

Medical Therapy for IBD

I. INTRODUCTION

The treatment of Crohn's disease and ulcerative colitis involves a number of different approaches, including: medication, nutritional therapies, surgery, psychological support, and cancer screening. For most patients, the primary initial treatment involves medications. This discussion will review the more common medications used in treating Crohn's disease and ulcerative colitis. It should be noted that medications have two primary roles: induction therapy and maintenance therapy. Induction therapy refers to using stronger medications for a short time to get a sick patient with a flare (symptoms) under control. Maintenance therapy refers to medications used long term to keep a well patient from developing flares of their disease (relapses).

II. TREATMENT OF CROHN'S DISEASE

Treatment of Crohn's disease requires knowledge of the extent and severity of the disease, which is usually determined through a combination of x-ray and endoscopic studies. The location of the disease (for example small intestine vs. colon) may determine what medicines are used. In addition, different complications of the disease are treated with different strategies. For example, a patient with inflammation of the lining of the bowel (inflammatory Crohn's) is probably best treated with medication, whereas a patient who has a scarred and narrow piece of bowel (stricture) causing obstruction is usually best treated with surgery.

Crohn's Disease - Induction Therapy

Patients who come in with a flare of their disease typically undergo induction therapy with either prednisone or enteral nutrition. Prednisone is an anti-inflammatory medication that is usually taken in pill form, but is also available as a liquid. It is usually taken once a day. Approximately 75% of children treated with prednisone will experience improvement in their symptoms within two weeks. However, prednisone treatment can have side effects (see below). For this reason, prednisone is generally not used as a long term drug, but rather as a "bridge" to a maintenance treatment.

Enteral nutritional therapy (more commonly used in Europe than in the United States or Canada) requires the patient to stop eating food, and drink a special liquid formula by mouth usually as the sole source of nutrition. Because most children do not like the taste of these special formulas, often a feeding tube is used to deliver the formula that passes down the nasal cavity and into the stomach (nasogastric, or NG tube). The period of exclusive enteral nutrition usually lasts about 6 weeks to 8 weeks and then food is slowly reintroduced. Children treated with enteral nutrition for Crohn's disease are less likely to respond to enteral nutrition than to prednisone, and many children are reluctant to have the feeding tube placed. However, enteral nutrition as primary induction therapy is effective in about 60% of patients, and does not have the side effects associated with prednisone treatment.

For very mild flares of Crohn's disease, aminosalicylates (e.g. Pentasa®, Asacol®,) and antibiotics (e.g. ciprofloxacin, metronidazole [Flagyl®]) are utilized as induction treatment. While clinical studies have not convincingly shown that these medications are effective, patients and physicians often report that these medications can treat mild flares of the disease. Budesonide, a newer steroid preparation, is another option for mild Crohn's disease of the terminal ileum and cecum.

Crohn's Disease - Maintenance Therapy.

Once a patient improves after induction therapy, they generally need to stay on a medication to prevent relapses (flares) of the disease. The two principal maintenance therapies utilized are aminosalicylates and immunomodulators (medications that decrease the activity of the immune system).

Aminosalicylates include medications more active in the colon (balsalazide - Colazal®, olasalazine-Dipentum®, sulfasalazine), and medications that work both in the small intestine and the colon (mesalamine - Pentasa®, Asacol®). Because most patients have disease involving both the small intestine and the colon, usually me-

salamine is utilized as maintenance therapy. Currently, medical studies suggest that at best, aminosaliclates only help maintain remission in a small number of patients with Crohn's disease. However, because these medications are quite safe, they are often used as first line treatment in patients with mild Crohn's disease. The primary disadvantage of these medications is that children often have to take a large number of pills (up to 16 tablets a day).

For patients with moderate to severe disease, extensive disease, or who have persistently active Crohn's despite aminosaliclate use, immunomodulators are the main medication utilized as maintenance therapy. The immunomodulator medications most frequently used to treat Crohn's disease are 6-mercaptopurine (e.g. Purinethol®) or azathioprine (e.g. Imuran®). Another immunomodulator with proven effectiveness in Crohn's disease is the medication methotrexate. Immunomodulator treatments have been shown in many clinical studies to prevent flares of Crohn's disease and to heal the intestinal lining. They are also easier to take than salicylates: 6-mercaptopurine or azathioprine are usually taken once a day, while methotrexate is taken once weekly. However, in approximately 5% of patients, these drugs may be associated with significant side effects, including infections and lowering of the blood count (see below). These medications also can take between 1-4 months to work, so they are not effective to treat flares of the disease (not used as induction agents).

Treating Resistant Crohn's Disease

For patients whose disease does not respond to corticosteroids, or does not stay under control despite an immunomodulator, infliximab (Remicade®) is a very effective drug. Studies of patients with resistant Crohn's disease suggest that infliximab will get the disease under control 50-70% of the time. This medication is administered intravenously (by vein) three times in the first two months of treatment, then approximately every 2 months thereafter. Patients who respond to infliximab will usually feel better within 2-4 weeks after their first treatment. Infliximab has been proven to heal the intestinal lining, close fistulas, and reduce the need for prednisone in patients with resistant Crohn's disease. However, infliximab also has the potential for serious side effects, including severe infections and allergic reactions (see below). Therefore, it is generally reserved

for patients with more severe or resistant disease who have not responded to immunomodulators.

A small number of patients will have persistently active Crohn's disease despite prior treatment with corticosteroids, salicylates, immunomodulators, and infliximab. Treatment of these patients is highly individualized, and should be carried out by a physician with special expertise in treating resistant inflammatory bowel disease. For some patients whose disease is limited to a small section of the bowel, surgery may be the best option. For others with more extensive disease, treatment may include a prolonged course of enteral nutritional therapy, other medications (including cyclosporine, tacrolimus, adalimumab, or thalidomide), or a combination of medicine and surgery.

III. TREATMENT OF ULCERATIVE COLITIS

The medications used to treat Crohn's disease and ulcerative colitis are similar. As with Crohn's disease, the location and the severity of the disease (as determined by endoscopic studies) will determine the type of medication used. Most ulcerative colitis in children involves the entire large intestine. However, approximately 20% of children will have disease limited to the lower part of the colon (rectum or rectosigmoid). This latter group of patients can often be treated with steroid or aminosaliclate enemas.

Induction Therapy Of Ulcerative Colitis

For **mild colitis** (e.g. 3 or fewer bowel movements a day, small amounts of blood, mild inflammation on colonoscopy), aminosaliclates are the first-line treatment. The available aminosaliclates in the United States include sulfasalazine (Azulfidine®), mesalamine (Pentasa®, Asacol®), balsalazide [Colazal®]), and olsalazine (Dipentum™). These medications are generally all well tolerated, with few side effects. Sulfasalazine has been utilized the longest by physicians, and offers the added benefit of treating IBD-associated arthritis. However, it also has a higher incidence of side-effects, including allergic reactions, hepatitis, and increased skin sensitivity to sunlight. Mesalamine is also available in a suppository form (Canasa®) and an enema form (Rowasa®).

Patients with mild colitis who respond to salicylates usually improve within 2 weeks. It is important to note that up

to 10% of patients will develop worsening of symptoms (more blood and diarrhea) on salicylates; symptoms will improve once the medication is stopped. In this small group of patients, a rechallenge with salicylates will once again produce worsening of symptoms, and some other medication (e.g. an immunomodulator) should be used for maintenance.

A few reports suggest that concurrent treatment with an antibiotic such as ciprofloxacin (Cipro®) or metronidazole (Flagyl®) might also be of benefit in treating mild colitis. Therefore, physicians will sometimes prescribe antibiotics for mild colitis flares.

For moderate to severe colitis (e.g. 4 or more bowel movements a day with more blood), prednisone is used as initial induction treatment. If a patient is hospitalized, an intravenous form of prednisone (methylprednisolone) is often used. Prednisone and other corticosteroids are usually very effective for moderate to severe colitis, with a 75% response rate. Improvement usually occurs within the first two weeks (often within a few days). Again, because of long-term side effects, physicians try to limit exposure to prednisone. Therefore, once a patient has improved (within 2-4 weeks), physicians start tapering this medication, aiming to get a patient off of prednisone within 3 months. Patients who flare as they are being tapered should be considered candidates for surgery or immunomodulator treatment.

Patients with severe colitis unresponsive to corticosteroids should be strongly considered for surgical therapy (colectomy). For patients who are unprepared to undergo surgery, a number of other medications (including cyclosporine, infliximab, and tacrolimus) have been utilized to induce remission. All these medications have been shown to be effective at getting the disease under control in the short term. However, children who are treated with these medications still have a high likelihood of needing surgery within the first two years after their treatment.

Maintenance Therapy of Ulcerative Colitis (UC)

Because these medications are very safe, aminosalicylates are the first line maintenance therapy for patients with ulcerative colitis. Ideally, the physician goal should be to get the disease under control (induce remission), either with aminosalicylates alone, or with prednisone

and aminosalicylates. Once the disease is under control, steroids are gradually reduced, with the hope of leaving a patient on the salicylates alone. Salicylates have been shown to be effective in preventing flares of ulcerative colitis. If taken consistently and on a daily basis, they also reduce the long-term risk of colon cancer in colitis patients. As mentioned previously, sulfasalazine also offers the added benefit of reducing joint pains (arthralgia) in children with colitis and joint symptoms.

Approximately 50% of children with ulcerative colitis will have persistent active disease (diarrhea and rectal bleeding) despite the use of aminosalicylates as maintenance therapy. In these children, azathioprine or 6-mercaptopurine are frequently added as maintenance medications to help keep the disease under control. Approximately two-thirds of patients will respond to this class of medications. Patients with UC in whom azathioprine or 6-mercaptopurine is ineffective should be considered surgical candidates. Infliximab (Remicade®) has been attempted as maintenance treatment in some patients with UC, but the long-term success of this strategy has not yet been determined.

IV. SPECIFIC MEDICATIONS USED IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

A. Corticosteroids - Prednisone, Prednisolone, Methylprednisolone

These medications are induction therapies for moderate to severe IBD, and have been used for over 50 years. They are usually used short term (a few weeks to a few months) to get moderate to severe CD or UC under control. Prednisone is usually given as a single dose in the morning. Most patients treated with corticosteroids will improve within 2 weeks of treatment. Patients who respond will have improved appetite and a decrease in pain, diarrhea, and bleeding. Short-term side effects (seen in the first month) can include moodiness, altered sleep patterns, water retention, and hunger. These usually improve as the dose is lowered. Long-term side effects (most commonly seen in patients who have been taking these for several months) can include high blood pressure, high blood sugar, stomach irritation (gastritis), weakening of the bones and hip, eye cataracts, and facial swelling. Patients on steroids are also at increased risk for viral infections, especially chicken pox.

Recommended monitoring for patients on corticosteroids: Patients treated with daily steroids should undergo routine follow-up visits in which blood pressure measurements, physical examinations and lab work are performed. Patients who have symptoms of gastritis may benefit from being treated with an acid blocking drugs such as ranitidine (Zantac®), or omeprazole, (Prilosec®). Patients on corticosteroids should be up to date on immunizations, receive a flu shot annually, and undergo yearly eye examinations.

B. Aminosalicylates - Sulfasalazine, Olsalazine, Mesalamine, Balsalazide

These are among the safest medications used to treat IBD, but are generally effective only in milder cases. They usually come as pills or capsules, and are given two or three times a day. They are most effective as maintenance therapies in mild to moderate ulcerative colitis.

Sulfasalazine (Azulfidine®), the oldest of the medications, has been used for over 40 years to treat IBD. It is very effective, but also carries an increased risk of allergic reactions (including skin rashes, hives, liver inflammation, and a more severe reaction called Stevens-Johnson syndrome). It can also lower the levels of a vitamin called folic acid in the blood, so patients on sulfasalazine should also receive a daily folic acid supplement. Sulfasalazine can cause a lowering of the white blood cell count, so patients treated with this medication should have their blood counts checked every 3-6 months. Sulfasalazine can sometimes cause hair loss. In adult males, sulfasalazine can lower the sperm count, but the count usually returns to normal after the medication is stopped.

Mesalamine (Pentasa®, Asacol®), balsalazide (Colazal®), and olsalazine (Dipentum®) are sulfasalazine derivatives that carry a lower risk of allergic reactions, because they are not sulfa-based drugs. They have been used for over 15 years. They are effective in treating ulcerative colitis (and perhaps in Crohn's disease). These medications can also be associated with allergic reactions, including pancreatitis (inflammation of the pancreas), and loss of protein in the urine.

Recommended monitoring for patients on aminosalicylates: Patients treated with salicylates should be seen every 3-6 months, and have to undergo a physical

examination and laboratory studies, including complete blood count, sedimentation rate, and liver function tests. Consideration should also be given to checking a urine specimen once a year to look for protein loss. Patients taking sulfasalazine should wear sun block during the summer to reduce the risk of skin rashes or burns.

C. Antibiotics – Metronidazole, Ciprofloxacin

Antibiotics (ie Metronidazole - Flagyl®, Ciprofloxacin – Cipro®) are often used to treat infectious complications of inflammatory bowel disease, such as abscesses in the abdomen or around the anus (perianal). They also may have an effect, comparable to aminosalicylates, in the treatment of mildly active CD, especially in patients with perianal infections. While studies have not demonstrated a consistent benefit of antibiotic use in UC patients, they are sometimes utilized to treat mild flares of ulcerative colitis.

A common side effect of many antibiotics is gastrointestinal discomfort, such as nausea, vomiting, and diarrhea. When taking metronidazole, patients may complain of a metallic taste. Rarely, with long-term use, patients can develop a problem with their nerves (peripheral neuropathy). A physician should be notified immediately if any numbness or tingling were to develop in hands or feet. Metronidazole may reduce the effectiveness of birth control pills and should not be taken by pregnant women. Patients must also avoid alcohol when taking this medication. Ciprofloxacin can sometimes be associated with skin rashes nausea. Rare reports of tendonitis and tendon rupture have also been reported with ciprofloxacin.

D. Azathioprine AZA And 6-mercaptopurine (6MP)

These two medications are very similar, because azathioprine is converted to 6-mercaptopurine in the body. They are primarily used as maintenance treatment in Crohn's disease, and have been used for over 25 years. They are also used in patients with ulcerative colitis whose symptoms persist despite salicylates. These medications typically take 3-6 months to be effective. Because of their slow onset of action, they are not effective induction agents. They are among the most effective agents we have to treat CD and UC. Approximately 75% of patients respond, and fewer than 5% develop significant side effects.

Side effects of these medications include lowering of the blood count, pancreatitis (inflammation of the pancreas), and hepatitis (inflammation of the liver). These medications may also increase the risk of serious viral infections, including chicken pox or mononucleosis. A recent study suggests that patients on AZA or 6MP may also be at an increased risk of lymphoma (a tumor of the lymph glands). The risk is approximately twice that of someone who is not taking these medications, but is still very small (approximately 1 in 4500 patient-years).

Recommended monitoring for patients on AZA or 6MP: Because a small number of patients will develop significant side effects on these medications, frequent visits are needed initially. A patient's physician may draw a blood test before starting called a thiopurine methyltransferase (TPMT) activity level or thiopurine methyltransferase genotype. This test will help the physician to more accurately predict how the body breaks down (metabolizes) AZA or 6MP. In addition, the patient should undergo frequent monitoring of blood counts and liver function tests in the first 3 months, then approximately every 3 months thereafter. Patients should be kept up to date on immunizations, including chicken pox immunization, and be given a flu shot annually.

E. Methotrexate

Methotrexate is another immunomodulatory medication used as a maintenance therapy for Crohn's disease. It is considered an alternative to azathioprine and 6-mercaptopurine and has been used for over 20 years. It is also used to treat patients with IBD who have significant joint complications. Methotrexate is usually given once a week, either as pills or as an injection. Patients receiving methotrexate need to be supplemented with daily folic acid in order to prevent complications.

Side effects of methotrexate are similar to those of azathioprine and 6-mercaptopurine and primarily involve lowering of the blood count and liver inflammation. As with azathioprine and 6-mercaptopurine, serious infections are rare, but may occur. Pancreatitis is usually not seen. Rare severe complications of long-term use include liver and lung scarring. Pregnant women, or women planning to become pregnant, should not take methotrexate, as it can cause miscarriages and birth defects.

Recommended monitoring for methotrexate is the same as for patients on azathioprine or 6-mercaptopurine.

F. Infliximab (Remicade®)

Infliximab is an antibody to a protein called tumor-necrosis factor (TNF). TNF is thought to trigger some of the bowel inflammation seen in inflammatory bowel disease, so by blocking this protein, inflammation is decreased. Infliximab is usually used in patients with Crohn's disease who have not responded to corticosteroids and immunomodulators. It also may be utilized in patients with ulcerative colitis who have not responded to these medications. Infliximab has been widely utilized to treat Crohn's disease since 1998, and was given FDA approval to treat ulcerative colitis in 2006.

Infliximab is given as an intravenous infusion over 2-4 hours. It is usually begun for a patient with active disease (induction treatment). The first three doses are given in a 6 week period. The second dose is given 2 weeks after the first dose, and the third dose is given 6-weeks after the first dose. If a patient responds, they usually feel better by the third dose. If they respond, they should be continued on infusions given approximately every 6-8 weeks, depending on symptoms. About 70% of patients with active Crohn's disease and 50% of patients with ulcerative colitis will respond initially.

Side effects of infliximab occur in about 10% of patients. These include reactions during the time the drug is being given (infusion reactions). The most common infusion reactions are skin rashes, hives, chest tightness, and difficulty breathing. Patients who develop such a reaction may sometimes tolerate the medication if they are premedicated with steroids. Lowering of the blood count may occur. Serious infections, particularly tuberculosis have been reported. This medication may also cause an increased risk of lymphoma, but because this medication has only been in use for under a decade, the true risk of lymphoma is unclear.

Suggested monitoring for patients on infliximab: All patients to be treated with infliximab should undergo a PPD (TB skin test) prior to being started on this medication. Patients at high risk for TB or with symptoms such as a cough should also undergo a chest x-ray. Patients should also undergo monitoring for the complete blood count, sedimentation rate, and liver function tests during each infusion. It is generally recommended that patients treated with infliximab be kept on another immunomodulator such as azathioprine or 6-mercaptopurine in addition to the infliximab, in order to decrease the risk

of forming antibodies to infliximab. In addition, patients maintained on infliximab should receive their medication at regular intervals (i.e. about 8 weeks), to decrease risk of antibody formation.

G. Cyclosporine (Gengraf[®], Neoral[®], Restasis[®], and Sandimmune[®]) and Tacrolimus (Prograf[®])

Cyclosporine and tacrolimus are medications that may be used short term to induce a remission in Crohn's or UC patients with severe symptoms and persistently active disease despite conventional treatments. They act to suppress immune system activity, thus decreasing the inflammatory process causing active symptoms in IBD. These medications are usually used to treat hospitalized patients that have not responded to intravenous steroid treatment.

While quite effective, these drugs require close monitoring due to the risk of side-effects. The side effects of these medications include infections, kidney problems, high blood sugar, headache, and (rarely) seizures. The risk of these complications can be decreased if blood levels are followed. There may also be an increased risk of lymphoma, (a cancer of lymph glands), though the precise risk is unknown.

Recommended monitoring for patients treated with cyclosporine or tacrolimus:

Patients with Crohn's disease or ulcerative colitis undergoing treatment with these medications should undergo close followup by a physician experienced in the use of these medications. Ideally, they should be utilized for a short time (3-6 months). Patients treated with these medications require frequent visits and blood tests to

monitor blood counts and kidney function. In addition, patients treated with these medications should also be placed on an antibiotic to reduce the risk of Pneumocystis pneumonia (a serious lung infection). Certain medications (such as erythromycin and ketoconazole) can raise blood levels of cyclosporine and tacrolimus, and patients should consult their physician if they get placed on new medications during the course of treatment.

Overview and summary.

Physicians who care for children with inflammatory bowel disease are constantly working on ways to try to improve their health. Over the last 20 years, the number of medications utilized to treat this illness has increased, which has resulted in improved well being for most people with IBD. The current document outlines the most common medications utilized to treat IBD in 2006. However, this is not an all-inclusive list of medical treatments. In addition, as new medications are discovered to be effective, patients with IBD will hopefully have an increasing number of options with regards to their treatment.

To prove a medication is safe and effective in treating IBD, it usually needs to be studied in both adults and children. Clinical trials are studies conducted by physicians and pharmaceutical companies to try to determine which new treatments are effective, how they work, and how safe they are. In some cases, your physician may offer you the opportunity to participate in such a study. While participation is always optional, taking part in a clinical trial may help your doctors find out what are the best treatments for IBD, and also help other patients who have the disease.

To find out more about clinical trials go to <http://www.clinicaltrials.gov/>