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REVIEW

New developments in ulcerative colitis: latest evidence on management, treatment, and maintenance

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Abstract

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disorder that involves any part of the colon starting in the rectum in a continuous fashion presenting typically with symptoms such as bloody diarrhea, abdominal pain, and rectal urgency. UC is diagnosed based on clinical presentation and endoscopic evidence of inflammation in the colon starting in the rectum and extending proximally in the colon. The clinical presentation of the disease usually dictates the choice of pharmacologic therapy, where the goal is to first induce remission and then maintain a corticosteroid-free remission. There are multiple classes of drugs that are available and are used based on the clinical severity of the disease. For mild-to-moderate disease, oral or rectal formulations of 5-aminosalicylic acid are used. In moderate-to-severe UC, corticosteroids are usually used in induction of remission with or without another class of medications such as thiopurines or biologics including anti-tumor necrosis factor, anti-integrins, or Janus kinase inhibitors for maintenance of remission. Up to 15% of the patients may require surgery as they fail to respond to medications and have risk of developing dysplasia secondary to longstanding colitis.

Keywords: colitis, inflammatory bowel disease, ulcerative colitis.

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Introduction

Ulcerative colitis (UC) was first described in mid-1800s.[1] It is an idiopathic, chronic inflammatory disorder of the colonic mucosa that commonly involves the rectum and may extend in a proximal and continuous fashion to involve other parts of the colon.[2] The disease typically affects individuals in the second or third decade of life with hallmark clinical symptoms of bloody diarrhea and rectal urgency with tenesmus.[3,4] The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes.[5,6] There are multiple drug classes discussed in this review that can be used to treat acute exacerbation of the disease and for maintenance of remission. However, even with medical therapy, up to 15% of patients will require surgery to treat UC or disease complications of dysplasia.

Overall, the incidence of inflammatory bowel disease (IBD) has traditionally been highest in North America and Western Europe with increasing incidence in the mid-20th century. However, incidence of IBD is increasing in emerging populations in continental Asia.[7,8] In North America, the incidence of UC is 2.2–14.3 cases per 100,000 persons per year, and its prevalence is 37–246 cases per 100,000 per year.[7] The exact pathogenesis of the disease is not well understood but there are genetic factors that are attributed to the risk of developing the disease accompanied by epithelial barrier defects and environmental factors. Currently, a number of genetic and environmental factors that increase the risk of developing UC are identified.[9] A westernized lifestyle and diet including cessation of tobacco use, fatty diet, stress, and medication use and high socioeconomic status are all associated with the development of IBD.[10] Among many such factors, tobacco smoking and appendectomy are linked to milder disease, fewer hospitalizations, and decreased incidence of UC but the reverse is true for Crohn's disease.[11,12]

The diagnosis of UC is based on the clinical presentation and symptoms consistent with the disease and findings on colonoscopy or sigmoidoscopy showing continuous colonic inflammation starting in the rectum. Pathologic findings of chronic colitis confirm the diagnosis.

Disease approach, assessment of clinical severity, and disease management

Initial treatment is based upon disease severity and extent. Patients can present with mild, moderate, or severe disease – stratification based on clinical severity is used to guide medical and pharmacologic management. The goals of treatment are induction of remission followed by maintenance of remission in conjunction with steroid-free treatments in the long-term management.[6] Historically, the Truelove and Witts criteria are utilized to stratify patients with mild, severe, or fulminant colitis (Table 1). Patients categorized as having mild clinical disease have less than four stools per day with or without blood with no signs of systemic toxicity. Mild crampy abdominal pain and tenesmus are common clinical symptoms. In moderate–severe disease, patients have abdominal pain, frequent loose bloody stools (typically more than four per day), and mild anemia not requiring blood transfusions. They also have minimal signs of systemic toxicity such as low grade fever. In contrast, patients with fulminant disease present with over six loose bloody stools with severe abdominal cramps and systemic toxicity such as fever or tachycardia. They also have manifestations such as anemia or an elevated erythrocyte sedimentation rate (ESR)/c-reactive protein (CRP). In addition to assessing patients with the Truelove and Witts criteria, the colon should be evaluated endoscopically either with a sigmoidoscopy or colonoscopy, depending on the clinical presentation and any validated score such as Mayo Endoscopy score or Ulcerative Colitis Endoscopic Index of Severity (UCEIS) should be utilized[13] (Tables 2 and 3). The endoscopic Mayo score classifies disease as mild, moderate, or severe based on the erythema, erosions, ulcers, and/or severe friability. The management of severe and fulminant clinical disease differs from that of mild-to-moderate disease. Historically, step-up therapy was used for treating any flare ups of UC. However, recent evidence suggests a top down approach using effective therapy such as anti-tumor necrosis factor (TNF) often with immunomodulator to control severe disease; thus, patients with severe clinical disease on presentation may be treated with biologics early on as opposed to use of mesalamines that are effective only in mild-to-moderate disease.

Mild-to-moderate disease

5-Aminosalicylate

There are multiple 5-aminosalicylate (5-ASA) compounds available. One of the first drugs available was sulfasalazine. Sulfasalazine is a prodrug that is partially absorbed in the jejunum and passes to the colon where it is reduced by coliforms to sulfapyridine and its active form, 5-ASA.[14] 5-ASA is primarily responsible for efficacy of sulfasalazine. Other 5-ASA products (i.e. mesalamine) are formulated to release in the colon via a number of different mechanisms including both bacterial-mediated release and pH-mediated release. In azo-bond prodrug, the mesalazine is synthesized as a prodrug binding via an azo-bond to a transport molecule. Due to the presence of an azo-bond, it is not absorbed in the upper gastrointestinal tract. The bond is subsequently cleaved by bacterial action in the colon by azoreductase, releasing the active mesalazine component of the drug. In pH-mediated release formulations, the active drug is encapsulated in an enteric coating to control the site of drug release. Other available formulations include time-dependent release, which consists of microspheres of mesalazine encapsulated within a semipermeable membrane that produces time and moisture-dependent release of active drug. Although the different release mechanisms may be of benefit for certain patients, the recent American Gastroenterological Association (AGA) guidelines on mild-to-moderate UC do not suggest changing mesalamine based on release formulation in someone who is not responding adequately to the initial mesalamine release mechanism.[15]

The dosing per pill is variable but in general, these medications can be taken once a day or in twice daily regimens. The initial

Table 1. Truelove and Witts' severity index.

	Mild	Moderate	Severe
Bowel movements (no. per day)	Fewer than 4	4–6	Six or more plus at least one of the features of systemic upset (marked with *)
Blood in stools	No more than small amounts of blood	Between mild and severe	Visible blood
Pyrexia (temperature greater than 37.8°C) *	No	No	Yes
Pulse rate greater than 90 bpm *	No	No	Yes
Anemia *	No	No	Yes
Erythrocyte sedimentation rate (mm/hour) *	30 or below	30 or below	Above 30

Adapted from Sturm et al.[13]

Table 2. Endoscopic Mayo score.

Mucosal appearance at endoscopy	Normal or inactive disease	0
	Mild disease (erythema, decreased vascular pattern, mild friability)	+1
	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	+2
	Severe disease (spontaneous bleeding, ulceration)	+3

Adapted from Sturm et al.[13]

approach for mild-to-moderate disease is to start oral and topical 5-ASA. Oral 5-ASA is started at a full-strength dose of 4.8 g/day for induction of remission. Over time, this can be reduced to a maintenance dose of 2.4 g/day. In patients who have not achieved remission on oral therapy, combining oral and rectal therapy is more effective in inducing remission.[16–18]

In patients with more limited disease of the rectum and/or sigmoid colon, some patients may opt for only topical rectal treatments and defer oral therapy due to cheaper costs, quicker response time, and typically requiring lesser frequent dosing when compared to oral therapy. However, if the patient fails to respond to topical therapy, then oral therapy should be added to the regimen. Topical therapy with 5-ASA can be given via suppository or enema.[19–21]

In left-sided colitis and pancolitis, combination therapy has proven to be more effective in achieving remission and its maintenance than isolated oral therapy or isolated topical therapy.[22] In general, 5-ASA drugs start working within 2–4 weeks and they show response in up to 80% of patients (when selected appropriately).[19] Once remission is achieved, patients are continued on the drug for maintenance therapy. Given the safety of the drug and lack of any dose-dependent side-effect profile, some practitioners opt to keep patients on the 4.8 g/day dose while others will lower the dose to 2.4 g/day when dosing for maintenance. There are no data to support doses that are less than 2.4 g/day, and these doses should be avoided.[15]

In patients with only mild-to-moderate disease who fail to respond to mesalamine, one can consider adding a steroid-containing foam or enema in combination with 5-ASA therapy.[23] In patients who have an inadequate response to the combination of oral 5-ASA and topical 5-ASA/steroids in 2–4 weeks, the budesonide multimatrix (MMX) formulation can be considered.[24,25] Although these steroid formulations are relatively safe given their lack of systemic absorption, they are not as effective as oral prednisone. The initial study importantly compared budesonide MMX to mesalamine and not prednisone.[26] Additionally, none of these steroid formulations are approved for long-term maintenance of remission.[15]

Although side effects can happen with both sulfasalazine and 5-ASA, sulfasalazine appears to have a wider range of more serious adverse events. Both anemia and abnormal liver tests are associated with sulfasalazine use and, to that end, patients should have routine complete blood counts (CBC) and liver function tests (LFTs) checked while on sulfasalazine. Additionally, to reduce the risk of anemia, patients should take folic acid 1 mg daily. Other side effects include nausea, headaches, fevers, and rash. Headaches and nausea are often dose dependent but slow titration of the dose can minimize these issues. However, sulfasalazine should be discontinued if the patient experiences idiosyncratic drug reactions such as skin rash, pancreatitis, pneumonitis, and agranulocytosis, and the patient should not be rechallenged. Approximately, 25% of patients stop using sulfasalazine due to its broader side-effect profile compared to mesalamine.

In contrast, mesalamine is a very safe and effective medication. It is extremely rare to develop any side effects on the drug. Up to 3% of patients may experience paradoxical worsening of diarrhea, and stopping the drug may be helpful.[27] Interstitial nephritis is a very rare side effect occurring in less than 0.2% of cases. Routine monitoring of kidney function is recommended to screen for interstitial nephritis.[28]

Oral budesonide and rectal budesonide formulations carry little to no risk. Rectal budesonide foam was more efficacious in inducing remission in patients when compared to placebo.[29] Studies show that there is a small change in systemic cortisol levels, but classic steroid-related side effects are not seen with these drugs. There are case reports of steroid-related side effects with oral budesonide when used in high doses for long term.[30]

Moderate-to-severe disease

Systemic corticosteroids are typically given first line for induction of remission in cases of moderate-to-severe disease. Oral steroids are used in most cases, but in up to 15% of patients, the disease may present as acute severe ulcerative colitis necessitating hospitalization and intravenous steroids.[31] Steroids are used in the acute inflammatory phase of the disease to assist with induction of remission but should always be bridged with a steroid-sparing agent for a goal of long-term steroid-free maintenance of remission.[6] Intravenous or oral steroids should never be used for long-term therapy as they are associated with a myriad of irreversible side effects such as weight gain, cataracts, osteoporosis, hypothalamic pituitary axis suppression, and immunocompromised state. Several classes of drugs can be used for maintenance of remission including thiopurines, anti-TNF agents, anti-integrins, and Janus kinase inhibitors that are discussed in detail in this review.

Corticosteroids

As stated earlier, corticosteroids are only used for induction of remission. Oral prednisone is usually the first choice of

Table 3. UCEIS (Ulcerative Colitis Endoscopic Index of Severity) descriptors and definitions.

Descriptor	Likert scale (anchor points)	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliteration (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderator severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

Adapted from Sturm et al.[13]

treatment at a dose of 40–60 mg daily.[6] Higher doses have not been shown to be more effective. In most patients, oral steroids are useful for induction of remission; however, if symptoms do not respond adequately, intravenous steroids should be used and the patient should be hospitalized.[32] These patients are at risks of developing complications, and close monitoring in the hospital setting is recommended. Intravenous methylprednisone is usually preferred at a dose of 40–60 mg daily (e.g. 20 mg every 8 hours) over intravenous hydrocortisone that may cause sodium retention.[31] Approximately two-thirds of the patients respond to this treatment. There are no specific recommendations for tapering the steroid dose, but it is advised to transition to an oral prednisone dose of 40–60 mg daily until significant clinical improvement occurs and then taper with a dose of 5–10 mg weekly until a dose of 20 mg is reached, then a tapering of 2.5–5 mg every week is advised.[6,33]

If there is no meaningful response to the intravenous steroids in acute severe disease within 3–5 days as determined by the Oxford index, steroid-refractory disease should be considered and rescue therapy with other therapeutic entities – either infliximab or cyclosporine – should be initiated.[34]

Steroids are very effective in inducing remission but have a number of adverse effects. In addition, they are ineffective in maintaining remission.[35] The frequency and severity of steroid toxicity are substantial and may involve virtually any organ system and many of these complications are irreversible[6,36] such as obesity, hypertension, diabetes, cataracts, glaucoma, depression, anxiety, insomnia, irritability, and avascular necrosis. Additionally, the risks of opportunistic infections in patients with inflammatory bowel disease patients using steroids are increased three-fold and are more common over the age of 50 years.[6,37] The risks are increased synergistically when steroids are used concomitantly with other immunosuppressive therapies such as infliximab or thiopurines.[37]

Thiopurines

Thiopurines (azathioprine [AZA] and 6-mercaptopurine [6-MP]) have a steroid-sparing effect and are used for maintenance of remission when steroids are withdrawn. Thiopurines have no role for induction of remission. AZA and 6-MP are slow-acting medications, and it can take 3 months before therapeutic concentrations are achieved. Hence, a longer course of steroids is often required until the pharmacologic effect of thiopurines is exerted.

AZA and 6-MP have multiple side effects where leukopenia and elevation in transaminases are the most common. These are dose-dependent side effects of the medication and are typically related to the activity of thiopurine methyltransferase (TPMT) enzyme. These adverse effects occur in 10% of the patients and usually in the first month of therapy.[38] It is recommended to monitor CBC and LFTs in patients on treatment with thiopurines frequently when first starting the drug and then periodically thereafter. Given that there is a small risk of mortality secondary to severe leukopenia and infections, the current guidelines recommend testing for TPMT enzymatic activity before starting thiopurines.[39–41] Another limiting side effects is intractable nausea. There is 0.3% of the population

with homozygous mutations for TPMT, and they have negligible enzyme activity. In these cases, one should avoid using a thiopurine. If the enzymatic activity is intermediate, the starting dose should be reduced by 25–50%.[39,42]

Thiopurines are also associated with an increased risk of malignancy. There is a risk of non-melanoma skin cancer, and an annual skin exam is advisable to mitigate this risk. Patients should be advised to wear sunscreen and avoid prolonged exposures to the sun. Additionally, there is also an increased risk of lymphoma in patients treated with thiopurines. The incidence is small and is quantified as 1 in 1000-person years.[43] The risk of developing lymphoma is most pronounced in patients with negative Epstein Barr virus at the time drug is initiated, and it is advised to not use thiopurines in these patients.[44] Use of thiopurines over 2 years appears to be a common denominator in cases of hepatosplenic T-cell lymphomas. This is particularly significant in young men under the age of 35.[45]

Other nonspecific side effects include abdominal pain, nausea, vomiting, and pancreatitis. Most of these side effects aside from the pancreatitis are self-limited and often dissipate over time. In cases of pancreatitis, however, the drug should be stopped and not reinstituted.

Anti-TNF agents (infliximab, adalimumab, and golimumab)

Different from thiopurines, anti-TNFs can be used for both induction and maintenance of remission.[46,47] They are most often used with corticosteroids to induce remission.[48] The American College of Gastroenterology (ACG) and the European Crohn's and Colitis Organisation (ECCO) recommend the use of infliximab for induction of remission in patients with glucocorticoid-refractory or glucocorticoid-dependent disease.[6,49] The recommendations also suggest use in patients with severe disease where standard treatment has failed or is not responding to high-dose steroids in hospital.[6] There are three anti-TNF agents that are approved to be used in moderate-to-severe UC: infliximab, adalimumab, and golimumab.[46,50,51]

Infliximab is a chimeric (combination of human and murine) IgG1 monoclonal antibody that binds with affinity to TNF-ά and neutralizes its biologic activity.[52] Adalimumab and golimumab are 100% human antibodies. There are several clinical trials on infliximab evaluating its efficacy and its use in UC.[50] The number-needed-to-treat is four to induce one case of remission.[53] All anti-TNF agents are effective, with infliximab being slightly more efficacious than adalimumab with regard to inducing a clinical response or mucosal healing, but these results are not well established.[54] Infliximab is an infusion that is typically infused over 2 hours. In contrast, both adalimumab and golimumab are subcutaneous injectables. All of these agents are effective for induction and maintenance of remission in UC. However, only infliximab dosing is weight based and has efficacy in acute severe UC refractory to intravenous steroids.[55]

Anti-TNF agents are safe but there are many recognized adverse effects associated with them, which can be minimized by preinitiation testing and careful monitoring after starting the treatment. Injection site reactions are seen in less than 10% of the patients and these reactions are usually mild. Infusion reactions with infliximab can be acute or delayed. Acute reactions occur in the first 24 hours of infusion. True anaphylaxis (IgE mediated) may occur in some patients; however, in most patients it is nonallergic or an anaphylactoid reaction.[56,57] If allergic reaction is suspected, the drug should be discontinued, and the patient should not be rechallenged with infliximab.

The most common significant side effect of anti-TNF agents are infections. Most infections are mild, such as common cold, otitis media, and sinusitis. However, these patients are at increased risk of developing serious infections due to their immunocompromised state. All patients must undergo tests to eliminate latent tuberculosis (TB) and chronic hepatitis B infection before starting therapy as both are at increased risk of reactivation if found to be latent in the patient.[58] There are numerous rare side effects associated with anti-TNF therapy. One of the rare but more commonly seen side effects is the nonspecific elevation of liver enzymes. The elevated liver enzymes can be a reaction to the infliximab itself and considered a drug reaction that should reverse with cessation of the drug, but a second condition potentially brought out by infliximab is autoimmune hepatitis that may or may not be directly related to the infliximab. Often in this scenario, the condition persists even with cessation of the infliximab.[59] Periodic testing of liver function tests is recommended. Liver enzymes usually tend to normalize once the drug is discontinued. Although rare, there are case reports of acute liver failure requiring liver transplantation with the use of infliximab.[60]

The risk of cancer with anti-TNF therapy is debatable. There appears to be an increased risk of melanoma skin cancer, and a yearly skin exam is advisable. There is conflicting evidence about increased risks of lymphoma; therefore, there are no specific screening recommendations for this while on anti-TNF therapy.

Anti-TNF agents can take up to 6–12 weeks to achieve initial response and mucosal healing. Therapeutic drug monitoring is the new standard of care in treatment of IBD patients. In addition, all anti-TNF agents have risks of developing antibodies altering its efficacy.[61] Hence, checking drug levels and levels of antibodies may allow tailoring of drug dosage or choice of medication to achieve a clinical response or remission.[61,62]

Calcineurin inhibitors

Cyclosporine has a role in induction of remission in severe-to-fulminant steroid-refractory colitis. Although there are some

limited data for the use of tacrolimus, they are not recommended for typical use. Cyclosporine is used as a rescue therapy at select IBD centers, but it does not have a role for long-term therapy. Transition to oral cyclosporine from a continuous infusion is typically performed after patients show response to intravenous cyclosporine. When transitioning to oral cyclosporine, patients are also started on a long-term maintenance plan consisting of thiopurines or anti-integrins.[6] The oral cyclosporine is usually discontinued within 3 months. Even though, over 60% of patients with severe UC respond to intravenous cyclosporine, most will still ultimately require colectomy in 5–7 years.[63]

Cyclosporine is administered as a continuous infusion at a dose of 2–4 mg/kg per 24 hours. As studies show similar efficacy and lesser toxicity with the lower dose of 2 mg/kg, many clinicians start with this dose.[64,65] It is recommended to maintain intravenous use of glucocorticoids in these patients. Because of the extent of immunosuppression given the steroids, cyclosporine, and a long-term maintenance drug, prophylaxis against pneumocystis pneumonia (PCP) is recommended.

Conversion from the continuous infusion of cyclosporine to oral cyclosporine should be sought early in the course of treatment once a patient shows adequate response to the intravenous dose. Blood levels of cyclosporine should be checked every day to every alternate day with goal levels ranging between 200 and 400 ng/mL in doses 2–4 mg/kg, respectively. Doses can be adjusted based on efficacy and toxicity and rounded off to nearest 25 mg to aid oral conversion, which is calculated by doubling the intravenous dose that led to resolution of symptoms and is administered 12 hours apart. Trough levels are checked before the fourth dose. Levels of 200–300 ng/mL are optimum as levels that are less than 200 ng/mL are associated with loss of response.[66]

Patients receiving intravenous cyclosporine should show initial response in 2–3 days of starting treatment, evidenced by clinical resolution of symptoms of abdominal pain, blood in stool, and may have formed stools with normalization of laboratory tests. Before transitioning to oral cyclosporine, patients should be able to tolerate an oral diet. In patients who fail to show resolution of symptoms of severe disease in 72 hours, *Clostridioides difficile* should be tested and treated if positive. Unfortunately, patients failing to respond within 72 hours likely will need a colectomy.

Patients responding to intravenous cyclosporine and successfully transitioned or oral cyclosporine can be discharged on oral cyclosporine, oral steroids, a long-term steroid sparing drug (e.g. thiopurine or anti-integrin) and PCP prophylaxis with a tapering regimen of steroids over the 4–6 weeks followed by tapering of oral cyclosporine over the ensuing 3 months. Patients who cannot get off steroids should be evaluated for surgery.

Adverse effects are common with use of cyclosporine and sometimes, life threatening. Patients must be monitored for electrolyte abnormalities like hyperkalemia and hypomagnesemia. Nephrotoxicity is a common side effect and is usually reversible after discontinuation of the drug. Neurotoxicity may manifest as mild tremor or sometimes, severe headache, visual abnormality or seizures.[67] Calcineurin-inhibitor pain syndrome is characterized by symmetrical pain in feet and ankles. Symptoms may improve once the drug is stopped or by use of calcium channel blockers.[68]

Anti-integrins

Integrins are proteins that regulate migration of leucocytes to the intestines. Vedolizumab is a fully humanized recombinant monoclonal antibody that binds to alpha4–beta7 integrin and prevents migration of leucocytes to the gut. Vedolizumab has shown to be effective and is approved for use to induce and maintain remission in moderate-to-severe active UC.[69,70] It is the first anti-integrin approved for use in UC. The initial therapeutic response is usually seen in 6 weeks of treatment, but it can take up to 6 months for the full maximal benefit to be seen.

With regard to safety, vedolizumab is the safest biologic available with minimal side effects such as intestinal infections – attributed to its mechanism of action that is very gut therapeutic.[71] There is a small theoretical risk of developing progressive multifocal leukoencephalopathy (PML), which is a viral infection of the brain resulting in severe disability and death and has been associated with the use of anti-integrins. However, in the initial studies there are no reported cases of PML with vedolizumab.[71,72] Upper respiratory tract infections are the most common infections in patients on treatment with vedolizumab. There is no increased incidence of abdominal infections and lower respiratory tract infections with vedolizumab when compared to placebo.[71] Infusion-related reactions are also identified as an adverse event of vedolizumab with an incidence of <5% with most of these reactions being mild to moderate.[71,72] These are mostly self-limiting and do not usually require the discontinuation of the drug.

Tofacitinib

Tofacitinib is a Janus kinase inhibitor and was recently licensed in 2018 for treatment of moderate-to-severe active UC.[73] The timing and decision to use is similar to that of anti-TNFs or vedolizumab. It is indicated for treatment of adult patients with moderate-to-severe UC, but it is not recommended for use in combination with other biologics or potent immunosuppressants such as a thiopurine or calcineurin inhibitor.[73] A decision to start treatment with tofacitinib should be based on the patient's compliance with drug therapy and comfort with the drug's adverse events profile. In the United States insurance coverage and costs also need to be considered. Initial drug response can be seen in 6 weeks.

Tofacitinib is the first oral formulation of a small molecule that is taken twice a day. It is available in doses of 5 mg and 10 administered twice a day. The lowest effective dose should be used to maintain the response. If adequate therapeutic benefit is not achieved after 16 weeks of 10 mg twice a day dosing, it must be discontinued. Dose adjustment is required in

moderate-to-severe renal impairment and it is recommended to cut down to a half-daily dose compared with the dose given to patients with normal renal function. It is not recommended to use tofacitinib in patients with severe hepatic impairment. Half-dosing should also apply to those patients receiving concomitant CYP 3A4 inhibitors such as ketoconazole.[73]

Adverse effects of tofacitinib are similar to anti-TNF agents.[74] Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in the clinical trials with tofacitinib.[73] Patients with UC on 10 mg twice daily were associated with a greater risk of serious infections compared with those on 5 mg twice daily. Additionally, opportunistic herpes zoster infections including meningoencephalitis, ophthalmologic, and disseminated cutaneous were seen in patients on 10 mg twice daily.[73] To mitigate the risk of zoster activation, it is recommended that these patients should be vaccinated against zoster.

Before starting tofacitinib, patients should be evaluated and tested for latent or active TB. In patients who are tested positive for latent TB, it is recommended to consult an infectious disease specialist to whether or not to initiate anti-TB therapy before starting the treatment with tofacitinib. Other side effects include neutropenia and it is recommended that patients should undergo episodic checking of a CBC with differential. It is also associated with an increase in liver enzymes of up to three times the upper limit of normal. Reduction of dose of tofacitinib in these patients resulted in normalization of liver enzymes.[75]

Conclusion

UC is a chronic inflammatory condition where medications are used to induce remission and maintain a steroid-free remission. Up to 15% patients may require colectomy due to inability to control the disease. The choice of medication depends upon the clinical stage of the disease. Contrary to the historical treatment paradigm of a bottom-up *versus* top-down strategy, now the recommendation is to treat the underlying severity of disease with medications that are most appropriate for that level of disease severity. In cases of mild-to-moderate disease severity, mesalamine is preferred as it is the safest available drug for the management of UC with a 0.2% risk of interstitial nephritis. However, if the disease is not responding adequately to mesalamine or if the disease is categorized as moderate-to-severe, then one should utilize immunosuppressants, and biologics including anti-TNF, anti-integrin, or a small molecule Janus kinase inhibitors. Thiopurines including azathioprine and mercaptopurine have been utilized for decades in the management of UC, but they only have a role in maintenance of remission and can take up to 3 months to achieve efficacy. In contrast, anti-TNF medications including infliximab, adalimumab, and golimumab all have efficacy for induction of remission and maintenance of remission. The drugs are fairly equivalent, but infliximab has greater bioavailability, as it is administered intravenously, and can be dosed based on one's weight. These drugs have side effects from the immunosuppression but no more than a thiopurine. The safest available biologic is vedolizumab that is a gut-specific anti-integrin. Given its gut specificity it does not carry many side effects. The newest group of drugs is the small molecule Janus kinase inhibitors. Tofacitinib is an oral pill taken twice a day that is likely to be quite desirable to patients given the mode of administration. However, it still retains a side-effect profile that is equal to, or more significant than, anti-TNF medications. All of these drugs should be considered in the appropriate setting based on the severity of the UC. Most importantly, though, no patients should be left on long-term corticosteroids.

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