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Review

Impact of Extraintestinal Manifestations on Inflammatory Bowel Disease Treatment

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Abstract

Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD) and can significantly impact disease management. The choice of treatment for EIMs depends on the specific manifestation, its severity, and the activity of the underlying IBD. Ocular manifestations, such as uveitis, scleritis, and episcleritis, often require tailored treatment approaches. Systemic corticosteroids, biologic agents, and topical medications are commonly used to manage these conditions. Hepatobiliary manifestations, including primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH), are often treated with anti-TNF agents, corticosteroids, or immunosuppressants. Musculoskeletal manifestations, such as axial and peripheral spondyloarthritis, are typically managed with anti-TNF agents or other biologic therapies. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution due to the risk of exacerbating intestinal inflammation. Mucocutaneous manifestations, including pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, and oral lesions, often respond to anti-TNF agents or other immunosuppressants. Treatment selection for EIMs requires a multidisciplinary approach involving gastroenterology, rheumatology, dermatology, and ophthalmology. The specific choice of treatment depends on patient factors, disease severity, and response to previous therapies.
Keywords: Extraintestinal manifestations, inflammatory bowel disease, treatment

EXTRAINTESTINAL MANIFESTATIONS

Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD). These systemic manifestations can arise from a complex interplay of immunological, genetic, and environmental factors. The precise mechanisms underlying EIMs remain elusive, but several factors are implicated. Immune dysregulation, a hallmark of IBD, plays a pivotal role. Aberrant T-cell responses and dysregulated cytokine production can contribute to systemic inflammation and tissue damage. Autoantibodies targeting extraintestinal organs, such as the skin, joints, eyes, and liver, have also been identified in some patients. Additionally, the release of inflammatory mediators, including cytokines and chemokines, can promote inflammation and tissue injury in distant sites. Genetic predisposition may further influence susceptibility to EIMs, with certain human leukocyte antigen (HLA) alleles and other genetic variants associated with increased risk.

The spectrum of EIMs is broad, encompassing a wide range of organ systems. Skin manifestations, including erythema nodosum, pyoderma gangrenosum, and aphthous ulcers, are among the most common. Joint involvement, such as arthritis and spondylitis, can significantly impair quality of life. Ocular manifestations, including iritis and uveitis, can lead to vision loss if not promptly treated. Hepatobiliary involvement, particularly primary sclerosing cholangitis (PSC), is a serious complication with potential long-term consequences. Other EIMs may affect the lungs, cardiovascular system, and nervous system. The presence of EIMs can impact treatment decisions and overall disease management.[1-3]

OCULAR MANIFESTATIONS

Uveitis

The management of uveitis in patients with IBD is influenced by the activity status of their intestinal disease. In patients with inactive intestinal disease, topical and systemic corticosteroids or infliximab may be considered first-line therapies. For patients with active intestinal disease, systemic corticosteroids and biologic agents, such as infliximab, adalimumab, or ustekinumab, may be preferred due to their potential to simultaneously control both uveitis and intestinal inflammation. The choice of biologic agent should be individualized based on patient factors, disease severity, and response to previous therapies.[4]

Scleritis

The management of scleritis in patients with IBD depends on the severity of the ocular involvement and the activity of the underlying IBD. For patients with scleritis and inactive IBD, nonsteroidal anti-inflammatory drugs (NSAIDs), topical corticosteroids, or systemic corticosteroids may be considered. These options offer effective control for less severe scleritis. However, in patients with scleritis and active IBD, immunomodula-

tory therapy (IMM), anti-TNF agents, or ustekinumab are often preferred. These medications can simultaneously address both the ocular inflammation and active IBD. The specific choice of therapy should be tailored to the individual patient based on disease severity, response to previous treatments, and potential drug interactions.[4]

Episcleritis
Episcleritis typically responds well to topical NSAIDs. This approach minimizes systemic exposure to medications while providing symptomatic relief.[4]

HEPATOBILIARY MANIFESTATIONS

Primary Sclerosing Cholangitis
Anti-TNF agents like infliximab and adalimumab, vedolizumab, or ustekinumab are often preferred treatment options for PSC in IBD patients.[4]

Autoimmune Hepatitis
Treatment for AIH in IBD patients depends on whether remission needs to be induced or maintained. Corticosteroids are typically the first-line therapy for inducing remission of both IBD and AIH. Thiopurines are the preferred first-line therapy for maintaining remission in both IBD and AIH. However, infliximab or ustekinumab may also be effective options, particularly if thiopurines are not tolerated or fail to control the disease.[5] A very recent study has demonstrated that infliximab may be an effective and safe therapy in autoimmune hepatitis treatment.[6]

PSC-AIH Overlap
In cases where both PSC and AIH are present, a combination of corticosteroids and/or immunosuppressants might be necessary to manage the overlapping inflammatory processes affecting the liver and bile ducts.[5]

MUSCULOSKELETAL MANIFESTATIONS

Axial Spondyloarthritis
Axial spondyloarthritis (AS) is the most common form of musculoskeletal manifestation in IBD, characterized by inflammation of the sacroiliac joints and spine. Treatment for AS in IBD patients typically involves anti-tumor necrosis factor (TNF) agents, such as adalimumab and infliximab.[7] Upadacitinib and secukinumab may also be considered. Vedolizumab and ustekinumab are not recommended for AS in IBD patients.[8] Etanercept, a TNF inhibitor commonly used for AS, should be avoided in IBD patients due to the risk of paradoxical gastrointestinal inflammation.[7]

Peripheral Spondyloarthritis
Peripheral spondyloarthritis involves inflammation of peripheral joints, such as the hands, wrists, ankles, and feet. Treatment for peripheral spondyloarthritis in IBD patients typically includes anti-TNF agents, similar to AS.[4] Additionally, ustekinumab, upadacitinib, methotrexate, and sulfasalazine may be used for peripheral spondyloarthritis in IBD.4 Vedolizumab is not recommended for this manifestation.[4]

The use of NSAIDs for pain management in IBD patients is controversial due to the potential risk of exacerbating intestinal inflammation. If NSAIDs are deemed necessary, they should be used for short durations (less than 15 days) and with caution.

MUCOCUTANEOUS MANIFESTATIONS

Pyoderma Gangrenosum
Pyoderma gangrenosum (PG) is a severe ulcerative skin lesion characterized by a painful, rapidly expanding area of necrosis. Treatment for PG in IBD patients typically involves anti-TNF agents, particularly infliximab.[4] Systemic steroids, ustekinumab, tofacitinib, cyclosporine, and metronidazole may also be considered. Topical steroids and topical calcineurin inhibitors may be used as adjunctive therapy.

MAIN POINTS

- Extraintestinal manifestations (EIMs) are common in inflammatory bowel disease (IBD) and can significantly impact treatment.
- The management of EIMs depends on the specific manifestation and the activity of the underlying IBD.
- Ocular manifestations, hepatobiliary manifestations, musculoskeletal manifestations, and mucocutaneous manifestations are all common EIMs in IBD.
- Anti-TNF agents, systemic corticosteroids, and other medications are often used to treat EIMs in IBD.
- A multidisciplinary approach involving gastroenterology, rheumatology, dermatology, and ophthalmology is often recommended for the management of EIMs in IBD.

Erythema Nodosum
Erythema nodosum (EN) is characterized by tender, red, subcutaneous nodules. Treatment for EN in IBD patients typically involves anti-TNF agents, ustekinumab, or vedolizumab.4 If lesions are very painful, short-term oral corticosteroids and hydroxychloroquine may be considered.

Sweet's Syndrome
Sweet's syndrome (SS) is a rare inflammatory disorder characterized by fever, neutrophilic leukocytosis, and painful erythematous skin lesions. Treatment for SS in IBD patients typically involves anti-TNF agents, IMM, systemic corticosteroids, and topical corticosteroids.[4]

Oral Lesions
Oral lesions in IBD can manifest in various forms, including aphthous ulcers and angular cheilitis. Treatment for oral lesions in IBD patients typically involves anti-TNF agents, systemic corticosteroids, and topical corticosteroids.[4]

Treatment Selection for Extraintestinal Manifestations: General Approach

- Anti-TNF agents are contraindicated in patients with IBD and concurrent multiple sclerosis or other central demyelinating pathologies.[4]
- IBD is rarely associated with peripheral neuropathy. In the presence of peripheral neuropathy, consider complications associated with metronidazole use, nutritional deficiencies, and metabolic causes.[9]
- Anti-TNF agents should be the first-line treatment for axial spondyloarthritis.
- For the treatment of extraintestinal manifestations, a multidisciplinary approach involving gastroenterology, rheumatology, dermatology, and ophthalmology is recommended, with joint drug/dosage selection if possible.

Table 1 summarizes the effectiveness of biological agents in various EIMs across different types of IBD, highlighting the specific agents that can be considered for each EIM and IBD type.

Table 1. Effectiveness of biological agents in various extraintestinal manifestations

Medication	EIM (Preferred Choice)	IBD
Infliximab	Excluding PSC	CD+UC
Adalimumab	Excluding PSC	CD+UC
Ustekinumab	Excluding AxSpa	CD+UC
Tofacitinib	Axial and peripheral spondyloarthritis	UC
Vedolizumab	Excluding axial and peripheral spondyloarthritis	CD+UC
Certolizumab pegol	Excluding PSC	CD

EIM: extraintestinal manifestations, IBD: inflammatory bowel disease, PSC: primary sclerosing cholangitis, AxSpa: axial spondyloarthritis, CD: Crohn's disease, UC: ulcerative colitis

CONCLUSION

EIMs are a common complication of IBD and can significantly impact disease management. The choice of treatment for EIMs depends on the specific manifestation, disease severity, and activity of the underlying IBD. A multidisciplinary approach involving gastroenterology, rheumatology, dermatology, and ophthalmology is often recommended to ensure optimal management. By addressing both the intestinal inflammation and EIMs, healthcare providers can improve the overall quality of life for patients with IBD.

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REFERENCES

1. Kayar Y, Dertli R, Konür Ş, et al. Mucocutaneous Manifestations and Associated Factors in Patients with Crohn's Disease. *Turk J Gastroenterol*. 2022;33(11):945-954. [CrossRef]
2. Kilic Y, Kamal S, Jaffar F, Sriranganathan D, Quraishi MN, Segal JP. Prevalence of Extraintestinal Manifestations in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis*. 2024;30(2):230-239. [CrossRef]
3. Turkcapar N, Toruner M, Soykan I, et al. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. *Rheumatol Int*. 2006;26(7):663-668. [CrossRef]
4. Gordon H, Burisch J, Ellul P, et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis*. 2024;18(1):1-37. [CrossRef]
5. Lohse AW, Sebode M, Jørgensen MH, et al.; European Reference Network on Hepatological Diseases (ERN RARE-LIVER); International Autoimmune Hepatitis Group (IAIHG). Second-line and third-line therapy for autoimmune hepatitis: A position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. *J Hepatol*. 2020;73(6):1496-1506. [CrossRef]
6. Efe C, Lytvyak E, Eşkazan T, et al. Efficacy and safety of infliximab in patients with autoimmune hepatitis. *Hepatology*. Published on Sep 6, 2024. doi: 10.1097/HEP.0000000000001089. [CrossRef]
7. Kaufman I, Caspi D, Yeshurun D, Dotan I, Yaron M, Elkayam O. The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int*. 2005;25(6):406-410. [CrossRef]
8. Narula N, Aruljothy A, Wong ECL, et al. The impact of ustekinumab on extraintestinal manifestations of Crohn's disease: A post hoc analysis of the UNITI studies. *United European Gastroenterol J*. 2021;9(5):581-589. [CrossRef]
9. Goolsby TA, Jakeman B, Gaynes RP. Clinical relevance of metronidazole and peripheral neuropathy: a systematic review of the literature. *Int J Antimicrob Agents*. 2018;51(3):319-325. [CrossRef]