

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Management of Arthritis in Patients with Inflammatory Bowel Disease



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G&H How frequently does arthritis occur in patients with inflammatory bowel disease?

TRO There are 2 types of joint problems that can occur in patients with inflammatory bowel disease (IBD): arthritis, which is inflammation, and arthralgia, which is pain without inflammation. Arthralgia is more common among patients with IBD, occurring in 40–50% of patients, which is a rate similar to that of the general population; arthritis occurs in approximately 15–20% of Crohn's disease (CD) patients and approximately 10% of ulcerative colitis (UC) patients at some stage during their disease course.

G&H What types of arthritis are most common in patients with IBD?

TRO Approximately 60–70% of the arthritis seen in IBD patients is peripheral arthritis, in which the large joints are affected, and this arthritis is typically an oligoarthritis, meaning that fewer than 5 joints are affected. The most commonly affected joints are the knees, ankles, wrists, elbows, and hips. A smaller proportion of IBD patients have symmetrical polyarthritis, which has a presentation similar to that of rheumatoid arthritis; these patients can develop inflammation in any joints, but typically the small joints of the hands are affected. Finally, 1–6% of all IBD patients develop ankylosing spondylitis, which is a progressive inflammatory arthropathy affecting the sacroiliac joints and the spine. These patients develop gradual fusion of the spine over a period of time. While large joint arthritis is nearly always associated with active

IBD, ankylosing spondylitis and small joint polyarthritis can flare up independently of the patient's IBD.

G&H How does arthritis in IBD patients differ from arthritis in the general population?

TRO The arthritis that occurs in IBD patients is very unlike rheumatoid arthritis. Patients who have rheumatoid arthritis have an erosive and deforming arthropathy that gradually destroys the joints, and a number of these patients require joint replacement surgery. In contrast, the arthritis associated with IBD is not erosive or deforming and should do no long-term damage to the joints. In general, IBD patients with peripheral arthritis present with acute, hot, swollen joints, and with the large joint arthritis, patients often present with pain and swelling that migrate from joint to joint. Compared to large joint arthritis, the peripheral polyarthritis tends to be more persistent, lasting for 1–2 years, and affecting the same joints consistently.

In some cases, clinicians may mistake large joint arthritis for reactive arthritis, which is a type of arthritis that can develop in response to infections—for example, *Shigella* or *Yersinia* infections in the gut or chlamydial infections of the genitourinary system. Diagnosis can sometimes be quite confusing in these cases, as reactive arthritis in the context of a gut infection can very closely mimic the arthritis that occurs in patients with IBD. In patients known to have IBD, a presentation with diarrhea and arthritis could be due to reactive arthritis secondary to a gut infection, or it could be a flare of the IBD associated

with arthritis. For patients not known to have IBD, this clinical presentation can be the first presentation of IBD, as joint problems are the first symptom of the disease in some IBD patients.

G&H How does the type of IBD affect the development of arthritis?

TRO The patterns of arthritis are actually the same in CD and UC; however, there appears to be a slightly greater prevalence of arthritis in CD compared to UC. Patients who have CD that affects the large bowel probably have the most arthritis. Some evidence suggests that the most important areas of the gut in terms of the development of arthritis are the right-hand side of the colon and the bottom of the small bowel, but this association has not been conclusively demonstrated.

G&H What mechanism underlies the development of arthritis in patients with IBD?

TRO The development of arthritis in these patients definitely involves a genetic component, which probably makes patients susceptible to luminal microbiota that can trigger arthritis. The arthritis associated with IBD is classified as a seronegative spondyloarthropathy; all the conditions in this group involve the development of arthritis without the presence of autoantibodies, and all these conditions are associated with an increased risk of developing ankylosing spondylitis. Ankylosing spondylitis is known to be strongly associated with *HLA-B27*, which is a particular variant of an *HLA* gene that controls the immune response, and peripheral arthritis in IBD patients is also associated with *HLA-B27*, although less strongly; this common association probably accounts for the increase in ankylosing spondylitis among patients with seronegative spondyloarthropathy. However, peripheral arthritis in IBD patients has an even stronger association with a rare *HLA* allele called *HLA-DR103*. This allele is present in approximately 35% of patients with large joint arthritis and in up to 65% of patients who have more than 1 episode of large joint arthritis. In comparison, this allele occurs in only 1–3% of the general population. How this genetic association results in arthritis among IBD patients is largely speculation. My hypothesis is that episodic bouts of arthritis are triggered by the combination of a leaky, inflamed gut, which is found in IBD, plus a genetic susceptibility to certain bacteria that patients may encounter. This susceptibility is determined by the *HLA* genes (and possibly other genes) that patients have inherited, and it allows an uncontrolled inflammatory response to develop, specifically targeting the joints.

Interestingly, ankylosing spondylitis is very strongly associated with *HLA-B27* overall (with over 90% of idiopathic ankylosing spondylitis patients possessing this allele), but this association is actually much weaker among patients with IBD (50–80%). My interpretation of this finding is that the genetic association between *HLA-B27* and ankylosing spondylitis is less important in patients with IBD because of the environmental susceptibility provided by gut inflammation. Thus, if patients have the genetic predisposition (*HLA-B27*) that makes them susceptible to ankylosing spondylitis, then they have a 1–10% chance of developing this condition. If they have gut inflammation, which makes the gut very leaky, then their immune system is exposed to many antigens they would not otherwise encounter, and IBD can trigger ankylosing spondylitis in the absence of *HLA-B27*. If patients have the combination of both *HLA-B27* and a leaky gut, then their chances of developing axial arthritis are very high: In a small study my coauthors and I conducted, magnetic resonance imaging scans showed abnormalities in the sacroiliac joints in every single person who had both *HLA-B27* and a diagnosis of CD. In summary, the development of arthritis is probably the result of both a genetic predisposition and exposure to luminal bacteria, but direct mechanistic evidence to support this hypothesis is not yet available.

G&H Which IBD therapies are most likely to provide a benefit in terms of reducing patients' arthritis symptoms?

TRO The treatments that clinicians would normally use to treat ankylosing spondylitis overlap with IBD therapy; specifically, anti-tumor necrosis factor (TNF) α therapies such as infliximab (Remicade, Janssen Biotech), adalimumab (Humira, Abbott), and certolizumab pegol (Cimzia, UCB) are effective for both conditions. Steroids are not particularly effective for the treatment of ankylosing spondylitis, and immunomodulators do not help in terms of the axial disease, although they may help in the treatment of peripheral arthritis.

Some data suggest that sulfasalazine might be a better anti-inflammatory medication than mesalamine for peripheral arthritis associated with IBD, but this benefit has not been definitively proven. Steroids obviously have an anti-inflammatory effect on the peripheral joints and can be quite effective, but these drugs have substantial long-term side effects, so the amount of steroids prescribed in IBD patients should be kept to a minimum. Again, anti-TNF α drugs are very effective for patients who have troublesome and persistent inflammatory arthritis associated with IBD.

G&H Which additional therapies could be added to manage arthritis in patients with IBD?

TRO In general, clinicians should try to use anti-inflammatory drugs that can treat the joint problems and also provide benefit for the gut. Large joint arthritis normally resolves once the gut disease is under control, so it is unusual that clinicians would need to add medications beyond those used to treat the underlying IBD. For patients who have more persistent arthritis—for example, small joint polyarthritis—adding an immunosuppressant such as methotrexate or possibly azathioprine may be effective. In some patients with active gut disease, joint disease may be the factor that pushes a clinician to start biologic therapy.

G&H Which drugs are contraindicated in this population?

TRO Nonsteroidal anti-inflammatory drugs (NSAIDs) are the main group of drugs that should be avoided in patients with IBD. Evidence suggests that these drugs can trigger flare-ups of the underlying IBD, so I would not recommend using NSAIDs to treat arthritis if a patient's IBD is active. If a patient has quiescent IBD and the joint pain is very troublesome, then clinicians can cautiously try an NSAID; in this situation, clinicians need to inform patients of the risk that the drug will upset the gut.

G&H How much research is available regarding the management of arthritis in patients with IBD?

TRO A small case series of anti-TNF α therapy in IBD-associated arthropathies was published in *The Lancet* in 2000, which demonstrated in 4 patients that articular manifestations were effectively treated by TNF α blockade, and an article published in *Alimentary Pharmacology & Therapeutics* in 2003 looked at cyclooxygenase-2 (COX-2) inhibitors as a treatment for IBD-associated arthritis. This latter study using rofecoxib suggested that this drug was reasonably safe, but only 41% of patients had a clinical response to the drug in terms of their arthritis. However, a later study of COX-2 antagonists in general in IBD patients suggested that these drugs were associated with a high risk of IBD relapse—in addition to the safety issues raised more widely by this class of drugs. My coauthors and I also conducted genetic studies several years ago at Oxford in which we looked at possible mechanisms for arthritis in IBD patients, and we published a study in *Alimentary Pharmacology & Therapeutics* in 2009 in which we assessed the risk of ankylosing spondylitis among patients with CD.

Aside from these small studies, very little research has focused on the management of IBD and arthritis, partly because recruiting patients for such studies is difficult: Although 10–20% of patients will develop arthritis at some stage during their disease course, this arthritis is very episodic, so gathering enough patients for a study is actually quite difficult. Also, because the arthritis that occurs in IBD patients is not erosive or deforming, it does not have major long-term sequelae that can be studied.

G&H What further research is needed regarding the treatment of arthritis in patients with IBD?

TRO Perhaps the most pressing need is further research into how ankylosing spondylitis develops in patients with IBD. Although peripheral arthritis can be very troublesome, only a very small minority of patients have peripheral arthritis that is persistent and debilitating over long periods of time; in contrast, ankylosing spondylitis is a lifelong, progressive condition that can be quite debilitating. I think understanding the relationship between intestinal inflammation and the development of ankylosing spondylitis will be key to this research; thus, studies looking at intestinal permeability, inflammation, and luminal bacteria to see how these factors might trigger ankylosing spondylitis will be important. Also, research has already revealed that the *HLA-DR103* allele is a strong genetic determinant for arthritis in patients with IBD, so a logical step would be to see what triggers arthritis in patients who have this allele.

Suggested Reading

- Orchard TR, Holt H, Bradbury L, et al. The prevalence, clinical features and association of *HLA-B27* in sacroiliitis associated with established Crohn's disease. *Aliment Pharmacol Ther.* 2009;29:193-197.
- Orchard TR, Thiyagaraja S, Welsh KI, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. *Gastroenterology.* 2000;118:274-278.
- Van den Bosch F, Kruithof E, De Vos M, De Keyser F, Mielants H. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. *Lancet.* 2000;356:1821-1822.
- Reinisch W, Miehsler W, Dejaco C, et al. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther.* 2003;17:1371-1380.
- De Vos M. Joint involvement associated with inflammatory bowel disease. *Dig Dis.* 2009;27:511-515.
- Rodríguez-Reyna TS, Martínez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World J Gastroenterol.* 2009;15:5517-5524.