CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Biologics Dose Escalation for the Treatment of Inflammatory Bowel Disease: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	August 28, 2018
Report Length:	30 Pages

CADTH

Authors: Yi-Sheng Chao, Sarah Visintini

Cite As: Biologics dose escalation for the treatment of inflammatory bowel disease: A review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa: CADTH; 2018 Aug. (CADTH Rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Context and Policy Issues

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterized by the inflammation conditions involving colon and small intestines.[1] Ulcerative colitis (UC) and Crohn's disease (CD) are the primary constituents of IBD.[1] IBD is more prevalent in northern and industrialized countries and in specific races, particularly Caucasians and Ashkenazic Jews.[1] In in 2006, the incidence for CD in Canada was estimated to range from 8.8 per 100,000 in British Columbia to 20.2 per 100,000 in Nova Scotia,[2] based on a study that analyzed data from five Canadian provinces. In the same study, the incidence of UC was estimated to range from 9.9 per 100,000 in British Columbia to 19.5 per 100,000 in Nova Scotia.[2] The prevalence of UC and CD were similar in Canada in 2006.[2] It was estimated that 0.5% of Canadians had some form of IBD in 2006.[2]

UC and CD have distinct characteristics. UC is a mucosal disease that usually involves the rectum and all or part of the colon.[3] Common symptoms are diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain.[3] CD affects any part of the gastrointestinal tract from the mouth to the anus.[3] CD can be acute or chronic bowel inflammation.[3] The inflammation usually leads to one of two patterns of disease: a fibrostenotic obstructing pattern or a penetrating fistulous pattern.[3] The differential diagnosis of UC and CD can be difficult and may require clinical, endoscopic and radiological investigation.[3]

Conventional treatment for IBD includes 5-aminosalicylic acid agents, glucocorticoids, antibiotics, azathioprine and 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus depending on the disease severity and symptoms.[3]

Biologics

More recently, there are biologics or biologic agents or biologic therapies available for patients with moderate to severe IBD.[3] Biologics or biologic agents are large, protein-based molecules that can block inflammation for several immune-related diseases.[4] For example, the first biologic approved for CD is infliximab, a chimeric immunoglobulin (IgG)1 antibody against tumor necrosis factor (TNF)-α.[3] For patients with moderately or severely active UC, about one third can obtain complete remission and 40% can maintain remission for at least one year.[3] The recommended dose for infliximab is to repeat infusion 5mg/kg every eight weeks.[3] In 2016, there were three types of biologics approved for the treatment of IBD: anti-TNF agents (infliximab, adalimumab, and golimumab), anti-integrin agents (vedolizumab) and anti-interleukin (IL) 12/23 IgG1 kappa agents (Ustekinumab).[5,6]

Safety and dosing

There are adverse effects of biologic therapies that can develop with the ongoing treatment. Antibodies to the biologics may develop and decrease the effectiveness of biologics.[3] New-onset psoriasiform skin lesions may develop in 5% of IBD patients treated with anti-TNF biologics.[3] This is called paradoxical reactions.[7] Such reactions are pathological conditions that can occur even while IBD is well controlled.[7] These reactions originate from patients' reactions to the biologics and multiple immunological pathways are found to be involved.[7] Common paradoxical reactions include palmoplantar pustular and psoriasiform reactions, psoriatic arthritis, and hidradenitis.[7] Due to their potential to cause morbidity and mortality, paradoxical reactions should be closely monitored.[7] Clinical practices, such as managed switching[8] and therapeutic drug monitoring,[9] have been used for individual patients.

In addition, patients treated with biologics are at greater risk of infection.[3] There have been other rare conditions reported, such as non-Hodgkin's lymphoma, hepatospenic T cell lymphoma, acute liver injury, and the development of anti-integrins.[3]

Dose, frequency, and duration of treatment that can affect the effective concentration in the blood[10] are considered important for IBD treatment.[11] Shorter intervals, increased doses or switching to other biologics may help patients to maintain remission and avoid adverse effects and paradoxical reactions.[3]

Benefits of higher than standard doses

Up to one-third of IBD patients can experience that biologics become less effective and fail to maintain disease remission.[12] In these cases, dose intensification or more frequent dosing have been considered and tried.[12] However, the safety profile of intensified dosing and the effects on paradoxical reactions remain a subject of research. There is a need to review the effectiveness and risks of the biologics that are infused more frequently or at higher doses.

To answer this question, we aim to review the literature and compare the clinical utilities and cost-effectiveness of higher or more frequent than standard dosing of biologics with standard dosing for the treatment of IBD.

Research Questions

1. What is the clinical effectiveness of higher or more frequent versus standard dosing of biologics for the treatment of inflammatory bowel disease?
2. What is the clinical effectiveness of higher or more frequent than standard dosing versus switching biologics for the treatment of inflammatory bowel disease?
3. What is the cost-effectiveness of higher or more frequent versus standard dosing of biologics for the treatment of inflammatory bowel disease?
4. What is the cost-effectiveness of higher or more frequent than standard dosing versus switching of biologics for the treatment of inflammatory bowel disease?
5. What are the evidence-based guidelines regarding higher or more frequent than standard dosing of biologics for the treatment of inflammatory bowel disease?

Key Findings

There is limited evidence to comparing the effectiveness of different doses of the following biologics in patients with inflammatory bowel disease (IBD): vedolizumab, adalimumab, infliximab. There were no studies on golimumab or ustekinumab identified. The sample sizes of the primary studies ranged from 33 to 778. Weekly and biweekly adalimumab doses were associated with similar clinical responses and frequencies of serious infectious adverse events. Biweekly adalimumab 40 mg or 80 mg was associated with comparable trough concentrations. The sample sizes for the trials on vedolizumab were not enough to compare the effectiveness of high and standard doses. For infliximab, dose intensification based on a multiple-criteria algorithm was similarly effective as symptom-based dose intensification in a RCT. Two of the three retrospective cohort studies provided conflicting evidence regarding the needs for colectomy. One study found that an accelerated infliximab induction strategy reduced the need for early colectomy, while another discovered that an

accelerated infliximab doses after initial standard infusion was associated with higher colectomy rates for patients with acute ulcerative colitis. In the third retrospective cohort study by Nagata et al., doubling the infliximab dose and shortening the intervals of infliximab infusion were similarly effective to achieve clinical response, compared to switching to adalimumab in the short or long run. The included guideline indicated that for those who are considered secondary non-responders, dose escalation or switching may be appropriate. No relevant cost-effectiveness studies regarding higher or more frequent versus standard dosing or switching of biologics for the treatment of inflammatory bowel disease.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and July 30, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1 : Selection Criteria

Population	Adult and pediatric patients with moderate to severe Crohn's disease Adult and pediatric patients with moderate to severe ulcerative colitis
Intervention	Higher than standard doses of adalimumab, infliximab, golimumab, ustekinumab, or vedolizumab at the regular dosing interval Standard doses of the biologics at more frequent dosing intervals Higher than standard doses at more frequent dosing intervals Standard doses and dosing intervals: Adalimumab (regular dosing for adults is 1 40mg injection every 2wks) [13] Infliximab (standard dosing for adults is 5 mg/kg; every 8 weeks)[14] Golimumab (standard dosing for adults is 200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 50 mg every 4 weeks)[15] Ustekinumab, subcutaneous or intravenous administration available, doses depending on body weight and age, see monograph for details[16] Vedolizumab (standard dosing for adults is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter)[17] *golimumab is not used for Crohn's disease; ustekinumab is not used for ulcerative colitis
Comparator	Q1. Q3. Standard doses of same biologic agents discussed above Q2. Q4. Switching to an alternative biologic agent Q5. No comparator

Outcomes	Q1, Q2: Efficacy/effectiveness, clinical benefit including: Clinical Remission; Clinical Response, Health Related Quality of life, Surgery. Other efficacy outcomes may include: mucosal testing for inflammation/mucosal healing; physical function/disability; days of missed work or school; corticosteroid free clinical remission. - Safety – serious infections, cancers are some of the main ones; withdrawals due to adverse events and serious adverse events Q3. Q4 cost-effectiveness, Q5. evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, economic evaluation, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. Studies included in a selected systematic review were also excluded.

Critical Appraisal of Individual Studies

For the comparisons between biologics of different doses, the quality of randomized clinical trials (RCTs) was assessed using the Cochrane Risk of Bias Tool.[18] The quality of non-randomized studies was assessed using the Newcastle-Ottawa scale.[19] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations assessed in each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 511 citations were identified in the literature search. Following screening of titles and abstracts, 484 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search and one relevant publication was identified from other sources. Of these potentially relevant articles, 20 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection. Additional citations that may be of interest are included in Appendix 5.

Summary of Study Characteristics

Additional details describing the characteristics of the included studies are reported in Appendix 2.

Study Design

There were four RCTs,[20-23] three retrospective cohort studies,[24-26] and one evidence-based guideline.[27]

Year of Publication and Country of origin

The RCTs were published between 2009 and 2018.[20-23] One of the five RCTs was from France,[20] one from the Netherlands,[21] one from the USA,[22] and one from Japan.[23] The corresponding authors of Parikh et al. was based in the USA and the trial sites were in Canada and the Russian Federation.[22]

The retrospective cohort studies were published in 2015 and 2018.[24-26] One of them was from the USA,[26] one from Japan,[25] and one from Ireland.[24]

The evidence-based guideline was published in 2018 by the American College of Gastroenterology in the USA.[27]

Study population

The sample sizes of four RCTs ranged from 46 to 778.[20-23] The mean ages of all participants were not reported.[20-23] The RCTs recruited patients aged 18 years or older,[20-22] except for Watanabe et al. that included individuals aged 15 years and over.[23] Four RCTs focused on patients with CD[20,21,23] and one studied patients with UC.[22]

The sample sizes of the retrospective cohort studies ranged from 33 to 146.[24-26] The mean ages were not reported.[24-26] The median ages in Gibson et al. were 34 and 38 in two groups.[24] The minimum age in Nagata et al. was 13 years.[25] The age range in Shah et al. was eight to 86 years.[26] Shah et al. and Gibson et al. studied patients with UC.[24,26] Nagata et al. focused on CD.[25] Gibson et al. compared patients experiencing different dosing policies at an academic center.[24] Nagata et al. reported the disease history of two groups of patients treated with two different dosing strategies.[25] Shah et al. matched patients treated with high and standard doses based on propensity scores.[26]

The evidence-based guideline aimed to review the evidence for the management of adult patients with Crohn's disease.[27] There were no limitations on disease severity, publication languages, or countries where trials were conducted.[27]

Interventions and Comparators

Two RCTs compared the effectiveness of different doses of adalimumab,[20,23] one studied vedolizumab,[22] and one studied infliximab.[21] Adalimumab was infused more frequently, 40 mg weekly, after induction therapy was compared to standard dose (40 mg biweekly, after induction) or induction only (see Appendix 2).[20] In the 148-week subcohorts of Watanabe et al., high-dose adalimumab, 80 mg, was infused every other week and compared to the standard dose (40 mg every other week).[23] Parikh et al. studied three doses of vedolizumab, 2, 6, and 10 mg/kg infused on days 1, 15, 29, and 85, and compared to placebo.[22] D'Haens et al. adopted two dose increase schemes for infliximab based on a pre-specified algorithm and compared them with symptom-based dose increase scheme.[21]

Three retrospective cohort studies compared the effectiveness of different doses of infliximab.[24-26] Gibson et al. compared the effectiveness of two dosing policies implemented before and in 2011, 5 mg/kg at weeks 0, 2, and 6 and accelerated dosing, respectively.[24] Nagata et al. included three groups: doubling the infliximab dose, shortening dose intervals to every four to seven weeks, and switching to adalimumab.[25] Shah et al. compared the effectiveness of high-dose infliximab, 10 mg/kg, with standard dose, 5 mg/kg.[26]

The evidence-based guideline did not limit the review on any specific interventions.[27] The interventions identified from the primary studies included sulfasalazine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptourine, and anti-TNF agents (infliximab, adalimumab, certolizumab pegol), however, only the recommendations regarding biologics are relevant to this review.[27]

Outcomes

The outcomes evaluated by the four RCTs included the Crohn's Disease Activity Index (CDAI) scores,[20,21] reduction in CDAI scores,[23] ulcer development,[21] clinical remission defined as CDAI less than 150,[20,21,23] endoscopic remission,[21] quality of life,[20] hospitalization,[20] pharmacokinetics,[22] and adverse events.[20,22] The follow-up time was 253 days,[22] 54 weeks,[21] 56 weeks,[20] and 148 weeks.[23]

The outcomes assessed by the three retrospective studies included clinical remission defined as CDAI less than 150,[25] symptom improvement,[24] CDAI scores,[25] C-reactive protein levels,[24,25] rebound in inflammation,[24] colectomy rates,[26] hospitalization,[26] need for additional infliximab,[26] infection,[26] and complications.[26]

The follow-up lasted for a maximum of 56 days,[24] 48 weeks,[25] and one year.[26]

The evidence-based guideline did not have a restriction on the types of outcomes.[27] The outcomes retrieved from the primary studies included hospitalization, surgical complications, steroid use, and mortality.[27]

Summary of Critical Appraisal

Additional details describing the critical appraisal of the included studies are reported in Appendix 3.

Three of the four RCTs did not mention the method to randomly assign participants to different groups.[20,22,23] In the RCT by D'Haens et al., randomization was centrally conducted online.[21] Allocation concealment was not described in the four RCTs.[20-23] Three RCTs were double-blind[20,21,23] and Parikh et al. did not mention blinding.[22] Patient attrition was described in detail in the four RCTs.[20-23] The primary outcomes were reported in the four RCTs.[20-23]

Three retrospective cohort studies adopted inclusion and exclusion criteria to select patients somewhat representative of the average target populations.[24-26] Gibson et al. selected hospitalized patients.[24] Nagata et al. and Shah et al. included patients visiting clinics.[25,26] Gibson et al. used a historical cohort before accelerated dosing was initiated in 2011as comparator.[24] Nagata et al. and Shah et al. used patients visiting the same centres as comparator.[25,26] The strength of the three retrospective cohort studies was the use of medical records as the source of information.[24-26] Though the limitation was that the information on the outcomes were also available to the investigators at the time of study.[24-26] Different cohorts were comparable in the sources of speciality care.[24-26] The information on outcomes was available from the medical records and could be identified at the time of study.[24-26] The lengths of follow-up seemed to be sufficient for outcomes to develop.[24-26] All eligible patients were included for analysis.[24-26]

The evidence-based guideline specified the overall objectives, health questions, intended populations, and target users.[27] A systematic literature search was conducted.[27] The health benefits, sides effects and risks were considered in formulating the recommendations.[27] The recommendations were specific and easy to identify with treatment options available.[27] Authors' conflict of interest was declared, however, the public and patients were not consulted for guideline development.[27] Further limitations included that the exact search terms were not published, only the limitation on data availability was considered by the authors, the mechanism to derive summaries was not well explained, and the review and validation of the guideline was not described.[27] There was no mechanism about updating

the review and facilitators and barriers to application, implementation recommendations, resource limitations, and monitoring methods were not addressed, however this does not affect the confidence in the recommendations themselves.[27] It remained unclear whether the funding agency had a role in the guideline development.[27]

Summary of Findings

1. *What is the clinical effectiveness of higher or more frequent versus standard dosing of biologics for the treatment of inflammatory bowel disease?*

Further detail regarding the outcomes reported in the primary studies is included in Appendix 4.

Adalimumab

Two poor-quality RCTs tested adalimumab in patients with Crohn's disease.[20,23] Colombel et al. compared two dosing strategies after the completion of induction therapy, 40 mg weekly or biweekly, to induction therapy only.[20] The induction included adalimumab 80 mg subcutaneously at week 0 and 40 mg at week 2.[20] After the stratification at week 4 according to the disease severity, individuals were assigned to different dosing strategies.[20] The median CDAI scores and the incidence of serious infectious adverse events were similar between the groups receiving standard/biweekly or weekly doses.[20] Other outcomes of the two dosing strategies were only compared to the group receiving induction only.[20] After 56 weeks of follow-up, it was found that the two dosing strategies continuously administered after induction therapy were associated with less disease severity in terms CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ), larger proportions of clinical remission, fewer flares and surgeries, and less hospitalization than induction only.[20]

The RCT by Watanabe et al. consisted of two parts, a double-blind randomized trial and an open-label maintenance trial.[23] After the double-blind randomized trial that compared biweekly adalimumab 40 mg with placebo, the participants that did not discontinue after 52 weeks of follow-up were randomly assigned to two of the subcohorts in the open-label trial.[23] Two doses were compared in the two subcohorts: adalimumab 40 mg or 80 mg biweekly.[23] The mean trough concentrations were comparable between these two doses.[23] It was found that approximately 30% of patients experienced clinical remission, defined as CDAI less than 150, with any of the adalimumab doses.[23] The improvement in quality of life could be found in patients treated with any doses of adalimumab.[23] Specifically, 75% of the eight patients experienced clinical remission after 48 weeks of dose escalation.[23] It was concluded that adalimumab was effective to maintain long-term clinical remission in Japanese patients with moderate to severe Crohn's diseae.[23]

Vedolizumab

Parikh et al. compared three doses of vedolizumab (2, 6, and 10 mg/kg) to placebo in a poor-quality dose-ranging RCT that recruited UC patients.[22] The authors reported that vedolizumab "demonstrated dose-proportional pharmacokinetics and maximally saturated α4β7 receptors over the tested dose range".[22] Vedolizumab was also well tolerated up to 10 mg/kg and there was no related adverse event or death observed.[22] Clinical response, defined as Partial Mayo Score less than or equal to two, could be found in over 50% of vedolizumab-treated patients and less than 34% of placebo-treated patients.[22] This study was not powered for clinical efficacy.[22]

Infliximab

Infliximab was evaluated in a fair-quality RCT in CD patients by D'Haens et al.[21] and two good-quality retrospective cohort studies in UC patients.[24,26]

D'Haens et al. had patients infused with standard induction doses and adjusted the doses based on three strategies.[21] Two dose-intensification strategies with different increase in magnitudes were based on a pre-specified multi-criteria algorithm, compared to one dose-increase strategy based on symptoms only.[21] It was found that an infliximab dose increase based on a multiple-criteria algorithm was as effective to achieve corticosteroid-free remission as a dose increase based on symptoms of CDAI greater than 220.[21]

In Gibson et al., three doses of infliximab given at weeks 0, 2, and 6 were compared with accelerated induction therapy adopted infusion of three doses within a median period of 24 days.[24] It was found that an accelerated infliximab induction strategy could effectively reduce the need for early colectomy in patients hospitalized for acute severe UC, compared to standard induction implemented before 2011.[24] This conclusion could be supported by lower rates of colectomy during induction therapy, longer time to colectomy, and subsequent need to colectomy among those completed induction therapy, compared to standard induction therapy.[24] Gibson et al. also found that the factors associated with successful induction therapy were level of albumin at the time of treatment, and accelerated induction therapy.[24]

Shah et al. used propensity scores to match patients receiving high doses with those given standard doses of infliximab.[26] Patients were retrospectively categorized based on the dose of the induction strategy while hospitalized, (5 mg/kg or 10 mg/kg at weeks 0, 2, and 6).[26] Compared to standard dose (at least one 5 mg/kg induction dose), a 10 mg/kg induction dose was associated with higher 30-day colectomy rates in patients hospitalized for acute UC.[26] The factors associated with the need for accelerated infliximab induction were female sex and low albumin levels in blood.[26]

2. *What is the clinical effectiveness of higher or more frequent than standard dosing versus switching biologics for the treatment of inflammatory bowel disease?*

Infliximab

Nagata et al. conducted a good-quality retrospective cohort study that compared intensified infliximab doses with switching to adalimumab.[25] CD patients were assigned to different doses according to physicians' judgment.[25] Nagata et al. assessed three interventions among patients who had already undergone standard maintenance therapy of infliximab (5mg/kg every 8 weeks).[25] It was found that doubling infliximab dose, shortening the interval of infliximab, and switching to adalimumab were associated with similar short-term and long-term effectiveness.[25] This was supported by the similar proportions of clinical response (decrease in the CDAI score of at least 25% or 70 points from baseline), clinical remission (CDAI score of less than 150), and sustained remission at 48 weeks.[25]

3. *What is the cost-effectiveness of higher or more frequent versus standard dosing of biologics for the treatment of inflammatory bowel disease?*

There were no cost-effectiveness studies regarding higher or more frequent versus standard dosing of biologics for the treatment of inflammatory bowel disease identified.

4. *What is the cost-effectiveness of higher or more frequent than standard dosing versus switching biologics for the treatment of inflammatory bowel disease?*

There were no cost-effectiveness studies regarding higher or more frequent than standard dosing versus switching biologics for the treatment of inflammatory bowel disease identified.

5. *What are the evidence-based guidelines regarding higher or more frequent than standard dosing of biologics for the treatment of inflammatory bowel disease?*

The evidence-based guideline recommends the use of anti-TNF agents (infliximab, adalimumab, certolizumab pegol) to treat Crohn's disease resistant to corticosteroids.[27] In addition to switching to other anti-TNF agents or drugs of other classes, dose escalation is considered an option for patients who have developed resistance to initial anti-TNF agents; the strength or grading of the evidence was not provided for this statement.[27] Further detail is included in Appendix 4.

Limitations

There are several limitations to this report. The samples sizes were small; six of the seven studies included fewer than 150 participants.[20-23] One was underpowered for clinical efficacy based on a power calculation.[22] There is considerable heterogeneity in the clinical settings and the dosing strategies. Only three types of biologics were tested: adalimumab, vedolizumab, and infliximab.[20-23] There were no studies on golimumab or ustekinumab. The RCTs were of fair to poor quality.[20-23] None of the RCTs described allocation concealment. Randomization methods were described only in one RCT.[21] The outcomes were not uniform across studies.[20-23] The group assignment was determined by physicians in a good-quality retrospective cohort study.[25] This practice might include selection bias. There might not be sufficient sample sizes to detect adverse events. Additionally, the relevant recommendation included in the guideline was not clearly associated with supporting evidence.

Conclusions and Implications for Decision or Policy Making

There is limited evidence to compare the effectiveness of different doses of the four biologics in patients with IBD. For adalimumab in CD patients, high and standard doses were tried and the two RCTs confirmed the effectiveness of adalimumab at standard or higher dosing.[20,23] However, there was insufficient sample size to test the significance of the differences between two doses.[20,23]

Three doses of vedolizumab were tested in the RCT on UC patients by Parikh et al.[22] This RCT confirmed that vedolizumab was well tolerated and verified the dose-response relationship in pharmacokinetics.[22] However, this RCT was also underpowered for effectiveness comparison.[22]

Infliximab was tested in one RCT on CD patients[21] and in two retrospective cohort studies on patients hospitalized for UC.[24,26] Dose intensification based on a multiple-criteria algorithm was similarly effective as symptom-based dose intensification in the RCT.[21] By comparing cohorts of different time periods, before 2011 or in 2011, Gibson et al. found that more frequent induction of three doses of infliximab were associated with less need for colectomy.[24] Though it was not mentioned whether there were other differences in clinical practices between the two time periods.[24] In contrast, Shah et al. found that high-dose

induction therapy was associated with higher 30-day colectomy.[26] These two retrospective cohort studies provided somewhat conflicting evidence.

In the retrospective cohort study by Nagata et al., doubling the infliximab dose and shortening the intervals of infliximab infusion were similarly effective to achieve clinical response, compared to switching to adalimumab between weeks 4 and 48 after initial treatment.[25]

The included studies were limited by small sample sizes, heterogeneity in study settings, diverse interventions, and different patient characteristics. The quality of the RCTs was fair to poor.[20-23] There was no information on allocation concealment in the RCTs.[20-23] There might not have been sufficient sample sizes to detect adverse events. The three retrospective cohort studies had the limitation that outcome data were available in the medical records at the time of study.[24-26]

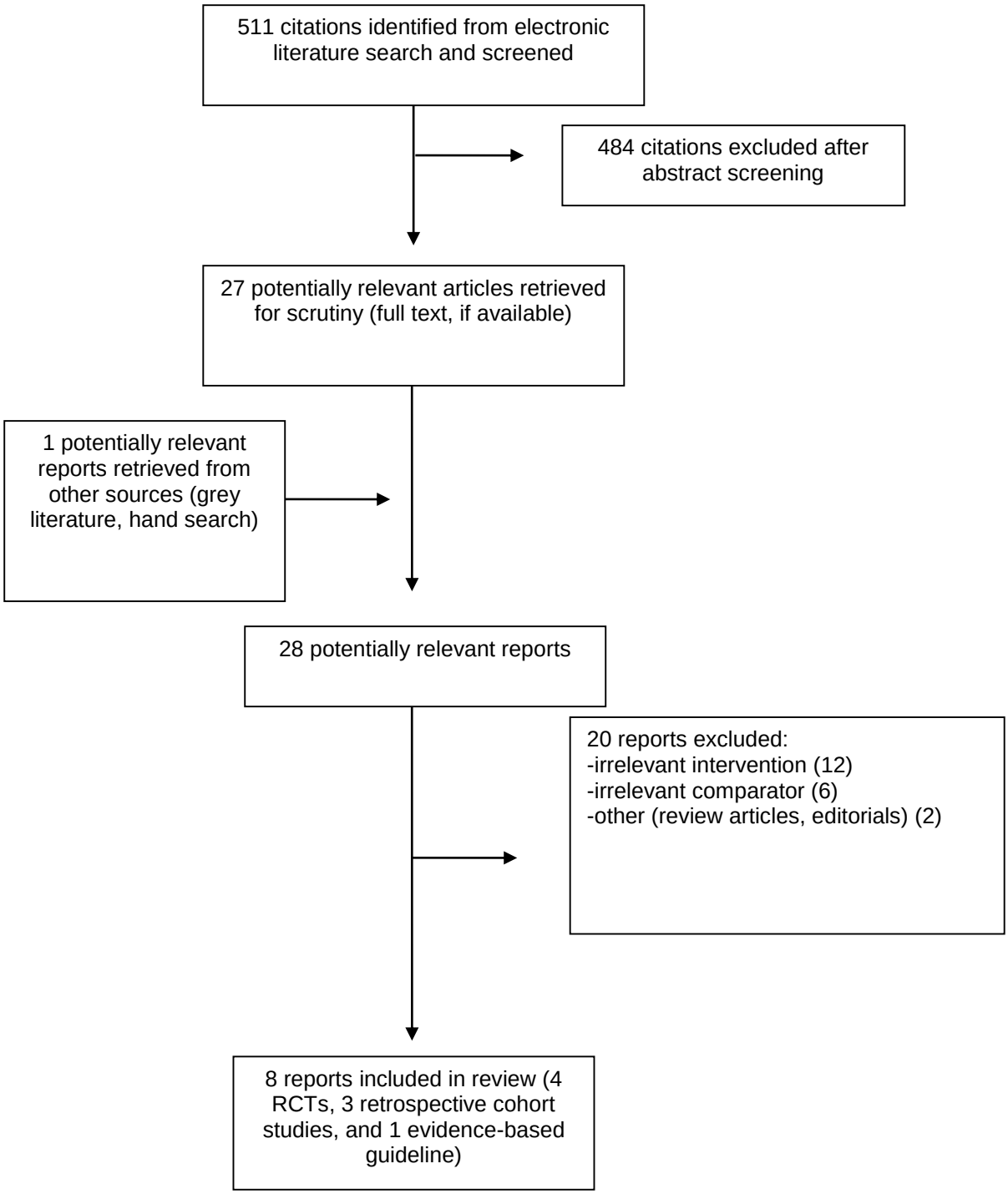
For policy making, there is limited evidence to guide both evidence-based policy development and clinical practice. The sample sizes for the trials on adalimumab and vedolizumab were not enough to compare the effectiveness of high and standard doses.[20,22,23] For infliximab, two of the retrospective cohort studies provided somewhat conflicting evidence regarding the needs for colectomy.[24,26] As Shah et al. [26] suggested, there is a need for prospective randomized studies to assess the effectiveness of different dosing strategies. Once clinical effectiveness is established, economic evaluations in the Canadian setting are needed in order to determine the cost-effectiveness for Canadians with IBD.

References

1. Hanauer SB. Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis.* 2006;12(suppl_1):S3-S9.
2. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, et al. The Epidemiology of inflammatory bowel disease in Canada: A population-based study. *Am J Gastroenterol.* 2006;101:1559.
3. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. *Harrison's principles of internal medicine, 18th Edition.* New York (NY): McGraw-Hill Education; 2011.
4. Switching from innovator to biosimilar (subsequent entry) infliximab: An updated review of the clinical effectiveness, cost-effectiveness, and guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/switching-innovator-biosimilar-subsequent-entry-infliximab-review-clinical-effectiveness-cost-1.
5. Cingoz O. Ustekinumab. *MAbs.* 2009;1(3):216-221.
6. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol.* 2015;12(9):537-545.
7. Puig L. Paradoxical reactions: Anti-tumor necrosis factor alpha agents, ustekinumab, secukinumab, ixekizumab, and others. *Curr Probl Dermatol.* 2018;53:49-63.
8. Razanskaite V, Bettey M, Downey L, Wright J, Callaghan J, Rush M, et al. Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme. *J Crohns Colitis.* 2017;11(6):690-696.
9. Restellini S, Chao CY, Lakatos PL, Aruljothy A, Aziz H, Kherad O, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. *Inflamm Bowel Dis.* 2018;24(7):1531-1538.
10. Chao YS, Brunel L, Faris P, Veugelers PJ. The importance of dose, frequency and duration of vitamin D supplementation for plasma 25-hydroxyvitamin D. *Nutrients.* 2013;5(10):4067-4078.
11. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology.* 2015;148(7):1320-1329.e1323.
12. Qiu Y, Chen BL, Mao R, Zhang SH, He Y, Zeng ZR, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFalpha dose intensification in Crohn's disease. *J Gastroenterol.* 2017;52(5):535-554.
13. PrHUMIRA® (adalimumab) [product monograph]. St-Laurent (QC): AbbVie Corporation; 2018: https://www.abbvie.ca/content/dam/abbviecorp/ca/en/docs/HUMIRA_PM_EN.pdf. Accessed 2018 Aug 27.
14. PrREMICADE® (infliximab): 100 mg/vial sterile lyophilized powder for solution [product monograph]. Toronto (ON): Janssen Inc.; 2018: https://www.janssen.com/canada/sites/www_janssen_com_canada/files/prod_files/live/remicade_cpm.pdf. Accessed 2018 Aug 23.
15. PrSIMPONI® (golimumab): 50 mg/4.0 mL solution for infusion [product monograph]. Toronto (ON): Janssen Inc.; 2018: http://www.janssen.com/canada/sites/www_janssen_com_canada/files/prod_files/live/simponi_cpm.pdf. Accessed 2018 Aug 27.
16. PrSTELARA® (ustekinumab) [product monograph]. Toronto (ON): Janssen Inc. ; 2018: http://www.janssen.com/canada/sites/www_janssen_com_canada/files/prod_files/live/stelara_cpm.pdf. Accessed 2018 Aug 27.
17. ENTYVIO® (vedolizumab): 300 mg/vial powder for concentrate for solution for infusion. Oakville (ON): Takeda Canada Inc.; 2017: https://www.takeda.com/siteassets/en-ca/home/what-we-do/our-medicines/entyvio-pm-eng-03-may-2017-c.pdf. Accessed 2018 Aug 27.
18. Higgins JPT, Green S, (editors). 12.4.1 Confidence intervals. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. London: The Cochrane Collaboration; 2011: https://handbook-5-1.cochrane.org/chapter_12/12_4_1_confidence_intervals.htm. Accessed 2018 Aug 27.
19. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): The Ottawa Hospital Research Institute; 2013: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2018 Aug 27.
20. Colombel JF, Sandborn WJ, Rutgeerts P, Kamm MA, Yu AP, Wu EQ, et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. *Am J Gastroenterol.* 2009;104(5):1170-1179.
21. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology.* 2018;154(5):1343-1351.e1341.
22. Parikh A, Leach T, Wyant T, Scholz C, Sankoh S, Mould DR, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis.* 2012;18(8):1470-1479.
23. Watanabe M, Hibi T, Mostafa NM, Chao J, Arora V, Camez A, et al. Long-term safety and efficacy of adalimumab in Japanese patients with moderate to severe Crohn's disease. *J Crohns Colitis.* 2014;8(11):1407-1416.

24. Gibson DJ, Heetun ZS, Redmond CE, Nanda KS, Keegan D, Byrne K, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol.* 2015;13(2):330-335.e331.
25. Nagata Y, Esaki M, Umeno J, Fuyuno Y, Ikegami K, Maehata Y, et al. Therapeutic strategy for Crohn's disease with a loss of response to infliximab: a single-center retrospective study. *Digestion.* 2015;91(1):50-56.
26. Shah SC, Naymagon S, Panchal HJ, Sands BE, Cohen BL, Dubinsky MC. Accelerated infliximab dosing increases 30-day colectomy in hospitalized ulcerative colitis patients: A propensity score analysis. *Inflamm Bowel Dis.* 2018;24(3):651-659.
27. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: Management of crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.
28. Consortium ANS. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 1800 Mth DD.
29. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet.* 2015;385(9976):1406-1417.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of included primary studies

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Colombel et al. 2009,[20] France	RCT, 3-arm, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial Setting: a multi-center study conducted at 92 sites in Europe, the United States, and Canada	778 patients randomized Inclusion criteria: 1) ages of 18 and 75 years 2) moderate-to-severe CD (defined by a CDAI score of 220 to 450) for at least 4 months prior to the start of the trial 3) not treated with other TNF antagonist therapies for at least 12 weeks prior to the start of trial	Induction treatment for all: 1. Week 0: open-label adalimumab 80 mg subcutaneously 2. Week 2: adalimumab 40 mg 3. Week 4: stratified by treatment response (decrease in CDAI of ≥ 70 points) Intervention: 1) adalimumab 40 mg weekly followed up to week 56	1) Induction only 2) adalimumab 40 mg every other week (standard dose) after induction therapy	1) CDAI scores at each visit 2) Clinical remission defined as CDAI < 150 3) Numbers of flares 4) Disease-specific, health-related quality of life, measured by the IBDQ at baseline and weeks 4, 12, 26, and 56 5) all-cause and CD-related hospitalization risks assessed based on the review of serious adverse events 6) All-cause hospitalization defined as any hospitalization 7) CD-related hospitalization due to adverse outcomes / complications related to CD or for the treatment of CD. 8) summaries of the patients' dispositions, reasons for discontinuation from the trial, and exposures to the study medication 9) adverse events 56 weeks of follow-up
D'Haens et al.	RCT, 3-arm, proof-of-	122 biologic-naïve	Induction common	Dose increase	Primary outcomes:

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
2018,[21] the Netherlands	concept, double-blind 27 centers from Belgium, France, and the Netherlands from July 2012 to September 2015 "a randomized controlled trial investigating tailored treatment with infliximab for active luminal Crohn's disease," TAILORIX trial	adult patients with active luminal CD (71 female, median age 29.8 years) Inclusion criteria: 1) adults with active luminal CD naïve to biologics 2) indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria 3) Disease activity by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 mg/g) and visible ulcers at baseline ileocolonoscopy. Infections were ruled out with fecal culture and an ELISA for Clostridium difficile toxins.	to all: infliximab intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Dose increase based on a pre-specified algorithm 1) every 8 weeks from week 14 to week 54 (end of the study period) as follows: infliximab dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) 2) infliximab dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2)	based on symptoms alone: Iinfliximab dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of infliximab (control group) (p 1345)	corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula. Secondary endpoints: proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CD Endoscopic Index of Severity <3) at weeks 12 and 54, and others Follow-up: weeks -3 to -1, 0, 2, 4, 6, 12, and 14, and every 4 weeks thereafter until week 54
Gibson et al. 2015,[24] Ireland	Retrospective cohort study At a single academic center from September 2005 through 2013	50 hospitalized patients who received infliximab for steroid-refractory acute severe ulcerative colitis Median ages: 34 (before 2011) and 38 (in 2011)	In 2011, an accelerated dosing induction strategy: patients received their 3 induction doses (5 mg/kg), with the timing of each infusion guided by clinical need (worsening	Before 2011, all patients requiring rescue infliximab received a standard dosing schedule of 5 mg/kg at weeks 0, 2, and 6. Responders continued to receive	1) improvement in symptoms or CRP, 2) rebound in inflammation during the induction period Follow-up: 56 days maximal

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		Inclusion criteria: 1) Hospitalized patients requiring rescue therapy with infliximab for acute severe ulcerative colitis 2) from a prospectively maintained database of patients with IBD (n = 3214). 3) not receiving rescue cyclosporine 4) diagnosis of UC by using standard clinical, endoscopic, radiographic, and histologic criteria 5) lower gastrointestinal endoscopy with biopsy on admission 6) laboratory parameters measured	symptoms or inflammatory markers), permitting induction dosing during a much shorter period.	maintenance dosing every 8 weeks.	
Nagata et al. 2015,[25] Japan	Retrospective cohort study, single-centre	N = 33 Age > 13 years Inclusion criteria: 1) clinical visits for CD between October 2004 to May 2014 2) history of infliximab infusion therapy Exclusion criteria: 1) clinical remission under standard infliximab maintenance therapy (every 8 weeks at a dose	Standard infliximab maintenance therapy (every 8 weeks at a dose of 5 mg/kg) 1) doubling the infliximab dose in 13 patients (DD group) 2) shortening the infliximab interval in 13 patients (SI group: every 4 to 7 weeks) according to the attending physician's judgment	1) switching to adalimumab in 7 patients (SA group; 160, 80 and 40 mg on week 1, 2, and 4 respectively)	1) clinical response, short-term or long-term: CDAI scores, CRP levels, and clinical remission Follow-up: 48 weeks

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		of 5 mg/kg) 2) discontinued infliximab therapy 3) lost to follow-up			
Parikh et al. 2012,[22] USA	RCT, phase 2, multi-centre 11 clinical sites in Canada and in the Russian Federation	N = 46 Inclusion criteria: 1) 18–70 years old 2) diagnosis of UC confirmed both endoscopically and/or histopathologically 3) minimum disease duration of 2 years 4) PMS of 1–7 at the time of screening 5) Acceptable treatment options: oral 5-aminosalicylates, corticosteroids, and/or purine antimetabolites or methotrexate. See the article for exclusion criteria	Vedolizumab 10 mg/kg 30 to 60 minute period on days 1, 15, 29, and 85	Placebo and vedolizumab 2 or 6 mg/kg	Primary outcomes: 1) pharmacokinetics, pharmacodynamics, and Immunogenicity including serum concentration of vedolizumab 2) safety: adverse events, vital signs, physical findings, clinical laboratory investigations, and electrocardiograms 3) efficacy: PMS, though underpowered Follow up: 253 days
Shah et al. 2018,[26] USA	Retrospective cohort study, propensity-score matching, single-centre	N = 146 Age range = 8 to 86 years Inclusion criteria: 1) diagnosis of UC confirmed before admission 2) hospitalized for acute UC 3) infliximab - naive before admission 4) at least 1 induction dose of infliximab during hospitalization	High dose: infliximab 10 mg/kg	Standard dose: infliximab 5 mg/kg	Primary outcomes: 1) 30-day colectomy rate from the time of admission Additional outcomes 1) length of stay 2) need for an additional infliximab 3) 90-day colectomy rate 4) 1-year colectomy rate 5) infectious and/or noninfectious complications

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Watanabe et al. 2014,[23] Japan	RCT, maintenance trial, partly double-blind and partly open-label, placebo control with a subcohort of dose escalation	N = 79 Inclusion criteria of induction trial: 1) older than 15 years but younger than 75 2) Crohn's disease for longer than 4 months 3) diagnosis confirmed by endoscopic or radiologic evaluation 4) CDAI of 220 to 450 Inclusion criteria of maintenance trial: 1) clinical response, defined as a decrease in CDAI of ≥70 points versus baseline (CR-70), at the end of the 4-week induction trial	1) all-adalimumab cohort: at least 1 injection of adalimumab 40 mg in the maintenance trial 2) adalimumab 80 mg every other week: dose-escalation subcohort (148-week follow-up subcohort)	3) adalimumab 40 mg every other week (148-week follow-up subcohort): patients who completed 148 weeks of follow-up after the first dose of adalimumab	Primary outcome: 1) proportion of patients achieving clinical remission (CDAI <150) 2) proportion of patients achieving CR-70 and CR-100 (defined as a decrease in CDAI score of at least 100 points compared with baseline) Other outcomes: 1) mean change from baseline in CDAI 2) Mean change from baseline in IOIBD, IBDQ, and SF-36 summary scores. Follow-up: 148 weeks

CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IBD =inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; IOIBD = International Organization of Inflammatory Bowel Disease; PMS = partial Mayo score; RCT = randomized controlled trial; TNF = tumor necrosis factor; UC = ulcerative colitis

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Lichtenstein et al. 2018[27]						
Health-care providers, adult patients with Crohn's	Diagnosis, biomarkers, treatment, and therapy for Crohn's disease Identified interventions including sulfasalazine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptourine, and anti-TNF agents (infliximab, adalimumab, certolizumab pegol)	No limitations on clinical outcomes Identified outcomes including hospitalization surgical complication, patient-reported outcomes, and mortality	Literature search using MEDLINE, EBASE, and SCOPUS; search terms not listed; data synthesis not mentioned	Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system	Descriptive summary statements	No mentioned

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of RCTs using the Cochrane Risk of Bias checklist[14]

Strengths	Limitations
Colombel et al. 2009[20]	
• Patients blinded to treatment • Physicians blinded to treatment • Attrition reported in Figure 1 • Missing data imputed by carrying forward last observations • Selective outcome reporting not likely	• Randomization method unclear • Allocation concealment not mentioned
D'Haens et al. 2018[21]	
• Randomization method described • Patients blinded to treatment • Physicians blinded to treatment • Attrition reported in Figure 1 • Selective outcome reporting not likely	• Allocation concealment not mentioned
Parikh et al. 2012[22]	
• Attrition reported in Figure 1 • Selective outcome reporting not likely	• Randomization method unclear • Allocation concealment not mentioned • Blinding not mentioned
Watanabe et al. 2014[23]	
• Patients blinded to treatment • Physicians blinded to treatment • Attrition reported in Figure 1 and 2 • Missing data imputed by carrying forward last observations • Selective outcome reporting not likely	• Randomization method unclear • Allocation concealment not mentioned

CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; LBC = liquid-based cytology; RCT = randomized controlled trial

Table 5: Strengths and Limitations of non-randomized studies using Newcastle-Ottawa scale[15]

Strengths	Limitations
Gibson et al. 2015[24]	
• Hospitalized patients sampled at an academic centre in Ireland • Historical controls before accelerated dosing implemented in 2011 • Exposure documented in medical records • Control cohort sampled in the same centre • Outcome documented in medical records • Follow-up adequate for acute control of disease flares • All patients included for outcome assessment	• Outcome of interest available at the start of the study
Nagata et al. 2015[25]	
• Patients visiting an academic centre sampled • Controls from the same centre • Exposure documented in medical records • Outcome documented in medical records • Follow-up for more than four weeks for assessing clinical response • Patient comparison available in Figure 1 and 2	• Outcome of interest available at the start of the study • Group assignment according to the attending physician's judgment
Shah et al. 2018[26]	
• Patients visiting an academic centre sampled • Controls from the same centre, matched according to propensity scores • Exposure documented in medical records • Outcome documented in medical records • Follow-up for 30 days for assessing the outcome • Patient comparison available in Figure 1 and 2	• Outcome of interest available at the start of the study

Table 6: Strengths and Limitations of Guidelines using AGREE II[28]

Item	Guideline
	Lichtenstein et al. 2018[27]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Strongly agree
2. The health question(s) covered by the guideline is (are) specifically described.	Partly agree
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Strongly agree
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Partly agree, health-care providers only
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Strongly disagree, no patient consultation mentioned
6. The target users of the guideline are clearly defined.	Strongly agree
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Strongly agree, MEDLINE, EBASE and SCOPUS searched
8. The criteria for selecting the evidence are clearly described.	Partly agree, the exact search terms not listed
9. The strengths and limitations of the body of evidence are clearly described.	Partly agree, limitation due to data availability mentioned
10. The methods for formulating the recommendations are clearly described.	Partly disagree, the mechanisms to derive summaries not explained
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Strongly agree
12. There is an explicit link between the recommendations and the supporting evidence.	Strongly agree
13. The guideline has been externally reviewed by experts prior to its publication.	Strongly disagree, no external review declared
14. A procedure for updating the guideline is provided.	Strongly disagree, no update procedures mentioned
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Strongly agree
16. The different options for management of the condition or health issue are clearly presented.	Strongly agree
17. Key recommendations are easily identifiable.	Strongly agree
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Strongly disagree
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Strongly disagree

Item	Guideline
	Lichtenstein et al. 2018[27]
20. The potential resource implications of applying the recommendations have been considered.	Strongly disagree
21. The guideline presents monitoring and/or auditing criteria.	Strongly disagree
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Strongly disagree, the influence of the funding agency not described
23. Competing interests of guideline development group members have been recorded and addressed.	Strongly agree

Appendix 4: Main Study Findings and Author's Conclusions

Table 7: Summary of Findings of RCTs

Main Study Findings	Author's Conclusions
Colombel et al. 2009[20]	
• CDAI and IBDQ: continuously high or standard doses of adalimumab (40 mg weekly or biweekly) associated with significantly greater improvements vs. the induction only/reinitiation group ($P < 0.05$) The median CDAI scores were similar between the groups receiving standard or weekly doses. • Clinical remission: at week 56, high or standard doses of adalimumab associated with a significantly greater percentage (51 % for every other week and 49 % for weekly) than induction only/reinitiation group (38 % $P < 0.05$). • Flares and surgeries: high or standard doses of adalimumab associated with fewer flares and fewer CD-related surgeries ($P < 0.05$) • CD-related and all-cause hospitalizations: high or standard doses of adalimumab associated with significantly lower risks than induction only/reinitiation group ($P < 0.05$) • Serious infectious adverse events: similar frequencies in the three treatment groups (3.9 % for biweekly dose, 4.7 % for weekly, and 5.0 % for induction only/reinitiation). • Subgroup analysis: "Approximately 85 % (34 / 40) of patients re-established response after switching to open-label weekly therapy." (p. 1174)	• Clinical response measured by CDAI scores and the incidence of serious infectious adverse effects were similar between weekly and biweekly doses • "continuous treatment with adalimumab was more effective than a strategy of induction dosing followed by reinitiation of adalimumab with clinical deterioration for maintenance of clinical remission, improved quality-of life outcomes, reduced flares, and a decrease in number of surgeries and risk of hospitalization" (p. 1171)
D'Haens et al. 2018[21]	
• Corticosteroid-free remission (CDAI <150): 15 (33%) of 45 patients in the DIS1 group, 10 (27%) of 37 patients in the DIS2 group, and 16 (40%) of 40 patients in the control group (P = .50) (p. 1343)	• "increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone" (p. 1343)
Parikh et al. 2012[22]	
• Serum concentration: monoexponential decline until concentrations reached 1 to 10 µg/mL, and nonlinear decline • Maximum serum concentration (Cmax) and area under the curve (AUC): increase approximately proportionally as a function of dose • Safety: well tolerated with no deaths and no adverse events leading to discontinuation • Clinical response: day 29 through day 253, over 50% for vedolizumab-treated patients and 22% and 33% for placebo-treated patients • Fecal calprotectin level: vedolizumab reduced the level compared with placebo" (p. 1470)	• "Vedolizumab demonstrated dose-proportional pharmacokinetics and maximally saturated α4β7 receptors over the tested dose range." • "Multiple dosing up to 10 mg/kg was well tolerated." • "Over the course of follow-up a greater proportion of patients treated with vedolizumab were in clinical response than those who were assigned to placebo." (p. 1470)
Watanabe et al. 2014[23]	
• Mean adalimumab trough concentrations: comparable between the patients receiving 40 mg biweekly and those receiving 80 mg biweekly	• Comparable mean trough concentrations for 40 mg and 80 mg biweekly after 52 weeks of treatment • "Adalimumab is effective for maintaining long-term clinical

Main Study Findings	Author's Conclusions
• Clinical remission rates: approximately 30% after 36 weeks of exposure to adalimumab and for the remainder of the study (35%, 33%, and 28% for weeks 48, 108, and 144, respectively) in the all-adalimumab cohort (n = 79) • Quality of life: an improvement in was also maintained over the same period in the all-adalimumab cohort (n = 79). • Dose-escalation: clinical remission rate 75% (6/8) clinical remission achieved in the dose-escalation subcohort (n = 40) 48 weeks after dose escalation • Safety: adalimumab tolerated and no deaths reported (p. 1408)	remission in Japanese patients with moderate to severe Crohn's disease" (p. 1408)

CDAI = Crohn's Disease Activity Index

Table 8: Summary of Findings of Non-Randomized Studies

Main Study Findings	Author's Conclusions
Gibson et al. 2015[29]	
• Baseline: no differences between groups in median levels of C-reactive protein, albumin, or hemoglobin • Rate of colectomy during induction therapy: significantly lower with the accelerated regimen (6.7%, 1 of 15) than with the standard regimen (40%, 14 of 35) (Fisher exact test, P = 0.039) • Time to colectomy: standard regimen associated with shorter time (log-rank test, P = 0.042) • Subsequent need for colectomy among patients who completed induction therapy: similar between the groups during the follow-up period • Factors associated with successful induction therapy based on multivariate analysis: level of albumin (g/L) when the treatment began (P = 0.003) and the accelerated dosing regimen (P = 0.03).	• "In patients with acute severe UC, an accelerated infliximab induction strategy reduces the need for early colectomy."(p. 330)
Nagata et al. 2015[25]	
• Clinical response: 62% in the DD group, 77% in the SI group, and 57% in the SA group (p = 0.59) • Rate of clinical remission: 54% in the DD group, 62% in the SI group, and 43% in the SA group (p = 0.90) • Rate of sustained remission at 48 weeks: 44% in the DD group, 54% in the SI group and 33% in the SA group (p = 0.88)	• "The short- and long-term efficacy of doubling the dose of infliximab, shortening the interval of infliximab or switching to adalimumab is similar for CD patients who no longer respond to infliximab."(p. 50)
Shah et al. 2018[26]	
• Colectomy: 25 (17.1%) treated with colectomy by 30 days, 33 (22.6%) by 90 days, and 41 (28.1%) by 1 year in 146 (120 SD/26 HD) patients • Colectomy rates and length of stay: similar in 21 propensity score matched dyads (n = 42) treated with SD or HD • Accelerated infliximab induction needs: more SD patients compared to HD patients (23.8% vs. 0%, P = 0.048) • Progression to colectomy: more rapidly in AD patients within 30 days compared to non-AD (P = 0.001) • Odds of needing accelerated infliximab induction: female sex and hypoalbuminemia significantly associated with increased odds on both univariate and multivariate analyses.	• "receiving accelerated infliximab dosing after an initial SD infusion was associated with significantly higher 30-day colectomy rates in hospitalized acute UC patients." • "The most effective dosing strategy in this population remains unclear and prospective randomized studies are needed."(p. 651)

AD = accelerated dose; CD = Crohn's disease; DD = doubling dose; HD= high dose; SA = switching to adalimumab; SD = standard dose; SI = shortening interval; UC = ulcerative colitis

Table 9: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Lichtenstein et al. 2018[27]	
• Recommendation 24: "anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids (strong recommendation, moderate level of evidence)" • Recommendation 25: "anti-TNF agents should be given for Crohn's disease refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence)" • Recommendation 26: "combination therapy of infliximab with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab alone in patients who are naive to those agents (strong recommendation, high level of evidence)" (p. 484)	In addition to switching to other anti-TNF agents or drugs of other classes, dose-escalation could considered as an option for secondary non-responders (those who developed resistance to initial anti-TNF agents), but there was no reference to support this statement (see page 508 for details) Biosimilar anti-TNF agents • Summary statement 43: "Biosimilar infliximab and biosimilar adalimumab are effective treatments for patients with moderate-to-severe Crohn's disease and can be used for de novo induction and maintenance therapy • Summary statement 44: "Insufficient data exist to support the safety and efficacy of switching patients in stable disease maintenance from one biosimilar to another of the same biosimilar molecule" (p. 486)

TNF = tumor necrosis factor

Appendix 5: Additional References of Potential Interest

Non-systematic review

Hindryckx P, Novak G, Vande Casteele N, et al. Review article: dose optimisation of infliximab for acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2017;45(5):617-630.

Studies comparing standard doses with lower doses

Dretzke J, Edlin R, Round J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. *Health Technol Assess.* 2011;15(6):1-244.

Dubinsky MC, Rosh J, Faubion WA, Jr., et al. Efficacy and Safety of Escalation of Adalimumab Therapy to Weekly Dosing in Pediatric Patients with Crohn's Disease. *Inflamm Bowel Dis.* 2016;22(4):886-893.

Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology.* 2012;143(2):365-374.e362.

Jiang XL, Cui HF, Gao J, Fan H. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. *J Clin Gastroenterol.* 2015;49(7):582-588.

Pouillon L, Ferrante M, Van Assche G, et al. Mucosal Healing and Long-term Outcomes of Patients With Inflammatory Bowel Diseases Receiving Clinic-Based vs Trough Concentration-Based Dosing of Infliximab. *Clin Gastroenterol Hepatol.* 2018;16(8):1276-1283.e1271.

Sharma S, Eckert D, Hyams JS, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis.* 2015;21(4):783-792.

Wu KC, Ran ZH, Gao X, et al. Adalimumab induction and maintenance therapy achieve clinical remission and response in Chinese patients with Crohn's disease. *Intestinal research.* 2016;14(2):152-163.

Studies on individualized dose management

Steenholdt C, Brynskov J, Thomsen OO, et al. Individualized Therapy Is a Long-Term Cost-Effective Method Compared to Dose Intensification in Crohn's Disease Patients Failing Infliximab. *Dig Dis Sci.* 2015;60(9):2762-2770.

Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut.* 2014;63(6):919-927.

Minar P, Saeed SA, Afreen M, Kim MO, Denson LA. Practical Use of Infliximab Concentration Monitoring in Pediatric Crohn Disease. *J Pediatr Gastroenterol Nutr.* 2016;62(5):715-722.

Ghaly S, Costello S, Beswick L, et al. Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response. *Intern Med J.* 2015;45(2):170-177