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REVIEW

Indeterminate Colitis – Update on Treatment Options

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Abstract: Indeterminate colitis (IC) is described in approximately 5–15% of patients with inflammatory bowel disease (IBD). It usually reflects a difficulty or lack of clarity in distinguishing between ulcerative colitis (UC) and Crohn's disease (CD) on biopsy or colectomy specimens. The diagnostic difficulty may explain the variability in the reported prevalence and incidence of IC. Clinically, most IC patients tend to evolve over time to a definite diagnosis of either UC or CD. IC has also been interchangeably described as inflammatory bowel disease unclassified (IBDU). This review offers an overview of the available limited literature on the conventional medical and surgical treatments for IC. In contrast to the numerous studies on the medical management of UC and CD, there are very few data from dedicated controlled trials on the treatment of IC. The natural evolution of IC more closely mimics UC. Regarding medical options for treatment, most patients diagnosed with IC are treated similarly to UC, and treatment choices are based on disease severity. Others are managed similarly to CD if there are features suggestive of CD, including fissures, skin tags, or rectal sparing. In medically refractory IC, surgical treatment options are limited and include total proctocolectomy (TPC) and ileal pouch–anal anastomosis (IPAA), with its associated risk factors and complications. Post-surgical complications and pouch failure rates were historically thought to be more common in IC patients, but recent meta-analyses reveal similar rates between UC and IC patients. Future therapies in IBD are focused on known mechanisms in the disease pathways of UC and CD. Owing to the lack of IC-specific studies, clinicians have traditionally and historically extrapolated the data to IC patients based on their symptomatology, clinical course, and endoscopic findings.

Keywords: indeterminate colitis, medical treatment, ulcerative colitis, Crohn's disease, total proctocolectomy, ileal pouch–anal anastomosis

Introduction

Inflammatory bowel disease (IBD) consists of a spectrum of immune-mediated bowel diseases that usually manifest in genetically predisposed individuals. Although primarily a luminal bowel disease with two defined ends of the spectrum – Crohn's disease (CD) and ulcerative colitis (UC) – there are multiple extraintestinal manifestations (EIMs) and a variant described as indeterminate colitis (IC). IC has also been referred to as inflammatory bowel disease unclassified (IBDU).

In this review, we use the term IC for consistency to refer to IC/IBDU.

The distinction between CD and UC is important and could have significant implications on the choice, type, and timing of disease-related surgery, disease course, prognosis, and medical treatment.[1] UC is characterized by superficial inflammation involving the rectum and extending proximally in a variable, diffuse, and typically

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continuous distribution. CD is characterized by transmural inflammation in any part of the gastrointestinal tract with intervening normal areas, and is typically rectal sparing. IC may have characteristics of both CD and UC, often with eventual differentiation over the course of time. A few older studies have examined the proportion of patients evolving from IC to either CD or UC. In the study by Meucci et al, 80% of IC patients eventually acquired a definitive diagnosis of UC or CD, within 8 years of diagnosis.[2]

Indeterminate colitis (IC) was proposed as a provisional classification prior to establishing a definitive diagnosis of either CD or UC, and represents a subtype of IBD involving mucosal inflammation with clinical and pathological features that are not easily distinguished.[3,4]

The term inflammatory bowel disease unclassified (IBDU) has been used interchangeably with IC, specifically defined as IBD with no definitive features of CD or UC. It was introduced by Kent et al in instances where there were inadequate clinical data or histopathological examination showing some features of CD and other changes indistinguishable from UC.[5] In 2005, the International Classification of Diseases, 10th revision (ICD-10) included IC as a diagnosis, separate from CD and UC. In the clinical setting, it is not uncommon to have patients initially labeled as having IC eventually evolve to UC or CD.

This review article provides a comprehensive review of IC, with a primary focus on its medical and surgical treatment. The available data are predominantly from studies in adult patients, which focused on patients with UC and CD with relatively small cohorts of IC patients included in the trials. We opted to include data from the occasional references in the pediatric literature owing to limited studies on IC in adult cohorts. In instances where we reference the pediatric literature, we offer our thoughts and discuss limitations on generalizability of the data. In addition, we briefly discuss the management of complications associated with IC, surgical management and its complications, and future therapeutic options.

Our thoughts on each section are highlighted at the end of the section.

Epidemiology, Diagnosis, and Clinical Features of Indeterminate Colitis

The prevalence rate of IC is estimated to be 22/100,000, and it has a higher incidence in females and Caucasian patients.[6] Several previous studies have shown that a diagnosis of IC is present in 5–15% of IBD cases.[1,3] However, the diagnosis can be highly variable among institutions and individual pathologists owing to diagnostic difficulties.[7,8] The frequency of establishing a diagnosis is dependent on the awareness of the broad spectrum of pathology seen in UC and CD. The classic endoscopic and histological features of UC or CD do not always conform to the traditional findings, which can lead to the diagnosis of IC.[9] The location and distribution of the disease are important in differentiating UC from CD. Sequential biopsy changes in the mucosa of UC can evolve with time, leading to variation in the extent of involvement over time and a lack of an endoscopic–histological correlation. In quiescent disease, only minimal histological changes are found, making a histological differentiation of CD and UC difficult. Backwash ileitis can also present with a mild degree of inflammation in the distal ileum.[9] Significant inflammation in such settings in the terminal ileum may raise the possibility of a diagnosis of CD. There also appears to be a lack of consistency and clarity among pathologists regarding the definition of IC. A previous study evaluated the biopsy results of pathologists from 24 medical centers on colonic specimens from IBD patients, followed by an experienced IBD pathologist's review. The expert review resulted in a changed diagnosis in 45% of the specimens.[10] Common causes for uncertainty in IBD pathology are fulminant colitis, insufficient endoscopic specimens, and failure to incorporate and utilize the major diagnostic features for CD and UC.[11]

Compared to UC, patients with IC have a younger age of onset and have more extensive and severe disease. The male to female ratio is usually close to 1. IC patients tend to use immunosuppressive medications more frequently, and have a higher risk of colorectal cancer, colectomy, and pouch failure compared to UC patients.[12] In addition, a family history of IBD is more common in IC compared to both UC and CD. Associated EIMs are similar and equally common in IC patients compared to UC and CD.[13]

It is important for clinicians to provide a relevant and concise history to pathologists in patients with suspected IC to help to establish a diagnosis. If needed and clinically relevant, a second opinion from an expert gastrointestinal pathologist should be sought.

Medical Treatment of Indeterminate Colitis

There is insufficient evidence on specific medical management of IC owing to a lack of large randomized prospective

treatment trials. This may also be partly due to the uncertain diagnosis and relatively small numbers of patients. Thus, patients with IC are typically treated similarly to UC patients based on the clinical disease severity, as well as the extent and severity of endoscopic and histological findings.[12] Some clinical trials of adult patients with IBD have included small numbers of patients with IC, but have not specifically addressed treatment response in IC patients as a subgroup. The spectrum of conventional treatments previously studied includes corticosteroids, thiopurines (azathioprine or mercaptopurine), aminosalicylates (eg, 5-aminosalicylic acid [5-ASA]), calcineurin inhibitors, biologics, and small molecules.

Conventional treatments and advances in the treatment paradigm of IC are discussed in the next sections and are summarized in Table 1.

The discussion includes the use of these medications in UC and CD as a segue into their use in IC. In each of the sections on treatment options, we review and summarize the available literature on the use of each agent across the spectrum of IBD and opine on the specific use in IC.

5-Aminosalicylic Acid Preparations

Aminosalicylates such as 5-ASA remain the first line therapy for both induction and maintenance of mild to moderate UC, but have not been shown to be particularly effective in the management of CD. The exception is sulfasalazine, which is superior to placebo in colonic CD.

The proposed mechanisms of action of aminosalicylates include increased expression of peroxisome proliferator-activated receptors in the gastrointestinal epithelial cells, which results in anti-inflammatory properties. They also decrease colonic inflammation by inhibiting the cyclo-oxygenase enzymes.[14] Both oral and rectal 5-ASA therapies are effective in inducing and maintaining remission in UC.[15] Sulfasalazine was the first developed aminosalicylate and was shown to be highly effective for the treatment of UC, with some efficacy in colonic CD. However, it is not well tolerated, which was a restrictive factor for optimizing dosage and led to the development of newer formulations.[16] There is insufficient evidence regarding differences in effectiveness between the different oral 5-ASA formulations.[17] In patients with mild to moderate UC, low- and standard-dose mesalamine has been shown to be effective for the induction and maintenance of remission.[18] A meta-analysis of 15 studies indicated that the use of mesalamine and probiotics together had improved clinical efficacy in patients with UC.[19] The magnitude of benefit was small when using high-dose mesalamine compared with standard dosage, and it was associated with higher costs.[18]

Based on these studies, 5-ASAs were extended to treat patients with mild IC, especially with features more suggestive of UC. Therapy usually includes 5-ASA suppositories for proctitis and proctosigmoiditis. Adequate doses of 5-ASA or sulfasalazine (3.6–4.8 g/day for 5-ASA and 4–6 g/day for sulfasalazine) were used for moderately active disease.[20]

It is worth noting that there are insufficient dedicated trial data to support the efficacy of these medications in IC. However, in clinical practice, 5-ASAs have been used in IC, ostensibly based on the extrapolation of data from trials in UC and CD.

Table 1 Different Classes of Medical Treatment for Indeterminate Colitis

Therapy	Strength of Evidence	First Line: Yes/No	Risk of Side Effects: Low, Intermediate, High	Disease Severity
Anti-TNF-alpha agents	Inadequate	No	Intermediate	Severe and refractory
Thiopurines: azathioprine/6-MP	Inadequate	No	Intermediate	Moderate
Steroids	Moderate	No	High	Moderate to severe
Vedolizumab	Inadequate	Unknown	Low	Unknown
Ustekinumab	Inadequate	Unknown	Low	Unknown
Mesalamines	Moderate	Yes	Low	Mild

Notes: We reviewed all available literature using the following databases: PubMed, Medscape, and UpToDate. Owing to the scarce data, IC has been looked at as a subgroup in larger IBD studies.

Corticosteroids

Steroids are effective in both luminal UC and CD for inducing remission. Budesonide is most commonly used in patients with CD because of its activity in the distal ileum and right colon.[21] Other steroids, including hydrocortisone and prednisolone, are commonly used and were previously the mainstay of IBD treatment. However, steroids have no role in maintaining remission in either UC or CD.[22] Patients are usually classified as "steroid responsive", "steroid dependent", or "steroid resistant". Long-term steroid use is associated with significant toxicities, including weight gain, increased risk of diabetes mellitus, adrenal suppression, bone loss, eye disease, and hypertension. These side effects, in combination with the known lack of efficacy for steroids as maintenance therapy in IBD, have resulted in the development and more frequent use of immunomodulatory therapies.[22] One study showed that an early response to intravenous steroids and maintenance therapy with biologics was associated with a lower rate of relapse in severe UC.[23]

The role of steroids is limited to controlling symptoms in flares in IBD, as a bridge to more definitive therapy, or the induction of remission. Their use has been extended similarly to include patients diagnosed with IC.

Thiopurines

Thiopurines have been shown to maintain remission in both UC and CD.[21] Previous studies have investigated the use of thiopurine independent of concurrent anti-tumor necrosis factor (anti-TNF) therapy.[24] The available data call into question the overall benefits of thiopurine monotherapy in patients with IBD, especially when balanced against the known risks, which include lymphomas. There is some benefit in patients with perianal disease. Both azathioprine (AZA) and 6-mercaptopurine (6-MP) have been used in moderate to severe IBD as monotherapy or as part of combination therapy in patients with steroid-dependent disease.[21] They can cause myelosuppression, especially in patients with low levels of thiopurine methyltransferase (TPMT) enzyme activity. It is standard clinical practice to check the TPMT levels in patients with IBD contemplating thiopurine therapy. Pancreatitis is one of the contraindications for continued use of these agents.[21] There is a slight increase in the risk of development of non-Hodgkin's lymphoma and non-melanoma skin cancer.[17]

In our opinion, these side effects and the scanty available literature limit the utility of thiopurines as monotherapy in patients with IC. Furthermore, there are other available therapies with more data on their efficacy in IC patients.

Methotrexate

Methotrexate (MTX) is a folate analog which interferes with DNA synthesis and has anti-inflammatory effects. It has been used in both UC and CD.[14] McDonald et al conducted a systemic review of large randomized trials, which suggested that MTX provided a benefit for induction of remission and complete withdrawal from steroids in refractory CD.[25] Although several retrospective studies have shown favorable effects of MTX in UC,[26,27] two randomized controlled trials did not show any difference in either induction or maintenance.[28,29] Overall, based on the meta-analysis and randomized studies, MTX monotherapy is not recommended for induction therapy.[30] The use of MTX in IC has been studied in the pediatric population. Assa et al conducted a retrospective study which showed that IBDU patients had similar outcomes to CD patients at final follow-up in terms of the efficacy, tolerance, and safety of MTX.[31] MTX was also recommended for use in children with IC who are intolerant or refractory to AZA/6-MP. Hepatotoxicity, which presents with elevated aminotransferase levels and significant risk of teratogenicity in pregnancy, remains a concern associated with MTX. Somewhat reassuringly, liver fibrosis is uncommon.[32]

To the best of our knowledge, there are no convincing data on the use of MTX as monotherapy in IC.

Calcineurin Inhibitors

Navazo et al showed that oral microemulsion cyclosporine was an effective drug in the initial management of patients with UC and IC flare unresponsive to steroids.[33] Cyclosporine has been used to treat both moderate and severe UC. One small randomized placebo-controlled study reported efficacy in using cyclosporine in steroid-refractory UC in hospitalized patients.[34] Another randomized trial from Japan showed higher rates of mucosal healing with tacrolimus but low clinical remission rates.[35] More recently, clinicians have favored using infliximab as rescue therapy in hospitalized patients with acute severe UC, perhaps because of concerns over the narrow therapeutic window for cyclosporine.[36]

The narrow therapeutic window for cyclosporine, including potential renal toxicity, may have contributed

to infliximab being favored in severely active UC and refractory IC as well.

Vedolizumab

Vedolizumab is a second generation humanized anti-adhesion medication that blocks the interaction between $\alpha_4\beta_7$-integrin and MadCAM-1.[37] The GEMINI trials I and II were randomized, placebo-controlled studies that compared vedolizumab to placebo in patients with UC and CD, respectively.

In GEMINI I, UC patients were randomized to either placebo or vedolizumab at weeks 0 and 2. At week 6, the response rates were 47.1% and 25.5% among patients in the vedolizumab and placebo groups, respectively ($p<0.001$). The clinical remission rates were 16.9% in the active group and 5.4% in the control group. There was also a significant difference in mucosal healing between the active and control placebo groups (40.9% vs 24.8%). Responders following induction were re-randomized to receive vedolizumab every 8 weeks (Q8W) or every 4 weeks (Q4W), or placebo, and followed up to week 52. For the maintenance phase of the trial, the clinical remission rates at week 52 were 41.8% and 44.8% for patients assigned to vedolizumab Q8W and Q4W, respectively, compared with 15.9% for placebo patients. Results from the maintenance therapy showed that durable clinical response, durable clinical remission, mucosal healing, and glucocorticoid-free remission at week 52 were all higher among patients assigned to vedolizumab regimens compared to the placebo group.[38]

In GEMINI II, patients with active CD were randomized to either vedolizumab or placebo at weeks 0 and 2. During the induction phase, clinical remission rates were 14.5% and 6.8% for the vedolizumab and placebo groups, respectively, at week 6 ($p=0.02$). Responders from the induction phase were re-randomized to receive vedolizumab Q8W or Q4W, or placebo, for the maintenance phase of the trial. At week 52, the clinical remission rates were 39%, 36.4%, and 21.6% for patients who received vedolizumab Q8W and Q4W, and the placebo group, respectively.[39]

The VISIBLE I trial compared the efficacy of subcutaneous/intravenous vedolizumab to a placebo group. The results showed statistical significance, with clinical remission following both subcutaneous and intravenous infusions.[40] Another trial compared vedolizumab to adalimumab, and showed higher rates of endoscopic improvement (39.7% vs 27.7%), and clinical (31.3% vs 22.5%) and histopathological remission (10.4% vs 3.1%) in patients who received vedolizumab at week 52.[41] It is worth noting that none of these trials reported an increase in the rate of infections. However, there was a mild increase in the risk of infusion reactions and malignancy in less than 5% of the patients.[38,39,41]

To date and to the best of our knowledge, there have been no studies specifically evaluating the use of vedolizumab exclusively in patients with IC. Their use in patients in IC is based on extrapolated data from studies on patients with UC and CD.

Ustekinumab

Ustekinumab is a monoclonal immunoglobulin G (IgG) antibody that targets the p40 subunit of the inflammatory cytokines interleukin-12 (IL-12) and IL-23.[37] Two identical randomized placebo-controlled trials evaluated the efficacy of ustekinumab in moderate to severe CD patients: UNITI-1 and UNITI-2. Patients who either had a primary or secondary non-response to TNF or had adverse effects were included in the UNITI-1 trial, while patients who either failed or had severe side effects from conventional treatment but were largely anti-TNF therapy naïve were included in the UNITI-2 trial. In both trials, patients received one of two doses of ustekinumab or placebo. Both trials showed higher clinical response rates at week 6 with both doses of ustekinumab compared to the placebo group. Patients who responded were included in the IM-UNITI trial for maintenance therapy with ustekinumab for either Q8W or Q12W. In both groups, the clinical remission rates were 53.1% and 48.8% in patients who received ustekinumab Q8W and Q12W, respectively, and 35.9% in the placebo group ($p=0.04$).[42]

The UNIFI trial evaluated the efficacy of ustekinumab as 8-week induction and 44-week maintenance therapy in patients with moderate to severe UC. The rate of clinical remission was higher among patients who received ustekinumab compared to the placebo group (15.5% vs 5.3%, $p<0.001$). Patients who responded in the induction phase underwent second randomization and received maintenance therapy with ustekinumab Q12W or Q8W, or placebo. The clinical remission rate at week 44 was significantly higher among patients who received 90 mg subcutaneous ustekinumab Q12W (38.4%) and ustekinumab Q8W (43.8%) compared with the placebo group (24.0%). The UNIFI trial showed that there were significant benefits in clinical remission, endoscopic improvement, and reduction in fecal calprotectin in patients with

UC who received ustekinumab.[43] Another study also evaluated the role of ustekinumab as a rescue treatment option for refractory moderate to severe UC.[44]

Although these studies indicate the efficacy and durability of response of ustekinumab in both UC and CD patients with areassuring safety profile, there are inadequate data available on the efficacy of ustekinumab in IC. By extension of the data in UC and CD, we opine that it could be offered as atherapeutic option to the appropriate patient after discussion as part of shared decision making.

Treatment of Refractory Indeterminate Colitis

Infliximab

Infliximab, a chimeric monoclonal IgG_1 antibody directed against human TNF-alpha, has been explored as a potential therapy for medically refractory IC. Papadakis et al evaluated infliximab in a cohort of 20 patients with IC who had steroid-resistant or steroid-dependent colitis. All patients had failed 5-ASA, 14 were refractory to thiopurines, and three had failed cyclosporine therapy. Fourteen patients (70%) showed a complete clinical response, defined as the cessation of colitis-related symptoms (abdominal cramping, diarrhea, and bleeding), two patients (10%) showed a partial response, defined by a reduction in the same symptoms, while four (20%) showed no response.[45] Herrlinger et al evaluated infliximab salvage therapy in 24 patients with either steroid-refractory or steroid-dependent disease who had failed induction with tacrolimus treatment. They noted that six of 24 tacrolimus-resistant patients (17%) achieved clinical remission after infliximab infusion, while an additional four (17%) had an initial response but ultimately required colectomy. Furthermore, 14 of 24 (58%) had no response and required colectomy.[46]

Based on the results of these few, small studies, the utility of infliximab in medically refractory IC is inconclusive but could be considered after weighing the risks and benefits of treatment versus surgical intervention.

Total Proctocolectomy and Ileal Pouch–Anal Anastomosis

Total proctocolectomy (TPC) and ileal pouch–anal anastomosis (IPAA), first reported in 1933, is now part of the spectrum of standard surgical treatment of UC patients who are acutely non-responsive to medical therapy, chronically refractory to medical treatment, or steroid dependent with adverse side effects, or in whom neoplastic transformation has occurred. The study by Yu et al suggests that approximately 15% of patients with IC undergoing TPC and IPAA are reclassified as CD on long-term follow-up. It is reasonable to infer that the natural history of IC tends to overlap more with UC.[47] In addition, the data lend some comfort in offering surgical intervention as a potential treatment option for IC patients. However, IC patients who undergo IPAA appear to be more likely than UC patients to have complications, including pouch failure.[9,47–50]

While the earliest studies evaluating pouch complications showed a significantly increased risk of pouch failure in IC compared to UC patients, more recent data contrast with these findings. One retrospective study noted that after surgical classification as UC or IC, there was no significant difference in the incidence of acute pouchitis, chronic pouchitis, or de novo CD between UC and IC groups.[51] Numerous other studies noted similar pouch failure rates between IC and UC.[52–54] Another retrospective case-matched analysis found that post-IPAA Crohn's disease rates were significantly increased in IC patients, although pouch failure rates were similar.[55] An additional analysis of IC patients showed high rates of pouchitis (57%) among both CD-like and non-CD disease-like behavior, with the CD-like patients requiring more medications (95% vs 18%), dilations (41% vs 0%), and pouch reoperations (32% vs 6%) compared to the non-CD group.[56] Of note, there was no difference in the Pouch Function Score between the two groups, which contrasts with the poor results previously published for patients with CD undergoing IPAA.[57,58]

To further clarify the outcomes of IPAA in patients with IC, a meta-analysis published in 2020, including 17 studies of IPAA outcomes, found a weighted mean pouch failure rate of 7.5% and weighted mean pouch complication rate of 67% in patients with IC. Patients with IC and UC had similar rates of pouch failure, pouchitis, anastomotic leak, stricture, and small bowel obstruction. IC patients had significantly higher odds of developing pouch fistula, pelvic sepsis, pelvic or cuff abscess, perineal complications, and an ultimate diagnosis of CD compared to their UC counterparts.[59]

Given the relatively suboptimal results in patients with IC who eventually evolve into CD, IBD serological tests have been explored to help differentiate between CD and UC. These tests include perinuclear anti-neutrophil cytoplasmic antibody (pANCA), anti-*Saccharomyces*

cerevisiae antibody (ASCA), anti-outer membrane porin C antibody (anti-OmpC), bacterial flagellin antibody (anti-cBIR-1), and *Pseudomonas fluorescens*-related protein antibody (anti-I2). It is worth noting that these tests have been studied in patients with defined UC and CD, and not extensively studied in IC patients. A prospective study of 97 IBD patients using pANCA and ASCA as potential differentiators revealed that 50% of patients with IC were negative for both markers, and the remaining patients tested positive on one or both tests; Furthermore, more CD patients showedASCA positive, ANCA negative whiles UC patients showed ASCA negative, ANCA positive..[60] ASCA and pANCA have shown sensitivity rates of only 40–60% when differentiating between UC and CD, limiting their utility in practice. Another observational study of IC patients over 12 months showed that a positive pANCA was associated with a likelihood ratio of 1.4 for a subsequent diagnosis of UC at 1 year, but neither ASCA nor anti-OmpC was associated with a subsequent diagnosis of CD.[61] Additional larger, multicenter prospective studies are needed to explore the predictive value of IBD serology in patients with IC evolving into UC or CD.

Based on the current limited evidence, it is reasonable to offer patients IPAA for IC as long as they are informed of the operative risks and potential pouch complications, including CD-like disease.

Management of Complications Associated with Indeterminate Colitis

IC symptoms include abdominal pain, abdominal cramping, persistent diarrhea, blood in the stool, rectal bleeding, weight loss, reduced appetite, fatigue, and changes in bowel patterns. Management involves a constellation of analgesics, medical therapy, and surgical options, depending on the response to treatment and disease severity. Providers typically refrain from using non-steroidal anti-inflammatory drugs (NSAIDs), because of their association with IBD flares, and opioids, because of challenges associated with long-term use. Other options include antidepressants, anticonvulsants, acetaminophen, and local therapy, depending on patient-specific factors.

Some complications arise from surgery, as in patients undergoing TPC with IPAA. A meta-analysis of 13 studies comparing outcomes of pouch surgery between patients with UC and IC found that UC patients developed complications of pouchitis (24.4%), small bowel obstruction (7.4%), anastomotic structure (4.9%), pouch fistula (2.7%), pelvic sepsis (2.5%), perineal complications (1.9%), pelvic or cuff abscess (1.4%), and an ultimate diagnosis of CD (0.67%). It also found that compared with UC patients, IC patients had higher odds of developing pouch fistula, pelvic sepsis, pelvic or cuff abscess, perineal complications, and an ultimate diagnosis of CD.[59]

Pouchitis is the most common complication following IPAA. Symptoms typically involve increased stool frequency, increased defecation urgency, pelvic pain, or bowel incontinence. Primary prevention of pouchitis typically involves avoidance of NSAIDs, given their higher association with chronic pouchitis.[62] Initial treatment usually consists of 2 weeks of ciprofloxacin, despite only a few studies exploring antibiotic efficacy, with other options including metronidazole or tinidazole.[63] Chronic pouchitis may develop in patients who are unresponsive to antibiotics or in whom they are ineffective. In those instances, considering other potential etiologies, including atypical infection and immune-mediated diseases, requiring the addition of 5-ASA, steroids, and vedolizumab or ustekinumab, is an alternative approach.[64,65] Probiotics have been examined in a few, small trials, which failed to show any significant benefit from probiotics alone, but they may provide an improvement in symptoms or remission in patients who had previously been treated with antibiotics.[66] Surgical management, including redo or takedown of the pouch, is considered in medication-refractory patients whose quality of life has been significantly affected by symptomatology.

Small bowel obstruction can be initially treated with nasogastric decompression (NGD). If NGD fails, then surgical management could be considered.

Anastomotic pouch strictures can result in bacterial overgrowth, pouch dilatation, defecatory challenges, and bowel obstruction. Management ranges from benign procedures of evaluation under anesthesia (EUA) and dilatation to endoscopic balloon/needle knife therapy and medical therapy, with the most severe treatment options including stricturoplasty, proximal diversion and stricture resection, or pouch excision.[67]

Fistula formation is a more common complication of CD but can still occur after IPAA. Fistulas may be pouch–vaginal, pouch–vesical, or pouch–anal fistulas. Pouch–vaginal fistulas can be treated conservatively with seton placement and fistula plugs, but owing to the poor success rates, surgical intervention is typically required. Pouch–vesical or pouch–anal fistulas can typically be treated with

serial EUA, abscess drainage, and sphincter-preserving surgery.[66] There is emerging evidence that stem cell therapy may be useful in the treatment of fistulas. A meta-analysis analyzing 29 studies found a higher rate of fistula healing with stem cell therapy compared to placebo, with higher healing rates in perianal and transsphincteric fistulas compared to rectovaginal fistulas.[68]

Based on the available data, similar approaches to the treatment of complications in patients with UC and CD can be applied to patients with IC in the appropriate clinical setting.

Extraintestinal Manifestations

IBD can involve multiple organ systems, including the joints, skin, biliary tract, and eyes in 25–40% of IBD patients.[69] These EIMs are more common in CD than UC, and in adults more so than children, but have not been well defined in IC.[70] Other EIMs and associated conditions include pyoderma gangrenosum, erythema, nodosum, Sweet syndrome, psoriasis, atopic dermatitis, hidradenitis suppurativa, axial and peripheral spondyloarthropathies, dactylitis, enthesitis, primary sclerosing cholangitis, uveitis, and episcleritis.[71] Two systematic reviews exploring the diagnosis and treatment of EIMs confirmed not only that anti-TNF agents were the primary treatment for EIMs, but also that they were effective in achieving a clinical response in over 50% of cases, except for primary sclerosing cholangitis.[72,73] Vedolizumab was not found to be efficacious in treating pre-existing EIMs but could have potential use for reducing the incidence of new EIMs. Minimal data exist for ustekinumab and tofacitinib.

There are also no clear guidelines available for the evaluation and follow-up for each EIM, and this should be studied further in patients with IC. Future large multicenter studies or registry-derived data are required.

Evaluation and Treatment of Associated Conditions, Age-Appropriate Screening, and Preventive Care

Infections and Vaccinations

IBD patients have an increased risk of infection not only due to their disease, but also due to the immunosuppressive therapies necessary for disease control. Therefore, age-appropriate vaccination should be discussed at the time of diagnosis. The risk of gastrointestinal infection is higher among IBD patients compared to control groups, with studies showing that enteric infections were responsible for 10.5% of all IBD relapses.[74,75] *Clostridium difficile* is the most common cause of infection and has been shown to increase the risk of colectomy, postoperative infectious complications, and mortality.[76,77] It is also important to check for cytomegalovirus (CMV) superinfection in moderate to severe colitis flares, specifically in those with corticosteroid-refractory disease or receiving immunomodulatory therapy.[78] A meta-analysis by Ford and Peyrin-Biroulet found that 0.9% of 4135 patients on anti-TNF therapy in randomized controlled trials developed an opportunistic infection, with a two-fold increased risk of infection with *Mycobacterium tuberculosis* (TB), herpes simplex and zoster, oral/esophageal candidiasis, CMV, Epstein–Barr virus (EBV), and *Nocardia*.[79]

In the absence of data specific to IC, age-appropriate vaccinations should remain a key aspect of treatment in all patients with IBD, including IC. In addition, testing and pretreatment screening for hepatitis B and C (HBV, HCV), human immunodeficiency virus (HIV), and TB infection is vital.

Osteoporosis and Osteopenia

Both CD and UC patients are at increased risk for bone disease. This is thought to be due to active inflammatory states resulting in increased bone resorption, calcium and vitamin D malabsorption/deficiency, as well as prolonged steroid use. Estimated rates of osteopenia and osteoporosis are reported as 35% and 15% of patients, respectively.[80–82] Bone density should be assessed prior to initiation of glucocorticoid therapy, as well as counseling for exercise and lifestyle modifications, including smoking cessation. Treatment with vitamin D and calcium should be initiated in appropriate clinical settings. Patients with osteopenia and significantly increased risk of fractures or prior fractures, as well as frank osteopenia, should be comanaged with endocrinology and/or rheumatology.

We recommend a similar approach in patients with IC.

Vascular Disease

IC patients are at a higher risk of cardiovascular disease given the nature of the systemic inflammation. The study by Paschou et al found a decrease in insulin levels and insulin resistance in non-obese, non-diabetic patients who received biological therapy.[83]

We recommend assessing and controlling factors related to cardiovascular disease in all IBD patients.

Cancer Screening

Historically, IC patients have been excluded from population-based analyses of cancer risk calculations in IBD patients. UC patients have an elevated risk of colon cancer and should therefore begin screening colonoscopy 8 years after disease onset. In patients with associated primary sclerosing cholangitis, screening colonoscopies should begin at diagnosis and yearly thereafter.

In patients with IC, clinicians should consider a similar approach to UC patients described above, keeping in mindthat there are no strong data specific to the IC cohort..

Future Therapeutic Options

Patients with IC are managed similarly to those diagnosed with UC, including both medical regimens and surgery for those who are non-responsive to medication. Newer therapies showing some efficacy, including drugs targeting IL-12, IL-23, and the janus kinase/signal transducer and activator of transcription proteins (JAK/STAT) pathway, as well as sphingosine-1-phosphate receptor modulators (S1P), have been approved or are in development for the management of IBD.

IL-12 and IL-23, both of which contain a p40 subunit in their overall structure, have become therapeutic targets owing to their downstream effects on TNF and T1 cell differentiation/IL-17 secretion, respectively.[84] These include ustekinumab, as mentioned in an earlier subsection, and brazikumab. In a phase IIa study, brazikumab, which selectively inhibits IL-23, showed clinical improvement in CD patients who had failed anti-TNF therapy in 49% of 119 patients with moderate to severe CD.[85] Mirikizumab, guselkumab, and tildrakizumab are all currently being studied and may be useful for both UC and CD, pending further exploration.

The most well-known JAK/STAT therapy, tofacitinib, mainly targets JAK1/JAK3 and has shown to be effective in UC through the OCTAVE trials.[86,87] These trials were phase III, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in moderate to severe UC patients after failure with conventional/anti-TNF therapy, eventually showing effectiveness for induction and maintenance therapy compared to placebo. In the OCTAVE Induction 1 and 2 trials, the primary endpoint was remission at 8 weeks, while in the OCTAVE Sustain trials the primary endpoint was remission at 52 weeks. The most common reported side effects were nasopharyngitis, arthralgia, and headache, which seemed to occur at similar rates in both drug and control groups. Other more concerning adverse events noted included thrombosis, herpes infection, and dose-dependent dyslipidemia.

Indicators from ongoing trials with filgotinib and upadacitinib (JAK1 inhibitors) show favorable results regarding symptom improvement, clinical remission, and histological evaluation. Filgotinib was tested in the FITZROY study, a phase II, randomized, double-blind, placebo-controlled trial, which found clinical remission in patients with moderate to severe CD.[88] The primary endpoint of clinical remission was defined as a Crohn's Disease Activity Index (CDAI) of less than 150 at week 10. Although side effects were similar between the study and control groups, serious infections occurred in the treatment but not the control group. Filgotinib was also evaluated in SELECTION, a phase IIb/III, randomized, double-blind, placebo-controlled trial that found efficaciousness for the induction and maintenance of clinical remission in moderate to severe UC compared to placebo.[89] The primary endpoint was clinical remission by Mayo endoscopic criteria, rectal bleeding, and stool frequency scores at 10 and 58 weeks. Adverse events were similar between the treatment groups in all three studies and the control group, with infection leading all other events.

The U-ACCOMPLISH trial, a phase III, randomized, double-blind, placebo-controlled trial for upadacitinib, confirmed clinical, endoscopic, and histological improvement in moderate to severe UC patients, as shown in the U-ACHIEVE trial, but the data have yet to be published. The primary endpoint was clinical remission via the Adapted Mayo Score. The most common side effects were acne, increased blood creatinine phosphokinase, and anemia, but overall safety findings were consistent with previous studies of the drug. The CELEST trial, a phase II, randomized, double-blind, placebo-controlled trial for patients with moderate to severe CD with inadequate response to immunosuppressants or TNF-alpha inhibitors, found endoscopic, but not clinical remission.[39]

Sphingosine-1-phosphate receptor modulators are effective by inactivating lymphocytes before they are able to leave lymphoid tissue, preventing them from reaching their end-organ targets. The TOUCHSTONE study was a phase II, randomized, double-blind, placebo-controlled trial with ozanimod for moderate to severe UC, with a primary endpoint of clinical remission (Mayo Clinic Score ≤ 2) at 8 weeks. In this trial, ozanimod was more effective than placebo for induction of clinical remission, and it has been approved for clinical use in UC.[90]

Further advances in therapy will likely rely on the accuracy of diagnosis of IC, with possible identification of certain biomarkers that could predict subsets of patients and future disease behavior. Importantly, randomized controlled trials involving IC patients are needed to provide more definitive answers and guidance for effective therapeutic options. In the absence of any data, we cannot opine on the utility of any of the newer molecules in the treatment of IC.

Pediatric Population

IC is twice as common in pediatric populations compared to their adult counterparts, with as many as 10% of children receiving IC as an initial diagnosis.[91] Similarly to adults, rates of IC diagnosis decrease over time. As in adults, treatment of UC and CD has well-developed guidelines, but no guidelines exist for IC in pediatric populations. One retrospective, multicenter analysis analyzing 23 centers of pediatric IBD found that the most common first line treatment for active IC was mesalamine. Other treatments, including thiopurines, methotrexate, cyclosporine, and infliximab, were not clearly defined but were generally used based on clinical response to 5-ASA.[92]

Disclosure

The authors report no relevant conflicts of interest related to this review.

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