Extraintestinal Manifestations of IBD


Summary

Inflammatory bowel disease (IBD) manifests not only in the gastrointestinal (GI) tract, but also affects joints, skin, eyes, liver, lung, and pancreas. Atypical conditions, such as cardiovascular morbidities, fatigue, mental health disorders, and pain are also increasingly identified to be related to IBD. Up to half of patients with IBD have extraintestinal manifestations (EIMs). Therapies for intestinal inflammation can treat some EIMs directly due to shared inflammatory pathways or indirectly due to improvement of the bowel inflammation and related improvement of EIMs, but in some cases these therapies do not address the EIMs at all. Examples of the EIMs commonly not addressed by these therapies include anterior uveitis, ankylosing spondylitis, and primary sclerosing cholangitis (PSC), which usually occur independent of bowel inflammatory activity. Rogler and colleagues reviewed the epidemiology, pathophysiology, clinical presentation, and treatment of different types of EIMs in patients with IBD. The authors also review the genetic and environmental factors that can lead to development of IBD and its EIMs, as well as the immune system and intestinal microbiome alterations associated with each.

The extra-intestinal symptoms of IBD most commonly involve the musculoskeletal system (peripheral and axial arthritis and enthesitis), skin (pyoderma gangrenosum, erythema nodosum, Sweet syndrome, and aphthous stomatitis), hepatobiliary tract (PSC), and eyes (episcleritis, anterior uveitis, and iritis).

EIMs differ from the extra-intestinal complications of IBD, which are direct or indirect sequelae of intestinal inflammation. EIMs are the result of inflammation that develops outside of the GI tract in patients with IBD, caused by disrupted immune regulation and possibly the same environmental or genetic factors that cause gut inflammation.

EIMs can occur before or after the diagnosis of IBD; 26% of all patients with EIMs report the occurrence of EIMs up to 25 months (median 5 months) before IBD diagnosis. Some patients with IBD develop more than 1 EIM, either before or after the onset (or diagnosis) of IBD.

Clinical Practice Take-Home Points

- The most common extraintestinal manifestations (EIMs) of IBD are musculoskeletal disorders (affecting up to 46% of patients with IBD), skin disorders, and ophthalmologic disorders.
- Identification of co-existing EIMs is a critical component to the management of IBD. Treatment of EIMs in IBD should be aimed at addressing the inflammatory bowel condition, but also, when possible, to identify shared immune pathways and mechanisms for management. Additional treatments, however, may be required to address these challenges.
- Patients with Crohn’s disease who smoke are more likely to present with EIMs than nonsmokers. Smoking cessation may be associated with a reduced prevalence of EIMs in Crohn’s disease.
- Patients with IBD also have an increased risk of acute myocardial infarction and heart failure, as well as a 3-fold increase in risk of venous thromboembolic events such as deep vein thrombosis, splanchnic thromboembolism, and lung embolism.
- Fatigue and pain are frequently reported by patients with IBD—more than 50% of patients with IBD have pain for more than 5 years. Up to 60% report abdominal pain, 38% report back pain, 29% report knee pain, and 26% report hip pain (26%). Most patients state that these pain attacks affect their activities of daily living.

Although the EIMs of IBD occur more frequently in certain organs, almost any organ can be affected, and EIMs are not always obvious or easy to detect. For example, acute or chronic pancreatitis associated with IBD (and not with IBD medications such as azathioprine) is rare, whereas asymptomatic exocrine insufficiency, pancreatic duct abnormalities, and hyperamylasemia occur in up to 18% of patients with IBD. Disorders such as pneumonitis or PSC can persist in patients with ulcerative colitis even after proctocolectomy.
Figure 1. Extraintestinal manifestations of IBD affect many organs. *green*: frequent EIMs; *blue*: rare EIMs.
Several biologic therapies are currently FDA-approved for the treatment of moderate to severe Crohn’s disease, including monoclonal antibodies targeting tumor necrosis factor (TNF)-alpha, leukocyte adhesion, and interleukin-12/23. Unfortunately, a large proportion of patients with moderate to severe Crohn’s disease will require sequential therapies during their disease course due to either primary non-response or secondary loss of response to a given therapy. Currently, there is a paucity of head-to-head clinical trial data to assist clinicians in determining the ideal order in which to best utilize these therapies toward maximizing patient quality of life. In silico analyses, such as network meta-analyses or Markov simulation modeling using best available randomized controlled trial and observational study data can augment this knowledge gap.

In this study, Scott and colleagues employed Markov simulation modeling to determine the ideal position of ustekinumab among existing treatment algorithms in the post-SONIC era. In the base algorithm, individuals would initially receive combination therapy with infliximab and azathioprine. Individuals without a clinical response or with a subsequent loss of response would transition to a second anti-TNF agent combined with a thiopurine modeled after adalimumab. With failure to respond or loss of response to adalimumab and azathioprine, individuals would cycle to vedolizumab monotherapy, and then to surgery if necessary. Inserting ustekinumab prior to each medication transition yielded 4 algorithms: Algorithm 1: ustekinumab prior to other biologics, Algorithm 2: ustekinumab prior to a second anti-TNF agent, Algorithm 3: ustekinumab prior to vedolizumab, and Algorithm 4: ustekinumab prior to surgery. For each therapy, simulated individuals could experience clinical remission, response, or therapy-related adverse events such as serious infection or other adverse events. Transition probabilities were derived from relevant clinical trials for each medication, including, but not limited to, SONIC, GEMINI, and UNITI. Individuals not responding to therapy were at increased risk of surgery. Outcomes were measured in quality adjusted life years (QALYs). The base case was assumed to be a 35-year-old individual with steroid-dependent moderate to severe Crohn’s disease. Primary analyses simulated the first year of therapy. Sensitivity analyses explored all model inputs, as well as time horizons of up to 7 years and ages from 25 to 65 in 10-year increments.

In this simulation, using ustekinumab as a first-line biologic therapy yielded the greatest estimated QALYs at the end of 1 year compared with the algorithms inserting ustekinumab after other biologic therapies. Further, this algorithm resulted in a greater percentage of simulated individuals in clinical remission or response, and fewer adverse events and surgeries than later ustekinumab use. The incremental benefit in QALYs increased with time horizons of 3, 5, and 7 years, and was appreciated for all simulated ages.

In summary, this study using unique Markov modeling methods to assess where in current treatment algorithms ustekinumab might yield the greatest quality of life benefit for patients with moderate to severe Crohn’s disease, demonstrated that incorporating ustekinumab as first-line biologic therapy may yield the greatest potential QALYs. Future prospective research assessing therapy sequencing over time in Crohn’s disease is required to confirm these findings.
Figure 1. Base model structure incorporating ustekinumab into 4 treatment algorithms for Crohn’s disease. Four algorithms incorporating ustekinumab in different positions were simulated. AZA, azathioprine; CD, Crohn’s disease; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

Table 1. Mean effectiveness and incremental effectiveness of 4 algorithms incorporating ustekinumab.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Algorithm treatment order</th>
<th>Mean effectiveness (in QALYs) (95% confidence intervals)</th>
<th>Incremental effectiveness of Algorithm 1 compared with other algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UST -&gt; IFX+AZA -&gt; ADA+AZA -&gt; VDZ -&gt; surgery</td>
<td>0.7598 (0.7593–0.7602)</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>IFX+AZA -&gt; UST -&gt; ADA+AZA -&gt; VDZ -&gt; surgery</td>
<td>0.7399 (0.7395–0.7403)</td>
<td>−0.020</td>
</tr>
<tr>
<td>3</td>
<td>IFX+AZA -&gt; ADA+AZA -&gt; UST -&gt; VDZ -&gt; surgery</td>
<td>0.7404 (0.7399–0.7408)</td>
<td>−0.019</td>
</tr>
<tr>
<td>4</td>
<td>IFX+AZA -&gt; ADA+AZA -&gt; VDZ -&gt; UST -&gt; surgery</td>
<td>0.7437 (0.7433–0.7441)</td>
<td>−0.016</td>
</tr>
</tbody>
</table>

NOTE: Mean and incremental effectiveness for the 4 treatment algorithms at 1 year. Bold and underline emphasizes the position of ustekinumab in each treatment algorithm.
ADA, adalimumab; AZA, azathioprine; CD, Crohn’s disease; IFX, infliximab; UST, ustekinumab; VDZ, vedolizumab.