

BIOLOGIC THERAPY

Muffling the
Molecular Messenger



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& COLITIS**

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ABOUT CROHN'S AND COLITIS CANADA

Crohn's and Colitis Canada wants to help you on your journey of discovery. Our promise reflects our determination to cure Crohn's disease and ulcerative colitis and improve the lives of children and adults affected by these chronic diseases.

We are committed to helping you learn more about Crohn's and colitis. Our patient information booklets can help you make informed decisions. Knowledge is most often the key to managing your health.

Please go to crohnsandcolitis.ca for the complete list of patient information brochures. You can download them at your convenience or contact your local Crohn's and Colitis Canada chapter and a free copy will be mailed out to you!

This particular booklet addresses the topic of biologic therapy. Biologics are among the different medical treatment options that help individuals in the management of their disease.



One of the exciting developments arising from inflammatory bowel disease (IBD) research (which includes Crohn's disease and ulcerative colitis) is in the field of biologic therapy. Also known as biotherapy, biologics in IBD are medications that have been engineered to target specific activity in the immune system.

To really understand what biologics are about, we need to take a step back and understand the inflammatory processes in Crohn's and colitis.

INFLAMMATION AND IMMUNITY IN CROHN'S AND COLITIS

If you live with Crohn's or colitis you are likely familiar with the term "inflammation". But what is it?

Inflammation is the body's normal, natural response to things like injury, infection (e.g., bacteria, viruses), certain types of stress, and pain. Any of these triggers will set off activity at the injured site, as well as in your vascular system (veins, arteries, blood flow) and your immune system.

When inflammation occurs (for whatever reason), cells in the area release chemicals which act like a 911 emergency call. These signals help the body deal with the injury at the site. As a result, there will be swelling in the area, which may result in pain and heat; this is what is referred to as inflammation. Inflammation in the short-term is essential to start repairing the injured area, protecting it against further injury, and healing it.

For reasons not fully understood, sometimes the immune system does not switch off after its initial response. When not switched off, the inflammatory responses that were initially beneficial in repairing tissue damages begin to damage healthy tissue. When this happens, the medical condition is known as an immune-mediated disease, of which Crohn's, colitis, rheumatoid arthritis, and multiple sclerosis are examples.

The symptoms of Crohn's and colitis are associated with this ongoing inflammation that is occurring in the gastrointestinal tract and its inner lining. Severe gut pain, diarrhea, nausea, vomiting and fatigue are the results of an immune system that no longer knows friend from foe, and is attacking otherwise healthy tissue.

MEDICATIONS TO TREAT CROHN'S AND COLITIS

Many medications are prescribed to control inflammation. There are five types, or classes, of these medications:

1. AMINOSALICYLATES

- Usually prescribed for milder attacks of IBD, particularly ulcerative colitis
- Help reduce the risk of relapses in people with colitis

2. GLUCOCORTICOIDS (STEROIDS)

- Prescribed for moderate to severe attacks
- Not used for prolonged periods or prevention of relapses
- Suppress immune responses throughout the entire body

3. IMMUNOSUPPRESSANTS AND IMMUNOMODULATORS

- Used for long-term treatment and for helping people reduce the use of steroids
- Help prevent relapse for people with Crohn's disease
- Suppress immune responses throughout the entire body

4. ANTIBIOTICS

- Sometimes used as a treatment for Crohn's patients
- Prescribed when a patient has an abscess, fistula or infection

5. BIOLOGICS

We'll talk more about biologics in the next section.

If you would like to know more about the other classes of medications mentioned above, please check out our brochure, *Prescription for Health*.

WHAT ARE BIOLOGICS?

A biologic is a drug that is derived from living cells. Vaccines, insulin and monoclonal antibodies are examples of biologics. They often have large, complex molecular structures. Due to the complexity in manufacturing biologics from living cells, they tend to be higher in cost and are relatively difficult to replicate precisely in comparison to conventional (“small molecule”) drugs, which are composed of simple chemical structures. Biologics are generally administered by injection, subcutaneously or intravenously.

Biologic medications currently approved for treatment of Crohn’s and colitis in Canada have been developed to target specific molecules within the inflammatory processes in order to control inflammation.

Biologics may target different parts of immune responses in controlling inflammation, such as mop up some of the inflammatory signals or stop some cells from travelling to the areas of inflammation in the gut, thereby allowing the gut to heal.

Anti-TNF Biologics

One of the signals involved in causing inflammation in people with Crohn’s and colitis is called tumour necrosis factor alpha, or TNF-alpha. Biologic medications that block those signals are known (not surprisingly) as anti-TNF biologics.

$\alpha_4\beta_7$ Integrin Blockers Biologics or selective adhesion molecule inhibitors (SAM).

These biologic medications attempt to block the movement of some inflammatory cells to areas of inflammation in the gut, allowing time for the gut to heal.

BIOLOGICS APPROVED FOR USE

The following table describes the biologics used in Canada for treatment of Crohn’s and colitis, as well as the method of drug administration.

Name	Used for	Administered
Generic name: Adalimumab Trade name: Humira® Type: Anti-TNF	Treatment of moderate to severe Crohn’s (adult and pediatric) and colitis (adult). It is used for people who have not responded well to conventional therapies.	By subcutaneous injection (SC)
Generic name: Infliximab Trade name: Remicade® Type: Anti-TNF	Treatment of moderate to severe Crohn’s (adult and pediatric), and fistulizing Crohn’s. Treatment of moderate to severe colitis (adult and pediatric). It is used for patients who have not responded well to conventional therapies.	By intravenous (IV)
Generic name: Golimumab Trade name: Simponi® Type: Anti-TNF	Treatment of moderate to severe colitis in adults. It is used when conventional colitis medicines have not worked well or cannot be tolerated, or in patients who have demonstrated steroid dependence.	By subcutaneous injection (SC)
Generic name: Vedolizumab Trade name: Entyvio® Type: Integrin Blocker	Treatment of moderate to severe colitis in adults. It is used when conventional colitis medicines have not worked well enough or cannot be tolerated, and in patients who have not had satisfactory response with infliximab.	By intravenous (IV)

HOW THESE MEDICATIONS ARE TAKEN

Adalimumab can be self-administered by subcutaneous injection, either by a pen (similar to the “epi” pen used by people with allergies) or by a pre-filled syringe, commonly injected bi-weekly. Adalimumab needs to be refrigerated. As an exception, for example when travelling, the medication may be kept at room temperature (25°C) for up to 14 days. The product must be used within 14 days even if it is put back in the refrigerator, otherwise it must be discarded. Patients may contact the patient support program, AbbVie Care, to arrange for a nurse to give the injection or provide training at the location of their choice, to assist with reimbursement issues, or to provide a travel letter as well as tips for traveling with your medication.

Infliximab infusions are most often administered at a BIOADVANCE® Clinic under nurse supervision, but can sometimes be available at your doctor’s office. The dosage is based on weight so not every patient takes the same dose. Once a patient is on maintenance therapy, the IV (or infusion) sessions are scheduled approximately every eight weeks; each session takes about two hours. A BIOADVANCE® Coordinator assists patients with coverage issues, locating and setting up appointments at a suitable clinic as well as making the necessary arrangements for patients to travel if needed.

Golimumab can be self-administered by subcutaneous injection, either by a pen (similar to the “epi” pen used by people with allergies) or by a pre-filled syringe, commonly injected every 4 weeks during maintenance therapy. If patients prefer, they can contact the integrated patient care program, BIOADVANCE®, to arrange for a nurse to give the injection or provide training at the location of their choice. Golimumab needs to be kept refrigerated until use.



Vedolizumab infusions are administered at one of YOURVANTAGE™ network clinics, under nurse supervision. Once a patient is on maintenance therapy, the IV (or infusion) sessions are scheduled approximately every eight weeks; each session takes about 30 minutes. Should you plan to travel for an extended period of time, YOURVANTAGE™ can help you locate and make arrangements at a suitable clinic within Canada.

If your doctor is considering biologic therapy for your moderate to severe IBD, you should discuss with your physician about which biologic therapy is most appropriate for you. It is not advisable to switch from one biologic to the other if the one you’re taking is working for you. So it is better to start off with the most appropriate therapy from the beginning.

Also, the patient support programs, available through the companies that manufacture biologics, offer varying levels of service options for patients. These programs offer a wide variety of help including coordination of injections/infusions services and investigation of reimbursement options.

Stopping Biologic Treatment?

When biologic medication is able to keep your disease in remission, the current guidelines are to continue the biologic medication, adhering to the dosage and dosing schedules that you are prescribed. Please speak with your physician before stopping treatment or missing doses.

COMMON SIDE EFFECTS

It is important to be aware that with every medication you take, there are benefits and risks. On the plus side there are positive effects which are intended by your physician to help manage your IBD. The minuses are the unintended side effects you might experience.

When any medication is prescribed there is a need to balance the benefits versus the risks. If the main action of the drug is doing what it is supposed to do, but is also causing you difficulties due to side effects, you and your doctor need to discuss the risks and benefits of the prescription and the dosage you are taking. A workable balance needs to be established so that your symptoms can be controlled. Do not stop your medications without consulting with your doctor and discussing alternatives, as this may lead to flare-ups.

The safety profile for anti-TNF is well established. Side effects may include:

- Redness, swelling, bruising and/or itching at the IV or injection site (allergic reactions)
- Rash on parts of the body
- Infections of any type – including upper respiratory tract, skin, urinary tract, etc.
- Chills, fever, muscle aches

RARE POTENTIAL SIDE EFFECTS

There are some issues that pose a small, but serious risk when taking anti-TNF biologics. Reactivation of pre-existing tuberculosis (TB) infection has been associated with patients taking anti-TNF biologics. Therefore, patients should not start these medications without a TB test, because if you have an inactive case of TB, biologics can potentially reactivate the disease.

Because biologics lower your immune-fighting reactions, infections – some of which may be serious – have also been reported by people taking these medications. If you develop any signs of a general infection such as fever, fatigue or coughing you should contact your doctor.

People with HIV, AIDS, leukemia or lymphoma, heart failure or an organ transplant are generally not considered to be good biologic candidates.

On rare occasions, people taking anti-TNF biologics have developed blood disorders, nervous system disorders and cancer of the lymphatic system (lymphoma). These instances are very rare, however they do occur more often than in the general population. For example, four to six patients out of every 10,000 have developed lymphoma while taking a biologic compared to the two to three patients not taking a biologic.

TREATMENT APPROACHES

Two approaches that are currently being used to manage Crohn's and colitis include:

1. The right time for biologic use in your treatment journey – a personalized approach:

The conventional approach to controlling Crohn's and colitis employs aminosaliclates and steroids as the first line of defense; if these approaches are not effective, then medication is stepped up to immunosuppressants. If these do not work, then patients are again stepped up, this time to biologic medication.

In your physician's "personalized treatment care" approach, a patient-fitting specific criteria begins immunosuppressants and biologic therapy when recommended and not necessarily "stepped up" when other treatments fail. Research is being conducted to determine whether this accelerated form of treatment care is more effective for both the short and long-term health of the Crohn's and colitis patients, but current information suggests that earlier treatment with biologics is likely to be more effective at preventing bowel damage and complications.

Keep in mind – drug plans for biologic medication vary across Canada. Check out the Biologics Report Card on our website for details. Check with your insurer or reimbursement specialists/support program to find out what the particular requirements are for your drug plan and whether or not a biologic treatment care plan outlined by your physician will be covered.



2. Combination Therapy

Another treatment approach is to combine an immunosuppressant with a biologic; in some patients this appears to enhance the effectiveness of the drugs more than either one alone could achieve.

We want to stress that both of these approaches are only applicable to carefully selected patients who fit certain criteria. Talk to your gastroenterologist for more details and information.

WHAT DOES THE FUTURE HOLD?

Subsequent Entry Biologics

As patent protections expire for biologics, manufacturers are working to develop subsequent entry biologics (SEBs), drugs that are similar to the innovator biologic drug. Currently in Canada, there are no SEBs approved for the treatment of Crohn's and colitis, however this may change as research and regulations evolve.

In Canada, SEBs are not considered 'generic biologics'. They are considered similar, but not identical, to the innovator biologic drugs. Like innovator biologics, SEBs are generated from living cells. Because their molecular structures are large and manufacturing processes complex, it is challenging to produce exact replica of innovator drugs. Differences between SEB and innovator drug may result in differences in clinical effects.

Individuals on a biologic innovator drug should be aware of the risks and benefits of switching to an SEB. In some cases, substitution may lead to the formation of anti-drug bodies that will cause both the SEB and the innovator drug to stop working. Talk to your doctor if you are considering using an SEB.

New treatments

Researchers are constantly finding better ways to treat Crohn's and colitis. Not only are researchers discovering new treatment approaches, they are also finding improved ways to use the medications already employed in the fight against IBD.

If biologic therapy is not an ideal treatment for you, consider speaking to your gastroenterologist about participating in one of many clinical trials available in various locations across Canada.

WE'RE HERE FOR YOU

Crohn's and Colitis Canada hopes that you found this brochure on biologic therapy helpful in explaining this relatively new generation of IBD medication. As you have learned, biologics offer a whole new way of treating the chronic inflammation that plagues people with Crohn's disease and ulcerative colitis.

Because continuing research is offering better ways of treating IBD, we are optimistic that one day, a cure will be found. In the meantime, Crohn's and Colitis Canada hosts education events across Canada to provide you with information about a variety of topics related to Crohn's and colitis. You can learn more about our organization and our education events by visiting crohnsandcolitis.ca, and by signing up for our free e-newsletter *Talk About Guts*.

ABOUT CROHN'S AND COLITIS CANADA

Crohn's and Colitis Canada is the only national, volunteer-based charity focused on finding the cures for Crohn's disease and ulcerative colitis and improving the lives of children and adults affected by these diseases. We are one of the top two health charity funders of Crohn's and colitis research in the world, investing over \$88 million in research to date. We are transforming the lives of people affected by Crohn's and colitis (the two main forms of inflammatory bowel disease) through research, patient programs, advocacy, and awareness. Our **Crohn's & Colitis – Make it stop. For life.** Campaign will raise \$100 million by 2020 to advance our mission.

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For more information on Crohn's disease or ulcerative colitis visit our website crohnsandcolitis.ca or call 1-800-387-1479

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