions and classifications, epidemiology, pathogenesis, clinical manifestations, diagnostic approaches, and current management modalities—including novel therapies. This serves as a comprehensive reference for clinicians managing this condition in daily practice.

II. METHODS

This study is a systematic review conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review aims to evaluate current scientific evidence regarding the pathogenesis, clinical manifestations, diagnosis, and management of inflammatory bowel disease (IBD)-associated arthritis, including recent advancements in biologic and targeted therapies.

A systematic literature search was performed across several electronic databases, namely PubMed, Scopus, ScienceDirect, and Google Scholar. Articles published between January 2014 and December 2025 were identified using the following combinations of keywords and Boolean operators: ("Inflammatory Bowel Disease" OR "Crohn's Disease" OR "Ulcerative Colitis") AND ("Enteropathic Arthritis" OR "IBD-associated Arthritis" OR "Spondyloarthritis") AND ("Treatment" OR "Management" OR "Biologic Therapy" OR "JAK Inhibitor" OR "Ustekinumab" OR "Vedolizumab"). Additionally, a manual search of the reference lists of relevant articles was conducted to identify further literature.

Inclusion criteria comprised original research articles, randomized controlled trials, cohort studies, case-control studies, observational studies, systematic reviews, meta-analyses, and international clinical guidelines discussing IBD-associated arthritis. Articles were required to be available in full text and published in either English or Indonesian. Exclusion criteria encompassed duplicate articles, conference

abstracts without full texts, letters to the editor, commentaries, and articles that did not specifically address musculoskeletal involvement or arthritis management in IBD patients.

The article selection process was conducted in stages, including identification, title and abstract screening, full-text eligibility assessment, and final selection of articles meeting the inclusion criteria. Selected articles were subsequently extracted and analyzed based on study characteristics, study populations, types of arthritic manifestations, diagnostic methods, therapeutic modalities, and reported clinical outcomes.

The methodological quality of the included articles was evaluated using instruments appropriate for their respective study designs. Subsequently, the extracted data were synthesized narratively and categorized into several main themes: the pathogenesis of IBD-associated arthritis, clinical manifestations, diagnostic approaches, conventional management, biologic therapies, Janus kinase (JAK) inhibitors, and developments in novel targeted therapies.

III. RESULT AND DISCUSSION

The following is a literature synthesis on IBD-associated arthritis encompassing eight primary themes. Each theme is discussed based on current evidence from the literature identified through the established search strategy.

Definition

IBD-associated arthritis can involve both peripheral and axial joints. This condition is categorized under spondyloarthritis (SpA). Spondyloarthritis, which encompasses ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthritis, is characterized by inflammatory involvement of the axial and peripheral joints and typically presents with a negative rheumatoid factor (Arvikar & Fisher, 2011).

Spondyloarthritides share similar genetic factors, including an association with HLA-B27. Extra-articular features such as dermatological manifestations, dactylitis, enthesopathy, and ocular disease may also be observed. IBD-associated arthritis more closely resembles ankylosing spondylitis than other SpA subtypes, as it tends to be symmetric and continuous. Conversely, reactive arthritis or psoriatic arthritis may present asymmetrically or cause non-continuous lesions in the spine. The criteria established by the European Spondyloarthropathy Study Group (ESSG) remain the most widely used for classifying SpA (Ashrafi et al., 2021; Dougados et al., 1991).

Orchard et al. classified IBD patients with peripheral arthritis into two categories. Type 1 is characterized by pauci/oligoarticular arthritis, causing pain and swelling in a maximum of five joints, predominantly the large joints of the lower extremities. Type 1 arthritis is typically acute, self-limiting, and correlates with IBD disease activity. Joint symptoms may precede the diagnosis of IBD. Type 2 peripheral arthritis features a more polyarticular distribution (affecting more than five joints), is symmetrical, and primarily involves the upper limbs (most frequently the metacarpophalangeal [MCP] joints). Type 2 peripheral arthritis may run a chronic course and is less likely to parallel IBD activity. In both types, peripheral arthritis tends to be non-deforming and non-erosive. Alternative diagnoses, such as rheumatoid arthritis or psoriatic arthritis, should be considered in IBD patients presenting with erosive arthritis (Ashrafi et al., 2021; Orchard, 2012).

In separate publications, Arnold Bargen in 1929 and Philip Hench in 1935 observed and studied 1,500 patients with chronic ulcerative colitis; 60 suffered from arthritis, which was noted as the most common complication of colitis aside from polyposis. These publications expanded the descriptions that catalyzed early appreciation of the heterogeneous nature of IBD-associated arthritis (Ashrafi et al., 2021).

Bargen and Hench classified the arthritis into four types: (1) Arthritis manifesting long before ulcerative colitis, resembling an atrophic form (an early term for rheumatoid arthritis) and considered unrelated to colitis. (2) Atrophic arthritis and colitis occurring simultaneously but progressing independently. (3) Arthritis resembling atrophic arthritis that emerges during colitis remission but remains absent during bowel disease exacerbations. (4) The most common type, presenting as subacute arthritis that flares concurrently with colitis exacerbations and improves when the colitis enters remission. This type

demonstrates a clear correlation between the simultaneous remission and exacerbation of both conditions (Ashrafi et al., 2021).

They regarded the first three types as coincidental associations between rheumatoid arthritis and IBD. However, the fourth and most prevalent type was concluded to be a specific complication of colitis rather than a mere coincidental association with another disease (Ashrafi et al., 2021).

Epidemiology

Arthritis occurs more frequently in Crohn's disease than in ulcerative colitis. Risk factors for developing arthritis may include active bowel disease or a family history of IBD. Women may carry a higher risk for peripheral arthritis, whereas men tend to exhibit axial involvement more frequently. The presence of other EIMs, such as erythema nodosum or pyoderma gangrenosum, can also serve as risk factors (Arvikar & Fisher, 2011).

Arthralgia is more common in IBD patients, affecting 40–50% of the patient population, which is comparable to the rate in the general population. Active arthritis occurs in approximately 15–20% of patients with Crohn's disease and about 10% of those with ulcerative colitis at some point during their disease course (Orchard, 2012).

Risk Factors

Enteropathic arthritis is a subset of spondyloarthritis associated with IBD. Approximately 50% of SpA patients exhibit microscopic intestinal inflammation, and 7% progress to overt IBD. In patients with ankylosing spondylitis, the prevalence of IBD ranges from 4% to 14%. The risk of developing IBD is elevated three- to five-fold in ankylosing spondylitis patients compared to healthy individuals. The incidence of IBD occurs at a similar frequency in both non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis populations. Furthermore, IBD is more frequently observed in male patients with ankylosing spondylitis, and its prevalence tends to decrease with advancing age (Perhimpunan Reumatologi Indonesia, 2021).

Clinicians should maintain a high index of suspicion for enteropathic arthritis in spondyloarthritis patients with a family history of IBD, chronic diarrhea lasting more than 4 weeks accompanied by weight loss, chronic abdominal pain, unexplained rectal bleeding, prolonged fever, a history of perianal fistulas or abscesses, anemia, malabsorption symptoms, or EIMs such as erythema nodosum, pyoderma gangrenosum, oral thrush, and cholangitis, as well as dermatological signs like maceration or laceration (Perhimpunan Reumatologi Indonesia, 2021).

In SpA patients lacking the aforementioned signs, enteropathic arthritis should be suspected if the patient meets at least two of the following criteria: (1) chronic abdominal pain lasting over 4 weeks, whether persistent or intermittent; (2) iron deficiency with or without anemia; (3) the presence of extraintestinal manifestations; (4) unexplained fever lasting more than 1 week; (5) unexplained weight loss; and (6) a family history of IBD (Perhimpunan Reumatologi Indonesia, 2021).

Pathogenesis

Extension of the Intestinal Immune Response

Extraintestinal manifestations arise as a result of an immune response to intestinal antigens that subsequently affects other organs, or through inflammatory processes devoid of direct intestinal involvement. These mechanisms are triggered by genetic predisposition, environmental factors, or the underlying presence of IBD itself (Ashton et al., 2024; Faggiani et al., 2024).

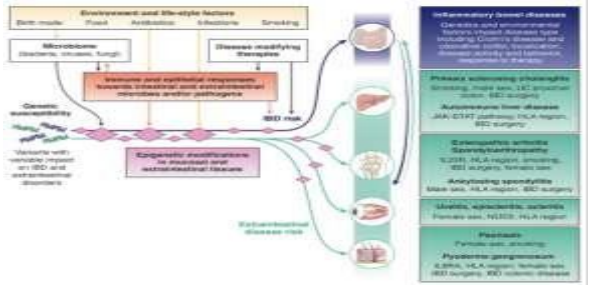

Fig. 1. Risk Factors for the Development of IBD and Extraintestinal Diseases (Ashton et al., 2024).

A potential factor contributing to EIMs is the ectopic expression of chemokines and adhesion molecules in extraintestinal organs and tissues. T cells are recruited to the gut due to the expression of α4β7 integrin and the CCR9 receptor, which bind to MAdCAM-1 and CCL25, respectively, both expressed on the intestinal endothelium. Alterations in lymphocyte homing in IBD may facilitate the upregulation of MAdCAM-1 and CCL25 in the liver and the migration of gut-tropic T cells to extraintestinal sites, driving the progression of inflammation (Faggiani et al., 2024).

Independent Inflammatory Processes

The specific role of the microbiota in extraintestinal manifestations has not been entirely elucidated or definitively established. The potential contribution of molecular mimicry between gut microbiota antigens and non-microbial epitopes on cells within target organs in driving T-cell clonal activation and immune cross-reactivity remains inconclusively proven. Individuals with IBD and psoriatic arthritis (PsA) exhibit a relative decrease in the prevalence of *Coprococcus* and *Ruminococcus* species. These species play a crucial role in maintaining intestinal homeostasis by producing short-chain fatty acids (SCFAs), which exert metabolic and immunomodulatory effects. Generally, SCFA levels are diminished in patients with IBD and concomitant psoriatic arthritis. Conversely, IBD patients with spondyloarthritis demonstrate elevated levels of the genus *Dialister*, which correlates positively with joint disease activity. Furthermore, patients with both IBD-associated arthritis and rheumatoid arthritis (RA) exhibit high levels of *Clostridiaceae*, suggesting a potential shared microbial link in inflammatory arthritides (Faggiani et al., 2024).

Dysbiosis in IBD patients can enhance lipopolysaccharide expression, subsequently triggering the activation of various pro-inflammatory molecules, such as interleukin-6 (IL-6), interferon-γ (IFN-γ), and vascular endothelial growth factor (VEGF). This cascade potentially contributes to the development of EIMs (Faggiani et al., 2024).

Genetics

There is substantial overlap in genetic risk loci between IBD and its extraintestinal manifestations. The identification of associated genetic mutations and polymorphisms in key immune pathways may enable a molecularly based classification of EIMs, which would be more precise than traditional organ-based classifications. This paradigm shift would also facilitate a more comprehensive understanding of therapeutic targets, thereby optimizing treatment efficacy (Faggiani et al., 2024).

Genetic factors account, at least partially, for the predisposition of certain IBD patients to develop arthritis via alterations in both innate and adaptive immune pathways. The HLA-B27 gene is postulated to contribute to arthritis pathogenesis in IBD by facilitating the presentation of arthritogenic peptides to T cells. Additionally, this genotype may heighten susceptibility to protein misfolding, thereby triggering an inflammatory response. However, HLA-B27 explains only a minor fraction of the overall genetic susceptibility to arthritis in IBD (Turner et al., 2005).

Over 71 susceptibility loci have been identified in IBD. Genome-wide association studies have consistently demonstrated the involvement of NOD2/CARD15 on chromosome 16q12, which accounts for up to 20% of the overall genetic susceptibility to Crohn's disease. NOD2/CARD15 functions in the innate immune response as an intracellular receptor for bacterial molecular patterns on monocytes, ultimately leading to NFκB activation. Alterations in host-microbe interactions within the gut may play a pivotal role in Crohn's disease pathogenesis. In SpA patients, the overall prevalence of CARD15 polymorphisms is not increased, although it is associated with a higher risk of intestinal inflammation (Reveille, 2011).

The IL-23R polymorphism, which confers strong protection against IBD, has also been found to be protective against ankylosing spondylitis. STAT3 is similarly implicated in gene studies linking Crohn's disease with ankylosing spondylitis. STAT3 is activated in response to signaling through IL-23R within the Th17 pathway. Furthermore, IL12B, which encodes the p40 subunit shared by IL-12 and IL-23, has been identified, underscoring the critical role of the Th17 pathway in SpA pathogenesis (Danoy et al., 2010). It remains unclear whether any of these specific genes inherently increase susceptibility to arthritis within the context of IBD. Further robust studies are required to identify specific genetic variants that amplify the risk of arthritis in IBD (Arvikar & Fisher, 2011).

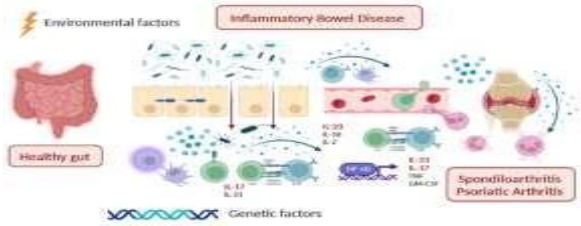

Fig.2. The Gut-Joint Axis in the Pathogenesis of IBD and SpA.

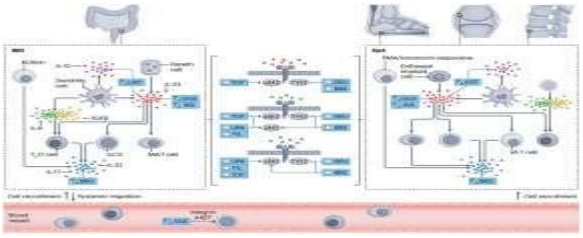

Fig.3. IL-23 and IL-17 Pathways and Therapeutic Targets in Spondyloarthritis and Inflammatory Bowel Disease.

Clinical Manifestations

Enteropathic arthritis should be suspected in IBD patients presenting with spinal pain lasting over 3 months, peripheral joint pain or swelling, enthesitis, and dactylitis. Spondyloarthritis occurs in 10–39% of IBD patients as an extraintestinal manifestation. It is more prevalent in Crohn's disease than in ulcerative colitis. Axial arthritis manifestations occur in approximately 20% of cases, with ankylosing spondylitis estimated at 2–16% and sacroiliitis at 12–46%. The prevalence of HLA-B27 positivity is 25–78% in patients with both IBD and ankylosing spondylitis, and 7–15% in those with IBD and sacroiliitis. Peripheral SpA manifestations in IBD range from 0.4% to 34.6%, with higher incidences observed in younger demographics (Perhimpunan Reumatologi Indonesia, 2021).

Axial arthritis in IBD may encompass isolated sacroiliitis (often asymptomatic), inflammatory back pain (IBP), and ankylosing spondylitis. Because the terms ankylosing spondylitis, sacroiliitis, and IBP exhibit some phenotypic overlap, distinguishing them can be clinically challenging. Ankylosing spondylitis requires radiographic evidence of sacroiliitis in conjunction with back pain and stiffness lasting more than 3 months that does not improve with rest but is relieved by exercise, or limitation of motion in the sagittal and frontal planes, or restricted chest expansion relative to age- and sex-matched norms. Sacroiliitis is defined strictly as inflammation of the sacroiliac joint, which may be symptomatic or asymptomatic. Inflammatory back pain is a clinical diagnosis and does not inherently mandate imaging. The Calin criteria can differentiate IBP from mechanical back pain, being fulfilled if at least 4 of the 5 following parameters are met: (1) age of onset <40 years, (2) duration >3 months, (3) insidious onset, (4) morning stiffness, and (5) improvement with exercise (Calin, 1977). The newer IBP criteria developed by the Assessment of SpondyloArthritis international Society (ASAS) in 2010 may offer superior specificity compared to the Calin criteria (Sieper et al., 2009).

IBD-associated ankylosing spondylitis is considered an entity distinct from idiopathic ankylosing spondylitis, demonstrating a weaker association with male sex and HLA-B27 positivity. The 1984 modified New York criteria for ankylosing spondylitis base the diagnosis on the presence of inflammatory back pain combined with radiological evidence of grade 2 bilateral or grade 3 unilateral sacroiliitis. Asymptomatic sacroiliitis can be detected in up to 32% of IBD patients, though its clinical significance remains ambiguous. Patients with axial involvement frequently report back pain accompanied by morning stiffness that alleviates with exercise. Axial symptoms typically do not correlate with bowel disease activity. Axial disease can occur in isolation or in combination with peripheral arthritis (Arvikar & Fisher, 2011).

Other musculoskeletal manifestations in IBD encompass enthesitis (inflammation at tendon insertion sites), dactylitis (sausage-like swelling of the digits), and arthralgia (joint pain without clinical signs of inflammation). Furthermore, IBD complications and treatment-related adverse effects, such as septic arthritis or osteonecrosis, must be meticulously evaluated in IBD patients presenting with joint pain, particularly in monoarticular or oligoarticular scenarios (Arvikar & Fisher, 2011).

Diagnosis

There is no singular gold standard for diagnosing enteropathic arthritis. The diagnosis fundamentally relies on clinical findings of spondyloarthritis based on ASAS criteria, supported by laboratory investigations, radiological imaging, and gastrointestinal biopsy results as the standard for the underlying bowel disease (Perhimpunan Reumatologi Indonesia, 2021).

Ancillary investigations that aid in diagnostic formulation include: 1) Inflammatory markers (Erythrocyte Sedimentation Rate [ESR], C-reactive protein [CRP]); 2) Stool culture and microscopy; 3) Fecal Calprotectin (FC); 4) Endoscopy and colonoscopy. Ileocolonoscopy remains the cornerstone diagnostic evaluation for IBD to assess the entire lower gastrointestinal tract, including the terminal ileum. Mucosal biopsies must be obtained from all macroscopically visible lesions; 5) Conventional radiography of the spine and sacroiliac joints; 6) Musculoskeletal ultrasound; 7) Abdominal (lumbosacral) MRI/computed tomography, beneficial as adjunctive tools to assess the extent of Crohn's disease; 8) Video capsule endoscopy (VCE), utilized to evaluate tissues inaccessible via standard endoscopy or colonoscopy; 9) Intestinal biopsy as the diagnostic gold standard for differentiating ulcerative colitis and Crohn's disease (Perhimpunan Reumatologi Indonesia, 2021).

No single laboratory test can definitively diagnose IBD-associated arthritis or be used in isolation to quantify disease activity. The diagnosis remains predominantly clinical, predicated on the presence of peripheral or axial arthritis within the context of IBD. Inflammatory markers such as CRP, ESR, platelet count, or white blood cell count may be elevated solely due to the underlying IBD activity without concurrent arthritis, complicating their interpretation in IBD-associated joint disease. Conversely, inflammatory markers may remain within normal limits despite active arthritis; thus, a normal ESR or CRP does not rule out active joint inflammation (Arvikar & Fisher, 2011).

Although the prevalence of HLA-B27 in idiopathic ankylosing spondylitis exceeds 90%, an overall increased frequency of HLA-B27 is not observed across the general IBD population. However, within the subgroup of patients with concurrent IBD and ankylosing spondylitis, up to 78% test positive for HLA-B27. In contrast, isolated sacroiliitis lacks a significant correlation with HLA-B27. HLA typing does not play a direct diagnostic role in IBD-associated arthritis; nevertheless, HLA-B27 positive individuals with IBD are at an elevated risk of developing axial arthritis. Imaging is generally unnecessary for diagnosing IBD-associated peripheral arthritis, though it may assist in excluding alternative pathologies. Plain radiographs of peripheral joints may reveal effusions or periarticular osteopenia, akin to findings in other inflammatory arthritides. Frank erosions and joint destruction are exceedingly rare (Arvikar & Fisher, 2011).

Unlike peripheral arthritis, diagnosing axial arthritis may necessitate imaging. The hallmark of axial spondyloarthritis is the presence of inflammation coupled with proliferative bone changes, culminating in syndesmophyte formation in the spine or ankylosis of the sacroiliac joints. Idiopathic ankylosing spondylitis and IBD-associated arthritis exhibit virtually identical radiographic presentations in the spine and sacroiliac joints. The lower thoracic spine is the region most frequently affected in ankylosing spondylitis. In advanced stages, the disease may manifest as sclerosis, syndesmophytes, or vertebral fusion, producing the classic "bamboo spine" appearance. While erosive or destructive lesions can occur in axial spondyloarthritis, they are substantially less common than osteoproliferative lesions (Braun & Baraliakos, 2011).

Anteroposterior (AP) plain radiography of the pelvis and spine serves as the standard modality for evaluating sacroiliitis and ankylosing spondylitis in patients with suspected axial involvement. This examination is the traditional gold standard for detecting structural alterations. However, such radiographic changes typically emerge in the advanced stages of the disease and may require several years of progression before becoming radiologically apparent (Arvikar & Fisher, 2011).

Magnetic Resonance Imaging (MRI) is widely regarded as the superior technique for detecting active inflammation in the spine and sacroiliac joints, facilitating much earlier diagnosis. For decades, diagnostic radiological criteria, such as the modified New York criteria, mandated the presence of grade 2 bilateral or grade 3 unilateral sacroiliitis on plain radiographs as a primary parameter for confirming ankylosing spondylitis. The updated ASAS classification criteria for axial spondyloarthritis now incorporate the detection of sacroiliac inflammation via MRI as acceptable definitive evidence for diagnosing sacroiliitis.

Beyond detecting active inflammation, MRI also holds the potential to identify early structural bone changes and is instrumental in predicting and longitudinally monitoring therapeutic response (Braun & Baraliakos, 2011; Peluso et al., 2013; Rudwaleit et al., 2009).

Management of IBD-Associated Arthritis

General Principles of Management

Overall, studies specifically investigating the treatment of IBD-associated arthritis remain sparse, highlighting a critical need for larger-scale randomized controlled trials. Because oligoarticular peripheral arthritis often parallels the clinical course of IBD, therapies targeting the intestinal disease frequently alleviate this form of arthritis concurrently. In ulcerative colitis, a colectomy can serve as a curative intervention for the bowel disease and may simultaneously resolve peripheral arthritis, particularly Type 1. However, case reports have documented the *de novo* development of arthritis post-proctocolectomy in UC patients, specifically in those undergoing ileal pouch-anal anastomosis. The pouch procedure, performed to preserve anal sphincter function and improve quality of life relative to a stoma, may leave behind residual inflamed colonic tissue. This remnant tissue can exacerbate or trigger arthritis due to persistent gastrointestinal inflammation (Balbir-Gurman et al., 2001).

Spondyloarthritis (SpA) represents the most common extraintestinal manifestation in IBD patients. When IBD and SpA coexist, the clinical characteristics of both the musculoskeletal and intestinal diseases must be carefully integrated when designing a therapeutic strategy. While treatment armaments for IBD and SpA have expanded rapidly in recent years, randomized controlled trials with SpA-specific endpoints are conspicuously absent within the IBD management literature. In recent developments, the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and the Italian Society of Rheumatology (SIR) collaboratively formulated updated therapeutic recommendations for IBD-associated arthritis using the pseudo-Delphi method. The overarching goal is to provide a standardized reference guide for gastroenterologists and rheumatologists co-managing these complex cases (Macaluso et al., 2024).

The recent 2024 consensus by the IG-IBD and SIR recommends that, as an overarching principle, patients with IBD-associated SpA must receive integrated, multidisciplinary care driven jointly by rheumatology and gastroenterology. Drug dosing must be meticulously individualized on a case-by-case basis, anchored in the patient's clinical history. Furthermore, clinical decision-making must be rooted in shared decision-making between the physician and the patient. Key recommendations from this consensus include: 1) IBD-associated SpA should be classified strictly according to the ASAS criteria into either axial or peripheral SpA; 2) Within the context of SpA, the diagnosis of IBD and the differentiation between Crohn's disease, ulcerative colitis, and IBD unclassified (IBD-U) must rely on globally accepted criteria as established by the European Crohn's and Colitis Organisation (ECCO); 3) The presence of specific "red flags" warrants immediate referral of patients with suspected IBD and SpA to a gastroenterologist or rheumatologist; 4) In axial SpA, joint disease activity must be evaluated at baseline and longitudinally during therapy using the Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP; 5) In peripheral SpA, joint disease activity must be assessed at baseline and longitudinally using the Disease Activity Index for Psoriatic Arthritis (DAPSA); 6) For Crohn's disease, bowel disease activity must be evaluated at baseline and monitored using the Harvey-Bradshaw Index (HBI); 7) For ulcerative colitis, bowel disease activity must be assessed at baseline and monitored using the Partial Mayo Score (PMS) (Macaluso et al., 2024).

Treatment Modalities for Spondyloarthritis and IBD

For patients presenting with active axial SpA and active IBD, TNF inhibitors (infliximab and adalimumab for both Crohn's disease and UC, or golimumab specifically for UC) are strictly recommended as first-line therapy. The treatment algorithm for active axial SpA with concurrent active IBD is illustrated below (Macaluso et al., 2024):

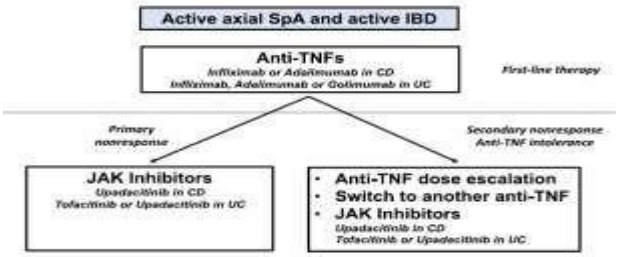

Fig.4. Therapeutic Algorithm for Active Axial SpA and Active IBD.

In the setting of active Crohn's disease or ulcerative colitis associated with axial SpA, anti-TNF agents are the undisputed first-line treatment. The robust efficacy of anti-TNF therapy for both axial SpA and IBD is extensively documented in the literature. The prioritization of these agents is further bolstered by the widespread availability of infliximab and adalimumab biosimilars, which deliver equivalent efficacy and safety profiles to the originators at a substantially reduced economic cost. Etanercept, another anti-TNF agent, lacks efficacy in active Crohn's disease and has been implicated as a potential trigger for paradoxical *de novo* Crohn's disease. Certolizumab pegol is FDA-approved for Crohn's disease and represents a viable, effective alternative for axial SpA. In the event of primary non-response to an initial anti-TNF agent, a direct switch to a JAK inhibitor is strongly recommended. Sulfasalazine (SSZ) and methotrexate (MTX) are not indicated for isolated axial disease due to proven lack of efficacy (Macaluso et al., 2024).

For patients with active axial SpA but inactive IBD (in remission), TNF inhibitors (infliximab and adalimumab for CD and UC, or golimumab for UC) remain the recommended intervention. The corresponding algorithm is presented below (Macaluso et al., 2024):

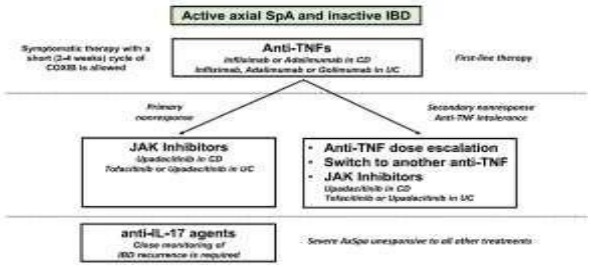

Fig. 5. Therapeutic Algorithm for Active Axial SpA and IBD in Remission.

In cases where axial SpA is active but IBD is in stable remission, therapeutic targeting must pivot to prioritize the rheumatic disease. Axial symptoms can be profoundly debilitating. While nonsteroidal anti-inflammatory drugs (NSAIDs) are generally contraindicated in IBD populations, the expert panel concedes that short courses (2–4 weeks) of selective COX-2 inhibitors (COXIBs) are clinically acceptable for IBD patients in established remission. Existing literature supports the safety of this approach, demonstrating no statistically significant difference in IBD flare rates between patients receiving celecoxib for 2 weeks or etoricoxib for 3 months compared to their respective placebo controls. In this cohort (active axial SpA/inactive IBD), a primary non-response to anti-TNF therapy necessitates a switch to a JAK inhibitor. For patients who maintain long-term stable IBD remission but present with severe axial SpA refractory to all aforementioned treatments, anti-IL-17 agents may be carefully considered, provided there is stringent clinical and biomarker monitoring for potential intestinal flare. Furthermore, patients who successfully achieve long-term stable remission of their axial disease should be maintained on long-term continuous therapy, given the exceptionally high relapse rate associated with axial SpA withdrawal (Macaluso et al., 2024).

For patients with active peripheral SpA associated with active ulcerative colitis, sulfasalazine is an appropriate consideration for mild disease, and may serve strictly as adjunctive therapy to control peripheral SpA in Crohn's disease. The therapeutic algorithm for this cohort is detailed below (Macaluso et al., 2024):

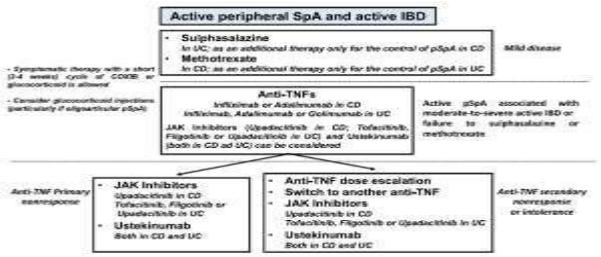

Fig. 6. Therapeutic Algorithm for Active Peripheral SpA and Active IBD.

Mesalamine (5-ASA) remains a foundational therapeutic option for the majority of ulcerative colitis patients, particularly in mild disease phenotypes. Sulfasalazine (SSZ) emerges as the treatment of choice for mild UC coupled with mild-to-moderate peripheral musculoskeletal manifestations, dosed typically at 2–3 g/day. Conversely, all 5-aminosalicylates, including SSZ, lack therapeutic efficacy in Crohn's disease and are not indicated for its primary management. However, SSZ may be utilized as an adjunct, layered alongside CD-effective agents, specifically to attain therapeutic control of articular manifestations in patients with concurrent peripheral SpA. Localized therapy via intra-articular glucocorticoid injections is highly effective for curbing localized inflammation in peripheral SpA. Short-term systemic glucocorticoid courses may be deployed to induce rapid remission in moderate-to-severe symptomatic flares, serving as a temporal bridge to steroid-free maintenance regimens. Methotrexate (MTX) is a viable option for controlling mild-to-moderate peripheral SpA in CD. In UC, MTX is relegated strictly to the role of adjunctive therapy aimed exclusively at peripheral joint control (Macaluso et al., 2024).

In the clinical scenario of active peripheral SpA coupled with moderate-to-severe active IBD, or in cases refractory to sulfasalazine or methotrexate, TNF inhibitors (infliximab and adalimumab for CD and UC, or golimumab for UC) are the mandated first-line biologics. JAK inhibitors and ustekinumab also emerge as valid considerations. If a primary non-response to an initial anti-TNF agent occurs in this cohort (active peripheral SpA/moderate-severe active IBD), a switch to ustekinumab is recommended. Conversely, in the event of secondary loss of response or intolerance to an anti-TNF, clinicians should consider dose escalation or switching within class to an alternative anti-TNF. JAK inhibitors or ustekinumab remain viable downstream options. For patients successfully achieving sustained, stable remission of both musculoskeletal and intestinal domains, careful, individualized consideration may be given to withdrawing advanced therapies on a case-by-case basis. In UC, 5-ASA compounds should be maintained indefinitely. Thiopurines (for CD and UC) or methotrexate (for CD) may be utilized for long-term maintenance (Macaluso et al., 2024).

For patients presenting with active oligoarticular peripheral SpA and IBD in remission, first-line therapy firmly rests on localized intra-articular steroid injections. Should this approach fail to yield an adequate response, sulfasalazine serves as the primary systemic alternative. The algorithm for active peripheral SpA and inactive IBD is outlined below (Macaluso et al., 2024):

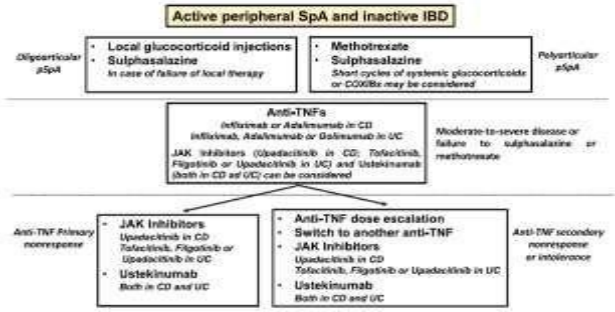

Fig. 7. Therapeutic Algorithm for Active Peripheral SpA and IBD in Remission.

When addressing active peripheral SpA in the setting of inactive IBD, the therapeutic trajectory is heavily dictated by the specific rheumatic phenotype. The fundamental distinction between oligoarticular and polyarticular peripheral SpA delineates the boundary for local steroid utility, whereas systemic therapies—including conventional DMARDs—become necessary for mild-to-moderate polyarticular disease. Rapid symptomatic suppression can be achieved via short courses of systemic glucocorticoids or selective COXIBs

for 2–4 weeks, a strategy particularly suited for polyarticular flares. For patients with active peripheral SpA and inactive IBD who prove refractory to sulfasalazine or methotrexate, TNF inhibitors are the recommended first-line advanced therapy. JAK inhibitors and ustekinumab serve as potent alternatives. A primary non-response to an initial anti-TNF agent should prompt an immediate pivot to ustekinumab or a JAK inhibitor. In scenarios of secondary non-response or intolerance, dose optimization or switching to a second anti-TNF agent is advised, with JAK inhibitors and ustekinumab remaining robust fallback options (Macaluso et al., 2024).

Novel Therapies for IBD-Associated Arthritis

Janus Kinase Inhibitors - Tofacitinib

Tofacitinib is a potent, selective inhibitor of the JAK-1 and JAK-3 pathways, holding regulatory approval for the treatment of ulcerative colitis. Beyond gastroenterology, tofacitinib demonstrates high efficacy across a spectrum of chronic inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, and psoriatic arthritis. Given its proven broad-spectrum efficacy in autoimmune pathophysiology, it harbors significant potential as a definitive treatment for IBD-associated arthritis (Sęk et al., 2024).

In a compelling case study by Wang et al. (2019), the dual biologic/small-molecule approach utilizing tofacitinib combined with vedolizumab (VDZ) successfully induced deep remission of both aggressive synovitis and the underlying ulcerative colitis. Prior to this, vedolizumab monotherapy had failed to achieve durable articular remission. Corroborating this, Le Berre et al. reinforced the clinical viability of VDZ and tofacitinib combination therapy in UC patients suffering from highly refractory axial and peripheral spondyloarthritis. Furthermore, Majumder et al. documented the successful induction of remission in severe IBD-associated lower extremity arthritis and ulcerative colitis utilizing a triple-therapy regimen of tofacitinib, methotrexate (MTX), and mesalamine. This success occurred in a patient previously completely refractory to sulfasalazine, etanercept, adalimumab, and infliximab. Another case report highlighted the dramatic efficacy of tofacitinib in steroid-refractory peripheral IBD-associated arthritis following the failure and subsequent discontinuation of salazopyrin and golimumab (Sęk et al., 2024).

Janus Kinase Inhibitors - Upadacitinib

Upadacitinib is a highly selective oral JAK-1 inhibitor approved by both the FDA and EMA for ulcerative colitis, and has recently secured EMA approval for Crohn's disease. Its established efficacy in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis strongly positions it as a highly promising agent for targeting articular EIMs in IBD (Sęk et al., 2024).

Pooled data from Phase III, multicenter, double-blind randomized controlled induction trials substantiates the premise that upadacitinib is highly effective in resolving extraintestinal manifestations, specifically articular involvement, in UC patients. During the induction phase, 41 out of 75 patients (54.7%) treated with upadacitinib at 45 mg/day achieved complete resolution of peripheral or axial spondyloarthritis. By comparison, only 16 of 38 patients (42.1%) in the placebo arm achieved resolution. In the maintenance extension, 10 out of 15 patients (66.7%) on a 30 mg/day upadacitinib regimen and 5 out of 13 patients (38.5%) on 15 mg/day achieved sustained resolution of their SpA, sharply contrasting with the placebo group, where only 4 of 18 patients (22.2%) maintained articular remission (Sęk et al., 2024).

In summary, while current robust data specifically evaluating JAK inhibitors for IBD-associated arthritis remains in its infancy, both tofacitinib and upadacitinib exhibit immense promise as future cornerstone therapies for articular EIMs. Moreover, highly selective next-generation JAK inhibitors—such as filgotinib for IBD and baricitinib for rheumatologic disorders—are currently under intense investigation. These emerging findings will likely reshape the therapeutic horizon for IBD-associated arthritis. Rigorous further research, unequivocally demanding large-scale prospective randomized controlled trials (RCTs), is imperative to formally codify the exact positioning of JAK inhibitors within the EIM treatment algorithm (Sęk et al., 2024).

Ustekinumab

Ustekinumab is a fully human monoclonal antibody that antagonizes the p40 subunit shared by IL-12 and IL-23, pivotal cytokines driving Th1 and Th17 mediated immune cascades. Ustekinumab is FDA-

approved for moderate-to-severe TNFα-refractory Crohn's disease and moderate-to-severe ulcerative colitis. Crucially, it also holds FDA approval for psoriatic arthritis and plaque psoriasis—conditions that share deep pathophysiological homology with IBD (Sęk et al., 2024).

A robust prospective cohort study by Biemans et al., assessing the real-world efficacy and safety of ustekinumab in Crohn's disease, revealed that 44 of the 221 enrolled patients reported baseline arthralgia. Longitudinally, 24 of those 44 patients (54.5%) achieved complete joint remission. Conversely, a *de novo* onset of arthralgia was documented in 37 patients, notably clustered among those who failed to achieve clinical remission of their underlying Crohn's disease. The prospective architecture, substantial cohort size, and extended follow-up fortify this study's value in evaluating ustekinumab's impact on articular EIMs. However, the study is critically limited by its failure to distinguish between non-inflammatory arthralgia and true inflammatory IBD-associated arthritis, thus preventing definitive conclusions regarding ustekinumab's true anti-arthritic efficacy (Sęk et al., 2024).

A clinical report by Matsumoto et al. detailed a patient presenting with Crohn's-associated sacroiliitis, peripheral arthritis, a concurrent IBD-related cutaneous rash, and scleritis. Following NSAID failure, ustekinumab initiation resulted in the rapid, complete resolution of both the cutaneous and ocular EIMs, accompanied by gradual but definitive remission of all articular manifestations. Of particular clinical interest, ustekinumab induced complete resolution of the sacroiliitis—a hallmark of axial SpA. This is a highly provocative finding, as ustekinumab is currently formally contraindicated/not recommended for the treatment of pure axial SpA (Sęk et al., 2024).

A subsequent case study by Matsumoto et al. described a patient who developed paradoxical psoriasis secondary to infliximab therapy, alongside simultaneous IBD-associated peripheral arthritis in the knee. Transitioning the patient to ustekinumab induced rapid remission of the arthritis and complete clearance of the dermatological lesions within 2 months of induction (Sęk et al., 2024).

Vedolizumab

Vedolizumab (VDZ) is a humanized monoclonal antibody targeting the α4β7 integrin, FDA-approved for the induction and maintenance of remission in both Crohn's disease and ulcerative colitis. VDZ functions by binding the α4β7 integrin expressed on gut-homing T lymphocytes, thereby blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Because MAdCAM-1 is expressed almost exclusively on mucosal endothelial cells, VDZ confers highly gut-selective targeted therapy. However, this profound gut selectivity raises critical questions regarding its capacity to control systemically driven EIMs, including IBD-associated arthritis. Predicated on the hypothesis that IBD-associated arthritis is secondarily driven by uncontrolled intestinal mucosal inflammation, inducing deep mucosal healing via VDZ could theoretically extinguish the joint disease. Conversely, if IBD-associated arthritis is propelled by independent systemic immune activation, systemic agents like TNF antagonists or corticosteroids would possess a distinct mechanistic advantage over VDZ (Sęk et al., 2024).

The 2023 ECCO guidelines on extraintestinal manifestations explicitly recommend against the use of vedolizumab for both axial and non-axial spondyloarthritis, citing an elevated risk of paradoxical *de novo* arthritis and the severe exacerbation of pre-existing joint disease. Furthermore, recent data evaluating VDZ's efficacy and safety in managing IBD-associated arthritis remain highly polarized and contradictory (Sęk et al., 2024).

A retrospective chart review by Uri Kopylov et al. suggested potential VDZ efficacy in resolving or improving peripheral SpA. Following 12 months of VDZ therapy, symptomatic resolution was achieved in 7 out of 21 patients (33.3%) with peripheral spondyloarthritis. In stark contrast, zero resolution was observed in the 10-patient axial SpA sub-cohort. Additionally, among 69 patients presenting solely with arthralgia, 18 (26.1%) experienced resolution after 12 months of VDZ. The data presented are statistically underpowered to draw definitive conclusions due to the small sample size. Furthermore, the confounding use of concomitant articular therapies (e.g., COX-2 inhibitors and aspirin) severely limits the interpretability of these findings (Sęk et al., 2024).

Conversely, several case reports highlight striking therapeutic triumphs in managing articular EIMs with VDZ. VDZ administration has been documented to induce complete resolution of ankylosing

spondylitis and sacroiliitis in Crohn's disease, polyarthritis in CD, and intractable joint/back pain and polyarticular arthritis in ulcerative colitis. In all these cases, the resolution of articular EIMs strongly correlated with the achievement of deep mucosal control of the underlying IBD. The reported resolution of axial SpA under VDZ is a profoundly important clinical observation, as axial disease is traditionally considered to run completely independent of bowel activity. Although case reports reside at the nadir of the evidence hierarchy, they uncover crucial clinical signals regarding VDZ's potential efficacy in articular EIMs (Sęk et al., 2024).

In synthesis, available data suggest VDZ may hold therapeutic utility for a specific subset of patients with IBD-associated arthritis—most likely those whose joint symptoms perfectly mirror their luminal inflammation, which VDZ successfully heals. Nonetheless, the current paucity of robust literature precludes the formulation of definitive, evidence-based conclusions regarding VDZ's efficacy and safety for articular EIMs. The glaring discordance between retrospective cohorts and the absolute lack of large-scale prospective RCTs underscores a critical mandate for future rigorous investigation (Sęk et al., 2024).

IV. CONCLUSION

IBD-associated arthritis is a highly prevalent musculoskeletal manifestation affecting both the peripheral and axial joints. Categorized under the umbrella of spondyloarthritis (SpA), it shares a complex pathophysiological relationship with IBD driven by intertwined genetic predispositions, environmental triggers, and profound immune dysregulation. The diagnosis of IBD-associated arthritis remains heavily reliant on astute clinical evaluation, bolstered by advanced imaging modalities such as MRI to facilitate early detection of axial involvement. While peripheral joint inflammation frequently parallels the clinical activity of the underlying bowel disease, axial involvement typically follows an independent trajectory. Consequently, therapeutic strategies must concurrently address the distinct phenotypic demands of both the IBD and the musculoskeletal manifestations. Sulfasalazine and localized intra-articular steroid injections are the recommended mainstays for mild peripheral arthritis. In contrast, TNF-α inhibitors remain the indisputable first-line biological therapy for active axial disease and moderate-to-severe IBD. The strategic deployment of JAK inhibitors and anti-IL-17 agents may be considered for patients failing conventional biologics, provided there is vigilant clinical surveillance for potential IBD exacerbations. Unwavering multidisciplinary collaboration between gastroenterologists and rheumatologists is absolutely paramount in the management of IBD-associated SpA to tailor optimal therapeutic interventions and systematically prevent irreversible long-term complications. Ultimately, this review aims to equip clinicians with a deeper, evidence-based understanding of IBD-associated arthritis to elevate the standard of patient care.

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