



# Positioning biologics in the management of moderate to severe Crohn's disease

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## Purpose of review

Since there is a lack of head-to-head randomized controlled trials, little direction is provided from guidelines on the positioning of biologics for the treatment of Crohn's disease (CD). This review utilizes comparative effectiveness and safety results from real-world data and network meta-analyses to inform clinical practice for positioning of biological therapies in the treatment of moderate-to-severe CD.

## Recent findings

We summarize the results of studies pertaining to the identification of predictors for response to biologics in CD. Recently published studies about the management of moderate-to-severe CD are discussed and a positioning algorithm is proposed for the therapeutic approach of these patients.

## Summary

Different classes of biologics are comparable with regards to safety and almost similar in effectiveness in the management of CD. There are certain clinical scenarios in which one biologic is more effective than another. For instance, patients with a more aggressive disease phenotype such as fistulizing disease would benefit from infliximab over other biologics, whereas in older patients at a higher risk for infectious complications, it may be more appropriate to use ustekinumab or vedolizumab over the anti-tumor necrosis factor (TNF) agents. More data pertaining to identifying predictors of response to the different available therapies and head-to-head comparison trials are needed to personalize our therapeutic approach of CD patients.

## Keywords

biologics, Crohn's disease, moderate-to-severe, positioning

## INTRODUCTION

To guide the choice of treatment in patients with Crohn's disease (CD), identification of potential predictors of response to the different available medications and patient risk stratification based on disease severity are extremely important factors to consider. At initial evaluation, CD patients are categorized into low-risk (mild) versus high-risk (moderate-to-severe) for the development of CD-related complications. A risk stratification index has been proposed based on the disease burden (biomarkers of disease activity, extent and endoscopic appearance, i.e. size/depth of ulcers), the impact of the disease on the patient (symptoms, quality of life, disability), and disease course (perianal complications, prior intestinal resection, extra-intestinal manifestations) [1]. High-risk CD patients may have the following features: diagnosed at a young age <30 years, have tobacco use, elevated C-reactive protein (CRP) and/or fecal calprotectin levels, deep and large mucosal ulcers on colonoscopy or imaging, have a long segment of bowel involvement, have the perianal disease, extra-intestinal manifestations, and/or prior bowel resections [1–3].

The medical management of patients with CD has changed over recent years. In the past, physicians followed a 'step-up' therapy approach for all CD patients starting with the least potent medications and escalating in a stepwise manner, reserving the more potent and potentially more toxic biologic agents for last resort. More recently, due to a better understanding of the natural history of CD, it has been demonstrated that early and rapid control of inflammation (endoscopic and clinical remission) modifies the disease trajectory and yields better outcomes. This fundamental concept has supported the 'top-down' therapy approach, particularly for patients with moderate-to-severe (high-risk) CD,

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**KEY POINTS**

- Multiple predictors of response to different biologics have been investigated, but to date, none are reliable.
- Ongoing research is focused on personalizing the therapeutic approach and selecting the right medication for each unique person.
- When selecting treatment options for patients with moderate-to-severe Crohn’s disease, in addition to categorizing them into high and low-risk patients, we take into account the presence of fistulizing disease, extra-intestinal involvement, age of the patient, the risk for frequent infections, current and prior history of malignancy, as well as the extent of bowel involved, to make the biologic selection.
- In older patients who are at increased risk of infection and malignancy, we opt for using vedolizumab or ustekinumab, unless these patients suffer from the extensive disease with fistulizing complications, in which case, we would use anti-tumor necrosis factor (TNF) agents.
- Anti-TNFs, especially infliximab, is used in patients with fistulizing Crohn’s disease.

while reserving the ‘step-up’ approach for patients with mild (low-risk) CD [4].

The therapeutic armamentarium is expanding (Table 1). Previously, the only available biologics for CD included the antitumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) agents, but recently, vedolizumab and ustekinumab have become approved and are readily available for the treatment of moderate-to-severe CD. Due to the lack of head-to-head randomized controlled trials, little direction is provided from guidelines on the positioning of the available biologics. As such, we have been relying on real-world data, observational comparative effectiveness, and network meta-analyses to inform comparative effectiveness and safety of the different biologics and serve as a guide for their positioning in the treatment of moderate-to-severe CD.

We hereby discuss these results and propose a positioning therapeutic algorithm for these patients.

**PREDICTORS OF RESPONSE TO DIFFERENT BIOLOGICS**

Approximately two-thirds of CD patients have an initial response to their first biologic drug and many will lose this response with time, either due to immunogenicity or mechanistic failure of the biologic [5<sup>\*\*\*</sup>]. Those who have initial nonresponse to a certain biologic may respond to a different class of biologics. Therefore, it is important to identify predictors of response to the available biologics to optimize efficacy, gain time at achieving remission, reduce cost, and minimize unnecessary drug adverse effects. Many predictors of response, or no response, have been investigated including a patient’s clinical characteristics, disease behavior, serologic biomarkers of inflammation, proteomic markers, as well as pharmacogenetic biomarkers amongst others.

For anti-TNF biologics, almost all clinical characteristics including age, sex, weight, duration of disease as well as disease location and extent, CRP levels, and fecal calprotectin were not shown to predict response to treatment [5<sup>\*\*\*</sup>]. In addition, although serum TNF levels were not found to predict response to infliximab [6], higher intestinal mucosal expression of TNF [7] as well as interleukin (IL)-17 and IL-23 [8] was associated with higher short-term response whereas oncostatin M expression was associated with failure of response [9]. Many genes have been explored using genome-wide association studies (GWAS) and despite the presence of some potential predictive factors for response in some polymorphisms in the members of the TNF family, more studies are needed to prove their use in clinical practice [10]. On the other hand, five mucosal differentially expressed genes in patients with colonic CD predicted infliximab response with 100% accuracy [11]. Protein extracts of peripheral blood mononuclear cells from 30 outpatients diagnosed with

**Table 1.** Approved biologics for the treatment of inflammatory bowel disease

Biologic	Mechanism of action	Route of administration	Approved for
Infliximab (Remicade)	Anti-TNF	Intravenous	CD, UC
Adalimumab (Humira)	Anti-TNF	Subcutaneous	CD, UC
Certolizumab pegol (Cimzia)	Anti-TNF	Subcutaneous	CD
Golimumab (Simponi)	Anti-TNF	Subcutaneous	UC
Vedolizumab (Entyvio)	Anti-integrin $\alpha$ -4 $\beta$ 7	Intravenous	CD, UC
Natalizumab (Tysabri)	Anti-integrin $\alpha$ -4	Intravenous	CD
Ustekinumab (Stelara)	Anti-IL-12/IL-23	Intravenous induction; subcutaneous maintenance	CD, UC

Anti-IL, anti-interleukin; anti-TNF, antitumor necrosis factor; CD, Crohn’s disease; UC, ulcerative colitis.

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ulcerative colitis or CD predicted response to anti-TNF therapy in 96% [12]. The personalised anti-TNF therapy in Crohn's disease Consortium described a significant association between the presence of human leukocyte antigen -DQA1\*05 and the development of immunogenicity with the use of anti-TNF agents [13<sup>¶</sup>].

Similar to anti-TNF biologics, no clinical characteristics have been found to predict response to vedolizumab. One study showed that the expression of  $\alpha 4\beta 7$  in blood as well as the presence of T, B, and natural killer (NK) cells was a good marker for vedolizumab response [14]. However, high levels of circulating IL-6 [15] and low or absent  $\alpha 4\beta 7$  integrin expression in colonic mucosa are associated with nonresponse [16]. A clinical decision support tool (CDST) for vedolizumab, taking into account prior bowel surgery, prior anti-TNF therapy, history of the fistulizing disease, baseline albumin and baseline CRP, was able to identify patients in clinical remission, corticosteroid-free remission, and mucosal healing with an area under the receiver operator curve of 0.67, 0.66, and 0.72, respectively [17<sup>¶</sup>]. In this CDST, the low probability cutoff value identified patients at a low likelihood of responding to vedolizumab with high sensitivity, whereas the high probability cut-off value identified patients at a higher likelihood of responding to therapy with moderate specificity. In a subsequent analysis, this model predicted vedolizumab drug concentration with good accuracy in the Study of Vedolizumab in Patients With Moderate to Severe Ulcerative Colitis trial cohort, and predicted a two-fold increase in surgery risk over 12 months of vedolizumab therapy in the vedolizumab for health outcomes in inflammatory bowel diseases consortium among low to intermediate probability versus high probability patients [17<sup>¶</sup>].

Predictors of response to ustekinumab are inconsistent [5<sup>¶¶</sup>]. Although some studies showed that previous anti-TNF therapy is a risk factor for treatment failure, other studies have reported that the response is independent of previous anti-TNF failure [18,19].

Future research is needed to develop a comprehensive predictive model incorporating patient and disease-related factors including genetic, clinical, biochemical, proteomic, and endoscopic/mucosal factors to personalize the treatment approach. This is where artificial intelligence and machine learning technology may play a critical role in advancing these predictive models [20].

## COMPARATIVE EFFECTIVENESS AND COMPARATIVE SAFETY

There is a lack of head-to-head randomized controlled trials comparing the efficacy and safety of

different biologics in the treatment of moderate-to-severe CD. For that reason, we rely on different network meta-analyses comparing different biologic agents to placebo, observational comparative effectiveness and safety studies, as well as real-world data to try to position the different medications for the treatment of CD [21<sup>¶</sup>].

Similar to several registry-based and multicenter cohort studies, an observational population-based study comparing the different anti-TNF agents amongst biologic-naïve CD patients, showed no differences in CD-related hospitalizations or major abdominal surgeries between infliximab and adalimumab treated patients [22]. Also, there were no significant differences in safety between infliximab and adalimumab treated patients. However, a US administrative claims-based study of biologic-naïve CD patients showed that infliximab was associated with lower CD-related hospitalizations, corticosteroid use, and less abdominal surgeries compared to adalimumab [23]. When compared to certolizumab pegol, infliximab treated patients had lower rates of all-cause hospitalization and CD-related hospitalization [23]. All three biologic agents had comparable rates of serious infections.

In a network meta-analysis, Singh *et al.* [24] separately analyzed the comparative efficacy of the first biologic (biologic naïve) agents and second biologic (prior anti-TNF exposure) agents. For the biologic naïve patients, eight randomized controlled trials on the moderate-to-severe luminal CD were included. Results showed that infliximab and adalimumab were most effective, followed by ustekinumab and vedolizumab as first-line treatments for inducing clinical remission and clinical response in biologic-naïve patients. In moderate-to-severe patients with luminal CD and prior anti-TNF exposure, six randomized controlled studies were included and concluded that adalimumab and ustekinumab were superior to vedolizumab for inducing clinical remission in patients with prior exposure to anti-TNF agents [24]. Patients with primary nonresponse to infliximab were excluded from the analysis. After selecting patients who had a clinical response to induction therapy, adalimumab and infliximab ranked highest for maintenance of remission. On network meta-analysis, none of the biologics caused significant serious adverse events compared to placebo in the maintenance trials, and ustekinumab had the lowest risk of serious adverse events and infection.

Real-world data showed that CD patients receiving vedolizumab as first-line therapy have higher clinical remission rates compared to nonbiologic naïve patients receiving vedolizumab [25,26]. Bohm *et al.* [27<sup>¶</sup>] compared anti-TNF agents to vedolizumab in CD using a retrospective observational cohort

propensity score-weighted comparison and showed no significant difference between vedolizumab and anti-TNF agents with regards to clinical remission, steroid-free clinical remission and endoscopic remission. Rates of noninfectious serious adverse events, but not serious infections, were significantly lower with the use of vedolizumab compared to anti-TNF agents [27<sup>\*</sup>]. Interestingly, in a separate observational study of elderly inflammatory bowel disease (IBD) patients, Adar *et al.* [28] found no significant difference in safety or rates of CD clinical remission between vedolizumab and anti-TNF agents.

Regarding ustekinumab, Scott *et al.* [29] used clinical trials and observational data to identify an ideal therapy sequence for patients with CD, including patients who used ustekinumab for at least 1 year. Incorporating advanced simulation methods, a Markov model was constructed. The base case used was that of a young male with moderate-to-severe CD who is naïve to biologics and immunomodulatory drugs. The standard of care treatment algorithm was defined as initial therapy with infliximab and azathioprine, followed by adalimumab and azathioprine, vedolizumab, and lastly surgical resection. The model assessed different positions for ustekinumab; before the standard of care or between the different treatment modalities. Clinical outcomes were calculated in quality-adjusted life years (QALYs), taking into account remission, response, surgical events, adverse events, infection, and lymphoproliferative disorders. Ustekinumab as first-line therapy yielded the greatest QALYs, resulting in 10% more patients in remission or response, fewer serious or infectious adverse events, and 2% fewer surgeries at 1 year, compared with other algorithms.

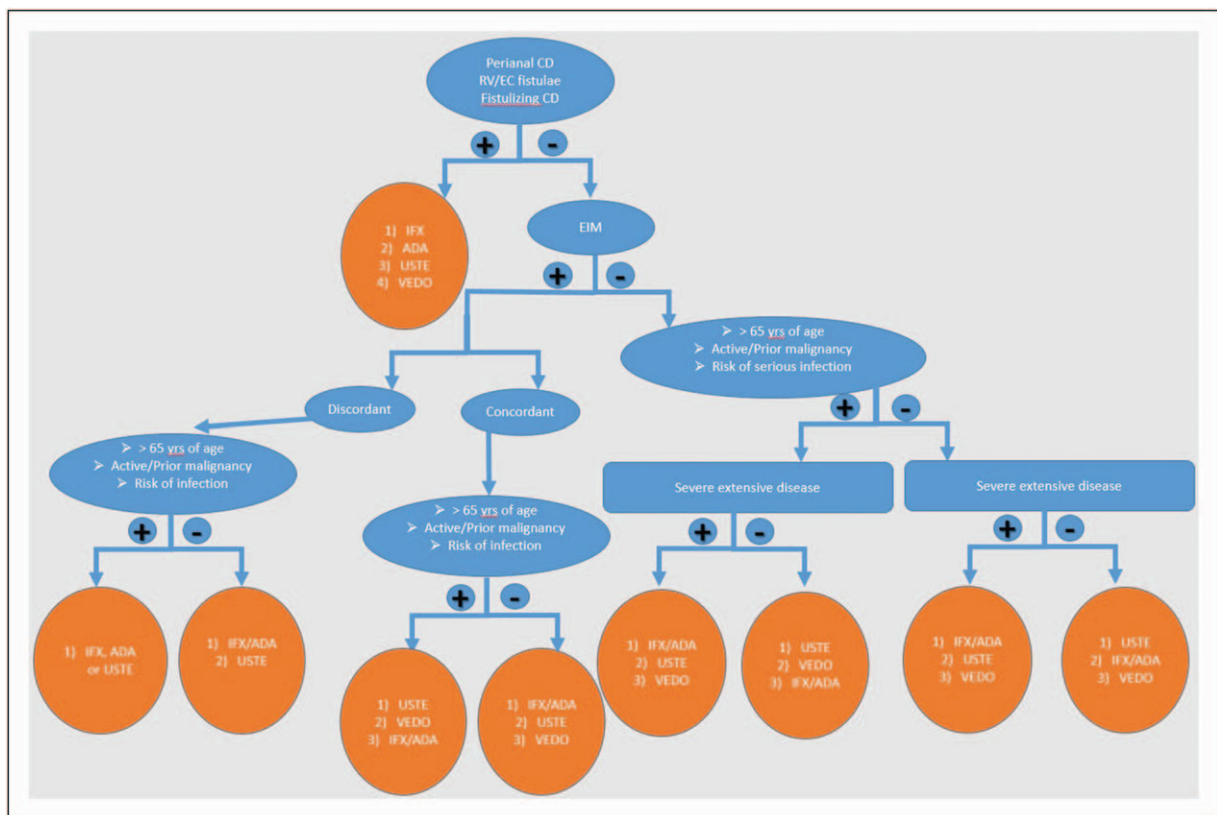
## POSITIONING ALGORITHM

The expanding therapeutic armamentarium for the treatment of patients with moderate-to-severe CD allows patients different treatment options. Ongoing research is focused on personalizing the therapeutic approach and selecting the right medication for each unique person. By risk stratifying patients according to their disease severity and prognosis for the development of CD-related complications and by identifying predictors of response to certain biologics, personalized medicine becomes possible. Of course, other factors that affect the selection of the medication includes patient preference as well as the cost to the patient promoting the importance of shared decision making.

The most updated American College of Gastroenterology (ACG) Clinical Guidelines for the Management of CD in Adults makes a strong recommendation for the use of anti-TNF agents,

ustekinumab, and vedolizumab for the induction and maintenance of patients with moderate-to-severe CD [4]. For patients with severe/fulminant CD, the ACG makes a strong recommendation to consider using anti-TNF agents, particularly infliximab. As for CD patients with the perianal fistulizing disease, enterocutaneous or rectovaginal fistulas, the ACG makes a strong recommendation that infliximab should be considered with a moderate level of evidence. Although adalimumab and certolizumab may be effective and should also be considered, there is a low level of evidence supporting this strong recommendation. The current available American Gastroenterological Association (AGA) guidelines on the management of inflammatory CD have been published in 2013, before the approval of ustekinumab and vedolizumab for the management of CD [30]. More updated guidelines on the management of moderate-to-severe CD are in the press and have been circulated for public comment. These updated guidelines by Feuerstein *et al.* recommend the use of anti-TNF (strong recommendation), ustekinumab (strong recommendation), or vedolizumab (conditional recommendation) for the induction and maintenance of remission of patients with moderate-to-severe luminal CD. In biologic naïve patients, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol (strong recommendation) and suggests the use of vedolizumab over certolizumab pegol (conditional recommendation). In those patients who are primary nonresponders to anti-TNF agents, the AGA recommends the use of ustekinumab (strong recommendation) and suggests the use of vedolizumab (conditional recommendation). For CD patients with active perianal fistula, the AGA makes a strong recommendation for the use of infliximab. In a conditional recommendation, the use of adalimumab, ustekinumab, and vedolizumab is suggested.

After reviewing the available guidelines and the comparative effectiveness and safety results, we propose the following algorithm (Fig. 1). In our algorithm, and similar to what has been previously published by several other groups, we take into account special patient populations which influence the choice of biologic and these include: high-risk patients with the fistulizing disease, especially perianal disease, those with extra-intestinal manifestations, elderly patients over the age of 65 years, patients at a higher risk of infections, and those with an active or past diagnosis of malignancy. An expert opinion meeting from Canada evaluated physicians' preferences for the use of specific biologic agents in different CD clinical scenarios using RAND/University of California Los Angeles appropriateness methodology and included factors similar to what we



**FIGURE 1.** Algorithm for positioning biologics in the treatment of patients with moderate-to-severe Crohn's disease. The above algorithm guides therapeutic decisions for patients with moderate-to-severe Crohn's disease. The algorithm does not reflect the use of monotherapy vs. combination therapy. If there is an overlap in a patient's clinical scenario, we suggest treating according to the higher risk phenotype (e.g. disease severity outweighs the presence of extra-intestinal manifestations). ADA, adalimumab; anti-TNF, antitumor necrosis factor; CD, Crohn's disease; EC, enterocutaneous; EIM, extra-intestinal manifestations; IFX, infliximab; RV, rectovaginal; USTE, ustekinumab; VEDO, vedolizumab.

propose in our algorithm [31<sup>11</sup>]. Additional factors that they considered to influence biologic choice included the presence of antidrug antibody status and consideration of potential pregnancy.

## CONCLUSION

To date, there are no reliable predictors of response to the different biologic agents and as previously mentioned, head-to-head clinical trials comparing biologics are lacking. These results are needed to better tailor therapy choice and objectively personalize treatments for the different phenotypes of patients with moderate-to-severe CD. Until then, physicians and patients may select the biologic agent based on physician experience and patient preference.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Peyrin-Biroulet L, Panes J, Sandborn WJ, *et al.* Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol* 2016; 14:348.e17–354.e17.
2. Siegel CA, Whitman CB, Spiegel BMR, *et al.* Development of an index to define overall disease severity in IBD. *Gut* 2018; 67:244–254.
3. Torres J, Caprioli F, Katsanos KH, *et al.* Predicting outcomes to optimize disease management in inflammatory bowel diseases. *J Crohns Colitis* 2016; 10:1385–1394.
4. Lichtenstein GR, Loftus EV, Isaacs KL, *et al.* ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018; 113:481–517.
5. Gisbert JP, Chaparro M. Predictors of primary response to biologic treatment ■ [anti-TNF, vedolizumab, and ustekinumab] in patients with inflammatory bowel disease: from basic science to clinical practice. *J Crohns Colitis* 2020; 14:694–709.

This is a comprehensive review of the predictors of primary response to the available biological therapies that are used to treat inflammatory bowel diseases. Although no single marker serves as a prognostic indicator of response to a biologic agent, the manuscript reviews all the potential predictors.

6. Billiet T, Cleynen I, Ballet V, *et al*. Evolution of cytokines and inflammatory biomarkers during infliximab induction therapy and the impact of inflammatory burden on primary response in patients with Crohn's disease. *Scand J Gastroenterol* 2017; 52:1086–1092.
7. Atreya R, Neumann H, Neufert C, *et al*. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. *Nat Med* 2014; 20:313–318.
8. Zhang X, Hu J, Suo L, *et al*. IL-17 and IL23 expression as a predictor of response to infliximab treatment in Crohn's disease. *Zhonghua Nei Ke Za Zhi* 2015; 54:940–944.
9. West NR, Hegazy AN, Owens BMJ, *et al*. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. *Nat Med* 2017; 23:579–589.
10. Linares-Pineda TM, Canadas-Garre M, Sanchez-Pozo A, Calleja-Hernandez MA. Pharmacogenetic biomarkers of response in Crohn's disease. *Pharmacogenomics J* 2018; 18:1–13.
11. Arijis I, Quintens R, Van Lommel L, *et al*. Predictive value of epithelial gene expression profiles for response to infliximab in Crohn's disease. *Inflamm Bowel Dis* 2010; 16:2090–2098.
12. Eftekhari P, Glaubitz L, Breidert M, *et al*. Physiological intermolecular modification spectroscopy for the prediction of response to antitumor necrosis factor therapy in patients with inflammatory bowel diseases. *Dig Dis* 2014; 32:446–454.
13. Sazonovs A, Kennedy NA, Moutsianas L, *et al*. HLA-DQA1\*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology* 2020; 158:189–199.  
This is the first study to describe an association between HLA-DQA1\*05 and development of antidrug antibodies when anti-TNF agents are used.
14. Boden EK, Shows DM, Chiorean MV, Lord JD. Identification of candidate biomarkers associated with response to vedolizumab in inflammatory bowel disease. *Dig Dis Sci* 2018; 63:2419–2429.
15. Soendergaard C, Seidelin JB, Steenholdt C, Nielsen OH. Putative biomarkers of vedolizumab resistance and underlying inflammatory pathways involved in IBD. *BMJ Open Gastroenterol* 2018; 5:e000208. doi: 10.1136/bmjgast-2018-000208.
16. Rath T, Bojarski C, Neurath MF, Atreya R. Molecular imaging of mucosal alpha4beta7 integrin expression with the fluorescent antiadhesion antibody vedolizumab in Crohn's disease. *Gastrointest Endosc* 2017; 86:406–408.
17. Dulai PS, Amiot A, Peyrin-Biroulet L, *et al*. A clinical decision support tool may help to optimise vedolizumab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2020; 51:553–564.  
This study proposes a validated clinical decision support tool specific to vedolizumab to help physicians optimize treatment of patients with Crohn's disease.
18. Greenup AJ, Rosenfeld G, Bressler B. Ustekinumab use in Crohn's disease: a Canadian tertiary care centre experience. *Scand J Gastroenterol* 2017; 52:1354–1359.
19. Harris KA, Horst S, Gadani A, *et al*. Patients with refractory Crohn's disease successfully treated with ustekinumab. *Inflamm Bowel Dis* 2016; 22:397–401.
20. Waljee AK, Wallace BI, Cohen-Mekelburg S, *et al*. Development and validation of machine learning models in prediction of remission in patients with moderate to severe Crohn disease. *JAMA Netw Open* 2019; 2:e193721. doi: 10.1001/jamanetworkopen.2019.3721.
21. Nguyen NH, Singh S, Sandborn WJ. Positioning therapies in the management of Crohn's disease. *Clin Gastroenterol Hepatol* 2020; 18:1268–1279.  
This is a recently published review paper on the positioning of therapies for the treatment of Crohn's disease. This manuscript takes in to account comparative efficacy studies, comparative safety studies, and also proposes an algorithm for the positioning of therapies.
22. Singh S, Andersen NN, Andersson M, *et al*. Comparison of infliximab with adalimumab in 827 biologic-naive patients with Crohn's disease: a population-based Danish cohort study. *Aliment Pharmacol Ther* 2018; 47:596–604.
23. Singh S, Heien HC, Sangaralingham LR, *et al*. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naive patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2016; 14:1120.e6–1129.e6.
24. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018; 48:394–409.
25. Feagan BG, Lasch K, Lisssoos T, *et al*. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019; 17:130.e7–138.e7.
26. Kopylov U, Verstockt B, Biedermann L, *et al*. Effectiveness and safety of vedolizumab in anti-TNF-naive patients with inflammatory bowel disease – a multicenter retrospective European study. *Inflamm Bowel Dis* 2018; 24:2442–2451.
27. Bohm M, Xu R, Zhang Y, *et al*. Comparative safety and effectiveness of vedolizumab to tumour necrosis factor antagonist therapy for Crohn's disease. *Aliment Pharmacol Ther* 2020; 52:669–681.  
This is a robust, large, comparative effectiveness and safety study comparing vedolizumab to anti-TNF therapy amongst patients with Crohn's disease.
28. Adar T, Faleck D, Sasidharan S, *et al*. Comparative safety and effectiveness of tumor necrosis factor alpha antagonists and vedolizumab in elderly IBD patients: a multicentre study. *Aliment Pharmacol Ther* 2019; 49:873–879.
29. Scott FI, Hans AK, Gerich ME, *et al*. Identification of the most effective position for ustekinumab in treatment algorithms for Crohn's disease. *Clin Gastroenterol Hepatol* 2020; S1542-3565(20)31130-7. [Online ahead of print]
30. Terdiman JP, Gruss CB, Heidelbaugh JJ, *et al*. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013; 145:1459–1463.
31. Weizman AV, Nguyen GC, Seow CH, *et al*. Appropriateness of biologics in the management of Crohn's disease using RAND/UCLA appropriateness methodology. *Inflamm Bowel Dis* 2019; 25:328–335.  
Excellent manuscript providing practical guidance by displaying different clinical Crohn's disease scenarios and the appropriateness to select amongst the available biologics.

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