Journal of the Canadian Association of Gastroenterology, 2025, **8**, S1–S5
https://doi.org/10.1093/jcag/gwae053
Supplement Article

What is first-line and what is second-line therapy in adult patients with moderate to severe Crohn's disease?

Remo Panaccione*

Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB T2N 4Z6, Canada

*Corresponding author: Remo Panaccione, MD, Inflammatory Bowel Disease Unit, University of Calgary, Rm 6D32, Calvin Wenzel Precision Health Building, 3280 Hospital Dr NW, Calgary, AB T2N 4Z6, Canada (rpanacci@ucalgary.ca).

Abstract

Crohn's disease, a chronic inflammatory bowel disease, necessitates a comprehensive treatment approach tailored to the individual's specific disease characteristics and overall health. Treatment strategies aim to induce and maintain remission, alleviate symptoms, normalize biomarkers, improve the endoscopic appearance of the intestine, and improve quality of life. Key therapeutic options include pharmacotherapy, featuring corticosteroids, immunomodulators, monoclonal antibodies, and more recently Janus Kinase inhibitors (JAKi) which target different mechanisms of inflammation. Additionally, surgical interventions may be required for complications or when medical therapy fails. The recent introduction of novel therapies, such as the interleukin-23 (IL-23) anti-p19 inhibitor risankizumab and the selective JAKi upadacitinib, raises pertinent questions regarding the optimal sequencing of advanced therapeutic options. This review evaluates current data to address these questions and reflects the author's perspectives based on a presentation at the 27th Annual University of Manitoba Key Topics in Gastroenterology 2024.

Key words: therapies; Crohn's disease; decision making

Introduction

Over the past 2 decades, 4 classes of monoclonal antibodies; often referred to as biologics have been approved for use in moderate to severe Crohn's disease by Health Canada. More recently, the first selective Janus kinase inhibitor (JAKi), upadacitinb (UPA) has also been approved for this indication.[1] For many years, the anti-tumour necrosis factor-α (anti-TNF) agents (infliximab [IFX] and adalimumab [ADA]) were commonly used as the first-line therapy in clinical practice.[2] Physicians became accustomed to and comfortable with these agents as experience grew. Vedolizumab (Vedo), an alpha-4 beta-7 antagonist was a welcome addition because of the perceived safety benefit due to its gut specificity.[2] This appealed to both health care providers and patients despite an initial lack of endoscopic data in the phase 3 program and initial non-significant results in anti-TNF-exposed patients. Ustekinumab (USTE), an IL-12/23 inhibitor held the promise of improved efficacy over anti-TNF based on the experience in psoriasis as well as a favourable safety profile.[2] However, the head-to-head SEAVUE study failed to show superiority over USTE over ADA.[3]

With the approvals of risankizumab (RZB),[4] a selective p19 inhibitor, and UPA,[1] the first advanced oral option, determining the optimal first-line and second-line treatments for moderate to severe Crohn's disease becomes crucial.

This review integrates pivotal phase 3 program data, network meta-analyses, and recent head-to-head trials to provide a comprehensive, evidence-based, patient-centric approach to selecting first and second-line therapies for Crohn's disease.

Key considerations when deciding on first- and second-line advanced therapies

There are important clinical considerations when making treatment decisions of what therapy to use first-line versus second-line. We also must remember that these considerations may be somewhat different if we consider the physician's view versus the patient's view.[5]

From a physician's standpoint, we often consider disease location, disease severity, and duration of disease.[5] Other clinical considerations include the presence or absence of extra-intestinal manifestations (EIMs), the presence of perianal fistulizing diseases as well as individual patient comorbidities.[5] Patients may consider convenience or mode of administration, safety concerns, and overall impact on quality of life. In the end, both physicians and patients desire therapies that act rapidly to control symptoms while providing durable efficacy while sparing the need for corticosteroids.[5] Therapies should have robust data to support their ability to achieve modern-day treatment targets including "mucosal healing." Simply stated, a therapy should demonstrate a favourable benefit to the risk profile whether it is first line or second line.

Clinical settings where advanced therapies should be considered

There's been an evolution in the clinical scenarios where an advanced therapy such as a monoclonal antibody (biologic) or a JAKi would be considered in a patient with moderate to severe Crohn's disease. Historically, patients were required

to fail what was termed "conventional therapy" such as corticosteroids and immunomodulators (thiopurines or methotrexate) before a biologic would be entertained. However, recent data would suggest that any patient requiring a course of corticosteroids should be considered for advanced therapy.[6] This would be consistent with our longstanding knowledge of the natural history of patients who are on corticosteroids where a fair proportion will be steroid refractory within the first 3-4 months and a higher percentage will be steroid dependant.[7] A clinical decision to start corticosteroids should prompt a clinician to consider starting an advanced therapy.

A second cohort of patients that should be considered for advanced therapies are those deemed to be at high risk of disease progression. This includes patients with young age of onset, the need for corticosteroids, extensive small bowel disease, upper intestinal disease, rectal disease, perianal fistulizing disease, and those patients with deep ulcers at endoscopic evaluation.[8]

Evaluating the evidence for positioning therapies

In examining the evidence, we can look at the results of the pivotal phase 3 clinical trials with the different advanced therapies available. Making indirect comparisons is often difficult because of differences in baseline patient characteristics, trial design, and timing of endpoints. Regardless this does give us a sense of absolute efficacy and placebo-adjusted rates. Systematic reviews, meta-analysis, and network meta-analysis do provide a more scientific way of making these indirect comparisons and have become more reliable in their interpretation especially when head-to-head studies are available and can be added into the network. Fortunately, the last several years have seen both head-to-head studies and phase 3 trials with active comparator arms which help answer the questions at hand.

Phase 3 studies

The primary endpoint of the majority of phase 3 trials has been clinical remission as measured by the Crohn's disease activity index at the end of induction and maintenance. The majority of these trials employed randomized withdrawal design for enrolling patients into the maintenance portion. When looking at the results with the anti-TNF agents, VEDO, and USTE clinical remission at the end of induction ranged from 15% to 40%.[9–14] Clinical remission at the end of maintenance in the randomized responders ranged from 30% to 54%.[9–14] The phase 3 UPA trials resulted in high rates of clinical remission after 12 weeks in the mixed population of ~50% and clinical remission rates of ~40% in the UPA 15 mg and ~50% in the UPA 30 mg during maintenance.[15] Similar results were seen in the RZB phase 3 studies with clinical remission rates being between 35% and 40% at the end of induction and approximately 60% at the end of maintenance.[16,17]

As treatment targets have evolved we have gained a better appreciation of the importance of endoscopic response, endoscopic remission, and mucosal healing. Infliximab was able to achieve mucosal healing (absence of mucosal ulceration) rates of 44% in the ACCENT 1 and SONIC trials.[10,18] ADA demonstrated mucosal healing rates of approximately 25% in the EXTEND trial.[19] There is no endoscopic data for VEDO in the GEMINI program and when evaluated in a small uncontrolled cohort in VERSIFY endoscopic remission (simple endoscopic score of severity in Crohn's disease [SES-CD] score of 4 or less) at week 26 was 11.9%.[20] Similarly, in the phase 3 USTE endoscopic sub-study, 17% of the subjects achieved endoscopic remission (SES-CD score of 2 or less) at week 44.[21]

Endoscopic response has become a co-primary endpoint at the end of both induction and maintenance in more recent registrational trials with endoscopic remission being a key secondary endpoint. At week 12, endoscopic remission (SES-CD 4 or less) rates with UPA were 36% in the bio-naive and 20% in the bio-exposed and ranged between ~16% and 34% during 52 weeks of maintenance in the responders.[15] With RZB, the absolute rates are very similar ranging between ~20%-55% at week 12 and ~21%-50% at week 52 of maintenance.[16,17] Absolute rates depend on whether patients are bio-naive or inadequate responders to biologic therapy and appear to be dose-dependent. In the recently reported treat-through design trials of guselkumab (GUS) and mirkizumab (MIRI), two other IL-23 ant-p19 agents; the endoscopic remission rates appeared to be in a similar range at the end of week 12 and 48-52 weeks of maintenance.

Meta-analysis in moderate to severe CD

Meta-analysis integrates findings from many individual studies (often RCTs), applying objective statistical formulas to make indirect comparisons between agents often using placebo as the anchor. A recent network meta-analysis by Barberio et al.[22] ranked IFX, RZB, and UPA as the most effective therapies in patients with moderate to severe CD. Infliximab was only studied in bio-naive patients. When data are analyzed separately, RZB 600 mg ranked first for both the bio-naive and bio-exposed groups, suggesting that the ranking of IFX 5 mg/kg in the pooled analysis was driven by use in biologic-naive patients.[22] The total data for UPA, GUS, and MIRI were not included. In addition, and likely more importantly Vuyyuru et al.[23] published a network meta-analysis specifically looking at endoscopic outcomes at the end of induction and maintenance. Agents were pooled by the mechanism of action and demonstrated that IL-23 ant-p19 inhibitors are more effective among the advanced therapies for achieving both endoscopic response and remission. This is a very intriguing analysis and certainly should shape our thinking around the positioning of therapy.

Head-to-head trials in moderate to severe Crohn's disease

Head-to-head trials can provide a wealth of information when informing the positioning of therapies. However, there are several critical factors that need to be considered when interpreting the results which include what is an acceptable clinically meaningful difference, how the trial mirrors clinical practice, how corticosteroids are handled within the trial, what endpoints are being used, and finally overall trial design and whether it is powered as a non-inferiority or superiority trial.

The first head-to-head trial in moderate to severe CD was the SEAVUE trial.[3] This was a treat-through design powered for the superiority of USTE over ADA using standard approved dosing regimens in patients who were naive to advanced therapies. The primary endpoint was the achievement of clinical remission at week 52 as defined by the Crohn's

disease activity index (CDAI). The trial failed to achieve the primary endpoint. Subjects treated with both USTE and ADA and achieved high rates of clinical remission at 65% and 61%, respectively. This was largely attributed to the relatively short disease duration, less severe endoscopic disease, and the fact that all participants were bio-naive at baseline. There were no differences among the groups in key secondary endpoints including endoscopic remission. Although a negative trial, at the time this did increase the use of USTE in clinical practice because it was perceived as working similarly well as ADA and enjoyed a favourable safety profile as well as requiring fewer injections.

More recently, the results of the SEQUENCE trial were reported.[24] This was an open-label head-to-head comparison of RZB to USTE in moderate to severe CD patients who had failed at least one anti-TNF. It was designed to assess co-primary endpoints at week 24 (powered for non-inferiority for CDAI remission) and the superiority of RZB over USTE at week 48 for endoscopic remission. Although open-label, the assessments were blinded, in particular, the endoscopic scores were determined by central readers who were blinded to the treatment allocation as well as when the endoscopy was being performed (baseline, week 24, or week 48). The trial demonstrated that RZB was non-inferior for achieving clinical remission at week 24 compared to USTE and superior to USTE for achieving endoscopic remission (32% RZB vs 16% USTE; P <.0001). Several key secondary endpoints were tested demonstrating the superiority of RZB over USTE including clinical remission at week 48, endoscopic response at weeks 24 and 48, corticosteroid-free clinical remission at week 48, and steroid-free endoscopic remission at week 48. Overall all the deltas favouring RZB over USTE were approximately 20% across all endpoints. Certainly, this will serve as a landmark study and it is difficult to see a clinical scenario outside of access where USTE would be preferred over RZB in patients exposed to anti-TNF.

Finally, the phase 3 programs for both GUS and MIRI have been presented.[25,26] Although not fully published the findings are informative. Both trials enrolled patients with moderate to severe Crohn's disease including patients who had failed conventional therapies and advanced therapies (USTE failures were excluded). These were large multi-centre, randomized, double-blind, double-dummy, placebo- and active-controlled, treat-through studies with USTE as the active comparator. The primary endpoints were composite clinical and endoscopic endpoints and these endpoints were met for both GUS and MIRI over placebo. However, the key secondary endpoints included comparisons against USTE.

In the pooled analysis (GALAXI 2 and GALAXI 3) in the GUS program, both evaluated doses of GUS (100 mg subcutaneous [sc] every 8 weeks or 200 mg sc every 4 weeks) demonstrated statistical superiority over USTE for achieving endoscopic response at week 48, endoscopic remission at week 48, and the composite endpoints of clinical remission and endoscopic response at week 48 and deep remission (clinical and endoscopic remission) at week 48.[25] The deltas favouring GUS over USTE were in the 15% range. However, in the VIVID evaluating similar endpoints with MIRI compared to USTE, no difference was observed.[26] Further evaluations of both of these datasets are needed to get a full understanding of the results but at this moment the data would suggest that in Crohn's disease, both RZB and GUS are superior to USTE whereas MIRI is not. This certainly has implications with biosimilar USTE being already available.

General concepts when positioning therapies in IBD

Several fundamental concepts are essential in the management of Crohn's disease. Firstly, early treatment initiation is crucial, as highlighted by Ben-Horin's review,[27] which demonstrated that the efficacy of advanced therapies decreases with disease duration. The PROFILE trial further emphasized the importance of early intervention, showing high rates of clinical and endoscopic remission within the first year of diagnosis with the early introduction of anti-TNF therapy.[28]

Secondly, therapy efficacy should drive treatment decisions. Uncontrolled disease is associated with disease progression and other adverse events, such as infections. Opting for a therapy perceived as "safer" but sacrificing efficacy is a common pitfall that clinicians and patients must avoid. Effective therapies should be prioritized to prevent long-term complications and improve patient outcomes.

Thirdly, the first choice of advanced therapy is critical. Previous exposure to other advanced therapies has been associated with reduced efficacy of subsequent treatments. Therefore, selecting a highly effective first-line therapy is essential to maximize patient benefits and minimize the time spent on less effective treatments.

Lastly, individual patient characteristics, including the presence of EIMs, history of perianal fistulizing disease, co-existing immune-mediated diseases, and comorbidities that may limit the use of certain therapies, must be carefully considered when making treatment decisions.

What should be considered as first-line therapy in moderate to severe Crohn's disease?

Although all advanced therapies are approved for first-line use after the failure of conventional therapy, considering all available data (phase 3 trials, meta-analyses, and head-to-head comparisons), the most effective first-line therapies for moderate to severe Crohn's disease are anti-TNF agents, anti-p19s (RZB and GUS), and UPA.

RZB and GUS have demonstrated superiority to USTE, suggesting they should be preferred as first-line options, barring access issues. Vedolizumab, although safe, lacks robust endoscopic data and has lower clinical efficacy, suggesting limited first-line use in Crohn's disease. In contrast, IFX is preferred over ADA for its endoscopic data and benefits in fistulizing Crohn's disease, although it may need to be paired with a purine anti-metabolite for optimal efficacy.

In clinical practice, patients with significant EIMs such as uveitis, peripheral arthritis, ankylosing spondylitis, or pyoderma gangrenosum should consider anti-TNF therapy as first-line, specifically IFX. Patients with perianal fistulizing disease should also prefer IFX as the first-line option. For patients without significant EIMs or perianal fistulizing disease, RZB emerges as the ideal first-line agent due to its superior benefit-risk ratio and will likely become the preferred first-line agent within the next 3 years. The data for UPA is similar to RZB and should be considered a first-line option for patients who are steroid-refractory, intolerant to

steroids, require rapid symptom resolution, or prefer an oral option.

What should be considered as second-line therapy in moderate to severe Crohn's disease?

Second-line therapy considerations after VEDO or USTE failure align with first-line decisions, focusing on EIMs and perianal disease. Twenty percent of the patients enrolled in the RZB phase 3 program had been exposed to USTE, and overall, the efficacy and placebo-adjusted deltas for clinical outcomes in this cohort favoured RZB.

Due to the fact that anti-TNFs were the first class of advanced therapy approved, many decisions revolve around what therapy to use after anti-TNF failure. VEDO performed poorly in this patient population in GEMINI 2, with extremely low rates of clinical remission, and could not be differentiated from placebo. The SEQUENCE study clearly showed RZB to be superior to USTE in this clinical scenario. The only other consideration for second-line therapy in anti-TNF failures is UPA, which would be the author's preference in patients with EIMs other than psoriasis or perianal fistulizing disease.

Final recommendations

When making choices about first- and second-line advanced therapy in Crohn's disease, considerations should begin and end with the patient. This includes a comprehensive evaluation to understand the nature of the disease, risk assessment, and a discussion around patient preferences.

Emerging data are reshaping the positioning of advanced therapy. IL-23 anti-p19s are highly effective and safe first- or second-line therapies, likely emerging as the preferred first-line treatment for the majority of patients. The selective JAKi UPA is highly effective, rapidly acting in Crohn's disease, and provides the first oral advanced option for patients. Anti-TNFs continue to play an important role after 25 years of clinical experience.

Overall, the optimal management of Crohn's disease requires a nuanced approach that integrates the latest clinical evidence, patient-specific factors, and the evolving landscape of therapeutic options. By prioritizing early and effective interventions, clinicians can improve patient outcomes and enhance the quality of life for individuals living with Crohn's disease.

Supplement sponsorship

This article appears as part of the supplement "27th Anniversary Key Topics in Gastroenterology in 2024." The symposium and this supplement were funded by grants from the following sponsors:

- Platinum: Abbvie Canada, Janssen Inc, Pfizer Canada, Takeda Canada, Fresenius-Kabi
- Silver: Boston Scientific, Ferring Pharmaceuticals, Organon, Eli Lilly and Company

Conflicts of interest

R.P. has served as a consultant for Abbott, AbbVie, Abbivax, Alimentiv (formerly Robarts), Amgen, AnaptysBio, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Fresenius Kabi, Genentech, Gilead Sciences, Glaxo-Smith Kline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Spyre Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Union Biopharma, Viatris, Ventyx, UCB; received speaker's fees from AbbVie, Amgen, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Gilead Sciences, Janssen, Merck, Organon, Pfizer, Roche, Sandoz, Shire, Takeda Pharmaceuticals.

Conflict of interest disclosure forms (ICMJE) have been collected for all co-authors and can be accessed as supplementary material here.

Data availability

No new data were generated or analysed in support of this research.

References

1. https://health-products.canada.ca/noc-ac/nocInfo?no=31974
2. Panaccione R, Steinhart AH, Bressler B, et al. Canadian association of gastroenterology clinical practice guideline for the management of luminal Crohn's disease. *Clin Gastroenterol Hepatol*. 2019;17(9):1680–1713. https://doi.org/10.1016/j.cgh.2019.02.043
3. Sands BE, Irving PM, Hoops T, et al.; SEAVUE Study Group. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. *Lancet*. 2022;399(10342):2200–2211. https://doi.org/10.1016/S0140-6736(22)00688-2
4. https://health-products.canada.ca/noc-ac/nocInfo?no=29238
5. Rubin DT, Sninsky C, Siegmund B, et al. International perspectives on management of inflammatory bowel disease: opinion differences and similarities between patients and physicians from the IBD GAPPS survey. *Inflamm Bowel Dis*. 2021;27(12):1942–1953. https://doi.org/10.1093/ibd/izab006
6. Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology*. 2021;161(1):47–65. https://doi.org/10.1053/j.gastro.2021.04.063
7. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol*. 2010;105(2):289–297. https://doi.org/10.1038/ajg.2009.579
8. Siegel CA, Bernstein CN. Identifying patients with inflammatory bowel diseases at high vs low risk of complications. *Clin Gastroenterol Hepatol*. 2020;18(6):1261–1267. https://doi.org/10.1016/j.cgh.2019.11.034
9. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;337(15):1029–1035. https://doi.org/10.1056/NEJM199710093371502
10. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541–1549. https://doi.org/10.1016/S0140-6736(02)08512-4

11. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130(2):323–33; quiz 591. https://doi.org/10.1053/j.gastro.2005.11.030
12. 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;132(1):52–65. https://doi.org/10.1053/j.gastro.2006.11.041
13. Sandborn WJ, Feagan BG, Rutgeerts P, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711–721. https://doi.org/10.1056/NEJMoa1215739
14. Feagan BG, Sandborn WJ, Gasink C, et al.; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946–1960. https://doi.org/10.1056/NEJMoa1602773
15. Loftus EV Jr, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2023;388(21):1966–1980. https://doi.org/10.1056/NEJMoa2212728
16. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet*. 2022;399(10340):2015–2030. https://doi.org/10.1016/S0140-6736(22)00467-6
17. 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. *Lancet*. 2022;399(10340):2031–2046. https://doi.org/10.1016/S0140-6736(22)00466-4
18. Colombel JF, Sandborn WJ, Reinisch W, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383–1395. https://doi.org/10.1056/NEJMoa0904492
19. Rutgeerts P, Van Assche G, Sandborn WJ, et al.; EXTEND Investigators. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012;142(5):1102–1111.e2. https://doi.org/10.1053/j.gastro.2012.01.035
20. Danese S, Sandborn WJ, Colombel JF, et al. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. *Gastroenterology*. 2019;157(4):1007–1018.e7. https://doi.org/10.1053/j.gastro.2019.06.038
21. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology*. 2018;155(4):1045–1058. https://doi.org/10.1053/j.gastro.2018.06.035
22. 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*. 2023;72(2):264–274. https://doi.org/10.1136/gutjnl-2022-328052
23. Vuyyuru SK, Nguyen TM, Murad MH, et al. Comparative efficacy of advanced therapies for achieving endoscopic outcomes in Crohn's disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2024;22(6):1190–1199.e15. https://doi.org/10.1016/j.cgh.2023.12.023
24. Peyrin-Biroulet L, Chapman C, Colombel JF, et al. Risankizumab versus Ustekinumab in moderate to severe Crohn's disease. *NEJM*. 2024;391(3):213.
25. Panaccione R, Danese S, Feagan B. Efficacy and safety of Guselkumab therapy with moderately to severely active Crohn's disease: results of the GALAXI 2 & 3 phase 3 studies. *DDW*. 2024.
26. Jairath V, Sands BE, Bossuyt P, et al. Efficacy of Mirikizumab in comparison to Ustekinumab in patients with moderate-to-severe Crohn's disease: results from the phase 3 VIVID-1 study. *ECCO*. 2024.
27. Ben-Horin S, Novack L, Mao R, et al. Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease: a systematic review and an individual-patient data meta-analysis of randomized controlled trials. *Gastroenterology*. 2022;162(2):482–494. https://doi.org/10.1053/j.gastro.2021.10.037
28. Noor NM, Lee JC, Bond S, et al.; PROFILE Study Group. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024;9(5):415–427. https://doi.org/10.1016/S2468-1253(24)00034-7