Curr Gastroenterol Rep (2016) 18: 51
DOI 10.1007/s11894-016-0522-0



# Next-Generation Therapeutics for Inflammatory Bowel Disease

**Parambir S. Dulai**[1] · **William J. Sandborn**[1]

Published online: 26 July 2016


**Abstract** Tumor necrosis factor (TNF) antagonists are the cornerstone of therapy for moderately to severely active inflammatory bowel disease (IBD). Although our understanding of pharmacokinetics, pharmacodynamics, and treatment optimization for these agents has evolved considerably over the past decade, a substantial majority of individuals fail to respond or lose response to TNF-antagonists over time. A need therefore remains for efficacious treatment options in these patients. Alternative immunological targets have now been identified, and several novel therapeutic agents are in development for IBD. In this review article, we discuss these novel therapeutic agents, with a particular focus on those demonstrated to be efficacious in phase 2 and 3 clinical trials. We further discuss considerations to be made when integrating these agents into routine practice over the next decade.

**Keywords** Biologics · Vedolizumab · Etrolizumab · Tofacitinib · Ustekinumab

## Introduction

Tumor necrosis factor (TNF) antagonists have now become the cornerstone of therapy for moderately to severely active IBD. Considerable strides have been made towards the optimization of their use, through the early use of combination immunosuppressive therapy [1–3], or pro-active drug and disease monitoring with accompanying adjustments in therapy [4, 5]. Despite this, nearly a third of patients will be primary non-responders and another third will be secondary non-responders, leaving only a third of patients in clinical remission after 1 year of therapy [6]. Furthermore, these agents are not without risk and the off-target effect of TNF antagonists may result in serious and sometimes life-threatening adverse events [7, 8]. A need therefore remains for efficacious treatment options in these patients, with alternative mechanisms of action.

## Anti-trafficking

Mucosal barrier dysfunction is felt to be one of the earliest, and potentially most important, events in the pathogenesis of IBD [5]. The occurrence of mucosal barrier dysfunction leads to the presentation of luminal bacterial antigens to the innate immune system and T cells which, under specific environmental circumstances, become activated. Once activated, T cells undergo proliferation and expansion in regional lymph nodes, eventually returning to the gut as mature antigen-differentiated lymphocytes. This process of proliferation, maturation, and release from regional lymph nodes has become the potential site of action for a new biologic agent, ozanimod.

### Ozanimod

Ozanimod is a small molecule inhibitor that modulates the sphingosine 1-phosphate receptor (S1P), which is needed for activated lymphocytes to leave lymph nodes. By causing internalization of the $S1P_{1R}$ on lymphocytes so they are unable to respond to S1P expressed along the lymphatic endothelium,

This article is part of the Topical Collection on *Inflammatory Bowel Disease*

✉ William J. Sandborn
wsandborn@ucsd.edu

[1] Division of Gastroenterology, University of California at San Diego, La Jolla, CA, USA

ozanimod effectively blocks downstream inflammatory processes by "trapping" lymphocytes at their earliest phase of trafficking. Treatment efficacy for ozanimod is largely limited to a phase 2 study of 186 UC patients [9•], where it was demonstrated that once daily dosing of ozanimod at 1 mg resulted in significantly higher rates of clinical remission and mucosal healing at 8 weeks (Table 1). Of importance, within this trial, the investigators looked at histologic remission as defined by the Geboes score (<2) and noted that the rates of histologic remission at week 8 (0.5 mg 14 %, 1.0 mg 22 %) were lower than endoscopic mucosal healing rates at week 8 (0.5 mg 28 %, 1.0 mg 34 %), but at week 32, these were more comparable (histologic remission 0.5 mg 23 %, 1.0 mg 31 %; endoscopic mucosal healing 0.5 mg 32 %, 1.0 mg 33 %). This, along with the overall increase in clinical remission rates and treatment effect size by week 32, would suggest that treatment efficacy is time dependent, and extended treatment may be associated with improved healing [9•]. Phase 3 trials in ulcerative colitis and phase 2 trials in Crohn's disease are currently underway and should help to address this question.

## Anti-adhesion

Once activated lymphocytes have left lymph nodes to return to the gut as mature antigen-differentiated lymphocytes capable of secreting pro-inflammatory cytokines and chemokines, the next potential therapeutic target is inhibition of lymphocyte adhesion. This homing and adhesion require a dynamic interaction between surface ligands on leukocytes and adhesion molecules on the epithelial cell surface. Three molecules have been of particular interest for drug development in IBD and three new biologics are emerging as next-generation therapeutics.

### Vedolizumab

Vedolizumab, a monoclonal antibody that targets the α4β7 integrin, was approved for use in UC and CD and is now widely used in routine practice [10•, 11•] (Tables 1 and 2). For UC, treatment outcomes in clinical practice have mirrored those seen in the RCT with rates of clinical remission after induction ranging from 24 to 36 % [12–15]. A multi-center cohort study has reported on long-term outcomes with vedolizumab in 114 moderately severely active UC patients, and the cumulative rates of clinical remission and mucosal healing at 6 months were observed to be 26 and 31 %, with corresponding rates at 12 months being 72 and 67 %, respectively [16]. Within this multi-center consortium, the single predictor identified for failing to achieve clinical remission with vedolizumab in UC was prior exposure to a TNF antagonist (hazard ratio (HR) 0.33, 95 % CI 0.18–0.61).

For CD, rates of clinical remission after induction therapy in clinical practice have ranged from 24 to 31 %, with prior exposure to TNF antagonists ($p = 0.011$), prior hospitalization within the preceding 12 months ($p = 0.015$), and less severe disease ($p = 0.019$), being important predictors of treatment efficacy [12–15]. A multi-center cohort study has reported on long-term outcomes with vedolizumab in 212 moderately severely active CD patients, and the cumulative rates of clinical remission and steroid-free remission at 6 months were observed to be 18 %, with corresponding rates at 12 months being 34 % [17]. Within this multi-center consortium, individuals with prior exposure to TNF antagonists (HR 0.40, 95 % CI 0.20–0.81), those with more severe disease activity (HR 0.54, 95 % CI 0.31–0.95), those with active perianal disease at baseline (HR 0.49, 95 % CI 0.27–0.88), and those who were previous or current smokers (HR 0.47, 95 % CI 0.25–0.89) were less likely to achieve clinical remission. The impact of prior exposure to TNF antagonists on treatment efficacy in CD is further supported by a phase 3 RCT (GEMINI III) which demonstrated that rates of clinical remission at week 6 were not significantly different between vedolizumab and placebo among individuals with prior exposure to TNF antagonists (15.2 vs. 12.1 %, $p = 0.433$) [18•]. Rates of clinical remission were however significantly different at week 10 (26.6 vs. 12.1 %, $p = 0.001$), which would suggest that the time-dependent efficacy of vedolizumab is more pronounced among individuals with prior exposure to TNF antagonists [18•].

### Etrolizumab

Etrolizumab, a monoclonal antibody that selectively binds the β7 subunit of the α4β7 and the αEβ7 integrins, has recently completed a phase 2 trial in UC [19]. In this small study of 124 UC patients, etrolizumab was demonstrated to be considerably more efficacious as compared to placebo for achieving clinical remission with induction therapy (Table 1). Although this would appear to be twice as efficacious as vedolizumab for induction of clinical remission, it should be noted that the study end-point for induction was week 10 compared to week 6 for vedolizumab. This is of importance as week 6 clinical remission rates between the placebo group (5 %), 100 mg etrolizumab group (10 %, $p = 0.66$), and the 300 mg etrolizumab group (8 %, $p = 0.97$) were not statistically significant. Furthermore, this study had no maintenance data, it used a modified intention-to-treat analysis, and it was a relatively small study with only 39 patients analyzed in each active treatment arm. Nonetheless, these data are quite promising and phase 3 trials in UC and CD are currently underway, including a head to head comparison against adalimumab.

**Table 1** Phase 2 and 3 clinical trials in ulcerative colitis

| | S1P modulation (Phase 2) | Anti-α4β7 (Phase 3) | Anti-β7 (Phase 2) | Anti-MAdCAM-1 (Phase 2) | JAK inhibition (Phase 3) |
|---|---|---|---|---|---|
| Drug characteristics | | | | | |
| Drug | Ozanimod; oral SMI | Vedolizumab, IV monoclonal | Etrolizumab, SQ monoclonal | PF-00547659, SQ monoclonal | Tofacitinib; oral SMI |
| Mechanism | $S1P_{1R}$ internalization | Anti-integrin (α4β7) | Anti-integrin (β7 subunit) | Anti-adhesion (MAdCAM-1) | Anti-cytokine (JAK inhibitor) |
| Effect | Sequestration of T cells in lymph nodes | Inhibition of leukocyte trafficking | Inhibition of leukocyte trafficking | Inhibition ofleukocyte adhesion | Inhibition of multiple cytokines |
| Trial characteristics | | | | | |
| Design | DBPCRCT, OL arm stratified for TNF-antagonist use | DBPCRCT, OL arm stratified for TNF-antagonist use | DBPCRCT, stratified for TNF-antagonist use | DBPCRCT | DBPCRCT; stratified for TNF-antagonist use |
| Score | MCS 6–12; MES 2–3, blinded, central | MCS 6–12; MES 2–3 sigmoidoscopy | MCS 5–12; MES 2–3, blinded, central | MCS 6–12; MES 2–3 | MCS 6–12; MES 2–3, blinded, central |
| Dosing | 0.5 or 1.0 mg daily | 300 mg at 0, 2, and 6 wks induction; Q8 wk maintenance | 100 mg wks 0, 4, and 8; 420 mg wk 0 then 300 mg wks 2, 4, and 8 | 7.5, 22.5, 75 mg, or 225 mg Q4 wk for 3 doses | 10 mg BID 8 wks |
| Induction therapy | | | | | |
| Clinical remission[a] | 1 mg, 10 %<br>0.5 mg, 8 % | 12 % | 100 mg:, 21 %<br>300 mg, 10 % | 7.5 mg, 8.6 %<br>22.5 mg, 14 %<br>75 mg, 12.8 %<br>225 mg, 3.0 % | 10–13 % |
| Mucosal healing[a] | 1 mg, 22 %<br>0.5 mg, 16 % | 16 % | 100 mg, 11 %<br>300 mg, 6 % | 22.5 mg, 19.6 %<br>75 mg, 17.2 % | 16–17 % |
| Maintenance therapy | | | | | |
| Clinical remission[a] | 1 mg, 15 %<br>0.5 mg, 20 % | Q8 wk, 26 %<br>Q4 wk, 29 % | NR | NR | NR |
| Mucosal healing[a] | 1 mg, 21 %<br>0.5 mg, 20 % | Q8 wk, 32 %<br>Q4 wk, 36 % | NR | NR | NR |
| Comments | Possible cardiac and hepatic effects | Similar efficacy in clinical practice | Identified mucosal expression predictors | | Results similar in TNF-antagonist naïve and exposed |

*SMI* small molecule inhibitor, *mg* milligram, *wk* week, *IV* intravenous, *SQ* subcutaneous, *MCS* Mayo clinical score, *MES* Mayo endoscopic sub-score, *DBPCRCT* double-blind placebo-controlled randomized controlled trial, *OL* open label, *TNF* tumor necrosis factor, *Q4* every 4, *Q8* every 8

[a] Delta difference between within study intervention and placebo arms; maintenance data is week 32 data for ozanimod, week 52 data for vedolizumab. Mucosal healing: endoscopic sub-score of 0 or 1. Clinical remission: Mayo clinical score 2 or less with no sub-score greater than 1

**Table 2** Phase 2 and 3 clinical trials in Crohn's disease

| | Anti-α4β7 (Phase 3) | Anti-MAdCAM-1 (Phase 2) | Anti-IL-12/23 (Phase 3) | Anti-SMAD7 (Phase 2) |
|---|---|---|---|---|
| Drug characteristics | | | | |
| Drug | Vedolizumab, IV monoclonal | PF-00547659, SQ monoclonal | Ustekinumab, IV monoclonal | Mongersen, oral SMI |
| Mechanism | Anti-integrin (α4β7) | Anti-adhesion (MAdCAM-1) | Anti-cytokine (p40 subunit) | Anti-sense (SMAD 7/ TGF-β1) |
| Effect | Inhibition of leukocyte trafficking | Inhibition of leukocyte adhesion | Inhibition of cytokine mediation inflammation | Disinhibition of TGF-β1 mediation anti-inflammatory effect |
| Trial characteristics | | | | |
| Design | DBPCRCT, OL arm stratified for TNF-antagonist use | DBPCRCT | DBPCRCT, 2 trials in TNF-antagonist naïve or exposed | DBPCRCT |
| Score | CDAI 220-450 | CDAI 220-450 | CDAI 220-450 | CDAI 220-400; ileocolonic ds |
| Dosing | 300 mg at 0, 2, 6 wks induction; Q8 wk maintenance | 7.5, 22.5, 75, or 225 mg Q4 wk for 3 doses | 130 or 6 mg/kg | 10, 40, and 160 mg for 2 wks |
| Induction therapy | | | | |
| Clinical remission[a] | 7.7 % | 22.5 mg, 1 % | TNF-failure<br>130 mg, 8.6 %<br>6 mg/kg, 13.6 % | 160 mg, 55 % |
| | | 75 mg, 1.5 % | TNF-naïve/non-failure<br>130 mg, 11 % | 40 mg, 45 % |
| | | 225 mg, 1 % | 6 mg/kg, 21 % | 10 mg, 2 % |
| Maintenance therapy | | | | |
| Clinical remission[a] | Q8 wk: 17.4 % | NR | NR | 160 mg, 46 % |
| | Q4 wk: 14.8 % | | | 40 mg, 42 % |
| | | | | 10 mg, 8 % |

*SMI* small molecule inhibitor, *mg* milligram, *wk* week, *IV* intravenous, *SQ* subcutaneous, *CDAI* Crohn's disease activity index, *DBPCRCT* double-blind placebo-controlled randomized controlled trial, *OL* open label, *TNF* tumor necrosis factor, *Q4* every 4, *Q8* every 8

[a] Delta difference between within study intervention and placebo arms; maintenance data is 84 days for Mongersen, and week 52 data for vedolizumab

### Anti-MAdCAM-1

Another strategy to inhibit leukocyte adhesion is to block the adhesion molecule on endothelial cells as opposed to its integrin ligand. PF-00547659 is a monoclonal antibody that targets mucosal addressin cell adhesion molecule 1 (MAdCAM-1), and this drug has undergone phase 2 studies in both UC and CD. In UC, a phase 2 trial of 357 individuals demonstrated that PF-00547659 resulted in a significantly higher rate of remission and mucosal healing as compared to placebo, and this was most significant for the 22.5 and 75 mg dosing regimen [20] (Table 1). In CD, however, the phase 2 trial of 267 individuals failed to meet its primary end-point (Table 2). Despite this, there was a trend towards a higher response rate among individuals with an elevated baseline CRP and PF-00547659-treated individuals demonstrated a sustained dose-related reduction in soluble MAdCAM [21]. Given the trial was only 12 weeks in duration, and prior studies for anti-trafficking and anti-adhesion molecules have demonstrated a duration dependent efficacy that is more pronounced in CD as compared to UC, an extended duration study may be required to demonstrate a significant treatment effect size for this biologic in CD.

## Anti-cytokine

### Ustekinumab

Once activated lymphocytes return to the gut, they begin to secrete various cytokines and chemokines which are responsible for the local inflammatory micro-environment and cross-talk between immune cells. Beyond tumor necrosis factor-α, several other cytokines and cytokine pathways have now been implicated in the pathogenesis of IBD. An important pro-inflammatory cytokine pathway that induces Th1 and Th17 differentiation is IL-12 and IL-23, and a monoclonal antibody that targets this pathway through a common p40 subunit is ustekinumab. Within the phase 2b trial of CD patients who had failed prior TNF-antagonist therapy, ustekinumab resulted in a higher rate of maintaining clinical remission (41.7 vs.

27.4 %, $p = 0.03$) and steroid-free remission (30.6 vs. 17.8 %, $p = 0.048$) among patients who had responded to Ustekinumab induction therapy, as compared to placebo at week 22 [22]. Phase 3 trials have recently been completed in TNF-antagonist naïve and experience patients with promising results [23, 24] (Table 2). The improvement in clinical remission seen within these phase 3 induction trials was accompanied by improvements in biomarkers of inflammation (CRP, fecal calprotectin, fecal lactoferrin), and biochemical remission (normalization of CRP) was achieved in 21–26 %, 17–21 %, and 8–9 % of patients receiving 6 mg/kg of ustekinumab, 130 mg of ustekinumab, and placebo, respectively. In clinical practice, similar promising results have been seen with cohorts reporting a clinical benefit in over two thirds of patients after induction therapy, and the majority of these patients maintaining treatment response for up to 12 months [25, 26]. In these studies, the only significant predictor identified for achieving a clinical response with ustekinumab was the use of concomitant immunosuppressive therapy (odds ratio (OR) 5.43, 95 % CI 1.14–25.77), which is known to impact treatment outcomes with anti-cytokine biologics [3].

### Mongersen

Transforming growth factor (TGF)-β1, another important cytokine linked to the pathogenesis of mucosal inflammation in IBD, is an immunosuppressive cytokine that negatively regulates T cell immune responses. It has been demonstrated that an inhibitor of TGF-β1, SMAD7, is overexpressed in CD patients and the inhibition of SMAD7 (disinhibition of TGF- β1) restores basal negative feedback loops on cytokine production [27]. Phase 2 trials for mongersen, an oral SMAD7 antisense oligonucleotide, have now been completed, and phase 3 trials are underway [28•] (Table 2). Although this trial demonstrated the largest treatment effect size ever seen in CD, it should be noted that the inclusion criteria were very strict in large part due to the fact that the active compound of mongersen is only released in the terminal ileum and proximal colon. Thus, the clinical efficacy and therapeutic benefit of this agent in patients with more extensive disease, penetrating or stricturing complications, and prior surgical resections remain to be determined.

### Tofacitinib

Janus kinases (JAKs) are important mediators and regulators of cellular differentiation, immune cell function, and signaling pathways. By targeting JAKs, a common signaling pathway for several pro-inflammatory cytokines, therapeutic agents have the potential to inhibit both T and B cell functions, while preserving regulatory T cell function. Tofacitinib, an oral small molecule that inhibits JAK 1 and 3 (and JAK 2 at higher doses), has undergone phase 2 and 3 studies in UC. Phase 2 data demonstrated a significant treatment effect for tofacitinib with the 10-mg twice daily dosing being associated with maximum treatment effect size for clinical remission (38 %) and mucosal healing (28 %). Phase 3 data were recently presented and quite promising, with a significant treatment effect being demonstrated for both clinical and endoscopic remission [29, 30] (Table 1). It is worth noting that within one of the phase 3 induction trials (OCTAVE 1), the treatment effect size for clinical remission and mucosal healing were higher in the TNF-antagonist-exposed group (clinical remission 11 % and mucosal healing 18 %) as compared to the TNF-antagonist-naïve group (clinical remission 9 % and mucosal healing 13 %). This was not the case in the other phase 3 induction trial (OCTAVE 2) which followed more traditional outcomes for biologics and demonstrated a slightly higher treatment effect size in the TNF-antagonist naïve as compared to the TNF-antagonist exposed. Taken together, tofacitinib was efficacious in both groups and may potentially be more efficacious in TNF-antagonist-exposed patients. Furthermore, treatment effect was seen as early as 2 weeks suggesting a rapid onset of action for this biologic.

## Clinical Considerations and Future Trends

Within this review, we have highlighted several novel therapeutic agents that are currently in the process of completing or have completed phase 2 and phase 3 clinical trials. As these agents come to market, several considerations will need to be made with regard to their integration and use. Perhaps, one of the most important is drug clearance, pharmacokinetics/pharmacodynamics, and the potential advantages of small molecule inhibitors. Small molecule inhibitors, such as ozanimod, tofacitinib, and mongersen, have a distinct advantage over parenterally administered biologics in that the small molecular weight of these agents allows for rapid uptake, steady-state concentrations, and reductions in the potential for immunogenicity. An example of this can be seen within the phase 3 induction studies for tofacitinib in UC, where a very similar rate of remission was seen among all four quartiles of plasma concentrations [31]. In contrast, within the phase 3 trials of ustekinumab in CD and the phase 3 trials of vedolizumab in UC, there was a clear exposure-response relationship for serum ustekinumab and vedolizumab concentrations and remission [32, 33]. Thus, small molecule inhibitors are potentially less likely to need concomitant immunosuppressive therapy to prevent immunogenicity, and may be more favorable in individuals with a higher baseline risk for enhanced drug clearance.

Another important consideration to be made when integrating these agents into practice is the latency of onset and time to maximal efficacy. Drugs that target lymphocyte migration, ozanimod, vedolizumab, and anti-MAdCAM-1 appear to have a more gradual onset of action, which is particularly more pronounced in CD as compared to UC. This is likely

in part due to the inability of these to target local immune cell populations within sites of inflammation. In patients with more severe disease or those who are at an increased risk for immediate complications (i.e., colectomy for severe UC), anti-trafficking agents may be less effective in the short term, and anti-cytokine or anti-sense therapy may be more effective for achieving a rapid response and induction of remission. If anti-trafficking agents are to be used in these clinical settings, consideration will need to be given to concomitant administration of immunosuppressive agents or prolonged steroid tapers, to help bridge the latency of onset for treatment efficacy. Recently, the idea of combining biologics, particularly biologics with alternative mechanisms of action (i.e., infliximab + vedolizumab) has been entertained [34]. As we enter into an era of biosimilar therapy, which would make the TNF antagonist part of combination therapy more affordable, this approach may be given more consideration.

## Conclusions

In summary, several therapeutic agents will soon be coming to market in both UC and CD. These agents have distinct biologic mechanisms and modes of drug delivery, which impact their overall efficacy, latency of treatment effect, and pharmacokinetic/pharmacodynamic profiles. Alongside, this evolution in our treatment armamentarium will need to identify better strategies for optimization of patient profiling and personalization of treatment decisions.

### Compliance with Ethical Standards

**Conflicts of Interest** PSD has no conflicts or potential competing interests. WJS reports grant support from Pfizer, Exact Sciences, Amgen, the American College of Gastroenterology, and the Broad Foundation; grant support and personal fees from Prometheus Laboratories, AbbVie, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; and personal fees from Kyowa Hakko Kirin, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, Am Pharma BV, Dr. August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, Index Pharmaceuticals, Nestle, Lexicon Pharmaceuticals, UCB Pharma, Orexigen, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast Inc., Shire, Ardelyx Inc., Actavis, Seattle Genetics, MedImmune (AstraZeneca), Actogenix NV, Lipid Therapeutics Gmbh, Eisai, Qu Biologics, Toray Industries Inc., Teva Pharmaceuticals, Eli Lilly, Chiasma, TiGenix, Adherion Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx Inc., Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos, Seres Health, Ritter Pharmaceuticals, Theravance, Palatin, Biogen, and the University of Western Ontario (owner of Robarts Clinical Trials).

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Grant Support** PSD is supported by a training grant through the National Institute of Diabetes and Digestive and Kidney Diseases (5T32DK007202).

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet (Lond Engl). 2008;371(9613):660–7.
2. Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet (Lond Engl). 2015;386(10006):1825–34.
3. Dulai PS, Siegel CA, Colombel JF, Sandborn WJ, Peyrin-Biroulet L. Systematic review: monotherapy with antitumour necrosis factor alpha agents versus combination therapy with an immunosuppressive for IBD. Gut. 2014;63(12):1843–53.
4. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148(7):1320–9.e3.
5. Dulai PS, Levesque BG, Feagan BG, D'Haens G, Sandborn WJ. Assessment of mucosal healing in inflammatory bowel disease: review. Gastrointest Endosc. 2015;82(2):246–55.
6. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease—algorithm for practical management. Aliment Pharmacol Ther. 2016;43(1):30–51.
7. Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol. 2014;12(9):1443–51. **quiz e88-9**.
8. Dulai PS, Siegel CA. The risk of malignancy associated with the use of biological agents in patients with inflammatory bowel disease. Gastroenterol Clin North Am. 2014;43(3):525–41.
9.• Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016;374(18):1754–62. **Pivotal phase 2 trial of a first in class biologic agent that modulates sphingosine-1-phospate receptors and inhibits T cell release from lymph nodes**.
10.• Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710. **Phase 3 trial that led to the approval of vedolizumab in ulcerative colitis**.
11.• Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–21. **Phase 3 trial that led to the approval of vedolizumab in Crohn's disease**.

12. Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice—a nationwide consecutive German cohort study. Aliment Pharmacol Ther. 2016;43(10):1090–102.
13. Amiot A, Grimaud JC, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2016.
14. Vivio EE, Kanuri N, Gilbertsen JJ, Monroe K, Dey N, Chen CH, et al. Vedolizumab effectiveness and safety over the first year of use in an ibd clinical practice. J Crohns Colitis. 2016;10(4):402–9.
15. Shelton E, Allegretti JR, Stevens B, Lucci M, Khalili H, Nguyen DD, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. Inflamm Bowel Dis. 2015;21(12):2879–85.
16. Peerani F, Narula N, Dulai PS, Chaudrey K, Whitehead D, Hudesman D, et al. Sa1888 Efficacy and predictors of outcomes of vedolizumab for ulcerative colitis in clinical practice. Gastroenterology.150(4):S392-S3.
17. Dulai PS, Peerani F, Narula N, Chaudrey K, Whitehead D, Hudesman D, et al. Sa1889 Efficacy and predictors of outcomes of vedolizumab for Crohn's disease in clinical practice. Gastroenterology.150(4):S393.
18.• Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618–27.e3. **This study demonstrated that rates of clinical remission in Crohn's disease with vedolizumab were significantly influenced by the duration of therapy, and this more pronounced among individuals with prior exposure to anti-TNF therapy.**
19. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet (Lond Engl). 2014;384(9940):309–18.
20. Reinisch W, Sandborn W, Danese S, Cataldi F, Hebuterne X, Salzberg B, et al. 901a A randomized, multicenter double-blind, placebo-controlled study of the safety and efficacy of anti-MAdCAM antibody PF-00547659 (PF) in patients with moderate to severe ulcerative colitis: results of the TURANDOT Study. Gastroenterology.148(4):S-1193.
21. Sandborn W, Lee SD, Tarabar D, Louis E, Klopocka M, Klaus J, et al. 825 Anti-MAdCAM-1 antibody (PF-00547659) for active refractory Crohn's disease: results of the OPERA study. Gastroenterology.148(4):S-162.
22. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367(16):1519–28.
23. Sandborn W, Gasink C, Blank M, Lang Y, Johanns J, Gao L-L, et al. O-001 a multicenter, double-blind, placebo-controlled phase3 study of ustekinumab, a human IL-12/23P40 mAB, in moderate-service Crohn's disease refractory to Anti-TFN[alpha]: UNITI-1. Inflamm Bowel Dis. 2016;22:S1.
24. Late-breaking abstracts. United European Gastroenterology Journal. 2015;3(6):561-71.
25. Wils P, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, et al. Subcutaneous ustekinumab provides clinical benefit for two-thirds of patients with Crohn's disease refractory to anti-tumor necrosis factor agents. Clin Gastroenterol Hepatol : Off Clin Pract J Am Gastroenterol Assoc. 2016;14(2):242–50. **e1-2**.
26. Kopylov U, Afif W, Cohen A, Bitton A, Wild G, Bessissow T, et al. Subcutaneous ustekinumab for the treatment of anti-TNF resistant Crohn's disease—the McGill experience. J Crohns colitis. 2014;8(11):1516–22.
27. Monteleone G, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT. Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. J Clin Invest. 2001;108(4):601–9.
28.• Monteleone G, Neurath MF, Ardizzone S, Di Sabatino A, Fantini MC, Castiglione F, et al. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. N Engl J Med. 2015;372(12):1104–13. **Pivotal phase 2 trial of a first in class biologic anti-sense agent**.
29. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367(7):616–24.
30. OP019. Efficacy and safety of oral tofacitinib as induction therapy in patients with moderate-to-severe ulcerative colitis: results from 2 phase 3 randomised controlled trials. J Crohn's Colitis. 2016;10 suppl 1:S15–S.
31. DOP071. Tofacitinib plasma concentration monitoring is not needed for optimisation of induction therapy in moderate-to-severe ulcerative colitis: results of pooled exposure-response analyses of phase 3 induction studies. J Crohn's Colitis. 2016;10 suppl 1:S73–4.
32. OP028. Pharmacokinetics and exposure-response relationships of intravenously administered ustekinumab during induction treatment in patients with Crohn's disease: results from the UNITI-1 and UNITI-2 studies. J Crohn's Colitis. 2016;10 suppl 1:S23–4.
33. Osterman MT, Roblin X, Glover SC, Navaneethan U, Popa MA, Wyant T, et al. 512 Association of vedolizumab drug concentrations at or before week 6 with remission at week 14 in moderately to severely active ulcerative colitis patients from GEMINI 1. Gastroenterology.150(4):S105.
34. Hirten R, Longman RS, Bosworth BP, Steinlauf A, Scherl E. Vedolizumab and infliximab combination therapy in the treatment of Crohn's disease. Am J Gastroenterol. 2015;110(12):1737–8.