

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Overview of Extraintestinal Manifestations of Inflammatory Bowel Disease



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### G&H What are the various types of extraintestinal manifestations associated with inflammatory bowel disease?

**ML** There are a wide variety of extraintestinal manifestations. One category consists of manifestations that tend to occur classically with active inflammatory bowel disease (IBD). Examples of these types of manifestations include joint manifestations (eg, arthralgias and arthritis) and skin manifestations (eg, erythema nodosum and pyoderma gangrenosum). Joint manifestations are the most common type of extraintestinal manifestation of IBD and can affect multiple joints, peripherally or centrally. Skin manifestations are also common. Less common manifestations that correlate with inflammatory activity include ocular manifestations, such as episcleritis, scleritis, and anterior uveitis. Some of the extraintestinal manifestations within this category can even develop prior to the diagnosis of bowel inflammation.

Other extraintestinal manifestations are completely independent of disease activity. One example is primary sclerosing cholangitis.

Another category of extraintestinal manifestations consists of those that develop as a complication of IBD or of IBD therapies. For example, when a patient has ongoing inflammation of the gut, this can lead to blood loss, and then anemia. The ongoing inflammation can also trigger an increased clotting risk and can be associated with pulmonary embolus. An example of a drug-induced extraintestinal manifestation is when a treatment for IBD, such as an anti-tumor necrosis factor (TNF) agent, causes a paradoxical psoriasis. Ironically, anti-TNF agents themselves can treat psoriasis independently, but in patients who are taking these agents for other conditions, there have been reports of de novo psoriasis. Other

de novo paradoxical complications associated with IBD therapies include the rare manifestations of demyelination and vasculitis.

Thus, physicians should think systemically when managing IBD, as nearly every organ system may be involved.

### G&H What has recent research found regarding the incidence and risk factors of extraintestinal manifestations of IBD?

**ML** The most recent data from the population-based Swiss IBD Cohort Study found that nearly half of patients with Crohn's disease and approximately one-third of patients with ulcerative colitis had 1 to 5 extraintestinal manifestations. Some of the more common ones were arthritis, aphthous stomatitis, uveitis, erythema nodosum, and ankylosing spondylitis. In the Swiss IBD cohort, family history of IBD and disease activity were associated with extraintestinal manifestations, particularly among patients with Crohn's disease.

Interestingly, some of the risk factors for developing these extraintestinal manifestations appear to be linked with having colonic inflammation rather than inflammation elsewhere.

### G&H Have there been any recent trends regarding the incidence of these manifestations? Is awareness of them increasing?

**ML** There has likely been an increased awareness that these manifestations can be linked to IBD. Thus, it is difficult to know whether the actual incidence is increasing. I often educate my patients at diagnosis that they may have extraintestinal manifestations so that should the

manifestations arise, patients know to tell me. I am not sure that this awareness existed a decade or two ago. With this increased awareness, physicians are starting to target therapies that will manage all of their patients' inflammatory symptoms, not just inflammation in the bowel.

### **G&H** Are the underlying mechanisms of these extraintestinal manifestations understood yet?

**ML** No, we do not know the underlying pathophysiology as to why these specific extraintestinal manifestations develop. However, this is an area currently undergoing further study. There are several ongoing studies looking at genetic components that may be predictive of some of these manifestations.

### **G&H** Are some extraintestinal manifestations more likely to occur with Crohn's disease as opposed to ulcerative colitis, or vice versa?

**ML** Yes, some extraintestinal manifestations appear to be linked more to one disease than the other. For example, primary sclerosing cholangitis is seen more often in ulcerative colitis as compared to Crohn's disease. However, other manifestations, such as those involving the joints, are seen more often in patients who have Crohn's disease. Of the various types of Crohn's disease (ie, with small bowel, colonic, or upper gastrointestinal tract involvement), patients who have colonic involvement tend to have more extraintestinal manifestations.

### **G&H** Does the presence of a manifestation increase the risk of developing another one?

**ML** Among patients with extraintestinal manifestations, many have more than one. The Swiss IBD Cohort Study showed that extraintestinal manifestations appear to track somewhat together. That being said, if a patient has an extraintestinal manifestation, it does not necessarily mean that he or she will definitively have more.

### **G&H** When do extraintestinal manifestations typically occur?

**ML** They can occur at any time. However, if they occur prior to gastrointestinal inflammation or symptoms, they can be somewhat more difficult to diagnose. In the workup, the physician would need to find other clues to determine whether the patient could have underlying IBD that could be associated with the manifestation. It is not infrequent that I receive a referral from a specialist who is wondering whether a patient may have underlying IBD (eg, from an ophthalmologist who found episcleritis

in a patient who did not improve with traditional topical treatment or from a rheumatologist who found sacroiliitis in a patient with mild gastrointestinal symptoms). Thus, communication among physicians is important, as is the awareness that the timing of these manifestations can differ. It is somewhat more common for the gastrointestinal symptoms of IBD to occur first, although we have also seen extraintestinal manifestations come earlier.

Interestingly, in the Swiss study, it was more common for some extraintestinal manifestations to occur before the diagnosis of IBD in children than in adults.

### **G&H** Were there any other differences in the extraintestinal manifestations seen in children vs adults?

**ML** No. The same extraintestinal manifestations were seen in children and in adults. For children, manifestations were more common with Crohn's disease. Peripheral arthritis appeared to be the most common manifestation, followed by aphthous stomatitis.

### **G&H** Does the presence of IBD affect the treatment of extraintestinal manifestations?

**ML** Often yes. For example, if a patient has been diagnosed with IBD as well as an extraintestinal manifestation such as ankylosing spondylitis, physicians try to prescribe a medication with a mechanism of action that can treat both the joint inflammation and the bowel inflammation.

For many manifestations (such as generalized arthralgias or aphthous stomatitis), controlling the bowel inflammation often leads to the extraintestinal manifestation improving as well. In this scenario, any drug with a mechanism of action that heals the bowel can be used. However, it is important to keep in mind that there are times when bowel inflammation is fully controlled and the extraintestinal manifestation is still active. Therefore, it should not necessarily be assumed that the two go hand in hand.

It is also sometimes assumed that medications that are more specific to the gut may not treat extraintestinal manifestations. Although this may be true, if the drug gets the bowel inflammation under control, it may also have benefit for the extraintestinal manifestation.

Thus, the key take-home message is to follow the patient's symptoms, both extraintestinal and gastrointestinal, as well as confirm endoscopic healing in the bowel to select the right therapies for each individual patient.

### **G&H** How have recent trends in IBD treatment affected the management of extraintestinal manifestations?

**ML** As mentioned previously, we are seeing paradoxical reactions in some patients being treated for IBD with anti-TNF agents who are developing extraintestinal manifestations such as anti-TNF-induced psoriasis. This is a puzzling situation because anti-TNF agents are approved for the treatment of psoriasis, yet individuals who are on this therapy for another condition can develop psoriasis. Medications such as topical agents are often added to the anti-TNF agent to control the psoriasis. However, if the psoriasis is particularly bothersome, in a difficult location such as the scalp or face, or does not respond to the therapy, the patient may have to move off of the anti-TNF agent to another class of drugs. It is rare that this happens, but it may. It is estimated that up to 90% of individuals with paradoxical psoriasis will respond to topical agents and/or the addition of immunomodulators. When these therapies are not effective, it can be difficult to want to change therapy because the anti-TNF agent may have been controlling the patient's bowel symptoms and inflammation quite well. In these scenarios, a change of class can often improve the paradoxical psoriasis. In my practice, I try to use an interleukin 12/23 inhibitor in these instances, as this type of agent can be effective for both Crohn's disease and psoriasis.

Another paradoxical reaction is demyelination in the brain related to anti-TNF therapy, which can mimic multiple sclerosis. Often, the condition improves with corticosteroids and stopping the anti-TNF agent.

As anti-TNF agents are being used more frequently, increased awareness of these potential reactions is important so that patients can be treated appropriately.

### G&H What is the role of specialist care?

**ML** A key aspect of the treatment of extraintestinal manifestations is using a multidisciplinary approach and collaborating with dermatology, ophthalmology, and/or rheumatology colleagues. In many instances, there are medications that can be used to control multiple ongoing inflammatory symptoms, which is ideal. There may be challenges surrounding the exacerbation of one disorder with the treatment of another (eg, some medications used for the treatment of rheumatoid arthritis can worsen Crohn's disease or ulcerative colitis). Thus, collaboration over a treatment plan is important. This is particularly true when potentially changing a class of medication. If that class is very effective for one disorder but not the other, multidisciplinary collaboration can help find the next best choice.

### G&H When is referral to a specialist necessary?

**ML** Many of the extraintestinal manifestations, such as aphthous stomatitis or arthralgias, can be managed

primarily by the gastroenterologist treating the underlying IBD. However, eye symptoms (eg, pain with light that is associated with redness in the eye) should be taken very seriously and require urgent ophthalmologic referral to ensure prompt treatment and the prevention of ocular complications.

### G&H How should IBD patients be monitored for the development of extraintestinal manifestations?

**ML** It should be part of routine clinical care that each time an IBD patient is seen in the clinic, he or she is asked a series of questions regarding the presence of any extraintestinal manifestations. This can help guide treatment algorithms. In addition, it can help improve patients' quality of life by directly addressing any manifestations. Patients may not bring up extraintestinal manifestations on their own; they may not even be aware that their symptoms are linked to their underlying IBD.

### G&H What are the next steps in research?

**ML** Several studies are currently looking at rare phenotypes to better understand whether there are genetic, microbial, or other risk factors for the development of extraintestinal manifestations. If this can be determined, it may be possible to better define treatment algorithms or even prevent these complications. The more data that are collected, the better patients with these manifestations can be managed.

*Dr Long has done consulting for AbbVie, Takeda, Pfizer, Janssen, UCB, and Valeant Pharmaceuticals and has received research support from Pfizer and Takeda.*

### Suggested Reading

Ditisheim S, Fournier N, Juillerat P, et al; Swiss IBD Cohort Study Group. Inflammatory articular disease in patients with inflammatory bowel disease: result of the Swiss IBD Cohort Study. *Inflamm Bowel Dis*. 2015;21(11):2598-2604.

Fraga M, Fournier N, Safroneeva E, et al; Swiss IBD Cohort Study Group. Primary sclerosing cholangitis in the Swiss Inflammatory Bowel Disease Cohort Study: prevalence, risk factors, and long-term follow-up. *Eur J Gastroenterol Hepatol*. 2017;29(1):91-97.

Greuter T, Bertoldo F, Rechner R, et al; Swiss IBD Cohort Study Group. Extraintestinal manifestations of pediatric inflammatory bowel disease: prevalence, presentation, and anti-TNF treatment. *J Pediatr Gastroenterol Nutr*. 2017;65(2):200-206.

Hedin CRH, Vavricka SR, Stagg A, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis and therapy [published online November 15, 2018]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjy191.

Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss Inflammatory Bowel Disease cohort. *Am J Gastroenterol*. 2011;106(1):110-119.

Vavricka SR, Gubler M, Gantenbein C, et al; Swiss IBD Cohort Study Group. Anti-TNF treatment for extraintestinal manifestations of inflammatory bowel disease in the Swiss IBD Cohort Study. *Inflamm Bowel Dis*. 2017;23(7):1174-1181.