Anti-adhesion molecule therapy for inflammatory bowel disease

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Abstract: Although biologic agents directed against tumor necrosis factor alpha (TNF α) continue to be an effective therapeutic strategy for patients with inflammatory bowel disease (IBD), approximately 30% of patients with Crohn's disease (CD) who are refractory to standard treatment do not respond to induction therapy with TNF α inhibitors and, of those who initially respond, 50% or more cease to respond within a year. Moreover, their use can be associated with significant safety issues. Clearly, there is a need to target alternative pathways involved in the inflammatory process. IBD is driven by the trafficking of lymphocytes from the circulation into the gut tissue that is mediated by adhesive interactions between the lymphocytes and endothelial cells. The adhesion molecules involved represent attractive targets for the development of new therapeutics which should aid in the resolution of existing inflammation, prevent recurrence of inflammation, and may potentially lead to long-term control of disease. In this article we review current opportunities and challenges facing anti-adhesion therapy in IBD, and discusses recent clinical development efforts that have focused on having an impact on two particular adhesive interactions: α_4 -integrin/MAdCAM-1 and β_2 -integrin/ICAM-1. Of particular interest is natalizumab, a humanized monoclonal antibody against human α_4 integrin that is approved for the treatment of patients with moderately-to-severely active CD and evidence of active inflammation. This agent represents an efficacious therapeutic option for patients who do not respond to, or have failed, a TNF- α inhibitor.

Keywords: Crohn's disease, inflammatory bowel disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) represents a chronic inflammatory disorder of the gastrointestinal tract encompassing Crohn's disease (CD) and ulcerative colitis (UC) [Cho, 2008; Baumgart and Carding, 2007]. The precise etiologies of these disorders are largely unknown, but the prevailing theory supports an abnormal immune response to an unknown environmental factor, commensal intestinal bacteria, or other disease-precipitating cofactors in a genetically susceptible host. This ultimately leads to an immune response that is inappropriate and sustained, which leads to tissue damage and the signs and symptoms of IBD [Sandborn and Yednock, 2003].

Despite significant advances in the therapeutic strategies over the last decade, there remains an unmet therapeutic need in the therapy of both CD and UC. A significant proportion of patients with CD and UC will fail to respond to, or lose

response to, traditional nonbiologic therapy, resulting in impaired quality of life (QoL) and complications such as fibrostenosis or internal penetrating disease that may necessitate surgical intervention [Bernklev *et al.* 2005; Cosnes *et al.* 2005]. In the era of antitumor necrosis factor (anti-TNF) therapy, clinical trial data suggest that 30–40% of patients will fail to have an initial response if such therapy is introduced after the failure of nonbiologic therapy, and a further 50% may lose response in the first year alone [Colombel *et al.* 2007; Sandborn *et al.* 2007a; Hanauer *et al.* 2002]. Current therapeutic options are also hampered with undesirable side effects such as metabolic changes, increased risk of mortality and infections with corticosteroids, a documented increase in lymphoma with the purine antimetabolites, and intolerance to methotrexate. Therefore, it comes into question what the benefit–risk equation really is with traditional nonbiologic therapy [Van Assche and Rutgeerts, 2005]. Anti-TNF strategies have also been associated

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with safety issues which include immunogenicity, hypersensitivity reactions, and increased risk of infection, as well as rare reports of malignancies (including hepatosplenic T-cell lymphoma), demyelinating disorders, hematologic abnormalities, and exacerbation of congestive heart failure [Elan Pharmaceuticals and Biogen Idec, 2010; Van Assche and Rutgeerts, 2005]. Targeting other potential pathways which are involved in the development and perpetuation of inflammation are severely needed and would offer patients and physicians alternative therapeutic options.

Lymphocytes play a central role in the pathogenesis of IBD [Eksteen *et al.* 2008]. The overall lymphocyte population is expanded in IBD, particularly in CD. Their journey from the vascular space into the gut tissue is regulated by a series of adhesion molecules that represent attractive targets for drug development. The ability to disrupt mechanisms central to the adhesion and trafficking of T lymphocytes into the inflamed gut, should aid in the resolution of existing inflammation and prevent recurrence of inflammation which would potentially lead to long-term control of disease. In this article we review current

opportunities and challenges facing anti-adhesion therapy in IBD.

The role of adhesion molecules in lymphocyte trafficking in the intestine

Leukocytes originate in the bone marrow and mature in the primary lymphoid organs. To patrol antigens in the gut lumen or assist in intestinal inflammatory reactions, they need to be directed toward the gastrointestinal tract. This journey requires several steps which are guided by an elaborate system of adhesion molecules [Van Assche and Rutgeerts, 2005; Von Adrian and Mackay, 2000]. The first step in the migration of leukocytes from the circulation into the tissue is the interaction of these lymphocytes with the endothelium of postcapillary vessels. This interaction is hampered by the high relative speed at which leukocytes travel that creates a shear stress in the blood stream. To overcome this, a sequential adhesion system has evolved which results in the tethering, rolling, firm adhesion, spreading, and migration of lymphocytes from the vascular space into inflamed tissue [Yonekawa and Harlan, 2005; Springer, 1994] (Figure 1). Tethering occurs through the

Figure 1. Leukocyte trafficking and post-trafficking events: tethering, rolling, firm adhesion, spreading, and migration. [Adapted with permission from Yonekawa and Harlan, 2005.]

interaction of selectins (L-, P-, and E-selectins) and oligosaccharide moieties that act as ligands [Vestweber and Blanks, 1999]. L-selectins are expressed on leukocytes, and P- and E-selectins are found on the endothelium. Although strong, these selectin bonds are short-lived and, consequently, the T cells roll over the endothelium from one selectin bond to the next [Lawrence and Springer, 1991]. This results in slowing of the lymphocytes and allows for transient interactions which enable the cell to encounter the cytokine-rich microenvironment that triggers subsequent firm adhesion and consequent migration through the blood vessel wall [Campbell *et al.* 1998, 1996; Bevilacqua, 1993].

Secondary adhesion molecules, all members of the integrin family, function to stop the rolling lymphocytes and allow migration. Integrins are cell-surface adhesion molecules that mediate both cell-cell and cell-extracellular matrix interactions [Hynes, 1992]. They consist of transmembrane α and β subunits that associate as heterodimers to form more than 24 different functional integrin receptors. The integrins involved in lymphocyte migration include $\alpha_2\beta_2$ (or lymphocyte function-associated antigen 1 [LFA-1]), and 2 α_4 integrins ($\alpha_4\beta_1$ and $\alpha_4\beta_7$) [Berlin *et al.* 1995]. Integrins are activated by chemokines on the endothelial surfaces that bind to G-protein-coupled receptors on lymphocytes [Van Assche and Rutgeerts, 2005]. The integrins on the lymphocytes bind to specific ligands on the endothelium called addressins. The $\alpha_2\beta_2$ integrin (or LFA-1), expressed on neutrophils, interacts with intercellular adhesion molecule-1 (ICAM-1) and -2 (ICAM-2). The $\alpha_4\beta_1$ integrin binds to vascular cell adhesion molecule-1 (VCAM-1) and the $\alpha_4\beta_7$ integrin to mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) [Sandborn and Yednock, 2003; Hamann *et al.* 1994; Lobb and Hemler, 1994; Springer, 1994; Postigo *et al.* 1993; Hemler *et al.* 1990]. There is evidence indicating that $\alpha_4\beta_1$ /VCAM-1 and $\alpha_4\beta_7$ /MAdCAM-1 operate independently to support lymphocyte adhesion, with chemokines selectively triggering adhesion and promoting motility and migration [Miles *et al.* 2008]. MAdCAM-1 is typically linked with gut-associated lymphoid tissue [Sandborn and Yednock, 2003; Briskin *et al.* 1997]. Owing to this specificity in distribution, adhesion molecules are thought to not only facilitate lymphocyte migration, but also contribute to tissue-specific trafficking.

Adhesion molecules in IBD

The migration of leukocytes into inflamed bowel tissue is central to the pathogenesis of IBD. Cytokines, including TNF- α and interleukin-1 (IL-1), secreted by inflammatory cells activate integrins on leukocytes and upregulate the expression of ICAM-1, MAdCAM and E-selectin on the vascular endothelium of inflamed tissue [Van Assche and Rutgeerts, 2005; Bernstein *et al.* 1998]. The intestinal endothelium in IBD patients has a higher adhesiveness for α_4 -integrins indicating the importance of this interaction in inflamed gut tissue [Van Assche and Rutgeerts, 2005]. In surgical resection specimens from patients with CD and UC, ICAM-1 and -2 expression is increased on the endothelium. Interestingly, clinical responses to anti-TNF- α therapy in CD patients are associated with a marked decrease in ICAM-1 expression in intestinal endothelium [Baert *et al.* 1999].

Once cells have successfully migrated in the tissues, the inflammatory process is propagated through increased local lymphocyte activation and proliferation, and decreased exit of lymphocytes from the mucosa. The expression of ICAM-1 in CD is not only increased in the intestinal mucosa, but also in the submucosa and muscle layers, and this may contribute to local interactions with lymphocytes that have penetrated the deeper layers of the intestinal wall as is characteristic of CD [Hogaboam *et al.* 1996]. Evidence also exists for a role for adhesion molecules in interactions between T cells and resident dendritic cells or mesenchymal cells in the intestinal mucosa and submucosa, thereby facilitating T-cell activation [Sandborn and Yednock, 2003]. α_4 integrins continue to play an important role in the inflammatory process through interactions with a number of tissue ligands, including the matrix protein fibronectin, the matricellular protein thrombospondin, the cytokine-like matrix molecule osteopontin, and metalloprotease, a disintegrin and metalloprotease domain 28 or metalloprotease disintegrin cysteine-rich protein expressed in lymphoid tissue [Sandborn and Yednock, 2003; Bridges *et al.* 2002; Li *et al.* 2002; Yakubenko *et al.* 2000; Bayless *et al.* 1998; Lehnert *et al.* 1998]. Such interactions induce costimulatory signals that lead to T-cell proliferation and adhesion, cytokine production, and an increase in the T-cell expression of matrix metalloproteinases that degrade the extracellular matrix and facilitate cell migration. Clearly, the disruption of adhesion molecule interactions may

prove to be effective due to decreased T-cell recruitment, inhibition of costimulatory signals in local T-cell activation, or a combination of both.

Approaches to targeting adhesion molecules and their associated ligands

There is a strong scientific rationale for targeting the integrins and their receptors as a way of impacting leukocyte trafficking. First, integrins are critically involved in several steps of the adhesion cascade, and preclinical studies have demonstrated that leukocyte integrin blockade is effective in a wide range of disease models including asthma, IBD, multiple sclerosis (MS), myocardial infarction, psoriasis, rheumatoid arthritis, and stroke [Cornejo *et al.* 1997]. Second, many details of integrin structure and function have been elucidated, thereby facilitating and directing drug development. Third, platelet integrin antagonists have already been shown to be effective drugs, thereby validating the integrins as targets [Yonekawa and Harlan, 2005]. Strategies being pursued that are part of 'anti-adhesion' therapy are summarized in Figure 2 and include: (1) receptor-ligand blockade (typically with an antibody or small molecule ligand mimetic antagonist); (2) allosteric inhibitors affecting affinity/avidity (typically small molecule antagonists); (3) inhibitors of 'inside-out' and 'outside-in' signaling pathways (typically small molecule inhibitors); and (4) inhibitors of the intracellular

pathways (transcription–translation) that regulate ligand expression (typically antisense molecules or small molecule inhibitors).

Anti-adhesion molecule strategies in animal models of IBD

Multiple animal models of mucosal inflammation are available for studying the pathogenesis and treatment of IBD [Strober *et al.* 2002]. While aspects of human IBD are reflected in each model, no animal model is ideal and numerous aspects need to be considered when data are evaluated [Rivera-Nieves *et al.* 2008].

A monoclonal antibody to α_4 integrin was evaluated in the cotton-top tamarin (CTT), a primate that spontaneously develops chronic colitis characterized by acute flares that is histologically and clinically reminiscent of human UC [Podolsky *et al.* 1993]. The monoclonal antibody (specific to $\alpha_4\beta_1$) significantly reduced acute colitis compared with baseline ($p=0.005$) and control group ($p<0.01$). Colitis activity was reduced in 11 of 12 antibody-treated animals at the end of a 10-day period, with 8 animals demonstrating complete quiescence of acute inflammation. The attenuation of colitis was related to the ability of the antibody to disrupt the recruitment of lymphocytes and monocytes, as evidenced by an increase in concentration of circulating leukocytes within a few days of antibody injections. In the same CTT model, clinical disease

Figure 2. Approaches to targeting leukocyte integrins and their ligands. [Adapted with permission from Yonekawa and Harlan, 2005.].

(as assessed by stool consistency) was rapidly improved by an antibody to the $\alpha_4\beta_7$ heterodimer [Hesterberg *et al.* 1996]. Treatment with this antibody also reduced the colonic infiltration of leukocytes. In another animal model of induced colitis, the dextran sodium sulfate (DSS)-colitic mouse, a pyridazinone-based $\alpha_4\beta_7$ selective antagonist demonstrated oral in-vivo activity [Gong *et al.* 2006].

The importance of the $\alpha_4\beta_7$ integrin was further evaluated through the manipulation of an integrin regulatory domain (adjacent to metal ion-dependent adhesion site [ADMIDAS]), a domain that normally serves to raise the activation threshold of $\alpha_4\beta_7$ and stabilize it in the non-adhesive state [Park *et al.* 2007]. Lymphocytes from mice harboring a disrupted ADMIDAS expressed an $\alpha_4\beta_7$ integrin that persistently adhered to MAdCAM-1 and also exhibited improper de-adhesion. *In vivo*, lymphocytes demonstrated enhanced adhesion to Peyer's patch venules, but suppressed homing to the gut. These results underline the importance of balance in adhesion and de-adhesion.

In a CD8(+) T-cell-dependent TNF^{ΔARE} mouse model of spontaneous CD, the requirement of intestinal-specific homing molecules, the chemokine/chemokine receptor pair CCL25/CCR9, and β_7 integrin was evaluated in animals genetically lacking these molecules [Apostolaki *et al.* 2008]. Although CCL25/CCR9 has been implicated in the recruitment of T-lymphocytes to the small intestine, intestinal inflammation developed unperturbed in animals lacking CCL25/CCR9. In contrast, genetic ablation of β_7 integrin resulted in the complete absence of intestinal pathology.

Strategies to block/disrupt MAdCAM-1 have also been evaluated *in vivo*. In the DSS model of induced colitis, anti-MAdCAM-1 treatment with an antibody reduced both colonic injury and the infiltration of β_7 -integrin-positive lymphocytes in the colonic mucosa [Kato *et al.* 2000] and led to a reduction in leukocyte sticking and extravasation that was paralleled by a significant reduction (45%) in intestinal inflammation [Farkas *et al.* 2006]. In trinitrobenzene sulfonate (TNBS)-induced colitis in mice, MAdCAM-1 inhibition through an antisense oligonucleotide reduced the number of $\alpha_4\beta_7$ -positive lymphocytes in the inflamed colonic mucosa, and significantly suppressed the development of colitis [Goto *et al.* 2006]. Interestingly, a soluble

lymphotoxin- β receptor (LT β R) Ig fusion protein, a competitive inhibitor of LT β R activation, significantly attenuated the development and histologic manifestations of chronic inflammation in the DSS mouse model of induced colitis. LT β R-Ig treatment significantly downregulated MAdCAM-1 expression, resulting in reduced leukocyte rolling and sticking in venules and reduced extravasation in the intestinal mucosa [Stopfer *et al.* 2004].

Anti-ICAM strategies, including blocking anti-ICAM-1 antibodies and ICAM-1 antisense oligonucleotides, have been evaluated in animal models of IBD. In DSS-induced murine colitis and in SAMP-1/Yit adoptive transfer-induced murine spontaneous ileitis, anti-ICAM antibodies were effective at reducing inflammation [Burns *et al.* 2001; Hamamoto *et al.* 1999]. Interestingly, in the mouse SAMP-1/Yit spontaneous ileitis model, ICAM-1 antibodies were only effective if administered in combination with anti-VCAM-1 or anti- α_4 -integrin-blocking antibodies. This suggests a redundancy in the adhesion pathway during acute inflammation. It is also important to note that anti-adhesion molecule therapy did not affect the signs of chronic inflammation such as architectural changes in the mucosa.

GI270384X, an oral inhibitor of ICAM-1 and E-selectin, was evaluated in two experimental models of colitis [Panés *et al.* 2007]. In severe forms of colitis (2% and 3% DSS-treated mice and IL-10 deficient mice, respectively), colonic inflammation was not modified by GI270384X. In less-severe forms of disease (1% DSS treatment), GI270384X ameliorated the clinical signs of colitis, colonic pathological changes, and serum biomarkers in a dose-dependent fashion. In addition, GI270384X abrogated the upregulation of ICAM-1 (with no effect on VCAM-1 or E-selectin), with an associated significant decrease in the number of rolling and firmly adherent leukocytes in colonic venules. In a study using DSS-induced colitis in mice, leukocyte adhesion was abrogated by VCAM-1 and MAdCAM-1 antibodies, but not by an anti-ICAM-1 antibody. Only the administration of an anti-VCAM-1 antibody resulted in significant attenuation of colitis [Soriano *et al.* 2000].

Anti-adhesion molecules in the treatment of IBD

In IBD, clinical development efforts have focused on making an impact on two particular

interactions: α_4 -integrin/MAdCAM-1 and β_2 -integrin/ICAM-1.

Anti- α_4 -integrin therapy

Two monoclonal antibodies have progressed through drug development programs and into clinical trials in IBD: a humanized monoclonal α_4 -integrin IgG4 antibody (TYSABRI [natalizumab]; Elan Pharmaceuticals, South San Francisco, CA and Biogen Idec, Cambridge, MA) and a specific humanized $\alpha_4\beta_7$ -integrin monoclonal antibody (vedolizumab/MLN0002; Millennium Pharmaceuticals, Cambridge, MA). In addition, an orally active small molecule antagonist to α_4 -integrin is in early clinical development in Japan (AJM300; Ajinomoto Co., Inc.), and an antibody to the β_7 integrin subunit is also under early clinical development by Genentech (rhuMab β_7) with recruitment currently ongoing for a phase 1 study in UC.

Natalizumab

Structure and mechanism of action

Natalizumab (TYSABRI; Elan Pharmaceuticals and Biogen Idec) is a humanized monoclonal antibody against human α_4 integrin. Natalizumab contains human framework regions and the complementary-determining regions of a murine antibody that binds to the α_4 -subunit of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins expressed on the surface of all leukocytes, except neutrophils, and inhibits the α_4 -mediated adhesion of leukocytes to their counter-receptors, including VCAM-1 and MAdCAM-1 [Elan Pharmaceuticals and Biogen Idec, 2010].

Indication

Natalizumab was approved on 14 January 2008 by the US Food and Drug Administration (FDA) for inducing and maintaining clinical response and remission in patients with moderately-to-severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional therapies and inhibitors of TNF- α (Table 1). In the United States, natalizumab is available only to patients enrolled in the risk minimization plan called the TOUCHTM (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program for close monitoring for the occurrence of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections. Natalizumab should not be used in combination with immunosuppressants (e.g. 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α . Natalizumab is also approved as monotherapy for the treatment of patients with relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations (initial approval date: 23 November 2004; current indication statement approved: 5 June 2006) [Elan Pharmaceuticals and Biogen Idec, 2010].

Development

Initial studies were performed with the antibody before humanization (AN100226m) and demonstrated that it was a potent inhibitor *in vitro* of the interactions between $\alpha_4\beta_1$ and VCAM, and that it suppressed and reversed experimental autoimmune encephalomyelitis (EAE) in a guinea pig model for MS [Kent *et al.* 1995]. The antibody

Table 1. Natalizumab therapy: indication and contraindications [Elan Pharmaceuticals and Biogen Idec, 2010].

Natalizumab therapy indications
<ul style="list-style-type: none"> • Inadequate response to conventional therapies • Unable to tolerate conventional therapies • TNF-α inhibitor primary nonresponder • TNF-α inhibitor secondary nonresponder • Unable to tolerate inhibitors of TNF-α • Elimination of corticosteroids is not possible with inhibitors of TNF-α • Following cessation of any concomitant immunosuppressive therapy other than corticosteroids
Natalizumab therapy contraindications
<ul style="list-style-type: none"> • In combination with immunosuppressants • In combination with inhibitors of TNF-α • Signs of liver injury (elevated serum hepatic enzymes and total bilirubin) • Increased risk of malignancy • Increased risk of developing PML
TNF- α , tumor necrosis factor alpha, PML, progressive multifocal leukoencephalopathy.

was then humanized to reduce potential immunogenicity, increase its half-life *in vivo*, and to allow repeat administration and consequently increase therapeutic benefit [Leger *et al.* 1997]. Grafting of the complementary-determining regions of AN100226m onto a human immunoglobulin (IgG₄) framework resulted in a new antibody (AN100226; natalizumab) that was approximately 95% human-derived. The choice of IgG₄ as the framework was important, as it does not activate complement, has a low affinity for Fc receptors, and persists longer in the circulation than other forms of human IgG [Mountain and Adair, 1992]. Importantly, the humanized antibody was equivalent to the murine antibody in terms of binding to $\alpha_4\beta_1$ and blocking cell adhesion, and reversing active EAE in guinea pigs.

Efficacy in Crohn's Disease

Induction In a pilot, placebo-controlled study, natalizumab (3 mg/kg infusion) was administered to 30 patients with mild-to-moderately active CD (Crohn's Disease Activity Index [CDAI] ≥ 151 and ≤ 450) [Gordon *et al.* 2001]. By week 2, natalizumab-treated patients demonstrated a significantly decreased CDAI from baseline, a higher rate of remission, and a lower requirement for rescue medication. The single infusion was well tolerated, and the increased circulating lymphocytes observed were indicative of interrupted lymphocyte trafficking. In a subsequent, double-blind, placebo-controlled study in 248 patients with moderate-to-severe CD, significantly higher rates of clinical response at weeks 4, 6, 8, and 12 were demonstrated in patients who received two infusions of 3 or 6 mg/kg of natalizumab compared with patients who received placebo. The onset of treatment effect was rapid and response was sustained for up to 8 weeks after the last infusion. In addition, natalizumab-treated patients who received two infusions of 3 mg/kg demonstrated a significantly higher rate of clinical remission at weeks 4, 6, 8, and 12 compared with the placebo group. Although the rate of remission in the patients in the 6 mg/kg treatment group was not significantly different compared with the rate in the placebo group at week 6 (the primary endpoint), significant differences were achieved at weeks 4 and 8 [Ghosh *et al.* 2003].

While weight-based dosing had been used in both CD and MS trials, a study was undertaken to determine the optimal dosing regimen for the phase 3 program [Bennett *et al.* 2002].

Population pharmacokinetic modeling was applied to the pharmacokinetic and α_4 integrin binding data from phase 2 studies of natalizumab in patients with CD or MS. The analyses demonstrated that fixed dosing of natalizumab every 4 weeks achieved more consistent serum concentrations across a wide range of body weights compared with weight-based dosing, and resulted in exposures overlapping those produced by the 3 and 6 mg/kg doses used in the phase 2 trials.

The effects of natalizumab on the induction of response in patients with CD were subsequently evaluated in two phase 3 studies. The randomized, placebo-controlled ENACT-1 (Efficacy of Natalizumab as Active Crohn's Therapy) trial involved 905 patients and demonstrated that natalizumab treatment resulted in a small, but significant, improvement in response at week 10 (56% versus 49% in the placebo group; $p = 0.05$) and a small, but insignificant, improvement in remission (37% versus 30% in the placebo group; $p = 0.12$) following three (300 mg) infusions at weeks 0, 4, and 8 (Table 2) [Sandborn *et al.* 2005]. The second phase 3 induction trial, ENCORE (Efficacy of Natalizumab in Crohn's disease respOnse and REmission), involved patients ($n = 509$) with moderately-to-severely active CD and objective evidence of inflammation as characterized by elevated C-reactive protein (CRP; defined as >2.87 mg/l) and demonstrated that natalizumab was effective as induction therapy [Targan *et al.* 2007]. The primary endpoint, a response (decrease in CDAI score ≥ 70 points) at week 8 that was sustained through week 12, was achieved in 48% of natalizumab-treated patients compared with 32% of placebo-treated patients ($p < 0.001$) (Figure 3 and Table 2). It is also important to note that a more rigorous response endpoint (decrease in CDAI score ≥ 100 points) was also sustained at

Table 2. Natalizumab: response and remission data from phase 3 trials [Targan *et al.* 2007; Sandborn *et al.* 2005]. © 2005 Massachusetts Medical Society. All rights reserved.

Study	Week	Response	Remission
ENACT-1	Week 10	56%	37%
ENCORE	Week 12 [sustained]	48%	26%
ENACT-2	Week 36	61%	44%

ENACT, efficacy of natalizumab as active crohn's therapy; ENCORE, efficacy of natalizumab in crohn's disease response and remission.

Figure 3. Proportion of patients with elevated C-reactive protein (CRP) levels who achieved clinical response in the ENCORE natalizumab induction trial. The primary endpoint was induction of response (≥ 70 -point decrease from baseline Crohn's Disease Activity Index [CDAI] score) at week 8 that was sustained through week 12. Reprinted from Targan *et al.* 2007 with permission from Elsevier.

every time point evaluated. The proportion of patients with a 100-point response at week 8 and sustained through week 12 was significantly ($p < 0.001$) higher for natalizumab-treated patients (39%; 102 of 259) compared with placebo-treated patients (22%; 56 of 250).

Maintenance In ENACT-2, a large, phase 3, randomized, placebo-controlled maintenance study, 339 patients who responded to natalizumab (decrease in baseline CDAI ≥ 70 points) in the ENACT-1 induction trial were re-randomized to receive placebo or 300 mg natalizumab every 4 weeks from weeks 12 to 56, with follow up through week 60 [Sandborn *et al.* 2005]. At week 36, response (decrease in baseline CDAI ≥ 70 points, with an absolute score < 220 points) was continuously maintained by 61% of natalizumab-treated patients compared with 28% of patients in the placebo group ($p < 0.001$), and remission (CDAI < 150 points) was maintained at all assessed time points in 44% of natalizumab-treated patients compared with 26% of placebo-treated patients ($p = 0.003$) (Figure 4 and Table 2). The rates of sustained remission were significantly higher in the natalizumab group at every point from week 20 through 60 (39% versus 15% in the placebo group; $p < 0.001$).

Over the course of ENACT-1, natalizumab responders demonstrated clinically meaningful improvements in health-related quality of life (HRQoL). During subsequent maintenance therapy, both Inflammatory Bowel Disease Questionnaire (IBDQ) and Short-Form 36 (SF-36) scale scores of patients who responded to natalizumab induction and then received the agent in ENACT-2 remained stable, while those re-randomized to placebo worsened [Feagan *et al.* 2007]. At week 60 (48 weeks after the initiation of maintenance therapy), the mean change from ENACT-1 baseline of all scales of the IBDQ and SF-36 was significantly higher for those who continued to receive natalizumab ($p < 0.001$). Importantly, the scores of patients who received maintenance natalizumab treatment were not statistically different for six of eight scales of the SF-36 from those in a cross section of the US population.

Patients who completed the ENACT-2 trial were eligible to enroll in the long-term, open-label extension study ENABLE (Evaluation of the Natalizumab AntiBody for Long-term Efficacy), which was designed to evaluate the safety and efficacy of natalizumab as continuous maintenance therapy over an additional 12 months in patients

Figure 4. Proportion of patients in the ENACT-2 natalizumab maintenance trial with a sustained response (a) and sustained remission (b) at each visit. [Adapted with permission from Sandborn *et al.* 2005; copyright © 2005 Massachusetts Medical Society. All rights reserved.].

in remission at the end of ENACT-2 (total exposure >2 years) [Panaccione *et al.* 2006]. At the end of ENACT-2 (month 15), 146 of the 339 patients in the ENACT-2 population were in remission (CDAI score <150) and enrolled in ENABLE. Of these patients, 87 (60%) had received uninterrupted natalizumab for a total of 15 months in the ENACT trials. Overall, 75 of the 87 patients (86%) remained in remission after 12 additional months of natalizumab treatment. Moreover, 85% of patients who were corticosteroid-free and in remission on entry maintained their corticosteroid-free remission after the 12 additional infusions in ENABLE. Similar results were demonstrated

among those subsets of patients with previous exposure or failure to anti-TNF therapy, with 91% and 82% in remission after the additional 12 months, respectively. Importantly, long-term natalizumab therapy was safe and well-tolerated, with a low rate of immunogenicity.

Subgroups

Corticosteroids A total of 42% (143 of 339) of the natalizumab responders in ENACT-1 were on baseline oral corticosteroids or budesonide. Among responders re-randomized to natalizumab, 58% had eliminated corticosteroids at

Figure 5. Proportion of patients in the ENACT-2 natalizumab maintenance trial who were able to both sustain remission and discontinue corticosteroid use. [Adapted with permission from Sandborn *et al.* 2005; copyright © 2005 Massachusetts Medical Society. All rights reserved.].

week 36, compared with 28% of responders who had been re-randomized to placebo ($p < 0.001$). At week 36, 45% of natalizumab-treated patients who were on baseline steroids had discontinued steroids and were in remission, compared with 22% of patients in the placebo group ($p = 0.003$). This effect was maintained throughout the trial and, at week 60, 42% of natalizumab-treated patients who were on baseline steroids had discontinued steroids and were in remission, compared with 15% of patients in the placebo group ($p < 0.001$; Figure 5) [Sandborn *et al.* 2005].

Prior exposure to anti-TNF- α antibody
Response in patients previously exposed to TNF- α inhibitors is most relevant, as natalizumab is only approved for this group of patients. The induction (ENACT-1, ENCORE) and maintenance (ENACT-2) trials included a large number of patients with prior exposure to a TNF- α inhibitor, many of whom were considered TNF- α failures. In ENACT-1, 40% of patients had previously received a TNF- α inhibitor. Of these, 55% of natalizumab-treated patients experienced a response and 33% were in remission at week 10 versus 35% ($p = 0.003$) and 22% ($p = 0.046$) of placebo-treated patients, respectively [Sandborn *et al.* 2005]. Nearly half (48%) of the patients in the ENCORE induction trial had prior exposure to a TNF- α inhibitor, most of whom (71%) were considered by the investigator to have failed this therapy [Present *et al.* 2007].

A post-hoc analysis of the efficacy of natalizumab in the ENCORE subpopulation of patients who had failed treatment demonstrated that 38% of patients had a sustained response to natalizumab at both weeks 8 and 12, compared with 15% of patients treated with placebo ($p < 0.001$). Approximately 50% of natalizumab-treated patients with prior treatment failure were in response at either time point (52% at week 8 and 49% at week 12) compared with the placebo group (22% at week 8 and 29% at week 12; $p \leq 0.006$). Remission was sustained through weeks 8 and 12 in 17% of patients treated with natalizumab compared with 5% of patients in the placebo group ($p = 0.012$). Remission rates at week 8 were 21% and 8% ($p = 0.019$), and were 23% and 13% ($p = 0.095$) at week 12 for patients in the natalizumab and placebo groups, respectively (Figure 6) [Present *et al.* 2007].

In ENACT-2, 58% of patients treated with natalizumab and previously exposed to a TNF-inhibitor had a sustained response at all time points through month 9 compared with 10% treated with placebo ($p < 0.001$). Similarly, sustained remission was observed in 39% of patients treated with natalizumab and 8% of those treated with placebo ($p = 0.002$). Statistically significant treatment differences in the maintenance of sustained clinical response and remission between natalizumab and placebo were observed until the end of the study at month 15 [Panaccione *et al.* 2006].

Figure 6. Proportion of patients in the ENCORE natalizumab induction trial identified as having had a previous TNF α therapy failure and being in remission during the trial. [Adapted with permission from Present *et al.* 2007.].

Long-term data on natalizumab (>27 months) are also available for patients who had previously failed treatment with a TNF inhibitor. Patients who participated in the ENACT trials were eligible to enroll in a long-term open label extension study. A total of 86% (12 of 14 patients) of the patients in these trials who had previously failed therapy with a TNF- α inhibitor and were in remission at the end of 15 months of natalizumab therapy were in remission following an additional 12 months of natalizumab [Ghosh and Panaccione, 2007].

Safety

Adverse events Natalizumab has demonstrated a consistent safety profile within controlled clinical trials of CD, with the most frequently reported ($\geq 10\%$) adverse events (AEs) including headache, fatigue, upper respiratory tract infections, and nausea [Elan Pharmaceuticals and Biogen Idec, 2010; Sands *et al.* 2007; Targan *et al.* 2007; Sandborn *et al.* 2005; Ghosh *et al.* 2003; Gordon *et al.* 2001]. The most frequently reported AEs that resulted in discontinuation of natalizumab were exacerbation of CD (4.2%) and acute hypersensitivity reactions (1.5%). Natalizumab was also well tolerated in the long-term, open-label extension study ENABLE, in which patients received natalizumab for >2 years. The most frequently reported AEs included nasopharyngitis, headache, and exacerbation of CD, with 6% of patients discontinuing treatment due to an AE.

It should be noted that natalizumab-treated patients may have moderate and sustained elevations in median absolute circulating lymphocyte count [Sandborn *et al.* 2005]. It is important to note that these elevations are not above the upper limit of normal, are a predicted, pharmacologic effect, and are reversible upon cessation of treatment with natalizumab. Interestingly, there were no differences in total blood lymphocyte, T-cell, or B-cell counts between patients treated with a humanized antibody to $\alpha 4\beta 7$ (MLN02) and placebo [Feagan *et al.* 2005].

Immunogenicity In both short- and longer-term CD trials, immunogenicity has been consistently low ($\leq 11\%$ of patients) [Hyams *et al.* 2007; Sands *et al.* 2007; Targan *et al.* 2007; Sandborn *et al.* 2005; Ghosh *et al.* 2003; Gordon *et al.* 2001]. While the development of persistent antibodies against natalizumab (defined as two positive antibody tests occurring at least 6 weeks apart or a single positive test at the last measurement) is associated with a loss of clinical efficacy, 75% of patients with transient antibodies continued to maintain a response through week 60 [Sandborn *et al.* 2005]. Interestingly, none of the patients in the long-term study (>2 years of natalizumab) had detectable levels of persistent antibodies.

Infusion reactions/hypersensitivity Hypersensitivity reactions have occurred in natalizumab-treated patients, usually within 2 hours of the start of infusion, and are generally associated with

persistent antinatalizumab antibodies [Elan Pharmaceuticals and Biogen Idec, 2010]. In ENACT-1, acute infusion reactions occurred in 45% (24 of 53) of patients who tested positive for antibodies against natalizumab compared with 9% (54 of 597) of patients who tested negative for antibodies ($p < 0.001$). Of the five patients with a serious hypersensitivity-like reaction, three were positive for antinatalizumab antibodies. In ENACT-2, 19% (7 of 36) of patients who were positive for antibodies had either an acute infusion reaction (3 patients) or a hypersensitivity-like reaction (4 patients), compared with 7% (26 of 354) of patients who tested negative for antibodies ($p = 0.02$) [Sandborn *et al.* 2005]. Although the incidence of acute infusion reactions and hypersensitivity-like reactions was low, they did occur more frequently in patients with persistent antinatalizumab antibodies.

Hepatotoxicity Clinically significant liver injury has been reported in patients treated with natalizumab in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as 6 days after the first dose. Signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing further evidence that natalizumab caused the injury. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Importantly, there have been no liver-related deaths or liver transplants. [Elan Pharmaceuticals and Biogen Idec, 2010].

Infection A total of 477 of 1182 (40.4%) natalizumab-treated patients in short-term CD clinical trials experienced at least one infection, compared with 183 of 506 (36.2%) of placebo-treated patients [Biogen Idec and Elan Pharmaceuticals, 2007]. The rates of serious infections were similar between natalizumab- and placebo-treated patients (2.5% and 2.4%, respectively). Importantly, the rates of discontinuation were also similar between natalizumab- (0.6%) and placebo-treated (1%) patients. In a recent safety update (as of 30 June 2009), the most common serious AEs reported were infections (1.4%), including urinary tract, respiratory tract, and Herpes zoster virus [Pepio *et al.* 2009].

Progressive multifocal leukoencephalopathy PML, a rare and progressive demyelinating disease of the brain, is caused by infection of oligodendrocytes by reactivated JC virus (JCV) and typically causes permanent disability or death [Richardson-Burns *et al.* 2002]. The majority of healthy individuals are believed to be infected at an early age with JCV, with the seroprevalence of anti-JCV antibodies ranging from 10% to 80%, depending on the testing methodology [Knowles *et al.* 2003; Knowles and Sasnauskas, 2003].

A subsequent expert review of 3417 patients with MS, CD, or rheumatoid arthritis who received natalizumab in clinical trials estimated the risk of PML to be approximately 1 in 1000 patients for those treated with this agent for a mean of 17.9 months [Yousry *et al.* 2006]. In November 2009, the US package insert was updated due to postmarketing reports of additional cases of PML, which have been reported in patients with MS who were receiving no concomitant immunomodulatory therapy. In patients treated with natalizumab, the risk of developing PML increases with longer treatment duration, and for patients treated for 24–36 months is generally similar to the rates seen in clinical trials, as reported above. There is limited experience beyond 3 years of treatment. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of natalizumab will mitigate the disease, so clinical vigilance for signs or symptoms suggestive of PML is important. Dosing should be withheld immediately at the first sign or symptom suggestive of PML and a magnetic resonance imaging scan of the brain performed. If clinically indicated, polymerase chain reaction testing of cerebrospinal fluid for JC viral DNA may also be considered [Elan Pharmaceuticals and Biogen Idec, 2010]. Additional work is ongoing to identify potential risk factors and evaluate therapeutic options.

Owing to the risk of PML, TYSABRI is available in the United States only through the special restricted distribution TOUCHTM Prescribing Program. Under the TOUCHTM Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse natalizumab [Elan Pharmaceuticals and Biogen Idec, 2010]. The goals of the TOUCHTM program are to promote

informed benefit–risk decisions, to minimize the risk of PML, and to minimize death and disability due to PML. In addition, this program is used to determine the incidence and risk factors for PML and other serious opportunistic infections, as well as assess long-term safety in clinical practice. Owing to the TOUCHTM Prescribing Program, clinical vigilance has led to the early identification of signs and symptoms of possible PML, and subsequent testing and confirmation led to initiation of appropriate treatment. Plasma exchange may be effective in restoring immune effector function in natalizumab-treated patients [Khatri *et al.* 2009]. Indeed, approximately 3 weeks after plasma exchange of a natalizumab-treated MS patient with PML, JCV was no longer detectable and symptoms improved [Linda *et al.* 2009].

In any discussion of risk–benefit with CD therapies, it is important to note that patients with CD have an overall mortality rate that is increased relative to the normal population [Wolters *et al.* 2006]. In addition, as CD patients suffer from a substantially reduced HRQoL compared with healthy individuals [Irvine, 1997], they have well-defined preferences among treatment attributes and are willing to accept tradeoffs among attributes. Patients are willing to accept a considerable risk of serious AEs in exchange for clinical efficacy. Indeed, the patients' perspectives on balancing benefits and risks can assist in making treatment and regulatory decisions [Johnson *et al.* 2007]. It should also be noted that there are a number of interventions available for patients with PML, including antiviral treatment, immunomodulatory therapies, and plasma exchange [Stüve *et al.* 2007]. Moreover, there are ongoing efforts to identify possible aspects of the JC viral life cycle that might be used in a screening tool to identify those patients at risk of developing PML [Verbeeck *et al.* 2008].

Malignancy A total of 7 malignancies in 1182 CD patients who received natalizumab during short-term clinical trials have been reported. The seven malignancies included adenocarcinoma of the lung, bladder cancer, breast cancer, invasive breast cancer, colon cancer, malignant melanoma, and uterine cancer. In natalizumab-treated patients with CD, the rate of malignancy was 1.6 events/100 person-years, compared with 0.60 in the placebo group. However, the short duration of treatment, use of concomitant medications, and prior treatment

history make it difficult to predict the actual rate of malignancies [Biogen Idec and Elan Pharmaceuticals, 2007].

Vedolizumab/MLN0002

Vedolizumab/MLN0002 (formerly known as MLN02 and LDP-02; Millennium Pharmaceuticals) is a humanized monoclonal antibody that specifically recognizes the $\alpha_4\beta_7$ heterodimer without cross reacting with the individual component monomers [Feagan *et al.* 2005]. In a study in CTTs, rapid (24–72 hours) symptomatic improvements were observed with antibody administration, and were mirrored by improvements in histological changes and a reduction in mucosal T cells [Hesterberg *et al.* 1996]. A phase 1/2, double-blind, placebo-controlled, dose-ascending study in humans with moderate UC indicated that vedolizumab doses up to 2.0 mg/kg were safe and well tolerated [Feagan *et al.* 2000]. Complete endoscopic and clinical remission was observed in three of five patients in the 0.5 mg/kg vedolizumab treatment group.

In a follow-up, phase 2, multicenter, double-blind, placebo-controlled trial in 181 patients with active UC, vedolizumab was significantly more effective than placebo for the induction of clinical and endoscopic remission [Feagan *et al.* 2005]. At week 6, clinical remission rates were 33%, 32%, and 14% for the 0.5 mg/kg vedolizumab, 2.0 mg/kg vedolizumab, and placebo groups, respectively ($p=0.03$). Endoscopically evident remission was achieved in 28%, 12%, and 8% of the 0.5 mg/kg vedolizumab, 2.0 mg/kg vedolizumab, and placebo groups, respectively ($p=0.007$). Although vedolizumab did appear to be well tolerated, human antihuman antibodies developed in 44% of vedolizumab-treated patients by week 8. Overall, 24% of patients were positive for antibody at a titer of $>1:125$ and showed a loss of saturation of $\alpha_4\beta_7$ binding sites and a resultant clinical remission rate similar to that in the placebo group. Although the number of patients who achieved remission (approximately one-third) suggested that a higher dose of vedolizumab should be evaluated, such an approach may not be successful as a dose–response relationship was not observed and saturation of $\alpha_4\beta_7$ on peripheral T cells was observed at both doses when the primary endpoint was assessed.

Vedolizumab has also been evaluated in CD. In a 180-day randomized, placebo-controlled,

phase 2 study in 185 patients with mild-to-moderate CD, there was no difference in response at 2 months between the vedolizumab group and placebo, as defined by a decrease in CDAI of ≥ 70 points [Feagan *et al.* 2008; Millennium Pharmaceuticals, 2002].

Although the results from UC were favorable, clinical development was delayed in order to address manufacturing issues. In 2007, Millennium Pharmaceuticals announced the resumption of the vedolizumab clinical program to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of vedolizumab derived from a newly engineered, commercially scaleable cell line [Millennium Pharmaceuticals, 2007]. The new clinical development program using the updated molecule MLN0002 includes a phase 2 long-term safety study in UC and CD and phase 3 induction and maintenance trials in patients with UC (GEMENI I) and CD (GEMENI II).

AJM300

AJM300 is an orally active small molecule that is an antagonist to α_4 -integrin. One randomized placebo-controlled clinical trial has been presented at the 2009 Digestive Disease Week (DDW) Annual Meeting [Takazoe *et al.* 2009]. This study compared the efficacy and safety of placebo or AJM300 40 mg tid, 120 mg tid, or 240 mg tid orally for 8 weeks in patients with active CD. The primary endpoint was decrease in CDAI score from baseline to final evaluation at week 4 or later and the secondary endpoint was clinical response. The investigators found no significant difference in clinical response with AJM300 compared with placebo, but among those patients with a high CDAI at baseline there was a significant decrease in CDAI with AJM300 120 mg group ($p=0.0485$) compared with placebo and a trend toward decrease in the 240 mg group. AEs did not appear to be dose-related: 16.7% in the placebo group and 0%, 23.5%, and 22.2% in the AJM300 40 mg, 120 mg, and 240 mg groups, respectively. This very preliminary study will need replication in a larger study before any conclusion about the utility of the drug can be made.

Anti-ICAM-1 therapy: Alicaforsen

Alicaforsen (ISIS 2302; ISIS Pharmaceuticals) is a 20-base ICAM-1 antisense oligonucleotide that specifically reduces ICAM-1 mRNA and protein expression [Shanahan, 1999]. In a pilot study, 15 patients with mild-to-moderate CD on

corticosteroids received ISIS 2302 (0.5–2.0 mg/kg/day IV 13 times over 4 weeks). Promising results were achieved, including durable remissions, steroid sparing, and an acceptable safety profile [Yacyshyn *et al.* 1998]. Based on these favorable results, two larger multicenter trials were designed. In the first trial, patients with steroid-dependent moderate CD were treated subcutaneously with ISIS 2302 (0.5 mg/kg or placebo; 5 days per week for up to 4 weeks). However, treatment with ISIS 2302 was judged to be ineffective and enrollment was terminated early [Schreiber *et al.* 2001]. In the second trial, 299 patients in the US and Europe with moderately active steroid-dependent CD received an intensified regimen of ISIS 2302 (2 mg/kg IV three times per week) for up to 4 weeks or placebo [Yacyshyn *et al.* 2002]. After a 1-month interval without treatment, the same treatment schedule was repeated. While there were no significant differences in remission rates between ISIS 2302 and placebo treatment groups, when patients were regrouped in terms of total drug exposure (using the area under the curve [AUC] of plasma concentration over time), the highest AUC group showed consistent improvements in most of the clinical endpoints (remission, CDAI, and IBDQ). Unfortunately, disappointing results were also obtained from two further double-blind, placebo-controlled trials in 331 patients with active CD [Yacyshyn *et al.* 2007].

While ISIS 2302 may indeed demonstrate effectiveness if used at an adequate dose, it may well be that there is a redundancy in the adhesion pathways in the inflamed gut, thereby allowing alternative routes for leukocyte infiltration. Another explanation for the lack of efficacy is the inability of the agent to penetrate the inflamed bowel. Consequently, a rectal enema ISIS 2302 formulation has been clinically evaluated. In an open-label study, 15 patients with active UC received nightly enemas of ISIS 2302 (240 mg) for 6 weeks [Miner *et al.* 2006]. Interestingly, concentrations of the intact oligonucleotide in mucosal colonic tissue biopsies were significantly higher than those in plasma. At the end of treatment, there was a 46% reduction in mean Disease Activity Index (DAI) and a 33% rate of remission (as defined by complete mucosal healing). In a phase 2, dose-ranging, double-blind, placebo-controlled study, 112 patients with mild-to-moderate left-sided UC received one of four ISIS 2302 enema regimens or placebo daily for 6 weeks [Van Deventer *et al.* 2006].

While there were no significant differences between treatment and placebo in terms of DAI at week 6, there was a prolonged reduction in the mean percentage DAI relative to baseline from week 18 (51% versus 18%; $p=0.04$) to week 30 (50% versus 11%; $p=0.03$) in the 240 mg ISIS 2302 group compared with placebo.

The place of anti-adhesion therapies in the treatment of IBD

Current guidelines recommend a stepwise approach to the treatment of IBD, involving the addition of newer therapies as severity and refractoriness to therapy increases. Therefore, biologic therapies are typically used after corticosteroids and immunosuppressants have failed to achieve or maintain prolonged remission [Clark *et al.* 2007]. While TNF- α inhibitors continue to be an effective therapeutic strategy for patients who are refractory to corticosteroids and immunosuppressants, there remains a significant patient population that remains active in the short or long term despite anti-TNF therapy. This includes those patients for whom TNF- α inhibitors are contraindicated, those who do not respond to TNF- α inhibitors (primary nonresponders), and those who have a secondary loss of response or develop intolerance to TNF- α inhibitors (secondary nonresponders). Data from the ACCENT I and CHARM trials suggest that an option for those patients who are losing response to infliximab or adalimumab is to either double the dose of infliximab or increase the frequency of adalimumab injections. Alternatively, short-term data from the GAIN trial demonstrated that patients may be efficaciously switched from infliximab to adalimumab if they have lost response to or have become intolerant to infliximab. In addition, data from the WELCOME (26-week, open-label trial evaluating the clinical benefit and tolerability of certolizumab pegol induction and maintenance in patients suffering from CD with prior loss of response or intolerance to infliximab) study demonstrated the efficacy of certolizumab in patients who were no longer responding to infliximab [Vermeire *et al.* 2008]. However, previous exposure to therapy with a TNF- α inhibitor appears to result in lower absolute efficacy rates compared with patients who are TNF- α inhibitor naïve [Abreu, 2007; Colombel *et al.* 2007; Sandborn *et al.* 2007b; Hanauer *et al.* 2006].

Primary nonresponders to anti-TNF

There are no controlled data to support sequential use of TNF- α inhibitors in patients with a primary lack of response to any one of these agents. Scientifically, it makes little sense to continue to use agents within the same class. The risks associated with these agents remains the same; however, the benefit intuitively decreases dramatically. Therefore, natalizumab may be a viable alternative to treatment with second or third TNF- α inhibitors for primary nonresponders to anti-TNF therapy (Table 1).

Corticosteroid-dependent patient

Patients who enter remission for induction therapy for any of the anti-TNF- α agents should remain on that therapy to maintain remission. Sandborn and colleagues reported at the 2009 DDW Annual Meeting that among the 508 patients originally randomized in the SONIC trial, 46% of those receiving infliximab plus azathioprine (I + A) were in steroid-free remission at week 50, compared with 35% receiving infliximab alone (I) and 24% receiving azathioprine (A; $p < 0.001$ for I + A versus A; $p = 0.028$ for I versus A; $p = 0.035$ for I + A versus I) [Colombel *et al.* 2010]. However, if patients are treated with anti-TNF and fail to enter into remission or, more importantly, cannot enter and sustain remission in the absence of steroids, alternate therapeutic strategies should be explored. In this case, there is no evidence that a second TNF- α inhibitor would be of benefit for corticosteroid sparing or elimination, and following dose adjustment/optimization of the anti-TNF- α , patients who are still unable to discontinue corticosteroids should be switched to natalizumab following cessation of any concomitant immunosuppressive therapy (Table 1). Other possible options include methotrexate, surgery or participation in clinical trials for novel agents.

Conclusions

IBD is driven by lymphocytes that traffic from the circulation into the gut tissue. Such trafficking is mediated by a series of adhesive interactions between the invading lymphocyte and endothelial cells. Consequently, anti-adhesion molecule strategies represent an attractive concept for the development of new therapeutics in the management of IBD. Natalizumab, a humanized monoclonal antibody against human α_4 integrin, is approved for the treatment of patients with moderately-to-severely active CD. This agent represents an efficacious therapeutic

option for patients who do not respond to, or have failed, a TNF- α inhibitor. Evolving strategies for risk management to maximize the risk–benefit offers patients with IBD a new class of agents and widens options for physicians caring for such patients.

Conflict of interest statement

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Dr Ghosh has associations with Schering Plough (educational symposium, advisory board), Centocor (educational symposium, advisory board), Abbott (educational symposium, advisory board), UCB Pharma (educational symposium, advisory board), Elan (advisory board), and Novimmune (advisory board).

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