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THE ROLE OF UPFRONT SURGERY IN THE MANAGEMENT OF ILEAL CROHN'S DISEASE

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder characterized by transmural inflammation that can affect any part of the gastrointestinal tract. Among the various phenotypes of CD, involvement of the terminal ileum, known as ileal CD, poses unique challenges in management due to its potential for complications such as strictures, fistulas, and abscesses.[1] While medical therapy remains a cornerstone in the management of CD, the role of surgery, particularly upfront surgical intervention (early resection), has garnered increasing attention in recent years.[2]

The decision to pursue surgical intervention at the outset of disease management, rather than relying solely on medical therapy, is a subject of ongoing debate in the field. Upfront surgery (prior to advanced medical therapies) may offer benefits such as rapid resolution of symptoms, avoidance of long-term immunosuppressive therapy and prevention of disease progression. However, concerns regarding the postoperative morbidity and potential for recurrence associated with surgical intervention warrant careful consideration.[3]

Recent studies have provided valuable insights into the efficacy and safety of upfront surgery in ileal CD. The PREDICT study, conducted by Agrawal et al., demonstrated favourable outcomes with early surgical intervention in a cohort of patients with ileocecal CD, highlighting the potential for improved clinical outcomes and reduced healthcare utilization compared to medical management with anti-tumor necrosis factor (TNF) agents. More importantly, approximately half of patients did not need medical therapy after 5 years of follow-up, which demonstrates the durability of surgically-induced remission in early stage CD.[4] Additionally, the landmark LIRIC (Laparoscopic Ileocecal Resection versus Conventional Medical Management for Patients with Luminal Crohn's Disease) trial evaluated the role of laparoscopic ileocecal resection (LICR) versus

infliximab in patients with uncomplicated localized ileocecal CD, further informing the debate surrounding upfront surgery in this patient population.[5] The trial demonstrated that after 5 years of follow-up, 48% of patients using infliximab needed a surgical resection, implying that medical therapy does not prevent a surgical resection in all patients, but may delay surgery in many.[6]

In this narrative review, we aim to critically evaluate the existing literature on upfront surgery in ileal CD. Additionally, we seek to elucidate the optimal surgical management approach for patients with ileal CD and provide guidance for clinical decision-making in this challenging disease entity. Last, we discuss surgical approaches used in association with this strategy.

Rationale for Earlier Surgery in Terminal Ileum Crohn's Disease

While medical therapy remains a mainstay in the management of luminal CD, the limitations of pharmacological interventions, including the risk of adverse effects and the development of treatment refractoriness, underscore the importance of considering surgical intervention early in the disease course.[7] Currently, with optimal strategies using advanced therapies, mucosal healing is achieved in a limited proportion of patients. As an example, data from the CALM trial, using tight monitoring and early use of adalimumab, demonstrated that mucosal healing occurred in only 48% of patients.[8] As there is a lack of predictors of response to medical therapy, patient selection for advanced therapy or surgical resection occurs as a result of detailed discussion with patients around their objectives and expectations for their future disease course.

A compelling rationale for early surgical intervention in luminal terminal ileal CD lies in the potential for reducing disease-related morbidity and improving long-term outcomes. Kotze et al. conducted a retrospective cohort study evaluating postoperative morbidity in elective surgery for CD, highlighting a significantly lower rate of medical and surgical postoperative complications in patients with less than 5 years of disease duration.[9] Surgery after 5 years from diagnosis was associated with a higher risk of the need for a stoma (OR: 3.203; 95% CI: 1.011-10.151; P=0.048). Additionally, Avellaneda et al. reported favourable outcomes with earlier surgical intervention, demonstrating a reduction in the incidence of postoperative complications in patients with the luminal phenotype vs those with complicated disease, with fibrotic stenosis and penetrating complications.[10]

Potential advances and disadvantages of upfront surgery in ileal CD are detailed in **Table 1**. Earlier surgical intervention offers the advantage of addressing underlying pathology promptly, thereby mitigating the risk of disease progression and the development of irreversible complications such as stenosis or penetrating complications. Early surgery may prevent the need for repeated hospitalizations, invasive procedures and the long-term use of immunosuppressive medications, ultimately improving patient quality of life and reducing healthcare resource utilization.[11] Thus, the limited efficacy associated with optimized medical strategies, the reduced morbidity of surgery in the luminal phenotype, and the possibility of full disease control with no medications comprise the rationale of potential advantages of earlier surgical resection in localized terminal ileal luminal CD.

Early surgery in localized luminal ileal CD	
Advantages	**Disadvantages**
• Reset of inflammatory burden (no residual disease) • Durable remission • Possible avoidance of advanced therapies in the long term • Higher rates of minimally invasive procedures (laparoscopic, robotics) with low conversion rates • Lower direct and indirect costs	• Possibility of postoperative complications • Need for stomas when specific complications such as anastomotic leaks and obstruction occur • Body image and cosmesis

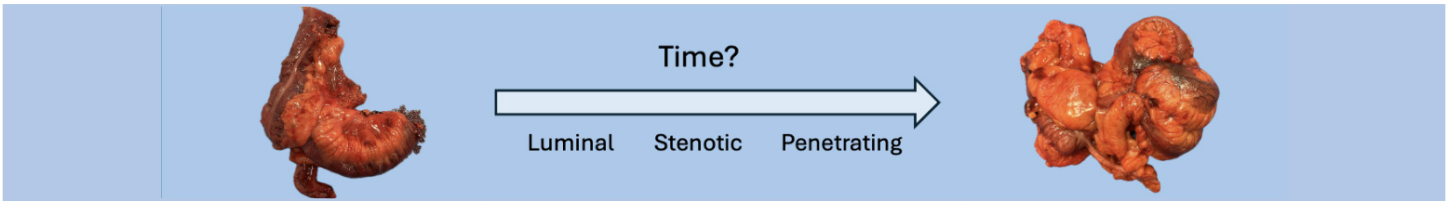
Table 1. Potential advantages and disadvantages of upfront surgery in luminal ileal CD; courtesy of Paulo Gustavo Kotze, MD.

Available Evidence in Favour of Earlier Surgery

The LIRIC trial, conducted by Ponsien et al., compared the efficacy of LICR with conventional medical management in patients with luminal CD.[5] The long-term evaluation of 134 (94%) of the 143 patients included in the LIRIC trial, of whom 69 were in the resection group and 65 were in the infliximab group, was described.[6] Median follow-up was 63.[5] months (IQR 39.0-94.5). In patients who underwent surgery, 18 (26%) of 69 patients were initiated on anti-TNF therapy and none required a second resection. A total of 29 (42%) patients in the resection group did not require additional CD-related medication, although 14 (48%) of these patients were given prophylactic immunomodulators. In the infliximab group, 31 (48%) of 65 patients had a CD-related resection, and the remaining 34 patients maintained, switched or escalated their anti-TNF therapy. These results position early laparoscopic resection as an effective and durable therapy in patients with limited ileal CD.

The PREDICT study, conducted by Agrawal et al., prospectively evaluated the outcomes of early surgical intervention vs anti-TNF agents as primary therapy in Danish patients with CD, after one year of diagnosis.[4] A total of 1279 patients were included. Of these, 45.4% underwent ileocolic resection and 54.6% received anti-TNFs. The composite outcome (defined as at least one of the following criteria: perianal CD, need for steroids, hospitalizations or re-resection) occurred in 273 individuals (incidence rate, 110/1000 person-years) in the surgery cohort and in 318 individuals (incidence rate, 202/1000 person-years) who used anti-TNFs. The risk of the composite outcome was 33% lower with surgery compared with anti-TNFs (adjusted hazard ratio, 0.67; 95% confidence interval, 0.54-0.83). Surgery was associated with a reduced risk of need for steroids and (additional) CD-related surgery. The proportion of individuals on no medical therapy 5 years after surgery was 49.7%, demonstrating the durable effect of surgery as primary therapy, with consistent disease control over time.

The SURGICROHN-LATAM consortium described postoperative morbidity after ileocecal resections comparing outcomes in patients who underwent earlier resection (luminal phenotype) with those with complicated disease (stenotic or penetrating phenotypes).[10] A total of 337 patients were included in the analysis, with 60 (17.80%) in the luminal phenotype. Patients with complicated disease had increased requirement of urgent surgery (26.71 vs 15%, P=0.056), longer operative time (164.25 vs 90.53 min, P< 0.01), lower rates of primary anastomosis (90.23 vs 100%, P=0.012), an increased incidence of overall postoperative complications (33.21 vs 16.67%, P=0.013), more re-operations (13.36 vs 3.33%, P=0.026), higher rates of major anastomotic leaks, and longer hospital stays. These findings demonstrate the reduced morbidity associated with surgery in luminal CD vs complicated disease, positioning surgery as a safer procedure if performed in expert hands before disease progression occurs. The increased complication rates in patients with delayed surgery are possibly associated with inadequate nutritional status, use of steroids, larger inflammatory masses, and intraoperative difficulties due to extensive disease. **Figure 1** describes in detail comparisons in different variables of upfront surgery with delayed procedures.



Upfront Surgey	Type of Approach	Delayed Surgey
Shorter	**Extent of procedures**	Longer
Lower	**Postoperative morbidity**	Higher
Higher	**Minimally invasive**	Lower
Lower	**Conversion rates**	Higher
Less likely	**Associated procedures**	More likely
Less likely	**Inflammatory masses**	More likely

Figure 1. Surgical characteristics of upfront (earlier) surgery vs delayed procedures in ileal CD; courtesy of Paulo Gustavo Kotze, MD.

Surgical Options in Upfront Surgery in Ileal Crohn's Disease

In the luminal phenotype, minimally invasive procedures with multiport laparoscopy, single-port or robotic platforms comprise the mainstay of the surgical approach.[12] The need for conversion to open surgery is reduced due to the preserved anatomy of the disease, in the absence of inflammatory masses or penetrating complications.

In most centres globally, multiport laparoscopy is the preferential method for ileocecal resections.[13] Typically, 4 ports are placed, followed by resection, releasing the terminal ileum, cecum, and proximal transverse colon from the retroperitoneal structures and omentum. The ileocolic vessels are ligated and resection can be accomplished. Anastomosis can be performed intra-corporeally (with endoscopic staplers and specimen withdrawal via a Pfannenstiel incision), or extra-corporeally (with small midline incisions to withdraw the specimen and perform the anastomosis with conventional linear staplers). Compared to conventional open surgery, laparoscopic procedures minimize surgical trauma, reduce postoperative pain, and accelerate recovery. Patients undergoing laparoscopic surgery experience shorter hospital stays and quicker return to normal activities, leading to improved patient satisfaction and quality of life. By avoiding large abdominal incisions and minimizing tissue manipulation, laparoscopy reduces the risk of wound complications, surgical site infections, and incisional hernias. Furthermore, the laparoscopic approach results in less intraoperative blood loss and lower rates of postoperative ileus, contributing to a smoother postoperative course and faster recovery.

Evidence supporting single-port surgery for ileocecal resection in CD continues to accumulate, demonstrating its feasibility, safety, and potential advantages over traditional multi-port laparoscopy.[14,15] Recent studies have shown that single-port laparoscopic surgery offers comparable surgical outcomes to multiport laparoscopy while providing additional benefits such as reduced postoperative pain, shorter hospital stays, and improved cosmetic results. Patients undergoing single-port resections require lower doses of analgesics compared to those undergoing multi-port laparoscopy, highlighting the potential for enhanced postoperative recovery with the use of single-port surgery. Furthermore, single-port surgery offers the advantage of a single, less conspicuous incision, resulting in improved cosmesis and patient satisfaction, which may be particularly relevant for younger patients or those with aesthetic concerns.

Robotic-assisted surgery has emerged as a promising option for ileocecal resections in CD, offering several potential advantages over traditional laparoscopic approaches. Studies investigating the use of robotic surgery, in CD have demonstrated its feasibility, safety and efficacy in achieving surgical goals.[15] Robotic platforms provide surgeons with enhanced dexterity, precision, and three-dimensional visualization, allowing for meticulous dissection and suturing in confined anatomical spaces. This can be particularly advantageous in complex cases of CD with dense adhesions, fistulas, or involvement of adjacent structures, where precise tissue manipulation is critical to minimize intraoperative complications and achieve optimal outcomes. Recent evidence suggests that robotic ileocecal resection in CD may lead to improved short-term outcomes compared to conventional laparoscopic techniques.[16] Studies have reported shorter operative times, reduced blood loss, and lower rates of conversion to open surgery with robotic-assisted approaches. Furthermore, robotic surgery offers the potential for faster postoperative recovery, shorter hospital stays, and decreased postoperative pain compared to traditional laparoscopy. These findings highlight the potential benefits of robotic-assisted surgery in optimizing perioperative outcomes and enhancing patient recovery following ileocecal resection for CD.

Personal Commentary on the Role of Upfront Surgery in Ileal Crohn's Disease

Burrill Crohn's seminal paper from 1932 included an initial case series of 14 patients, all of whom underwent ileocecal resections as part of disease treatment.[17] Currently, more than 90 years after this initial description, available data suggest that in localized terminal ileal CD, surgical resection still plays a significant role in multidisciplinary management.

Clearly, surgery performed in tertiary centres by experienced surgeons, with a minimally invasive approach, is safe and associated with reduced rates of postoperative complications. Therefore, it is important to at least discuss the surgical option with patients at the same level of advanced medical therapies, to highlight the potential advantages and disadvantages of each strategy. Still, the safety of medical therapies remains important in decision-making. Additionally, in modern everyday life where young individuals prefer to spend time working or enjoying themselves instead of going to infusion clinics, the practicality of surgery to potentially avoid medical therapy for some time may represent a preferred option for some patients. It is also extremely important to emphasize that despite the reduced risk of an anastomotic leak (approximately 3.5%), if that complication occurs a temporary ileostomy may be needed and patients' quality of life can be affected. Another point to be discussed in shared decision-making is that upfront surgery does not avoid the need for continuous tight monitoring with biomarkers, imaging, and endoscopic tests targeting early detection of recurrence, where medical therapy will be essential.

Therefore, in a discussion of the ideal multidisciplinary therapeutic strategy for luminal ileal CD, upfront surgery plays a solid role as a safe

and durable option, if performed by experienced inflammatory bowel disease (IBD) surgeons. The current challenge in clinical practice is that there are no validated biomarkers that can predict response to medical therapy. If one could precisely predict which patients have less likelihood of response to optimized medical therapy and direct them straight to upfront surgery, this could represent a more trustworthy algorithm to avoid medical undertreatment and surgical overtreatment. While a biomarker-driven strategy is still not available, individualized multidisciplinary discussions with clinicians including gastroenterologists, IBD surgeons, and patients with their families comprise the best approach to the treatment of luminal ileal CD at this point.

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UC=ulcerative colitis; CD=Crohn's disease.

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ACUTE SEVERE ULCERATIVE COLITIS: REVIEW OF MANAGEMENT AND EMERGING TREATMENTS

Key Takeaways

- ASUC has a considerable risk of colectomy and complications, therefore decisions about medical vs surgical treatment should be made early on during hospitalisation to minimize morbidity.
- Emerging data supports Janus kinase (JAK) inhibitors as a new treatment opportunity for ASUC.
- There is still lack of randomized controlled data to fully understand optimal timing and sequencing of advanced therapies in ASUC.

Introduction

Acute severe ulcerative colitis (ASUC) is a medical emergency, with an overall mortality rate of 1%.[1] Patients with ulcerative colitis (UC) have a 20–25% rate of severe exacerbation requiring hospitalization for urgent medical treatment and surgical consideration.[2-4] The rate of re-hospitalization for recurrent ASUC is 34.4%, and it typically occurs within 24 months of the index admission.[5] Treatment requires a patient-centred multidisciplinary approach that includes gastroenterology, colorectal surgery, and nutrition support, with the goal of minimizing disease complications, adverse events of treatment, and healthcare costs.[6] Clinicians and patients have an increasing number of treatment options and additional safety issues to consider. We review the current approach to management and summarize emerging data on the use of novel agents to treat ASUC.

Initial management:

ASUC is largely defined by the Truelove and Witts criteria (Table 1), requiring six or more bowel movements, and at least one marker of systemic

illness.[4] The number of positive markers correlates with the risk of colectomy.[7] Less commonly used criteria include the modified Mayo classification and the Montreal classification.[2] A recent study conducted by Adams et al. validated threshold values for C-reactive protein (CRP) ≥100 mg/L, albumin ≤25 g/L, and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) ≥4 as predictors of steroid non-response.[8] Patients with ASUC require hospital admission and a comprehensive evaluation to identify triggers, such as NSAID use and disease complications. The physical exam assesses nutritional status and screens for signs of an acute abdomen. The initial investigations include a complete blood count (CBC), extended electrolyte levels, a liver panel, albumin levels, CRP levels, and stool studies to identify coexisting infections, including *Clostridioides difficile (C. difficile)* enteric pathogens. An abdominal radiograph establishes baseline bowel dilation and detects free air from a perforation. Computed tomography should be ordered sparingly to minimize the cumulative radiation exposure in a predominantly young cohort. Within 72 hours, and ideally 24 hours, an unprepped flexible sigmoidoscopy is performed to assess the degree of mucosal inflammation and to obtain sufficient number of biopsies from severely effected areas for cytomegalovirus (CMV). Minimal insufflation is required to limit perforation risk and prevent worsening of symptoms. A pre-biologic work-up is initiated, including a TB skin test or interferon-gamma release assays, chest radiograph, and hepatitis B serologies.

Initial management involves fluid resuscitation and either a clear fluid diet or low-residue enteral diet. Enteral feeding is preferred; however, parental nutrition may be required in severely malnourished patients. To induce remission, patients receive methylprednisolone 60 mg/day in divided dosing; higher doses do not confer a lower colectomy rate.[2] Based on recent data, immediately implementing advanced therapy, potentially avoiding corticosteroids may be reasonable in patients with a high risk of corticosteroid failure.[8] An early surgical consultation is suggested to discuss colectomy as both first-line and rescue treatment.[9,10] Venous thromboembolism (VTE) prophylaxis is required given the substantial VTE risk compared to that of the general population.[2,9,10]

Response to treatment is evaluated daily with stool charting, a physical exam, CBC, and CRP levels. Any clinical worsening, including abdominal distention, warrants an urgent abdominal radiograph to evaluate for complications, including megacolon and perforation. A high level of clinical suspicion and close monitoring is required as corticosteroids may mask abdominal pain severity.

A special note on opiates:

Opiate use in hospitalized inflammatory bowel disease (IBD) patients does not improve pain scores and is associated with an increased risk of infections, bowel obstruction, perforation, and mortality.[11] Concerningly, opiate-naïve IBD patients are often prescribed similar doses to regular opiate users and are frequently discharged with new opioid prescriptions.[11] Best practices include analgesia with acetaminophen and opiate avoidance when possible. A pain service consultation is recommended if analgesia requirements escalate.

Response to corticosteroids

On day 3 of admission, patients are risk stratified using the Oxford criteria: those with more than 8 stools per day; or more than 3 stools per day and a CRP level of >45 mg/L are likely refractory to corticosteroids, and have an 85% colectomy rate.[3] One-third of patients are unresponsive to corticosteroids and require rescue medical therapy or surgery.[3] Predictors of a corticosteroid-refractory course include an albumin level of <30 g/L, a CRP level of >30 mg/L and endoscopic severity.[7] A recent validated risk prediction model, that incorporates CRP ≥100 mg/L (1 point), albumin ≤25 g/L (1 point) and UCEIS ≥4 (1 point) and UCEIS ≥7 (2 points) was accurate in predicting CS non-response.[8] Tools such as these may help with early identification of patients who are in need of rescue therapy.

Corticosteroid-responsive patients complete 3–5 days of methylprednisolone therapy before transitioning to an oral prednisone dose of 40–60 mg/day. Maintenance therapy is typically initiated within two weeks of discharge, along with a corticosteroid taper.[2] Although corticosteroid-responsive patients have lower colectomy rates, re-hospitalization rates are similar to corticosteroid-refractory patients.[5]

Rescue medical therapy

Infliximab

Infliximab (IFX) is an anti-tumour necrosis factor alpha (TNFα) agent and an established rescue treatment for corticosteroid-refractory ASUC. The short-term colectomy rate for patients receiving IFX at a dose of 5 mg/kg on weeks 0, 2, and 6, is 29% compared to 67% for those receiving the placebo.[12] In ASUC, substantial fecal losses of IFX occur, and accelerated dosing strategies have been evaluated. Strategies include an initial 10 mg/kg dose of IFX, or shortened infusion intervals.[13] A recent meta-analysis found no significant difference in short or long-term colectomy rates between the accelerated and standard treatment groups; although a subgroup analysis demonstrated a trend toward lower colectomy rates with IFX at a dose of 10 mg/kg at 3, 12, and 24 month follow-ups.[13] As such, current guidelines do not make recommendations on accelerated IFX dosing.[9] From a pragmatic perspective, accelerated IFX dosing may be required for some patients. If surgery

is required despite IFX rescue therapy, recent data found no significant difference in infectious or surgical complications, reoperation, readmission, or mortality.[13]

Cyclosporine

Cyclosporine (CsA) is a calcineurin inhibitor that initially become a mainstay rescue treatment after Lichtiger et al. reported a significant clinical response with intravenous CsA at a dose of 4 mg/kg compared to placebo in corticosteroid-refractory severe ulcerative colitis (UC).[14] Similar response rates were observed with CsA at a dose of 2 mg/kg intravenous (IV) compared to CsA at a dose of 4 mg/kg IV.[9,10,15] A meta-analysis, which included the CYSIF and CONTRUCT trials, compared CsA (2 mg/kg IV) to IFX (5 mg/kg) as rescue therapy for ASUC. Among a subgroup analysis of randomized controlled trials (RCTs), the pooled rates of treatment response were not significantly different between treatments for short-term treatment response (IFX: 43.8% vs. CsA: 41.7%), 3 month (IFX:26.6% vs. CsA:26.4%), 12-month colectomy rates, and adverse events.[16] However, in the subgroup analysis of non-randomized trials, IFX was favoured over CsA for short-term treatment response (74.8% vs. 55.4% respectively) and the 12-month colectomy rate (20.7% vs. 36.8%, respectively).[16] Adverse events include infections, hypertension, renal impairment, seizures, and malignancy, which require close monitoring.[16] Owing to the safety profile, and requirement for dose-adjustments, CsA is less frequently used than IFX in the management of ASUC.[17] Following a response to CsA, patients are typically maintained on thiopurines; however, emerging evidence suggests vedolizumab and ustekinumab as maintenance therapy for ASUC.[18]

Tacrolimus

Tacrolimus is a calcineurin inhibitor that has been demonstrated to improve clinical outcomes in patients with steroid-refractory UC. However, tacrolimus has worse long-term outcomes compared to IFX in corticosteroid-refractory UC.[18] Limited data exists for its use as rescue therapy in ASUC. A recent ASUC cohort study reported higher rates of short-term colectomy, medication discontinuation, and rehospitalizations with tacrolimus treatment compared to IFX.[19] Tacrolimus is not currently recommended in treatment guidelines.[9,10]

Tofacitinib

Tofacitinib is a small molecule oral agent that selectively targets Janus kinase (JAK) 1-3 signalling. There is mounting interest and use of tofacitinib in ASUC given its quick onset and particularly for IFX-exposed patients. A systematic review of 148 ASUC cases, including the GETAID trial, evaluated tofacitinib as rescue therapy in IFX-exposed patients or as sequential treatment after failed IFX or CsA rescue therapy. Induction doses of tofacitinib were 10 mg twice a day or three times a day, and the pooled 30, 90, and 180-day colectomy-free survival was 85%, 86%, and 69%, respectively.[20] At follow-up, the rates of clinical and endoscopic remission were 35–69% and 55%, respectively.[20] A single-center observational study suggested that a short course of tofacitinib at a dose of 10 mg TID followed by tofacitinib at a dose of 10 mg PO BID may be more effective than tofacitinib at a dose of 10 mg PO BID.[21] Earlier concerns regarding the risk of VTE, malignancy, and cardiovascular events have not been observed in long-term, real-world safety data.[22] With the exception of an increased Herpes Zoster risk, rates of adverse events are similar to those of other UC treatments.[22]

Upadacitinib

Upadacitinib is a novel, selective JAK-1 inhibitor with a rapid onset of action and clinical efficacy in UC patients with prior biologic and tofacitinib exposure.[23] Although the data is limited to case reports and small studies, the use of upadacitinib in anti-TNF-exposed ASUC patients is promising.[24,25] In a study that included six patients who had previous IFX exposure and corticosteroid-refractory ASUC, upadacitinib was administered at a daily oral dose of 45 mg as rescue therapy.[26] By day 7, all of the patients demonstrated a clinical response and by week 16, five patients remained colectomy-free.[26] Further studies are needed before upadacitinib can be recommended as a rescue therapy.

Vedolizumab

Vedolizumab specifically targets the gut by selectively inhibiting the α4β7 integrin and is a first line therapy in moderate to severe UC. Vedolizumab is not suitable as rescue therapy in ASUC given its prolonged onset of action. However, it may be an alternative to thiopurine maintenance therapy following calcineurin inhibitor induction. A recent review of 156 ASUC patients, many of whom had previous anti-TNF exposure, showed a colectomy-free rate of 65-69% when combined with CsA or tacrolimus as bridge therapy.[18] The largest study involved 71 patients with severe UC in which 76% of them had ASUC. Vedolizumab was administered following CsA or tacrolimus rescue therapy, and the colectomy-free rates at 3, 12, and 24 months were 93%, 67%, and 55%, respectively.[18] Currently, there are no RCTs evaluating vedolizumab in ASUC.

Ustekinumab

Ustekinumab is an IL12/23 antibody approved for treating moderate to severe UC. Its use in ASUC has garnered interest as many patients are previously exposed to anti-TNFs, vedolizumab, and small molecules. The literature is limited to three retrospective studies in which the majority of patients had previously been exposed to anti-TNFs and vedolizumab. Ustekinumab was initiated following calcineurin inhibitor rescue therapy and at follow-up, all patients were colectomy-free.[18] Although the small

sample sizes limit extrapolation to clinical practice, the foundation is laid for further evaluation.

Surgery

Increasingly, surgical options are discussed as an alternative to chronic medication management in UC. These options include a subtotal colectomy and ileostomy with potential re-anastomosis and formation of an ileal-pouch anal anastomosis later. However, patients remain wary of having a stoma and potential complications, such as pouchitis. Urgent colectomy carries greater risks of morbidity and mortality compared to elective colectomy, and understanding prognostic factors facilitates discussion about treatment outcomes. Predictors of colectomy include albumin levels of <30 g/L, CRP levels of >30 mg/L, *C. difficile* infection, endoscopic severity, previous thiopurine or anti-TNFα treatment, and the risk correlates to the number of predictors present.[5,7,13] Patients who avoid colectomy within 3 months of the index attack have a colectomy-free survival of 93.5%, 81.5%, and 79.4% at 1, 3, and 5 years, respectively.[5] Toxic megacolon, perforation, and massive hemorrhage are complications of ASUC and are indications for urgent colectomy.[2] Initial retrospective studies reported increased post-operative complications, such as infection, sepsis, and leak in patients with recent biologic use.[27] However, recent meta-analyses have not found an increased risk of post-operative complications in UC and Crohn's disease (CD) patients with anti-TNF and vedolizumab exposure.[27] Furthermore, the time interval from the last anti-TNF dose to surgery does not impact the risk of postinfectious complications and detectable serum levels are not associated with increased infection risk.[27] The use of advanced therapy should not impact surgical decision making.

Sequential Rescue Therapy:

Sequential rescue therapy refers to the use of IFX therapy following CsA rescue therapy, or vice versa, to avoid colectomy in ASUC. Gisbert et al. have shown that the colectomy-free rate of sequential therapy with IFX following CsA was 58%, and 42% when CsA was administered after IFX.[18] However, the sample size was too small to make a comparison of efficacy, and the overall adverse event rate and mortality was 26% and 0.88%, respectively, which is similar to the findings in previous meta-analyses.[18] Risks of this strategy include delaying necessary surgery and additive immunosuppression leading to increased infections.[18]

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) may be a useful strategy for guiding anti-TNF therapy dosing in moderate to severe UC. Optimizing drug levels in ASUC can theoretically improve outcomes. ASUC patients who are refractory to corticosteroids have improved clinical and endoscopic remission rates and colectomy-free rates when IFX levels are detectable.[28] Lower IFX levels are common in ASUC given the significant inflammatory burden and increased fecal loss and clearance of IFX. The development of strategies to optimize drug dosing remain challenging due to drug pharmacokinetics and limited availability of point of care TDM.[28] Furthermore, limited data exists on the use of TDM with accelerated IFX dosing and the optimal target levels for ASUC remain unknown.[28]

Antibiotics

The literature does not support the use of antibiotics to induce remission in UC. A recent Cochrane review, which mostly included severe UC patients, found no difference between antibiotics and placebo for induction.[29] Data specific to ASUC is lacking. Based on earlier studies in this review, North American guidelines recommend against the use of antibiotics for the treatment of ASUC.[9,10]

Conclusion:

ASUC has a considerable risk of colectomy and complications. Patients require close monitoring and early recognition of a limited response to corticosteroids, prompting early rescue medical therapy or surgery. For patients who are refractory to corticosteroids, CsA and IFX are the mainstay treatments. However, the recent availability of small molecule therapies and newer biologics has sparked renewed interest in innovative strategies for ASUC management. Increasingly, patients are exposed to more than one advanced therapy prior to hospitalization; therefore, deciding whether to attempt further therapy in the setting of ASUC is not straightforward. We recommend that all patients with ASUC be managed or transferred to an expert centre, when possible, in which both colorectal surgeons and gastroenterologists collaborate closely to optimize safety outcomes for this potentially life-threating condition.

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Y.L.: None declared

Diagnosis of ASUC using Truelove & Witts Criteria:		
• ≥6 BMs/day AND • HR ≥90 bpm;	• Temp ≥37.8°C: • Hemoglobin <105 g/L; or	• ESR >30 mm/hr
Investigations:		
• Labs: CBC, electrolytes, creatinine, urea, liver panel, albumin, CRP • Stool studies: culture & sensitivity, C. diff, ova & parasite • Imaging: AXR or CXR • Endoscopy: Flexible sigmoidoscopy within 72 hours • Preparation for rescue therapy: TB skin test, IGRA, Hepatitis B serologies, Cholesterol		
Treatment:		
• Fluid rescustitation • Clear fluid diet or low residue diet • Methylprednisolone 60 mg/day in divided BID or TID dosing • VT prophylaxis		
Day 3 Assessment using the Oxford Criteria:		
• BMs >8 / day or • BMs >3/day & CRP >45 mg/L		

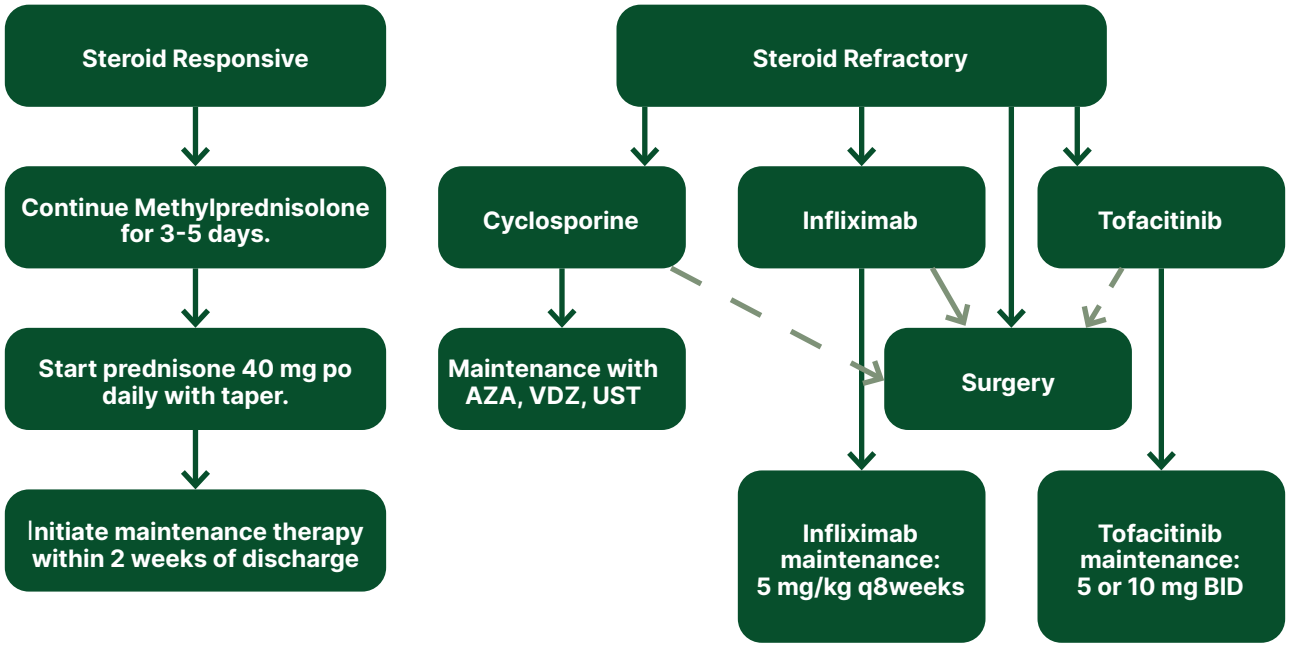

Table 1: Investigations & Management of ASUC; courtesy of Yvette Leung, MD and Natasha Klemm, MD

Clinical Pearls

- ASUC is a potentially life-threatening condition
- 1/3 of patients are steroid-refractory
- Predictors of a steroid-refractory course include: albumin <30 g/L; CRP >30 mg/L; and endoscopic severity
- Inflixmab & Cyclosporine are mainstay rescue medical therapy
- As patients become increasingly exposed to biologic therapies, newer agents are required as rescue medical therapy
- Newer agents, such as Tofacitinib, improve colectomy-free survival in steroid-refractory ASUC
- Predictors of colectomy after a steroid-refractory course include: albumin <30 g/L, CRP >30 mg/L, C. difficile infection, endoscopic severity, and previous thiopurine or anti-TNFa treatmentimproved colectomy-free
- Therapeutic Drug Monitoring may have a role in ASUC management, but further research is required before implementation in clinical practice

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- STELARA®/STELARA® I.V. should not be given to patients with any clinically important active infection. Patients should be evaluated for tuberculosis infection prior to therapy and monitored for active tuberculosis during and after treatment
- Potential to increase the risk of malignancy
- All patients, in particular those greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy, or those with a history of PUVA treatment, should be closely monitored for skin cancer
- Hypersensitivity reactions including serious allergic reactions (anaphylaxis and angioedema), allergic alveolitis, and eosinophilic pneumonia
- May cause allergic reactions in individuals sensitive to latex
- Concurrent use with live viral or bacterial vaccines is not recommended
- For infants exposed in utero, use of live vaccinations is not recommended under 6 months of age, unless the benefit of vaccination clearly outweighs the risk
- Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA®/STELARA® I.V.
- May affect allergy immunotherapy
- If reversible posterior leukoencephalopathy syndrome is suspected, administer appropriate treatment and discontinue STELARA®/STELARA® I.V.
- Should be given to a pregnant woman only if the benefit clearly outweighs the risk
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Reference:

1. STELARA/STELARA I.V. Product Monograph. Janssen Inc., April 5, 2023.

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TREATMENT RELATED ADVERSE EVENTS AND MONITORING OF PATIENTS RECEIVING BIOLOGIC OR SMALL MOLECULE THERAPY FOR INFLAMMATORY BOWEL DISEASE.

Key Takeaways

- Advanced therapies for IBD are generally safe but require treatment specific ongoing monitoring.
- Individual patient characteristics influence treatment choice and should be considered when implementing an ongoing monitoring strategy.
- Regular biochemical monitoring should be individualized to specific treatment requirements.
- Drug interactions must be considered when prescribing small molecule advanced therapy for IBD.

Introduction

The management of Inflammatory Bowel Disease (IBD) has evolved with the emergence of new treatment paradigms and the introduction of novel advanced therapies, including monoclonal antibodies (mAbs) and small molecules. These advanced therapies have improved disease control, but they necessitate careful pre-treatment assessment and ongoing monitoring to manage potential adverse effects and optimize patient outcomes. This review focuses on practical approaches to treatment-specific monitoring of currently available advanced therapies.

Treatment-associated adverse events

Infections

Patients with IBD, and those taking advanced therapies, are at an increased risk for infections. Maintaining vigilance for signs of infection, prompt evaluation and management, and therapy interruption, when necessary, are crucial in avoiding serious complications.

The risk of opportunistic infections is a significant concern with anti-tumor necrosis factor (TNF) therapy, because this treatment method doubles the risk of such infections among IBD patients.[1] In addition, the risk of tuberculosis reactivation can increase up to 25-fold depending on clinical circumstances.[2] The TREAT Registry showed a serious infection rate of 2.15 events per 100 patient-years (PY).[3] However, a meta-analysis of 21 placebo-controlled Crohn's disease (CD) trials did not show an increased risk of serious infections with anti-TNF therapy.[4] Excluding latent infections prior to treatment and ongoing monitoring, especially for opportunistic and atypical infections, is important when administering anti-TNF therapy.

In a phase 3 CD trial, nasopharyngitis was more frequent in the vedolizumab arm, along with apparently higher rates of both infections and serious infections.[5] However, subsequent long-term safety studies and meta-analyses did not show an increased infection risk with vedolizumab.[6-9] The EVOLVE study, a multicenter retrospective real-world study that included 1,095 IBD patients, found a significantly lower rate of serious infections and adverse events with vedolizumab versus anti-TNF.[10]

Ustekinumab therapy has not shown an increased risk for serious or opportunistic infections in long-term studies,[11] with its infection risk being similar to vedolizumab and lower than that of anti-TNF therapies.[12,13] Risankizumab and mirikizumab therapy have also shown no increased risk of serious or opportunistic infections in the registrational clinical trials.[14-16]

The introduction of Janus kinase (JAK) inhibitors has raised specific concerns around Herpes Zoster (HZ) reactivation. Long-term data on tofacitinib suggests that HZ occurs at a rate of 3.[24] events per 100 PY, with other serious infections occurring at a rate of 1.[8] events per 100 PY.[17] An upadacitinib trial reported similar serious infection rates to adalimumab, but a higher risk of HZ.[18] A recent network meta-analysis concluded that tofacitinib and upadacitinib significantly increase the risk of HZ infection,[19] although most cases were reported to be mild or moderate and had resolved without discontinuation of treatment.[20] Routine use of the adjuvanted recombinant zoster vaccine is recommended for adults requiring advanced IBD therapies.

In a phase 3 trial for UC, it was observed that ozanimod exhibited infection rates of 23% (compared to 11.9% with placebo), with low rates of serious infections (0.9% for ozanimod versus 1.8% with placebo) and HZ (2.2% for ozanimod versus 0.4% with placebo).[21] These results were confirmed by a long-term extension study that reported an infection rate of 24.[3] events per 100 PY, a serious infection rate of 1.9 events per 100 PY, and an HZ rate of 1.7 events per 100 PY.[22] Notably, an open-label study involving multiple sclerosis patients highlighted that opportunistic infections were predominantly driven by HZ.[23] Similarly, in a phase 3 trial for UC, it was found that etrasimod demonstrated minimal serious infection rates (1% for etrasimod versus 3% for placebo) and HZ rates (1% for etrasimod versus 0% for placebo), with no reports of opportunistic infections.[24] Consistent with these findings, long-term safety data from an etrasimod open-label extension trial indicated a low risk of infection.[25]

Vaccination Status

Live vaccines are contraindicated in patients receiving biologic and small molecule therapy. It is important to assess measles, mumps, and rubella (MMR) and varicella-zoster virus (VZV) vaccination history and immune status before initiating advanced therapy. If required, administer vaccines before starting therapy; however, do not delay urgent treatment for live vaccine administration.

Recommendations indicate that all IBD patients should receive the following inactivated vaccines, regardless of active treatment: influenza, meningococcal, Haemophilus influenzae type b, diphtheria, tetanus, pertussis, human papillomavirus, and pneumococcal.

Assess viral hepatitis status before initiating advanced therapy for IBD. Unimmunized patients should receive the hepatitis B vaccine. It is important to note that reactivation of hepatitis B is a known complication of anti-TNF therapy. Patients positive for hepatitis B surface antigen (HBsAg) are at the highest risk and should consider prophylactic antiviral therapy before initiating anti-TNF treatment.

All adult IBD patients should consider the recombinant zoster vaccine (non-live), especially those receiving immunomodulator, biologic, or small molecule therapy as it can mitigate HZ risk.

For further details on immunizations for IBD patients, refer to the 2021 Canadian Association of Gastroenterology Clinical Practice Guideline.[26]

Hematologic And Metabolic

Up to 19% of patients receiving anti-TNF therapy for immune-mediated diseases develop at least one episode of neutropenia, with 6% experiencing serious infections related to neutropenia.[27] Thrombocytopenia is infrequently associated with anti-TNF therapies, with data limited to case reports. In cases of significant thrombocytopenia, alternate causes, including autoimmune conditions or viral infections, should be considered.[28]

Weight gain has been observed in patients with IBD who are receiving anti-TNF therapy. However, long-term registry data has not established a direct link between anti-TNF therapy and weight gain, although patients who are underweight at treatment initiation may experience early weight gain.[29] Some patients gain weight due to an improvement in their nutritional status following effective therapy, as suggested by a small cohort study that showed an increase in both body mass index (BMI) and muscle mass parameters after anti-TNF therapy initiation.[30]

Vedolizumab therapy for IBD has not been associated with metabolic adverse effects. While leukocytosis and leukopenia were reported in a small proportion of patients in registration trials, subsequent long-term safety analyses have not confirmed these findings.[9] Therapies that target interleukins do not appear to cause significant adverse hematologic or metabolic effects.[15,16,31,32]

Neutropenia and lymphopenia occurred in upadacitinib-treated patients in the pivotal induction and maintenance trials, with no cases requiring treatment discontinuation. Neutropenia was observed in 6% of patients treated with 30 mg of upadacitinib, 3% of patients treated with 15 mg of upadacitinib, and in 1% of patients who received a placebo. Lymphopenia occurred in 2% of patients who were treated with both 30 mg and 15 mg doses of upadacitinib, and in 1% of placebo-treated patients. Anemia was more common in placebo-treated patients compared to those receiving upadacitinib.[33] With up to 9.2 years of safety data, significant cytopenias have not been reported with tofacitinib.[17] Creatine phosphokinase (CPK) elevations were observed in a small percentage of JAK inhibitor

patients and were mostly asymptomatic and non-serious.

S1P receptor modulators impair the migration of lymphocytes out of lymphoid tissue by blocking S1P receptors, leading to a relative reduction in circulating peripheral lymphocytes. There is generally an expected and measurable relative reduction in lymphocytes by approximately 40%–50%, which resolves after treatment discontinuation in most patients. Profound lymphopenia is rare, occurring in 1% of patients.[21,25,34]

Cardiovascular

Patients with IBD are at an increased risk of cardiovascular disease,[35] likely attributable to chronic inflammation and associated metabolic derangement.[36] While effective management of IBD and its underlying risk factors is key, there are specific treatment-related considerations.

Data from preclinical studies suggested potential benefits of TNFα inhibition for treating congestive heart failure, however, a subsequent clinical trial showed no such benefit, and had reported an increased risk of hospitalization and all-cause mortality.[37] Case reports also link anti-TNF therapy to heart failure exacerbations in patients with IBD.[38] Anti-TNF therapy is contraindicated in New York Heart Association Class III/IV heart failure and should be used with caution in patients at risk for heart failure.

Long-term safety data has not established an increased cardiovascular event risk with vedolizumab therapy.[9] Agents targeting IL-12 and -23 show a favourable safety profile with no significant increase in cardiovascular events compared to other therapies.[39]

Initiation of JAK inhibitor therapy can modestly increase both low density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels by approximately 20%, with the LDL-HDL ratio remaining stable.[33,40-42] It is not clear if increased cholesterol levels results in atherosclerosis. Interestingly, there is some evidence that tofacitinib may positively impact macrophage cholesterol metabolism, which could potentially mitigate the risk of atherosclerosis.[43]

In a long-term extension study of tofacitinib for treating UC, the risk of major adverse cardiovascular events was low, with a rate of 0.27 events per 100 PY.[17] A systematic review and meta-analysis of real-world studies also did not report any major adverse cardiovascular events or thromboembolic complications.[44]

The ORAL Surveillance open-label randomized trial compared tofacitinib at a dose of 5 mg or 10 mg twice daily to anti-TNF therapy in 4,362 patients older than 50 years with active rheumatoid arthritis and at least one additional cardiovascular risk factor. The results of the trial demonstrated a higher incidence of major cardiovascular events with tofacitinib.[45] Post-hoc analyses demonstrated that the increased risk of adverse cardiovascular events was limited to a high-risk patient cohort (age ≥65 years or those with a history of smoking)[46] and was predominantly observed in patients with prior atherosclerotic cardiovascular disease.[47] The SELECT-COMPARE trial compared the effects of upadacitinib and adalimumab for rheumatoid arthritis treatment, and found no difference in the incidence of cardiovascular events.[48]

S1PRMs pose specific cardiac safety concerns due to S1P1 receptors, which are found on cardiac myocytes, and their subsequent effects on cardiac conduction. Transient bradycardia is a common early side effect, within hours of the first dose, which is largely asymptomatic. In the True North induction and maintenance trials, one patient developed a type 1 second-degree heart block, and there were no cases of type II or third-degree heart block.[21,34] A large open-label extension trial of ozanimod for multiple sclerosis reported hypertension at a rate of 2.0 events per 100 PY and no cases of second- or third-degree heart block.[23]

Thromboembolic

IBD has long been recognized as a risk factor for venous thromboembolism (VTE) and arterial events, especially during disease exacerbation.[49-51] Corticosteroid use increases VTE risk, while anti-TNF agents have been associated with a decreased risk of VTE.[51,52]

Despite regulatory warnings prompted by the ORAL Surveillance study, long-term exposure data suggests that the risk of VTE and arterial thrombosis in those treated with JAK inhibitors remains low. Randomized trials and real-world studies have consistently found low rates of these adverse events that do not differ from those observed with anti-TNF therapy.[17,44,48,53,54] A recent consensus process concluded that there is no observable increased risk of VTE in IBD patients treated with tofacitinib.[51]

Hepatic

Anti-TNF therapies have been associated with a variety of liver injury patterns, with events ranging from transient and self-limited, to severe.[55] Anti-integrin and anti-interleukin therapies have a low risk of drug-induced liver injury, although there have been cases of idiosyncratic, clinically apparent liver injury that has resolved with discontinuation.[9,56]

Unlike monoclonal antibodies, small molecule drugs undergo hepatic metabolism through the cytochrome P450 enzyme system, which can result in drug-drug interactions. Elevations of transaminases have been observed with both JAKs and S1PRMs, although they are generally mild and do not require treatment discontinuation.[22,24,33,56]

Neurologic

Anti-TNF agents increase the risk of inflammatory demyelinating and non-demyelinating central nervous system (CNS) events, especially in patients with multiple sclerosis or a history of optic neuritis.[57] Other advanced therapies do not appear to increase the risk of inflammatory CNS events.

One case of progressive multifocal leukoencephalopathy (PML) has been reported in a vedolizumab-treated patient who was HIV-positive and on concomitant immunosuppression, another case of PML was reported in an infliximab-treated patient,[58] and there have been case reports of PML in S1PRM-treated multiple sclerosis patients.[23]

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients treated with anti-TNF agents[59,60] and ustekinumab.[61,62]

Ophthalmologic

Clinical trial data suggest that S1PRMs can trigger macular edema in 1:125 to 1:300 patients. [21,22,34] The cases generally resolve following drug discontinuation, however, patients with pre-existing uveitis or diabetes are at increased risk.

Immunologic

Anti-TNF therapy triggers a spectrum of immune-mediated adverse events, including infusion reactions, injection site reactions, delayed hypersensitivity reactions, paradoxical autoimmune disorders (e.g., lupus-like syndromes and psoriasis), and immunogenicity. Subsequent mAbs and small molecule therapies have largely attenuated these immunologic complications of treatment.

Malignancy

The use of anti-TNF agents has raised concerns around an increased risk of malignancy, specifically non-melanoma skin cancer (NMSC) and lymphoma,[63] although the evidence has been conflicting.[64,65] The S1PRM modulator fingolimod has a slightly increased risk of basal cell carcinoma,[66] which has not been conclusively demonstrated with ozanimod or etrasimod.[21,22,25] Findings on the malignancy risk of JAKs are also varied, with some studies suggesting a risk of malignancy and NMSC.[17,40,67,68]

Treatment Monitoring Strategy

Effective IBD management requires a baseline assessment and ongoing monitoring for treatment-related complications. Regular laboratory investigations, symptom monitoring, infection vigilance, cancer screening, and attention to treatment-specific concerns are crucial. Please see the table below for more information.

Therapeutic Class	Medication	Pre-Treatment Assessment	Ongoing Monitoring
Anti-tumour necrosis factor-α (TNFα)	Infliximab Adalimumab Golimumab Certolizumab	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Vaccine review (no live vaccination during treatment). Contraindicated if: • Active infection. • Profound cytopenia. • NYHA Class III or IV heart failure. • Pre-existing multiple sclerosis or optic neuritis.	CBC every 3–6 months. Liver panel every 3–6 months. Tb/viral hepatitis if high-risk travel or exposure. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider an annual pap-smear and skin exam, especially if concomitant immunosuppressive therapy. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
Anti-integrin	Vedolizumab	Vaccine review (no live vaccination during treatment). Consider TB status assessment.	CBC every 3–6 months. Liver panel every 3–6 months. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
Anti-interleukin	Ustekinumab Risankizumab Mirikizumab	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Vaccine review (no live vaccination during treatment).	CBC every 3–6 months. Liver panel every 3–6 months. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.

Janus Kinase inhibitor	Tofacitinib	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Baseline lipid panel and cardiovascular risk factor assessment. If age >65 years or history of cardiovascular disease, use lowest effective dose with careful consideration of risks and benefits. Family planning, if applicable. • Dose adjustment (5 mg BID) if: • eGFR <60. • Strong CYP3A4 inhibitors. • Moderate CYP3A4 inhibitor with a strong CYP2C19 inhibitor. Contraindicated if: • Pre-existing cytopenia (ANC <1.0 × 10^9 cells/L, HGB <90 g/L, ALC <0.5 × 10^9 cells/L). • Severe renal (eGFR <15 ml/min) or hepatic impairment. • Potent CYP3A4 inducers. Vaccine review (recombinant herpes zoster highly recommended, no live vaccines during treatment).	CBC every 3–6 months: • Interrupt treatment if HGB <80 g/L or decrease >20 g/L; or ANC 0.5–1.0 × 10^9 cells/L. • Discontinue if ANC <0.5 x 10^9 cells/L or ALC <0.5 × 10^9 cells/L. • Liver panel at 4–8 weeks, then every 3–6 months. Lipid panel at week 4–8 (tofacitinib)/ week 12 (upadacitinib); then every 6 months. Coordinate hypercholesterolemia management with primary care/ cardiology, per 2021 Canadian Cardiovascular Society Guidelines. Periodic confirmation of medication adherence. Periodic review of family planning, if applicable. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider an annual skin exam. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
	Upadicitinib		
Sphingosine-1-phosphate receptor (S1PR) modulators	Ozanimod	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Cardiac assessment: ECG, heart rate, blood pressure. Ophthalmology evaluation (if diabetes mellitus, uveitis, or retinal disease). Family planning, if applicable. Caution if: • Pre-existing pulmonary disease. • Drugs that slow the heart rate or AV conduction. Contraindicated if: • Concomitant use of MAO inhibitors. • Severe hepatic impairment. • Myocardial infarction, unstable angina, stroke, or transient ischemic attack, decompensated or advanced heart failure, within 6 months. • Cardiac conduction abnormalities (AV node block, SA block) without a pacemaker. • Macular edema. • Severe respiratory disease (pulmonary fibrosis, asthma, or chronic obstructive pulmonary disease); spirometry if indicated. Vaccine review (recombinant Herpes Zoster highly recommended, no live vaccines during treatment).	CBC every 3-6 months: • interrupt treament if ALC < 0.2 x 10^9 cells/L Liver panel every 3–6 months. Assess visual disturbances. Monitor blood pressure regularly. Periodic confirmation of medication adherence. Periodic review of family planning, if applicable. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider annual skin exam. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations
	Etrasimod		

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AV, atrioventricular; BID, twice a day; CBC, complete blood count; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HGB, hemoglobin; NYHA, New York Heart Association; SA, sinoatrial; Tb, tuberculosis; TNFα, tumour necrosis factor-α.

Table 1: Therapeutic class-based guide for advance therapy monitoring in the management of Inflammatory Bowel Disease ; courtesy of Michael Stewart, MD, FRCPC

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FARHAD PEERANI, MD

Farhad Peerani graduated from the University of British Columbia's medical program and completed residencies in internal medicine and gastroenterology at the University of Alberta. He pursued an advanced two-year clinical research Inflammatory Bowel Disease (IBD) Fellowship at both the University of Alberta and Mount Sinai Hospital in New York City. He was subsequently appointed Assistant Professor of Medicine at the University of Alberta on July 1, 2016. He is the IBD fellowship program director and serves as Treasurer for the Canadian IBD Research Consortium. His primary research interests are in real-world effectiveness of biologic and small molecule therapies, IBD in the elderly and the primary sclerosing cholangitis-IBD phenotype.

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MEDICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN THE ELDERLY

Introduction

The optimal management of inflammatory bowel disease (IBD) can be challenging at the best of times; however, this notion becomes more salient when treating the niche population of elderly IBD. The prevalence of IBD in elderly Canadians has almost doubled in a span of 5 years, increasing from 1/160 in 2018 to 1/88 in 2023.[1] While the majority of IBD patients are diagnosed between 20-40 years of age, 10-15% are diagnosed at >60 years of age.[2] Elderly-onset ulcerative colitis (UC) patients more commonly have left-sided colitis with less disease extension whereas elderly-onset Crohn's disease (CD) patients typically exhibit an inflammatory colonic phenotype. Although elderly-onset IBD patients typically demonstrate a less aggressive natural history overall, they have a similar risk of surgery compared to their adult-onset IBD counterparts with the majority being treated with non-advanced therapies.[3] A lack of physician knowledge and comfort level in treating elderly IBD likely contribute to patients being maintained inappropriately on long-term steroids and/or 5-aminosalicylates.

The existing literature on elderly IBD often fails to differentiate between aging pediatric or adult-onset IBD patients and elderly-onset IBD patients; therefore, this article will discuss the management of both groups together. Nevertheless, it is important to note that these two groups likely have different underlying pathophysiological mechanisms driving their respective diseases which can have implications for therapeutic decisions.[4] Unfortunately, the majority of evidence to help guide decision-making in elderly IBD is derived from retrospective analyses of real-world data or health administrative datasets, as well as post-hoc analyses of randomized controlled trials (RCTs). Drug efficacy aside, nuanced care of the elderly IBD patient involves an appreciation of frailty and comorbidity to help contextualize the risks of immunosuppressive therapy. Not only is the safety of therapies contingent upon the intrinsic immunosuppressive properties of the drug, but in addition, drug efficacy needs to be considered with respect to the effectiveness in controlling disease activity and achieving corticosteroid-free remission.

Frailty

Although the European Crohn's and Colitis Organisation refers to a cut-off of 60 years of age to define elderly-onset IBD, using chronological age alone is insufficient to appropriately assess a patient's suitability for IBD therapy. Frailty is a multifaceted concept that includes aspects of psychosocial well-being, social supports, cognition, comorbidities, nutrition, and functional status reflecting the physiologic resiliency of an individual to withstand stressors such as immunosuppression or surgery. A recent systematic review summarized that the majority of literature in IBD patients revolves around modified frailty indices that have not been validated in the IBD population.[5] This systematic review explored non-surgical IBD outcomes wherein frailty predicted hospitalizations, readmissions, length of stay, and mortality. Effective IBD treatment has been demonstrated to improve frailty, underscoring the importance of not undertreating elderly IBD patients in the right clinical context.[6] Future studies will help to elucidate frailty risk stratification tools for IBD therapy in the elderly; however, physicians can incorporate hand-grip strength measurements and the Clinical Frailty Scale[7] directly in the clinic to better understand the biologic age of their elderly IBD patients.

Safety

Infection

Although advanced age and comorbidities increase the risk of infection in patients on biologic or small molecule therapy, the type of advanced therapy also appears to play a role. The literature contains limited safety data in the elderly and the data that does exist stems primarily from the use of anti-TNF therapy in observational real-world cohorts. In the Mayo Clinic's reporting of 100 consecutive IBD patients with opportunistic infection, those on infliximab had an 11.1 OR (P = 0.07) of developing an infection with the greatest risk seen in patients >50 years of age.[8] In an Italian multicentre cohort study, 11% of patients >65 years of age on infliximab or adalimumab developed severe infections, compared to 0.5% of patients >65 years of age not on a biologic and 2.6% of patients <65 years of age on biologic therapy[9]. In contrast, in a post-hoc analysis of four RCTs, although UC patients ≥60 years of age had an increased baseline risk of serious adverse events, no increase in risk was attributed to anti-TNF therapy.[10] While real-world effectiveness data demonstrates confounding bias, RCT data is victim to a lack of generalizability given that clinical trial patients tend to be more robust than the patients we see in clinic. Although data on other advanced therapies in the elderly is sparse, vedolizumab, ustekinumab, risankizumab, and ozanimod generally have more favourable side effect profiles with respect to infectious risk than tofacitinib and upadacitinib.[11] Last, although combination therapy is often not used in the elderly due to safety concerns, a post hoc analysis of the REACT trial reported no increased adverse outcomes in CD patients ≥60 years of age who were exposed to early combined immunosuppression.[12]

Thrombosis/CV risk

Janus kinase (JAK) inhibitors such as tofacitinib and upadacitinib should be used with caution in the elderly IBD population after carefully weighing the risks and benefits of therapy. The ORAL Surveillance safety data revealed increased rates of major adverse cardiovascular events, malignancies (excluding non-melanoma skin cancers), serious infections, venous thromboembolisms (VTEs) and mortality in rheumatoid arthritis (RA) patients aged ≥50 years with ≥1 additional cardiovascular disease risk factor who were treated with tofacitinib compared to anti-TNF therapy.[13] Of note, this data was derived from a RA cohort and reassuringly 7.8 years of safety data from the tofacitinib UC clinical trial programs have failed to reveal similar risks.[14] For the sphingosine-1-phosphate receptor modulators, pre-existing cardiovascular conditions within 6 months prior to initiating therapy, such as myocardial infarction, stroke, decompensated heart failure, and Type II second or third degree AV block, need to be considered and would be contraindications to initiating ozanimod or etrasimod. Of note, while anti-TNF therapy is contraindicated in patients with New York Heart Association Class III or IV congestive heart failure, there may be a protective benefit where anti-TNF reduces the risk of VTEs and arterial events in IBD patients.[15]

Malignancy

Due to the risk of lymphoma with azathioprine that approaches 1:350 per year once patients are older than 50 years of age,[16] it is advisable to use methotrexate over azathioprine if an immunomodulator is clinically indicated in patients with a previous history of immunogenicity and/or refractory disease. The decision surrounding withdrawal of azathioprine therapy in an elderly IBD patient in remission is slightly more contentious with a 5-year cumulative relapse rate of 46% previously reported.[17] The risks of disease flares need to be weighed against the risks of infection and malignancy (non-melanoma skin cancer, lymphoma).

Drug Interactions

Polypharmacy is prevalent in older patients with IBD,[18] therefore it is incumbent upon the prescribing physician to be aware of potential drug interactions. For elderly IBD patients on azathioprine, it is important to be mindful that interactions with allopurinol, a commonly prescribed medication for gout, can dramatically increase the risk of bone marrow suppression.[19] Furthermore, when azathioprine and warfarin[20] are used together, the anticoagulation effect of warfarin is impaired. While ozanimod is primarily metabolized by the CYP2C8 pathway,[21] JAK inhibitors are metabolized via the CYP3A4 pathway.[22] One needs to be aware of concomitant prescriptions for major CYP2C8/CYP3A4 inducers such as rifampin, phenytoin and carbamazepine that can decrease the bioavailability of the small molecule therapies.

Efficacy

Efficacy data of advanced therapies in elderly IBD patients is sparse and is primarily centered around the use of anti-TNF therapy due to its long duration on the market. While some retrospective studies have suggested that elderly IBD patients are more likely to develop a secondary loss of response to anti-TNF therapies[23] and are less likely to achieve short-term clinical response,[24] a post-hoc analysis of RCTs in UC patients revealed no difference in inducing or maintaining remission between older and younger patients.[10] The real-world data could be confounded by the fact that elderly IBD patients are less likely to be initiated on advanced therapy and therefore may have more refractory disease upon initiation. In addition, clinicians are more likely to discontinue therapy due to adverse events in the elderly IBD population. Interestingly, a multicentre retrospective Japanese study revealed that anti-TNF therapy may be less effective in bio-naïve elderly-onset IBD patients[25] and

while immunosenescence may lead one to surmise that immunogenicity plays less of a role with age, a post-hoc analysis from the REACT trial contradicts this hypothesis.[26] When comparing the effectiveness of anti-TNF therapy to vedolizumab therapy in the elderly, mixed results have been reported.[27,28]

Conclusion

Treatment decisions in the elderly are complex and need to take into consideration frailty, comorbidities, quality of life, mobility restrictions (barrier to travel for intravenous infusions and clinic appointments), physical limitations (difficulties self-administering rectal therapies or subcutaneous injections), suboptimal response to vaccination, and psychosocial supports. As older IBD patients are at increased risk of post-operative morbidity and mortality,[29,30] it is imperative that ageism does not creep into the decision-making process for escalating IBD therapy or offering timely surgery. Proposed algorithms for treating elderly UC and CD patients are depicted in **Figure 1** and **Figure 2** respectively. Although the American Gastroenterological Association has published clinical practice guidelines on the topic of elderly IBD,[31] a large knowledge gap remains for physicians, which hopefully will be informed by future clinical trials.

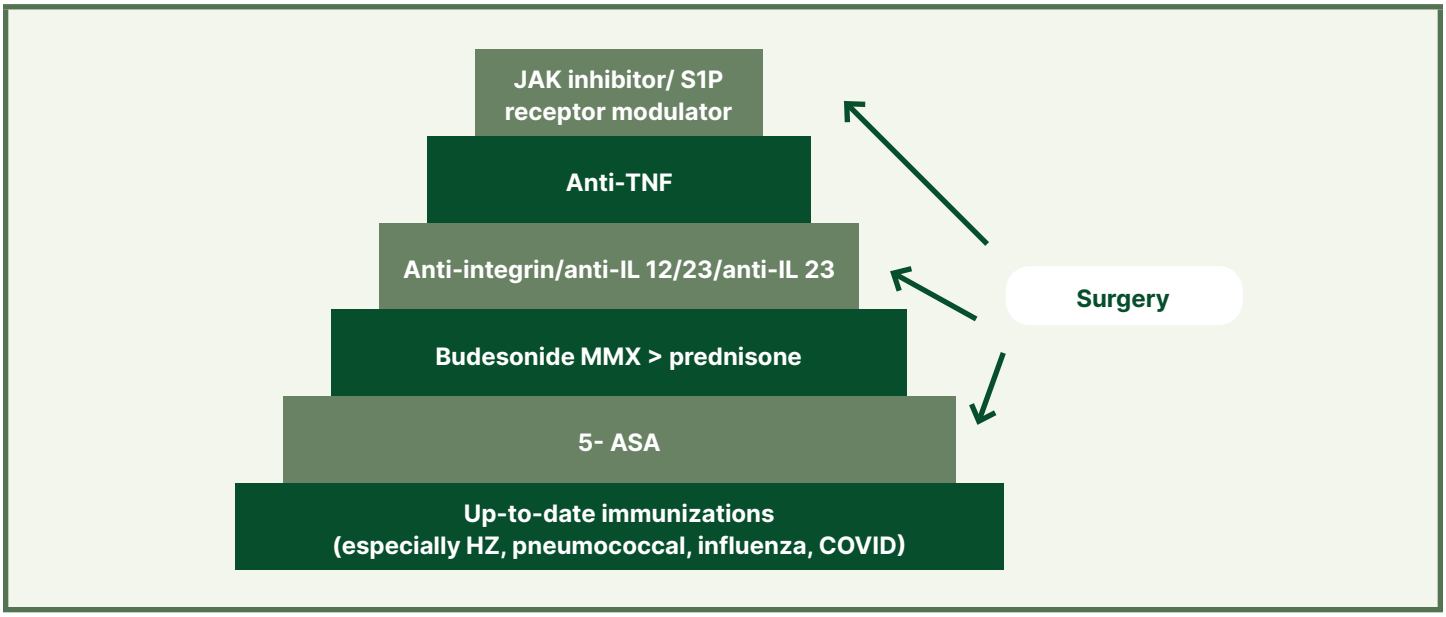

Figure 1. ELDERLY UC Proposed Treatment Algorithm; courtesy of Farhad Peerani, MD
JAK, Janus kinase; S1P, sphingosine 1-phosphate; TNF, tumour necrosis factor; IL, interleukin; MMX, multimatrix; ASA, aminosalicylate; HZ, herpes zoster

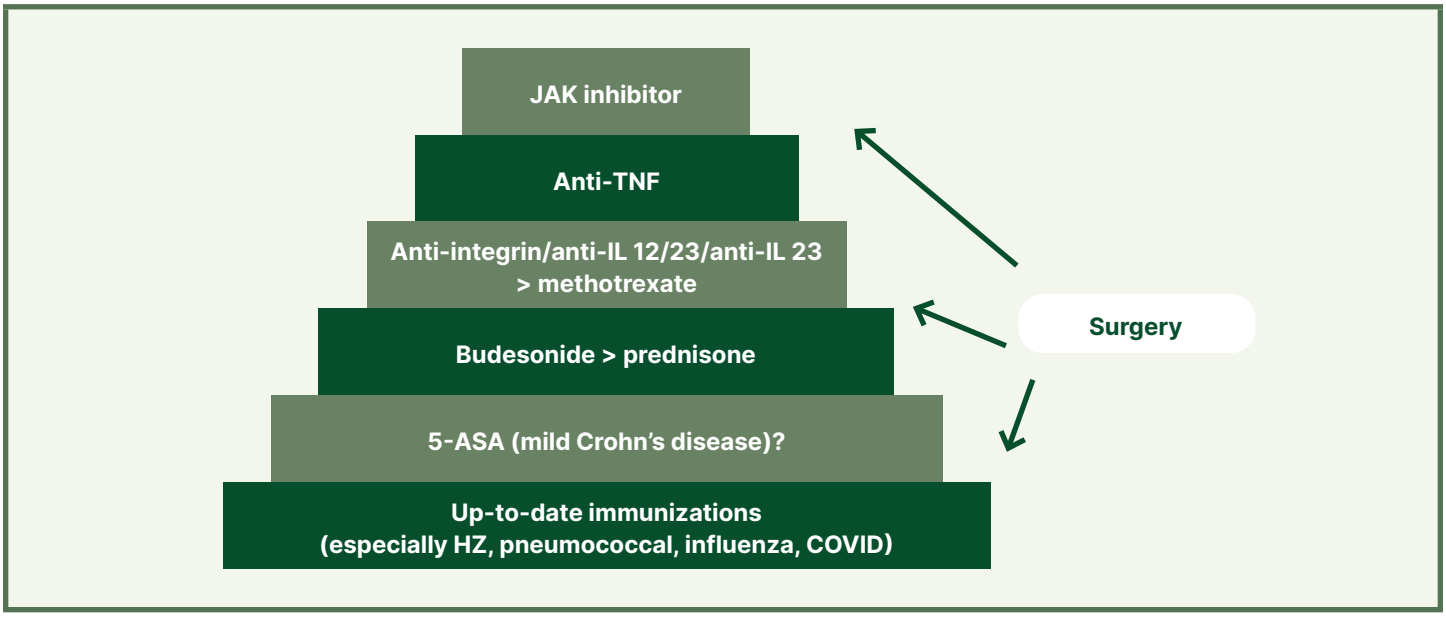

Figure 2. ELDERLY CD Proposed Treatment Algorithm; courtesy of Farhad Peerani, MD
JAK, Janus kinase; TNF, tumour necrosis factor; IL, interleukin; ASA, aminosalicylate; HZ, herpes zoster

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Clinical Pearls

- When considering therapy for elderly IBD patients, do not fall victim to ageism but rather assess whether your patient is “fit” vs “frail”
- Avoid initiating azathioprine in IBD patients ≥ 50 years of age
- Anti-TNF therapies are the most extensively studied advanced therapies in elderly IBD patients with a signal for increased infection and perhaps decreased efficacy, especially in elderly-onset IBD patients
- Order a baseline echocardiogram in elderly IBD patients prior to commencing anti-TNF therapy
- Consider using a lower induction dose of JAK inhibitors in those patients with a history of cardiovascular risk factors or thrombosis who are not on concomitant antiplatelet or anticoagulant therapy
- A multidisciplinary healthcare team including family physicians, IBD nurses, gastroenterologists, colorectal surgeons, dieticians, pharmacists, psychiatrists, and geriatricians is ideal in providing optimal care

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- reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of RENFLEXIS® have not been established in patients less than 6 years of age.

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† Comparative clinical significance unknown.
‡ IQVIA data from February 2023 to March 2024.
§The program was initially operated by Merck Canada Inc. under the name MERCK HARMONY. In June 2021, it transitioned to Organon Canada Inc. and is now operating under the name HARMONY BY ORGANON™.
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OPHTHALMIC COMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

Key Takeaways

- Ocular EIMs are more common in CD than UC
- Episcleritis and uveitis are the most common ocular EIMs
- All patients living with IBD must check their eyes regularly and be aware to consult a physician if experiencing ocular redness, pain, light sensitivity or blurred vision
- When ocular manifestations are present, prompt treatment can avoid blindness, and patient awareness and education contribute enormously to this
- Ocular complications may arise from the natural history of the disease, from treatment or from non-related but concurrent conditions. Awareness is the key for proper management.
- Collaboration between gastroenterologists and ophthalmologists is essential when selecting therapy for patients with ocular inflammation and IBD

Introduction

The prevalence of inflammatory bowel disease (IBD), estimated at 843 per 100,000 people (95% PI 828-859) (i.e., 0.843% of the population) in 2023 is increasing in Canada and is expected to reach 1.1% of the Canadian population by 2035.[1] Consequently, extraintestinal manifestations and complications will also increase. Up to 50% of patients suffering from IBD will develop an extraintestinal manifestation (EIM) during the course of their disease, patients with Crohn's disease (CD) being more often affected then those with ulcerative colitis (UC).[2] Ocular manifestations are the third most common EIM after articular and dermatological involvements.[3] Ocular complaints in patients with IBD can represent an EIM, a complication of systemic treatment or an unrelated affection. All patients presenting with a red eye, light sensitivity, loss of vision or any acute ocular symptom(s) should be promptly evaluated by an eye specialist. Early detection of ophthalmologic diseases and appropriate management require collaboration between specialists and are of utmost importance to avoid permanent visual loss.

The most common ocular manifestations reported in IBD patients are episcleritis (2-5%) and anterior uveitis (0.5-3.5%).[3] Other less common manifestations include scleritis, intermediate and posterior uveitis, retinal vasculitis, retinal vascular occlusions, orbital inflammatory syndrome, and optic neuritis.[4] Ocular manifestations can also be associated with malabsorption syndromes encountered in some patients with IBD.[5] Secondary vitamin A deficiency can result in night blindness and keratoconjunctivitis sicca.[6,7]

Episcleritis and Scleritis

Episcleritis, the most common ophthalmic complication of IBD, consists of an inflammation of the superficial episcleral vessels. It presents as sudden eye discomfort, sectorial or diffuse redness, tearing, minimal or no pain, and no change in visual acuity. It is generally unilateral and can also present in its nodular form. In episcleritis, redness will blanch with the diagnostic test consisting of instillation of a drop of phenylephrine 2.5%. Like other ocular manifestations, episcleritis can present before or after the diagnosis of IBD. Episcleritis is associated with active CD and can be considered an indicator of intestinal disease activity.[8] Treatment of active IBD is generally sufficient to resolve episcleritis but some topical treatment can be added, such as lubricants, topical corticosteroids or topical non-steroidal anti-inflammatories (NSAIDs). Sometimes oral NSAIDs are needed but should be used cautiously because of their effect on intestinal inflammation.

Scleritis

Scleritis is a rare manifestation of IBD, occurring in less than 1% of cases[3] **(Table 1)**. Contrary to episcleritis, scleritis is not considered an index of IBD activity and may develop even when the intestinal disease is inactive. Scleritis has a more severe presentation than episcleritis. Patients with scleritis typically complain of severe redness and deep pain (typically wakening up at night due to pain). Redness will not blanch with topical phenylephrine. There is generally no discharge or photosensitivity and visual acuity remains normal unless it is a severe form of the condition or there is an associated posterior component. Scleritis can be associated with multiple systemic diseases, some life-threatening. Due to its severity, scleritis needs to be treated aggressively to avoid blindness. Treatment requires systemic therapy, initiating with NSAIDs and frequently requiring systemic corticosteroids and immunosuppression.

	Uveitis	Episcleritis	Scleritis
Presentation	Perilimbal flush, photosensitivity, blurry vision	Red eye, minimal pain, blanches with phenylephrine	Red eye, deep pain, violet hue, does not blanch with phenylephrine
First-line Treatment	Topical steroids	Observation, NSAIDs, topical corticosteroids	Systemic NSAIDs, systemic corticosteroids
Differential diagnosis for underlying disease	Idiopathic, trauma, HLA-B27 associated systemic diseases like IBD, other systemic conditions, postoperative	Idiopathic, herpes zoster, rarely systemic disease	Connective tissue disease, herpes zoster, syphilis, gout

Table 1: Uveitis versus episcleritis versus scleritis; courtesy of Marie-Lyne Belair, MD, FRCSC and Evangelina Esposito, MD CHM

Uveitis

Uveitis is the second most common ocular manifestation of IBD (0.5-3.5%) and is twice as frequent in patients with CD than in patients with UC.[9,10] Uveitis signifies acute inflammation of the uveal tract or middle layer of the eye, which includes the iris, ciliary body and choroid. It is classified as anterior, intermediate, posterior or panuveitis. Anterior uveitis (also referred as iritis or iridocyclitis) occurs when the inflammation is predominantly in the anterior chamber; intermediate uveitis when the vitreous is involved; posterior uveitis when it affects the retina and/or choroid; and panuveitis when the inflammation is equally present in all three parts of the eye.[11] In patients with IBD, uveitis is typically anterior and does not correlate with gastrointestinal tract activity.[12] However, anterior uveitis might be considered a marker of a more severe disease course.[13] Anterior uveitis is often associated with other EIMs such as erythema nodosum and arthralgias. There is a well-established association between CD, ankylosing spondylitis and anterior uveitis. These patients tend to be HLA-B27 positive.[4] Clinically, anterior uveitis symptoms are redness, light sensitivity, pain, and decreased vision. If severe, anterior uveitis can present with an accumulation of inflammatory cells in the anterior chamber called a hypopyon (**Figure 1**). Treatment of an anterior uveitis episode need to be initiated promptly to avoid potential blinding complications such as posterior synechiae, glaucoma, macular edema, cataracts, band keratopathy, and retinal involvement. Initial treatment is with topical corticosteroids and cycloplegic drops. Periocular injection or systemic corticosteroids may be required for more severe cases. In cases of multiple recurrences or chronic evolution, or if topical treatment leads to intolerable side effects, immunosuppression therapy may be considered.

Special considerations must be taken in the pediatric population. Often, children do not complain of blurred vision and uveitis can be less symptomatic. It is particularly important in this age group to proceed to regular ophthalmic follow-up. The prevalence of ocular manifestations of IBD in children is reported to be 0.62-1.82%, uveitis being the most common.[14]

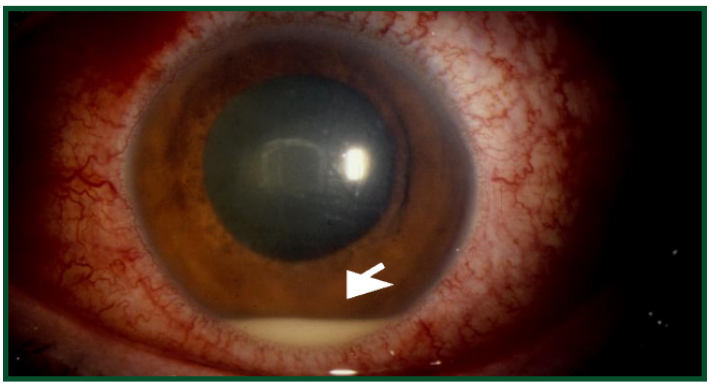

Figure 1. Photo showing the presence of a hypopyon (white line – arrow): sign of severe anterior uveitis ; courtesy of Marie-Lyne Belair, MD, FRCSC and Evangelina Esposito, MD CHM

Differential Diagnosis

Uveitis can be associated with inflammatory diseases other than IBD. The most common association is with ankylosing spondylitis, a type of inflammatory arthritis associated with HLA-B27. It is important not to assume that all cases of IBD presenting with uveitis are from inflammatory causes. Infectious and other non-infectious causes need to be kept in mind and investigated appropriately. Among infectious causes are syphilis, herpetic group (HSV, VZV, CMV), Lyme disease, and tuberculosis. Ocular redness can also be associated with some non-urgent pathologies such as blepharitis, conjunctivitis and keratitis sicca, or more urgent pathologies such as corneal ulcer (a pathology that should always be considered in contact lens wearers), ocular trauma or endophthalmitis (in patients with recent ocular surgery or therapeutic injection for other causes).

Importance of Collaboration in Treatment Decision-making

As mentioned previously, most cases of ocular EIM can be treated with local or periocular corticosteroids. More severe cases or chronic ocular inflammation must be treated more aggressively and with a long-term approach. Uveitis with a chronic course or multiple recurrences requires immunosuppressive therapy to avoid prolonged use of corticosteroids and their associated side effects.[15] Various immunosuppressive agents are used in uveitis treatment. Anti-metabolites such as methotrexate, mycophenolate mofetil and azathioprine are frequently used for severe non-infectious uveitis. When a patient with IBD requires systemic therapy, the choice of the immunosuppressive agent should also consider the presence or absence of ocular EIM. Biological anti-tumor necrosis factor (anti-TNF) agents (mainly infliximab and adalimumab) are effective in treating both IBD and uveitis. These agents are approved for the treatment of isolated non-infectious intermediate, posterior and panuveitis forms of uveitis. In cases of anterior uveitis associated with ankylosing spondylitis, anti-TNF agents have been proven effective in reducing flares of uveitis and improving the control of chronic uveitis.[16,17] Vedolizumab has been introduced recently for the treatment of IBD but its gut-selective inflammatory control appears to limit its effect on EIM prevention as described in a study where patients receiving it were more likely to develop EIMs vs those receiving anti-TNF therapies.[18]

Conclusion

Ocular involvement is prevalent in CD and active IBD. Ophthalmologists must be aware that ocular inflammation can precede the diagnosis of IBD. Physicians treating patients with IBD must be aware of the presenting symptoms of ocular extra-intestinal manifestations. Patients must be informed to seek

medical attention if experiencing such symptoms. They should also have regular ocular examinations to detect eye involvement and potential side effects of IBD treatment. Timely diagnosis and treatment are important to prevent irreversible visual loss.

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