Treatment of arthritis associated with inflammatory bowel disease

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INTRODUCTION

Arthritis is a recognized extraintestinal manifestation of several illnesses and conditions, including inflammatory bowel disease (IBD) and other disorders. Management of this condition has similarities to the treatment of other forms of spondyloarthritis; it is complicated by the need to coordinate treatment interventions with those needed for concurrent inflammation of the gut due to the Crohn disease or ulcerative colitis that is also present. Other illnesses also have a propensity for causing inflammation of joints and the gut.

The treatment of arthritis associated with IBD is presented here. The clinical manifestations, diagnosis, and differential diagnosis of IBD-associated arthritis; and the pathogenesis, other clinical manifestations, diagnosis, and management of inflammatory bowel disease, including Crohn disease and ulcerative colitis, are reviewed in detail separately. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases" and "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases", section on 'Other diseases with bowel and joint involvement' and "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults" and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults" and "Management of the hospitalized adult patient with severe ulcerative colitis" and "Overview of the medical management of mild (low risk) Crohn disease in adults".)

TREATMENT APPROACH

The approach to the treatment of arthritis associated with inflammatory bowel disease (IBD) (algorithm 1) is very similar to and derived from the treatment of other forms of spondyloarthritis (SpA). Thus, it includes the use of nonsteroidal antiinflammatory drugs (NSAIDs) for initial therapy for peripheral and axial disease; selected conventional nonbiologic disease-modifying antirheumatic drugs (DMARDs) for peripheral arthritis resistant to initial therapy, if biologics are not already required for axial or gastrointestinal disease manifestations; and tumor necrosis factor (TNF) inhibitors for peripheral arthritis resistant to conventional nonbiologic DMARDs and for axial disease resistant to NSAIDs. (See 'Management of peripheral arthritis' below and 'Management of spondylitis and sacroiliitis' below.)

There is relatively limited direct evidence to support the efficacy of these or other treatment options for IBD-related arthritis. Support for this approach is largely indirect, derived from trials and observational studies involving patients with peripheral and axial SpA who have been diagnosed with ankylosing spondylitis, psoriatic arthritis, and other forms of SpA. Our approach is also generally consistent with expert opinion on the management of patients with coexisting SpA and IBD, as expressed by a multidisciplinary panel of specialists [1]. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Treatment of peripheral spondyloarthritis" and "Treatment of psoriatic arthritis".)

Effective treatment of the underlying IBD is often helpful in controlling the peripheral arthritis; in addition, it is not uncommon for the gastroenterologist to initiate glucocorticoids or TNF inhibitor therapy primarily for the IBD, which then also reduces the activity of the musculoskeletal symptoms concurrently. (See "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Medical management of moderate to severe Crohn disease in adults" and "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" and "Management of the hospitalized adult patient with severe ulcerative colitis".)

MANAGEMENT OF PERIPHERAL ARTHRITIS

Treatment of peripheral arthritis in patients with inflammatory bowel disease (IBD)-related arthritis is usually initiated with a nonsteroidal antiinflammatory drug (NSAID), and patients are treated with a conventional nonbiologic disease-modifying antirheumatic drug (DMARD), such as sulfasalazine or methotrexate (MTX), if NSAID therapy and local glucocorticoid injections are inadequate to provide relief of signs and symptoms of the inflammatory arthritis

(algorithm 1). (See 'Initial peripheral arthritis therapy/NSAIDs' below and 'Inadequate response to NSAIDs' below and 'Role of glucocorticoids' below.)

Control of the underlying IBD should also be optimized in patients with arthritis in collaboration with the patient's gastroenterologist, and patients with new-onset or persistent IBD-associated arthritis but quiescent gastrointestinal symptoms should be evaluated by their gastroenterologist to exclude asymptomatic gastrointestinal inflammation that may require treatment.

Patients with an inadequate response to NSAIDs and conventional nonbiologic DMARDs are generally treated with a TNF inhibitor, as are patients who have another indication for these biologic agents, such as axial disease unresponsive to NSAIDs or severe or resistant gastrointestinal disease activity. (See 'Use of TNF inhibitors in patients resistant to conventional DMARDs' below.)

There is only limited information from randomized trials to guide treatment decisions for arthritis associated with IBD; most of the available information is from small case series. Some agents, notably sulfasalazine (SSZ), azathioprine (AZA), 6-mercaptopurine (6-MP), MTX, glucocorticoids, and tumor necrosis factor (TNF) inhibitors, may be helpful for both bowel and joint inflammation [2-8]. Our recommendations are based upon the available limited direct evidence; inferences from studies of other forms of arthritis, including SpA and reactive arthritis; and our clinical experience.

Initial peripheral arthritis therapy/NSAIDs — In patients with mild or recurring transient peripheral arthritis, we suggest initial therapy with an NSAID in antiinflammatory doses (eg, the nonselective NSAID, naproxen, 375 to 500 mg twice daily or the COX-2 selective NSAID, celecoxib, 100 mg twice daily), but antiinflammatory doses of any NSAID or COX-2 selective agent may be effective. Naproxen or other nonselective NSAIDs should be administered together with a proton pump inhibitor (eg, omeprazole 20 mg daily) for gastroprotection. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity", section on 'Proton pump inhibitors'.)

NSAID therapy should be initiated collaboratively in consultation with the patient's gastroenterologist, because of their potential for causing gastrointestinal side effects, including worsening of bowel inflammation. Despite such concern, we have used agents from both NSAID classes successfully in patients with IBD, with therapeutic benefit and good tolerance clinically. In patients in whom symptoms or signs of IBD develop or worsen during use of either nonselective or COX-2 selective NSAIDs, the drug should be temporarily or permanently

discontinued; this problem should be jointly managed by the rheumatologist and the gastroenterologist.

In patients in whom a first NSAID does not control symptoms (a substantial reduction in inflammatory joint pain and stiffness over two weeks of therapy) or is poorly tolerated, a second NSAID should generally be tried before initiating therapy with a conventional nonbiologic DMARD such as SSZ. However, we usually avoid a second NSAID in patients in whom NSAID use has been associated with new or worsening symptoms or signs of active IBD. (See 'Inadequate response to NSAIDs' below.)

Local joint injection is also a therapeutic option in patients with a small number of affected joints (see 'Role of glucocorticoids' below). Septic arthritis should be excluded in patients with a possible joint infection before treatment for presumed IBD-associated arthritis with systemic or intraarticular therapies. (See "Septic arthritis in adults".)

Although careful epidemiologic studies investigating the possible link between NSAIDs and the development of IBD have not been performed, a number of reports in patients receiving both nonselective and COX-2 selective NSAIDs suggest that these agents increase the risk for the development of IBD and may exacerbate underlying IBD [3,9-12]. (See "NSAIDs: Adverse effects on the distal small bowel and colon" and "Definitions, epidemiology, and risk factors for inflammatory bowel disease".)

Possible exacerbation of IBD symptoms by NSAIDs are difficult to assess. Agents effective for treatment of idiopathic IBD may improve bowel inflammation due to NSAIDs [10]. Similarly, radiographic studies and even endoscopic findings and biopsies may not differentiate between these causes [10]. Thus, improvement in symptoms and the mucosal appearance following withdrawal of the potentially offending NSAID may provide the best support for NSAIDs being the cause in an individual patient. (See "NSAIDs: Adverse effects on the distal small bowel and colon", section on 'Management'.)

Because COX-2 activity promotes epithelial proliferation and wound healing, COX-2 inhibition could theoretically have deleterious effects in patients with IBD [13]. However, there is also evidence that COX-2 selective inhibitors can ameliorate the severity of experimental colitis [10], and two trials have suggested that the COX-2 selective inhibitors celecoxib and etoricoxib might not exacerbate IBD symptoms [14-16]. Both had small sample sizes. In the celecoxib trial, there was no significant difference in the rate of relapse of IBD after two weeks [15]. Similar results were found in a three-month randomized trial comparing etoricoxib with placebo in patients with IBD treated for rheumatologic symptoms [16].

One of the largest trials of a COX-2 selective NSAID included 45 patients with IBD and arthralgias who were treated for three days to three months with rofecoxib, which is no longer available [12]. Arthralgia relief was reported by 71 percent of patients (complete relief in 18 percent and partial relief in 53 percent). However, nine patients (20 percent) required discontinuation of therapy due to the development of gastrointestinal symptoms, which subsided after treatment was stopped. This was a higher rate of discontinuation than was observed in a control group of 30 patients with dyspepsia (3 percent). The percentage of patients who required discontinuation was similar for those with Crohn disease or ulcerative colitis. Whether this experience is generalizable to other COX-2 inhibitors remains unresolved.

Inadequate response to NSAIDs — In patients with peripheral arthritis who have an inadequate response to or are intolerant of NSAIDs, we use a conventional nonbiologic DMARD; the first-line drug in this setting is sulfasalazine (SSZ), which can also benefit IBD (see 'Sulfasalazine' below). However, if SSZ is inadequate or poorly tolerated, other options include methotrexate (MTX) and azathioprine (AZA) (see 'Alternatives to SSZ' below). The AZA metabolite, 6-mercaptopurine (6-MP) is sometimes used for the treatment of IBD and, like AZA, may be effective for arthritis.

Local glucocorticoid injection may be of benefit in patients with a small number of affected joints, or a short course of oral glucocorticoids or an intramuscular injection may be effective as bridging therapy in patients with severe symptoms or functional impairment requiring more rapid relief until the DMARD takes effect. (See 'Role of glucocorticoids' below.)

Sulfasalazine — In patients with peripheral arthritis in whom nonselective or COX-2 selective NSAIDs do not result in acceptable symptomatic relief, and who lack axial disease that is not controlled by NSAIDs, we suggest the addition of SSZ, rather than another nonbiologic or biologic DMARD. The initial dose of SSZ is 500 mg twice daily with an increase in daily dose of 1000 mg every two weeks until arthritis symptoms improve or a maximum dose of 1000 mg three times daily is reached. A trial of at least 12 weeks is required to adequately assess efficacy.

The use of SSZ in these patients is based upon evidence of efficacy in other forms of peripheral SpA, as well as in patients with IBD, by expert opinion [1], and by our clinical experience. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Treatment of peripheral spondyloarthritis" and "Treatment of psoriatic arthritis" and "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)

SSZ is an azo-bonded combination of 5-aminosalicylic acid and sulfapyridine [17]. SSZ is poorly absorbed in the small intestine. In the colon, SSZ is split by bacteria into its constituent moieties. The 5-amino compound lowers colonic prostaglandin E and alters gut flora. The sulfapyridine appears to be antiarthritic [17]. However, aminosalicylates (eg, mesalamine), which are useful for controlling intestinal inflammation, appear to have no direct antiinflammatory effect on the synovium [3]. (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease".)

Alternatives to SSZ

- Methotrexate – A trial of MTX is an option in patients in whom SSZ is not effective or poorly tolerated, using the same approach to MTX dosing and administration as in rheumatoid arthritis (RA). The usual initial dose is 10 mg once weekly, increased in 2.5 to 5 mg increments, at approximately weekly intervals, until joint inflammation is controlled or a dose of 25 mg per week is reached. Orally administered MTX is adequately absorbed, even in patients with active IBD [18]; however, subcutaneous injection of MTX is a treatment option that provides higher bioavailability of the drug, especially at doses greater than 15 mg. If dose-limiting gastrointestinal side effects from MTX develop during oral therapy, switching to subcutaneous administration is recommended. Patients receiving MTX should also be treated with folic acid (1 mg daily). (See "Use of methotrexate in the treatment of rheumatoid arthritis" and "Initial treatment of rheumatoid arthritis in adults", section on 'Pretreatment interventions' and "Initial treatment of rheumatoid arthritis in adults", section on 'Initial therapy with methotrexate'.)

- Azathioprine/6-mercaptopurine – Other immunomodulatory therapies used for IBD, including AZA and 6-MP, may also have beneficial effects on joint disease [3]. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases" and "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)

Use of TNF inhibitors in patients resistant to conventional DMARDs — In patients with peripheral joint disease resistant to NSAIDs and conventional nonbiologic DMARDs (eg, a three-month trial of SSZ or MTX), we suggest one of the monoclonal antibody TNF inhibitors, rather than another conventional nonbiologic DMARD or an alternative biologic agent. Either infliximab, adalimumab, golimumab, or certolizumab pegol may be employed, using the dosing regimens also used in other forms of SpA and in IBD (see "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors" and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults" and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults"). The following initial doses are typical:

- Infliximab – 5 mg/kg by intravenous infusion at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter
- Adalimumab – 40 mg by subcutaneous injection every other week
- Golimumab – 50 mg by subcutaneous injection once a month (loading doses may also be used in patients with active gut inflammation)
- Certolizumab pegol – Initial: 400 mg by subcutaneous injection, repeat dose 2 and 4 weeks after initial dose; maintenance: 200 mg every 2 weeks or 400 mg every 4 weeks

The choice of TNF inhibitor should be made in collaboration between the rheumatologist and gastroenterologist and may be determined in part by regulatory, cost, or insurance restrictions in different countries or geographic regions; such restrictions may also be affected by the specific IBD diagnosis (ie, whether the patient has Crohn disease or ulcerative colitis). These factors also influence the decision to use a biosimilar TNF inhibitor in this clinical setting. Coordinated treatment is also important because drugs that are effective for one manifestation, particularly either bowel inflammation or arthritis, may not be effective for the other. As an example, the TNF inhibitor etanercept is used less often than the other agents, as it is not effective for the gastrointestinal manifestations of Crohn disease. By contrast, vedolizumab, a monoclonal antibody that binds the alpha4/beta7-mucosal vascular addressin cell adhesion molecule 1 (MadCAM) complex in the gut, is effective in reducing the gastrointestinal manifestations of Crohn disease and ulcerative colitis but may be ineffective for treating the arthritis; one case series suggests it can induce or flare sacroiliitis or peripheral arthritis in some patients [19], but this remains unresolved. (See "Management of moderate to severe ulcerative colitis in adults" and "Medical management of moderate to severe Crohn disease in adults".)

Commonly, it is refractory gut inflammation rather than refractory joint inflammation which leads to initiating TNF inhibitor therapy. TNF inhibitors are also used in patients with axial disease with inadequate symptomatic relief with NSAIDs. (See 'Management of spondylitis and sacroiliitis' below.)

> In addition to the evidence of their efficacy in other forms of SpA, a number of small case series and other observational studies have also provided evidence in support of the benefit of TNF inhibition in patients with both IBD and peripheral arthritis [4,7,20,21].

Screening for latent tuberculosis and baseline chest radiography should be performed because of the risk of reactivation of latent tuberculosis in patients receiving TNF inhibitor therapy. Patients with evidence of latent, previously untreated tuberculosis should begin antituberculous therapy prior to beginning anti-TNF-alpha therapy. (See "Risk of mycobacterial infection associated with biologic agents and JAK inhibitors" and "Treatment of tuberculosis infection (latent tuberculosis) in nonpregnant adults without HIV infection".)

The risks and adverse effects of TNF inhibitors are described in detail separately (see "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects"). The presence of active infection is an absolute contraindication to the use of either of these agents. This is a particular concern in fistulizing Crohn disease, as abscess formation can accompany that process in the gut. There should be an ongoing dialogue between the gastroenterologist and the rheumatologist when considering biologic agents in such a patient.

Resistant to initial TNF inhibitor — In patients who have an inadequate response to a three-month trial of a first TNF inhibitor, we generally try switching to a second TNF inhibitor before trying another biologic agent, such as the interleukin (IL) 12/23 inhibitor, ustekinumab, which is in use for both Crohn disease and psoriatic arthritis.

An open-label, single-arm study of ustekinumab in patients with ankylosing spondylitis suggested efficacy of this agent [22]; however, target outcomes were not achieved in subsequent trials of ustekinumab in patients with ankylosing spondylitis and with nonradiographic axial spondyloarthritis [23]. Efficacy of IL-23 inhibitors and Janus kinase (JAK) inhibitors in IBD has been encouraging, but these studies have not directly addressed effects on IBD-related peripheral arthritis. Despite the lack of evidence to directly evaluate JAK inhibitor therapy in IBD-related arthritis, a JAK inhibitor may be a reasonable alternative option to consider following TNF inhibitor failure; tofacitinib has been approved by US Food and Drug Administration (FDA) for both ankylosing spondylitis and ulcerative colitis. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Janus kinase (JAK) inhibitors'.)

While secukinumab has been ineffective for bowel disease in IBD trials, flares of new or pre-existing IBD after initiation of secukinumab have been rare in our clinical experience. Use of non-TNF inhibitor biologics for IBD-related arthritis should be a collaborative decision of the rheumatologist and the gastroenterologist. (See "Medical management of moderate to severe Crohn disease in adults".)

In this group we also try to assure full mucosal healing of the gut, even in patients who are not symptomatic with respect to gastrointestinal tract symptoms. Improvement in gut inflammation may also be associated with reduced joint symptoms, in our experience, just as increased gut inflammation may be associated with flares of the arthritis. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases", section on 'Type I arthropathy'.)

Role of glucocorticoids — There are several clinical settings in which a short course of glucocorticoids or intra-articular administration may be useful for relief of joint inflammation or

as bridging therapy until a systemic agent is effective in patients with IBD-related peripheral arthritis:

- Patients with a limited number of swollen joints amenable to arthrocentesis and joint injection may benefit from intra-articular glucocorticoid injections. Such injections may reduce the need for systemic therapy, in our experience. (See "Intraarticular and soft tissue injections: What agent(s) to inject and how frequently?" and "Joint aspiration or injection in adults: Technique and indications".)

  In patients in whom the addition of conventional nonbiologic DMARDs (eg, SSZ, MTX, or AZA/6-MP) has not successfully controlled the arthritis, intraarticular glucocorticoid injection may also be beneficial.

- Acute flares of arthritis may be treated by methylprednisolone (80 to 120 mg administered by an intramuscular injection) or by a short course of oral glucocorticoids (prednisone, initially 20 mg per day, then tapered over two weeks). We avoid the use of long-term systemic glucocorticoids because of the infection-related risks already imposed by the IBD. Administration, dosing, and adverse effects are similar to those in patients with RA and are discussed in detail separately. (See "Initial treatment of rheumatoid arthritis in adults", section on 'Glucocorticoids' and "Use of glucocorticoids in the treatment of rheumatoid arthritis".)

MANAGEMENT OF SPONDYLITIS AND SACROILIITIS

The axial disease associated with IBD is treated using the same approach (algorithm 1) as for other forms of axial SpA (eg, ankylosing spondylitis, nonradiographic axial SpA [nr-axSpA], or SpA associated with psoriatic arthritis). The goal of treatment for spinal and sacroiliac involvement is the control of symptoms, as it is for the peripheral arthritis. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

NSAIDs are used to treat spinal pain and stiffness, and patients benefit from an exercise program. Patients with inadequate control of their symptoms require a biologic agent, usually a TNF inhibitor. The same concerns and cautions noted for patients with peripheral arthritis apply to the use of NSAIDs and biologics for spondylitis and sacroiliitis. (See 'Initial peripheral arthritis therapy/NSAIDs' above and 'Use of TNF inhibitors in patients resistant to conventional DMARDs' above.)

Initial treatment of axial disease — Patients should be managed with both nonpharmacologic and pharmacologic treatment, which are complementary for patients with spinal involvement:

- We suggest that all patients with axial symptoms be referred to a physical therapist for instruction in back exercises. These are cornerstones for the long-term management of spondylitis and contribute to maintenance of flexibility and posture.

- In patients with axial symptoms we suggest NSAIDs in antiinflammatory doses (eg, naproxen 375 to 500 mg twice daily or celecoxib 100 mg twice daily), but antiinflammatory doses of any NSAID or COX-2 selective agent may be effective for symptoms of spondylitis or sacroiliitis. Naproxen or other nonselective NSAIDs should be administered together with a proton pump inhibitor (eg, omeprazole 20 mg daily) for gastroprotection. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity", section on 'Proton pump inhibitors'.)

  In patients in whom a first NSAID does not control symptoms (a substantial reduction in inflammatory back pain and stiffness over two weeks of therapy) or is poorly tolerated, a second NSAID should be tried.

This approach is based upon the benefits of this strategy for patients with ankylosing spondylitis and our clinical experience. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

Resistant to initial therapy for axial symptoms — In patients whose axial symptoms are not well controlled with NSAIDs, with a substantial reduction in inflammatory back pain and stiffness, we suggest a monoclonal antibody TNF inhibitor (eg, infliximab, adalimumab, certolizumab pegol, or golimumab), as in patients with peripheral arthritis resistant to nonbiologic DMARDs or with severe disease. (See 'Use of TNF inhibitors in patients resistant to conventional DMARDs' above.)

Sacroiliac and spinal inflammation associated with IBD will generally respond to TNF inhibitor therapy as it does in primary ankylosing spondylitis, although direct evidence to support this is limited. However, in patients with isolated axial disease refractory to nonselective or COX-2 selective NSAIDs alone, there is no evidence to support the use of SSZ or MTX, as such nonbiologic conventional DMARDs have been shown ineffective in controlling axial inflammation. (See "Treatment of psoriatic arthritis" and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

Published experience with infliximab in arthritis associated with IBD is limited to small case series in which it has been associated with improvement in symptoms of spondylitis as well as peripheral arthritis during treatment with this agent [21] (see 'Use of TNF inhibitors in patients resistant to conventional DMARDs' above). Whether TNF inhibitor therapy has any long-term benefit in reducing the progression of IBD-related spondylitis remains to be determined, but there is a growing consensus that early, sustained TNF inhibitor therapy in ankylosing spondylitis can modify radiographic progression over time. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'Effects of treatment on radiographic progression'.)

In selecting among the available TNF inhibitors, it should be noted that while etanercept may be used safely and is reported to be effective for arthritis and spinal involvement in Crohn disease, it is of no benefit for the intestinal manifestations of that disorder [24,25], unlike the monoclonal antibody TNF inhibitors, which are often used for Crohn disease and ulcerative colitis. (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors" and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults".)

Patients with axial disease resistant to an initial TNF inhibitor are managed in the same fashion as patients with peripheral arthritis who have an inadequate response to initial TNF inhibitor therapy. (See 'Resistant to initial TNF inhibitor' above.)

However, similar to etanercept, despite efficacy in SpA, secukinumab, a monoclonal anti-interleukin (IL) 17A antibody, has not proven effective in Crohn disease; thus, we would generally undertake trials of at least two TNF inhibitors before considering a trial of secukinumab in refractory axial disease, and this decision should be jointly discussed by both the rheumatologist and the gastroenterologist. (See 'Resistant to initial TNF inhibitor' above.)

MANAGEMENT OF ENTHESITIS AND DACTYLITIS

The treatment approaches to both enthesitis and dactylitis use the same strategies employed for the management of these conditions in other patients with peripheral SpA but have not been well studied. Treatment is initiated with NSAIDs. Heel orthoses and physical therapy, with local modalities can also be of benefit for enthesitis; a prolonged course of therapy may be required. Further pharmacologic management depends in part upon the other manifestations present; TNF inhibitors may improve symptoms in patients being treated with these agents. (See "Treatment of peripheral spondyloarthritis", section on 'Enthesitis' and "Treatment of peripheral spondyloarthritis", section on 'Dactylitis'.)

MONITORING AND DURATION OF THERAPY

Monitoring of patients after initiation of nonbiologic or biologic treatment follows the same approach as in other forms of spondyloarthritis, with the caveat that management should be done in collaboration with the patient's gastroenterologist. (See "Treatment of peripheral spondyloarthritis", section on 'Monitoring' and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

PROGNOSIS

The musculoskeletal prognosis of peripheral and axial spondyloarthritis in the setting of inflammatory bowel disease (IBD) mirrors that seen in the absence of IBD, by general consensus, but has not been formally evaluated. The long-term patient outcomes are commonly defined more by the course of the IBD than the arthritis, with the exception of the subset of patients with progressive spondylitis. The course of the peripheral arthritis is often fluctuating, but typically nonerosive and nondeforming.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Spondyloarthritis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Crohn disease in adults (The Basics)" and "Patient education: Ulcerative colitis in adults (The Basics)" and "Patient education: Nonsteroidal antiinflammatory drugs (NSAIDs) (The Basics)")

- Beyond the Basics topic (see "Patient education: Crohn disease (Beyond the Basics)" and "Patient education: Ulcerative colitis (Beyond the Basics)" and "Patient education: Nonsteroidal antiinflammatory drugs (NSAIDs) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Effective treatment of the underlying inflammatory bowel disease (IBD) is often helpful in controlling the peripheral arthritis of IBD, which is generally nondestructive; therapy is primarily directed at symptomatic relief. Drug choices should be made with close coordination of the patient's rheumatologist and gastroenterologist to optimize the efficacy and safety of pharmacotherapy for the patient's multiple clinical manifestations (algorithm 1). Treatment required for highly active gut inflammation is frequently also effective for the musculoskeletal disease. (See 'Treatment approach' above.)

- In patients with peripheral arthritis or axial disease, we suggest initial treatment with a nonsteroidal antiinflammatory drug (NSAID, eg, naproxen 375 to 500 mg twice daily or celecoxib 100 mg twice daily), rather than systemic glucocorticoids or a disease-modifying antirheumatic drug (DMARD). NSAID therapy should be initiated collaboratively in consultation with the patient's gastroenterologist, because of their potential for causing gastrointestinal side effects, including worsening of bowel inflammation. Naproxen or other nonselective NSAIDs should be administered together with a proton pump inhibitor (eg, omeprazole 20 mg daily). (See 'Initial peripheral arthritis therapy/NSAIDs' above and 'Initial treatment of axial disease' above.)

- In patients with peripheral arthritis resistant to or intolerant of NSAIDs, we suggest sulfasalazine (SSZ), rather than another nonbiologic or biologic DMARD. The initial dose is 500 mg twice daily with an increase in daily dose of 1000 mg every two weeks until arthritis symptoms improve or a maximum dose of 1000 mg three times daily is reached. Alternatives to SSZ include methotrexate (MTX) and azathioprine (AZA) or 6-mercaptopurine (6-MP). In patients resistant to these therapies, we use a tumor necrosis factor (TNF)-alpha inhibitor. (See 'Management of peripheral arthritis' above.)

- In patients with peripheral joint disease resistant to NSAIDs and conventional nonbiologic DMARDs (eg, a three-month trial of SSZ or MTX), we suggest one of the monoclonal

antibody TNF inhibitors, rather than another conventional nonbiologic DMARD or an alternative biologic agent. Either infliximab, adalimumab, golimumab, or certolizumab pegol may be employed, using the dosing regimens also used in other forms of SpA and in IBD (see 'Use of TNF inhibitors in patients resistant to conventional DMARDs' above). The following doses are typical:

  - Infliximab – 5 mg/kg by intravenous infusion at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter
  - Adalimumab – 40 mg by subcutaneous injection every other week
  - Golimumab – 50 mg by subcutaneous injection once a month (loading doses may also be used in patients with active gut inflammation)
  - Certolizumab pegol – Initial: 400 mg by subcutaneous injection, repeat dose 2 and 4 weeks after initial dose; maintenance: 200 mg every 2 weeks or 400 mg every 4 weeks

- Local glucocorticoid injection may be of benefit in patients with a small number of affected joints, or a short course of oral glucocorticoids or an intramuscular injection may be effective as bridging therapy in patients with severe symptoms or functional impairment requiring more rapid relief until the DMARD takes effect. (See 'Role of glucocorticoids' above.)

- We suggest that all patients with axial symptoms be referred to a physical therapist for instruction in back exercises. (See 'Initial treatment of axial disease' above.)

- In patients whose axial symptoms are not well controlled with NSAIDs, with a substantial reduction in inflammatory back pain and stiffness, we suggest a monoclonal antibody TNF inhibitor (eg, infliximab, adalimumab, certolizumab pegol, or golimumab) rather than a conventional DMARD or another biologic agent. Dosing is similar to that used for peripheral arthritis. (See 'Management of spondylitis and sacroiliitis' above and 'Use of TNF inhibitors in patients resistant to conventional DMARDs' above.)

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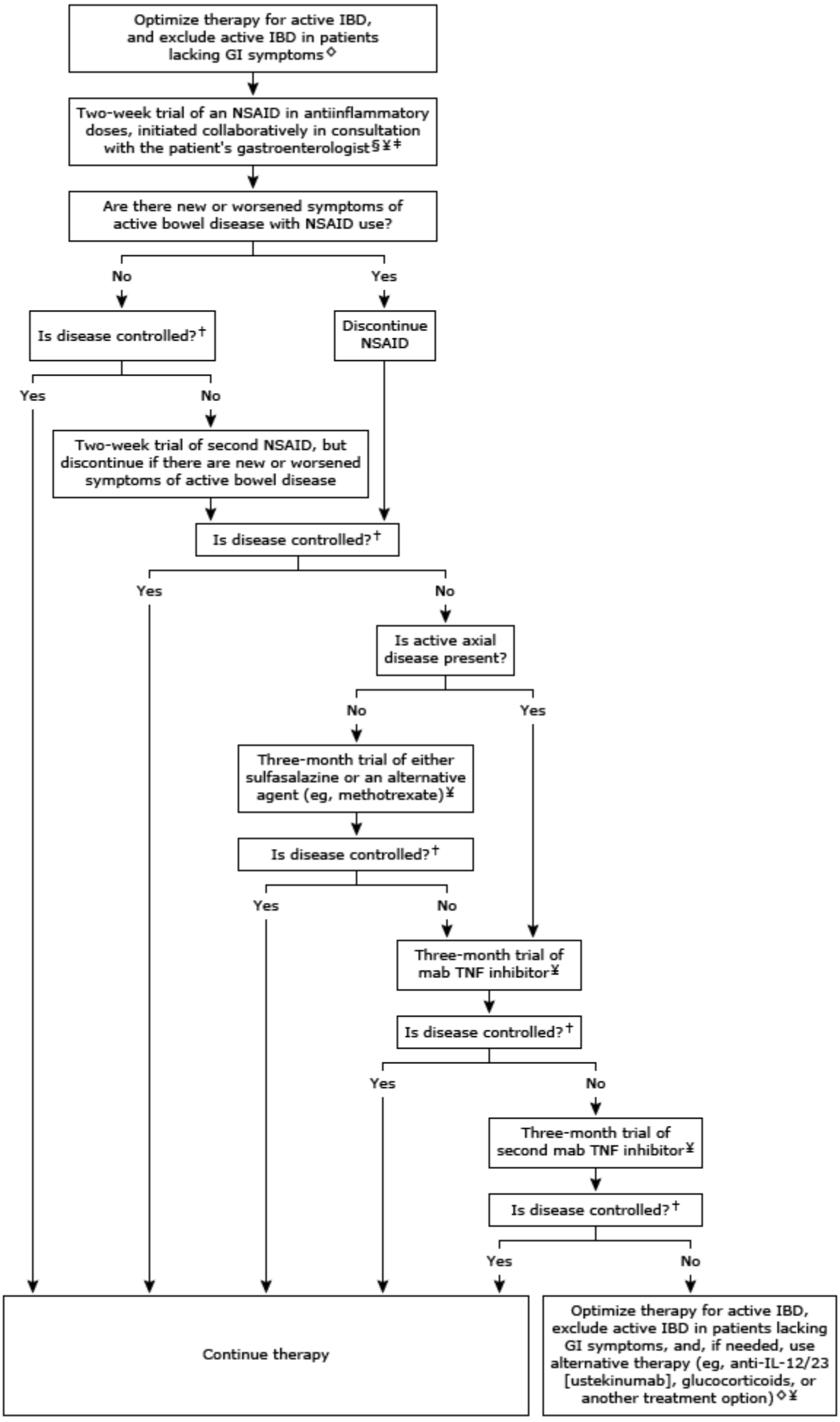
GRAPHICS

Systemic medical management of peripheral and axial arthritis in patients with inflammatory bowel disease*¶Δ


Optimize therapy for active IBD, and exclude active IBD in patients lacking GI symptoms◇
Two-week trial of an NSAID in antiinflammatory doses, initiated collaboratively in consultation with the patient's gastroenterologist§¥‡
Are there new or worsened symptoms of active bowel disease with NSAID use?
No
Yes
Is disease controlled?†
Discontinue NSAID
Yes
No
Two-week trial of second NSAID, but discontinue if there are new or worsened symptoms of active bowel disease
Is disease controlled?†
Yes
No
Is active axial disease present?
No
Yes
Three-month trial of either sulfasalazine or an alternative agent (eg, methotrexate)¥
Is disease controlled?†
Yes
No
Three-month trial of mab TNF inhibitor¥
Is disease controlled?†
Yes
No
Three-month trial of second mab TNF inhibitor¥
Is disease controlled?†
Yes
No
Continue therapy
Optimize therapy for active IBD, exclude active IBD in patients lacking GI symptoms, and, if needed, use alternative therapy (eg, anti-IL-12/23 [ustekinumab], glucocorticoids, or another treatment option)◇¥

IBD: inflammatory bowel disease; GI: gastrointestinal; NSAID: nonsteroidal antiinflammatory drug; mab: monoclonal antibody; TNF: tumor necrosis factor; IL: interleukin.

* Refer to UpToDate topic on treatment of arthritis associated with inflammatory bowel disease.

¶ Patients should be treated in collaboration with the patient's gastroenterologist.

Δ Intraarticular glucocorticoid injection is a potential added treatment option in a patient with a small number of affected joints.

◇ Refer to UpToDate topics on the management of ulcerative colitis and Crohn disease in adults.

§ Patients with axial disease should receive physical therapy for back exercise program.

¥ Refer to UpToDate topic on treatment of arthritis associated with inflammatory bowel disease for drug and dosing regimens.

‡ NSAIDs should not be administered for peripheral arthritis without excluding septic arthritis as the cause of joint inflammation (refer to UpToDate topic on septic arthritis in adults).

† Symptoms and signs of peripheral arthritis and inflammatory back pain and stiffness are well controlled.

Graphic 115015 Version 1.0

Contributor Disclosures

Robert D Inman, MD, FRCPC, FACP, FRCP Edin Consultant/Advisory Boards: AbbVie [IBD-related arthritis]; Janssen [IBD-related arthritis]; Lilly [Spondyloarthritis]; Novartis [Spondyloarthritis]. All of the relevant financial relationships listed have been mitigated. **Joachim Sieper, MD** Consultant/Advisory Boards: AbbVie [Spondyloarthritis]; UCB [Spondyloarthritis]. Speaker's Bureau: AbbVie [Spondyloarthritis]; Merck [Spondyloarthritis]; Novartis [Spondyloarthritis]. All of the relevant financial relationships listed have been mitigated. **Siobhan M Case, MD, MHS** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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