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Endoscopy Gastrointestinal Medicine Nutrition

The Centre for GI Health

IBD THERAPY FOR CROHN'S DISEASE AND ULCERATIVE COLITIS

In Australia, inflammatory bowel disease (IBD) is becoming more prevalent. It affects approximately 1 in 250 people aged 5-40 years. About 80,000 Australians have Crohn's disease or ulcerative colitis, with this number projected to increase to 100,000 by the next decade. The burden of disease is significant and the difficulties experienced by patients managing symptoms may be highly disruptive to their quality of life.

TREATMENT PRODUCTION

Biological therapies are produced within living organisms such as special yeasts, bacteria as well as mammalian cells which are engineered to create the active medications now available. There are five different biologic medications available in Australia to treat moderately severe Crohn's disease and Ulcerative colitis.

These therapies and variations of them also have application in other branches of medicine such as rheumatology, dermatology and respiratory medicine.

They include:

- Infliximab
- Adalimumab
- Golimumab
- Ustekinumab and
- Vedolizumab

The new classes of Small Molecules available are produced by chemical processes in a laboratory and include molecules referred to as:

Janus Kinase Inhibitors including

- Tofacitinib
- Filgotinib (not on the PBS) and
- Upadacitinib (not on the PBS)

Sphingosine-1-Phosphate Receptor Modulators including : Ozanimod (recently approved on the PBS as Zeposia)

TREATMENTS AVAILABLE

A variety of medical and surgical treatments have been available to manage these inflammatory bowel conditions since the 1950's and more recently a new class of very helpful and effective therapies referred to as biologic agents and the evolution of novel small molecules including the rather complicatedly named Janus Kinase inhibitors and Sphingosine 1-phosphate (S1P) receptor modulators have emerged as effective treatments especially for patients with moderate to severe disease .

WHAT ARE BIOLOGICS AND SMALL MOLECULES

An improved understanding of cell biology, the molecular pathophysiology of inflammation and our immune system has led to the development of specific therapies directed at influencing some of the known pro inflammatory proteins our own immune system makes in the setting of IBD.

These proteins have been shown to play important roles in the development of intestinal inflammation for both Crohn's disease and ulcerative colitis.

HOW DO THERAPIES WORK?

1. BIOLOGICAL THERAPIES

Essentially **Biologic therapies** work by blocking or neutralising different molecular components of the immune system referred to as cytokines that are known to contribute to the inflammatory process inducing inflammation of the gut lining .

During inflammation a cascade of chemicals are released from white blood cells called T lymphocytes and some of these called TNF (tumour necrosis factor) and specific interleukins (IL 12 and 23) are targeted by Biologic therapies .

Infliximab, Adalimumab and Golimumab are directed against TNF .
Ustekinumab is an antibody directed against the p40 subunit of IL-12 and IL-23 which are messenger chemicals discovered to recruit white blood cells into the gut to cause inflammation . Anti- p40 medications block the messenger signal of both IL-12 and IL-23 to reduce inflammation.

In contrast Vedolizumab is referred to as an anti-integrin . It is a gut specific monoclonal antibody that specifically targets the α4β7 integrin complex and blocks the attachment of white blood cells to tissues, preventing them from entering the lining of the gut and causing inflammation.

2. JAK INHIBITORS

Cytokine mediators of inflammation in IBD are reliant on the Janus Kinase receptors positioned on the cell membrane and responsible once activated for the Signal Transducer and Activator of Transcription (JAK-STAT) pathway signalling .

This is complicated as there are several such JAK receptors that have been identified belonging to the same family including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) .

Tofacitinib is a JAK 1 and JAK 3 inhibitor available on the PBS for use in moderate to severe Ulcerative colitis.

3. SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATORS

Sphigosine-1-phosphate is responsible for controlling the egress of lymphocytes from lymphoid organs which leads to decrease lymphocyte release from the lymphoid tissue into the circulation.

Ozanimod is an example of this class of drug and has only recently been approved for use in moderate to sever ulcerative colitis on the PBS .

SIDE EFFECTS & RISKS OF USE

All medications are associated with risk and benefits. Risks of using **biologics** may include injection or infusion site reactions, allergic reactions, and infection. Your doctor will work with you to determine proper dosage to help balance your symptoms and potential side effects.

For **JAK inhibitors**: The risk of infection including shingles, cold like symptoms ,diarrhoea and thromboembolic events is still being assessed

For **Sphingosine 1-Phosphate Receptor Modulators** may include infection, cardiac arrythmia, headache, pain on urination

BIOSIMILARS

As with other medicines, once a patent expires for a biologic, it is legal for other manufacturers to reproduce the drug.

Most medicines, such as aspirin, are small molecule products, which mean they have simple molecular structures that are easy to reproduce or copy. Such copies are called generic drugs. By comparison, biologics are very large and have complex molecular structures.

It is impossible to produce an exact copy without using the exact same ingredients, the living cell lines, and manufacturing conditions. Therefore, the drug that is produced by another manufacturer can never be considered identical to the initial biologic and is referred to as a ‘biosimilar’ (and not a ‘generic’).

HOW EFFECTIVE ARE THESE TREATMENTS?

Monoclonal antibodies have limitations in terms of efficacy, safety and cost. The available biologics are not effective in every patient with up to 30% of patients showing a lack of improvement after induction therapy with anti-TNF drugs for example. Additionally between 13% and 25% per year may develop a loss of response to anti-TNF agents .This loss of response may be due to pharmacodynamic, pharmacokinetic and/or immunogenic factors.

JAK inhibitors appear to induce a remission in up to 50% of patients with a clinical response on about 64% at 3 months.

Sphingosine-1-Phosphate Receptor Modulators are still being assessed but studies demonstrate up to 37 % of patients entering a clinical remission at one year with Ozanimod

IMMUNOGENICITY

Individuals doing well on a biologic drug may observe the benefits of treatment wearing off over time. Because biologics are 'foreign' proteins that were not produced by the patient's own genes, the body can develop antibodies to the biologic over time. This immune response is called immunogenicity.

Once antibodies to a biologic are formed by a patient's body, the biologic may stop working or cause an allergic-like reaction.

Whether immunogenicity is made more likely by switching among biologics and biosimilars remains unclear.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is available for some of the Biologic treatments in use and allows the doctor to more specifically adjust drug dosing appropriately to attain the best therapeutic outcome possible and to monitor for immunogenicity which may render the drug unhelpful and prompt a switch to an alternative treatment.

FEACAL CALPROTECTIN

Calprotectin is a protein found in white blood cells and is released when there is inflammation of the intestinal lining. Assessment for calprotectin not only indirectly demonstrates the presence of inflammation but is a practical test aiding assessment of how well Biologics and the small molecules selected are working and may limit the need for repeat colonoscopy exams.

CONCLUSION

In conclusion, the armamentarium of IBD therapeutic agents is ever expanding.

The recent significant development in the small molecules class of agents such as JAK inhibitors and S1P receptor modulators has opened up new possibilities for management and these agents offer the advantages of ease of administration (as they are oral agents) and do not have the downside of immunogenicity and antibody formation seen with some of the biologics.

Additionally, some of these agents will likely have the potential of having a more favourable safety profile compared to anti-TNF agents.

In the era of increasing therapeutic agents to treat IBD, the challenge will be the ability to select the best agent for the individual patient and for the development of a precision/personalised medicine approach to the treatment of IBD.