REVIEW ARTICLE

# Osteopathic Primary Care Treatment Options for Ulcerative Colitis

Amanda Fernandez, OMS IV[1]; Ronald Januchowski, DO, FACOFP[1]

[1]Edward Via College of Osteopathic Medicine-Carolinas Campus, Spartanburg, SC

**KEYWORDS:**

Drug Therapy

Osteopathic Manipulative Medicine

Ulcerative Colitis

ABSTRACT:

Introduction: Ulcerative colitis is a multifactorial, chronic inflammatory disease of the bowel that can cause physical, social and emotional injury to the patient. While perhaps not always making the initial diagnosis or providing primary treatment, the primary care physician can play a critical role in providing direction and clarity to the overall treatment plan for the patient. In addition, monitoring for complications or side effects of treatment will help maintain the patient's optimal health.

Methods: A literature search using PubMed, NCBI and WorldCat.org was done using the terms ulcerative colitis treatment, psychosocial association of ulcerative colitis, surgical management of ulcerative colitis, epidemiology of ulcerative colitis, the pathophysiology of ulcerative colitis, probiotics in ulcerative colitis, OMT for ulcerative colitis, and diagnosis of ulcerative colitis. A primary date range of 2015-2019 was used with a secondary search extending back to 1985.

Discussion: An Osteopathic approach to the treatment of ulcerative colitis will help the patient remain highly functioning and reduce complications of this disease. By being aware of the various pharmaceutical and non-pharmaceutical treatment options available, one can collaborate with the patient to create a treatment plan to minimize morbidity and increase functional days.

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the intestinal mucosa that begins in the rectum and progresses proximally, usually not extending beyond the colon. The annual incidence rate in North America for UC is approximately 12.2 cases per 100,000 person-years with a gradual increase in incidence over time.[1] There is little difference in disease incidence concerning sex; however, there is a slight male predominance. The influence of race on disease incidence is also important to consider. In the United States, Caucasians have a higher incidence of UC than African Americans and other races. In addition, the incidence of UC is higher among Jewish populations everywhere worldwide.[2] A cohort study showed that racial and ethnic minority patients with UC, specifically Asians and Hispanics, had a more severe disease presentation than Caucasians.[3]

**CORRESPONDENCE:**
Ronald Januchowski DO, FACOFP
rjanuchowski@carolinas.vcom.edu

 Print ISSN: 1877-573X
DOI:10.33181/12031

Patients with UC most commonly present between 15 and 30 years of age with abdominal pain and discomfort, increased frequency of bowel movements, urgency of bowel movements, chronic and bloody diarrhea, and mucorrhea.[4] Extraintestinal manifestations include inflammatory arthropathies, osteoporosis, primary sclerosing cholangitis (PSC), erythema nodosum, pyoderma gangrenosum, uveitis, and nephrolithiasis. Common physical exam findings include diffuse abdominal tenderness without rebound or guarding, signs of anemia, signs of dehydration, gross or occult blood on digital rectal exam, and anal fissures present on rectal inspection. Additional physical exam findings include Chapman Reflex Points associated with the colon, particularly the anterior iliotibial band.

UC is understood to be a multifactorial immune-mediated disease due to genetic predisposition, defects in mucosal defense mechanisms, and environmental factors, such as immigration and depression.[5] The genetic component of UC is most closely associated with anti-neutrophil cytoplasmic antibodies (ANCA). ANCA positivity has a high specificity in the diagnosis of UC and is associated with more severe clinical symptoms. Psychosocial stress and depression have not only been shown to influence the pathogenesis of UC but also increase the risk of relapse. Patients with UC have an increased risk of colorectal cancer.

In a population-based meta-analysis the risk of colorectal cancer in IBD patients was over twofold compared to the general population.[6]

Diagnosis of UC is made by the combination of history, physical examination, endoscopy, histology, and ultimately by exclusion of all other differential diagnoses. Biomarkers, such as ANCA, and complete blood counts (CBC) can be performed to support diagnosis. Endoscopic evaluation by ileocolonoscopy and gastroduodenoscopy, followed by biopsies taken from all segments of the intestine, provides definitive diagnosis of UC. Endoscopic findings include diffuse continuous mucosal inflammation that involves the rectum with possible proximal intestinal involvement limited to the colon, loss of haustral folds, and pseudopolyps. Histologic features include crypt abscesses, goblet cell and mucin depletion, and mononuclear inflammation of the lamina propria. Endoscopic evaluation and biopsy help to definitively diagnose UC by identification of the hallmark features associated with the disease and by exclusion of features pathognomonic for alternate diagnoses.

The factors which mediate UC include genetic predisposition, autoimmune disease processes, psychosocial influences, and dietary triggers.[7] Utilizing an integrative approach when treating UC through consideration of each of these mediating factors is paramount to optimal patient outcomes.

## NON-PHARMACOLOGICAL TREATMENT

UC is a multifactorial disease, which can be treated using non-pharmacological therapeutic modalities to augment pharmacological treatment. Osteopathic manipulative treatment (OMT), diet modification, probiotics and psychosocial interventions have proven successful in managing UC. The principle is that in treating the patient as a whole, the chronic inflammatory disease can be managed, and flares minimized.

### OMT

In considering OMT, no reviews were published for the specific treatment of UC. However, a review was published for the treatment of generalized chronic inflammatory diseases. On a physiologic level, clinical studies of OMT proved to reduce cytokines, including substance P, demonstrating an anti-inflammatory effect of this non-invasive treatment modality.[8] The benefit of OMT is that it is a drug-free therapeutic modality that offers little side effect profile if any, with muscle soreness being the most common. OMT uses manual manipulation to treat somatic dysfunctions to restore physiologic function. Its ability to tune the autonomic nervous system and increase parasympathetic activity supports how OMT can be an alternative therapy in treating chronic inflammatory diseases such as UC. In patients with irritable bowel syndrome (IBS), who share similar somatic dysfunctions with UC patients, visceral, sacral, and other direct and indirect osteopathic techniques were shown to reduce symptoms of abdominal pain, diarrhea and cramps among others.[9] Although there is limited data on the direct effect of OMT on UC, the symptomatic improvement for patients with IBS who were treated with various osteopathic techniques is promising for the effects OMT may have on patients with UC.

### Diet

Diet plays a major role in both the pathophysiology and management of IBD. Managing UC from a dietary standpoint requires the avoidance and addition of dietary triggers and therapies, respectively.

Tight junctions, found in the gut lumen, mediate the absorption of nutrients. These tight junctions are disrupted in IBD. An in vitro study showed that the addition of n-6 polyunsaturated fatty acids (PUFA), which include linolenic acid, arachidonic acid and docosapentaenoic acid, results in a decreased expression of tight junctions along the gut lumen, thereby worsening IBD. The study showed that the ingestion of n-6 PUFA is associated with a higher risk of developing IBD.[10] In a prospective, observational study evaluating the effects of certain compounds on UC patients in remission, intake of myristic acid and alpha linolenic acid (ALA) was associated with an increased risk of relapse. Myristic acid is a component of palm oil, coconut oil, and dairy fats, while ALA is a precursor to omega-3 fatty acids. UC patients should be advised to avoid foods and food products containing myristic acid and ALA in order to reduce the risk of relapse and flares. In addition, all patients should be advised to avoid n-6 PUFA as a preventative measure.

A case-control study investigating the link between diet and UC found that UC patients had a higher intake of total energy, protein, carbohydrates, total fat, SFA (saturated fatty acids), monounsaturated fatty acids (MUFA), and PUFA than those in the control group. Although this does not directly correlate a link between those food compounds and the development of UC, it does suggest that healthy patients and those with risk factors for developing UC should limit their consumption of them. The study also emphasized the importance of a diet rich in Vitamin C and folate, as consumption of these micronutrients in a nutrient-rich diet were found to lower the risk of UC.[11]

Curcumin, a component of the turmeric plant, is widely recognized for its health benefits, from its anti-inflammatory and antioxidant properties to its neuroprotective and cardioprotective uses. A less commonly recognized herbal medicine is asafetida (ASF); it is a common ingredient in Indian cuisine and is known to enhance the activities of digestive enzymes found in the pancreas and the small intestine. In an animal study, an encapsulated gut health product (GHP) was formulated using curcumin and ASF complexed onto turmeric nanofiber (TNF), a nanofiber prepared from turmeric containing dietary fiber. This novel GHP reduced the clinical symptoms of UC, the disease activity index, histopathologic lesions, and inflammatory mediator activity, such as myeloperoxidase, thereby elucidating the anti-inflammatory and antioxidant benefits of curcumin, ASF and turmeric.[12] This study suggests the supplementation of curcumin, ASF and turmeric into the diet can aid in managing flares and relapse of the disease. However, because this was an animal study, the authors cannot confidently recommend changes in patient management until human trials are performed.

### Probiotics

Probiotics are living organisms that provide health benefits to the host, when consumed as part of a healthy diet. VSL#3 is unlike most probiotics, it is a highly concentrated probiotic consisting of eight live, freeze-dried bacterial strains, including Lactobacilli (L paracasei, L plantarum, L acidophilus, and L delbrueckii subspecies bulgaricus), Bifidobacteria (B longum, B breve, B infantis), and Streptococcus thermophilus. A meta-analysis demonstrated the effectiveness of VSL#3 at inducing remission in active UC and as a possible alternative to 5-aminosalicylic acid for maintenance therapy.[13] Moreover, there was a reduction in stool frequency and hematochezia, and an improvement in mucosal appearance. Escherichia coli Nissle 1917 (EcN), another type of probiotic, has been recommended for the treatment of ulcerative colitis (UC). It has proven to be equivalent to mesalazine in preventing relapse and inducing remission, as well as improving the composition of the natural gut microbiota in UC patients.[14]

The addition of probiotics to a UC treatment plan as a pharmacological adjuvant is not only beneficial for the possible synergistic effects, but also for its low side effect profile. Across multiple studies, the side effects were limited to abdominal bloating and discomfort for the first few days. Less common adverse effects were an unpleasant taste and an increase in flatulence.[13] Overall probiotics do not impose serious side effects, encouraging its addition to the pharmaceutical regimen of UC. The role of probiotics is efficacious in both the induction and maintenance of UC and should be utilized, in combination with other treatment modalities, in the treatment of UC.

### Psychosocial

The Osteopathic principle which states that the body is a unit, in which the person is a combination of mind, body, and spirit requires consideration when treating patients with chronic illnesses, such as UC. Changes in body and behavior have psychological implications, just as the mind has effects on the body. Therefore, it is important to assess a patient with UC for the psychosocial effects that this lifelong and physically demanding condition can have on a person. There is a high prevalence of anxiety and depressive symptoms in IBD patients, particularly in adolescent and young adult patients.[15] In an animal study, experimental stress and depression negatively impacted immune function, by causing a reactivation of inflammation and altering the number and function of CD4 and CD8 lymphocytes. The treatment of those animal models with antidepressants such as the tricyclic antidepressants prevented reactivation of colitis, suggesting that treatment of UC through a biopsychosocial model helps to maintain remission.[16] In a study evaluating patient feedback about psychotherapy, patients reported improvement in their disease course as a result of reduced stress.[17] Psychological screening in adolescent and young adult IBD patients is recommended to improve the patient's quality of life and lessen health care costs. Screening for anxiety and depressive symptoms ensures early recognition and therefore early treatment of psychological conditions as a means to provide patients with the best chance at remission of UC.

## PHARMACOLOGICAL TREATMENT

The pharmacological treatment of UC follows a step-up approach. Therapy should begin with the medications with the least invasive and lowest side effect profile and increase to the next management option only when intolerant or refractory to a particular therapy. Treatment options are separated into severity of symptoms and disease stage, i.e. acute versus maintenance. While not all medications mentioned will be used in the primary care setting, it is important to recognize complications or side effects from medications that may be prescribed by a referral physician.

### *Mild to Moderate Disease*

### Glucocorticoids

Glucocorticoids work to decrease inflammation by increasing the transcription of genes, which code for anti-inflammatory proteins, in addition to inhibiting the expression of various inflammatory cytokines. First generation glucocorticoids such as prednisone, methylprednisolone and hydrocortisone have been used for the induction of clinical remission of IBD since the 1970's. Systemic glucocorticoids serve as first line therapy for both acute flares as well as severe UC. [18]

Drawbacks associated with first generation glucocorticoids, limiting their long-term use, are their side effect profile. The most important adverse effects to be aware of include weight gain, Cushing's syndrome, steroid-induced diabetes, cataracts, glaucoma, gastric ulcer, gastrointestinal bleeding, osteoporosis, hypertension, insomnia, anxiety, and immunosuppression. This severe side effect profile drove the innovation of second-generation glucocorticoids.

Second-generation glucocorticoids include budesonide, budesonide MMX and beclomethasone dipropionate. Budesonide MMX works via a colonic delivery technology known as Multi-Matrix System (MMX), which allows for extended release in the colon. Budesonide MMX induces remission in patients with mild to moderate UC and is currently utilized for patients non-responsive to traditional maintenance therapy. The benefits of second-generation over first-generation glucocorticoids are their mild side effect profile, of which most commonly include headache, nausea and urinary tract infection.[18]

### Aminosalicylates

Aminosalicylates represent a class that is inclusive of many preparations, with 5-aminosalicylic acid, mesalamine, balsalazide, sulfasalazine and olsalazine being the most commonly used. As a class, they have antibacterial and anti-inflammatory properties, making them effective for the short- and long-term treatment of IBD. Aminosalicylates decrease inflammation by preventing leukocyte recruitment in the bowel wall. These medications are available in both oral and topical forms for the purpose of achieving and maintaining remission of mild-moderate UC.

The most significant adverse effects in this class concern sulfasalazine. Due to its sulfapyridine moiety, patients commonly experience nausea, vomiting, dyspepsia, anorexia, headache, and abnormal sperm counts, motility and morphology. Less common reactions include allergic reactions, pancreatitis, hepatotoxicity,

drug-induced connective tissue disease, bone marrow suppression, interstitial nephritis and hemolytic anemia or megaloblastic anemia. Nephrotoxicity is not commonly seen, however it is recommended that serum creatinine be measured and followed, before and during treatment, respectively.[19]

Topical therapy has less systemic absorption and is thus better tolerated. Combination therapy with topical and oral aminosalicylates allows patients the ability to possibly achieve maximal response and remission.

### *Moderate to Severe Disease*

#### Purine analogs

Azathioprine and 6-mercaptopurine are the two most commonly used purine analogs, also known as thiopurines, targeted for moderate-severe UC. Azathioprine and 6-mercaptopurine are effective maintenance therapies for those who have failed aminosalicylates. Purine analogs work to inhibit the immune response through a series of mechanisms including inhibiting cell receptors, inducing T cell apoptosis, inhibiting lymphokine release, reducing monocyte production and blocking lymphocyte and monocyte interaction. In a 20-year retrospective study, thiopurine therapy allowed patients to achieve long-term steroid-free remission and mucosal healing.[20]

Adverse effects associated with thiopurines most commonly include neutropenia and leukopenia, hypersensitivity, and liver dysfunction. Additional less common adverse effects include fever, alopecia, and indigestion. It is important to monitor liver function as well as complete blood count levels in patients on azathioprine or 6-mercaptopurine therapy.[21]

#### Methotrexate

Methotrexate works to decrease inflammation associated with IBD through various mechanisms including enhancing adenosine concentrations, inhibiting cellular proliferation, limiting the production of inflammatory mediators, and inducing apoptosis. Previous studies have shown methotrexate to be effective in the management of UC for those who failed or were intolerant to thiopurines and have a steroid sparing effect.[22] Newer studies indicate that methotrexate might not be indicated for induction or maintenance therapy in UC.[23] At present, the results from medical trials do not support the use of low dose oral methotrexate for the production of remission in active ulcerative colitis. It is not known whether a higher dose of oral methotrexate, or giving methotrexate by a different route (e.g. by injection), would increase the likelihood of remission.[24]

Although methotrexate is well tolerated in the majority of patients, due to the low dosage requirement for therapeutic benefit in IBD patients, it does bear significant adverse effects that should be closely monitored. The most commonly noted adverse effects associated with methotrexate include hepatotoxicity, dyspnea, bone marrow suppression, osteomyelitis, nausea, vomiting, hair loss, arthralgias and myalgias. Long-term use of methotrexate is more significant for a high side effect profile. In a study evaluating the long-term hepatic and hematologic effects of methotrexate adverse effects included leukopenia, pancytopenia, megaloblastic anemia, thrombocytopenia, elevated liver enzymes, hepatic fibrosis, portal hypertension, and fatty liver disease. Other systemic effects include pulmonary fibrosis, nephrotoxicity, and mucocutaneous reactions. It is important to monitor liver and kidney function as well as complete blood count levels in patients on methotrexate therapy.

#### Anti-Tumor Necrosis Factor

Antibodies against tumor necrosis factor (anti-TNF) include several formulations, with the most commonly used for the treatment of UC being infliximab and adalimumab. Anti-TNF therapies are useful for UC patients who fail conventional therapy. Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that plays a strong role in the pathogenesis of several autoimmune diseases, such as IBD. Therefore, anti-TNF therapy has been utilized to suppress the inflammatory cascade driven by TNF. Treatment with these agents show good short-term and long-term resolution of clinical signs and symptoms, as well as decrease the colectomy rate.[25]

Mild adverse effects associated with anti-TNF agents include abdominal pain, nausea, arthralgias and upper respiratory tract infections, while severe adverse effects include pneumonia, sepsis, tuberculosis, drug-induced lupus and malignant tumors. Other adverse effects include tuberculosis, worsening neurological disease, psoriasis exacerbations, liver function test abnormalities, hepatitis, thrombocytopenia and neutropenia. In addition, patients can experience infusion reactions that can present with symptoms of fever, chills, headache, pruritis, nausea, flushing, dizziness, dyspnea, chest pain, changes in blood pressure and anaphylaxis.

#### Anti-Integrins

Anti-integrins, also known as selective leukocyte adhesion molecule inhibitors, like TNF antagonists, are another type of infusion therapy useful for the induction and maintenance of UC. This treatment option is superior to anti-TNF agents for patients with an increased risk of infection, such as the elderly or those with immunocompromised states and is indicated for those who have failed or are intolerant to TNF antagonists.[26] Anti-integrins work by disrupting intravascular lymphocyte adhesion to the gastrointestinal tract thereby inhibiting the inflammatory immune cascade. The most commonly used anti-integrins indicated for UC induction and maintenance include natalizumab and vedolizumab.

Reported adverse effects associated with natalizumab include worsening of UC symptoms, headache, vomiting, lethargy, sore throat, Campylobacter jejunii enteritis and opportunistic infections such as progressive multifocal leukoencephalopathy (PML). Adverse effects associated with vedolizumab most commonly include lethargy, headache, arthralgias, nausea, pyrexia, nasopharyngitis, upper respiratory tract infection, cough, sinusitis, oropharyngeal pain, bronchitis, influenza, rash, pruritis, back pain and extremity pain. Mild infusion-related and hypersensitivity reactions have also been reported. Serious infections associated with vedolizumab therapy include abscess, sepsis, tuberculosis,

Salmonella, listeria meningitis, giardiasis and cytomegaloviral colitis. While no cases of PML have been reported with vedolizumab to date, the risk of PML cannot be ruled out; signs and symptoms for this disease process should be monitored.

#### Tofacitinib

Tofacitinib was approved for use in patients with moderate to severe rheumatoid arthritis in 2012 and was approved in 2018 for the treatment of treatment-resistant UC. Tofacitinib works by inhibiting janus kinase (JAK), most specifically JAK1 and JAK3. It decreases the signaling of inflammatory cytokines, thereby reducing inflammation associated with inflammatory diseases such as rheumatoid arthritis and IBD. Onset of action is rapid showing significant improvement in symptoms in just two weeks, with a reduction in baseline C-reactive protein levels in four weeks.[27]

Adverse effects reported in recent studies include increased overall rate of infections, especially herpes zoster, nonmelanoma skin cancer, cardiovascular events, and abnormal lipid levels. Tofacitinib remains a new UC therapy and therefore its studies are limited. The long-term safety and efficacy of tofacitinib for the treatment of UC requires close follow-up and ongoing data collection.[27]

### *Fulminant Disease*

#### Cyclosporine

Cyclosporine is most commonly utilized as rescue therapy for UC patients who are steroid-resistant. It is effective at inducing remission in UC patients due to its rapid response time, as well as lasting effects. Cyclosporine works by mediating anti-inflammatory effects by lowering T cell activity and inducing apoptosis of lamina propria mononuclear cells. Severe adverse effects associated with cyclosporine include nephrotoxicity, infection, seizures and death. Less severe adverse effects include paresthesias, hypertension, hypertrichosis, headache, abnormal liver function tests, hyperkalemia and gingival hyperplasia. Renal function monitoring is important in patients receiving cyclosporine therapy.

#### Tacrolimus

Tacrolimus is used for patients with moderate to severe active UC whom are resistant to most therapies. It has proven to be a safe long-term therapeutic option that should be utilized prior to considering surgery for the management of UC. Tacrolimus is a macrolide antibiotic with an immunosuppressive role that works by inhibiting calcineurin, which results in the interruption of T cell signal transduction and prevention of inflammatory cytokine transcription.

Tacrolimus and cyclosporine share a similar side effect profile and thus patients on either therapy should be monitored the same way.[28] Adverse effects associated with tacrolimus include elevations in creatinine, tremor, cytomegalovirus colitis and esophagitis, herpes zoster, urinary tract infections, venous thrombosis, hypertension, headache, nausea, acquired thrombotic thrombocytopenia, and hypomagnesemia. *(Table 1, page 15)*

## SURGICAL REFERRAL

Medical management of UC has advanced over time, however many patients that become refractory to pharmaceutical intervention or develop serious complications require surgery for definitive treatment. The indications for surgical referral include acute colitis associated with severe complications or nonresponsive to medical management, chronic disease resulting in steroid dependency in adults, chronic disease resulting in growth or pubertal delay in children, colon dysplasia or cancer, and reconstruction after previous colectomy.[29] Absolute indications for surgery in the case of acute colitis are toxic megacolon, perforation, and severe colorectal bleeding. Cancer of the colon or rectum is an absolute indication for surgical management, with the standard procedure being ileal pouch anal-anastomosis (IPAA). Although surgical intervention carries its own risks, when indicated and utilized appropriately, surgery can prevent further complications, improve quality and longevity of life, and in some circumstances even save lives. Surgery, as a treatment option, should be viewed as an additional treatment modality that complements other forms of therapy rather than a 'failure of medical management.' Close communication between the primary care physician, gastroenterologist, and colorectal surgeon is imperative in order to achieve safe and efficacious outcomes that improve the quality of life for patients with UC.

## DISCUSSION

Ulcerative colitis is a disease that will be commonly encountered in the primary care setting. An Osteopathic approach to treatment will involve collaborating with the patient to develop a comprehensive, patient-centered treatment care plan that minimizes side effects and improves overall function. Monitoring for adverse effects to pharmaceutical treatment along with providing additional treatment options beyond medications will help the patient have reduced symptoms and an improved quality of life. The osteopathic family physician can provide excellent care to patients with ulcerative colitis to reduce the emotional and social impact associated with this lifelong illness.

## TABLE 1 :

Summary of Pharmacological Treatment

| Pharmaceutical | Mechanism of Action | Adverse Effects | Notes |
|---|---|---|---|
| *Mild to Moderate* | | | |
| **Glucocorticoids**<br>First generation: prednisone, methylprednisolone, hydrocortisone<br>Second generation: budesonide, beclomethasone | Increase transcription of genes that code for anti-inflammatory cytokines. | Weight gain, Cushing's syndrome, steroid-induced diabetes, cataracts, glaucoma, gastric ulcer, gastrointestinal bleeding, osteoporosis, hypertension, insomnia, anxiety, immunosuppression, urinary tract infection. | Second generation glucocorticoids have a milder side effect profile as opposed to first generation glucocorticoids. |
| **Aminosalicylates**<br>5-aminosalicylic acid, mesalamine, balsalazide, sulfasalazine and olsalazine | Decrease inflammation by preventing leukocyte recruitment in the bowel wall. | Dyspepsia, anorexia, abnormal sperm counts, motility and morphology, allergic reactions, pancreatitis, hepatotoxicity, drug-induced connective tissue disease, bone marrow suppression, nephrotoxicity, hemolytic anemia, megaloblastic anemia. | Topical formulations are better tolerated. Monitor serum creatinine. |
| *Moderate to Severe* | | | |
| **Purine analogs**<br>Azathioprine, 6-mercaptopurine | Inhibit the immune response through a series of mechanisms. | Neutropenia, leukopenia, hypersensitivity, liver dysfunction, fever, alopecia and indigestion. Hepatotoxicity associated with 6-mercaptopurine. | Monitor liver function and complete blood |
| **Methotrexate** | Enhance adenosine concentrations, inhibit cellular proliferation, limit the production of inflammatory mediators, and induce apoptosis. | Hepatotoxicity, dyspnea, bone marrow suppression, megaloblastic anemia, elevated liver enzymes, hepatic fibrosis, portal hypertension, fatty liver disease, osteomyelitis, hair loss, arthralgias, myalgias, pulmonary fibrosis, nephrotoxicity, muco-cutaneous reactions. | Monitor liver and kidney function, as well as complete blood count levels |
| **Anti-Tumor Necrosis Factor**<br>Infliximab, adalimumab | Suppress the inflammatory cascade driven by TNF | Infusion reactions, abdominal pain, nausea, arthralgias, upper respiratory tract infections, pneumonia, sepsis, tuberculosis, drug-induced lupus, malignant tumors, liver function test abnormalities, hepatitis, thrombocytopenia and neutropenia. | |
| **Anti-Integrins**<br>Infliximab, adalimumab | Disrupt intravascular lymphocyte adhesion to the gastrointestinal tract thereby inhibiting the inflammatory immune cascade. | Lethargy, upper respiratory tract infections, Campylobecter jejunii enteritis, opportunistic infections such as PML, and arthralgias. Serious infections associated with vedolizumab therapy include abscess, sepsis, tuberculosis, Salmonella, Listeria meningitis, giardiasis and cytomegaloviral colitis. | Monitor for signs and symptoms of PML. |
| **Tofacitinib** | Inhibitor of janus kinase (JAK), thereby inhibiting the signaling of inflammatory cytokines. | Increase in the overall rate of infections, especially herpes zoster, non-melanoma skin cancer, cardiovascular events, and abnormal lipid levels. | Long-term safety and efficacy require close follow-up. |
| *Fulminant* | | | |
| **Cyclosporine** | Suppresses T cell activity and induces apoptosis of lamina propria mononuclear cells. | Nephrotoxicity, infection, seizures, death, paresthesias, hypertension, hypertrichosis, headache, abnormal liver function tests, hyperkalemia and gingival hyperplasia. | Monitor kidney function. |
| **Tacrolimus** | Macrolide antibiotic that prevents transcription of inflammatory cytokines. | Elevated creatinine, tremor, cytomegalovirus colitis and esophagitis, herpes zoster, urinary tract infections, venous thrombosis, hypertension, headache, nausea, acquired thrombotic thrombocytopenia, and hypomagnesemia. | Monitor kidney function. |

**AUTHOR DISCLOSURES:**
No relevant financial affiliations or conflicts of interest.

**REFERENCES:**


1. Shivashankar, R., Tremaine, W., Harmsen, W., & Loftus, E. (2017). Incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota from 1970 through 2010. Clinical Gastroenterology and Hepatology, 15(6), 857-863. doi:10.1016/j.cgh.2016.10.039
2. Karlinger, K., Györke, T., Makö, E., Mester, A., & Tarján, Z. (2000). The epidemiology and the pathogenesis of inflammatory bowel disease. European Journal of Radiology, 35(3), 154-167. doi:10.1016/S0720-048X(00)00238-2
3. Castaneda, G., Liu, B., Torres, S., Bhuket, T., & Wong, R. (2017). Race/ethnicity-specific disparities in the severity of disease at presentation in adults with ulcerative colitis: A cross-sectional study. Digestive Diseases and Sciences, 62(10), 2876-2881. doi:10.1007/s10620-017-4733-5
4. Ungaro, R., Mehandru, S., Allen, P., Peyrin-Biroulet, L., & Colombel, J., Department of Gastroenterology, University Hospital of Nancy-Brabois, Vandoeuvre-les-Nancy, France. (2017). Ulcerative colitis. The Lancet, 389(10080), 1756-1770. doi:10.1016/S0140-6736(16)32126-2
5. Bye, W., Ma, C., Nguyen, T., Parker, C., Jairath, V., & East, J. (2018). Strategies for detecting colorectal cancer in patients with inflammatory bowel disease: A cochrane systematic review and meta-analysis. The American Journal of Gastroenterology, 113(12), 1801-1809. doi:10.1038/s41395-018-0354-7
6. Hartnett, L., & Egan, L. (2012). Inflammation, DNA methylation and colitis-associated cancer. Carcinogenesis, 33(4), 723-731.
7. Barnes, E., Nestor, M., Onyewadume, L., De Silva, P., Korzenik, J., Aguilar, H., Waldholtz, B., Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts. (2017). High dietary intake of specific fatty acids increases risk of flares in patients with ulcerative colitis in remission during treatment with aminosalicylates. Clinical Gastroenterology and Hepatology, 15(9), 1390-1396.
8. Licciardone JC, Kearns CM, Hodge LM, Bergamini MV. Associations of cytokine concentrations with key osteopathic lesions and clinical outcomes in patients with nonspecific chronic low back pain: results from the OSTEOPATHIC Trial. J Am Osteopath Assoc. 2012; 112: 596–605.
9. Cicchitti, L., Martelli, M., Cerritelli, F., & D'Acquisto, F., Academic Editor. (2015). Chronic inflammatory disease and osteopathy: A systematic review. Plos One, 10(3).
10. Balzola, F., Cullen, G., Ho, G., & Russell, R. (2013). Effect of polyunsaturated fatty acids on tight junctions in a model of the human intestinal epithelium under normal and inflammatory conditions. Inflammatory Bowel Disease Monitor, 14(1), 28-29.
11. Hou, Jason, Abraham, Bincy, El-Serag, Hashem (2011). Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. The American Journal of Gastroenterology, 106 (4), 563-573.
12. Gopi, S., Amalraj, A., Jude, S., Varma, K., Sreeraj, T., Haponiuk, J., & Thomas, S. (2017). Preparation, characterization and anti-colitis activity of curcumin-asafoetida complex encapsulated in turmeric nanofiber. Materials Science & Engineering C, 81, 20-31. doi:10.1016/j.msec.2017.07.037
13. Derwa, Y., Gracie, D., Hamlin, P., & Ford, A. (2017). Systematic review with meta-analysis: Efficacy of probiotics in inflammatory bowel disease. Alimentary Pharmacology and Therapeutics, 46(4), 389-400.
14. Graziani, C., Petito, V., Del Chierico, F., Mangiola, F., Pecere, S., Schiavoni, E.,et al. Bologna Italy 20170329-20170401. (2017). Oc.14.6: Escherichia coli Nissle 1917 modulate gut microbiota composition in ulcerative colitis patients. Digestive and Liver Disease, 49, 119. doi:10.1016/S1590-8658(17)30390-0
15. Van den Brink, G., Stapersma, L., Vlug, L., Rizopolous, D., Bodelier, A., Wering, H., Escher, J. (2018). Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics, 48(3), 358-369.
16. Ananthakrishnan, A., Khalili, H., Pan, A., Higuchi, L., De, S., Richter, J.,Chan, A. (2013). Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: Results from the nurses' health study. Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association,11(1), 57-62.
17. Mikocka-Walus, A., Gordon, A., Stewart, B., & Andrews, J. (2013). 'Just to get it off my chest': Patients' views on psychotherapy in inflammatory bowel disease. Counselling and Psychotherapy Research, 13(3), 227-234.
18. Dubois-Camacho K, Ottum PA, Franco-Muñoz D, De la Fuente M, Torres-Riquelme A, Díaz-Jiménez D, Olivares-Morales M, Astudillo G, Quera R, Hermoso MA. Glucocorticosteroid therapy in inflammatory bowel diseases: From clinical practice to molecular biology. World J Gastroenterol 2017, 23(36): 6628-6638.
19. Kornbluth, A., Sachar, D., & Practice Parameters Committee of the American College of Gastroenterology. (2010). Ulcerative colitis practice guidelines in adults: American college of gastroenterology, practice parameters committee. The American Journal of Gastroenterology, 105(3), 501-23.
20. Daniela, P., Annalisa, A., Stefano, F., Pietro, M., Rita, M., Luisa, G., Alessandro, A. (2018). Sustained clinical efficacy and mucosal healing of thiopurine maintenance treatment in ulcerative colitis: A real-life study. Gastroenterology Research and Practice, (2018). doi:10.1155/2018/4195968
21. Kakuta, Y., Kawai, Y., Okamoto, D., Takagawa, T., Ikeya, K., Suzuki, Y. (2018). Nudt15 codon 139 is the best pharmacogenetic marker for predicting thiopurine-induced severe adverse events in Japanese patients with inflammatory bowel disease: A multicenter study. Journal of Gastroenterology, 53(9), 1065-1078. doi:10.1007/s00535-018-1486-7.
22. Wahed, M., Louis-Auguste, J., Baxter, L., Limdi, J., McCartney, S., Lindsay, J., & Bloom, S. (2009). Efficacy of methotrexate in crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine / mercaptopurine. Alimentary Pharmacology and Therapeutics, 30(6), 614-620.
23. Herfarth, H., Barnes, E., Valentine, J., Hanson, J., Higgins, P., Isaacs, K., Lewis, J. (2018). Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. Gastroenterology, 155(4), 1098-1108. doi:10.1053/j.gastro.2018.06.046
24. Macaluso, F., Renna, S., Cottone, M., & Orlando, A. (2016). The meteor trial: The burial of methotrexate in ulcerative colitis? Gastroenterology, 151(1), 211-2. doi:10.1053/j.gastro.2016.02.085
25. Ruxi, L., Weiguang, Q., Zhiyong, W., Yinjun, W., Shixue, D., Qiang, L., & Xuebao, Z. (2014). Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: A meta-analysis. Plos One, 9(1). doi:10.1371/journal.pone.0086692
26. Khanna, R., Mosli, M., & Feagan, B. (2016). Anti-integrins in ulcerative colitis and Crohn's disease: What is their place? Digestive Diseases (Basel, Switzerland), 34(1-2), 153-9.
27. Pouillon, L., Bossuyt, P., & Peyrin-Biroulet, L. (2017). Tofacitinib is the right octave for ulcerative colitis. Gastroenterology, 153(3), 862-864. doi:10.1053/j.gastro.2017.07.027
28. Weigmann, B., Mott, S., Atreya, R., & Neurath, M. (2017). A mechanism of action for cyclosporine a in ulcerative colitis: The role of the TEC kinase ITK in disease pathogenesis. Gastroenterology, 152(5), 758.
29. Gallo, G., Kotze, P., & Spinelli, A. (2018). Surgery in ulcerative colitis: When? how? Best Practice & Research Clinical Gastroenterology, 32-33, 71-78. doi:10.1016/j.bpg.2018.05.017