Navigating the complexity of ulcerative colitis

Challenging case example

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Diagnosis ...

Mr E.K. is a 42-year-old construction worker who was diagnosed with ulcerative colitis (UC) 3 years ago after presenting to the emergency department with a 2-week history of bloody diarrhea, lower abdominal pain, and tenesmus. A gastroenterology consultation resulted in flexible sigmoidoscopy with findings supporting the diagnosis of colitis, including fibropurulent exudate found continuously from the rectum to 30 cm. No risk factors for infectious or *Clostridium difficile*–associated colitis were identified. Mr E.K. denied any extraintestinal features of inflammatory bowel disease (IBD). He was admitted to hospital for rehydration, symptom control, and medical management of presumed UC. Biopsies obtained during sigmoidoscopy were consistent with a diagnosis of IBD. Oral prednisone, 40 mg once daily, was initiated and he was discharged 1 week later with substantial improvement in his symptoms and a plan to taper the prednisone by 5 mg weekly.

First remission ...

At a follow-up gastroenterology appointment 6 weeks later, Mr E.K. reported that although he was feeling much better, he continued to experience frequent, bloody bowel movements (up to 8 per day). His prednisone dose had been tapered to 10 mg once daily. Findings of physical examination were unremarkable. Oral 5-aminosalicylic acid (5-ASA), 1 g 3 times a day, was initiated, as was supplementation with the probiotic VSL#3. He continued tapering his prednisone by 2.5 mg weekly without a reoccurrence of symptoms. The 5-ASA dose was also eventually changed to a maintenance dose of 1.5 g twice daily.

Bringing evidence to practice

- **Table 1**[1-7] provides an overview of common drugs used in the treatment of UC.* Oral corticosteroids are usually reserved for UC patients who do not respond to oral sulfasalazine or 5-ASA with or without topical 5-ASA, although they are also suitable for systemically ill patients. The time to effect is 7 to 14 days.[2] Following this, a gradual tapering of the dose is important to reduce symptom relapse.
- If 5-ASA is used for acute UC, the combination of both oral and topical rectal formulations is more effective than either alone.[8,9] While oral 5-ASA is given daily, 5-ASA enemas might only be necessary twice weekly (for both acute and maintenance UC treatment). Combination oral and rectal therapy also allows for lower oral 5-ASA doses, which might reduce the risk of adverse events such as blood dyscrasias and hepatotoxicity.[10] Both oral and rectal 5-ASA products vary in their formulations, affecting their activity in various areas of the lower bowel. Sulfasalazine and 5-ASA are similarly effective; sulfasalazine is less expensive but might be poorly tolerated.
- The probiotic VSL#3 has limited evidence suggesting possible benefit in maintenance treatment of mild to moderate UC.[6]

Difficult year ...

Mr E.K. continued to be closely followed by his family physician and gastroenterologist. He experienced multiple exacerbations of his IBD symptoms, each managed with a tapering course of prednisone. During his fourth exacerbation, the decision was made to initiate azathioprine at a dose of 50 mg once daily, with plans to add 25 mg weekly to a target dose of 100 mg/d. He continued taking the 5-ASA. Prednisone was restarted at 30 mg once daily and successfully tapered by 5 mg every week without a reoccurrence of his symptoms. At a follow-up appointment with his gastroenterologist, his azathioprine dose was increased to 150 mg once daily. Mr E.K.'s dose of 5-ASA was increased to 1.5 g 3 times daily in hopes of maintaining remission.

Three months after starting the azathioprine, Mr E.K. developed diffuse myalgia and subjective muscle weakness of the upper and lower extremities. At work, he had difficulty with overhead lifting and climbing ladders. His serum creatine kinase level was elevated at 589 U/L. Complete blood count, creatinine, electrolyte, liver enzyme, and thyroid-stimulating hormone levels were within normal limits. Mr E.K.'s azathioprine was stopped, with resolution of his muscle symptoms during the next 4 weeks. His creatine kinase level decreased slightly to 524 U/L. Mr E.K.'s gastroenterologist considered initiating a biologic response modifier such as infliximab.

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*The full version of the RxFiles Inflammatory Bowel Disease chart is available at www.cfp.ca. Go to the full text of the article online, then click on CFPlus in the menu at the top right-hand side of the page.

Table 1. Overview of common drugs for the treatment of UC

DRUG	TIME TO EFFECT	ROLE	COMMENTS
SSZ Salazopyrin	2-4 wk	Acute and maintenance therapy for UC	Dose-related side effects; less expensive than 5-ASA
5-ASA (mesalamine) Asacol Pentasa Mesasal Salofalk	2-4 wk	Acute (higher doses) and maintenance therapy (lower doses) for UC[1]	Often better tolerated than SSZ All oral formulations are active in rectum and proximal and distal colon; some products are also active higher in the gastrointestinal tract. Foam, enema, and rectal suppository formulations are useful for distal or rectal disease. Effective reach of effect: • suppository: 10 cm • foam: 15-20 cm • enemas: splenic flexure[2] Foam might be preferred for patients who have difficulty retaining enemas
Corticosteroids Prednisone, oral Budesonide (Entocort) Hydrocortisone (Cortifoam, Hycort, Cortenema) Hydrocortisone, IV (Solu-Cortef) Methylprednisolone, IV (Solu-Medrol)	< 7-14 d	Acute exacerbations of UC when severe or unresponsive to 5-ASA or SSZ	Higher initial doses required until clinical improvement is seen, then taper gradually and discontinue; other maintenance agents safer for maintenance of remission Oral or IV administration; IV administration useful in more severe or fulminant disease Anti-inflammatory dose equivalency: prednisone 5 mg = methylprednisolone 4 mg = hydrocortisone 20 mg Topical enemas and foams useful for distal colon and rectal disease Budesonide less bioavailable than prednisone; less effective, fewer side effects, more expensive
Purine antimetabolites AZA (Imuran) 6MP (Purinethol)	3-6 mo	Moderate to severe UC, for patients not responding to corticosteroids and for those unable to adequately wean from corticosteroids (eg, steroid sparing)	Maintenance doses are the same as induction doses Requires monitoring of CBC, LFTs, and for symptoms of pancreatitis Methotrexate lacks evidence in UC but can be tried if AZA is ineffective or not tolerated[3]
Biologic response modifiers (TNFα inhibitors) Infliximab (Remicade) Adalimumab (Humira)	Within 2 wk	Acute and maintenance therapy for UC in moderate to severe disease that is not responsive to standard treatment; avoid in active infection, acute heart failure, or hypersensitivity	Very effective in some, but also considerable potential harms, including increased risk of infection (eg, viral [especially varicella], fungal, or bacterial and reactivation of tuberculosis or hepatitis B), infusion reactions (especially with infliximab),[4] and rare lymphoma or drug-induced lupus. Recent meta-analysis found that in the short term, biologics had a higher rate of total adverse reactions vs control (NNH = 30, 95% CI 21-60), but the rate of serious adverse events was not different.[5] Long-term research is lacking
Cyclosporine	2-3 wk	Effective as surgery-sparing agent in acute, severe, steroid-refractory UC; useful as interim therapy while waiting for effect of purine antimetabolite	Rarely used with availability of the biologics
Probiotic VSL#3	NA	Maintenance therapy of mild to moderate UC	Limited evidence suggests benefit in maintenance therapy of mild to moderate UC[6]

5-ASA—5-aminosalicylic acid, 6MP—mercaptopurine, AZA—azathioprine, CBC—complete blood count, CI—confidence interval, IV—intravenous, LFT—liver function test, NNH—number needed to harm, SSZ—sulfasalazine, TNF—tumour necrosis factor, UC—ulcerative colitis.
Adapted from Sutherland and MacDonald.[7]

Bringing evidence to practice

- Azathioprine (1.5 to 2.5 mg/kg daily) might be effective in addition to 5-ASA as maintenance therapy for UC patients who require ongoing or frequent steroid treatment (off-label use).[11] As the onset of effect is slow, allow up to 6 months before reassessing therapy. In Mr E.K.'s case, was the dose too high too soon? It is possible that a longer trial at the 100-mg daily dose might have resulted in further benefit without the increased risk of adverse events associated with an increased dose.[12]
- With the frequent use of prednisone, consideration should be given to the need for osteoporosis prevention measures such as lifestyle modifications (eg, smoking cessation, exercise) and supplementation with vitamin D (eg, 1000 IU daily) and calcium (to ensure 1200 mg total daily intake of elemental calcium). A thorough fracture risk assessment is important and would guide evaluation of the need for a bisphosphonate.[13]
- Biologics such as infliximab suppress the immune system and increase infection risk. This risk is further increased if a patient is concomitantly taking other immune suppressants. When diagnosing UC, the eventual need for a biologic response modifier and the resulting immunosuppression should be considered. With this potential, consider the need for chest x-ray scan, tuberculosis and hepatitis screening, and administration of any necessary live vaccines. Standard vaccines should be administered when appropriate, including tetanus, diphtheria, poliomyelitis, human papillomavirus, varicella, herpes zoster, influenza, pneumococcal, hepatitis A and B, and measles-mumps-rubella. Thereafter, patients should receive annual inactivated influenza vaccines.[14-16]

Another admission and another medication ...

Within weeks of discontinuing the azathioprine, Mr E.K. experienced a severe flare of IBD symptoms, with up to 16 bloody bowel motions per day, disabling fatigue, and left lower quadrant pain relieved with defecation. He was admitted to hospital for further investigation and treatment. He received 2 units of packed red blood cells for anemia (hemoglobin 85 g/L). A limited colonoscopy revealed severe colitis and numerous scattered pseudopolyps and surrounding ulcerations. Biopsy results demonstrated florid acute and chronic inflammation. The acute exacerbation was treated with intravenous (IV) corticosteroids, and infliximab induction began with the first of 3, 300-mg IV doses. After 1 week he was discharged taking prednisone, 20 mg twice daily, to be tapered slowly during the next 2 months. Arrangements were made for Mr E.K. to receive follow-up infliximab infusions at 2, 6, and 14 weeks after induction, then to continue receiving infusions every 8 weeks if the prednisone was successfully tapered. With his third and fourth infliximab infusions, Mr E.K. experienced acute transfusion reactions, with symptoms of fever, headache, flushing, and hypotension. This occurred despite pretreatment with 50 mg of oral diphenhydramine and 100 mg of IV hydrocortisone. He was reluctant to continue with the infliximab. As a result, therapy with adalimumab was initiated at 160 mg subcutaneously every other week for 2 doses, then 40 mg subcutaneously every 2 weeks. He continued to take 1.5 g of oral 5-ASA 3 times daily.

Bringing evidence to practice

- Fulminant, severe UC exacerbations can be managed by IV corticosteroids.[17] A significant clinical

effect would be expected within 7 to 10 days. In patients who do not improve with this treatment, there is evidence that infliximab might be effective in inducing remission (number needed to treat is 5 at 8 weeks).[18-20] Biologic therapies usually take effect within 2 weeks.

- Infusion reactions and delayed hypersensitivity-like reactions (after 3 to 14 days) are common (approximately 10% of patients) with IV infliximab. Slowing the rate of infusion (over 2 to 4 hours) as well as pretreatment with acetaminophen, diphenhydramine, and IV hydrocortisone can reduce the incidence of reactions. Such reactions are uncommon with adalimumab, which is administered subcutaneously.
- Monitoring of patients using biologic therapies should include careful surveillance for infection.[21] Early detection, routine history and physician examination, and immediate initiation of supportive care are critical, as signs and symptoms might be blunted as a result of the anti-inflammatory effects of the biologic therapies. Tumour necrosis factor–α antagonists should be discontinued when there is clinical suspicion of infection and should not be restarted until the patient has stabilized. It is essential that the patient be educated about the early signs and symptoms of infection.
- Probiotics should likely be stopped once a biologic agent is started, as continuation could theoretically increase the risk of infection.
- With poor response to drug treatment or emergence of adverse events, the option of total colectomy as "curative" in UC should be entertained.

Serious complication ...

One month after beginning adalimumab therapy, the patient once again reported a near complete resolution of his symptoms and a successful taper off of his prednisone. This remission lasted only 3 months, and Mr E.K. was restarted on 60 mg of prednisone for a severe flare of his symptoms. One week later, he began to complain of malaise, fever, and difficulty with balance. Over the following day, the fever worsened and he developed uncontrollable shaking of his upper limbs. That evening he slept on a reclining chair; the following morning he was found unresponsive by his wife and was transferred to hospital by ambulance with possible seizure activity en route. He was admitted to the intensive care unit and was eventually diagnosed with a limbic viral encephalitis. He remained in hospital for many months, experiencing numerous sequelae and complications, including ongoing gastrointestinal bleeding, recurrent sepsis, acute renal failure secondary to acute tubular necrosis, multiple deep vein thromboses, dysphonia, urinary incontinence, disequilibrium, and lower extremity weakness.

Three years after diagnosis, after several hospital admissions and numerous exacerbations, Mr E.K. underwent a total colectomy for definitive treatment of his UC.

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