EXPERT OPINION

New biologic therapeutics for ulcerative colitis and Crohn's disease

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Introduction: Some inflammatory bowel disease (IBD) patients especially those with refractory Crohn's disease (CD) or relapsing ulcerative colitis (UC) do not respond to current therapies. The newly introduced biological drugs have got some interest due to their specificity and selectivity in modulation of inflammatory elements.

Areas covered: In 46 included randomized, placebo-controlled clinical trials, the efficacy and safety of different biologic drugs have been evaluated in moderately to severely active CD or UC patients. Current investigated drugs include new anti-TNF drugs (adalimumab, certolizumab pegol, etanercept, onercept and golimumab), anti-CD20 (rituximab), T-cell inhibitors (abatacept) and anti-α4 integrins (natalizumab and vedolizumab). Adalimumab, certolizumab, and golimumab showed significant efficacy in induction of remission and maintenance in CD and UC patients with a rate of adverse events similar to placebo in the major trials. Natalizumab and vedolizumab were effective in the treatment of moderately to severely active CD and UC patients. However, vedolizumab caused less adverse effects than natalizumab. onercept, etanercept, rituximab and abatacept were all well tolerated but were not effective in CD or UC patients.

Expert opinion: Anti-TNF drugs, except for onercept and etanercept, and anti-α4 integrins exhibit beneficial therapeutic effects. Although they were all well tolerated, the incidence of progressive multifocal leukoencephalopathy associated with natalizumab should not be missed.

Keywords: adalimumab, anti-TNF drugs, certolizumab, Crohn's disease, golimumab, infliximab, natalizumab, remission, systematic review, ulcerative colitis

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1. Introduction

Inflammatory bowel disease (IBD) is regarded as a gastrointestinal (GI) inflammation, principally in the whole bowel wall or in the mucosa and epithelial lining of the gut, colon and the rectum. IBD shows itself in two forms of ulcerative colitis (UC) and Crohn's disease (CD) that are differentiated by the spread and extent of inflammation and also the complications [1-3].

5-Amino salicylate [4,5], corticosteroids [6], immunosuppressive agents and anti-TNF [7-9], antibiotics [10,11], antioxidants [12], probiotics [13,14], phosphodiesterase inhibitors [15], potassium channel openers [16], adenosine triphosphate donors [17], melatonin [18] and some natural products [19,20] are some of the current available therapeutic options for IBD. However, these therapies are involved with more or less insufficient efficacy or have somehow safety concerns. Therefore, except for non-responders, discontinuation of treatment due to lack of drug potential to maintain patients in remission in long term is usually observed in clinical practice.

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Article highlights.

- Inflammatory bowel disease (IBD) is regarded as a gastrointestinal inflammation, principally in the whole bowel wall or in the mucosa and epithelial lining of the gut, colon and the rectum.
- The overactive immune system has been known in IBD pathogenesis, supporting the use of biological immunomodulators in management of IBD.
- Several pro-inflammatory cytokines including TNF-α, IL-12 and IL-23 appear to be critical in amplification of mucosal inflammation in patients with Crohn's disease (CD). Accumulative levels of TNF-α are found in the blood, colonic tissue and stools of patients with ulcerative colitis (UC).
- Inhibition of TNF-α production and activity is a new therapeutic strategy and numerous pharmaceutical companies are trying to design TNF-α-targeted molecules.
- The efficacy and safety of anti-TNF drugs, anti-CD20, T-cell inhibitors and anti-integrin in 46 studies including Phase II, Phase III/randomized, double–blinded, placebo-controlled trials have been evaluated in patients with CD or UC.
- Regarding rapid growth in development of new therapeutic options for CD and UC in the current decade, the results of efficacy and safety investigations on biologic drugs help introducing better drugs to market in near future.

This box summarizes key points contained in the article.

Besides, as addressed above, some toxic adverse events and sensitivity reactions make the conventional therapeutics intolerable for patients with chronic active CD or UC.

Although the exact etiology of CD and UC has not been clearly explained yet, with current knowledge, the role of genetic susceptibility, environmental factors, immune dysregulation, intestinal microbes and oxidative stress cannot be ignored [21-23].

As shown in **Figure 1**, the overactive immune system responses are believed to have the main role in IBD pathogenesis [24,25]. Interaction between immune system and encountered antigens has an important role in mucosal system of patients with IBD [24].

Several pro-inflammatory cytokines including TNF-α, IL-12 and IL-23 appear to be critical in the amplification of mucosal inflammation in patients with CD [26,27]. Likewise, accumulative levels of TNF-α has been found in the blood, colonic tissue and stools of patients with UC [28,29]. TNF-α has somehow provoking effects on the immune system comprising neutrophils and macrophages, B cells, production of IFN-γ by mucosal T-cells, the expression of adhesion molecules on vascular endothelial cells and secretion of tissue-altering enzymes such as matrix metalloproteinases, collagenase and elastase [30]. Therefore, inhibition of TNF-α production or activity is a new therapeutic strategy and numerous pharmaceutical companies are designing TNF-α-targeted molecules.

Infliximab is an IgG-1 monoclonal antibody that binds to TNF-α [31]. Infliximab is the first approved TNF-α inhibitor for CD by inducing and maintaining remission in steroid-refractory, steroid-dependent and immunomodulator-refractory inflammatory CD as demonstrated during ACCENT studies (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease). It is demonstrated to exert its beneficial effects via treating complex fistula and preventing postoperative recurrence. Furthermore, as a new indication for anti-TNF drugs, it has been approved in 2006 for UC based on the results of the acute ulcerative colitis treatment trial (ACT)-I and -II trials that evaluated the safety and efficacy of infliximab for induction and maintenance therapy in adult patients with moderately to severely active UC [32-34]. Several other drugs with similar mechanism of action have been designed currently and evaluated in clinical trials such as adalimumab, a fully human anti-TNF monoclonal antibody that has been approved in 2012 for treatment of moderately to severely active UC and CD. Certolizumab pegol or CDP870, a TNF monoclonal antibody, is only approved in Switzerland for CD. Other newly introduced molecules are etanercept (targeting TNF receptor-IgG fusion protein) and onercept (targeting TNF receptor), which have failed to have a beneficial therapeutic effect. Golimumab is almost one of the latest introduced anti-TNF antibodies. It has demonstrated a higher affinity than adalimumab. Therefore, it is associated with promising efficacy in patients with moderately to severely active UC during Phase II and III of clinical trials, as expected. Golimumab has been approved by FDA in 2013 for treatment of moderately to severely active UC.

T-cells as one of the involved factors in the pathogenesis of inflammation could be a therapeutic target. T-cell CD28 and CD80 or CD86 signaling on the antigen-presenting cells can stimulate activation of T-cells. Cytotoxic T-lymphocyte antigen 4 can inhibit CD28 binding to CD80 or CD86 [35]. Therefore, designing a molecule with similar action to cytotoxic T-lymphocyte antigen 4 may be of value in blocking stimulatory signaling of CD28, resulting in modulation of T-cell activation. Referring to that mechanism, abatacept is a recombinant fusion protein that exerts its effect similar to cytotoxic T-lymphocyte antigen 4.

Inflammatory disorders comprise impairment in leukocyte circulation known as leukocyte trafficking. Therefore, inhibition and modulation of leukocyte trafficking in gut mucosa has been demonstrated as a promising target in IBD treatment. These types of drugs can reduce the recruitment of inflammatory cytokines and cells into the gut tissues. Different types of integrins, generally expressed on leukocytes, are believed to exert role in the adhesion, migration and activation of immune cells across the vascular endothelium. α4 integrin has the ability to attach the vascular cell adhesion

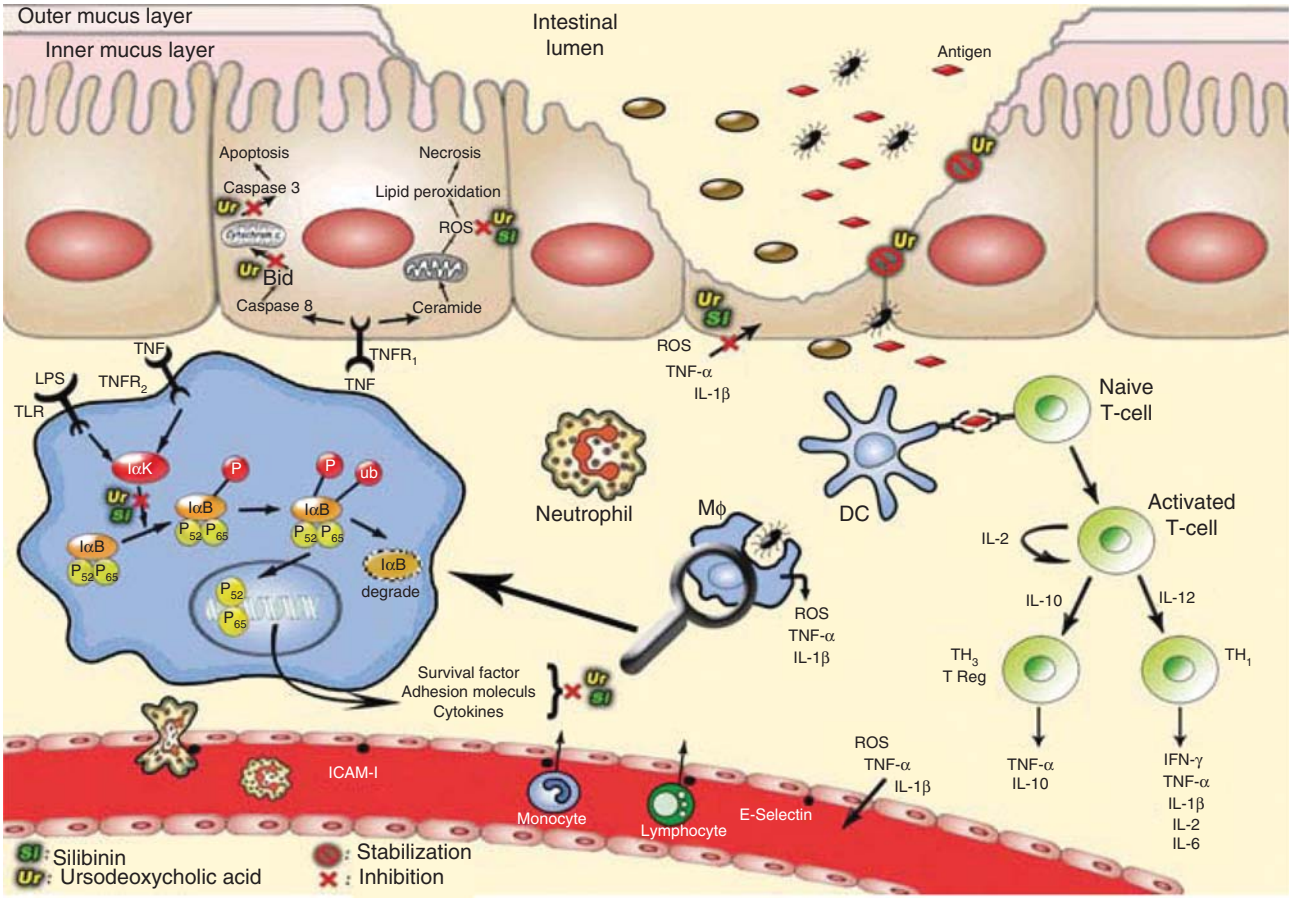

Figure 1. Role of inflammatory elements in inflammatory bowel disease.

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DC: Dendritic cell; LPS: Lipopolysaccharides; Mϕ: Interstitial macrophage; ROS: Reactive oxygen species; Si: Silibinin; TNFR: Tumor necrosis factor receptor; Ur: Ursodeoxycholic acid.

molecule (VCAM-1) and mucosal vascular addressin cellular adhesion molecule (MAdCAM-1), which is increased during the inflammation process. This interaction may be necessary for facilitating leukocyte migration to gut mucosa. In a tissue with chronic inflammation in the mucosa like GI in IBD, inhibition of α4 integrin could be a useful therapeutic target [36]. Referring to this mechanism of action, natalizumab and vedolizumab have been introduced that are recombinant humanized monoclonal IgG antibodies to α4 integrins that inhibit migration of leukocytes into GI [36]. Natalizumab has been approved by FDA in 2008 for both induction and maintenance of remission in patients with moderately to severely active CD. Forasmuch as natalizumab use is limited due to the observed risks of severe adverse events in patients, vedolizumab has been introduced with the similar mechanism of action but the higher selectivity. It is indicated to inhibit α4 integrins in the gut specifically. Thus, it results in reducing the α4 integrin-mediated lymphocyte trafficking within GI tract without adverse events in nervous system. Vedolizumab has the positive recommendation of management advisory committees of FDA for treatment of moderately to severely active UC and CD, based on the results of efficacy and safety trials. Among involved factors in leukocyte trafficking, CC chemokine receptor-9 (CCR9) has been proposed recently. CCR9 expresses on T-cells in the gut. The activation of this receptor results in T-cell binding to VCAM-1 and MAdCAM-1 with the mediation of integrins [37,38]. Considering this process, antagonizing this receptor may modulate the inflammation as vercirnon (GSK-1605786, CCX282-B), the selective antagonist of CCR9 does that by binding to the gut T-cells. This drug has been evaluated in Phase II trials (the prospective randomized oral-therapy evaluation in Crohn's disease trial-1 [PROTECT-1]) for treatment of patients with moderately to severely active CD [37,38]. The oral administration of this drug besides its confirmed efficacy through future Phase III clinical trials may introduce it as a beneficial treatment in CD. Overexpression, overactivation and B-cell dysfunction have been demonstrated in immune disorders including autoimmune diseases. CD20 is a protein that is expressed on the surfaces of B cells. Rituximab is an

antibody for the protein CD20, used in several malignancies and autoimmune diseases. IBD could be one of the inflammatory conditions that rituximab may be a beneficial treatment for [39].

2. Search strategy

Electronic databases, including PubMed, ClinicalTrial.gov, Google Scholar, Web of Science, Scopus and Cochrane Central Register of Controlled trials were searched for all clinical trials in which the efficacy and safety of novel biologic drugs for IBD (CD, UC) up to 2013 September were investigated clinically. The applied search terms were tumor necrosis factor, anti-TNF, efficacy, safety, biologic drugs, UC and CD. The reference lists of searched articles were brushed up for further applicable studies. The title and abstract of each article were examined to eliminate duplicates, reviews, case studies, non-clinical and pilot studies. All Phase II and III controlled clinical trials evaluating the efficacy and safety of novel biological molecules in IBD patients were considered. We excluded the studies in which the evaluated drug has been failed and did not continue, such as alicaforsen. We also did not summarize the details for infliximab that has the earlier approval for both UC and CD. However, adalimumab and certolizumab regarding updated trials (2011 – 2013) were included. According to the aim of this review, we focused on biological drugs other than IL-targeted therapies. Data were extracted according to study design, number and characteristics of included IBD patients, type of IBD, evaluated drug, control and outcomes of efficacy and safety.

3. Results

According to our searches, 46 studies were considered eligible (**Tables 1 – 4**). These 46 trials included 9 Phase II, 26 Phase III and 11 undefined randomized, double-blind, placebo-controlled trials. The efficacy and safety of different types of biologic drugs were evaluated in comparison with placebo, including anti-TNF drugs, anti-CD20, T-cell inhibitors and anti-integrins. The investigated drugs were certolizumab pegol, adalimumab, etanercept, onercept, golimumab, abatacept, natalizumab, vedolizumab and rituximab. The included population was moderately to severely active acute or chronic CD or UC patients who mostly experienced an inadequate clinical response and/or intolerance to prior treatments such as anti-TNF therapy (infliximab), steroids or other conventional medicines. CD patients with elevated C-reactive proteins (CRP) or with draining fistulas were also involved in some studies. Some of registered clinical trials that were sponsored by pharmaceutical companies have not reported the final results yet. However, all available characteristics of these trials were collected in the tables. Other trials reported the response and remission rates in drug- and placebo-receiving groups according to the observed changes in scores for the CD activity index (CDAI) or Mayo scoring system for UC activity assessment. The CD activity score of < 150 and improvement of CDAI ≥ 70 points from baseline were defined as clinical remission and response, respectively. Patients with active CD showed CDAI score of ≥ 150 (of 220 – 450 points), in whom the terminal ileum and/or colon were affected for at least 3 months. Remission was defined as a decrease in Mayo Clinic score to ≤ 2 points in UC patients.

3.1 Adalimumab

Adalimumab as an anti-TNF drug is generally prescribed and is thought to be effective and tolerable in CD and UC patients with inadequate response or loss of response in long term along with steroids and immunomodulator agents [40]. To evaluate the safety and efficacy of adalimumab for induction of remission in CD patients, the clinical assessment of adalimumab safety and efficacy studied as induction therapy in Crohn's disease (CLASSIC-I) study was carried out in 299 participants. In this Phase III dose-ranging trial, 160 mg subcutaneous injection of adalimumab at week 0, followed by 80 mg at week 2 was superior to placebo in induction of remissions in patients [41]. Responders to adalimumab induction at week 4 were followed-up to 56 weeks in a Phase II randomized, double-blind, placebo-controlled trial (CLASSIC-II) to assess the long-term efficacy of 40 mg adalimumab every other week or weekly. The CLASSIC-II results showed higher efficacy of adalimumab versus placebo during 56 weeks maintenance therapy [42]. The Crohn's trial of the fully human antibody adalimumab for remission maintenance (CHARM) trial also evaluated the efficacy and safety of adalimumab in a randomized, placebo-controlled Phase III clinical study. The effect of adalimumab treatment on health-related quality of life (HRQoL) during CHARM trial was also evaluated [43,44]. Further characteristics and outcomes are detailed in **Table 1**.

The ulcerative colitis long-term remission and maintenance with adalimumab (ULTRA 1) and ULTRA 2 are two Phase III multicenter, randomized, double-blind, placebo-controlled trials evaluating the efficacy of adalimumab in induction (ULTRA 1 and 2) and maintenance (ULTRA 2) of clinical remission in 576 and 494 moderately to severely active UC patients naïve to conventional treatments, respectively. The outcomes indicated the effectiveness of drug in comparison with placebo in clinical remission and maintenance during long-term treatment [45,46].

3.2 Certolizumab pegol

Certolizumab pegol, a pegylated conjugated Fab against TNF, is considered one of the effective choices for CD refractory as compared with other conventional medications [47-49]. We have summarized the characteristics of 10 Phase III, 2 Phase II and 3 undefined randomized controlled trials in **Table 2**.

Several clinical trials were conducted in order to evaluate the efficacy and safety of this drug. The pegylated antibody fragment evaluation in Crohn's disease: safety and efficacy

Table 1. Characteristics of clinical trials evaluating efficacy and safety of earlier anti-TNF dugs in patients with inflammatory bowel disease (adalimumab).

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/ duration	Response definition (end points)	Outcome (efficacy and safety)
Hanauer *et al.* 2006 [41]	R, DB, III (CLASSIC-I)	Adalimumab	Blocking TNF	Placebo	Moderate-to-severe CD	299	40 mg/20 mg, 80 mg/40 mg or 160 mg/80 mg s.c. at weeks 0, 2/4 weeks	Primary end point was sig difference in the rates of remission at weeks 4	Sig ↑remission in patient naïve to infliximab, optimal induction dosing was 160 mg/80 mg at weeks 0, 2, well tolerated
Sandborn *et al.* 2007 [42]	R, DB, II (CLASSIC-II)	Adalimumab	Blocking TNF	Placebo	Moderate-to-severe CD	55	40 mg s.c. every other week or weekly/56 weeks	Primary end point was maintenance of remission through weeks 56	Sig efficacy in induction and maintain clinical remission in patient naïve to anti-TNF treatment, well tolerated
Sandborn *et al.* 2007 [78]	R, DB, undefined	Adalimumab	Blocking TNF	Placebo	Moderate-to-severe CD	325	160 and 80 mg s.c. at weeks 0, 2/4 weeks	Primary end point was induction of remission at weeks 4, secondary end point was ↓CDAI score by 70 or more and 100 or more points	Sig ↑remission in patient naïve to infliximab
Colombel *et al.* 2007 [43]	R, DB, III (CHARM)	Adalimumab	Blocking TNF	Placebo	Moderately to severely activeCD	854	40 mg every other weeks or weekly/ 56 weeks	Primary end points were clinical remission at weeks 26, 56	Sig ↑remission rate at weeks 26, 56, sig ↑maintaining remission, no sig differences in efficacy between 2 adalimumab groups, well tolerated
Reinisch *et al.* 2011 [45]	R, DB, III (ULTRA 1)	Adalimumab	Blocking TNF	Placebo	Moderately to severely active UC	576	160 mg at weeks 0, 80 mg at weeks 2, 40 mg at weeks 4, 6 or 80 mg at week 0, 40 mg at weeks 2, 4, 6/8 weeks	Primary end point was clinical remission at weeks 8	Effective in induction of clinical remission with higher dose in patient naïve to conventional treatment
Sandborn *et al.* 2012 [46]	R, DB, III (ULTRA 2)	Adalimumab	Blocking TNF	Placebo	Moderately to severely active UC	494	40 mg every other weeks/52 weeks	Primary end points were remission at weeks 8, 52	Effective in induction and maintenance of clinical remission in patient naïve to conventional treatment, well tolerated
Sandborn *et al.* 2013 [79]	R, DB, III	Adalimumab	Blocking TNF	Placebo	Moderately to severely active UC	248	40 mg every other weeks/52 weeks	-	Sig improvements in disease activity, ↑clinical response

↑: Increase; CD: Crohn's disease; CDAI: Crohn's disease activity index; DB: Double-blind; NO: Number; R: Randomized; s.c.: Subcutaneous; Sig: Significant; UC: Ulcerative colitis.

Table 2. Characteristics of clinical trials evaluating efficacy and safety of earlier anti-TNF dugs in patients with inflammatory bowel disease (certolizumab pegol).

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/duration	Response definition (end points)	Outcome (efficacy and safety)
Winter *et al.* 2004 [80]	R, DB, II	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD	92	Single i.v. dose 1.25, 5, 10, 20 mg/kg/12 weeks	Primary end point was the percentage of patients achieving clinical response at weeks 4	No sig improvement in clinical response, ↑clinical benefit in terms of remission, well tolerated
Schreiber *et al.* 2005 [81]	R, DB, II	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD	292	100, 200, 400 mg at weeks 0, 4, 8/12 weeks	Primary end point was the percentage of patients with a clinical response at weeks 12	No sig effectiveness, well tolerated, adverse events incidence was similar in the treatment groups
Sandborn *et al.* 2007 [50]	R, DB, III (PRECISE 1)	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD	662	400 mg s.c. every 4 weeks/26 weeks	Primary end points were the induction of a response at weeks 6 and response at weeks 6, 26	↑Response rates, no sig improvement in remission rates
Schreiber *et al.* 2007 [51]	R, DB, III (PRECISE 2)	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD	668	400 mg s.c. every 4 weeks through weeks 24/26 weeks	ND	↑Efficacy (maintained response and a remission at weeks 26) in responders to induction therapy
Rutgeerts *et al.* 2008 [55]	R, DB, undefined	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe active CD	292	100, 200, 400 mg s.c. at weeks 0, 4, 8/12 6 weeks	ND	Sig improvements in HRQoL in 400 mg group
Feagan *et al.* 2009 [74]	R, DB, IIIb	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe active CD	425	400 mg s.c. every other weeks, responders were randomized to monthly maintenance therapy	ND	Sig improvements in HRQoL relative to baseline and to placebo
Lichtenstein *et al.* 2010 [53]	Single arm open label, III	Certolizumab pegol	Blocking TNF	Single arm	CD	241	400 mg s.c. every 4 weeks/26 weeks	ND	Sig efficacy in maintain remission for up to 18 months, more effectiveness in continuous therapy than interrupted therapy
Sandborn *et al.* 2010 [54]	R, DB, IIIb	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD naïve to anti-TNF therapy	539	400 mg s.c. every 2 or 4 weeks through weeks 24/26 weeks	Primary end point was response at weeks 6, secondary end points were remission at weeks 6 and response and remission at weeks 26	Similar efficacy in maintenance of response and remission in both doses of drug
Feagan *et al.* 2010 [77]	R, DB, IIIb	Certolizumab pegol	Blocking TNF	Placebo	Moderate-to-severe CD	668	400 mg s.c. every 4 weeks/26 weeks	ND	Sig improvement in work productivity
			Blocking TNF	Placebo		124		ND	

↑: Increase; CD: Crohn's disease; CRP: C-reactive protein; DB: Double-blind; EIS: Endoscopic index of severity; HRQoL: Health-related quality of life; i.v.: Intravenous; ND: Not determined; NO: Number; R: Randomized; s.c.: Subcutaneous; Sig: Significant.

Table 2. Characteristics of clinical trials evaluating efficacy and safety of earlier anti-TNF dugs in patients with inflammatory bowel disease (certolizumab pegol) (continued).

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/duration	Response definition (end points)	Outcome (efficacy and safety)
Sandborn *et al.* 2010 [52]	R, open label, III (PRECiSE 4)	Certolizumab pegol			Moderate-to-severe CD (who relapse during continuous or interrupted maintenance therapy)		400 mg s.c. every 4 weeks/52 weeks		↑Response and remission rates after reinduction in patients who relapsed after induction therapy
Schreiber *et al.* 2010 [68]	R, DB, undefined	Certolizumab pegol	Blocking TNF	Placebo	CD (responders to induction treatment with certolizumab pegol at weeks 6 in PRECiSE-2)	425	400 mg s.c./26 weeks	ND	↑Efficacy in earlier treatment with certolizumab
Sandborn *et al.* 2011 [49]	R, DB, IIIb	Certolizumab pegol	Blocking TNF	Placebo	Moderately to severely active CD	439	400 mg s.c. at weeks 0, 2, 4/6 weeks	Primary end point was clinical remission at weeks 6	No sig remission at weeks 6, sig improvement in patients with higher CRP
Schreiber *et al.* 2011 [82]	R, DB, undefined	Certolizumab pegol	Blocking TNF	Placebo	CD patients with draining fistulas (from PRECiSE-2)	108	400 mg every 4 weeks across weeks 8 – 24/ 26 weeks	ND	Sig improvement of sustained perianal fistula closure
Feagan *et al.* 2011 [83]	R, DB, IIIb (WELCOME study)	Certolizumab pegol	Blocking TNF	Placebo	CD	539	400 mg every 2 or 4 weeks through weeks 24/26 weeks	ND	Sig improvement in work productivity, daily activities, HRQoL
Hebuterne *et al.* 2013 [84]	Open label, single arm, IIIb	Certolizumab pegol	Blocking TNF	Single arm	Moderately to severely active CD	89	400 mg s.c. every 4 weeks up to weeks 52/ 54 weeks	Primary outcome was mean change in CD EIS score at weeks 10, secondary outcome was endoscopic response, remission, complete remission and mucosal healing at weeks 10, 54	Improvement of endoscopic lesions at weeks 10 and maintained through weeks 54

↑: Increase; CD: Crohn's disease; CRP: C-reactive protein; DB: Double-blind; EIS: Endoscopic index of severity; HRQoL: Health-related quality of life; i.v.: Intravenous; ND: Not determined; NO: Number; R: Randomized; s.c.: Subcutaneous; Sig: Significant.

(PRECiSE-1) study included 662 CD patients randomized to receive either certolizumab pegol or placebo to evaluate the efficacy and safety of drug through 26 weeks of treatment [50]. PRECiSE-2 trial was the evaluation of safety and efficacy of certolizumab pegol after induction therapy within 6 weeks. Patients were randomized to receive certolizumab pegol or placebo up to week 26 [51]. Patients who relapsed before week 26 (n = 124) were withdrawn from PRECiSE-2 and entered PRECiSE-4 to receive an extra certolizumab pegol dose in an open-labeled design followed by every 4 weeks injection as re-induction [52]. In addition, responders of PRECiSE-2 at week 26 were enrolled in PRECiSE-3 trial [53] that was an open-labeled extension trial. Patients received 400 mg certolizumab pegol every 4 weeks up to 54 weeks.

Certolizumab pegol treatment (induction and maintenance) for 26 weeks caused significant improvement in response rates in comparison with placebo, but not in remission rate [50]. Lichtenstein *et al.* evaluated the continuous therapy with certolizumab pegol to address the long-term efficacy and safety of maintenance therapy in CD patients. In maintenance remission with certolizumab pegol for up to 18 months, continuous therapy was shown to be more successful than the interrupted doses of drug [53]. In an evaluation of the effect of prior infliximab therapy on response and remission in CD patients involved in PRECiSE-2 trial, the efficacy of certolizumab pegol was higher in patients receiving it as a first-line treatment than the group with the experience of prior infliximab therapy [48]. In a Phase IIIb placebo-controlled trial, the difference between remission rate in certolizumab pegol and placebo-treated groups were evaluated in active CD patients naïve to anti-TNF therapy. The difference was not significant at week 6 (the primary end point). The higher concentration of CRP in the beginning of study was associated with significant difference in remission rate between the two compared groups [49]. In another clinical trial, enrolled CD patients with secondary failure to infliximab therapy and those responded to the induction therapy with certolizumab pegol expressed a similar response and remission rates to every 2 or 4 weeks maintenance therapies [54]. Rutgeerts *et al.* concluded that certolizumab pegol 400 mg improved HRQoL in CD patients in a multicenter, randomized, double-blind, placebo-controlled study [55].

Certolizumab pegol was generally well tolerated, and adverse effects incidences were similar in both certolizumab pegol and placebo-treated groups [48-50,52-54]. Some of the most frequently reported adverse effects were headache, nausea, arthralgia, abdominal pain, fatigue and pyrexia, in addition to a few numbers of adverse effects that led to withdrawal from the trials [49-52].

3.3 Onercept

We found one dose-ranging clinical trial assessing the efficacy and safety of onercept as a recombinant receptor for TNF. Two-hundred and seven CD patients received four doses of onercept or placebo for 8 weeks. The administered doses of onercept were not effective in induction of remission in patients with active CD. However, the drug was well tolerated and except for injection site reactions, there was no significant difference between all groups regarding frequency of adverse effects [56].

3.4 Etanercept

Etanercept, an antagonist for TNF receptor, has been compared with placebo in an efficacy and safety trial of 43 CD patients during 8 weeks. Etanercept was not more effective than placebo comparing clinical response at week 4. The incidence of adverse effects including either severe unwanted outcomes or other adverse effects was similar in drug- and placebo-received groups. The most frequent adverse effects were headache, abdominal pain, injection site reaction and skin disorders [57].

3.5 Golimumab

Golimumab is a human monoclonal antibody that targets TNF-α with a higher affinity than adalimumab. It has been evaluated for efficacy and safety in moderately to severely active UC patients. The results of program of ulcerative colitis research studies utilizing an investigational treatment-subcutaneous (PURSUIT-SC) induction study, containing a Phase II dose ranging followed by Phase III confirmatory study, showed the efficacy of golimumab in response and remission induction after 6 weeks of treatment. Furthermore, the responders in the mentioned study entered the 54 weeks PURSUIT-SC maintenance study. The prescribed doses were significantly effective in maintaining remission in patients. There were two Phase III randomized placebo-controlled trials performed and registered in ClinicalTrial.gov website. Although, the results of those trials have not been provided yet, we have summarized their characteristics in **Table 3** [58].

3.6 Natalizumab

Natalizumab, a recombinant humanized monoclonal IgG antibody to α4 integrin, a selective adhesion molecule, has been evaluated in nine randomized, double-blind, placebo-controlled clinical trials in 2662 moderately to severely active CD patients (**Table 4**). In order to investigate the efficacy of induction therapy, the international efficacy of natalizumab as active Crohn's therapy (ENACT-1) trial was performed in 905 patients with the end point of response demonstration at week 10 [59]. Results showed that natalizumab improved the response and remission rates in a non-significant manner. In an evaluation of effectiveness of drug in maintenance of remission, ENACT-2 study enrolled 339 responders of ENACT-1 study. Continuous therapy with 300 mg natalizumab every 4 weeks up to week 56, significantly maintained the response and remission rates in CD patients [59]. ENCORE study is another randomized placebo-controlled trial that evaluated the efficacy of natalizumab in induction

Table 3. Characteristics of clinical trials evaluating efficacy and safety of newer anti-TNF dugs in patients with inflammatory bowel disease.

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/ duration	Response definition (end points)	Outcome (efficacy and safety)
Rutgeerts *et al.* 2006 [56]	R, DB, undefined	Onercept	Recombinant receptor for TNF	Placebo	Moderate-to-severe acute or chronic active CD	207	10, 25, 35, 50 mg s.c. three times weekly/ 8 weeks	Primary outcome was induction of remission at weeks 8	No sig effectiveness, well tolerated
Sandborn *et al.* 2001 [57]	R, DB, undefined	Etanercept	TNF receptor antagonist	Placebo	Moderate-to-severe CD	43	25 mg s.c. twice weekly/8 weeks	Primary outcome was clinical response	No sig effectiveness, well tolerated
Sponsor: Janssen Pharmaceutical K.K (currently recruiting participants), NCT01863771 (2013 – 2015) [85]	R, DB, III	Golimumab	Blocking TNF	Placebo	Moderately to severely active UC	200	100 mg s.c. every 4 weeks from weeks 0 to weeks 52/68 weeks	Not provided	No results have been reported
Sponsor: Centocor, Inc. NCT00487539 (2007 – 2010) [86]	R, DB, II/III (PURSUIT-SC)	Golimumab	Blocking TNF	Placebo	Moderately to severely active UC	1065	100, 200 or 400 mg s.c. at weeks 0 followed a 50, 100 or 200 mg s.c., at weeks 2/6 weeks	Primary outcome was clinical response induction at weeks 6	Sig induction of clinical response, remission & mucosal healing, ↑quality of life, well tolerated
Sponsor: Janssen Research & Development, LLC (study is ongoing), NCT00488631 (2007 – 2011) [87]	R, DB, III (PURSUIT-SC Maintenance)	Golimumab	Blocking TNF	Placebo	Moderately to severelyactive UC	464	50, 100 mg s.c. every 4 weeks from weeks 0 to weeks 52/54 weeks	Primary outcome was maintaining clinical response through weeks 54	Sig efficacy in maintaining clinical response, well tolerated
Sponsor: Centocor, Inc. NCT00488774 (2007 – 2009) [88]	R, DB, II/III	Golimumab	Anti-TNF antibody	Placebo	Moderately to severely active UC	291	1, 2, 4 mg/kg i.v. infusion/6 weeks	Primary outcome was clinical response at weeks 6	No results have been reported

↑: Increase; CD: Crohn's disease; DB: Double-blind; i.v.: Intravenous; NO: Number; R: Randomized; s.c.: Subcutaneous; Sig: Significant; UC: Ulcerative colitis.

Table 4. Characteristics of clinical trials evaluating efficacy and safety of different biologic dugs in patients with inflammatory bowel disease.

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/ duration	Response definition (end points)	Outcome (efficacy and safety)
Gordon *et al.* 2001 [70]	R, DB, undefined	Natalizumab	Anti-α4 integrin	Placebo	Active CD	30	Single 3 mg/kg i.v. infusion	Primary end point was change in CDAI at weeks 2	Sig ↓CDAI at weeks 2, sig ↑circulating B & T lymphocytes, adverse events incidence was similar in the treatment groups
Ghosh *et al.* 2003 [36]	R, DB, undefined	Natalizumab	Anti-α4 integrin	Placebo	Moderate-to-severe CD	248	2 i.v. infusion of 3 or 6 mg/kg/4 weeks	Primary outcome was clinical remission at weeks 6, secondary outcomes were changes in scores of CDAI, HRQoL, & CRP levels	Sig ↑clinical remission & response rates, sig improvement in quality of life & CRP levels, adverse events incidence was similar in the treatment groups
Sandborn *et al.* 2005 [59]	R, DB, III, (ENACT-1, ENACT-2)	Natalizumab	Anti-α4 integrin	Placebo	Moderately to severely active CD	905	300 mg i.v. infusion every 4 weeks/ 56 weeks	Primary outcome was sustained response through weeks 36, secondary outcome was disease remission	Sig ↑rates of sustained response & remission through weeks 36, serious adverse events occurred in both groups
Sands *et al.* 2007 [69]	R, undefined	Natalizumab	Anti-α4 integrin	Placebo	Active CD	79	300 mg i.v. infusions every 4 weeks/ 8 weeks		↑Efficacy of combination of natalizumab & infliximab than treatment with infliximab alone, adverse events incidence was similar in the treatment groups
Targan *et al.* 2007 [60]	R, DB, undefined (ENCORE)	Natalizumab	Anti-α4 integrin	Placebo	Moderately to severely active CD	509	300 mg i.v. infusions every 4 weeks/ 8 weeks	Primary end point was induction of response at weeks 8 sustained through weeks 12, additional efficacy end points were the proportion of patients	↑Response & remission rates at weeks 4, 8 & 12, adverse events incidence was similar in the treatment groups

↑: Increase; ↓: Decrease; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; DB: Double-blind; HRQoL: Health related quality of life; IBDQ: Inflammatory bowel disease questionnaire; i.v.: Intravenous; ND: Not determined; NO: Number; R: Randomized; SF-36: Short form-36; Sig: Significant; UC: Ulcerative colitis.

Table 4. Characteristics of clinical trials evaluating efficacy and safety of different biologic dugs in patients with inflammatory bowel disease (continued).

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/ duration	Response definition (end points)	Outcome (efficacy and safety)
								with sustained remission & response or remission over time	
Feagan *et al.* 2007 [61]	R, DB, undefined	Natalizumab	Anti-α4 integrin	Placebo	CD	339	300 mg i.v. infusion every 4 weeks/ 48 weeks	ND	Sig improvement in HRQoL, sig ↑IBDQ & SF-36 (during ENACT-1) no change in IBDQ, SF-36 (during ENACT-2)
Sponsor: Elan Pharmaceuticals, NCT00055536 (2002 – 2003) [89]	R, DB, II	Natalizumab	Anti-α4 integrin	Placebo	CD	60	Not provided	Not provided	No results have been reported
Sponsor: Elan Pharmaceuticals, NCT00055367 (2002 – 2004) [90]	Non-R, open label, II	Natalizumab	Anti-α4 integrin	Single arm	Moderately to severely active CD (12 – 17 years)	30	3 i.v. Infusions	Not provided	No result have been reported
Sponsor: Elan Pharmaceuticals, NCT00078611 (2004 – 2005) [91]	R, DB, III	Natalizumab	Anti-α4 integrin	Placebo	Moderately to severely active CD	462	i.v. infusion every 4 weeks/22 weeks	Not provided	No result have been reported
Feagan *et al.* 2005 [62]	R, DB, II	Vedolizumab	Anti-α4integrin antibody	Placebo	Mildly to moderately active UC	181	0.5, 2 mg/kg i.v. infusion on days 1, 29/6 weeks	Primary end point was clinical remission at weeks 6	Sig efficacy in induction of clinical remission
Feagan *et al.* 2008 [63]	R, DB, II	Vedolizumab	Anti-α4 integrin antibody	Placebo	Active CD	140	0.5, 2 mg/kg i.v. infusion on days 1, 29/57 days	Primary end point was clinical response on day 57, secondary end points were the proportions of patients with clinical remission & with an enhanced clinical response	Sig dose-dependent efficacy in clinical remission, well tolerated
Parikh *et al.* 2012 [64]	R, DB, II	Vedolizumab	Anti-α4 integrin antibody	Placebo	UC	46	2, 6, or 10 mg/kg i.v. infusion on days 1, 15, 29, 85/253 days	Not available	Sig efficacy in maintaining clinical response
		Vedolizumab		Placebo	Active UC	895			

↑: Increase; ↓: Decrease; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; DB: Double-blind; HRQoL: Health related quality of life; IBDQ: Inflammatory bowel disease questionnaire; i.v.: Intravenous; ND: Not determined; NO: Number; R: Randomized; SF-36: Short form-36; Sig: Significant; UC: Ulcerative colitis.

Table 4. Characteristics of clinical trials evaluating efficacy and safety of different biologic dugs in patients with inflammatory bowel disease (continued).

Study	Design, clinical phase	Drug	Mechanism of action	Control	Patient population	Patients No	Drug dose (induction, maintenance)/ duration	Response definition (end points)	Outcome (efficacy and safety)
Feagan *et al.* 2013 [65]	R, open label, DB, III (GEMINI 1)		Anti-α4 integrin ng antibody				300 mg i.v. infusion every 4 or 8 weeks/ 52 weeks	Primary end point was clinical response at weeks 6	Sig efficacy in induction & maintaining clinical response
Sandborn *et al.* 2013 [66]	R, open label, DB, III (GEMINI 2)	Vedolizumab	Anti-α4 integrin ng antibody	Placebo	Moderately to severely active CD	1115	300 mg i.v. infusion every 4 or 8 weeks/ 52 weeks	Primary end point was clinical remission at weeks 6	Sig efficacy in induction & maintaining clinical remission, more incidence of adverse events than placebo
Sponsor: Millennium Pharmaceuticals, Inc., NCT01224171 (2010 – 2012) [92]	R, DB, III (GEMINI 3)	Vedolizumab	Anti-α4 integrin ng antibody	Placebo	Moderately to severely active CD	416	i.v. infusion at weeks 0, 2, 6/6 weeks	Primary end point was clinical remission at weeks 6	No result have been reported
Sponsor: Millennium Pharmaceuticals, Inc. (study is ungoing), NCT00790933 (2009 – 2016) [93]	Single group assignment, open label, III (GEMINI LTS)	Vedolizumab	Anti-α4 integrin ng antibody	Single arm	UC and CD	2200	Not provided	Not provided	No result have been reported
Leiper *et al.* 2011 [39]	R, DB, II	Rituximab	Anti-CD20	Placebo	Steroid-resistant moderately active UC	24	1 g i.v. infusions at 0, 2 weeks	Primary end point was remission at weeks 4	No sig effect on inducing remission, well tolerated
Sandborn *et al.* 2012 [67]	R, DB, III	Abatacept	Selective costimulation modulator	Placebo	Active UC & CD	451 CD, 490 UC	30, 10 or 3 mg/kg at weeks 0, 2, 4, 8/ 12 weeks for induction, 52 weeks for maintenance	Primary end point for CD was response at weeks 8, 12; remission at weeks 52, secondary end point was remission at weeks 8, 12, response at weeks 52, remission at weeks 24, 52 & corticosteroid-free remission at weeks 52	No sig therapeutic effect in UC and CD

↑: Increase; ↓: Decrease; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; DB: Double-blind; HRQoL: Health related quality of life; IBDQ: Inflammatory bowel disease questionnaire; i.v.: Intravenous; ND: Not determined; NO: Number; R: Randomized; SF-36: Short form-36; Sig: Significant; UC: Ulcerative colitis.

of response and remission in moderately to severely active CD patients [60]. Natalizumab's impact on the HRQoL besides its safety and tolerability has been investigated in several doses containing 3 and 6 mg/kg body weight or 300 mg by intravenous infusion. Except for some observed serious adverse effects such as progressive multifocal leukoencephalopathy [59], natalizumab was well tolerated and the frequency of adverse effect incidence was similar in drug- and placebo-treated groups (**Table 4**). In an assessment of natalizumab effect on HRQoL, outcomes were measured by the change from baseline on the IBD questionnaire, the short form-36, the EuroQol-5D and a subject global assessment. Results showed a significant improvement in drug-treated group during ENACT-1 trial. However, the measures remained constant during ENACT-2 and did not increase [61].

3.7 Vedolizumab

Vedolizumab is a human monoclonal antibody that specifically targets $\alpha 4\beta 7$ integrins. Thus, it exhibits lymphocyte trafficking inhibition specifically in the inflamed GI and does not affect other organs such as brain. In order to investigate its efficacy and safety, three Phase II [62-64] and four Phase III (GEMINI 1, GEMINI 2, GEMINI 3, GEMINI LTS) clinical trials have been performed in active UC and CD patients. Final results indicated that vedolizumab was significantly more effective in both induction and maintenance of clinical response and remission within clinical trials than placebo in UC patients. The results also showed vedolizumab to be a well-tolerated drug in patients [62,64,65]. In an integrated induction and maintenance trial, vedalizumab has been evaluated in comparison with placebo in moderately to severely active CD patients (GEMINI 2). The induction trial consisted of 368 randomized cohort and 747 open-label cohort, receiving 300 mg infusion of vedolizumab at week 0 and week 2. The patients (461) who showed response at week 6 entered in maintenance trial and received vedolizumab every 4 or 8 weeks up to week 52. The response rate analysis indicated that vedolizumab treatment resulted in higher rate of remission in patients during both induction and maintenance trials than placebo, however, it did not cause a CDAI-100 response at week 6. Safety assessment showed that vedolizumab-treated group reported more adverse effects than placebo group [66]. An ongoing open-label long-term safety assessment trial evaluating vedolizumab safety and tolerability has been started from 2009 and will be completed in 2016 (GEMINI LTS, NCT00790933).

3.8 Rituximab

Rituximab, an anti-CD20 antibody, has been administered in 24 steroid-resistant UC patients in a Phase II randomized placebo-controlled trial. The results showed that two rituximab infusions caused a significant response compared with placebo at week 4. However, it was not effective in induction of remission assessed by Mayo score system, an end point at week 4. Rituximab was well tolerated in patients [39].

3.9 Abatacept

Abatacept is a selective costimulation modulator, which has been evaluated in active CD and UC patients in four clinical controlled trials carried out by Sandborn *et al.* The responders to the induction therapy received the drug to be enrolled in maintenance assessment for up to 52 weeks. The observed clinical response and remission rates during both induction and maintenance studies were not significantly higher in abatacept-treated groups versus placebo [67].

4. Conclusion

Among earlier anti-TNF drugs, adalimumab, certolizumab pegol and golimumab were indicated to have significant efficacy in comparison with placebo in several clinical trials. However, certolizumab pegol as the first-line treatment was more effective in patients with prior infliximab therapy [68]. In addition, it was more effective in maintaining response and remission in responders to induction therapy that showed the importance of prior treatment in patients [51]. In one of the certolizumab pegol trials, the higher remission rate in placebo as compared with other studies has been reported [49]. Sandborn *et al.* stated that higher efficacy of anti-TNF drugs was related to higher CRP concentration and shorter duration of disease, in contrast to the involved patients in their trial [49]. Schreiber *et al.* reported that shorter duration of CD and earlier use of certolizumab pegol resulted in higher rates of treatment response and disease remission [68]. Etanercept and onercept have been evaluated in large randomized placebo-controlled trials in CD patients. The reported outcomes demonstrated that there was no significant difference between these drugs and placebo in disease management and remission induction [56,57]. Rutgeerts *et al.* mentioned that, in contrast to the mechanism of action of infliximab and adalimumab, etanercept and onercept were not associated with apoptosis of T-cells and monocytes. Therefore, the results of ineffectiveness of these drugs have been hypothesized via this mechanism of action [56]. However, they noted that although certalizumab pegol did not induce apoptosis, it was an effective therapeutic regimen. In addition, the potency of TNF inhibition may be discussable in different anti-TNF drugs [56]. Although the effective dose of etanercept in rheumatoid arthritis was administered, Sandborn *et al.* recommended applying higher doses in further studies to achieve clinical response in CD patients [57].

Several clinical trials have shown the effectiveness of natalizumab as an integrin inhibitor in moderately to severely active CD patients. Some clinical trials have compared the efficacy and safety of natalizumab alone or in combination with other treatments including infliximab [69]. Considering the mechanism of action of natalizumab that increases the circulating leukocytes, its administration may interrupt leukocyte

trafficking causing side effects in patients [70]. As well, vedolizumab is suggested to inhibit GI leukocyte trafficking; thus, it modulates leukocytes migration into the inflamed GI tissue. Its specificity for $\alpha4\beta7$ integrins leads to not interacting with leukocyte trafficking to the central nervous system. Natalizumab blocks both $\alpha4\beta1$ and $\alpha4\beta7$ integrins. It has been observed that natalizumab causes progressive multifocal leukoencephalopathy in brain. In contrast to natalizumab, vedolizumab acts specifically in the GI and does not affect other organs. Although adverse effects such as infections have been observed by the use of vedolizumab, its incidence has not been found significantly higher [65].

Rituximab is believed to remove B lymphocytes from the circulation. Therefore, it has been used in therapeutic regimen of several autoimmune diseases. In steroid-resistant active UC patients, rituximab administered at two infusions did not induce adequate remission [39].

Within four large randomized clinical trials, abatacept was compared with placebo in induction and maintenance of remission in patients with CD and UC. Lack of its efficacy in these trials has been explained by naming several limitations of study including not measuring CD activity from the beginning of trial in CD patients. Forasmuch as mechanism of action of abatacept is thought to inhibit T-cell activation, it might be beneficial in the modulation of inflammation in CD and UC patients. However, other factors are associated in disease progression such as GI barrier disruption and recruitment of leukocytes. By considering this pathogenesis, abatacept may not be helpful unless used in combination with other types of treatments [67].

Alicaforsen (ISIS2302) is an antisense molecule that inhibits intracellular adhesion molecule 1. Therefore, it plays the role of a modulator in the recruitment of leukocytes during inflammation process. Several placebo-controlled clinical trials have been conducted to examine its efficacy in chronic active CD and UC patients. Alicaforsen failed to induce significant higher remission in CD patients when compared with placebo [71,72]. However, administration of alicaforsen in enema dosage form resulted in a significant improvement in UC patients [73]. Forasmuch as CD activity has been known to be a factor involved in HRQoL and work productivity, several studies evaluate these factors in CD patients. The results of comparisons expressed a significant higher work productivity, daily activities and HRQoL in certolizumab-treated group [74-77].

5. Expert opinion

In this review, we have collected all Phase II and III clinical trials on the efficacy and safety of newly introduced biologic drugs in IBD besides a background data from earlier drugs used in this type of treatment. Among earlier anti-TNF drugs, adalimumab and certolizumab pegol besides golimumab as a newly introduced drug from this type of group, exhibit good therapeutic effects in both moderately to severely active CD and UC patients. Etanercept and onercept showed no significant efficacy in disease management and remission induction. No comparative trials on efficacy of etanercept and onercept in CD patients have been reported to date. Further dose-escalating studies are required to find the effective dose of onercept and etanercept. Effectiveness of natalizumab as an integrin inhibitor has been demonstrated in moderately to severely active CD patients.

In reviewed clinical trials, treatment was associated with improvement of HRQoL besides induction and maintenance of remission. This could be a valuable goal of the treatment, while almost a large number of recruited patients had used these therapeutic regimens as the second-line treatment due to failure of previously examined drugs. The efficacy of a drug as the first- or second-line treatment, duration and activity of disease in patients, the type of prior treatment and other involved factors such as CRP concentration have been compared and considered in performed clinical trials. The difference in those factors between various clinical trials is the source of controversy existing in the outcomes of studies. As mentioned before, the improvement of HRQoL is the ultimate goal of treatment that should be followed in design of clinical trials. Considering high frequency of inadequate response and lack of efficacy and tolerability in treated UC and CD patients, the necessity of examining new therapeutic options either with the same or even different target and mechanism of action is felt. For instance, infliximab that is commonly used in moderately to severely active CD patients may cause development of antibodies to drug in patient's circulation, resulting in a drop in efficacy. Furthermore, injection site reactions and delayed hypersensitivity are among common side effects. However, the outcomes of current clinical trials on new anti-TNF drugs exhibit beneficial therapeutic effects in patients with no response to prior treatments. The loss of efficacy of some anti-TNF drugs in clinical trials in comparison with placebo have been attributed to their different mechanism of actions. Therefore, further comparative studies between these drugs may be of value to know the mechanisms that must be targeted. In addition, more dose-escalating trials should be carried out to make a precise decision on the effectiveness of etanercept, onercept, rituximab and abatacept versus placebo. Regarding more acceptable safety profile of vedolizumab versus natalizumab, comparative efficacy and safety studies between these two integrin inhibitors may be helpful. Generally by an overview of the outcomes of reviewed clinical examinations, the effective dose and right duration of treatment to induce and maintain remission should be considered according to the disease activity index in both CD and UC patients. Due to approximately high costs of these types of recombinant drugs besides their serious side effects, a risk–cost–benefit analysis is required to prescribe the right medicine with the right dosage and duration to reach the optimized results. In future by collecting the efficacy and safety outcomes of more clinical trials, golimumab seems to be added to the list of beneficial anti-TNF drugs in UC and CD treatment. Anyway, we emphasize that prescribing these

drugs must be accompanied with full consideration of their risk, cost and benefit.

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Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Williams H, Walker D, Orchard TR. Extraintestinal manifestations of inflammatory bowel disease. Curr Gastroenterol Rep 2008;10:597-605
2. Walsh A, Mabee J, Trivedi K. Inflammatory bowel disease. Prim Care 2011;38:415-32
3. Xavier RJ, Podilsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007;448:427-34
4. Nikfar S, Rahimi R, Rezaie A, et al. A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. Dig Dis Sci 2009;54:1157-70
5. Rahimi R, Nikfar S, Rezaie A, et al. Comparison of mesalazine and balsalazide in induction and maintenance of remission in patients with ulcerative colitis: a meta-analysis. Dig Dis Sci 2009;54:712-21
6. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:590-9
7. Rahimi R, Nikfar S, Abdollahi M. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. Biomed Pharmacother 2007;61:75-80
8. Nikfar S, Mirfazaelian H, Abdollahi M. Efficacy and tolerability of immunoregulators and antibiotics in fistulizing Crohn's disease: a systematic review and meta-analysis of placebo-controlled trials. Curr Pharm Des 2010;16:3684-98
9. Ehteshami-Afshar S, Nikfar S, Rezaie A, et al. A systematic review and meta-analysis of the effects of infliximab on the rate of colectomy and post-operative complications in patients with inflammatory bowel disease. Arch Med Sci 2011;7:1000-12
10. Abdolghaffari AH, Nikfar S, Rahimi HR, et al. A comprehensive review of antibiotics in clinical trials for inflammatory bowel disease. Int J Pharmacol 2012;8:596-613
11. Rezaie A, Nikfar S, Abdollahi M. The place of antibiotics in management of irritable bowel syndrome: a systematic review and meta-analysis. Arch Med Sci 2010;6:49-55
12. Rezaie A, Eshghtork A, Zamani M, et al. Alterations in salivary antioxidants, nitric oxide, and transforming growth factor-beta1 in relation to disease activity in Crohn's disease patients. Ann NY Acad Sci 2006;1091:110-22
13. Rahimi R, Nikfar S, Rezaie A, et al. A meta-analysis of the benefit of probiotics in maintaining remission of human ulcerative colitis: evidence for prevention of disease relapse and maintenance of remission. Arch Med Sci 2008;4:185-90
14. Müllner K, Miheller P, Herszényi L, Tulassay Z. Probiotics in the Management of Crohn's Disease and Ulcerative Colitis. Curr Pharm Des 2013. [Epub ahead of print]
15. Salari P, Abdollahi M. Phosphodiesterase inhibitors in inflammatory bowel disease. Expert Opin Investig Drugs 2012;21:261-4
16. Hosseini-Tabatabaei A, Abdollahi M. Potassium channel openers and improvement of toxic stress: do they have role in the management of inflammatory bowel disease? Inflamm Allergy Drug Targets 2008;7:129-35
17. Salari P, Abdollahi M. Current opinion in the pharmaceutical management of irritable and inflammatory bowel diseases: role of ATP. Recent Patents Endocr Metabol Immune Drug Discov 2009;3:69-75
18. Mozaffari S, Abdollahi M. Melatonin, a promising supplement in inflammatory bowel disease: a comprehensive review of evidences. Curr Pharm Des 2011;17:4372-8
19. Rahimi R, Mozaffari S, Abdollahi M. On the use of herbal medicines in management of inflammatory bowel diseases: a systematic review of animal and human studies. Dig Dis Sci 2009;54:471-80
20. Rahimi R, Shams-Ardekani MR, Abdollahi M. A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. World J Gastroenterol 2010;16:4504-14
21. Bernstein CN, Fried M, Krabshuis JH, et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. Inflamm Bowel Dis 2010;16:112-24
22. Rezaie A, Parker RD, Abdollahi M. Oxidative stress and pathogenesis of inflammatory bowel disease: an epiphenomenon or the cause? Dig Dis Sci 2007;52:2015-21
23. Salari P, Abdollahi M. Current opinion in the pharmaceutical management of irritable and inflammatory bowel diseases: role of ATP. Recent Patents Endocr Metab Immune Drug Discov 2009;3:69-75
24. Dahan S, Roth-Walter F, Arnaboldi P, et al. Epithelia: lymphocyte interactions in the gut. Immunol Rev 2007;215:243-53
25. Rezaie A, Taghavi Bayat B, Abdollahi M. Biologic Management of Fistulizing Crohn's Disease. Int J Pharmacol 2005;1:17-24

26. Neurath MF. IL-23: a master regulator in Crohn's disease. Nat Med 2007;13:26-8

27. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology 2008;135:1130-41

28. Murch SH, Lamkin VA, Savage MO, et al. Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut 1991;32:913-17

29. Braegger CP, Nicholls S, Murch SH, et al. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. Lancet 1992;339:89-91

30. Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population based study. Gastroenterology 2001;123:255-60

31. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. Cytokine 1995;7:251-9

32. Miheller P, Lakatos PL, Horváth G, et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe–a Hungarian nationwide observational study. BMC Gastroenterol 2009;9:66

33. Ardizzone S, Colombo E, Maconi G, et al. Infliximab in treatment of Crohn's disease: the Milan experience. Dig Liver Dis 2002;34:411-18

34. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-76

35. Sandborn WJ, Colombel JF, Sands BE, et al. Abatacept for Crohn's disease and ulcerative colitis. Gastroenterology 2012;143:62-9

36. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24-32

37. Eksteen B, Adams DH. GSK-1605786, a selective small-molecule antagonist of the CCR9 chemokine receptor for the treatment of Crohn's disease. IDrugs 2010;13:472-81

38. Keshav S, Vaňásek T, Niv Y, et al. A randomized controlled trial of the efficacy and safety of CCX282-B, an orally-administered blocker of chemokine receptor CCR9, for patients with Crohn's disease. PLoS One 2013;8:e60094

39. Leiper K, Martin K, Ellis A, et al. Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. Gut 2011;60:1520-6

40. Sandborn WJ, Colombel JF, D'Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther 2013;37:204-13

41. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323-33

• **One of the pivotal clinical trials on adalimumab efficacy in patients with Crohn's disease (CD).**

42. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232-9

• **The following trial for CLASSIC-I to confirm adalilumab efficacy**

43. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65

44. Loftus EV, Feagan BG, Colombel JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol 2008;103:3132-41

• **A good article that analyzes the outcomes of CHARM trial, one of the pivotal trials of adalimumab.**

45. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780-7

46. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257-65

•• **The latest two Refs [45,46] evaluating adalimumab in patients with ulcerative colitis named 'ULTRA 1' and 'ULTRA 2'.**

47. Nikfar S, Ehteshami-Afshar S, Abdollahi M. Is certolizumab pegol safe and effective in the treatment of patients with moderate to severe Crohn's disease? A meta-analysis of controlled clinical trials. Iran Red Crescent Med J 2013;15:668-75

•• **A recent valuable meta-analysis on the safety and efficacy of certolizumab based on experiences through clinical trials in patients with CD.**

48. Hanauer SB, Panes J, Colombel JF, et al. Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. Aliment Pharmacol Ther 2010;32:384-93

49. Sandborn WJ, Schreiber S, Feagan BG, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. Clin Gastroenterol Hepatol 2011;9:670-8

50. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357:228-38

51. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357:239-50

52. Sandborn WJ, Schreiber S, Hanauer SB, et al. Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 Study. Clin Gastroenterol Hepatol 2010;8:696-702

• **The most important conducted clinical trials on certolizumab efficacy in patients with CD are PRECiSE 1, 2, 4 explained in Refs [50-52].**

53. Lichtenstein GR, Thomsen OØ, Schreiber S, et al. Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. Clin Gastroenterol Hepatol 2010;8:600-9

54. Sandborn WJ, Abreu MT, D'Haens G, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab.

Clin Gastroenterol Hepatol 2010;8:688-95

55. Rutgeerts P, Schreiber S, Feagan B, et al. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNF-alpha, improves health-related quality of life in patients with moderate to severe Crohn's disease. Int J Colorectal Dis 2008;23:289-96

56. Rutgeerts P, Sandborn WJ, Fedorak RN, et al. Onercept for moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2006;4:888-93

57. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088-94

58. Feagan B, Sandborn W, Marano C, et al. A phase 2/3 randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of subcutaneous golimumab induction therapy in patients with moderately to severely active ulcerative colitis: PURSUIT SC. CDDW/Annual CASL; 1 - 4 March 2013; Victoria, British Columbia

59. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353:1912-25

- **The ENACT-1 and -2 trials have been explained in this article by details on the evaluation of natalizumab in CD.**

60. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007;132:1672-83

61. Feagan BG, Sandborn WJ, Hass S, et al. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. Am J Gastroenterol 2007;102:2737-46

62. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7integrin. N Engl J Med 2005;352:2499-507

63. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. Clin Gastroenterol Hepatol 2008;6:1370-7

64. Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. Inflamm Bowel Dis 2012;18:1470-9

65. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710

66. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21

- **The pivotal clinical studies on the efficay and safety of vedolizumab, GEMINI 1, 2 are discribed in recently published articles as Refs [65,66].**

67. Sandborn WJ, Colombel JF, Sands BE, et al. Abatacept for Crohn's disease and ulcerative colitis. Gastroenterology 2012;143:62-9

68. Schreiber S, Colombel JF, Bloomfield R, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. Am J Gastroenterol 2010;105:1574-82

69. Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis 2007;13:2-11

70. Gordon FH, Lai CW, Hamilton MI, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology 2001;121:268-74

71. Schreiber S, Nikolaus S, Malchow H, et al. Absence of efficacy of subcutaneous antisense ICAM-1 treatment of chronic active Crohn's disease. Gastroenterology 2001;120:1339-46

72. Yacyshyn BR, Chey WY, Goff J, et al. Double-blind, placebo controlled trial of the remission inducing and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, c (ISIS 2302), in active steroid dependent Crohn's disease. Gut 2002;51:30-6

73. Van Deventer SJ, Tami JA, Wedel MK. A randomised, controlled, double-bind, escalating dose study of alicaforsen enema in ulcerative colitis. Gut 2004;53:1646-51

74. Feagan BG, Coteur G, Tan S, et al. Clinically meaningful improvement in health-related quality of life in a randomized controlled trial of certolizumab pegol maintenance therapy for Crohn's disease. Am J Gastroenterol 2009;104:1976-83

75. Rutgeerts P, Schreiber S, Feagan B, et al. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNFalpha, improves health-related quality of life in patients with moderate to severe Crohn's disease. Int J Colorectal Dis 2008;23:289-96

76. Feagan BG, Sandborn WJ, Wolf DC, et al. Randomised clinical trial: improvement in health outcomes with certolizumab pegol in patients with active Crohn's disease with prior loss of response to infliximab. Aliment Pharmacol Ther 2011;33:541-50

77. Feagan BG, Reilly MC, Gerlier L, et al. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECiSE 2 study. Aliment Pharmacol Ther 2010;31:1276-85

78. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829-38

79. Sandborn WJ, Colombel JF, D'Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther 2013;37:204-13

80. Winter TA, Wright J, Ghosh S, et al. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. Aliment Pharmacol Ther 2004;20:1337-46

81. Schreiber S, Rutgeerts P, Fedorak RN, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005;129:807-18

82. Schreiber S, Lawrance IC, Thomsen OØ, et al. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a

placebo-controlled study.
Aliment Pharmacol Ther 2011;33:185-93

83. Feagan BG, Hanauer SB, Coteur G, Schreiber S. Evaluation of a daily practice composite score for the assessment of Crohn's disease: the treatment impact of certolizumab pegol. Aliment Pharmacol Ther 2011;33:1143-51

84. Hébuterne X, Lémann M, Bouhnik Y, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut 2013;62:201-8

85. A safety and effectiveness study of golimumab in Japanese patients with Moderately to Severely Active Ulcerative Colitis. Janssen Pharmaceutical K.K. 2013. Available from: http://clinicaltrial.gov/ct2/show/NCT01863771?term=NCT01863771&rank=1

86. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85-95

87. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:96-109

88. An Efficacy and Safety Study of Golimumab in Participants with Ulcerative Colitis. Janssen Research & Development, LLC. 2007. Available from: http://clinicaltrial.gov/ct2/show/NCT00488774?term=NCT00488774&rank=1

89. Safety and Efficacy of Natalizumab in Combination with Remicade in the Treatment of Crohn's Disease. Elan Pharmaceuticals. 2003. Available from: http://clinicaltrial.gov/ct2/show/NCT00055536?term=NCT00055536&rank=1

90. Safety, Tolerability and Effectiveness of Natalizumab in Adolescents with Active Crohn's Disease. Elan Pharmaceuticals. 2003. Available from: http://clinicaltrial.gov/ct2/show/NCT00055367?term=NCT00055367&rank=1

91. A Clinical Trial of Natalizumab in Individuals With Moderately to Severely Active Crohn's Disease. Elan Pharmaceuticals. 2004. Available from: http://clinicaltrial.gov/ct2/show/NCT00078611?term=NCT00078611&rank=1

92. Study of Vedolizumab in Patients with Moderate to Severe Crohn's Disease (GEMINI III). Millennium Pharmaceuticals, Inc. 2010. Available from: http://clinicaltrial.gov/ct2/show/NCT01224171?term=NCT01224171&rank=1

93. An Open-label Study of Vedolizumab (MLN0002) in Patients with Ulcerative Colitis and Crohn's Disease (GEMINI LTS). Millennium Pharmaceuticals, Inc. 2008. Available from: http://clinicaltrial.gov/ct2/show/NCT00790933?term=NCT00790933&rank=1

94. Esmaily H, Vaziri-Bami A, Miroliaee AE, et al. The correlation between NF-kappaB inhibition and disease activity by co-administration of silibinin and ursodeoxycholic acid in experimental colitis. Fundam Clin Pharmacol 2011;25:723-33

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