The cause of IBD is unknown. The immune system of the intestine becomes overactive. Medicines to suppress the immune system have been used many decades. Prednisone is effective at getting most patients better, but using it for long periods may lead to side effects (discussed in the “Corticosteroid” handout).

**Immunomodulators**

Azathioprine and 6-MP  
(Azathioprine is turned into 6-MP in your body)  
Methotrexate

**What is Imuran® (Azathioprine) or 6-MP (6-mercaptopurine or Purinethol®) and Methotexate (MTX)?**

Azathioprine, 6-MP  and Methotrexate were developed for cancer chemotherapy, but when used in small doses, they can be helpful for treating chronic inflammatory diseases such as IBD and some forms of arthritis. These are medications that reduce (suppress) the activity of the immune system by suppressing the bone marrow where immune cells are formed. These  medications are called immunosuppressive or immunomodulators.

Azathioprine and 6-MP come in 50mg tablets, and are given every day. MTX is given once per week, by injection or as pills of 2.5 mg each.

**How can Azathioprine, 6-MP and MTX help IBD?**

Although Azathioprine, 6-MP and MTX cannot cure bowel disease, it can help reduce symptoms and prevent flare-ups.

Azathioprine, 6-MP and MTX are typically used when:

- Bowel disease is difficult to control
- Patient relapses frequently when Prednisone is decreased or stopped
Azathioprine, 6-MP and MTX do not work right away. It takes 8-12 weeks to achieve the desired dose and effect. During this time, you may still need to take Prednisone or other medications.

**What side effects are possible with Azathioprine and 6-MP?**

Together, you and your health care team will watch carefully for any side effects. To check your response to Azathioprine and 6-MP, you will need to visit the clinic and have blood tests regularly.

Some side effects are possible, especially when starting Azathioprine and 6-MP.

Although it is rare, a few people may develop an inflammation of the pancreas, called pancreatitis. Blood work is used to look for this complication before patients get sick from it. Typical symptoms are upper abdominal pain with vomiting.

Side effects may include:

- Pancreatitis
- Increased liver enzymes
- Bone marrow suppression
- Signs of infection, such as fever (a temperature greater than 38°C or 100.4°F), chills, sore throat, cough
- If you get chickenpox, stop 6-MP or Azathioprine and call your doctor
- Hair loss is not typically seen with the low dose 6-MP/Azathioprine
- GI upset is not typically seen

If you notice any side effects, call your doctor right away.

**What else should I consider before taking Azathioprine and 6-MP?**

Taking Azathioprine and 6-MP for a long time may increase the risk of cancer. After many years of study, the risk of cancer appears to be very small. You will need to consider this risk. Many patients feel the benefits of taking Azathioprine and 6-MP outweigh the risks, when their disease is hard to treat or control. **Skin cancer** may be increased, so sunscreen and avoiding excess sun is recommended. **Lymphoma** is a cancer that occurs in 1 in 100,000 people over a 10 year period. It is felt that Azathioprine or 6MP increase this risk to 3 or 4 per 100,000. There is a very rare lymphoma known as **hepatosplenic T-cell lymphoma** (less than 20 cases
reported in the world in IBD patients) that may be associated with azathioprine, 6-MP and with biologic therapy (below). This occurs primarily in young male patients, but it is difficult to provide an exact mathematical risk of this rare cancer as the total number of patients taking these medications is unknown. There is no test available to detect these cancers early or to see who may be at risk. Symptoms include fever, night sweats, unexplained weight loss and swollen glands.

**What side effects are possible with MTX (Methotrexate)?**

MTX given by weekly injection (typically for the first 12 weeks) may cause nausea and upset stomach, often made better by using anti-nausea medication.
Mild elevation of liver enzymes may occur and are monitored by your doctor.
Infection from immune suppression is rare.
Patients should use sunscreen and avoid excess sun exposure.

Lymphoma cancers have not been seen with MTX in IBD patients, however, many fewer children with IBD have been given MTX than the other immunomodulators so it may be too early to tell. Rheumatologists have a long experience treating certain arthritis patients with MTX without seeing a significant increase in lymphomas.

**What should I remember while taking Azathioprine, 6MP or MTX?**

If you are sexually active, use an effective birth control method. Talk with your doctor if you are planning to become pregnant.

If any worrisome side effect occurs, contact your doctor.

If you develop a fever, you should see your doctor.
Biologics

Anti-TNF Antibody Therapy (Remicade® and Humera,® others)

These are potent anti-inflammatory drugs given to counter-act one important mediator of inflammation known as TNF (Tumour Necrosis Factor). This is a key mediator of inflammation especially in Crohn’s disease.

Remicade is currently the most studied biologic in IBD. Remicade is given by intravenous infusion over several hours typically every 8 weeks. Humera is injected under the skin, typically once per week.

These medications are relatively new in the treatment of IBD, especially in children. Health Canada has place a “Black Box” warning on these medications in children because we recognize that some children have developed rare lymphoma (cancer of lymph nodes) while taking anti-TNF antibody. Many of these patients also had Azathioprine or 6-MP either before or during anti-TNF treatment, making it difficult to know which medication increases the risk; they may both increase the risk.

Some IBD experts have suggested that anti-TNF antibody treatment should be used first in IBD, especially Crohn’s, but much longer experience will be needed to know if this is the right approach.

Also, people now talk about the concept of “healing” of Crohn’s that occurs with anti-TNF antibody but not with other treatment. However, very few patients who are completely well on other treatment are re-scoped to see if they are ‘healed’ and only a small number of anti-TNF patients have been re-scoped in the clinical drug trials to see if they are healed. Overall, these medications have about a 60% effectiveness rate and are given long-term once they are started. My practice is to consider anti-TNF antibody therapy when all other treatment options including surgery have been exhausted.

In ulcerative colitis, anti-TNF antibody is used in the setting of overwhelming colitis in hospitalized patients who are facing surgery to remove the colon. In studies, 40-50 % of patients respond to this, although
our experience with sick colitis patients has not been as good and most patients have gone on to surgery.

Complications of anti-TNF include:

- Developing an allergic reaction to the medication
- Infection
  - New infection
  - Activation of existing infection (TB, CMV, herpes, HPV)
- Rare increased risk of cancer
- Local reaction to injection for Humera

**What should I remember while taking Biologics?**

You should be followed closely by your doctor if taking these medications. Rare adverse events may occur. If side effects or fever occur, contact your doctor.

This handout was written by Dr. Justinich as background information to facilitate discussion about these difficult treatment decisions and not to replace consultation with your practitioner.

More information can be found at the links provided in the Crohn’s and Colitis patient information sections.