MAY Y. CHOI
MD, MPH, FRCPC

Dr. May Choi is a rheumatologist and clinician scientist who started on faculty as an Assistant Professor at the Cumming School of Medicine, University of Calgary in 2020, and is a Member of the McCaig Institute for Bone and Joint Health. As an early career investigator, her research is focused on biomarker discovery and validation for prediction of clinical outcomes in autoimmune rheumatic diseases, and the prevention of autoimmune disease development and disease-related complications. She leads a research laboratory and biobank for local, national, and international collaborators. Her background and training include a Masters of Public Health in Epidemiology at Harvard University and a lupus fellowship at the Brigham and Women's Hospital (Boston, MA) under the supervision of Dr. Karen Costenbader (epidemiologist, lupus expert and Professor of Medicine at Harvard Medical School). Dr. Choi is also the Associate Director of MitogenDx Laboratory for novel autoantibody and biomarker testing for autoimmune diseases and the Associate Director of Research for the University of Calgary Lupus Centre of Excellence, which complement her research.

Affiliations:
Cumming School of Medicine, University of Calgary

DIANNE MOSHER
MD

Dr. Mosher is the Associate Dean of Indigenous, Local and Global Health and Professor of Medicine at the Cumming School of Medicine, University of Calgary . She is the past president of the Canadian Rheumatology Association and the Arthritis Alliance of Canada.She has over 30 years of clinical experience in Rheumatology with expertise in spondyloarthritis and Indigenous Health. Her research area of interest is in clinical outcomes, models of care and system level change.

Affiliations:
Cumming School of Medicine, University of Calgary

APPROACH TO MANAGEMENT OF INFLAMMATORY BOWEL DISEASE-RELATED ARTHRITIS

Introduction

The most common extraintestinal manifestation of inflammatory bowel disease (IBD) is arthropathy. These conditions have been reported in up to 50% of patients with IBD and are more common in Crohn's' disease (CD), particularly colonic disease, and in females.[1-6]

IBD-associated arthritis is classified as a type of spondyloarthritis (SpA). The treatment is dependent on the type of SpA involvement, which can be subdivided into peripheral and/or axial disease.[7,8] The treatment approach consists of a combination of non-pharmacological and pharmacological therapies managed by a multidisciplinary team and is based on collaborative decisions between gastroenterology and rheumatology. In light of rapidly expanding therapeutic armamentaria for both immune-mediated arthritis and IBD, this paper will provide an overview of an approach to the treatment of arthritis associated with IBD, considering recommendations by recent guidelines[1,9-11] and novel therapies.

Investigations

Peripheral arthropathies

Peripheral involvement in IBD includes type 1 and 2 peripheral arthritis, arthralgias, dactylitis, and enthesitis. Classification criteria for peripheral SpA based on the Assessment of SpondyloArthritis International Society (ASAS) include arthritis and/or enthesitis and/or dactylitis, plus (A) one or more of the following parameters: psoriasis, IBD, preceding infection, human leucocyte antigen [HLA]- B27, uveitis, sacroiliitis on imaging, or (B) two or more other parameters: arthritis, enthesitis, dactylitis, inflammatory back pain in the past, family history of SpA.[8] Concomitant IBD as a SpA feature with any peripheral arthropathy is sufficient for peripheral SpA classification.

Two types of peripheral arthritis in SpA have been identified based on articular involvement and natural history.[12] Type 1 arthritis (pauciarticular) is characterized by involvement of fewer than five joints, primarily in the large weight-bearing joints of the lower limb. These are usually acute and self-limiting (less than ten weeks) without permanent joint damage and tend to correlate with IBD activity. Type 2 (polyarticular) affects more than five joints, predominantly in joints of the upper limbs and is usually in a symmetrical distribution. These typically last for months or years and are independent of IBD flares. Diagnosis of peripheral arthritis is based on clinical examination and may be supplemented by imaging and blood tests (e.g., inflammatory markers) to exclude other forms of arthritis such as psoriatic arthritis (PsA), rheumatoid arthritis (RA), osteoarthritis, and other connective tissue diseases and causes of arthralgias. Unlike PsA and RA, for instance, peripheral arthritis in IBD patients is generally non-erosive; in this case, imaging may be helpful.

Enthesitis describes inflammation at the insertion of a tendon to bone, which can lead to erosions and bone proliferation (spur formation). Symptoms include pain, tenderness and swelling at the site. Enthesitis has a prevalence that ranges from 7%-50% in IBD.[2-6] It is often underdiagnosed on physical examination. Ultrasound has greater sensitivity as a diagnostic tool for enthesitis.[13]

Dactylitis is inflammation of the entire digit including soft tissue thickening, soft tissue edema, flexor tendon tenosynovitis, and joint synovitis. In addition to the clinical examination, it can be detected on MRI and ultrasonography. It has a prevalence of 2%-4% in individuals with IBD.[4,12]

Axial arthropathies

Sacroiliitis detected on plain radiographs has been reported in 2%-68% of patients with IBD.[14] However, in isolation, it is not diagnostic of axial SpA. According to the 2009 ASAS classification criteria for axial SpA, in patients <45 years of age with at least three months of back pain, sacroiliitis on imaging must be combined with at least one other SpA feature: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, IBD; favourable response to NSAIDs, family history of SpA; HLA-B27; and elevated C-Reactive protein (CRP).[7] Patients with non-radiographic sacroiliitis (no radiological evidence but can be detected on magnetic resonance imaging (MRI) can also be classified with axial SpA if they are HLA-B27 positive with at least two other SpA features. An MRI with T1-weighted spin-echo [TISE], short tau inversion recovery [STIR], and fat-saturated T2-weighted sequences is recommended. According to the European Crohn's and Colitis Organisation (ECCO) First European Evidence-based Consensus on Extra-intestinal Manifestations in IBD guideline, imaging in patients with inflammatory back pain is recommended, with the exclusion of patients who are HLA-B27-positive.[1] Only 25%-75% of patients with IBD-related axial SpA are HLA-B27 positive[2,4,15] vs 90% of patients with idiopathic ankylosing spondylitis (AS). In patients with AS, clinically evident IBD has been observed in 6%-14% [16,17] of patients; asymptomatic small bowel inflammation is found in up to 60% of patients with AS.[18,19]

Treatment of Peripheral Spondyloarthropathies

Non-steroidal anti-inflammatory drugs (NSAIDs) and conventional non-biologic disease modifying anti-rheumatic drugs (DMARDs)

Effective treatment of the underlying IBD is frequently sufficient to control peripheral arthritis without additional therapy. As the arthritis associated with IBD is generally non-erosive, the treatment objective is symptom control. The choice of therapy should be made collaboratively in consultation with the rheumatologist and gastroenterologist.

Following optimizing therapy of active IBD, in the presence of ongoing joint symptoms, a short course of NSAIDs is recommended. Although it has been generally thought that NSAIDs are contraindicated in IBD patients due to their potential adverse effects on disease activity,[20] recent clinical studies,[21] including a systematic review and meta-analysis of 18 studies did not find a consistent association between NSAIDs use and risk of CD and ulcerative colitis (UC) exacerbation.[22] In one large cohort study, patients receiving low-dose NSAIDs (aspirin ≤325 mg/day; ibuprofen ≤200 mg/day; naproxen <220 mg/day; or prescription NSAID used less than daily) did not have an increase in disease activity. Conversely, high-dose NSAID resulted in higher disease activity in CD patients with colonic involvement.[23] However, it is important to note that the clinical studies reviewed in the meta-analysis were observational. Therefore, the cautious use of short courses of NSAIDs with careful monitoring of IBD activity is reasonable.[23] In the presence of new or worsened symptoms of active bowel disease following the initiation of a NSAID, the NSAID should be discontinued.

In patients who cannot tolerate or are resistant to NSAIDs, a trial of a DMARD can be initiated. Methotrexate typically is used either in oral or subcutaneous form and is maximized to 25 mg weekly for the treatment of peripheral arthritis. Methotrexate frequently is used in low dose with an anti-TNF (tumor necrosis factor) agent to decrease drug resistance. A trial of sulfasalazine may also be initiated for peripheral arthritis.

Biologic agents or targeted synthetic disease modifying DMARDs

In patients resistant to NSAIDs and non-biologic DMARDs, a TNF-alpha inhibitor should be initiated (**Figure 1**). Infliximab, adalimumab, golimumab, or certolizumab pegol can be used. Etanercept is used less often as it is ineffective for the treatment of bowel disease. The decision to initiate or change biologic therapy should be collaborative between the rheumatologist and gastroenterologist.

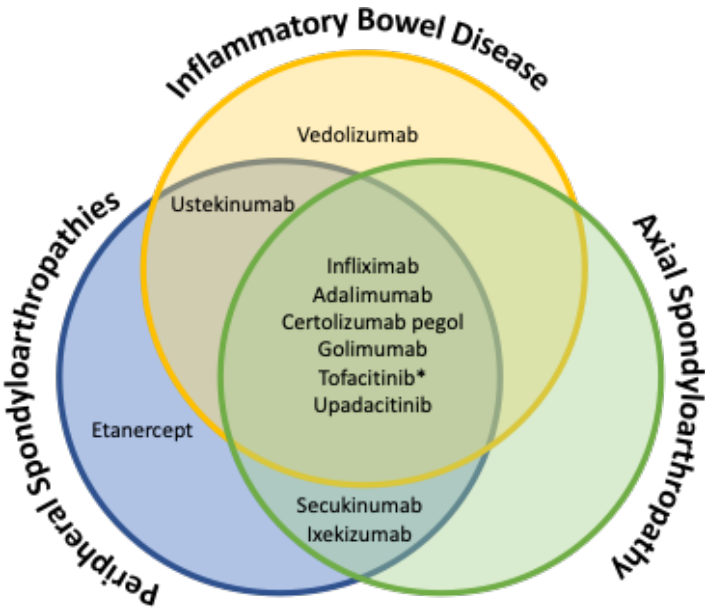

Figure 1. *Biologic agents and targeted synthetic DMARDs used in IBD and SpAs.*Tofacitinib is not effective for Crohn's disease.*

If a patient has tried more than one anti-TNF, alternatives include an interleukin (IL) 12/23 inhibitor (ustekinumab) and the Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib). While none of the clinical trials for these IBD therapies directly evaluated their effect on IBD-related peripheral arthritis, they are viable treatment options as they have been proven effective for other SpAs. Ustekinumab currently is indicated for both CD and PsA. Tofacitinib and upadacitinib are effective therapies for both IBD and SpA including AS, PsA and RA. Conversely, in a post hoc analysis of vedolizumab trials in patients with IBD, some patients demonstrate improvement in arthralgia/arthritis, possibly related to better control of gut inflammation.[24]

Short courses of systemic corticosteroids can be used to bridge therapy for patients who require rapid relief until the DMARD takes effect. Local steroid joint injections can also be utilized if a small number of joints are affected.

Enthesitis and dactylitis

Treatment of enthesitis and dactylitis is similar to that of axial arthritis in SpA. A trial of NSAIDs is the recommended initial therapeutic agent. Conventional non-biologic DMARDs are ineffective. Local peritendinous glucocorticoid injections may be beneficial, although they are associated with an increased risk of tendon rupture at the Achilles, patellar and quadriceps tendons; therefore, these locations should be avoided. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 recommendations state that local glucocorticoid injections may be considered for dactylitis.[11] Since the publication of these guidelines, additional therapies have become available, and injections should be considered only if other therapies have failed or are contraindicated.

For patients who are unresponsive to the NSAIDs or corticosteroid injections, biologic DMARDs are effective. Based on limited evidence,[25] an anti-TNF such as infliximab, golimumab or certolizumab may be initiated. Evidence from PsA clinical studies has demonstrated that enthesitis can be treated with other therapies that are effective in IBD as well. These include, tofacitinib and upadacitinib. Infliximab, certolizumab, ustekinumab, tofacitinib, and upadacitinib have been proven beneficial for dactylitis in patients with PsA.[26]

Treatment of Axial Spondyloarthropathies

The treatment of axial SpA in IBD is similar to that for idiopathic forms of axial SpA. Recent guidelines on the treatment of AS and non-radiographic axial SpA have been published. These include the 2019 edition by the American College of Rheumatology (ACR)/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network (SPARTAN)[9] and the 2016 update of the Assessment of SpondyloArthritis international Society (ASAS)-European League Against Rheumatism (EULAR) management recommendations for axial SpA.[10] Canadian guidelines are expected to be released in the near future.

Non-pharmacological therapies

Back exercises are a cornerstone of AS treatment to improve or maintain spinal and thoracic flexibility and posture. A recent Cochrane review of 14 randomized controlled trials with 1,579 participants with AS demonstrated some evidence to suggest that exercise programs slightly improve function, reduce pain and decrease global patient assessment of disease activity, when compared with no intervention.[27] Specifically, the 2019 ACR Guidelines recommend land-based over aquatic physical therapy interventions.[9]

Non-biologic DMARDs

For patients with IBD and axial SpA with controlled IBD and mild axial disease, a trial of NSAIDs may be considered. The 2019 ACR guidelines do not recommend any specific NSAID to decrease IBD symptoms.[9] For patients with axial disease who are intolerant or resistant to NSAIDs, there is no evidence to support the use of sulfasalazine or any other non-biologic conventional DMARD such as methotrexate, as the next line of therapy. If patients do not have prominent peripheral arthritis, these medications are not effective in controlling axial inflammation. The use of systemic corticosteroids is also strongly not recommended.

Biologic agents or targeted DMARDs

Anti-TNFs (e.g., infliximab, adalimumab, certolizumab pegol, and golimumab) (**Figure 1**) are the standard first-line biologic agents as they control axial disease, IBD and other extraintestinal manifestations of IBD. The choice of treatment should be a collaboration between the rheumatologist and the gastroenterologist as there are multiple factors to take into consideration. The 2019 ACR Guidelines conditionally recommend treatment of radiographic or non-radiographic axial SpA with an anti-TNF over treatment with other biologics.[9] Again, it should be noted that the exception in this context is etanercept as, although it can be used to treat axial disease, it

is not an effective treatment for IBD. Furthermore, while the monoclonal anti-IL-17A antibody therapies secukinumab and ixekizumab are recommended in idiopathic AS, they are not only ineffective in IBD, but have been associated with flares of new or pre-existing IBD following initiation. In patients resistant to or unable to take anti-TNF agents, tofacitinib and upadacitinib[28, 29] may be tried as they are effective therapies for both UC and AS. Upadacitinib is effective for CD. Ustekinumab and IL-23 inhibitors are not recommended due to their lack of effectiveness in axial SpA, as demonstrated in three placebo-controlled clinical trials.[30]

Combination biologic therapies

The use of combination therapy for IBD may be considered in difficult-to-control cases or in the presence of extra-articular features, predominately seen in arthritis. There are no efficacy or safety trials of combination therapy, only case series and case reports. The most frequently-used combination therapy for IBD and SpA is vedolizumab or ustekinumab with an anti-TNF agent. No serious safety signals have been reported in the case reports to date.[31] There is little evidence to support the use of tofacitinib and upadacitinib in combination with other biologics. Although clinical studies have demonstrated the efficacy of tofacitinib in axial SpA, it is not approved for this indication in Canada.

Conclusion

The management of IBD-associated arthritis has improved in the past two decades with the introduction of biologic and targeted synthetic DMARDs. Future research to increase practitioners' understanding of the disease pathogenesis of IBD-associated arthritis will lead to a broader choice of therapies for both immune-mediated arthritis and IBD, and an eventual cure.

Correspondence:
Dr. May Choi
Email: may.choi@ucalgary.ca

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