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CADTH Horizon Scan

An Overview of Emerging Trends and Technologies in Ulcerative Colitis

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Table of Contents

List of Tables

Abbreviations

5-ASA	5-aminosalicylate
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
CD	Crohn disease
CS	corticosteroid
ECCO	European Crohn's and Colitis Organization
HRQoL	health-related quality of life
HTA	health technology assessment
IBD	inflammatory bowel disease
IL	interleukin
JAK	Janus kinase
PRO	patient-reported outcome
STRIDE	Selecting Therapeutic Targets in Inflammatory Bowel Disease
TDM	therapeutic drug monitoring
TIM	targeted immune modulator
TNF	tumour necrosis factor
UC	ulcerative colitis

Key Messages

- This report provides an overview of the evolving therapeutic landscape for moderate to severe ulcerative colitis (UC), including recent changes to clinical practice guidelines, key trends in therapeutic strategies, and new or emerging treatment options, with a focus on biologics and small-molecule therapies.
- Recent guidelines on the medical management of patients with UC include those of the American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), and European Crohn's and Colitis Organisation (ECCO), which were published in 2019, 2020, and 2022, respectively. These guidelines provide an accurate reflection of how clinical practice has changed to incorporate newer therapies that have entered the market and newer evidence that has been published since the release of the Canadian guidelines in 2015. The ACG, AGA, and ECCO guidelines all recommend use of a tumour necrosis factor (TNF) antagonist, vedolizumab, or tofacitinib for induction of remission in patients with moderate to severe UC; the AGA and ECCO guidelines also recommend ustekinumab as an option and recommend vedolizumab over adalimumab, whereas the AGA guidelines recommend early use of biologic drugs over a step-up approach after failure of 5-aminosalicylates.
- Two important trends in therapeutic strategies for UC include changes in the use and definition of treatment targets and recommendations regarding therapeutic drug monitoring (TDM).
    - The 2021 Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) guidelines provide contemporary consensus recommendations for using new and updated targets throughout an individualized treatment timeline in patients with inflammatory bowel disease (IBD). Although histologic remission is not considered a formal UC treatment target in STRIDE-II, it is acknowledged as an adjunctive measure to endoscopic remission to represent a deeper level of healing and is the focus of many current studies.
    - The use of TDM emerged from challenges associated with the use of older biologics (primarily TNF antagonists), which posed difficulties related to immunogenicity and dosing. The relevance of TDM for newer biologics with different mechanisms of action, reduced immunogenicity, and fixed dosing (e.g., vedolizumab and ustekinumab) is a topic of ongoing debate. Although AGA guidelines on TDM in IBD and expert consensus statements support the use of reactive TDM for patients with UC who lose response to a TNF antagonist, evidence gaps remain regarding appropriate use of proactive TDM, utility of TDM for small molecules and biologics outside of the TNF antagonist class, and consistent target concentration thresholds to guide dose changes.
- There is a substantial pipeline of new and emerging drugs for the treatment of adults with moderate to severe UC, with many in phase IIb or III of clinical development; several notable trends of emerging pharmacotherapies exist, including an increasing number of Janus kinase inhibitors, several therapies with biologic targets that are new in UC (e.g., interleukin-23 antibodies, TNF-like ligand 1A inhibitors), an increasing number of oral therapies, and the first combination of 2 biologic therapies in UC.
- The Canadian health care system should be prepared to adapt to the rapidly evolving treatment landscape and potential clinical practice changes in moderate to severe UC. Drugs with new

mechanisms of action in the treatment area and the new paradigm of combination therapy with multiple biologics of different classes may lead to improved patient outcomes but can also further complicate the treatment decision-making process. Therefore, it is important for health care providers to stay up to date on new and upcoming treatment options, which may require educational initiatives for both providers and patients as well as updates to the Canadian treatment guidelines. Overall, potential changes on the horizon may have substantial implications for the health care system given the prevalence of UC in Canada, the costs of advanced therapies, and the increasing number of available treatment options.

Purpose

This report provides an overview of the evolving therapeutic landscape for moderate to severe ulcerative colitis (UC), including recent changes to clinical practice guidelines, key trends in therapeutic strategies, and new or emerging treatment options, with a focus on biologics and small-molecule therapies. This report does not provide a systematic review or critical appraisal of the clinical or economic evidence, of patient and stakeholder perspectives, or of ethical, legal, and social considerations of these technologies. As such, the information provided is not exhaustive or comprehensive of the considerations, issues, or implications posed by the use or adoption of new therapies for moderate to severe UC.

Methods

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international health technology assessment (HTA) database, the websites of Canadian and major international HTA agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Three search approaches were used to address the research objectives: a search of the concepts UC and UC pharmacotherapies in development; CADTH-developed search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials, HTAs, systematic reviews, meta-analyses, or indirect treatment comparisons for a secondary search of the concepts UC and UC emerging therapies; and a CADTH-developed search filter was applied to limit retrieval to guidelines for the concepts of UC or IBD and pharmacotherapies. The search was completed on December 19, 2022, and limited to English-language documents published since January 1, 2018. When possible, retrieval was limited to the human population. Conference abstracts were retrieved through a search of the Embase database limited to January 1, 2021, to December 19, 2022. The database searches were updated regularly until May 12, 2023.

In addition, the report authors conducted supplemental targeted internet searches using Google Scholar, PubMed (MEDLINE), and the US National Library of Medicine's ClinicalTrials.gov. Search concepts included

those relevant to the key themes of the report (i.e., clinical practice and treatment guidelines, treat to target, therapeutic drug monitoring [TDM], and emerging therapies in UC).

Study Selection

One author screened the literature search results and reviewed the full-text articles of potentially relevant studies. Sources were considered for inclusion if they provided evidence or supportive information for the key topics described in this report.

Peer Review

A draft version of this report was reviewed by 1 clinical expert.

Background

Inflammatory bowel disease (IBD) typically refers to Crohn disease (CD) and UC, both of which involve chronic inflammation of the gastrointestinal tract.[1,2] CD most commonly affects the small intestine, and often involves the deep layers of the bowel.[3] UC causes inflammation and ulcers exclusively in the colon and is generally characterized as a more superficial disease than CD because it affects the mucosa (inner lining).[4,5] Both types of IBD cause diarrhea, abdominal pain, rectal bleeding, nausea, vomiting, reduced appetite, and weight loss.[6,7] Patients with UC commonly experience severe, frequent, and bloody diarrhea, as well as tenesmus and urgency (feeling of the need to defecate immediately).[2,6-8] The prevalence of UC in Canada is among the highest in the world[9-13] and it is projected to increase from 210 per 100,000 persons in 2008 to 408 per 100,000 persons in 2030.[14] In a recently published 2023 report on the impact of IBD in Canada, it was estimated that approximately 322,600 Canadians are living with IBD in 2023 (0.8% of the population), a number that is projected to grow to 470,000 (1.1% of the population) by 2035.[13] New diagnoses are increasing the fastest in children younger than 6 years, and the most rapidly growing group of patients with IBD is seniors because of population aging and improvements in disease management.[13]

The main goals of UC management have traditionally included induction and maintenance of corticosteroid-free clinical and endoscopic remission,[15] although expert consensus initiatives have recommended considering other clinically relevant outcomes, including biomarker changes and histologic remission.[16] Treatment strategies for UC have conventionally followed a step-up approach in which more advanced systemic therapies are only initiated if a patient has a suboptimal response to an earlier line of therapy.[17,18] This approach may still be appropriate for some patients with UC as there is debate regarding the progressive nature of the disease and the timeline for cumulative damage because UC is generally characterized as a more superficial condition than CD.[19] However, there has been interest in adopting a treat-to-target approach in recent years, wherein adjustments to therapy are guided by the achievement of specific treatment goals, as suggested by consensus statements and international guidelines.[21-23]

Treatment for UC is determined by the site and extent of disease and by the severity of inflammation and symptoms.[15,20,21] Mild UC is typically managed using orally or rectally administered sulfasalazine and 5-aminosalicylates (5-ASAs); and conventional pharmacotherapy for moderate to severe UC entails an initial

induction of remission with a corticosteroid (CS).[15,21,22] In refractory IBD, thiopurines (e.g., azathioprine and 6-mercaptopurine [6-MP]) are used to maintain remission and decrease CS use, but they are ineffective as monotherapy in active IBD.[23] Methotrexate can induce and maintain remission in CD, but its effectiveness for UC has not been substantiated.[23] Importantly, all immunomodulators carry significant adverse effects, such as bone marrow suppression, cytopenias, and infections.[23] Should these therapies fail to provide a durable response, targeted immune modulators (TIMs), such as biologics and small-molecule drugs, are recommended.[15,20,21] Biologics approved in Canada for UC include tumour necrosis factor (TNF) antagonists (infliximab, adalimumab, and golimumab), an anti-integrin antibody (vedolizumab), and an anti-interleukin (IL)-12 and IL-23 inhibitor (ustekinumab).[1,21] The approved small molecules include a Janus kinase (JAK) inhibitor (tofacitinib) and a sphingosine-1-phosphate (S1P) receptor modulator (ozanimod).[20,21]

Over the past several years, the evidence base for biologics and small-molecule therapies in UC has grown substantially. As a result, major treatment guidelines are being updated and therapeutic strategies are evolving.[7,16,20,21,24-26] Further, there are many agents in mid or late stages of clinical development for UC, several of which may expand existing drug classes or introduce new ones in the therapeutic setting. This report provides an overview of these aspects of the evolving therapeutic landscape in moderate to severe UC.

Current Treatment Guidelines

Several of the biologics and small-molecule drugs available for the treatment of moderate to severe UC were approved by regulatory bodies within the past 5 years. In response, key clinical management guidelines in most regions have been updated to reflect these recent additions and provide recommendations regarding their appropriate use in clinical practice. In this section, recent guidelines for the treatment of moderate to severe UC in Canada, the US, and Europe are summarized, with a focus on recommendations regarding the use of biologics and small molecules to contextualize their potential place in therapy for emerging treatment options.

Canada

Clinical practice guidelines for the medical management of UC in Canada were last published in 2015 as the Toronto Consensus, supported by the Canadian Association of Gastroenterology.[15] The guidelines have not been updated since Health Canada approved tofacitinib (2018), ustekinumab (2020), and ozanimod (2022); therefore, these treatment options are not reflected in the recommendations. Further, results of the phase IIIb VARSITY trial — the only head-to-head clinical trial comparing 2 biologic therapies in patients with moderate to severe UC[27] — were published in 2019 and are not reflected in the recommendations. The results of this study showed superiority of vedolizumab compared with adalimumab in terms of achieving clinical remission and endoscopic improvement.[27] As a result of these important developments since the last update, the recommendations provided in the guidelines may not reflect the current clinical practice standards and may be considered outdated.

Overall, the consensus guidelines recommend that patients with moderate to severe UC undergo a course of oral CS therapy and those patients who achieve symptomatic remission should transition to 5-ASA, thiopurine, TNF antagonist (adalimumab, infliximab, or golimumab; with or without thiopurine or methotrexate), or anti-integrin (vedolizumab) maintenance therapy.[15] For patients with CS-resistant or dependent UC, the guidelines recommend a TNF antagonist or vedolizumab. In general, the guidelines only recommend vedolizumab for patients who have failed TNF antagonist therapy; however, as noted previously, the guidelines were published before the results of the VARSITY trial were available.

Notably, the recommendations in the 2015 Canadian clinical practice guidelines generally follow a "step-up" approach to treating patients with UC.

United States

The American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) have both published clinical practice guidelines that include recommendations for the treatment of moderate to severe UC.[7,21] The ACG guidelines were published before the FDA in the US approved ustekinumab in late 2019, and both guidelines were developed before ozanimod was approved in 2021. Therefore, the recommendations provided in these guidelines do not include all TIMs currently approved for the treatment of moderate to severe UC in the US. Nonetheless, the AGA and ACG guidelines may reflect how clinical practice has changed since the 2015 Canadian guidelines to incorporate newer therapies.

ACG Guidelines

The ACG recommends the use of a TNF antagonist (infliximab, adalimumab, or golimumab), vedolizumab, or tofacitinib for induction of remission in patients with moderately to severely active UC.[7] When TNF antagonist therapy is used for induction of remission in patients who have previously failed 5-ASAs, combination therapy with 5-ASA is not recommended. When infliximab is used for induction of remission, combination therapy with a thiopurine is recommended to reduce immunogenicity, increase drug exposure, and attain greater efficacy than infliximab monotherapy.[28] Vedolizumab or tofacitinib are recommended for induction of remission in patients who have previously failed TNF antagonist therapy, particularly for primary nonresponders.[7] Patients who initially respond to a TNF antagonist but subsequently lose efficacy may be switched to another TNF antagonist, but not a biosimilar of the original drug, rather than stopping treatment. In patients who successfully achieve remission with a biologic or tofacitinib, it is recommended that the same therapy be continued for maintenance of remission.

Although specific recommendations regarding the order of biologic or small-molecule therapy selection are not provided, the ACG guidelines note that it may be reasonable to consider the gut-selective anti-integrin therapy vedolizumab before more systemic therapies, such as TNF antagonists or JAK inhibitors, in some patient populations.[7]

AGA Guidelines

In adult patients with moderate to severe UC, the AGA recommends the use of a TNF antagonist (infliximab, adalimumab, or golimumab), vedolizumab, tofacitinib, or ustekinumab over no treatment.[21] Recommendations for a specific drug or class depend on a number of factors, including patient preferences

for attributes of therapy and previous biologic exposure. Further, if a drug is effective for induction of remission or response, it is assumed that it will be continued for maintenance therapy in line with standard of care in clinical practice.

For biologic-naive patients, the AGA recommends infliximab or vedolizumab over adalimumab for induction of remission.[21] As noted previously, the results of the VARSITY trial showed superior efficacy with vedolizumab compared with adalimumab.[27] The AGA guidelines note that patients who place higher value on convenience of a self-administered subcutaneous injection than on relative efficacy may choose adalimumab, particularly if they have less severe disease;[21] however, vedolizumab was not yet available in a self-administered subcutaneous formulation at the time the guidelines were published. In patients who have previously been exposed to infliximab, particularly those with primary nonresponse, the guidelines conditionally recommend ustekinumab or tofacitinib over vedolizumab or adalimumab. The AGA guidelines note that any use of tofacitinib in biologic-naive patients should be closely monitored in the setting of a clinical trial or registry study as per FDA guidance at the time of publication.

Monotherapy with a biologic or tofacitinib is also suggested over thiopurine monotherapy for induction of remission in the AGA guidelines, although no recommendation is provided for preference of these therapies in maintenance.[21] Further, the guidelines suggest a combination of a biologic or tofacitinib with thiopurines or methotrexate over either biologic or thiopurine monotherapy, although patients may choose biologic monotherapy if they place higher value on safety of monotherapy than on efficacy of combination therapy.

Notably, the AGA guidelines suggest early use of biologic drugs (with or without immunosuppressives) rather than the traditional step-up approach after failure of 5-ASAs.[21] The guidelines note that patients who place higher value on safety than on efficacy may reasonably choose gradual step-up therapy with 5-ASA over biologic or tofacitinib therapy. Overall, the AGA recommendations for the use of biologics and small molecules in patients with moderate to severe UC represent important updates from previous guidelines, which did not specify preferences for a particular drug compared with others within or between drug classes.

Europe

The ECCO guidelines on medical treatment for adults with UC were published in 2022.[20] Although these guidelines consider more recent evidence than those described previously, the document was finalized before the European Medicines Agency (EMA) approved ozanimod in late 2021 for the treatment of adults with moderately to severely active UC. Therefore, the biologics and small molecules included in the ECCO guidelines are similar to those in the previously described AGA guidelines.

ECCO recommends the use of a TNF antagonist (infliximab, adalimumab, or golimumab), vedolizumab, tofacitinib, or ustekinumab for patients with moderate to severe UC who have an inadequate response or intolerance to conventional therapy, including a 5-ASA, CS, or thiopurine.[20] The guidelines also suggest the use of vedolizumab rather than adalimumab for induction and maintenance therapy. As with other guidelines, maintenance therapy with the same drug used to induce remission is recommended for patients who achieve an initial response. For patients who lose response to a TNF antagonist, the guidelines note

there is insufficient evidence to provide a recommendation on the use of TDM (refer to the Therapeutic Drug Monitoring section for information and recommendations on TDM from other sources).

Future Considerations

There are many new and emerging biologic and small-molecule therapies in late stages of clinical development for UC (refer to the New and Emerging Drugs section). As these new therapies are introduced, treatment guidelines will need to be updated to provide recommendations regarding their optimal place in therapy for patients with moderate to severe UC. Several systematic literature reviews and network meta-analyses published after the guidelines described herein incorporated data for some emerging drugs compared with previously approved TIMs.[29-33] Results from these studies may be used to supplement data from randomized controlled trials to inform future treatment guideline updates.

Trends in Therapeutic Strategies

The clinical evidence for biologics and targeted small molecules in UC, as well as technological advances in diagnostics and outcome measurement, have drastically increased over the past decade. Such innovations have provided new opportunities to improve disease outcomes for patients with UC; however, they have also introduced complexity into clinical management algorithms, and therapeutic strategies have evolved to account for the abundant recent clinical evidence and to identify remaining gaps.

Treat to Target

An improved understanding of clinically relevant therapeutic targets and treatment end points is important to optimize management of patients with UC because timely initiation and adjustment of medications is dependent on well-defined treatment goals.[16] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program was initiated by the International Organization for the Study of Inflammatory Bowel Diseases and first provided consensus recommendations determining treatment targets for CD and UC in 2015.[24] This position statement constituted the guidance for a treat-to-target clinical management strategy, which has altered the treatment paradigm for patients with moderate to severe UC and is supported by many other sources.[25,26,34-36] The STRIDE recommendations for UC are primarily based on expert opinion, whereas recommendations for CD are mostly informed by evidence from randomized controlled trials. Further, there may be less emphasis on initiating advanced therapy early after diagnosis with UC, depending on severity and response to initial treatment, because it is generally characterized as a more superficial disease than CD.[19]

The original STRIDE-I guidance was subsequently updated in 2021 as STRIDE-II, which provides 13 contemporary consensus recommendations for using new and updated targets throughout an individualized treatment timeline.[16] The recommendations include clinical response as an immediate or short-term target; clinical remission and normalization of C-reactive protein and fecal calprotectin as intermediate or medium-term targets; and restoration of growth in children, endoscopic healing, absence of disability, and normalized health-related quality of life as long-term targets.[16] Histologic remission is not considered a formal UC

treatment target in STRIDE-II, but it is acknowledged as an adjunctive measure to endoscopic remission to represent a deeper level of healing. In addition, although C-reactive protein levels are typically elevated in patients with UC who are hospitalized and those with active disease,[37,38] they are not always elevated in outpatients with UC;[39] therefore, it may be less valuable as a treatment target in this setting.

Although this guidance document synthesized recommendations based on clinical expert opinion and a systematic review of the available evidence, it noted that clinical decisions may need to deviate from the suggested algorithm because there are major gaps in the evidence supporting some recommendations.[16] Areas for future research noted in STRIDE-II include development of patient-reported outcomes (PROs) specifically for use in clinical practice (as opposed to the clinical trial setting) as well as short tools for everyday use to measure health-related quality of life; prospective studies on histologic healing in UC to better understand whether its use as a treatment target may improve clinical outcomes; and additional studies to better link optimal thresholds for endoscopic healing with specific outcomes.

Histologic Healing

Some of the major evidence gaps noted in STRIDE-II are actively being addressed, with many studies seeking to better understand whether inclusion of histologic healing or remission as a treatment target for UC would improve patient outcomes.[40-44] One such study is the VERDICT trial, which is designed to identify an optimal treatment target for implementation into clinical practice, new clinical trials, and evidence-based guidelines for patients with moderate to severe UC. Enrolled patients are randomized into groups based on treatment target, including CS-free symptomatic remission, CS-free endoscopic remission plus symptomatic remission, or CS-free histologic remission plus endoscopic and symptomatic remission; enrolment is expected to be complete in late 2023.[43,44]

Reports from several studies conclude that the evidence continues to support associations between histology and clinical outcomes in UC, which may lead to histologic healing becoming a formal treatment target in the future, although additional work is needed to determine consistent criteria and definitions for its implementation.[25,34,43,45-49] Further, an international consensus to standardize integration of histopathology in clinical trials noted that achievement of histologic improvement or healing is an appropriate and realistic therapeutic target in UC.[50] In addition, several studies have shown that a combined end point of histologic and endoscopic healing may better predict long-term outcomes than either treatment target alone.[51-53]

Fecal Calprotectin

A number of studies have suggested that fecal calprotectin may be a clinically relevant biomarker of disease activity in IBD, and a reduced fecal calprotectin level in response to therapy has been reported to be associated with endoscopic, mucosal, and histologic healing in patients with UC.[54-64] Measurement of calprotectin through fecal testing has been proposed in some studies as a noninvasive, accessible, and cost-effective clinical assessment tool,[43-47,49] which may provide an opportunity for frequent monitoring of treatment response and disease activity.[58,59,62] Therefore, fecal calprotectin is a formal intermediate treatment target in STRIDE-II.[20,52] Further, the AGA recently published a clinical practice guideline on the role of biomarkers for the management of UC, which includes several recommendations regarding the use of fecal calprotectin measurements to inform treatment decisions and avoid routine endoscopic assessment

of disease for patients in symptomatic remission or with moderate to severe symptoms.[65] However, there is no direct evidence from randomized controlled trials in UC to conclusively demonstrate a benefit of fecal calprotectin measurement compared with symptom-based care, and endoscopy remains the standard for measurement of disease activity and monitoring of treatment response.

Despite its potential role in the medical management of IBD, it has been noted that there are limitations regarding the reproducibility, diagnostic accuracy, and appropriate threshold values of available fecal calprotectin tests.[56,57,59] In an international consensus statement, recommendations to address methodological issues in standardization of fecal calprotectin measurement included the use of quantitative tests, a consistent measurement method, and consideration of factors influencing the measurements.[57] Additional evidence is required to guide standardization for measurement of fecal calprotectin and interpretation of results, and to potentially further validate it as an appropriate independent treatment target. This may also affect its use in clinical trials, for which reducing variability is important for within-group and between-group comparisons.

Therapeutic Drug Monitoring

The development of TDM emerged from the challenges associated with the use of older biologic drugs, primarily TNF antagonists such as infliximab and adalimumab.[66,67] These drugs posed difficulties related to immunogenicity and dosing[66,67] because of the numerous patient-related and disease-related factors influencing a patient's plasma level of a biologic, a measure believed to align positively with the drug's therapeutic efficacy.[68-72] TDM entails assessing drug trough concentrations and anti-drug antibodies to better optimize drug concentrations and improve clinical outcomes.[68,69] Reactive TDM refers to the evaluation of drug concentrations and anti-drug antibodies in patients with suboptimal disease control or treatment failure, whereas proactive TDM refers to the measurement of drug trough concentrations and anti-drug antibodies during remission to guide dose adjustments that could achieve a target concentration.[68,70,71]

There has been ongoing debate about the application of TDM in IBD. The AGA has recommended reactive TDM for managing treatment changes but underscores the low quality of evidence supporting this recommendation because their study focused on TNF antagonists and thiopurines.[68] Conversely, ECCO states that evidence is insufficient to either support or oppose the use of TDM for improving clinical outcomes.[20] Recent expert consensus statements regarding TDM in IBD also support reactive TDM for patients who lose response to a TNF antagonist, and recommend reactive TDM for patients who lose response to vedolizumab or ustekinumab as well as proactive TDM for patients on a TNF antagonist.[70,71] However, studies have noted that evidence gaps remain regarding the appropriate use of proactive TDM, utility of TDM for small molecules and biologics outside of the TNF antagonist class, and consistent target concentration thresholds to guide dose changes.[68,69,71,73]

Given the introduction of newer biologics that have different mechanisms of action, reduced immunogenicity, and fixed dosing, such as vedolizumab and ustekinumab,[74,75] it is essential to assess the specific attributes of each therapy and determine the extent to which TDM is necessary. It is broadly acknowledged that longer-term, prospective studies, as well as additional randomized controlled trials, are needed to address these key questions.[68,70,71,76]

New and Emerging Drugs

There is a substantial pipeline of new and emerging drugs for the treatment of adults with moderate to severe UC, with many drugs in phase IIb or III of clinical development (Table 1; expanded in Appendix 1). Several notable trends exist, including an increasing number of JAK inhibitors, several therapies with biologic targets that are new in UC, an increasing number of oral therapies, and the first combination of 2 biologic therapies in UC.

Tofacitinib is currently the only JAK inhibitor approved by Health Canada for the treatment of adult patients with moderate to severe UC. There are 5 additional JAK inhibitors in phase IIb or phase III of clinical development (Table 1), most of which already have clinical data available (brepocitinib, ritlecitinib, filgotinib, and upadacitinib; refer to Appendix 1). Further, filgotinib has been approved for moderate to severe UC in Europe and Japan, and upadacitinib has been approved in the US and Europe. Although an increasing number of JAK inhibitors will become available in the near future, important safety signals have emerged with drugs in this class, leading to labelling recommendations by the FDA and Health Canada.[77,78] These recommendations include the implementation of a black box class warning across all JAK inhibitors emphasizing the potential cardiovascular risks associated with this class of medications; however, recent literature suggests that the cardiovascular risk with JAK inhibitors may not be significantly higher than that of other small-molecule drugs.[79]

Several drugs with new immunological targets are currently in phase IIb or phase III of clinical development for moderate to severe UC. This includes an IL-2 mutein Fc fusion protein that preferentially binds the high-affinity IL-2 receptor (efavaleukin alfa), an IL-36 receptor antagonist (spesolimab), and 3 IL-23 inhibitors (guselkumab, risankizumab, and mirikizumab). Other drugs with targets that are new in UC include RVT-3101 (formerly PF-06480605) and TEV-48574, both tumour necrosis factor–like ligand 1A (TL1A) and TNF superfamily member 15 (TNFSF15) inhibitors; obefazimod, a microribonucleic acid 124 (miR-124) upregulator; and cobitolimod, a toll-like receptor 9 (TLR9) activator.

The pipeline of emerging therapies in UC also includes an increasing number of orally administered drugs, including the 5 JAK inhibitors noted previously plus etrasimod, MORF-057, carotegrast methyl, and obefazimod. The only orally administered TIMs currently approved by Health Canada are tofacitinib and ozanimod.

Finally, the combination of guselkumab and golimumab is currently being tested in an ongoing phase IIb trial in patients with moderate to severe UC after final results from the phase IIa VEGA trial showed that this combination induced clinical response, clinical remission, and endoscopic improvement more effectively than monotherapy with either biologic at week 12 of treatment and without raising any new safety concerns up to week 50.[80] This is the first combination of biologic therapies to be assessed in patients with UC, and the positive results of the VEGA trial may lead to additional combination trials with the goal of improving efficacy by simultaneously targeting multiple pathways involved in the disease.[81]

Table 1: Pharmacological Products in Phase IIb or Phase III of Development for UC

Phase	Drug	Target	Mode of delivery
JAK/STAT inhibitor			
IIb	Brepocitinib	JAK and STAT, TYK2	Oral
IIb	Ritlecitinib	JAK and STAT	Oral
III	Filgotinib	JAK and STAT	Oral
III	Upadacitinib	JAK and STAT	Oral
III	Ivarmacitinib	JAK and STAT	Oral
Anti-IL and anti–IL receptor antibody			
IIb	Efavaleukin alfa	IL-2 receptor	Parenteral
II and III	Guselkumab	IL-23	Parenteral
II and III	Spesolimab	IL-36 receptor	Parenteral
II and III	Risankizumab	IL-23	Parenteral
III	Mirikizumab	IL-23	Parenteral
S1P-receptor modulator			
III	Etrasimod	S1P receptor	Oral
Anti-integrin			
IIb	MORF-057	Alpha 4 beta7 integrin	Oral
III	Carotegrast methyl	Alpha 4 integrin	Oral
III	Etrolizumab	Beta 7 integrin	Parenteral
Other			
IIb	RVT-3101 (PF-06480605)	TL1A and TNFSF15	Parenteral
IIb	TEV-48574	TL1A and TNFSF15	Parenteral
IIb	JNJ-4804 (guselkumab and golimumab combination therapy)	IL-23 (guselkumab) and TNF-alpha (golimumab)	Parenteral
III	Obefazimod	miR-124	Oral
III	Cobitolimod	TLR9	Oral, topical

IL = interleukin; JAK = Janus kinase; miR-124 = microribonucleic acid 124; S1P = sphingosine 1-phosphate; STAT = signal transducer and activator of transcription; TL1A = tumour necrosis factor–like ligand 1A; TLR9 = toll-like receptor 9; TNF = tumour necrosis factor; TNFSF15 = tumour necrosis factor superfamily member 15; TYK2 = tyrosine kinase 2; UC = ulcerative colitis.

Another important trend is the increasing number of biosimilars and generics expected to become available in the Canadian market in the next several years. Biosimilars of adalimumab and infliximab are already available, and patents expired for ustekinumab and golimumab in 2021. In addition, data protection expired for tofacitinib in 2022 and will be expiring for vedolizumab in 2023. These changes in exclusivity status of currently approved therapies will affect the therapeutic landscape in UC. Further, the availability of biosimilars could reduce the cost burden associated with biologic use, which can potentially influence the consideration of combination therapy of biologics with different targets in the future. This may also be a

consideration for drugs with new mechanisms of action because the availability of biosimilar or generic versions of drugs from different classes may increase the opportunity to assess combination therapy earlier in clinical development. Appendix 2 includes a list of phase III trials for biosimilars of biologics with expired data protection that are currently approved for UC in Canada (i.e., ustekinumab and golimumab). There is also the possibility of manufacturers marketing originator biologics under additional product names, as demonstrated by the recent approval of Finlius, a rebranded version of Stelara (ustekinumab).[82] However, it is unclear whether this will affect the treatment landscape in UC. The approval, coverage, and reimbursement of biosimilars is covered in greater detail in the CADTH Environmental Scan ES0366, *Formulary Management of Targeted Immune Modulators in Ulcerative Colitis*.[83]

Trends in Clinical Trial End Points

The design of clinical trials in moderate to severe UC has evolved since the first biologic was approved for the indication more than 15 years ago. One of the key changes is the inclusion of additional and modified end points, which largely align with the trends in therapeutic strategies described previously (refer to the Trends in Therapeutic Strategies section). In an international consensus document that communicated a set of core outcomes for randomized controlled trials in IBD (CORE-IBD), it was recognized that symptom-based measurements alone are not specific or sensitive enough to comprehensively assess disease activity in IBD, leading to the increased use of objective measures of inflammation, such as endoscopic evaluation.[84] The document noted that histologic remission has also been more frequently incorporated as an end point in clinical trials on UC, and there is an increasing emphasis on the importance of using validated PROs to capture the patient experience.[84] The overall aim of the consensus initiative, which involved an international collaboration between patients and clinical experts, was to assist in addressing the heterogeneity in outcome measures used to assess IBD drugs.[84] In brief, core domains for UC trials included PROs, quality of life, endoscopy, biomarkers, safety, and histopathology, and there was consensus to use a composite primary end point of symptomatic and endoscopic remission.[84]

Notably, pivotal clinical trials for the most recently approved UC therapies included end points that address the core domains outlined in the CORE-IBD consensus,[85,86] although some clinical trials for emerging therapies discussed previously (refer to the New and Emerging Drugs section and Appendix 1) do not include assessment of biomarkers and/or PROs as prespecified outcome measures on the trial registry at the time of this report. Including expanded, rigorous, and contemporary end points in clinical trials provides the opportunity for a more comprehensive assessment of a drug's clinical value by regulatory authorities and HTA bodies, and increases the evidence available to inform therapeutic strategies such as treat to target.

Conclusion

The treatment of moderate to severe UC is rapidly evolving. Many emerging therapies may expand existing drug classes, introduce new classes in UC, and facilitate combination therapy of biologics with different targets, which could in turn affect how the disease is managed. The health care system should

be prepared to adapt to these potential clinical practice changes. There are many JAK inhibitors currently in phase IIb or phase III clinical trials, and the introduction of some or all of these drugs may necessitate reconsideration of the place in therapy for this class. More orally administered TIMs for patients with UC may reduce the demand for infusion clinics and the resources associated with infusion services. Drugs with new mechanisms of action in the treatment area as well as the new paradigm of combination therapy with multiple biologics of different classes may lead to improved patient outcomes but could also further complicate the treatment decision-making process, especially considering there are already multiple safe and effective treatment classes available for patients with UC. Therefore, it is important for health care providers to stay up to date on new and upcoming treatment options, which may require educational initiatives for both providers and patients within the health care system as well as updated Canadian treatment guidelines to reduce the need for physicians to rely on guidelines from international organizations (e.g., ACG, AGA, ECCO). Further, strategies used to assess therapeutic effectiveness in real-world clinical practice are evolving, and efforts are being made to standardize and expand end points assessed in clinical trials of new UC therapies. One important consideration is the need to apply strategies such as TDM differently depending on the treatment because its application is generally accepted as important to TNF antagonists (particularly infliximab and adalimumab) but there is less evidence on its relevance to newer drugs such as vedolizumab and ustekinumab. In addition, the shift toward a treat-to-target approach and personalized medicine may result in better outcomes for patients with UC but could also require more sophisticated and individualized care, including enhanced diagnostic testing, patient monitoring, and patient education and engagement. Overall, these changes may have substantial implications for the health care system given the prevalence of UC in Canada, the costs of advanced therapies, and the increasing number of available treatment options.

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Appendix 1: UC Drugs in Phase IIb or III Trials

Table 2: Pharmacological Products in Phase IIb or Phase III of Development for UC (Expanded)

Phase	Drug	Manufacturer	Target	NCT number[a]	Completion	Regulatory	Mode of delivery
JAK and STAT inhibitor							
IIb	Brepocitinib	Priovant Therapeutics	JAK and STAT, TYK2	NCT02958865[87]	May 2021	—	Oral
IIb	Ritlecitinib	Pfizer Inc.	JAK and STAT	NCT02958865[87]	May 2021	—	Oral
III	Filgotinib	Gilead Sciences Inc.	JAK and STAT	NCT02914522[88-90] NCT02914535[91-93]	March 2020 November 2026	EU 2021-11 JP 2022-03	Oral
III	Upadacitinib	Abbvie Inc.	JAK and STAT	NCT03653026[94-96] NCT02819635[94-96] NCT03006068	January 2021 December 2021 August 2024	US 2022-03 EU 2022-07	Oral
III	Ivarmacitinib	Reistone Biopharma	JAK and STAT	NCT05181137	March 2025	—	Oral
Anti-IL and IL receptor antibody							
IIb	Efavaleukin alfa	Amgen, Inc.	IL-2 receptor	NCT04987307	August 2024	—	Parenteral
II/III	Guselkumab	Johnson & Johnson	IL-23	NCT04033445[97-99] NCT05528510	September 2029 April 2026	—	Parenteral
II/III	Spesolimab	Boehringer Ingelheim	IL-36 receptor	NCT03482635[100]	May 2020	—	Parenteral
II/III	Risankizumab	AbbVie Inc.	IL-23	NCT03398148 NCT03398135	May 2023 May 2024	—	Parenteral
III	Mirikizumab	Eli Lilly	IL-23	NCT03518086[101-106] NCT03524092[104-107]	March 2024 March 2025	—	Parenteral

Phase	Drug	Manufacturer	Target	NCT number[a]	Completion	Regulatory	Mode of delivery
S1P-receptor modulator							
III	Etrasimod	Pfizer Inc.	S1P-receptor	NCT03996369[108-110] NCT03945188[108-110] NCT04176588 NCT03950232	December 2021 February 2022 November 2022 August 2027	—	Oral
Anti-integrin							
IIb	MORF-057	Morphic Therapeutic Inc.	α4β7 integrin	NCT05611671	July 2025	—	Oral
III	Carotegrast methyl	EA Pharma Co	α4 integrin	NCT03531892[111]	October 2023	JP 2022-03	Oral
III	Etrolizumab	Hoffman-La Roche	β7 integrin	NCT02163759[112] NCT02165215[113] NCT02100696[114] NCT02171429[112] NCT02136069[115] NCT02118584	March 2020 April 2020 April 2020 May 2020 June 2020 August 2025	—	Parenteral
Other							
IIb	RVT-3101/ PF-06480605	Roivant Sciences/ Pfizer Inc.	TL1A and TNFSF15	NCT04090411	October 2022	—	Parenteral
IIb	TEV-48574	Teva Pharmaceuticals	TL1A and TNFSF15	NCT05499130 NCT05668013	October 2024 January 2025	—	Parenteral
IIb	JNJ-78934804 (guselkumab and golimumab combination therapy)	Johnson and Johnson	IL-23 (guselkumab) and TNFα (golimumab)	NCT05242484	September 2028	—	Parenteral

Phase	Drug	Manufacturer	Target	NCT number[a]	Completion	Regulatory	Mode of delivery
III	Obefazimod	Abivax	miR-124	NCT05507203 NCT05507216 NCT05535946	June 2024 June 2024 June 2025	—	Oral
III	Cobitolimod	InDex Pharmaceuticals	TLR9	NCT04985968	December 2024	—	Oral, Topical

EU = European Union; IL = interleukin; JAK = Janus kinase; JP = Japan; miR-124 = microribonucleic acid 124; PO = oral; S1P = sphingosine-1-phosphate; STAT = signal transducer and activator of transcription; TLR9 = toll-like receptor 9; TNF = tumour necrosis factor; TNFSF15 = tumour necrosis factor superfamily member 15; TYK2 = tyrosine kinase 2; UC = ulcerative colitis.

[a]Includes reference to published data for the associated clinical trial, where available.

Appendix 2: Phase III Clinical Trials for Ustekinumab Biosimilars

Note that this appendix has not been copy-edited.

Table 3: Phase III Clinical Trials Registered on ClinicalTrials.gov for Ustekinumab Biosimilars

Name	NCT	Conditions	Completion date
ABP-654	NCT04761627 NCT04607980	Psoriasis	March 20, 2023 June 3, 2022
AVT-04	NCT04930042	Psoriasis	October 11, 2022
BAT-2206	NCT04728360	Psoriasis	May 30, 2023 (Estimated)
BMAB-1200	NCT05335356	Psoriasis	October 30, 2023 (Estimated)
CT-P43	NCT04673786	Psoriasis	May 12, 2022
DMB-3115	NCT04785326	Psoriasis	November 2022
FYB-202	NCT04595409	Psoriasis	March 2022

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**