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Next generation therapeutics for inflammatory bowel disease

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Abstract

Tumor necrosis factor (TNF)-antagonists are the cornerstone of therapy for moderately-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

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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, 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 1mg resulted in statistically significant, 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 (0.5mg 14%, 1.0mg 22%) were lower than endoscopic mucosal healing rates at week 8 (0.5mg 28%, 1.0mg 34%), but at week 32 these were more comparable (histologic remission: 0.5mg 23%, 1.0mg 31%; endoscopic mucosal healing: 0.5mg 32%, 1.0mg 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 requires 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 3 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% - 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% - 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%), 100mg 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.

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 MAdCAM-1 (mucosal addressin cell adhesion molecule 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 22.5mg and 75mg 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 -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, remains 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 function, 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 10mg 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 regards 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 4 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.

Conclusion

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.

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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 of leukocyte 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	300mg at 0, 2, 6 wks induction; Q8 wk maintenance	100 mg wks 0, 4, and 8; 420 mg wk 0 then 300 mg wks 2, 4, 8	7.5mg, 22.5mg, 75mg or 225mg Q4 wk for 3 doses	10mg BID 8wks
Induction Therapy					
Clinical Remission *	1mg: 10% 0.5mg: 8%	12%	100mg: 21% 300mg: 10%	7.5mg: 8.6% 22.5mg: 14% 75mg: 12.8% 225mg: 3.0%	10-13%
Mucosal Healing *	1mg: 22% 0.5mg: 16%	16%	100mg: 11% 300mg: 6%	22.5mg: 19.6% 75mg: 17.2%	16-17%
Maintenance Therapy					
Clinical Remission *	1mg: 15% 0.5mg: 20%	Q8 wk: 26% Q4 wk: 29%	NR	NR	NR
Mucosal Healing *	1mg: 21% 0.5mg: 20%	Q8 wk: 32% 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

* 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

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

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(bt/)(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	300mg at 0, 2, 6 wks induction; Q8 wk maintenance	7.5mg, 22.5mg, 75mg or 225mg Q4 wk for 3 doses	130mg or 6mg/kg	10mg, 40mg, 160mg for 2 wks
Induction Therapy				
Clinical Remission *	7.7%	22.5mg: 1% 75mg: 1.5% 225mg: 1%	TNF-failure 130mg: 8.6% 6mg/kg: 13.6% TNF-naïve/non-failure 130mg: 11% 6mg/kg: 21%	160mg: 55% 40mg: 45% 10mg: 2%
Maintenance Therapy				
Clinical Remission *	Q8 wk: 17.4% Q4 wk: 14.8%	NR	NR	160mg: 46% 40mg: 42% 10mg: 8%

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

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