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REVIEW

Anti-cytokine therapy and small molecule agents for the treatment of inflammatory bowel disease

Yuancong Jiang[a], Deqiang Kong[a], Xiaolong Miao, Xing Yu, Zelai Wu, Han Liu, Weihua Gong

Department of Surgery, Second Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou 310009, China

Correspondence: W. Gong
<weihuagong@zju.edu.cn>
[a] These authors contributed equally to this work
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ABSTRACT. Inflammatory bowel disease (IBD), including Crohn disease and ulcerative colitis, with multifactorial etiologies has led to a global health-associated burden in many countries. Substantial efforts are devoted to understand the pathogenesis, behavioral and environmental triggers, which may be specifically valuable for the treatment of IBD. The specific pathogenesis underlying IBD is as yet incompletely understood. The use of anti-cytokine therapy and small molecule agents targeting the immune system is thought to restore the body's intestinal barrier function and relieve inflammation with manageable adverse effects. In this review, we report recent advances in anti-cytokine therapy and treatment with small molecule agents for the management of IBD.

Key words: inflammatory bowel disease, cytokines, small molecule therapy

Inflammatory bowel disease (IBD) is a term for two clinical conditions, Crohn disease (CD) and ulcerative colitis (UC), which are chronic relapsing inflammatory disorders of the gastrointestinal tract [1, 2]. The global prevalence and incidence of IBD continue to grow and contribute to an increasingly major health-associated burden in many countries, especially in North America, Oceania, and Europe, with a prevalence surpassing 0.3% and more than 6.9 million cases of this disorder (nearly 3.9 million for females and 3.0 million for males) worldwide in 2020 [3]. In newly industrialized countries, where the rapidly increasing incidence of IBD is associated with the transition to a more western industrial style, the peak incidence of IBD may not yet have been reached [2, 4, 5]. Of special interest, the incidence of pediatric-onset IBD patients who are diagnosed at age <18 years is approximately 10/100,000, with approximately 19% of incident cases present before age of 10 years [6, 7]. Generally, polygenetic and epigenetic susceptibility, environmental exposure, and immunologic factors have been implicated in IBD with the hallmarks of reshaped microbiome composition and impaired barrier function [8-10].

Over the past two decades, the therapeutic landscape of IBD has significantly changed. Traditionally, patients with structuring or penetrating disease are treated with 5-aminosalicylates, corticosteroids, immunomodulators, and even surgery [11], for maintenance therapy [12, 13]. The common therapeutic strategies in IBDs are summarized in *table 1*. However, due to their many adverse effects, as well as the incurable and recurring nature of IBD, there is an urgent need to explore alternative treatment options. The emergence of anti-cytokine therapy, as well as the development of small molecule agents, that target various signaling pathways in inmmunocompetent cells involved in the pathogenesis of IBD, has opened new perspectives for the treatment of IBD. Moreover, from the perspective of the etiology of IBD, more than 200 genetic-risk loci were identified, which provided a firm groundwork for the use of potential molecular targeted drugs [14-16]. However, even with these newer treatment strategies, recurrence may develop as well and more research is needed on the mechanisms of IBD and the development of anti-cytokine therapy and small molecule agents.

ANTI-CYTOKINE THERAPY IN IBD

Anti-tumor necrosis factor-α therapy

Tumor necrosis factor-α (TNF-α), a transmembrane protein, is widely thought to play a key role in the acute phase and mucosal healing of IBD, promoting the inflammatory process [17-19]. Since the first correlation of TNF-α and IBD was identified in 1991 [20], anti-TNF-α therapy has been implemented in clinical treatment with a significant therapeutic effect. To date, the use of anti-TNF-α monoclonal antibodies (mAbs) with neutralizing activity, such as infliximab, adalimumab, and certolizumab pegol, which activate the reverse signaling cascade, induce apoptosis and mediate cytotoxicity (ADCC), as well as complement-

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Table 1
Traditional therapeutic strategies in inflammatory bowel disease

Therapeutic strategies	Representative drugs or techniques
5-Aminosalicylic acid	Mesalazine, olsalazine, balsalazide, sulfasalazine
Glucocorticoids	Prednisone, hydrocortisone, methylprednisolone
Immunosuppressive drugs	Azathioprine, methotrexate, tacrolimus, thalidomide
Surgery	Laparoscopic or open abdominal surgery

dependent cytotoxicity, have been approved for IBD treatment as a first-line biologic agent with improved long-term patient outcomes [21, 22]. In a cohort study, adalimumab drug levels of at least 8.14 μg/mL were considered to indicate sufficient clinical and endoscopic remission/mucosal healing [23]. The use of infliximab and adalimumab was also reported, to have no deleterious effects on women during pregnancy and newborns in three independent clinical trials [24-26]. Consistent with the safety of infliximab and adalimumab in adults, pediatric patients with IBD demonstrated safety, efficacy, and growth rate normalization in several phase 3 trials [27-29], even at a high dose (infliximab 10 mg/kg) [30]. Considering the economic burden of anti-TNF-α therapy, the biosimilar infliximab CT-P13 was approved for switching therapy, which was effective and safe for long-term remission compared with infliximab in phase 3 to 4 trials [31-33]. However, rare but serious side effects, including cardiac failure and dermatologic complications, in addition to the development of opportunistic infections, including tuberculosis and even a risk for the development of malignancies, were reported in a small proportion of patients with IBD [34-37]. In a long-term real-world study by Lichtenstein *et al*. [38], infliximab was associated with a higher rate of serious infection, nonserious cerebrovascular accidents, and pulmonary embolisms, than other treatments, but similar mortality and malignancy rates. In addition, an estimated 30% to 40% of patients with IBD failed to achieve clinical remission primarily or lose response over time, which limits further applications [37, 39, 40]. In this respect, adalimumab dose escalation was required in a majority of patients for maintenance [41, 42]. In contrast, repeated administration with an anti-TNF-α agent may often result in treatment failure partly due to the immunogenicity and low-drug concentration at week 14 [43]. The results from a genome-wide association study within the framework of PANTS, a prospective cohort of 1240 patients with IBD, demonstrated that the risk of developing anti-TNF-α antibodies increased with the carriage of the HLA-DQA1*05 allele and therefore might provide an individualized choice for anti-TNF-α treatment [44].

Anti-integrin therapy

Lymphocyte Peyer patch adhesion molecule 1, a heterodimer of the intergrins α4 and β7, and a receptor expressed on the surface of T cells, facilitates lymphocyte recruitment to the intestinal mucosa *via* interaction with mucosal addressing cell adhesion molecule 1 (MAdCAM-1) [45, 46]. The humanized immunoglobulin G-1 (IgG-1) mAb vedolizumab selectively inhibits the interaction of $\alpha_4\beta_7$-binding MAdCAM-1 in the gut and alleviates intestinal inflammation [47, 48]. A large number of clinical trials have been initiated to evaluate the therapeutic effects of vedolizumab in patients with IBD. In particular, the GEMINI clinical trials provided evidence for the use of vedolizumab as an induction and maintenance treatment for patients with UC and Crohn disease (CD) and patients with CD who failed to respond to TNF-α antagonist treatment [49-51]. In two post-hoc analyses focus on the GEMINI 1 trial, both Sandborn *et al*. [52] and Feagan *et al*. [53] reported the trend that higher trough serum concentrations of vedolizumab were associated with higher rates of deep remission at week 52 and increased health-related quality of life (placebo 8.7–15.9% vs. vedolizumab 27–43.4% in different definitions of deep remission). In detailed, the placebo group achieved 8.7% at endoscopic remission and symptomatic improvement [Mayo Clinic endoscopic score (ES) = 0, rectal bleeding score (RBS) = 0, and decrease in stool frequency score (SFS) or no change from baseline], 13.5% at endoscopic improvement and symptomatic remission (Mayo Clinic ES $\leq$ 1, RBS = 0 and SFS = 0), 15.1% at endoscopic and symptomatic improvement [Mayo Clinic ES $\leq$ 1, RBS = 0, decrease in SFS or no change from baseline, and total score (ES + RBS + SFS) $\leq$ 1], and 15.9% at endoscopic and symptomatic improvement (Mayo Clinic ES $\leq$ 1, RBS = 0, and SFS $\leq$ 1). In contrast, the vedolizumab group achieved 27% at endoscopic remission and symptomatic improvement, 32.8% at endoscopic improvement and symptomatic remission, 36.1% at endoscopic and symptomatic improvement, and 43.4% at endoscopic and symptomatic improvement. A meta-analysis also demonstrated consistent results from GEMINI data and quantified the concentration of thresholds >20 μg/mL at week 6 and >12 μg/mL during maintenance with favorable outcomes in patients with UC [54]. For extra-intestinal manifestations (EIMs), the data from the GEMINI trials showed that, compared with placebo, vedolizumab is associated with a lower rate of new/worsening arthritis/arthralgia in CD. Notably, concomitant corticosteroid therapy with vedolizumab is positively correlated with the absence of EIM, as well as improved clinical response or remission in CD [55, 56]. However, paradoxical skin manifestations, such as worsen psoriatic lesions, psoriasiform eczema skin lesions or eczema skin

lesions, and inflammatory arthralgia/arthritis were reported in a small population during vedolizumab therapy in the OBSERV-IBD cohort study [57]. Collectively, the treatment of EIM with vedolizumab in quiescent CD was effective. In contrast, consistent results were not observed in UC [55].

In a large, real-world cohort study, vedolizumab was confirmed to be effective induction and maintenance therapy compared with placebo in both CD and UC, with clinical remission at 1 year being 22.1% and 61.9%, respectively [58]. In addition, trials comparing the efficacy of vedolizumab with other available biologic agents were conducted. Compared with adalimumab treatment, vedolizumab showed a significant benefit in patients with moderate to severe UC with clinical remission and endoscopic improvement at week 52, but a lower rate of corticosteroid-free clinical remission in phase 3b VARSITY trials that enrolled patients who had previously received TNF-α inhibitors [47]. Similar results were reported in two multicenter cohort studies [59, 60]. However, the rate of disease remission in patients with CD was similar between vedolizumab and TNF-α antagonist therapy [61]. A low rate of opportunistic infections (0.7–1.0/100 patients) was reported during 1 year of vedolizumab treatment, mostly with *Clostridium difficile* (0.5/100 patients), in some phase 3 clinical trials [62].

For outcomes of women during pregnancy and pediatric patients treated with vedolizumab, the data were limited. As reported by Moens *et al*. [63], several complications were reported in 25% of pregnancies and in 35% of infants among 24 pregnancies and 23 live births. Due to the potential blockage of MAdCAM-1 expressed in the placenta and lymphocyte recruitment [64], vedolizumab treatment should be implemented with caution. Nevertheless, a recent study presented the existence of a strong association exists between vedolizumab and changes in innate immunity, including alterations in macrophage populations and cell surface expression of molecules involved in microbial sensing, chemoattraction, and regulation of the innate effector response, with few effects on the interaction of $\alpha_4\beta_7$ with MAdCAM-1 [45]. For the pediatric patients, a clinical response was reached at week 6 to 31.6%, week 14 to 52.6%, and week 22 to 57.9%, and steroid-free remission was reached at week 22 to 20%. However, 12 serious adverse events occurred in 21 patients [65]. Larger prospective randomized trials are warranted to investigate the effect of vedolizumab therapy and the relation between adverse events and vedolizumab in obstetrical and pediatric patients.

Anti-interleukin 12/interleukin 23 agents

The production of interleukin 12 (IL-12) and IL-23 by dendritic cells is upregulated in IBD, contributing to the development of inflammation development by inducing a T helper 1 (Th1) and Th17 response, respectively [66, 67]. Ustekinumab, a human mAb that targets the shared p40 subunit of IL-12 and IL-23, showed a significant clinical response in patients with moderate to severe CD and UC by intravenous ustekinumab injection (single dose of 130 mg or 6 mg/kg) for induction and subcutaneous ustekinumab injection for maintenance therapy (every 8 weeks or every 12 weeks). Specifically, clinical remission was achieved in 15.6% of patients with the use of intravenous ustekinumab 130 mg/kg or in 15.5% of patients with the use of intravenous ustekinumab 6 mg/kg for induced therapy, and in 38.4% of patients with the use of subcutaneous ustekinumab every 12 weeks and in 43.8% patients with the use of subcutaneous ustekinumab every 8 weeks for maintenance therapy, compared with patients who received placebo (5.3% for induced therapy and 24.0% for maintenance therapy) [68]. The efficacy of ustekinumab was also demonstrated in the treatment of CD, regardless of whether patients previously received TNF-α antagonists [69, 70]. A low immunogenicity rate was reported in the maintenance of CD [71]. In a pilot study by Rowan *et al*. [72], subcutaneous ustekinumab induction (360 mg) was proposed as an alternative strategy in CD with trough concentrations of 6.1 μg/mL and a comparable rate of clinical remission (84.2%, 16/19) at week 8, and large population trials are needed for further confirmation. Several recent meta-analyses and clinical trials have claimed that the use of ustekinumab seems prior to the use of vedolizumab against IBD because of the higher rate of remission and endoscopic improvement in patients who are refractory to anti-TNF-α therapy [73-75]. However, the benefits of ustekinumab over vedolizumab remain controversial [76]. Nevertheless, ustekinumab is highly recommended for patients who have previously failed anti-TNF-α and anti-integrin therapy [77].

Risankizumab is a novel IgG-1 mAb that specifically targets the p19 subunit of IL-23 was launched in recent years. Compared with placebo, the use of intravenous risankizumab (600 mg) in patients with moderate to severe CD promoted the rates of clinical response (71%) and remission (47%) at week 26, and subcutaneous risankizumab (180 mg) was implemented for maintenance therapy at week 52. For these patients who received a placebo, switching risankizumab from placebo at week 12 may contribute to an increase in clinical remission [78, 79]. With the promising results of risankizumab in the treatment of IBD, the clinical trials on the comparison between risankizumab and ustekinumab in patients with IBD are ongoing [80]. In a phase 2 trial, Papp *et al*. [81] demonstrated that the therapeutic effect of risankizumab was superior to ustekinumab for moderate to severe plaque psoriasis. At present, a phase 3 trial (NCT04524611) involving in risankizumab and ustekinumab is ongoing, but no result is available on the therapeutic effect of both mAbs for treatment of IBD [81].

SMALL MOLECULES FOR THE TREATMENT OF IBD

JAK Inhibitors

The JAK-STAT pathway is widely involved in immune regulation, cancer pathophysiologic processes and

inflammation progression in many human diseases, including IBD [82, 83]. The development of small molecules targeting this pathway has permitted their use for therapeutic purposes notably in chronic inflammatory disease. Compared with mAb therapy, such compounds have the advantage to not elicit immunogenicity and have been shown clinical benefit in a series of phase 1 and 2 trials with patients with IBD [84]. Tofacitinib, an oral, nonselective JAK inhibitor, was implemented for the treatment of moderate to severe UC [85, 86]. Compared with placebo treatment, tofacitinib showed an effective benefit in the induction (10 mg twice daily) and maintenance (5 or 10 mg twice daily) of IBD in three phase 3 trials [87] (OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain). In two real-world retrospective cohorts, tofacitinib caused clinical remission in 41% of cases at week 12, in 32.5% at week 24, and in 27% after a year of treatment [88, 89]. Dose escalation of tofacitinib was a potential approach for patients who failed maintenance therapy (5–10 mg, but 15 mg twice daily was not regularly recommended) [86, 90]. The incidence of individual adverse events was generally consistent with the placebo group except for the higher incidence of herpes zoster, which was over 4% [91]. Moreover, patients treated with tofacitinib experienced a dose-dependent, increased risk of herpes zoster infection [86, 92].

Sphingosine-1-Phosphate Signaling (S1PR Agonists)

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that binds to five G protein-coupled receptors [16, 93]. Ozanimod, a novel S1P receptor modulator against subtypes 1 and 5, is currently being evaluated for induction therapy in patients with IBD in multinational phase 2 trials [94-96]. In a phase 2 trial enrolled in 197 patients with UC, treatment with 1 mg of ozanimod contributed to clinical remission in 16% of patients at 8 weeks and 21% of patients at week 32, slightly higher than the placebo group (6% and 6%, respectively) [96]. Another dose of 0.5 mg has been evaluated also in this trial. But no significant difference was observed in the clinical remission between the use of placebo and ozanimod, indicating that the dose of 0.5 mg may not be effective in induction therapy. Moreover, the absolute lymphocyte counts dropped dramatically in the ozanimod group. In another phase 2 trial, dose escalation was implemented from 0.25 mg (4 days) and 0.5 mg (3 days) to 1.0 mg (11 weeks) in the induction period for the treatment of CD. In total, 69 patients were included, and 27 patients were observed with clinical remission, pointing to a favorable prospect of alternative cures [94]. However, the rate of flares of CD developed in 26% of patients, and the overall rate of adverse events was reportedly high. In 2020, etrasimod, a novel S1PR agonist that selectively targets S1P1, S1P4, and S1P5 receptor modulators, was studied in a phase 2 clinical trial for patients with UC. Compared with placebo, clinical remission was achieved at week 12 by receiving 2 mg etrasimod (33.0% vs. 8.1%) [97]. However, the use of etrasimod also resulted in decreased absolute lymphocyte counts and serious treatment-emergent adverse events might limit its clinical application. In this respect, the safety and efficacy of S1PR agonists need to be further confirmed by large clinical trials.

SMAD Genes

Transforming growth factor (TGF)-β, a pleiotropic cytokine, has been demonstrated to be instrumental in maintaining mucosal homeostasis and enhancing anti-inflammatory effects *via* the activation of SMAD 2/3 proteins [98, 99]. However, the inhibitory protein SMAD7 negatively regulates the activation of SMAD 2/3 and competitively binds TGF-β receptor complex, thereby preventing the anti-inflammatory effect of TGF-β. Mongersen is an antisense oligodeoxynucleotide that can hybridize and degrade SMAD7 messenger RNA [98]. In a phase 2 trial, 166 patients with CD were enrolled and received three different doses of mongersen (10, 40, or 160 mg/day). Clinical remission at day 15 was achieved in 55% and 65% of the 40- and 160-mg mongersen groups, respectively, compared with 10% for placebo treatment [100]. Furthermore, post-hoc analysis indicated that for patients with a CD activity index >260, a dose of 160 mg/day was advised in the treatment instead of 40 mg/day [101]. The use of 160 mg mongersen daily was also supported by endoscopic improvement in participants at week 12 [102]. However, phase 3 clinical trials have shown that in active CD, mongersen has no strong therapeutic efficacy compared with placebo, which warrants more randomized clinical trials to confirm these conclusions [103].

Phosphodiesterase-4 Inhibitors

Phosphodiesterase (PDE) 4 is an enzyme that regulates cyclic adenosine monophosphate (cAMP), which is a basic intracellular second messenger involved in inflammation regulation and biochemical functions [104, 105]. Inhibition of PDE 4 reduces the production of TNF-α, IFN-γ, and IL-17 and increases the synthesis of the anti-inflammatory cytokine IL-10 by increasing cAMP levels [106]. Apremilast, an oral PDE-4 inhibitor agent, underwent a phase 2 trial for patients with active UC who had not been treated with biologic agents or had failed conventional therapies [107]. A treatment with apremilast at 30 mg twice daily resulted in a clinical remission of 31.6% at week 12 *versus* 12.1% in the placebo groups. Unexpectedly, dose escalation of apremilast showed minimal benefits. The use of 30 and 40 mg of the drug achieved clinical remission rates of 31.6% and 21.8% at week 12 and 40.3% and 32.7% at week 52, respectively. Headache and nausea were the most frequent adverse events, but severe weight loss (weight loss $\geq$10%) reported in a previous study of psoriatic disease was not observed [107, 108].

Table 2
Ongoing trials of anti-cytokine therapy for inflammatory bowel disease

Class	Drug	Route of administration	Clinical stage		Pharmaceutical Corporation	ClinicalTrials. gov reference	
			CD	UC		CD	UC
Anti-TNF-α therapy	Infliximab	Intravenous	Approved in USA		Johnson & Johnson	–	
	Adalimumab	Subcutaneous	Approved in USA		AbbVie	–	
	Certolizumab pegol	Subcutaneous	Approved in the USA		UCB	–	
	CT-P13	Intravenous or subcutaneous	Approved in USA/EU		Celltrion	–	
	AVX-470	Oral	–	Phase 1	Avaxia Biologics	–	NCT01759056
	Golimumab	Subcutaneous	Approved in the USA		Janssen	–	
Anti-integrin therapy	Natalizumab	Intravenous	Approved in the USA		Biogen Idec	–	
	Vedolizumab	Intravenous	Approved in the USA/EU		Takeda	–	
	Etrolizumab	Subcutaneous	Phase 3	Phase 3	Genentech	NCT02403323	NCT02165215
	Abrilumab	Subcutaneous	Phase 2	Phase 2	Amgen	NCT01696396	NCT01694485
	AJM300	Oral	–	Phase 3	EA Pharma	–	NCT03531892
Anti-IL-12/IL-23 agents	Ustekinumab	Intravenous or subcutaneous	Approved in the USA/EU		Janssen	–	
	Risankizumab	Intravenous	Phase 3	Phase 3	AbbVie	NCT03105128	NCT03398135
	Brazikumab	Intravenous or subcutaneous	Phase 3	Phase 2	AstraZeneca	NCT03961815	NCT03616821
	Mirikizumab	Intravenous or subcutaneous	Phase 3	Phase 3	Eli Lilly	NCT04232553	NCT03519945
	Guselkumab	Intravenous	Phase 3	Phase 2/3	Janssen	NCT04397263	NCT04033445

CD: Crohn disease; UC: ulcerative colitis; IL: interleukin.

Table 3
Ongoing trials of small molecule agents for inflammatory bowel disease

Class	Drug	Route of administration	Clinical stage		Pharmaceutical Corporation	ClinicalTrials. gov reference	
			CD	UC		CD	UC
JAK Inhibitors	Tofacitinib	Oral	Phase 3	Approved in USA	Pfizer	NCT04852666	-
	Filgotinib	Oral	Phase 3	Phase 3	Gilead Sciences	NCT02914561	NCT02914522
	Upadacitinib	Oral	Phase 3	Phase 3	AbbVie	NCT03345836	NCT03653026
	Peficitinib	Oral	-	Phase 2	Janssen	-	NCT01959282
	TD-1473	Oral	Phase 2	Phase 2/3	Theravance Biopharma	NCT03635112	NCT03920254
	PF-06651600	Oral	Phase 2	Phase 2	Pfizer	NCT03395184	NCT02958865
S1PR Agonists	Ozanimod	Oral	Phase 3	Phase 3	Celgene	NCT03467958	NCT03915769
	Etrasimod	Oral	Phase 2/3	Phase 3	Arena Pharmaceuticals	NCT04173273	NCT03996369
	Laquinimod	Oral	Phase 2	-	Teva Pharmaceutical Industries	NCT00737932	-
PDE Inhibitors	Apremilast	Oral	-	Phase 2	Amgen	-	NCT02289417

CD: Crohn disease; UC: ulcerative colitis.

CONCLUSIVE REMARKS

Accumulating evidence suggests that cytokine networks play a critical role in pathogenesis, and many clinical trials have addressed the possibility to manage IBD by targeting these pathways, either by neutralizing mAbs of small molecules [84, 109]. Ongoing trials of anti-cytokine therapy and small molecule agents for IBD are summarized in *tables 2 and 3*, and the diagram for the various molecular mechanisms underlying the success of anti-cytokine therapy is summarized in *figure 1*.

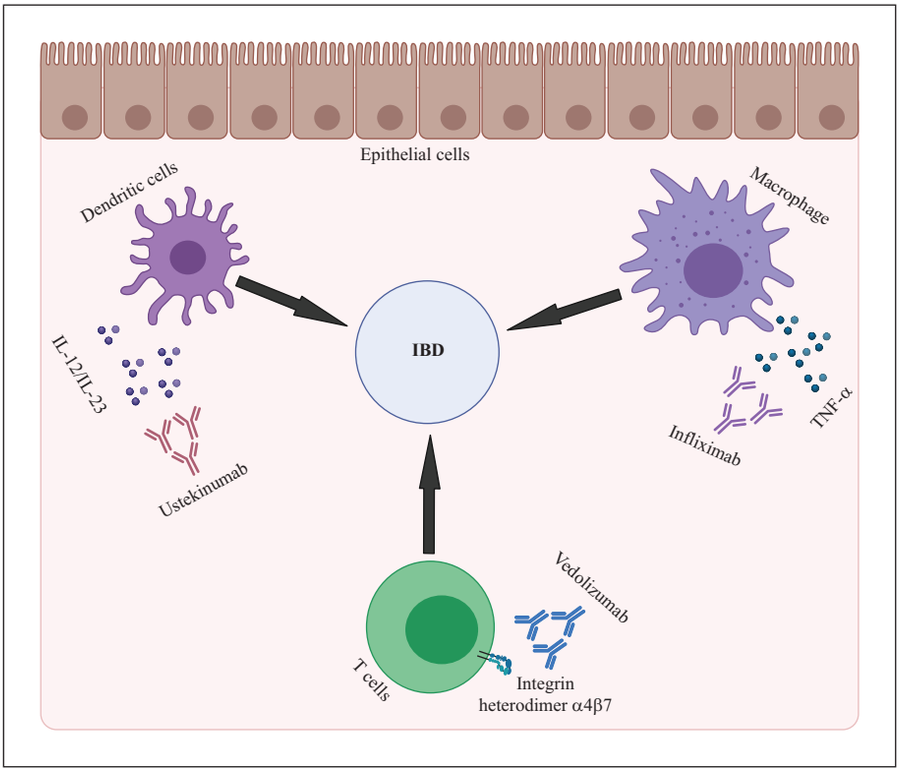

Figure 1
The diagram for the molecular mechanism of anti-cytokine therapy in inflammatory bowel diseases. Figure 1 was created with BioRender.com.

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