Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State: [redacted]	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Condition: Ulcertaive Colitis; Treatment: Biologic Therapies / Intravenous Medications

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

Please See Attachment A.

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

Please See Attachment B.

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

Please see attachment A & B.

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Please See Attachment C.

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Please see Attachment D

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

Please see Attachment D.

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

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Section J: Submission of Petition
In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so. • Attach additional pages as necessary.

I hereby certify that the above information is correct and complete.	
My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physici[redacted]	
Signature: [redacted]	Date Signed: November 14, 2014

Attachment A – From Mayo Clinic

http://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/basics/definition/con-20043763

Ulcerative colitis (UL-sur-uh-tiv koe-LIE-tis) is an inflammatory bowel disease (IBD) that causes long-lasting inflammation and ulcers (sores) in your digestive tract. Ulcerative colitis affects the innermost lining of your large intestine (colon) and rectum. Symptoms usually develop over time, rather than suddenly.

Ulcerative colitis can be debilitating and sometimes can lead to life-threatening complications. While it has no known cure, treatment can greatly reduce signs and symptoms of the disease and even bring about long-term remission.

Ulcerative colitis symptoms can vary, depending on the severity of inflammation and where it occurs. Therefore, doctors often classify ulcerative colitis according to its location.

You may have the following signs and symptoms, depending on which part of the colon is inflamed:

- Diarrhea, often with blood or pus
- Abdominal pain and cramping
- Rectal pain
- Rectal bleeding — passing small amount of blood with stool
- Urgency to defecate
- Inability to defecate despite urgency
- Weight loss
- Fatigue
- Fever
- In children, failure to grow

Most people with ulcerative colitis have mild to moderate symptoms. The course of ulcerative colitis may vary, with some people having long periods of remission.

Types

Ulcerative colitis is classified according to how much of your colon is affected. The condition can be mild and limited to the rectum (ulcerative proctitis). Or it can affect additional parts of your colon, generally with more severe symptoms. People who develop ulcerative colitis at a younger age are more likely to have severe symptoms.

When to see a doctor

See your doctor if you experience a persistent change in your bowel habits or if you have signs and symptoms such as:

- Abdominal pain
- Blood in your stool
- Ongoing diarrhea that doesn't respond to over-the-counter medications
- Diarrhea that awakens you from sleep
- An unexplained fever lasting more than a day or two

Although ulcerative colitis usually isn't fatal, it's a serious disease that, in some cases, may cause life-threatening complications.

Ulcerative colitis affects about the same number of women and men. Risk factors may include:

- **Age.** Ulcerative colitis usually begins before the age of 30. But, it can occur at any age, and some people may not develop the disease until after age 60.
- **Race or ethnicity.** Although whites have the highest risk of the disease, it can occur in any race. If you're of Ashkenazi Jewish descent, your risk is even higher.
- **Family history.** You're at higher risk if you have a close relative, such as a parent, sibling or child, with the disease.
- **Isotretinoin use.** Isotretinoin (Amnesteem, Claravis, Sotret; formerly Accutane) is a medication sometimes used to treat scarring cystic acne or acne. Some studies suggest it is a risk factor for IBD, but a clear association between ulcerative colitis and isotretinoin has not been established.

Possible complications of ulcerative colitis include:

- Severe bleeding
- A hole in the colon (perforated colon)
- Severe dehydration
- Liver disease (rare)

- Bone loss (osteoporosis)
- Inflammation of your skin, joints and eyes, and sores in the lining of your mouth
- An increased risk of colon cancer
- A rapidly swelling colon (toxic megacolon)
- Increased risk of blood clots in veins and arteries

Attachment B – Biologics from Crohns and Colitis Foundation of America

INTRAVENOUS (IV) MEDICATIONS

Infliximab (Remicade®) is the first FDA-approved biologic therapy for Crohn's disease, and was recently approved for ulcerative colitis. The medication is a chimeric monoclonal antibody. In other words, it's a hybrid consisting of 75 percent human, 25 percent mouse protein sequence. It works by binding to and preventing the activity of a specific protein in the body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is a cytokine, a specialized protein that promotes inflammation in the intestine and other organs and tissues.

It is given as a drip via intravenous infusion. Infusions take about two hours to complete and usually are given every eight weeks.

Infliximab has been approved for the treatment and maintenance of remission of moderately to severely active Crohn's disease and ulcerative colitis that is unresponsive to conventional therapy. It also has been approved for the treatment and maintenance of fistulizing Crohn's disease. (Fistulas are abnormal channels between two loops of intestine, or between the intestine and another structure, such as the skin.) Treatment with infliximab is often an effective method for tapering patients off steroids. Infliximab has been approved to treat ulcerative colitis in children six years and older.

Natalizumab (Tysabri®) has been approved for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies, including inhibitors of TNF-alpha.

Natalizumab (Tysabri®) is an antibody thought to inhibit certain types of white blood cells that are involved in the inflammatory process. It is infused into a vein at a certified infusion center and usually given once every 4 weeks. It takes about 1 hour to receive the entire dose.

Vedolizumab (Entyvio™) is an integrin receptor antagonist indicated for the treatment of adult patients with moderately to severely active ulcerative colitis and Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Vedolizumab is infused intravenously over approximately 30 minutes at zero, two and six weeks then every eight weeks thereafter.

SUBCUTANEOUS INJECTIONS

Adalimumab (Humira®) is a synthetic (man-made) protein, similar to human protein that blocks tumor necrosis factor alpha (TNF- α), a protein in your body that can cause inflammation. Adalimumab works by attaching to TNF- α and blocking its effects and thereby reducing the inflammation and relieving symptoms associated with Crohn's disease.

Adalimumab is taken by injection every other week. It can be administered at home by the patient or family member once instructed by a healthcare professional.

Adalimumab has been approved for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, and in those patients who did not benefit from treatment, or who were intolerant to previous treatment with infliximab. Adalimumab was approved in September 2014 for pediatric

patients six years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Adalimumab is also approved for adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants.

Certolizumab pegol (Cimzia ®) is the most recent biologic approved by the FDA for the treatment of Crohn's disease. Certolizumab pegol is used to reduce the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have not been helped enough by usual treatments.

Certolizumab pegol is the first and only PEGylated anti-TNF- alpha. The antibody portion of the drug is combined with a special chemical called polyethelyene glycol (PEG), which delays its excretion from the body.

Patients treated with Cimzia ® receive an injection every two weeks for the first three injections. Once benefit has been established, Cimzia® is usually given once every four weeks.

Golimumab (Simponi®) is indicated for the treatment of adult patients with moderate to severe ulcerative colitis (UC) who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-Mercaptopurine. Golimumab is used to induce and maintain clinical response, improve endoscopic appearance of the mucosa during induction, induce clinical remission and achieve and sustain clinical remission in induction responders.

Patients treated with golimumab receive an initial subcutaneous injection of 200mg at Week 0, followed by a 100mg injection at Week 2 and then 100mg every four weeks thereafter. The patient or family member, once instructed by a healthcare professional, can administer it at home.

IN THE PIPELINE

Additional biologic therapies under investigation for IBD include another antibody to TNF, CDP-870. Thalidomide and IL-11 are also being studied as biologic treatments. Drugs targeting a number of other cytokines and the inflammatory response, such as alpha 4 integrin, interleukin-6, interleukin-12, interferon gamma, and GM-CSF are being evaluated in clinical trials. Another experimental therapy for Crohn's disease is a mixture of colon-extracted proteins derived from the individual patient. Self-derived proteins represent an individualized approach to treatment.

SIDE EFFECTS

Because biologics are given either by intravenous infusions or subcutaneous injections, it may produce redness, itching, bruising, pain, or swelling on the injection site. Other side effects may include: headache, fever, chills, difficulty breathing, low blood pressure, and hives. Additionally, patients may experience stomach pain, back pain, rash, nausea, and upper respiratory infection (cough and sore throat).

DRUG INTERACTIONS

People taking several different medicines, whether prescription or over-the-counter, should always be on the lookout for interactions between drugs. Drug interactions may decrease a medication's effectiveness, intensify the action of a drug, or cause unexpected side effects. Before taking any medication, read the label carefully. Be sure to tell your doctor about all the drugs you're taking—even over-the-counter medications or complementary therapies—and any medical conditions you may have.

SPECIAL CONSIDERATIONS

There have been some reports of serious infections associated with infliximab, adalimumab, and certolizumab use, including tuberculosis (TB) and sepsis, a life-threatening blood infection. You should always have a TB test before you use infliximab, adalimumab or certolizumab because the drugs can increase the risk of re-activating TB for those

who have been exposed. It's not that you will "catch" TB when taking infliximab, adalimumab,or certolizumab but if you have latent (inactive) TB, the drug can reactivate the infection.

Cases of new infection with TB have also been reported. If you have prior exposure to TB, your doctor should begin TB treatment before you start infliximab, adalimumab or certolizumab. The same precaution should be taken before beginning treatment with corticosteroids.

Biologics may reduce the body's ability to fight other infections as well. If you are prone to infections or develop any signs of infection while taking these medications, such as fever, fatigue, cough, or the flu, inform your doctor immediately.

It may be inadvisable for people with heart failure to take any of these medications, so tell your doctor if you have any heart condition before starting this medication. Inform your doctor at once if you develop new or worsening symptoms of heart failure—namely shortness of breath or swelling of the ankles or feet.

On rare occasions, blood disorders have been noted with infliximab, adalimumab, and certolizumab. Inform your doctor if you develop possible signs such as persistent fever, bruising, bleeding, or paleness while taking infliximab, adalimumab, and certolizumab. Nervous system disorders also have been reported occasionally. Let your doctor know if you have or have had a disease that affects the nervous system, or if you experience any numbness, weakness, tingling, or visual disturbances while taking infliximab, adalimumab, and certolizumab.

Although reports of lymphoma (a cancer of the lymphatic system) in patients taking infliximab, adalimumab, certolizumab and other TNF-blockers are rare, they do occur more often than in the general population.

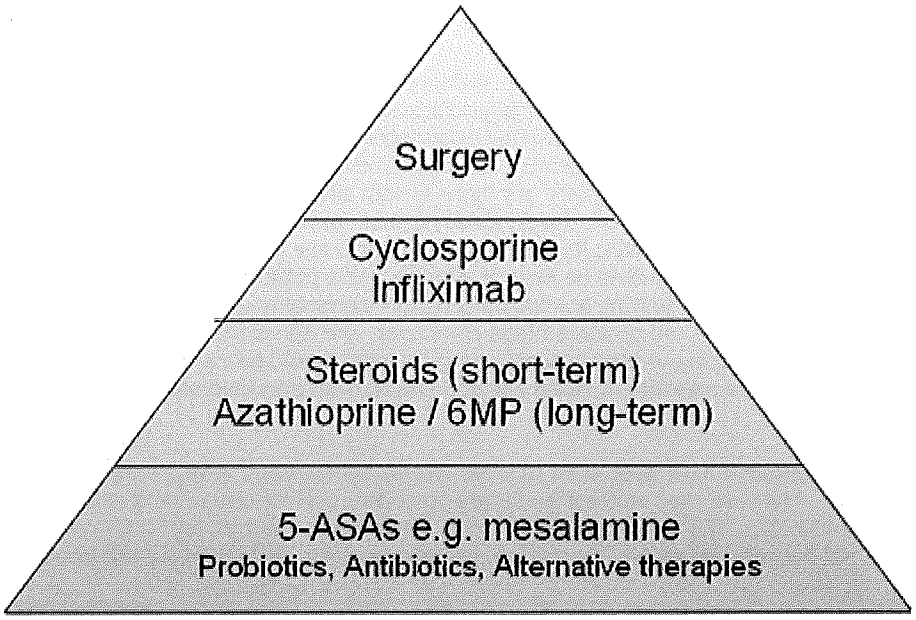
Progressive multifocal leukoencephalopathy (PML), a rare brain infection, has been reported with natalizumab use. Natalizumab may also cause liver damage and allergic reactions.

Your physician will monitor you closely while you are on biologic therapy. It is not advisable to stop and then try to restart infliximab. To achieve and maintain remission, it is advisable to stay on the medication.

From a more superficial standpoint, people with a significant fear of injections in general have to suffer through two hour infusions every two months.

Attachment C – Conventional Treatment from Beth Israel Deaconess Medical Center

The majority of patients with ulcerative colitis respond to conventional medical therapy; less than 20% need surgery to remove their colon (colectomy). Most patients will experience improvement in symptoms with medications taken by mouth, although those with disease limited to the rectum often do better with topical agents (enemas, suppositories). Only 15% require admission to hospital for intravenous medications, and this most commonly occurs shortly after diagnosis. With treatment, about 50% of patients remain in remission for periods of months to years. Figure 2 highlights the main therapies used in ulcerative colitis. They are described in detail below.



1. 5-amniosalicylates (5-ASAs)
5-ASA's are medications used to treat mild to moderate ulcerative colitis. Although it is uncertain exactly how they work, the 5-ASAs appear to act topically on the GI tract (not by being absorbed into the blood stream)and exert an anti-inflammatory effect. There are a number of these agents available which can be delivered both orally or rectally. Depending on how each specific drug is designed, the active 5-ASA is released at various locations throughout the GI tract.

The original 5-aminosalicylate, known as **sulfasalazine** (Azufidine), has been used to treat IBD for decades. It is most effective for mild to moderate Crohn's disease, particularly when the disease affects the colon. The 5-ASA is bound to a compound called sulfapyridine, from which it detaches when it reaches the colon. Unfortunately, sulfasalazine has a number of side effects due to the part of the sulfapyridine molecule (moiety) to which it is attached, including symptoms such as nausea and headache, and up to 1/3 of patients cannot tolerate it over the long-term. Patients who have allergies to sulfa medications will also be intolerant of sulfasalzine. Patients who take Sulfasalazine must also take folic acid 1 mg daily, as the Sulfasalazine depletes folic acid stores.

Because many patients cannot tolerate sulfasalazine, other methods of delivering 5-ASA to the small intestine and colon have been developed that do not contain a sulfapyridine moiety. Almost all of the patients intolerant of sulfasalazine are able to take these other 5-ASA agents, which are designed to release 5-ASA at specific locations throughout the GI tract.

These medications include a free 5-ASA, known as **mesalamine**, which is enclosed within special capsules that release the active drug only when they reach the small intestine or colon. Asacol, Asacol HD, Apriso, and Lialda release the mesalamine in the terminal ileum and colon. Pentasa releases mesalamine throughout the small intestine and colon.

Other agents include 5-ASA bound to another 5-ASA molecule (**olsalazine**, Dipentum) or a carrier molecule (**balsalazide**, Colazal). These drugs release 5-ASA specifically to the colon.

One of the main issues with 5-ASA therapy is compliance. The pill burden can be substantial (4-12 pills per day). While the older drugs were designed to be taken three to four times a day, most physicians prescribe these medications twice a day to make it easier for patients to take, and this strategy appears to be just as effective. The newer 5-ASA's, Lialda, and Apriso, are approved for ulcerative colitis for once daily dosing, with as few as four pills delivering 4.8g of mesalamine. Currently, other pharmaceutical companies are working on similar designs to make administration of this class of drugs as easy for patients as possible.

Mesalamine also comes in enema (Rowasa) and suppository (Canasa) forms, which is ideal for patients with disease limited to the lower third of the colon or rectum, respectively. These formulations are used quite commonly in patients with ulcerative colitis. They are actually more effective that oral 5-ASA. Often times the rectal therapies are used in conjunction with oral 5-ASA.

Side-effects from 5-ASA compounds are uncommon , but may include abdominal pain, gas, nausea, hair loss, headache, and dizziness. An important side effect for patients and physicians to recognize is a paradoxical worsening of diarrhea, which is due either to an allergic-type reaction or an increase in the secretion of water by the small bowel. If diarrhea worsens with initiation of these agents, this should be considered as a possible cause, and the drug should be stopped. There also are a number of rare but more serious side-effects from 5-ASA compounds, including allergic-type reactions in the pancreas, lungs, kidneys, skin, and bone marrow. Kidney function should be monitored annually in patients on 5-ASA. Reduced sperm counts have been noted in the majority of men on sulfasalazine (Azulfidine), so this should be kept in mind for male patients who are trying to conceive. Headache, nausea, loss of appetite, and vomiting are seen much more commonly with sulfasalazine therapy. Allergy to sulfa (rash, fever), a decreased red or white blood cell count, and abnormal liver tests can also be associated with sulfasalazine. Regular monitoring of blood counts and liver tests should be carried out in patients who are receiving this medication. The majority of these adverse effects are reversible once the drug is stopped.

2. Corticosteroids (Steroids)

Like sulfasalazine, corticosteroids (or "steroids") have been used to treat IBD for decades and have become a mainstay of treatment for active flares. They are used to treat moderate-to-severe Crohn's disease and when 5-aminosalicilates, and in some cases antibiotics, fail to control the disease. These drugs exert an anti-inflammatory and immunosuppressive effect and can be given by mouth, by rectum, or intravenously, depending on the location and severity of the disease.

Prednisone , the most commonly used oral steroid, produces consistent responses, and induces remission in about 70-80% of patients. Steroids also act quickly, with most patients noticing a response within one week.

Although steroids induce remission, they are not effective in the long-term to maintain remission. In addition, steroids are associated with a number of serious side-effects including low bone density (osteoporosis), diabetes, high blood pressure (hypertension), cataracts, psychosis, depression, increased risk of infections, acne, weight gain, difficulty sleeping (insomnia), and facial swelling. Steroids also cause the body's adrenal glands to stop producing their own endogenous steroid (cortisol). If the administered steroids are tapered off too quickly, the body can go into a "steroid withdrawal" or adrenal crisis. Once started, steroids are usually slowly reduced in dose over a number of weeks to prevent a sudden flare of the disease or adrenal crisis.

Patients who are on steroids also need to be on adequate amounts of calcium (1200mg) and vitamin D (800 IU). Some patients, with underlying osteopenia or osteoporosis, or patients who remain on steroids for prolonged periods of time, may require additional drugs (bisphosphonates) to prevent further bone loss. Bisphosphonates (alendronate or risidronate) have been shown to be useful in this situation, particularly in postmenopausal females and in those patients on long-term steroids.

Although steroids are effective in quickly inducing remission, a number of patients are unable to reduce their steroids without a worsening of their symptoms, and essentially become steroid-dependent. These patients require further medical or surgical therapy in order to help get them off of the steroids. In fact, studies have shown that one year after starting steroids approximately 25% of patients are steroid dependent and 25% of patients have required surgery. Less than 1/2 of patients are in remission and off steroids at one year. Therefore, once steroids are utilized to induce remission, other drugs are needed to help wean patients off of steroids, avoid surgery, and maintain remission. The agents typically used in this situation are known as immunomodulators,which will be discussed in greater detail below.

In addition to oral and intravenous formulations, corticosteroids are also available as intravenous (IV) and rectal formulations. Intravenous corticosteroids (methylprednisolone, hydrocortisone, dexamethasone) are used in patients with severe disease that require hospitalization. Steroids also come in rectal form and can be given as **enemas (Cortenema), hydrocortisone acetate foam (Cortifoam, ProctoFoam-HC)**, or **suppositories.**

3. Immunomodulators
Immunomodulators, or immunosuppressants, alter the body's immune response by inhibiting the inflammatory action of white blood cells. Since patients with ulcerative colitis are believed to have an overactive immune system as the cause of their uncontrolled GI inflammation, the use of a medication that tones down the immune response makes great sense. The immunomodulators used in the treatment of ulcerative colitis are azathioprine (Imuran) and 6-mercaptopurine (Purinethol).

These immunomodulators have a role in several circumstances. Most often they are used to maintain remission in those patients who initially required steroids, in those who have become steroid dependent, and in patients with perianal fistulae. In patients with milder symptoms, immunomodulators can also be used to induce remission. The reason that they are not used to induce remission in sicker patients is that they have a slow onset of action of up to three months before taking effect.

Azathioprine (AZA) is the pro-drug (precursor) of 6-mercaptopurine (6-MP) and breaks down to 6MP when it is absorbed into the bloodstream. These drugs may take six to 12 weeks to become effective. Over this time period, if patients are taking corticosteroids, the steroid dose is slowly reduced or tapered. These drugs appear to work to maintain remission in up to 2/3 of the patients. The dose of 6-MP/AZA is calculated based upon the patients' weight. Typically, prior to starting these drugs, a special blood test is checked to make sure the patient isn't at high risk for a low white blood count.

The most common side-effect of 6MP/AZA therapy is nausea. Interestingly, some patients who cannot tolerate 6MP due to nausea are able to tolerate AZA well, and vice-versa.

A small percentage of patients may be allergic to 6MP/AZA or develop inflammation of the pancreas known as pancreatitis. This occurs in 2% (2 out of 100 patients). The symptoms are an upper abdominal pain, and can be associated with nausea, and vomiting. If a patient develops this type of reaction to either drug, the other should not be used because the same reaction will develop. Once the medication is stopped, the pancreatitis usually quickly resolves.

Patients can also develop a low blood counts (typically white blood cells) or elevated liver tests (10% or 1 out of 10 patients) and therefore need frequent blood tests to monitor their blood cell counts and liver function. No matter how long one remains on the drug, these tests need to be continually monitored no less frequently than every three months, and more frequently at the initiation of therapy or after a dose change. There is now a test available that may identify those patients at greatest risk for developing a low white blood cell count. Also, it is now possible to measure the levels of the drug in the blood, known as metabolites. Assessing metabolite levels appears to be helpful in certain situations, such as assessing patients with suspected medication noncompliance, patients with abnormal liver tests, or patients who are not responding well to the 6MP/AZA.

Taking 6MP or AZA does put you at a slightly higher risk of both infection and lymphoma (a cancer of the lymph nodes. However, these potential risks are often outweighed by their benefits. Each individual considering these agents should discuss the pros and cons with their physician.

Cyclosporine (Neoral) is an oral medication used as "rescue therapy' when patients with severe disease fail (do not respond to) steroids and are facing surgical removal of the colon. When patients require admission to hospital and intravenous steroids fail to improve their symptoms within a few days, intravenous cyclosporine has been shown to obtain short-term response rates of about 80%. It initially is given intravenously, and then orally, but is used as a bridge to more long term therapy (mercaptopurine). It is not used routinely in those with milder disease, as the side-effects of tremor, kidney damage, hypertension (high blood pressure), seizures, and infections are significant. However, it can get patients over the severe episode of colitis and allow them to consider continued medical treatments or planned (elective) surgery.

4. Anti-tumor Necrosis Factor-alpha (TNF-α) Therapy
These drugs are specifically designed to bind to, and block the effects of TNFα, inflammatory protein or cytokine that is seen in high levels in patients with Crohn's disease and ulcerative colitis. There are currently three anti-TNF agents approved for the treatment of Crohn's disease, but only infliximab (Remicade), is approved for the treatment of moderate-to-severe ulcerative colitis.

Approximately 66% (2 out of 3) patients with ulcerative colitis will respond within the first two doses, and approximately 30-50% of those patients, will maintain response for up to one year.

Infliximab (Remicade) is a chimeric antibody, meaning that it is made up of material that is 25% mouse and 75% human. It is an antibody that binds to and blocks the effects of αTNF -- an inflammatory, protein (cytokine) that is seen in high levels in patients with inflammatory bowel disease. Infliximab has been in use to treat Crohn's disease

since 1998 and was approved for treatment of ulcerative colitis in 2005. Even some of the extra-intestinal manifestations of IBD (discussed above) may respond to infliximab therapy.

Infliximab is given intravenously. Administration typically takes place over two to three hours, and is usually well tolerated. After the initial infusion of infliximab, patients typically are given another IV dose two weeks and six weeks later, after which the drug is administered at consistent eight week intervals. This regimen of giving the drug more frequently at the beginning and then regularly thereafter has been shown to be more effective than receiving the drug just "on demand" when the patient has symptoms of a flare.

Although infliximab may prove highly effective in the initial stages of treatment, unfortunately some patients may lose response to infliximab over time. In such cases, the drug may need to be administered more frequently than every eight weeks or the dose may need to be increased. Patients can also develop reactions to the medication, which usually occur during the infusion. Most infusion reactions are mild and take the form of flushing, fevers, aches, and pains, but they can be more severe with associated chest pain, shortness of breath, hives, or a drop in blood pressure. Most of these reactions can be managed by slowing or stopping the infusion and giving intravenous fluids along with antihistamines, acetaminophen, or corticosteroids. Rarely the reactions can be delayed and occur a few days after the infusion. These types of reactions usually consist of joint pains, muscle aches, rash, and occasionally a fever. The vast majority of the infusion reactions are not true allergies. Hence, infusions can usually be completed and often do not preclude further use of the drug.

Although there are side effects associated with these medications, it is important to remember that anti-TNF therapy is both safe and extremely effective for the treatment of ulcerative colitis. There is a small increased risk of infections, including tuberculosis, as well as rare risks of heart failure, multiple sclerosis, lymphoma, autoimmunity (lupus-like reactions), and liver dysfunction, including reactivation of hepatitis B. These risks are relatively low, but should be considered.

Ongoing infection is an absolute contraindication to the treatment with any anti-TNF inhibitor. Prior to initiating treatment with infliximab or adalimumab, patients must be screened to make sure that they do not have an asymptomatic infection with tuberculosis. This is usually accomplished with a skin test (PPD test) and a chest x-ray. Patients who were born in countries where TB is more common may require treatment for TB before starting therapy with an anti-TNF agent. We recommend annual screening for TB while on anti-TNF therapy. We also recommend testing for previous exposure to hepatitis B virus prior to initiation of anti-TNF therapy.

5. Antibiotics

When one considers that bacterial elements are a trigger for the initial inflammation in ulcerative colitis, then manipulating colonic bacteria as a therapy makes sense. However, antibiotics such as Ciprofloxacin (Cipro) and Flagyl (Metronidazole) have shown minimal clinical benefits in ulcerative colitis and are not routinely used. Ciprofloxacin is better tolerated than metronidazole, but still has rare side effects including headaches, nausea, and sun-sensitivity. There is also a very rare risk of tendon rupture. Patients on Ciprofloxacin are also at increased risk for clostridium difficile colitis, a type of antibiotic-induced colitis that can be severe and requires specific therapy with metronidazole or vancomycin, another antibiotic.

Side effects with metronidazole are not uncommon, especially at higher doses. Side effects include nausea, loss of appetite, metallic taste, diarrhea, dizziness, headaches, and dark urine. Numbness or tingling of the hands (peripheral neuropathy) is rare, but may be irreversible. If this occurs, the drug must be discontinued. Metronidazole can also react with alcohol and cause a rare, severe reaction (antabuse-like) of nausea, vomiting, and shortness of breath. As a result, most patients on short courses of metronidazole are cautioned to avoid alcohol.

There is some emerging evidence that **Rifaxamin** (Xifaxan), a nonabsorbed antibiotic, is effective for the treatment of bacterial overgrowth and in small studies it has been shown to be effective in ulcerative colitis. It is a non-absorbed antibiotic that works by temporarily changing the mix of bacteria in the colon. There are no major side-effects, but it is unclear whether resistance by bacteria would become an issue in the long-term.

6. Complementary Therapies

The agents listed above (except for antibiotics) are considered standard medical treatments for ulcerative colitis. Additionally, a number of complementary therapies are used by patients although very few have actually been studied in clinical trials. Clinical trials have found some benefits in a few complementary therapies. They can be considered in mildy active disease if an alternative or addition to 5-ASA is desirable. Patients taking any complementary therapies should let their physicians know.

Probiotics are organisms, either bacteria or fungus, that promote beneficial effects in the colon. Lactobacillus, Bifidobacteria, Saccharomyces and Streptobacillus are considered to have such protective properties. Probiotics are not uncommonly used by patients with IBD. The normal colon contains billions of bacteria, which compete with

other detrimental organisms for survival in the "pea soup" of the normal colonic flora [5]. Single strains or combination of strains of some high-dose probiotics have been shown to produce similar results to mesalamine in inducing and maintaining a response in active ulcerative colitis. E.coli Nissle 1917, Bifidobacteria, Saccharomyces boulardii and a high-dose mix of Bififdobacteria, Lactobacilli and Stretptococcus ("VSL#3") had beneficial effects in clinical studies. However, many of the probiotics sold in stores and over the Internet have not been tested in ulcerative colitis, and may be at lower concentrations than those used in clinical studies.

Both germinated barley foodstuff and psyllium (Metamucil, Fybogel) stimulate the growth of beneficial colonic bacteria, and have been reported to improve symptoms in mildly active disease. Aloe vera capsules and curcumin were also shown in one study each to be better than placebo (dummy pill) in improving symptoms in mild ulcerative colitis. Other agents that may improve symptoms of ulcerative colitis include wheat grass juice, Jian Pi Ling tablets, Kui jie qing enemas, acupuncture with moxibustion, and bovine colostrum enemas [6]. In addition, some patients report benefits with a restricted carbohydrate diet, known as the "Specific Carbohydrate Diet". Most of these treatments have not been compared to placebo in measuring objective outcomes like colonic healing, which is considered the benchmark to assess any therapy.
Investigational treatments

Novel treatments for ulcerative colitis are currently under development or in **clinical trials** . The novel treatments include:

- Antibodies directed against specific types of immune cells (visilizumab, daclizumab, basiliximab)
- Inhibitors of cytokine activity (RDP58, alicaforsen)
- Inhibitors of migration of immune cells to the colon (MLN-02, ISIS-2302)
- Pig worm ova (Trichiuris suis)to influence the immune response
- Removal of certain immune cells (like dialysis) from the circulation (Adacolumn)
- Agents that work in a similar manner to 5-ASA (rosiglitazone)

Access to these therapies is currently only available through clinical trials as they are not F.D.A. approved for ulcerative colitis.
- See more at: http://www.bidmc.org/Centers-and-Departments/Departments/Digestive-Disease-Center/Inflammatory-Bowel-Disease-Program/Ulcerative-Colitis/How-is-ulcerative-colitis-treated.aspx#sthash.XkqHx5e8.dpuf

Attachment D – Cannabis study from National Center for Biotechnology Information

Cannabis use amongst patients with inflammatory bowel disease.

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Author information

Abstract

BACKGROUND:

Experimental evidence suggests the endogenous cannabinoid system may protect against colonic inflammation, leading to the possibility that activation of this system may have a therapeutic role in inflammatory bowel disease (IBD). Medicinal use of cannabis for chronic pain and other symptoms has been reported in a number of medical conditions. We aimed to evaluate cannabis use in patients with IBD.

METHODS:

One hundred patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD) attending a tertiary-care outpatient clinic completed a questionnaire regarding current and previous cannabis use, socioeconomic factors, disease history and medication use, including complimentary alternative medicines. Quality of life was assessed using the short-inflammatory bowel disease questionnaire.

RESULTS:

A comparable proportion of UC and CD patients reported lifetime [48/95 (51%) UC vs. 91/189 (48%) CD] or current [11/95 (12%) UC vs. 30/189 (16%) CD] cannabis use. Of lifetime users, 14/43 (33%) UC and 40/80 (50%) CD patients have used it to relieve IBD-related symptoms, including abdominal pain, diarrhoea and reduced appetite. Patients were more likely to use cannabis for symptom relief if they had a history of abdominal surgery [29/48 (60%) vs. 24/74 (32%); P=0.002], chronic analgesic use [29/41 (71%) vs. 25/81 (31%); P<0.001], complimentary alternative medicine use [36/66 (55%) vs. 18/56 (32%); P=0.01] and a lower short inflammatory bowel disease questionnaire score (45.1±2.1 vs. 50.3±1.5; P=0.03). Patients who had used cannabis [60/139 (43%)] were more likely than nonusers [13/133 (10%); P<0.001 vs. users] to express an interest in participating in a hypothetical therapeutic trial of cannabis for IBD.

CONCLUSION:

Cannabis use is common amongst patients with IBD for symptom relief, particularly amongst those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index. The therapeutic benefits of cannabinoid derivatives in IBD may warrant further exploration.

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