Medications on the Horizon for the Treatment of Moderate to Severe Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract for which there is no cure. IBD encompasses the main disease subtypes of Crohn's disease (CD) and ulcerative colitis (UC).[1] IBD follows a heterogeneous, relapsing and remitting course that is characterised by symptoms of diarrhoea, abdominal pain, rectal bleeding, faecal urgency and incontinence, and fatigue.[2,3] Other manifestations of IBD include anaemia, perianal fistulae in CD, colorectal cancer, and intestinal failure.[2,3] Thus, IBD is a progressive disease that can lead to bowel damage and disability and requires lifelong monitoring.

The epidemiology and burden of IBD

The prevalence of IBD has increased worldwide over the last 30 years.[4] The incidence of IBD is highest in the western world and ranges between 10.6/100,000/year to 29.3/100,000/year for CD and 17.4/100,000/year to 24.3/100,000/year.[2,3,5] Over 20,000 New Zealanders currently suffer from IBD and the burden is expected to double by 2030 due to a rising incidence and compounding prevalence.[6–8] There are also increasing rates of IBD amongst Māori compared to those seen historically (3-7% vs. 1%).[9–11] The peak age of onset of CD is between 20-40 years, with a smaller peak between 50-60 years.[3] For UC, the peak age of onset is between 30-40 years.[2] Thus, individuals with IBD live the majority of their lives with their disease.

IBD is a progressive disease associated with significant morbidity from cancer, infection, thrombosis and suicide.[12–15] IBD can also result in increased rates of hospitalisation for the treatment of disease relapses, surgical interventions, and to manage disease related- and treatment related-complications.[16] Annual IBD hospitalisation rates in New Zealand are between 20-28/100,000 persons.[8,10,17] Recurrent flares of inflammation in IBD lead to intestinal fibrosis with stricture and fistula formation (in CD), increasing the risk of surgery and stoma formation in young patients.[18,19] Chronic gastrointestinal inflammation also increases the risk of colorectal cancer with higher rates of this malignancy (1%, 3% and 7% at 10, 20 and 30 years, respectively) observed in individuals with colonic CD and UC compared to the general population (2-3 fold increase in risk).[20–22] Up to a third of individuals with IBD also have symptoms of significant anxiety and depression.[23] Patients with IBD are less able to undertake education[24] and have limitations in their ability to engage in employment.[25,26] Workplaces are often not able to accommodate aspects of IBD disability.[27,28] Thus, IBD can result in a significantly disabling disease course that has a major impact on the lives of patients, their whanau and society.

Principles of treating IBD

Treatments for IBD include diet and nutritional therapies, medications, and surgery.[29–31] Drugs to treat IBD include aminosalicylates (5-ASA; which result in anti-inflammatory actions by downregulating inflammatory cytokine production and cellular proliferation),[32] glucocorticoids (that inhibit the transcription of DNA sequences coding for inflammatory proteins and reduce signalling of these proteins through their interaction with transcription factors such as nuclear factor-kB),[33] immunomodulators such as methotrexate (inhibit nucleotide synthesis and cellular proliferation)[34] and thiopurines (suppress proinflammatory T lymphocyte responses),[35] and biological agents.[29]

Biological therapies that are efficacious for the treatment of IBD include anti-tumour necrosis factor antibodies (anti-TNFα; Infliximab and Adalimumab),[36–39] gut selective monoclonal antibodies to $\alpha_4ß_7$ integrin that reduce recruitment of T-cells and proinflammatory monocytes to the intestine (Vedolizumab),[40,41] and antagonists of IL-12 and IL-23 (Ustekinumab).[42,43] Newer biological agents for the treatment of moderate to severe IBD also include Risankizumab, Guselkumab and Mirikizumab, which are monoclonal antibodies that bind to the p19 subunit of IL-23 to antagonise the proinflammatory actions of this pathway.[44–46] These form of medications require either intravenous or subcutaneous dosing. The availability of infusion centres for intravenous

administration of IBD medications is highly variable throughout Aotearoa/New Zealand raising concerns surrounding regional inequities in access to these medications. Oral small molecule inhibitors have also been shown to be effective treatments for moderate to severe forms of IBD such as Ozanimod and Etrasimod (sphingosine 1-phosphate receptor modulators that limit tracking of lymphocytes to the intestinal epithelium),[47,48] and Tofacitinib, Filgotinib and Upadacitinib (janus kinase inhibitors (JAKi) that inhibit transduction of proinflammatory cytokine signalling pathways).[49–53] The goal of medical therapies for IBD is to target intestinal inflammation with the aim of achieving endoscopic and histological remission of disease.[54] Achieving gut mucosal healing has been associated with a reduced risk for future relapses, IBD-related surgeries and hospitalisations.[54,55] Disease activity in IBD is best assessed objectively through the use of endoscopic and radiological (magnetic resonance enterography, intestinal ultrasound) examination and the use of biomarkers such as C-reactive protein and faecal calprotectin.[54]

The standard therapeutic ladder for IBD medications usually commences with aminosalicylates (5-ASA agents) for mild mucosal inflammation and immunomodulators for moderate disease.[56] Biological therapies are usually reserved to treat moderate to severely active IBD but approximately 30% of patients (primary non-response) do not have an initial response to these treatments with up to 50% losing response over time (secondary non-response).[57,58] In these patients, response to therapy is best re-captured by switching to another therapeutic class in the setting of adequate drug concentrations and in the absence anti-drug antibodies.[57–59] As IBD is often diagnosed in adolescence and early adulthood, patients often require multiple lines of therapy over their lifetime.[2,3] Additionally, the optimal order for the use of biological therapies (sequencing of biological agents) is a growing field of research as efficacy of the first biological agent appears to be significantly greater than subsequent lines of therapy.[57–61] The major driver for the increasing direct health costs for caring for patients with IBD is the use of biological therapies.[62,63] However, the cost of these agents should be weighed against their potential utility at reducing the indirect costs of IBD and rates of healthcare utilisation from future hospital admissions, surgeries and outpatient visits.[63] Effective management of IBD can lead to improved work-related productivity, quality of life and societal contributions.[26,27,63,64] Additional cost savings can be gained by substituting expensive therapies which have minimal therapeutic response to those that are similarly priced but result in meaningful clinical improvement.

Medications on the horizon for patients with IBD in Aotearoa/New Zealand

Improved understanding of the pathogenesis of CD and UC will advance endeavours to break the therapeutic ceiling that exists with currently available classes of biological medications for the treatment of inflammatory bowel disease (IBD).[65] The following section will aim to highlight agents that have shown efficacy in the treatment of moderate-to-severe IBD that are not currently available in New Zealand but are in clinical use in other parts of the world or are in late-stage drug development. Pertinent results for these agents from Phase 3 randomized, controlled studies are summarised in Table 1. These data are from adult patients with IBD and efficacy and safety profiles of these newer biological medications on paediatric patients with IBD is still being investigated.

Janus kinase (JAK) inhibitors – Tofacitinib, Upadacitinib, Filgotinib

Janus kinase inhibitors (JAKi) are being increasingly used for the treatment of IBD and other immune-mediated disorders. These are oral, small molecule drugs that target the JAK-STAT pathway, have a rapid onset of action, short half-life and lack features of immunogenicity.[66,67] Tofacitinib, a pan-JAK inhibitor with higher inhibitory activity for JAK1 and JAK3 is approved for use for induction and maintenance in moderate-severe ulcerative colitis in many parts of the world.[49,52] JAKi can be effective therapies for moderate-severe IBD that is refractory to treatment with prior biological agents; however, the major concerns regarding Tofacitinib are in relation to excess rates of serious infections, herpes zoster infections and adverse cardiovascular events (Figure 1).[68]

Upadacitinib (UPA) is a JAK1 selective oral small molecule drug that has recently been approved for use in both UC and CD following the results of the pivotal phase 3 studies which demonstrated superior efficacy of UPA with placebo.[50,51] The results from these studies suggest a benefit with UPA for the treatment of extraintestinal manifestations that requires ongoing investigation in the long-term extension phase of these trials.[51,69] Filgotinib is an oral JAK1 preferential inhibitor that has also shown benefit as induction and maintenance treatment in moderate-severe UC.[53] JAK1 selectivity is hoped to limit the off-target effects of JAKi to improve their overall safety profile.[70] Early safety data from the U-ACHIEVE, U-ENDURE, and SELECTION trials have shown reduced rates of adverse events with JAK1 selective inhibitors compared to those seen for tofacitinib.[50,51,53] The utility and safety of JAKi in for the treatment of moderate to severe IBD in paediatric patients remains to be determined.

Given the rapid onset of action of JAKi and the reduced susceptibility of small molecules to drug loss associated with hypalbuminaemia and colonic protein loss, there is ongoing debate regarding their utility in the management of acute severe colitis.[71] This is not yet an approved indication for this class of medication but multiple case series have highlighted the benefits of tofacitinib as rescue therapy for acute severe colitis, including in those with corticosteroid and anti-TNF refractory disease.[71–74] Larger, prospective trials are required before this can be considered an approved indication for Jaki.

Subcutaneous infliximab and vedolizumab

Infliximab was the first biological agent approved for use in IBD but requires regular intravenous infusions which may be inconvenient for patients and challenging to facilitate in healthcare systems.[39,75,76] Biosimilars to infliximab such as CT-P13 have subsequently been developed which have shown efficacy in IBD.[77–79] Subcutaneous versions of this biosimilar (CT-P13 SC) have been shown to have a stable pharmacokinetic profile with reduced rates of clinically significant immunogenicity (neutralising antibodies) compared to intravenous preparations.[78,80] The efficacy of CT-P13 SC for maintenance therapy (following intravenous induction doses at Weeks 0, 2 and 6) is under ongoing investigation in the global phase 3 LIBERTY-CD and LIBERTY-UC trials.[81,82]

Vedolizumab offers gut-selective blockade of lymphocyte trafficking (anti-integrin) that is administered intravenously and currently available for use as a first or second line agent for CD and UC in New Zealand.[40,41] Subcutaneous preparations of vedolizumab (q2wkly after intravenous induction at Weeks 0 and 2) have been shown to be effective maintenance therapy for individuals with moderate-to-severe UC and CD.[83,84] There were no new safety concerns reported with subcutaneous preparations in these trials and efficacy was greater in anti-TNF naïve patients compared to those previously exposed to anti-TNF agents.[83,84]

Interleukin-23 (IL-23) p19 inhibitors – Guselkumab, Risankizumab, Mirikizumab

Interleukin-23 is believed to maintain the intestinal inflammation seen in IBD.[85] Blockade of this pathway is exploited by medications such as ustekinumab that are currently available for use in New Zealand as second line biologic agents for moderate-severe CD and UC.[42,43] There has been considerable drug development in relation to antagonism of the p19 subunit of IL23 in inflammatory disorders including IBD. Risankizumab, mirikizumab and guselkumab are all in various stages of phase 2/3 development for CD and UC.[44–46] These agents require intravenous induction followed by subcutaneous injections for maintenance therapy at various dose intervals (Risankizumab – q8wk, Mirikizumab – q4wk, Guselkumab – q8wk). Most of the cohorts recruited in these studies required an inadequate response or intolerance to prior conventional or biological therapies. Early safety data from these studies show limited serious adverse events compared with placebo.[44–46,86] The utility of these agents in the treatment of fistulising and perianal Crohn's disease and extra-intestinal manifestations remains to be determined.

S1P receptor modulators – Ozanimod, Etrasimod

Sphingosine-1-phosphate (S1P) receptor modulation leads to internalization of S1P1 receptors in lymphocytes and prevents mobilization of lymphocytes to inflammatory sites.[87,88] Ozanimod and etrasimod are oral S1P receptor modulators that have been shown to be effective for induction and maintenance therapy in patients with moderate-severe UC, including individuals with previous exposure to other biological agents.[47,48] Although these agents are well tolerated in general, bradycardia, lymphopenia, macular oedema (although rare), and liver transaminitis are the main safety issues that require consideration.[47,48,89,90] These agents are currently under ongoing investigation for the treatment of moderate-severe CD.

Combining biological therapies

Despite the increasing number of biological and small molecule agents that have been developed for the treatment of IBD over the past 20 years, a very real therapeutic ceiling exists regarding their efficacy. Clinical remission rates for medical IBD therapies seldom exceeds a therapeutic delta (difference between placebo and study drug) of 40%, except for UPA for moderate-severe UC.[50,65] Randomized, controlled studies are currently underway to examine the benefit of using various combinations of biological agents. Early reports from the VEGA study which investigated guselkumab plus golimumab (anti-TNF agent) combination therapy versus each of these agents as monotherapy in patients with moderate-severe UC showed some benefits with the combination strategy.[91] In this study, rates of endoscopic improvement, endoscopic normalisation and mucosal healing (histological remission and endoscopic normalisation) were greater at 38 weeks of follow up in the combination group compared to those who received monotherapy.[91] Although rates of clinical remission did not differ significantly between groups, this endpoint requires ongoing investigation and follow-up to assess the robustness of treatment responses in each arm.[91] Importantly, rates of adverse events were similar between groups suggesting that combination strategies may be safe and warrant ongoing investigation.[91]

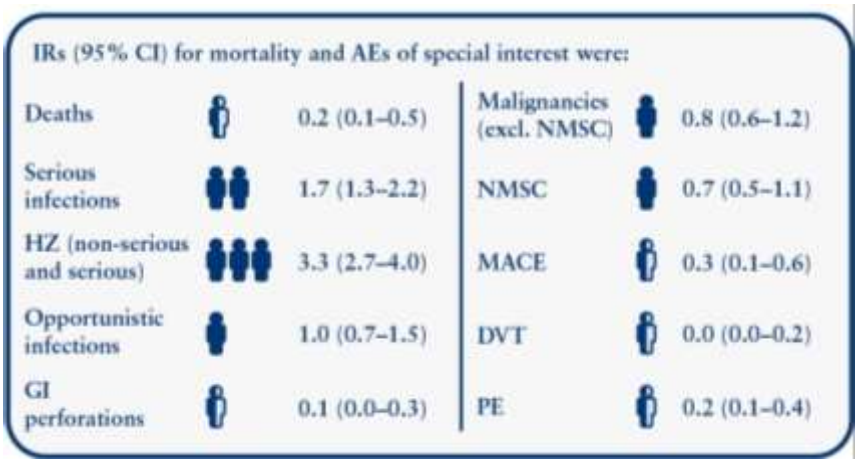
Table 1. Data from Phase 3, randomized, controlled studies of medications for the treatment of moderate-to-severe inflammatory bowel disease that are on the horizon for New Zealand.

Therapeutic agent	*Onset of action*	*Clinical remission rates*	*Endoscopic remission rates*	*Use for extraintestinal manifestations*	*Safety issues*
Subcutaneous infliximab biosimilar (CTP-13 SC) – Ulcerative colitis[81]	Weeks	Wk 54 - Placebo 20.8% - 120mg 43.2%	Not yet reported	Unclear (+ for infliximab IV)	• No new safety signals
Subcutaneous infliximab biosimilar (CTP-13 SC) – Crohn's disease[82]	Weeks	Wk 54 - Placebo 32.1% - 120mg 62.3%	Wk 54 - Placebo 10.7% - 120mg 34.6%	Unclear (+ for infliximab IV)	• No new safety signals
Subcutaneous vedolizumab – Ulcerative colitis[83]	Weeks to months	Wk 52 - Placebo 14.3% - IV 42.6% - SC 46.2%	Wk 52 - Placebo 12.5% - IV 27.8% - SC 29.2%	-	• No new safety signals
Subcutaneous vedolizumab – Crohn's disease[84]	Weeks to months	Wk 52 - Placebo 34.3% - SC 48%	Not reported	-	• No new safety signals
Tofacitinib (oral) – Ulcerative colitis[49,68,92,93]	Days to weeks	Wk 52 - Placebo 11% - 5mg BD 34.3% - 10mg BD 40.6%	Wk 52 - Placebo 4.0% - 5mg BD 14.6% - 10mg BD 16.8%	+	• Serious infection • Herpes zoster • Major cardiovascular events • Thromboembolic events
Upadacitinib (oral) – Ulcerative colitis[50,69]	Days to weeks	Wk 52 - Placebo 12% - 15mg 42% - 30mg 52%	Wk 52 - Placebo 6% - 15mg 24% - 30mg 26%	+	• No significant differences to placebo although no long term follow up available
Upadacitinib (oral) – Crohn's disease[51]	Days to weeks	Wk 52 - Placebo 15.1% - 15mg 37.3% - 30mg 47.6%	Wk 52 - Placebo 5.5% - 15mg 19.1% - 30mg 28.6%	+	• Herpes zoster • Neutropenia • Hepatic dysfunction
Filgotinib (oral) – Ulcerative colitis[53,94]	Weeks	Wk 58 - Placebo 11.2-13.5% - 100mg 23.8% - 200mg 37.2%	Wk 58 - Placebo 6.1-7.9% - 100mg 8.7% - 200mg 18.1%	+ (arthritis)	• No significant differences to placebo although long-term follow up not yet available
Risankizumab (IV/SC) – Crohn's disease[44]	Weeks	Wk 52 - Placebo 40.9% - 180mg 55.4% - 360mg 52.5%	Wk 52 - Placebo 13% - 180mg 30% - 360mg 39%	Unclear	• No significant differences to placebo
Mirikizumab (IV/SC)	Weeks	Wk 40	Wk 40	Unclear	• Infusion/injection reaction

Therapeutic agent	*Onset of action*	*Clinical remission rates*	*Endoscopic remission rates*	*Use for extraintestinal manifestations*	*Safety issues*
– Ulcerative colitis[86]		- Placebo 25.1% - 200mg 49.1%	- Placebo 29.1% - 200mg 58.6%		• Deranged liver function tests • Higher rates of depression noted in Mirikizumab group • Increased rates of opportunistic infections in Mirikizumab group vs. placebo
Ozanimod (oral) **– Ulcerative colitis**[47,89,95]	Weeks to months	Wk 52 - Placebo 18.5% - 1mg 37.0%	Mucosal healing (Wk52) - Placebo 14.1% - 1mg 29.6%	Unclear	• Bradycardia • Lymphopenia • Macular oedema • Elevated liver transaminases
Etrasimod (oral) **– Ulcerative colitis**[48]	Weeks	Wk 52 - Placebo 7% - 2mg 32%	Endoscopic improvement-histological remission (Wk 52) - Placebo 10% - 2mg 27%	Unclear	• Bradycardia • Lymphopenia • Macular oedema • Elevated liver transaminases

Wk, week; IV, intravenous; SC, subcutaneous

Figure 1. Safety profile of Tofacitinib for the treatment of ulcerative colitis in individuals with up to 7.8 years of safety data.[68]



IR, incidence rate; HZ, herpes zoster; GI, gastrointestinal; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event; DVT, deep vein thrombosis; PE, pulmonary embolism.

Adapted from: Sandborn WJ, D'Haens GR, Sands BE, et al. Tofacitinib for the Treatment of Ulcerative Colitis: An Integrated Summary of up to 7.8 Years of Safety Data from the Global Clinical Programme. J Crohns Colitis. 2023 Mar 1;17(3):338–51.

References:

1. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. N Engl J Med. 2020 Dec 31;383(27):2652–64.

2. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. The Lancet. 2017 Apr 29;389(10080):1756–70.

3. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. The Lancet. 2017 Apr;389(10080):1741–55.

4. Alatab S, Sepanlou SG, Ikuta K, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):17–30.

5. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015 Dec;12(12):720–7.

6. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021 Jan;18(1):56–66.

7. Kahui S, Snively S, Ternent M. Reducing the Growing Burden of Inflammatory Bowel Disease in New Zealand [Internet]. Wellington, New Zealand: Crohn's and Colitis Foundation Charitable Trust; 2017 [cited 2020 Jul 7]. Available from: https://issuu.com/crohnsandcolitisnz/docs/271017_master_formatted_bod_report_

8. Su HY, Gupta V, Day AS, Gearry RB. Rising Incidence of Inflammatory Bowel Disease in Canterbury, New Zealand. Inflamm Bowel Dis. 2016;22(9):2238–44.

9. Seleq S, Weilert F, Fulforth J. Inflammatory Bowel Disease (IBD) in Waikato, New Zealand: Incidence and Prevalence. Intern Med J [Internet]. [cited 2023 Mar 23];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.16072

10. Gearry RB, Richardson A, Frampton CMA, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. Inflamm Bowel Dis. 2006 Oct;12(10):936–43.

11. Qiu M, Patel RN, Kerrison C, Gearry RB. Low but increasing rates of inflammatory bowel disease in Māori: a report from Lakes District Health Board IBD. N Z Med J. 2022 May 20;135(1555):99–105.

12. Malham M, Jakobsen C, Paerregaard A, Virta LJ, Kolho KL, Wewer V. The incidence of cancer and mortality in paediatric onset inflammatory bowel disease in Denmark and Finland during a 23-year period: a population-based study. Aliment Pharmacol Ther. 2019 Jul;50(1):33–9.

13. Opstelten JL, Vaartjes I, Bots ML, Oldenburg B. Mortality After First Hospital Admission for Inflammatory Bowel Disease: A Nationwide Registry Linkage Study. Inflamm Bowel Dis. 2019 Oct;25(10):1692–9.

14. Jussila A, Virta LJ, Pukkala E, Färkkilä MA. Mortality and causes of death in patients with inflammatory bowel disease: a nationwide register study in Finland. J Crohns Colitis. 2014 Sep;8(9):1088–96.

15. Banerjee T, Gearry R. Editorial: suicide and IBD-a call to action. Aliment Pharmacol Ther. 2019 Jul;50(1):105–6.

16. Buie MJ, Quan J, Windsor JW, et al. Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review With Temporal Analyses. Clin Gastroenterol Hepatol. 2022 Jul;S154235652200670X.

17. King JA, Underwood FE, Panaccione N, et al. Trends in hospitalisation rates for inflammatory bowel disease in western versus newly industrialised countries: a population-based study of countries in the Organisation for Economic Co-operation and Development. Lancet Gastroenterol Hepatol. 2019 Apr;4(4):287–95.

18. Eglinton T, Reilly M, Chang C, Barclay M, Frizelle F, Gearry R. Ileal disease is associated with surgery for perianal disease in a population-based Crohn's disease cohort. Br J Surg. 2010 Jul;97(7):1103–9.

19. Eglinton TW, Gearry RB. Clinical factors predicting disease course in Crohn's disease. Expert Rev Clin Immunol. 2010 Jan 1;6(1):41–5.

20. Olén O, Erichsen R, Sachs MC, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. The Lancet. 2020 Jan;395(10218):123–31.

21. Olén O, Erichsen R, Sachs MC, et al. Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. Lancet Gastroenterol Hepatol. 2020 May;5(5):475–84.

22. Shah SC, Itzkowitz SH. Colorectal Cancer in Inflammatory Bowel Disease: Mechanisms and Management. Gastroenterology. 2022 Mar 1;162(3):715-730.e3.

23. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021 May 1;6(5):359–70.

24. Eloi C, Foulon G, Bridoux-Henno L, et al. Inflammatory Bowel Diseases and School Absenteeism. J Pediatr Gastroenterol Nutr. 2019 Apr;68(4):541–6.

25. Gearry RB, Frampton C, Inns S, Poppelwell D, Rademaker M, Suppiah R. VITALITY: impact of adalimumab on health and disability outcomes in patients with Crohn's disease, rheumatoid arthritis, or psoriasis treated in clinical practice in New Zealand. Curr Med Res Opin. 2019 Oct 3;35(10):1837–46.

26. Walter E, Hausberger SC, Groß E, Siebert U. Health-related quality of life, work productivity and costs related to patients with inflammatory bowel disease in Austria. J Med Econ. 2020 Oct;23(10):1061–71.

27. Paulides E, Daker C, Frampton C, et al. Overcoming Workplace Disability in IBD Patients: An Observational Study. Inflamm Intest Dis. 2020;5(2):84–92.

28. Paulides E, Cornelissen D, Vries AC de, Woude CJ van der. Inflammatory bowel disease negatively impacts household and family life. Frontline Gastroenterol. 2022 Sep 1;13(5):402–8.

29. Baumgart DC, Le Berre C. Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease. N Engl J Med. 2021 Sep 30;385(14):1302–15.

30. Bemelman WA, S-ECCO collaborators. Evolving Role of IBD Surgery. J Crohns Colitis. 2018 Jul 30;12(8):1005–7.

31. Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. Nutrients. 2019 Apr 26;11(5):947.

32. Desreumaux P, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid – new evidence. Aliment Pharmacol Ther. 2006;24(s1):2–9.

33. Irving PM, Gearry RB, Sparrow MP, Gibson PR. Review article: appropriate use of corticosteroids in Crohn's disease. Aliment Pharmacol Ther. 2007 Aug 1;26(3):313–29.

34. Herfarth HH, Kappelman MD, Long MD, Isaacs KL. Use of methotrexate in the treatment of inflammatory bowel diseases (IBD). Inflamm Bowel Dis. 2016 Jan;22(1):224–33.

35. de Boer NKH, Peyrin-Biroulet L, Jharap B, et al. Thiopurines in Inflammatory Bowel Disease: New Findings and Perspectives. J Crohns Colitis. 2018 Apr 27;12(5):610–20.

36. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007 Jan;132(1):52–65.

37. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2012 Feb 1;142(2):257-265.e3.

38. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2005 Dec 8;353(23):2462–76.

39. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. The Lancet. 2002 May 4;359(9317):1541–9.

40. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2013 Aug 22;369(8):699–710.

41. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2013 Aug 22;369(8):711–21.

42. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016 Nov 17;375(20):1946–60.

43. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1201–14.

44. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. The Lancet. 2022 May;399(10340):2031–46.

45. Sandborn WJ, D'Haens GR, Reinisch W, et al. Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study. Gastroenterology. 2022 May 1;162(6):1650-1664.e8.

46. Sands BE, Peyrin-Biroulet L, Kierkus J, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Crohn's Disease. Gastroenterology. 2022 Feb 1;162(2):495–508.

47. Sandborn WJ, Feagan BG, D'Haens G, et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2021 Sep 30;385(14):1280–91.

48. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. The Lancet. 2023 Apr 8;401(10383):1159–71.

49. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017 May 4;376(18):1723–36.

50. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. The Lancet. 2022 Jun;399(10341):2113–28.

51. Loftus EV, Panés J, Lacerda AP, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023 May 25;388(21):1966–80.

52. Panés J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut. 2017 Jun 1;66(6):1049–59.

53. Feagan BG, Danese S, Loftus EV, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. The Lancet. 2021 Jun 19;397(10292):2372–84.

54. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021 Apr 1;160(5):1570–83.

55. Colombel JF, D'haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2020 Feb 10;14(2):254–66.

56. Kobayashi T, Hibi T. Improving IBD outcomes in the era of many treatment options. Nat Rev Gastroenterol Hepatol. 2023;20(2):79–80.

57. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. J Crohns Colitis. 2018 May;12(6):635–43.

58. Papamichael K, Rivals-Lerebours O, Billiet T, et al. Long-Term Outcome of Patients with Ulcerative Colitis and Primary Non-response to Infliximab. J Crohns Colitis. 2016 Sep 1;10(9):1015–23.

59. Juillerat P, Grueber MM, Ruetsch R, Santi G, Vuillèmoz M, Michetti P. Positioning biologics in the treatment of IBD: A practical guide – Which mechanism of action for whom? Curr Res Pharmacol Drug Discov. 2022 Jan 1;3:100104.

60. Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2022 Jul 30;gutjnl-2022-328052.

61. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2022 Feb;7(2):161–70.

62. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. J Crohns Colitis. 2019 May 27;13(6):744–54.

63. Burisch J, Zhao M, Odes S, et al. The cost of inflammatory bowel disease in high-income settings: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2023 May 1;8(5):458–92.

64. van Gennep S, Evers SW, Rietdijk ST, et al. High Disease Burden Drives Indirect Costs in Employed Inflammatory Bowel Disease Patients: The WORK-IBD Study. Inflamm Bowel Dis. 2021 Mar 1;27(3):352–63.

65. Hirten RP, Iacucci M, Shah S, Ghosh S, Colombel JF. Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders. Clin Gastroenterol Hepatol. 2018 Sep 1;16(9):1374–84.

66. Ferrante M, Sabino J. Efficacy of JAK inhibitors in Ulcerative Colitis. J Crohns Colitis. 2020 Aug 1;14(Supplement_2):S737–45.

67. Rogler G. Efficacy of JAK inhibitors in Crohn's Disease. J Crohns Colitis. 2020 Aug 1;14(Supplement_2):S746–54.

68. Sandborn WJ, D'Haens GR, Sands BE, et al. Tofacitinib for the Treatment of Ulcerative Colitis: An Integrated Summary of up to 7.8 Years of Safety Data from the Global Clinical Programme. J Crohns Colitis. 2023 Mar 1;17(3):338–51.

69. Colombel JF, Cao Q, Ghosh S, et al. OP33 Effect of upadacitinib (UPA) treatment on extraintestinal manifestations (EIMs) in patients with moderate-to-severe Ulcerative Colitis (UC): Results from the UPA Phase 3 programme. J Crohns Colitis. 2022 Jan 1;16(Supplement_1):i036–7.

70. Danese S, Argollo M, Berre CL, Peyrin-Biroulet L. JAK selectivity for inflammatory bowel disease treatment: does it clinically matter? Gut. 2019 Oct 1;68(10):1893–9.

71. Berinstein JA, Sheehan JL, Dias M, et al. Tofacitinib for Biologic-Experienced Hospitalized Patients With Acute Severe Ulcerative Colitis: A Retrospective Case-Control Study. Clin Gastroenterol Hepatol. 2021 Oct;19(10):2112-2120.e1.

72. Jena A, Mishra S, Sachan A, Singh H, Singh AK, Sharma V. Tofacitinib in Acute Severe Ulcerative Colitis: Case Series and a Systematic Review. Inflamm Bowel Dis. 2021 Aug 19;27(9):e101–3.

73. Honap S, Pavlidis P, Ray S, et al. Tofacitinib in Acute Severe Ulcerative Colitis-A Real-World Tertiary Center Experience. Inflamm Bowel Dis. 2020 Oct 23;26(11):e147–9.

74. Kotwani P, Terdiman J, Lewin S. Tofacitinib for Rescue Therapy in Acute Severe Ulcerative Colitis: A Real-world Experience. J Crohns Colitis. 2020 Jul 30;14(7):1026–8.

75. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2005 Dec 8;353(23):2462–76.

76. Allen PB, Lindsay H, Tham TCK. How do patients with inflammatory bowel disease want their biological therapy administered? BMC Gastroenterol. 2010 Jan 10;10:1.

77. Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. The Lancet. 2019 Apr;393(10182):1699–707.

78. Schreiber S, Ben-Horin S, Leszczyszyn J, et al. Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease. Gastroenterology. 2021 Jun;160(7):2340–53.

79. Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakuraba A. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45(8):1043–57.

80. Roblin X, Veyrard P, Bastide L, et al. Subcutaneous injection of infliximab CT-P13 results in stable drug levels within 14-day treatment cycle in Crohn's disease. Aliment Pharmacol Ther. 2022;56(1):77–83.

81. Sands BE, Hanauer SB, Colombel JF, et al. P492 Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for ulcerative colitis: A Phase 3, randomized, placebo-controlled study: Results of the LIBERTY-UC study. J Crohns Colitis. 2023 Feb 1;17(Supplement_1):i623–4.

82. Colombel JF, Hanauer SB, Sandborn W, et al. DOP86 Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for Crohn's disease: A phase 3, randomised, placebo-controlled study (LIBERTY-CD). J Crohns Colitis. 2023 Feb 1;17(Supplement_1):i161–2.

83. Sandborn WJ, Baert F, Danese S, et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020 Feb;158(3):562-572.e12.

84. Vermeire S, D'Haens G, Baert F, et al. Efficacy and Safety of Subcutaneous Vedolizumab in Patients With Moderately to Severely Active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022 Jan 1;16(1):27–38.

85. Moschen AR, Tilg H, Raine T. IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. Nat Rev Gastroenterol Hepatol. 2019 Mar;16(3):185–96.

86. D'Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2023 Jun 29;388(26):2444–55.

87. Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature. 2004 Jan;427(6972):355–60.

88. Scott FL, Clemons B, Brooks J, et al. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. Br J Pharmacol. 2016;173(11):1778–92.

89. Panaccione R, Danese S, Wolf DC, et al. P405 Long-term safety of 3 years of ozanimod in moderately to severely active ulcerative colitis: an interim analysis of the True North open-label extension. J Crohns Colitis. 2023 Feb 1;17(Supplement_1):i534–5.

90. Vermeire S, Chiorean M, Panés J, et al. Long-term Safety and Efficacy of Etrasimod for Ulcerative Colitis: Results from the Open-label Extension of the OASIS Study. J Crohns Colitis. 2021 Jun 1;15(6):950–9.

91. Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised,

double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol. 2023 Apr 1;8(4):307–20.

92. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis. N Engl J Med. 2012 Aug 16;367(7):616–24.

93. Rubin DT, Reinisch W, Greuter T, et al. Extraintestinal manifestations at baseline, and the effect of tofacitinib, in patients with moderate to severe ulcerative colitis. Ther Adv Gastroenterol. 2021;14:17562848211005708.

94. Greuter T, Rieder F, Kucharzik T, et al. Emerging treatment options for extraintestinal manifestations in IBD. Gut. 2021 Apr;70(4):796–802.

95. Siegmund B, Axelrad J, Pondel M, et al. DOP43 Rapidity of ozanimod-induced symptomatic response and remission in patients with moderately to severely active Ulcerative Colitis: Results from the induction period of True North. J Crohns Colitis. 2022 Jan 1;16(Supplement_1):i092–3.