CARE GASTROENTEROLOGY FACULTY

GASTRO-TIMES

THE CHANGING LANDSCAPE OF INFLAMMATORY BOWEL DISEASE

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INTRODUCTION

WE ARE IN THE GOLDEN AGE OF INFLAMMATORY BOWEL DISEASE CLINICAL CARE

Biologics have revolutionized the treatment of chronic inflammatory conditions in the past two decades, leading to significant improvements in efficacy and manageable safety. In order to ultimately improve patient outcomes, research continues to consider how to optimize the use of current biologic agents (i.e. via dose optimization & therapeutic drug monitoring), drive innovation of new agents, and investigate how increased competition will affect practice, due to the introduction of biosimilars.

This issue of Gastro-Times will review these three key topics as they apply to the Canadian landscape. In order to provide real-world insight on IBD management, case studies will also be considered for pediatric patients, new patients (biologic naïve), and stable patients.

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A. OPTIMIZATION:
HOW TO ENHANCE CURRENTLY AVAILABLE BIOLOGICS

Research has demonstrated that currently approved biologics are effective therapeutic options for induction and maintenance of remission in moderate to severe ulcerative colitis (UC) and Crohn's disease (CD). There are several agents that are approved in Canada for UC and CD and can be considered for use in clinical practice (see *Table 1* for currently available therapies).

Table 1. Health Canada Approved Therapies for IBD

CROHN'S DISEASE	ULCERATIVE COLITIS
ANTI-TNF AGENTS	ANTI-TNF AGENTS
infliximab (Remicade®)	infliximab (Remicade®)
adalimumab (Humira®)	adalimumab (Humira®)
infliximab biosimilar (Inflectra®)	infliximab biosimilar (Inflectra®)
	golimumab (Simponi®)
ANTI-INTEGRIN AGENT	ANTI-INTEGRIN AGENT
vedolizumab (Entyvio®)	vedolizumab (Entyvio®)
ANTI-INTERLEUKEN AGENT	
ustekinumab (Stelara®)	

Biologic therapies have allowed treatment goals to evolve from symptomatic control, to altering the disease course by achieving remission (presence of sustained clinical remission, complete mucosal healing, and normalization of serological activity indexes).[i] There are several ways to optimize biologic therapy to achieve these goals, including selecting the appropriate patients, using concurrent immunosuppressants, and dose optimization.

1. Patient Selection

In order to determine who should be provided with early biologic therapy, patients should be risk stratified based on age, extent of disease, hospitalization, relapse/mortality rates, etc. (see *Table 2* for prognostic predictors for CD and UC). There are several studies that support the early use of biologics in CD & UC.[ii, iii, iv] Data suggests that certain patient subgroups with extensive disease activity/risk factors (i.e. severe rectal disease, young age, severe perianal disease, and steroid need at diagnosis) may benefit from early biologic treatment.[v] For patients with overlap irritable bowel syndrome (IBS) or who have mostly fibrotic disease, biologics often have lower remission rates.[vi]

Table 2. Prognostic Predictors for CD & UC

CD [vii]	
DISEASE ACTIVITY FACTORS	Intestinal symptom burden, disease related disability, objective measures of inflammation, fistulising CD
DISEASE RISK FACTORS	Age at diagnosis, endoscopic severity, smoking status, steroid exposure, disease behaviour, disease location
UC [viii]	
DISEASE ACTIVITY FACTORS	Intestinal symptom burden, disease related disability, endoscopic severity
DISEASE RISK FACTORS	Young age at diagnosis, extensive colitis, a high level of systemic symptoms, disease location, steroid exposure, need for hospitalization

"BIOLOGIC THERAPIES HAVE ALLOWED TREATMENT GOALS TO EVOLVE FROM SYMPTOMATIC CONTROL, TO ALTERING THE DISEASE COURSE BY ACHIEVING REMISSION."

2. Concurrent Immunosuppressants

Immunosuppressants may work synergistically with biologics, especially in immunosuppressant naïve IBD patients.[ix, x] The use of concurrent immunosuppressants such as azathioprine or methotrexate may be associated with higher remission rates and lower rates of anti-drug antibodies (ADAs), however there appears to be some conflicting results.

When infliximab was investigated with concurrent immunomodulators in the SONIC and UC SUCCESS trial, positive results were discovered in terms of remission. In the SONIC trial, patients with CD 57% of patients receiving infliximab with thiopurines, reached clinical remission at week 26 compared to the infliximab monotherapy group (44%).[xi] The UC SUCCESS trial in UC achieved a 40% remission rate with infliximab and azathioprine vs. 22% receiving infliximab alone.[xii]

While most data suggest immunosuppressants may be beneficial in combination, the COMMIT trial by Feagan et al., found different results. This study showed that starting infliximab with methotrexate was no more effective than infliximab monotherapy in patients with CD at 14 and 54 weeks but was still associated with improved infliximab pharmacokinetics in lower antibody production and higher infliximab drug concentrations.[xiii] Additionally, a recent Korean study (2016), found that both baseline immunomodulator and concurrent immunomodulator combination with adalimumab did not increase the efficacy of anti-TNF therapy.[xiv] Another trial looked at the trough levels of both infliximab or adalimumab in maintenance therapy, and found that concurrent immunomodulatory therapy did not influence trough levels of either agent. [xv]

Therapeutic decisions need to be made on an individualized basis, considering the risk-benefit profile especially in special populations such as paediatrics, young males, and the elderly.

3. Optimizing Dosage

Patients treated with biologic therapy often achieve clinical remission and mucosal healing. A small proportion of patients may experience a symptomatic recurrence. In the case of symptomatic recurrence, the first course of action is to consider optimization. This should be guided by therapeutic drug monitoring (TDM). Optimization may involve decreasing either the dose or the interval between treatments or adding an immunosuppressant. There is growing interest in serum drug levels and TDM to help assist with this decision. If a patient fails to respond and it appears that there is an appropriate amount of circulating drug, physicians may consider switching to another biologic therapy.[xvi]

Dose & Interval Adjustments

To recapture clinical remission, one option is to decrease the interval between doses. In a prospective study where patients relapsed after being given adalimumab, patients were treated with 40 mg weekly for 12 weeks before returning to the original bi-weekly regimen. 9 of the 14 CD patients achieved a clinical response/remission after 3 months of the standard dosing.[xvii] Another study of CD patients being treated with infliximab received a dose intensification (which is defined in this instance as an increase in infliximab dose, decrease in interval, or both). Results showed that 69.1% of patients were event-free from an interval decrease, 48.5% from a dose increase, and 45.7% from any dose intensification.[xviii] According to these studies, patients using a biologic can regain response to biologic treatment via changing the interval as well as dose. More frequent dosing as well as escalating dosing can also help to regain response in up to 80% of patients who have lost response.[xix,xx,xxi]

Therapeutic Drug Monitoring

The goal of TDM is to personalize biologic dosage in order to optimize clinical outcomes (ie. maintenance of remission and higher rates of mucosal healing). TDM is based on the principle that there is both a relationship between dose and serum drug concentration, and subsequently between concentration and therapeutic effects.[xxii] TDM has been studied with anti-TNF agents (ie. infliximab, adalimumab, golimumab), as well as thiopurines (azathioprine and 6-mercaptopurine).[xxiii] However, the majority of clinical experience with TDM stems from infliximab data.

The TAILORIX study (2016) prospectively evaluated TDM based dose escalation versus symptom based dose escalation with infliximab in biologic naïve adult patients with active CD to determine whether a TDM based strategy would lead to higher remission rates compared with symptom-based dose adjustments.[xxiv] This pilot study hypothesized that given the superior outcomes associated with serum drug concentrations in a 'therapeutic window', prospective TDM would lead to higher remission rates. Results show that dosing based on frequent, proactive trough-level adjustment was not superior to dosing based on symptoms alone, after 1 year of therapy. Furthermore, the prospective arm of the TAXIT trial (investigating stable patients receiving infliximab maintenance therapy) also failed to show a significant difference between TDM and conventional care. However, initial optimization was associated with increased clinical remission in CD and lower CRP levels.[xxv]

A post-hoc analysis of the ACT I and II studies (investigating UC patients) found that higher infliximab concentrations were associated with increased mucosal healing and clinical remission, with the highest proportion of patients in clinical remission having serum levels of infliximab between 2.4 and 6.8 ug/mL.[xxvi] Higher serum albumin levels also are associated with a prolonged infliximab half-life and increased efficacy.[xxvii]

Lastly, when TDM has been investigated in pediatric patients, it demonstrated that low infliximab levels were associated with the development of immunogenicity (measured by antibodies to infliximab), and that interval shortening vs. dose escalation resulted in higher infliximab levels.[xxviii]

Concluding Remarks

Evidently, there are a number of factors that need to be considered when optimizing therapy. These include selecting which patients are most suitable for biologic therapy, determining when is best to begin treatment, as well as managing their response to treatment accordingly. There is still much to be learned about targeted trough levels (ie. lowest serum concentration) and their impact in the long-term. It is important for researchers to continue investigating these concepts in order to incorporate learnings into practice and ultimately optimize patient outcomes.

CASE STUDY

A PEDIATRICIAN'S GUIDE TO OPTIMIZING TREATMENT

SEX: MALE **AGE:** 12

BACKGROUND: Ryan is a 12-year-old male who presented 6 months ago with a 12-month history of symptoms including weight loss (~5kg), lethargy, reduced appetite and intermittent abdominal pain. His stooling pattern was normal. Investigations at presentation revealed an iron-deficient anaemia and low albumin. Ileocolonoscopy was unremarkable, although MR enterography demonstrated about 12cm of inflammatory luminal disease in the distal ileum. He was initially induced on a course of exclusive enteral nutrition. His symptoms settled and his weight normalized. He commenced subcutaneous methotrexate as a maintenance agent. At 6-months he was asymptomatic with normal weight (39kg), however his height velocity remained sub-par and although his serum albumin had improved, it had not normalized. Repeat MR enterography demonstrated a persisting 8 to 10cm of active distal ileal disease with no evidence of fibrostenosis or fistulising disease.

CARE FACULTY TREATMENT CONSIDERATIONS:

Although in clinical remission and with evidence of some reduction in disease extent, this patient has not achieved mucosal remission. A re-induction with steroids could be considered, although the potential further impairment of linear growth and low likelihood of mucosal healing need to be considered. Anti-TNF therapy was recommended, and the patient was induced with 200mg (~5mg/kg/dose) at weeks 0, 2 and 6 with the first maintenance dose at week 14 and a plan for 8 weekly maintenance dosing. Although not particularly successful during the initial induction/maintenance attempt, methotrexate was continued subcutaneously in an attempt to reduce the likelihood of sensitization to the anti-TNF agent. Two weeks prior to the week 22 dose Ryan noticed some increased lethargy and reduced appetite. A trough drug level, taken immediately prior to the week 22 dose, revealed a drug level of 3ug/mL. This level was at the lower limit of the desired target range.

Dose optimization should be attempted and could involve either dose escalation or a reduction in dose interval. Ryan's schedule was altered to 6 weekly intervals with the dose remaining at 200mg. Ryan remained in complete continuous clinical remission thereafter. His trough was measured again 18 weeks later and was 7ug/mL. Over the next year his linear growth normalized. Repeat MR-enterography at 12 months demonstrated near complete resolution of the mucosal inflammatory changes.

B. INNOVATION:
THE ROLE OF NOVEL AND RECENTLY APPROVED THERAPIES

Innovation continues to drive the development of new molecules for use in Canada. There are a number of innovator biologics in late-stage development in the field of IBD that may build on the success of current therapy. This section provides an overview of each of the late-stage and recently approved innovator molecules, as well as considers their role, placement, and impact for patients with IBD in Canada.

Vedolizumab

Mechanism of Action

Vedolizumab is a humanized, IgG1 monoclonal antibody. It works by binding to the α4β7 integrin receptor, blocking its interaction with MADCAM1. Vedolizumab inhibits the migration of memory t-cells across the endothelium into inflamed gastrointestinal tissue, thereby inhibiting important contributors to chronic inflammatory diseases such as that UC and CD.[xxix] This mechanism of action holds the promise of a better safety profile than natalizumab (anti-α4 mAb) which has been associated with progressive multifocal leukoencephalopathy.[xxx]

Indication

Vedolizumab was approved in May 2015 for the treatment of UC for patients with an inadequate response to immunosuppressants, anti-TNF agents, or corticosteroids and in May 2016 for moderate to severe CD with an inadequate response to immunosuppressants, TNF agents, or corticosteroids.

CARE FACULTY PERSPECTIVE:

Vedolizumab appears to offer a favourable benefit/risk profile. Having a biologic agent with minimal systemic immunosuppression is attractive to both patients and physicians. Data regarding mucosal healing, efficacy in fistulising disease and extra-intestinal manifestations are eagerly awaited.

Ustekinumab

Mechanism of Action

Ustekinumab is a human immunoglobulin-1-kappa monoclonal antibody that binds to the p40 protein subunit shared by the interleukins (IL)-12 and IL-23.[xxxi] These cytokines are involved in inflammatory and immune responses (i.e. natural killer cell activation and CD4+ T-cell differentiation and activation).[xxxii] Several genomic studies have found a strong association between CD and a gene that encodes a subunit for the IL-23 receptor.[xxxiii]

Indication

Ustekinumab was approved on December 14, 2016 for the treatment of CD, based on a number of Phase 3 randomized controlled trials. The UNITI 1 and 2 Phase 3 induction trials showed that ustekinumab is effective for patients with and without prior anti-TNF failure.[xxxiv] Additionally, in the maintenance study presented at DDW 2016 (IMUNITI), results showed significant rates of clinical response and remission at one year for patients treated with ustekinumab every 8 weeks or every 12 weeks, over induction only with placebo maintenance.[xxxv] Further insights are anticipated into ustekinumab's impact on endoscopic healing.

CARE FACULTY PERSPECTIVE:

Ustekinumab was recently approved by Health Canada as induction and maintenance therapy for both anti-TNF naïve and exposed patients with CD. Ustekinumab is an effective treatment option for CD patients in both of these settings.

Tofacitinib

Mechanism of Action

Tofacitinib is the first in a new class of non-biologic disease-modifying anti-rheumatic drugs (DMARDs).[xxxvi] It is a once-daily oral Janus kinase (JAK) inhibitor that works by decreasing t-cell activation, pro-inflammatory cytokine production, and cytokine signaling by inhibiting type I cytokine receptors family and γ-chain cytokines to paired JAK1/JAK3 receptors.[xxxvii]

Indication

Tofacitinib is only currently approved for the treatment of rheumatoid arthritis (RA) in Canada, but is being studied in phase 3 trials in UC. Recent data in moderate-to-severe UC shows that tofacitinib has significantly greater efficacy data in both previously anti-TNF-treated and anti-TNF-naïve patients in terms of remission and mucosal healing, when compared to placebo.[xxxviii] Adverse events were not higher in the tofacitinib group vs. placebo, however signs of increases of serum lipid and creatine kinase levels were reported with tofacitinib.

CARE FACULTY PERSPECTIVE:

Tofacitinib is an oral agent that appears to be effective and safe for not only the management of moderate to severe UC, but several rheumatologic indications.[xxxix] Tofacitinib could offer patients a convenient once-daily, oral method of administration. It could be a valuable addition to current medical options and is currently being submitted for approval to Health Canada for moderate to severe UC.

Concluding Remarks

These novel agents provide patients and treating physicians with more options. In addition to these recently-approved and late-stage therapies, there are several others in early phase development (ie. mongersen, ozanimod, MEDI2070 to name a few) that we anticipate to see in the coming years. With the growing armamentarium of novel biologics as well as cost-saving alternative therapies (ie. biosimilars) that have recently entered the Canadian landscape, we can expect to see more therapeutic strategies and sequences that are individualized to each patient.

CASE STUDY

SEX: MALE **AGE:** 18

INTEGRATING NOVEL AGENTS INTO CLINICAL PRACTICE

BACKGROUND:

18-year-old male with a 9-month history of left-sided ulcerative colitis. Despite optimized 5ASA therapy he has required three steroid tapers, and is again symptomatic having completed his last course just 2 weeks ago. He has mild symptoms but flexible sigmoidoscopy reveals Mayo 2 disease activity extending to at least the splenic flexure. He is worried about the risks of immunosuppressive therapy and dislikes the idea of medication that isn't a pill. He is also moving away to start university in a month's time.

CARE FACULTY TREATMENT CONSIDERATIONS:

This patient is steroid dependent despite 5ASA therapy. He needs a more effective steroid-sparing maintenance regimen. Thiopurines can be considered, but carry risks of lymphoma and non-melanoma skin cancer that will be of concern to this patient. Anti-TNF agents can be considered, but have systemic effects and must be administered parenterally. Anti-integrin therapy is a new and appealing alternative given its potential safety advantage, but would require administration at an infusion centre. Tofacitinib may soon be approved for treatment of ulcerative colitis, and is orally administered. This agent has a favourable safety profile, although it has been linked to adverse effects on serum lipids. Our menu of options for treating UC is expanding, such that treatment can be better tailored to individual preferences and clinical circumstance.

C. COMPETITION:
THE IMPACT OF BIOSIMILARS

What are Biosimilars?

Biosimilars are similar but not identical to the Reference Biologic Drug (RBD), and may offer a reduction in drug cost in comparison to a RBD. They are estimated to generate a savings of more than $750 million per year in Canada.[xl,xli] This increase in options creates competition and could make it possible for the health care system to expand coverage/access to more patients. The drug cost savings that biosimilars offer have to be weighed against some potential concerns (ie. data extrapolation, immunogenicity, and non-medical switching).

In the last few years, biosimilars have been developed in several chronic disease categories. With the number of biologic agents going off patent in the coming years, there are several others expected to become available for patients. See *Table 3* for the biosimilars in development that are closest to being approved by Health Canada. Of note, there are approximately 3 other infliximab biosimilars and 11 other adalimumab biosimilars in earlier phase development.[xlii]

Table 3. Biosimilars in Development[xliii]

REFERENCE DRUG (BRAND NAME)	BIOSIMILAR	MANUFACTURER	STUDIED IN	DISEASE / INDICATION IN CANADA	CURRENT STATUS
INFLIXIMAB[xliv] (REMICADE)	CT-P13	Celltrion	RA, AS	Adult CD, Adult UC, RA, AS, PsA, and PsO	EU, FDA and Health Canada Approved
INFLIXIMAB[xlv] (REMICADE)	ABP710	Amgen	RA		Phase 3
INFLIXIMAB[xlvi] (REMICADE)	SB2	Samsung Bioepis	RA		EU approved
ADALIMUMAB[xlvii] (HUMIRA)	ABP501	Amgen	RA and PSO		FDA approved
ADALIMUMAB[xlviii] (HUMIRA)	SB5	Samsung Bioepis	RA		Phase 3
ETANERCEPT[xlix] (ENBREL)	GP2015	Sandoz	RA		FDA approved
ETANERCEPT[l] (ENBREL)	SB4	Samsung Bioepis	RA	RA, AS	EU approved, Health Canada Approved
CD = Crohn's Disease, UC = Ulcerative Colitis, RA = Rheumatoid Arthritis, AS = Akylosing Spondylytis, PsA = Psoriatic Arthritis, PsO = Psoriasis, JIA = Juvenile Idiopathic Arthritis					

CARE FACULTY PERSPECTIVE:

Biosimilars were developed to provide a more affordable option for patients suffering from immune mediated inflammatory diseases including CD and UC. Cost remains a concern for both public and private payers. Ideally, therapeutic decisions should be decided by patients and their health care providers with cost as one of many considerations.[li] Furthermore, cost encompasses components that extend beyond price, including patient support programs, prompt access, delivery, research and development, and education). We will see over the coming months how biosimilar impact the IBD treatment landscape.

Inflectra (CT-P13): Overview

The first and currently only biosimilar available in the field of gastroenterology in Canada is CT-P13 (Inflectra™ - infliximab's biosimilar).[lii] CT-P13 has been approved in a number of jurisdictions over the last few years.

In 2014, Health Canada approved CT-P13 for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and rheumatoid arthritis but not for IBD indications. The indications for CD and UC were initially not granted due to several observable differences between CT-P13 and its RBD. Two years later, (June 2016), CT-P13 was approved for CD, fistulizing CD and UC but not for pediatric UC and CD. Long-term safety results for this agent (as well as other biosimilars in development) are needed, as well as post-marketing monitoring.[liii]

"THE INDICATIONS FOR CD AND UC WERE INITIALLY NOT GRANTED DUE TO SEVERAL OBSERVABLE DIFFERENCES BETWEEN CT-P13 AND ITS RBD."

What are the Concerns Regarding Biosimilars?

Some of the potential concerns that have arisen surrounding biosimilars, include extrapolating data from one indication to another, immunogenicity, switching from a RBD to biosimilar, as well as substitutability.[liv] What follows is an overview of each of these concerns.

1. Extrapolation of Data to Other Disease Categories

Initial assessment of a biosimilar must be *in vitro*, then *in vivo,* and then in human clinical trials. Once the data has been collected in Phase 3 trials in one disease category, Health Canada deems it appropriate to extrapolate approval from one disease category, to others (for which each innovator drug has indications for). This is done after evaluating many components, including: similar MoA, target/receptor interactions and molecular signalling, product structure interactions with the target or receptor; PK, expected toxicities and information based on MoA. According to a number of regulatory agencies extrapolation could be a 'valid, evidence-based approach for the expedited development of new accessible agents,' however it must be considered on a case-by-case basis and thorough justifications/analyses must be conducted.[lv]

Extrapolation of the safety and efficacy data in one indication to another is how a number of biosimilars, such as CT-P13, are being approved. This process is used to limit the number of high cost clinical trials being conducted, in turn, allowing for a lower priced agent.[lvi] This suggests that there is less clinical data supporting the use of biosimilars in terms of safety and efficacy in these extrapolated disease categories.

Prior to CT-P13's approval in UC and CD, notable structural differences were found between the biosimilar and the RBD in *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC) and in binding with the FcγRIIIa receptor, that could correlate with mechanism of action. Failure to extrapolate across all clinical indications upfront could cause confusion and undermine the concept of biosimilars – ie. demonstrating that they're highly similar, notwithstanding minor differences in clinically inactive components.[lvii] It is expected that all extrapolated indications will be granted to biosimilars.[lviii]

2. Immunogenicity

Biologics can induce an immune response, with production of neutralizing antibodies that can render the drug ineffective, alter pharmacokinetics, cross-react with native proteins, or induce adverse reactions.[lix] Developing an immunogenic response with a biosimilar is dependent on both product factors and patient factors.

A. Product Factors

When developing biologics and biosimilars, they must both adhere to rigorous standards. Stringent requirements/guidelines have been imposed by health authorities in order to mitigate any significant changes in the final product.

Given the complexity in developing and/or replicating a monoclonal antibody, any small change in the manufacturing process (i.e. production, formulation, purification, handling/storage, etc.) and materials (ie. equipment, facilities) could cause variations in the final product. Manufacturing variations can be sensitive to any slight changes in buffer pH, temperature, pressure, design of bioreactor, and change of production site, which can result in differences in post-translational modifications.[lx]

These manufacturing changes are approved within a pre-specified margin and movement within those margins by the RBD and biosimilar can impact the degree of similarity between the two agents. These variations may or may not have an effect on efficacy or immunogenicity. Currently, there are no requirements for ongoing comparative testing, therefore similarity between an innovator drug and a biosimilar may not necessarily be maintained.[lxi]

B. Patient Factors

Components such as route of administration (SC, IM, IV), dose and treatment duration, co-morbidities and/or concomitant medication, and genetic factors can all contribute to different results in immunogenicity.

In a cross-immunogenicity study comparing infliximab with its biosimilar, comparable immunogenicity and presence of shared immuno-dominant epitopes in the two agents were discovered. Furthermore, the immunogenicity of CT-P13 was presented in two recently conducted clinical trials. The first is the Phase III PLANETRA clinical study, which discovered that 50% of patients treated with the methotrexate and the biosimilar, CT-P13, had developed anti-drug antibodies after 30 weeks of treatment.[lxiii] The effects of the antibody formation on treatment efficacy was clearly shown. No significant difference in response was found between infliximab and CT-P13. Secondly, in an early phase I trial, patients with active ankylosing spondylitis (PLANETAS) had antibody incidences of 9.1% with CT-P13 treatment, and 11.0% with infliximab treatment at 14 weeks. After 30 weeks, the incidences rose to 27.4% and 22.5%, respectively. Again, no specific differences were observed between the two agents. These higher rates of anti-drug antibodies compared to the RBD pivotal trials may be due to different assays and assay sensitivity.

Immunogenicity remains a concern with using both biosimilars and biologics. The continued and long-term impact on safety, efficacy, and immunogenicity of biosimilars requires post-marketing surveillance and additional follow-up studies.[lxiv]

3. Switching Therapy

During a course of therapy, patients may be switched from a RBD to a biosimilar. Switches from a RBD to a biosimilar can be described as automatic substitutions or one-way, non-medical switches.

Automatic substitution is when the original biologic is replaced with a biosimilar at the pharmacy level without the knowledge of a prescribing physician, based on interchangeability. Health Canada does not consider biosimilars and RBDs interchangeable (the expectation that a biosimilar is therapeutically equivalent to the RBD and able to provide the same clinical result); decisions regarding automatic substitution will be decided by individual provincial policies.

A *one-way non-medical switch* could also be made. This is defined as 'a change in a patient's medication to a distinct alternative that is expected to have similar effects for reasons other than lack of clinical efficacy or response, side effects, or poor adherence.' [lxv] The goal of non-medical switching is to reduce drug costs, however there are mixed results over how switching impacts patient adherence and clinical outcomes.[lxvi]

"THE GOAL OF NON-MEDICAL SWITCHING IS TO REDUCE DRUG COSTS, HOWEVER THERE ARE MIXED RESULTS OVER HOW SWITCHING IMPACTS PATIENT ADHERENCE AND CLINICAL OUTCOMES."

Patient Adherence

Patients become comfortable with their current regimen and the routine associated with it. In order to provide a customized and responsive support system tailored to each patient's needs, patient support programs (PSPs) are offered for most innovator biologic agents.

These programs provide various services including assistance with reimbursement, compassionate dosing, infusion and injection support, compliance monitoring, patient education, ancillary testing and communication with the healthcare team. It is expected that biosimilar manufacturers will provide similar PSP services.

Clinical Outcomes

A number of observational studies have been conducted in various immune-mediated inflammatory disorders (e.g. rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease) to assess the safety and efficacy of switching between infliximab RBD and CT-P13. In many trials across gastroenterology and rheumatology, both infliximab and CT-P13 have demonstrated comparable safety and efficacy, with no apparent increase in immunogenicity.[lxvii, lxviii,lxix,lxx]

Some studies have raised concerns over non-medical switching. In a Hungarian prospective, multicentre, nationwide cohort, bio-naïve patients and those previously given infliximab RBD were started on CT-P13.[lxxi] Those previously given infliximab, experienced lower response rates and more infusion reactions than those who were infliximab naïve. Similarly, within a cohort of patients starting CT-P13, Fiorino et al reported the highest rates of loss of response among those who were switched from RBD infliximab.[lxxii] Nguyen et al reported a systematic review that associated non-medical switching with adverse effects on health economic outcomes and medication-taking behaviours.[lxxiii] Observational studies such as these have limited ability to test true causal relationships, but make a strong case for careful prospective study of the long-term sequelae of switching between infliximab RBD and CT-P13.

A highly anticipated prospective study of non-medical switching to a biosimilar was the Norwegian NOR-SWITCH study. This randomized, double-blind, parallel-group, multicenter study compared the clinical efficacy and safety of switching from infliximab RBD to CT-P13 vs. continuation with infliximab RBD.[lxxiv] This study was unusual in that it combined patients across indications, including rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, UC, CD and chronic plaque psoriasis. This trial allowed for a 15% non-inferiority margin, however a 15% difference in disease worsening could be clinically important. Whether this design had sufficient sensitivity to detect small changes in health outcomes remains to be determined.[lxxv] The results from this trial were presented at United European Gastroenterology Week (UEGW) in October 2016 and the American College of Rheumatology (ACR) in November 2016. Overall, there were little differences between the biosimilar and RBD. However, in the CD subset, a 14.3% difference was discovered when switching, which could be clinically meaningful among ~100 CD patients in the study.

WATCH

The NOR-SWITCH Trial Interview with Dr. Marshall and Dr. Feagan at

www.CAREeducation.ca/gastroenterology/

Concluding Remarks

Given the potential cost savings that biosimilars may offer, their introduction into the Canadian landscape will certainly cause an element of competition among therapies offered in the field of gastroenterology. However, cost savings do need to be weighed against some of the potential concerns regarding biosimilars (ie. data extrapolation, immunogenicity, and non-medical switching).

CASE STUDY

SEX: FEMALE **AGE:** 27

TREATING A STABLE PATIENT - TO SWITCH OR NOT TO SWITCH?

BACKGROUND: 27-year-old female with a 6-year history of pan-ulcerative colitis. She had failed oral and topical mesalamine and required repeated courses of prednisone in the first three years after diagnosis. She had a severe flare in 2013 in which she required hospitalization and at that time infliximab was initiated along with azathioprine.
She has felt well since her discharge from hospital and has remained in symptomatic remission on infliximab 300 mg every 8 weeks. Her bloodwork has been stable including CRP. A flexible sigmoidoscopy done three months ago demonstrated she was in endoscopic remission with a Mayo endoscopy sub-score of 0.

CARE FACULTY TREATMENT CONSIDERATIONS:

In a competitive landscape in the era of biosimilars, the question arises – would one consider switching this patient from Infliximab® to CT-P13?
At the present time, there is not enough data to support non-medical switching of patients who are on stable innovator biologic. Ongoing studies are needed to determine whether this is a safe practice before putting stable patients at risk.

MOVING FORWARD

Researchers must continue to investigate how to optimize currently available therapies in order to provide patients with the best care available at this time. At the same time, innovation continues to drive the development of new molecules that will build on the success of current therapies. With the recent approval of vedolizumab for UC and CD, and ustekinumab in CD, as well as the awaited approval of tofacitinib, it is important to understand where they fit into the current treatment paradigm and how to optimize them. Furthermore, biosimilars have been developed to provide a cost-savings alternative and will likely spark competition in the market place. These cost savings need to be weighed against the potential concerns that exist regarding extrapolation, immunogenicity, switching, and interchangeability/substitutability.

Moving forward, there is still a lot of grey area when it comes to biosimilars because of their novelty to the Canadian landscape. It will be important to continue to study and discuss the impact they are having and whether the clinical outcomes for patients are being maintained at a high standard.

"RESEARCHERS MUST CONTINUE TO INVESTIGATE HOW TO OPTIMIZE CURRENTLY AVAILABLE THERAPIES IN ORDER TO PROVIDE PATIENTS WITH THE BEST CARE AVAILABLE AT THIS TIME."

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The CARE (Community. Academic. Research. Education) Faculty is a pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

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