CLINICAL UPDATE

Advances in Joint Pain and Arthritis in Inflammatory Bowel Disease

Recent Research on Joint Pain and Arthritis in Patients With Inflammatory Bowel Disease

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G&H Among the various extraintestinal manifestations of inflammatory bowel disease, how common are joint pain and arthritis?

DR Joint pain, or arthralgia, is the most common extraintestinal manifestation of inflammatory bowel disease (IBD) and occurs in up to one-third of patients. Arthritis is much less common. Other extraintestinal manifestations that are common are inflammatory conditions involving the skin or the eyes. Sometimes mouth sores are considered extraintestinal manifestations, but the mouth is actually an extension of the gut.

G&H What types of joint pain and arthritis are common in IBD patients?

DR The most common type of joint pain involves smaller joints, such as the wrists, knees, or ankles, and is usually symmetric. A less common, but still important, joint problem in IBD patients involves large joints and is usually unilateral. For example, a single knee or shoulder might be inflamed and swollen. In addition, it is important to distinguish arthralgia, which refers to pain of the joints, from an arthritis, which refers to inflamed joints or synovium. There are also parallel inflammatory processes such as ankylosing spondylitis or sacroiliitis that are truly independent disease states that can accompany IBD.

Small joint involvement is often related to inflammation of the bowel. Thus, when the intestinal inflammation is treated, the joint pain resolves. In contrast, larger joints and conditions such as ankylosing spondylitis and sacroiliitis are often independent of bowel inflammation. In these cases, treating the bowel or even performing surgery on the bowel does not resolve the joint pain.

G&H What is the etiology of joint pain and arthritis in IBD patients?

DR That is an important question that we still cannot answer. There are several different theories. One is that the inflammatory drive that leads to intestinal inflammation overlaps with an antigen that is commonly present in the joints or vice versa. Thus, when the patient develops an inflammatory reaction to whatever is happening in the intestine, there is an overlap with the expression of a similar protein or epitope in the joint that leads to a reaction there. This theory might also explain arthritis in IBD patients. However, the theory is not completely understood for either joint pain or arthritis in IBD patients.

More recently, there has been a suggestion that cytokine interleukin (IL)-23 might be a component of some of the extraintestinal manifestations, but that remains to be proven. This is of interest, however, because there are anti–IL-23 therapies that are available and others that are being developed for the treatment of IBD.

However, regardless of the pathogenesis of these manifestations, it is well known that some therapies used to treat the bowel also treat the joints themselves. When trying to treat IBD patients with joint pain, the first question should always be whether the intestinal inflammation is under sufficient control. If the intestines are treated appropriately, the second question should be whether the therapy being used is improving the joint pain because the bowel is improved, or whether the therapy being used is improving the joint pain because it happens to also treat joints. Therapies such as sulfasalazine and methotrexate work in the bowel as well as in the joints, as do anti–tumor necrosis factor (TNF), anti–IL-23, and Janus kinase inhibitors.

G&H Are there causes of joint pain in this setting other than IBD?

DR There are several. One of the more common side effects of corticosteroid withdrawal is joint pain. Thus,

it is important to distinguish a patient who has a true extraintestinal manifestation associated with IBD from a patient who is having a side effect from withdrawal of prednisone or another corticosteroid. This distinction can be made by taking a careful history, understanding the patient's history with IBD before receiving corticosteroids and whether the patient had joint pain, and examining the timing of the joint pain in relation to stopping the corticosteroid. In such a case, the patient sometimes needs to receive a low dose of corticosteroids to control the joints and slow down the taper until he or she recovers fully.

In addition, an allergy to thiopurines (ie, 6-mercaptopurine and azathioprine) can present with a severe, debilitating, acute-onset joint pain and high fever. In this case, the pain usually occurs 1 or 2 days after starting thiopurine as a new therapy, so it is clearly from the drug. Stopping the thiopurine resolves both the fever and the joint pain quite rapidly.

Another type of joint pain is related to the development of a lupoid reaction to anti-TNF therapies. After exposure to an anti-TNF therapy, some patients can develop double-stranded DNA antibodies or antihistone antibodies, which are associated with joint pain. This reaction resolves when the anti-TNF therapy is stopped and responds quite rapidly to low-dose prednisone.

G&H For a patient with IBD-associated joint pain and/or arthritis, what are the possible treatment options?

DR When a patient with IBD complains of joint pain, it is important to first perform a careful evaluation to determine the type of joint pain and whether the patient has a joint problem that is distinct from his or her IBD. Once it has been determined that the patient has a type of IBD arthropathy, then the therapy should be focused on controlling the bowel, at which point the joints will hopefully improve.

As previously mentioned, one treatment option is sulfasalazine, which controls ulcerative colitis and may have a small role in Crohn's disease of the colon. This therapy has been demonstrated to help the joints more than mesalamine. In addition, it is well known that anti-TNF therapies treat both joints and the bowel quite well.

As for novel IBD therapies, ustekinumab (Stelara, Janssen), which is an anti–IL-12 and anti–IL-23 agent, had already been approved by the US Food and Drug Administration to treat psoriatic arthritis and psoriasis when it received approval for the treatment of Crohn's disease. Similarly, tofacitinib (Xeljanz, Pfizer), a Janus kinase inhibitor that is expected to receive approval for treatment of moderate to severe ulcerative colitis next year, is already on the market for the treatment of rheumatoid arthritis. Thus, some of the therapies used to treat the bowel are also known to specifically treat the joints.

Occasionally, the bowel is treated, but the joints are still a problem. In this scenario, the therapy should be switched to treat both conditions with a different mechanism or an additional therapy should be used to better control the joints.

G&H Does the IBD drug vedolizumab also treat joint pain and/or arthritis?

DR Vedolizumab (Entyvio, Takeda) is a gut-selective therapy for Crohn's disease and ulcerative colitis that works by targeting the lymphocytes that are earmarked to migrate to the gut mucosa. Therefore, in part because it is a nonsystemic therapy, there has been some question as to whether it would uncover extraintestinal manifestations or whether, by treating the bowel, the extraintestinal manifestations would potentially be appropriately managed. In other words, if there is a shared antigen that is involved in joint pain and in the bowel, treating it with this drug would treat both problems, even though the drug is technically a selective therapy for the gut.

This has become of interest because vedolizumab works well for ulcerative colitis and has demonstrated good efficacy and excellent safety in Crohn's disease. However, some physicians have wondered whether it is causing or is associated with more joint pain. At this year's Digestive Disease Week, my colleagues and I presented findings from a post hoc analysis from GEMINI 2, one of the pivotal trials of vedolizumab in the treatment of moderate to severe Crohn's disease. We looked at the patients who had baseline arthritis or arthralgias and how they responded to either treatment with vedolizumab or placebo. In addition, we looked at whether the patients developed new or worsening joint pain or associated problems.

The results demonstrated increased rates of sustained resolution of arthritis and arthralgias and a reduced incidence of new or worsening arthritis or arthralgia in the patients who received vedolizumab. Also noted was arthralgia in both groups related to corticosteroid tapering, which was previously mentioned as a cause of joint pain. At least within the limits of this post hoc analysis, it appears that vedolizumab may both ameliorate existing cases and prevent the development of new cases of arthritis and arthralgia in patients with Crohn's disease. It is thought that these results would be applicable to ulcerative colitis as well.

However, these findings are not necessarily intuitive. There have been anecdotal experiences and case reports of patients on vedolizumab who developed worse joint pain, and there are likely exceptions to the findings of the post hoc analysis.

G&H Are there any other limitations or cautions that should be kept in mind regarding these findings?

DR One of the limitations is that GEMINI 2 was designed to look at the safety and efficacy of vedolizumab for the treatment of Crohn's disease. The capture of extraintestinal manifestations was limited according to how they were defined and recorded. They were part of the Crohn's Disease Activity Index and, thus, were limited by patient reporting more than any objective measure. The study was not powered to look at this particular endpoint.

Nonetheless, GEMINI 2 is a large study. There were 394 patients in the vedolizumab arm and 82 patients in the placebo arm. Therefore, these findings should not be ignored.

G&H Is it known why vedolizumab might provide a benefit for joint pain and/or arthritis?

DR If it does provide a benefit, it is probably related to the first cause of joint pain discussed here, the inflammation of the bowel. At this time, we do not have a better explanation, although there is currently work ongoing to try to better elucidate this issue.

G&H Was this analysis the first time this drug was studied in relation to these extraintestinal manifestations?

DR There has been discussion on this issue for some time, but this was the first extensive analysis performed. As for extraintestinal manifestations of IBD in general, there is a good deal of research that has been, and is currently being, conducted. Certainly, these manifestations are an important component of any trial that looks at management of IBD.

G&H What are the next steps in research in this area?

DR Better patient-reported outcomes are needed to improve capturing of the type of joint pain that patients are having and characterizing where it is located, when it occurs, and how to best manage it. To achieve this goal, we need to develop prospective studies that include joint pain and/or arthritis as accurately captured and important symptoms. By doing this, we will be able to analyze the data much more accurately and determine what is going on in these patients.

Dr Rubin is a consultant for and has received grant support from AbbVie, Janssen, Pfizer, and Takeda.

Suggested Reading

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