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


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.
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 Fistulating 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

### 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.
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 \( \alpha_4 \) 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 \( \alpha_4 \) 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 by 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, ClinicalTrials.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, oncept, 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).

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

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

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

1: 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.
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<th>Outcome (efficacy and safety)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandborn et al. 2010 [52]</td>
<td>R, open label, III (PRECiSE 4)</td>
<td>Certolizumab pegol</td>
<td>Moderate-to-severe CD (who relapse during continuous or interrupted maintenance therapy)</td>
<td>Placebo</td>
<td>CD (responders to induction treatment with certolizumab pegol at weeks 6 in PRECiSE-2)</td>
<td>425</td>
<td>400 mg s.c./26 weeks</td>
<td>ND</td>
<td>↑Response and remission rates after reinduction in patients who relapsed after induction therapy</td>
</tr>
<tr>
<td>Schreiber et al. 2010 [68]</td>
<td>R, DB, undefined</td>
<td>Certolizumab pegol</td>
<td>Blocking TNF</td>
<td>Placebo</td>
<td>CD patients with draining fistulas (from PRECiSE-2)</td>
<td>108</td>
<td>400 mg every 4 weeks across weeks 8 - 24/26 weeks</td>
<td>ND</td>
<td>↑Efficacy in earlier treatment with certolizumab</td>
</tr>
<tr>
<td>Sandborn et al. 2011 [49]</td>
<td>R, DB, IIIb</td>
<td>Certolizumab pegol</td>
<td>Blocking TNF</td>
<td>Placebo</td>
<td>Moderately to severely active CD</td>
<td>439</td>
<td>400 mg s.c. at weeks 0, 2, 4/6 weeks</td>
<td>Primary end point was clinical remission at weeks 6</td>
<td>No sig remission at weeks 6, sig improvement in patients with higher CRP</td>
</tr>
<tr>
<td>Schreiber et al. 2011 [82]</td>
<td>R, DB, undefined</td>
<td>Certolizumab pegol</td>
<td>Blocking TNF</td>
<td>Placebo</td>
<td>CD patients with draining fistulas (from PRECiSE-2)</td>
<td>539</td>
<td>400 mg every 2 or 4 weeks through weeks 24/26 weeks</td>
<td>ND</td>
<td>Sig improvement of sustained perianal fistula closure</td>
</tr>
<tr>
<td>Feagan et al. 2011 [83]</td>
<td>R, DB, IIIb (WELCOME study)</td>
<td>Certolizumab pegol</td>
<td>Blocking TNF</td>
<td>Placebo</td>
<td>Moderately to severely active CD</td>
<td>89</td>
<td>400 mg every 4 weeks up to weeks 52/54 weeks</td>
<td>ND</td>
<td>Sig improvement in work productivity, daily activities, HRQoL</td>
</tr>
<tr>
<td>Hebuterne et al. 2013 [84]</td>
<td>Open label, single arm, IIIb</td>
<td>Certolizumab pegol</td>
<td>Blocking TNF</td>
<td>Single arm</td>
<td>Moderately to severely active CD</td>
<td>510</td>
<td>400 mg s.c. every 4 weeks through weeks 24/26 weeks</td>
<td>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</td>
<td>Improvement of endoscopic lesions at weeks 10 and maintained through weeks 54</td>
</tr>
</tbody>
</table>

↑: 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-3 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 naive 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 Oneccept

We found one dose-ranging clinical trial assessing the efficacy and safety of oneccept as a recombinant receptor for TNF. Two-hundred and seven CD patients received four doses of oneccept or placebo for 8 weeks. The administered doses of oneccept 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 ClinicalTrials.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 drugs in patients with inflammatory bowel disease.

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

†: 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 drugs in patients with inflammatory bowel disease.

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

†: 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 drugs in patients with inflammatory bowel disease (continued).

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

: Increase; J: 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 drugs in patients with inflammatory bowel disease (continued).

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

* 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-2 and did not increase [61].

3.7 Vedolizumab

Vedolizumab is a human monoclonal antibody that specifically targets α4β7 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, vedolizumab 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 α4β7 integrins leads to not interacting with leukocyte trafficking to the central nervous system. Natalizumab blocks both α4β1 and α4β7 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.


45. The latest two Refs [45,46] evaluating adalimumab in patients with ulcerative colitis named ‘ULTRA 1’ and ‘ULTRA 2’.
54. The most important conducted clinical trials on certolizumab efficacy in patients with CD are PRECISE 1, 2, 4 explained in Refs [50-52].
New biologic therapeutics for ulcerative colitis and Crohn’s disease


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


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


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