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[†] Author for correspondence
Hôpital Huriez, Service d'Hépatogastro-Entérologie, Rue Polonovski
59037 Lille, Cedex, France
Tel.: +33 320 444 714
Fax: +33 320 444 713
jfcolumbel@chru-lille.fr

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Natalizumab: a promising treatment for Crohn's disease

Jean Frédéric Colombel[†] and Laurent Peyrin-Biroulet

A primary feature contributing to the pathology of Crohn's disease (CD) is inappropriate and persistent recruitment and migration of circulating leukocytes from the bloodstream to affected tissues and organs. These processes are mediated by interactions between α_4 integrin adhesion molecules expressed on leukocyte surfaces and cognate receptors on vascular endothelial cells. Natalizumab is a humanized immunoglobulin G₄ monoclonal antibody against α_4 integrins. Natalizumab has demonstrated efficacy in inducing and maintaining sustained remission in patients with moderately to severely active CD, including those intolerant of or unresponsive to infliximab. Maintenance therapy with natalizumab in adult patients allowed elimination of steroids in a significant number of patients and sustained patients' quality of life. Natalizumab has been well tolerated in the majority of patients. However, progressive multifocal leukoencephalopathy, a rare opportunistic infection associated with the JC polyomavirus, occurred in three natalizumab-treated patients; two multiple sclerosis patients and one CD patient. This article reviews the properties of natalizumab and addresses its potential benefits and risks in the treatment of CD.

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Crohn's disease (CD) is a common disease ranging in prevalence from 26 to 199 cases per 100,000 people in North America and from 8.3 to 214 cases per 100,000 people in Europe [1]. The incidence of CD continues to increase globally in many areas and, in Europe, the incidence of CD in children is increasing [1]. The course of CD is characterized by fluctuating periods of remission and relapse. CD is frequently progressive and patients with moderate to severe disease often require surgery. However, surgery is not curative and additional surgical intervention is commonly required.

Practice guidelines for the treatment of CD in adults were published in 2001 by the American College of Gastroenterology and its Practice Parameters Committee [2] and recently in Europe by the European Crohn's and Colitis Organization [3]. These guidelines suggest a 'step-up' or 'therapeutic pyramid' approach based on disease severity. Medications for induction of remission in mild-to-moderate disease include controlled-ileal release budesonide, antibiotics and aminosalicylates (5-ASA).

Induction of remission may be attempted in more severe cases with systemic corticosteroids or immunomodulators, such as azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate. Infliximab is usually reserved for refractory CD or patients with severe fistulizing disease.

Maintenance of medically or surgically induced remission may be difficult to achieve. AZA and 6-MP maintain medical remission effectively and are considered the benchmark by which other agents are measured [4]. However, these drugs may have significant side effects. Nausea, vomiting and abdominal pain are common adverse effects that occur usually early in therapy and improve with time. More serious side effects include pancreatitis, hepatitis, malignancies, myelosuppression and opportunistic infections. These may occur regardless of dose or duration of exposure to therapy. In clinical trials, up to 28% of patients discontinued AZA because of adverse effects [4]. Once AZA/6-MP are started, they should be continued indefinitely in most

patients. A recent study from the Groupe d'Etude Thérapeutique dans les Affections Inflammatoires du tube Digestif (GETAID) demonstrated that AZA withdrawal is not equivalent to continued therapy with AZA for maintenance of remission in patients with CD who have been in remission on AZA for less than 3.5 years [5]. However, the long-term benefits are tempered by the potential long-term consequences of AZA/6-MP treatment, which, in addition to the events noted above, has been associated with potential lymphoma-inducing effects [6]. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor (TNF)- α and the only approved biological therapy for CD to date, is proven to maintain remission among those with infliximab-induced remission and appears to have some steroid-sparing effects [7]. Long-term use of infliximab may be limited by immunogenicity and subsequent loss of response and remission [8]. As with AZA, infliximab use may be associated with an increased risk of potentially life-threatening infections and malignancies, including lymphoma [9].

Increasingly, data suggest that the current CD treatment paradigm may need revision [10]. Traditional step-up treatments do not alter the course of CD; up to 47% of CD patients relapse within a year of remission [11,12]. In one estimate, the risk of stenosing or penetrating complications was 40 and 70% at 5 and 20 years, respectively [13]. Surgery does not alter the disease's natural history; recurrent lesions have been observed endoscopically in the neoterminal ileum within 1 year of surgery in 73% of patients [12]. In the more than 60% of CD patients who require surgery, repeat surgery is common.

CD exerts significant costs on patients and society. The majority of these costs are associated with surgery and inpatient services [14]. Such estimates do not account for indirect costs, such as those associated with work absences or reduced quality of life (QoL). Clearly, therapies that are capable of reducing dependence on steroids, maintaining long-term remission, decreasing hospitalizations and reducing the need for surgical intervention would go a long way towards reducing morbidity and costs associated with CD.

The treatment of inflammatory bowel disease (IBD) has been revolutionized by the introduction of immune modulators and biological therapies. As recently as the 1990s, treatment was symptomatic and little control of the underlying disease process was possible. As more is known about the pathogenesis of IBD, the range of the therapeutic targets available has increased in parallel. These include agents that downregulate inflammatory cytokines, promote anti-inflammatory cytokines and inhibit leukocyte trafficking [15].

Adhesion molecules are a family of cell-surface glycoproteins critical to leukocyte adhesion, migration and activation. Adhesion molecules facilitate the movement of leukocytes from the blood stream into target organs, where they may proliferate and promote inflammatory cytokine production. Monoclonal antibodies against adhesion molecules, in particular α_4 integrins, are biological agents that can potentially restore imbalanced immune function by decreasing leukocyte migration and subsequent inflammation (FIGURE 1).

Most leukocytes, including lymphocytes, monocytes, eosinophils and basophils, express α_4 integrin adhesion molecules [16,17]. The integrins are a large family of heterodimeric, transmembrane glycoproteins that are capable of mediating both cell–cell and cell–matrix interactions [17]. α_4 integrin subunits are most frequently found adjoined with β_1 and β_7 subunits.

Endothelial ligands for α_4 integrins include members of the immunoglobulin superfamily (IGSF) of adhesion molecules, vascular cell adhesion molecule (VCAM)-1, and mucosal addressin cell adhesion molecule (MAdCAM)-1 [18–21]. Adhesive stability provided by α_4 integrin–IGSF interactions allows the leukocyte to resist the substantial shear forces of circulating blood. This firm adhesion, mediated by interactions between $\alpha_4\beta_1$ and $\alpha_4\beta_7$ and their endothelial cell ligands, is a requirement for their subsequent translocation, known as diapedesis, into inflamed tissue.

The potential utility of α_4 integrin as a therapeutic target and the ability of α_4 integrin antagonists to attenuate chronic inflammatory responses has been demonstrated in a number of animal models of chronic inflammation and autoimmunity, including IBD (colitis), experimental autoimmune encephalitis (EAE; an animal model of multiple sclerosis [MS]), adjuvant-induced arthritis, allergic airways inflammation, autoimmune thyroiditis, cutaneous contact hypersensitivity, pancreatic disease and diabetes [22].

Two humanized monoclonal antibodies targeted to α_4 integrins have been tested clinically for the treatment of IBD: MLN02 and natalizumab. MLN02 (formerly known as LDP-02; Millennium Pharmaceuticals, Inc., Cambridge, MA, USA) is a humanized, recombinant monoclonal antibody that binds specifically to $\alpha_4\beta_7$ integrin. The $\alpha_4\beta_7$ integrin interacts with MAdCAM-1 on gut mucosal cells and plays an important role in T-cell homing to the gut.

A 6-month, randomized, placebo-controlled, Phase II study of MLN02 in 185 patients with mild-to-moderate CD demonstrated a significant difference in remission but not response. Patients were randomized to receive MLN02 (0.5 or 2.0 mg/kg) or placebo on days 1 and 29. At 2 months, neither treatment group achieved the primary end point, which was a statistically significant difference from placebo in achieving clinical response (decrease of >70 points in CD Activity Index [CDAI] score). Remission, defined as a CDAI score of 150 or less, occurred in 36.9% of those given active drug, compared with 20.7% receiving placebo ($p < 0.05$) [23]. The efficacy of MLN02 for the treatment of active ulcerative colitis (UC) was also examined in a randomized, placebo-controlled study [24]. In this study, 181 patients with active disease (defined as an UC clinical score of 5–9 points) who had received either no therapy for UC or mesalamine, were randomized to receive two infusions of either 0.5 mg/kg ($n = 58$) or 2.0 mg/kg ($n = 60$) MLN02, or placebo ($n = 63$) at baseline and day 29. At week 6, clinical remission rates (defined as an UC clinical score of 0 or 1 and a modified Baron score of 0 or 1, with no evidence of rectal bleeding) were significantly greater in patients in the MLN02 treatment groups compared with patients in the

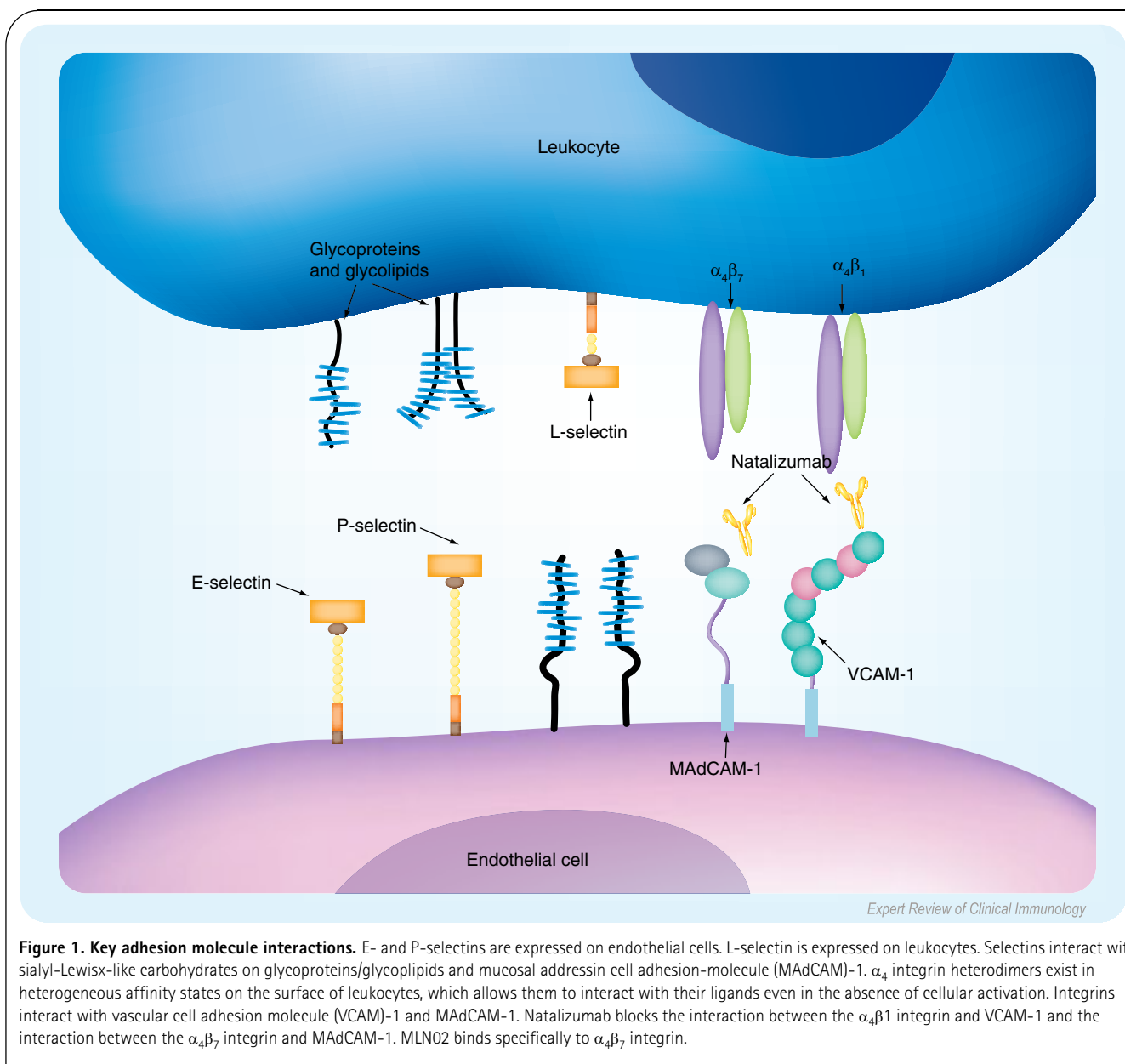


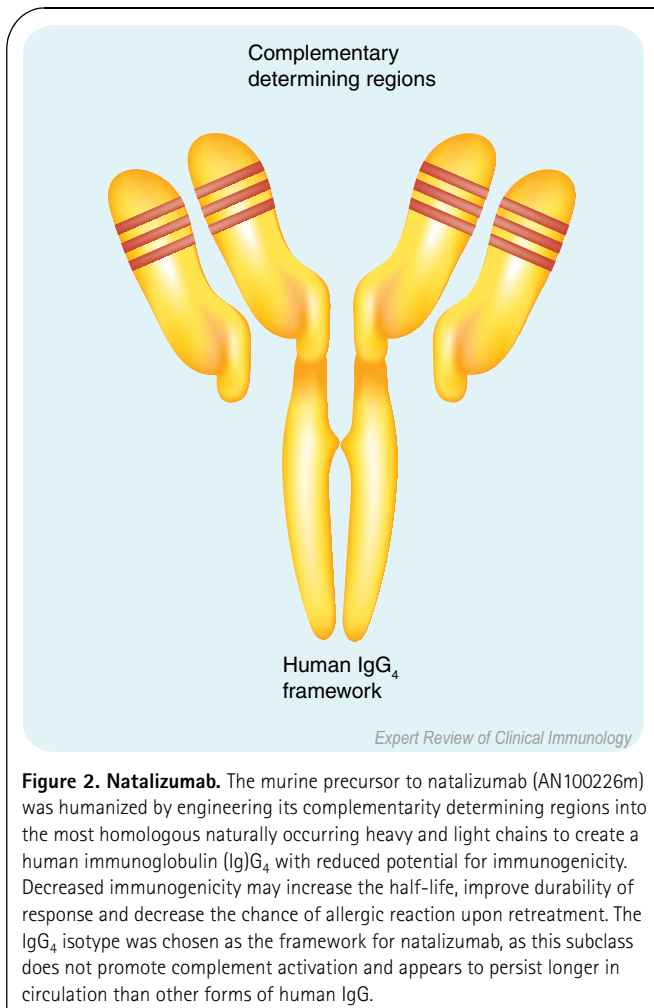
Figure 1. Key adhesion molecule interactions. E- and P-selectins are expressed on endothelial cells. L-selectin is expressed on leukocytes. Selectins interact with sialyl-Lewis-x-like carbohydrates on glycoproteins/glycolipids and mucosal addressin cell adhesion-molecule (MAdCAM)-1. α_4 integrin heterodimers exist in heterogeneous affinity states on the surface of leukocytes, which allows them to interact with their ligands even in the absence of cellular activation. Integrins interact with vascular cell adhesion molecule (VCAM)-1 and MAdCAM-1. Natalizumab blocks the interaction between the $\alpha_4\beta_1$ integrin and VCAM-1 and the interaction between the $\alpha_4\beta_7$ integrin and MAdCAM-1. MLN02 binds specifically to $\alpha_4\beta_7$ integrin.

placebo group (33% for the 0.5 mg/kg group, 32% for the 2.0 mg/kg group and 14% for placebo; $p = 0.03$). Rates of clinical response (defined as a decrease of at least 3 points on the UC clinical score) at week 6 were also significantly greater in the MLN02 treatment groups compared with placebo (66% for the 0.5 mg/kg group, 53% for the 2.0-mg/kg group, and 33% for placebo; $p = 0.002$).

Another strategy directed against trafficking of leukocytes has been blocking the endothelial cell adhesion molecules. Trials with the anti-intercellular adhesion molecule (ICAM)-1 antisense oligonucleotide ISIS-2302 (alicaforfen) in steroid-refractory CD have provided conflicting efficacy data [25,26]. Alicaforfen enema showed promising acute and long-term benefit in patients with mild-to-moderate descending UC [27,28].

Introduction to natalizumab

The humanized monoclonal antibody natalizumab recognizes both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins. Natalizumab contains more than 90% human sequences (FIGURE 2). To humanize the murine precursor to natalizumab (AN100226m), its complementarity determining regions (CDR) were engineered into the most homologous, naturally occurring heavy and light chains to create a human immunoglobulin (Ig)G₄ with reduced potential for immunogenicity. Decreased immunogenicity may increase the half-life, improve durability of response and decrease the chance of an allergic reaction upon retreatment [29]. The IgG₄ isotype was chosen as the framework for natalizumab as this subclass does not promote complement activation and appears to persist longer in circulation than other forms of human IgG [30].



Studies with AN100226m demonstrated that it was a potent inhibitor of interactions between $\alpha_4\beta_1$ and VCAM-1 *in vitro* and that it was capable of suppressing and reversing EAE [31]. The potential relevance of α_4 antagonist therapy to IBD was first shown in an animal model of colitis seen in cotton-top tamarin monkeys [32,33]. These studies demonstrated that modulation of leukocyte adhesion and migration was feasible in primate colitis and could disrupt chronic inflammation.

Pharmacodynamics

Natalizumab recognition of α_4 integrins allows for selective immune modulation, presumably by sparing neutrophil function. This proposed selectivity is supported by analyses of peripheral lymphocyte counts in the blood of patients with CD and UC following natalizumab infusion. Peripheral lymphocyte counts were increased owing to inhibition of transmigration out of the vascular space, while the numbers of neutrophils remained unaffected [34]. Increases in mean circulating lymphocyte counts (not above the upper limit of normal [ULN]) are expected because of the mechanism of action of natalizumab and have been observed in all clinical trials of natalizumab for IBD to date [35–40]; there have been no reported incidences of increased neutrophil levels.

Pharmacokinetics

A Phase I randomized, placebo-controlled, dose-escalation safety and tolerability study of a single intravenous dose of natalizumab was conducted initially in 28 volunteers with MS [41]. Five dose levels, ranging from 0.03 to 3.0 mg/kg of natalizumab, were administered. Pharmacokinetic samples were obtained at baseline, at 0.25–24 h and at the end of weeks 1, 2, 3 and 4. Additional samples were collected at the end of weeks 6 and 8 from the group receiving 3.0 mg/kg and from a subset of patients at weeks 10, 12 and 14.

Serum natalizumab levels fell below the detectable limits shortly after infusion in patients receiving doses of 0.03 and 0.1 mg/kg. Patients receiving an infusion of 0.3 mg/kg had detectable natalizumab concentrations for 1 week, while those in the 1.0 and 3.0 mg/kg groups had detectable concentrations for 3–8 weeks. These results suggested superior persistence of natalizumab at the high dosages and provided the rationale for the use of higher starting doses in larger Phase II MS and CD trials.

Descriptive pharmacokinetics and α_4 integrin saturation were assessed subsequently in a Phase II trial of natalizumab for active CD [42]. Patients in this trial were randomized to receive one of four possible treatments: a single natalizumab 3-mg/kg infusion followed by placebo infusion, two natalizumab 3-mg/kg infusions, two natalizumab 6-mg/kg infusions or two placebo infusions given 4 weeks apart. Natalizumab concentrations increased proportionally to the dose administered. There was minimal drug accumulation with repeated dosing. The volume of distribution was low and limited to the total blood volume. Systemic clearance was unchanged across dosing groups. The mean serum half-life of natalizumab ranged from 132 to 161 h. Maximal saturation of the α_4 -integrin receptor was achieved for all groups receiving natalizumab.

An open-label safety and tolerability study in adolescent patients (12–17 years of age) with moderate-to-severe CD also evaluated the pharmacokinetic parameters of three monthly natalizumab 3-mg/kg infusions. The apparent elimination half-life of natalizumab in this study ranged from 48.7 to 170.6 h. In contrast to studies in adult patients, mean α_4 integrin receptor percentage saturation fell from a peak of approximately 93 to not more than 34% or less over the course of each monthly dosing interval evaluated [39], suggesting that further studies may be necessary to define optimal dosing in adolescent CD patients.

Subsequent trials of natalizumab in adult patients with active CD and MS have employed fixed rather than weight-based dosing. Pharmacokinetic mixed-effect modeling, using data collected in Phase II studies, provided the rationale for this decision [43]. Drug clearance varied minimally across a range of body weights. These data indicated that a fixed 300-mg dose of natalizumab administered every 4 weeks should achieve a consistent serum concentration. This assumption was further confirmed by a comparison of natalizumab pharmacokinetics in the Phase II dose-finding study with those in a Phase III, randomized, multicenter, double-blind, placebo-controlled study of three monthly fixed doses of natalizumab 300 mg.

Maximal α_4 -integrin receptor saturation (100%) was achieved with all doses in both studies. α_4 integrin receptor saturation was generally maintained above 70% throughout each monthly dosing interval for the 6-mg/kg and fixed 300-mg dose regimens only, similar to previous natalizumab clinical trials [44].

Finally, a randomized, double-blind, placebo-controlled, multicenter, Phase II study investigating the safety and efficacy of natalizumab in patients with active CD (not in remission) despite ongoing therapy with infliximab demonstrated no drug–drug interactions between natalizumab and infliximab and natalizumab and infliximab serum concentrations were unaffected when administered concomitantly [40].

Clinical efficacy

Phase II studies

In the double-blind, placebo-controlled Phase II study of 30 patients with active CD (defined as CDAI 150–450) a single dose of natalizumab (3 mg/kg) resulted in a significant improvement in CDAI (mean decrease of 45 points), a result not seen in placebo-treated patients [35]. Among natalizumab-treated patients, 39% achieved remission (defined as a CDAI < 150) by week 2, compared with 8% among the placebo-treated group.

The larger, double-blind, placebo-controlled, Phase II dose-finding trial yielded similarly encouraging results [37]. Patients with moderate-to-severe CD were randomized to receive two infusions 4 weeks apart, consisting of either two infusions of placebo, one infusion of natalizumab 3 mg/kg followed by placebo, two infusions of natalizumab 3 mg/kg or two infusions of natalizumab 6 mg/kg. While the predefined study end point (remission at week 6 in the 6-mg/kg treatment group) did not differ between groups, the patients receiving two infusions of natalizumab 3.0 mg/kg had statistically significantly greater rates of response and remission compared with placebo. Other important improvements were seen among patients receiving natalizumab compared with placebo-treated patients. These included significantly improved QoL and better remission rates at multiple time points. Among those receiving two infusions of natalizumab, C-reactive protein (CRP) levels decreased significantly compared with placebo. Clinical benefit was rapid, often within 2 weeks and the effect was sustained up to 8 weeks after the last infusion.

The effects of combination biological therapy with natalizumab were also examined in the Phase II, randomized, placebo-controlled safety trial [40]. Patients with active CD who were not in remission, despite ongoing infliximab treatment were randomized 2:1 to receive natalizumab 300 mg or placebo along with infliximab 5 mg/kg throughout the 10-week study. While this study was designed to assess the safety of overlapping infliximab and natalizumab therapy, short-term efficacy end points were also studied. This small trial was not powered to detect differences in efficacy but efficacy analyses, while not statistically significant, generated some interesting results. Patients who were not in remission after receiving infliximab therapy and who were randomized to receive natalizumab showed improved efficacy

compared with those randomized to placebo. At week 10, 37% (19/52) of patients receiving both infliximab and natalizumab achieved remission compared with 30% (8/27) receiving infliximab alone. In addition, at week 10, 42% (22/52) of patients achieved clinical response in the infliximab and natalizumab group compared with 30% (8/27) of patients receiving infliximab alone. An analysis of durability of clinical response showed that 25% of patients receiving natalizumab and infliximab met the criteria for clinical response at all time points from weeks 6 to 10 compared with 11.1% of patients receiving infliximab only. Many patients from this trial enrolled in an open-label extension study where they had the opportunity to discontinue therapy with infliximab. The results of continued maintenance therapy in patients discontinuing infliximab have not yet been reported.

Phase III studies

Two large, international, randomized, Phase III controlled trials have also examined the efficacy of natalizumab as induction therapy [38,45]. The first of these trials, Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1), randomized 905 patients with moderately-to-severely active CD (CDAI 220–450) 4:1 to receive placebo or natalizumab 300 mg at weeks 0, 4 and 8. Patients were followed through to week 12. The primary end point for ENACT-1 examined the ability of natalizumab to induce a clinical response (≥ 70 -point decrease in baseline CDAI score from baseline) at week 10. A total of 56% of patients in the natalizumab group had a response (408/724) compared with 49% of patients in the placebo group (88/181; $p = 0.051$). Remission was achieved in 37% of the natalizumab group (267/724) compared with 30% of patients in the placebo group (55/181; $p = 0.12$).

ENACT-1 failed to achieve the primary end point of response at week 10, potentially owing to an unexpectedly high placebo response. However, there was evidence of an induction benefit for natalizumab in many patients, particularly those with biological evidence of inflammation (CRP > ULN; 2.87 mg/l) (FIGURE 3). CRP has been shown to be a useful marker for identifying CD patients whose symptoms are due to inflammation, rather than functional bowel disease [46]. The second Phase III induction trial, Efficacy of Natalizumab in CD response and REmission (ENCORE), was designed to test this hypothesis and enrolled 509 patients with moderately-to-severely active CD and biological evidence of inflammation (defined as CRP > 2.87 mg/l) [45] at the screening visit. In the ENCORE trial, patients were randomized 1:1 to receive natalizumab 300 mg or placebo infusions at weeks 0, 4 and 8. The primary end point examined the ability of natalizumab to induce a clinical response (≥ 70 -point decrease in baseline CDAI score) by week 8 that was sustained through to week 12. Additional efficacy end points included the proportion of patients achieving a clinical remission (CDAI < 150) by week 8 and through to week 12 and the proportion of patients in response or remission at any assessment. A significantly higher proportion of patients in the natalizumab group were in

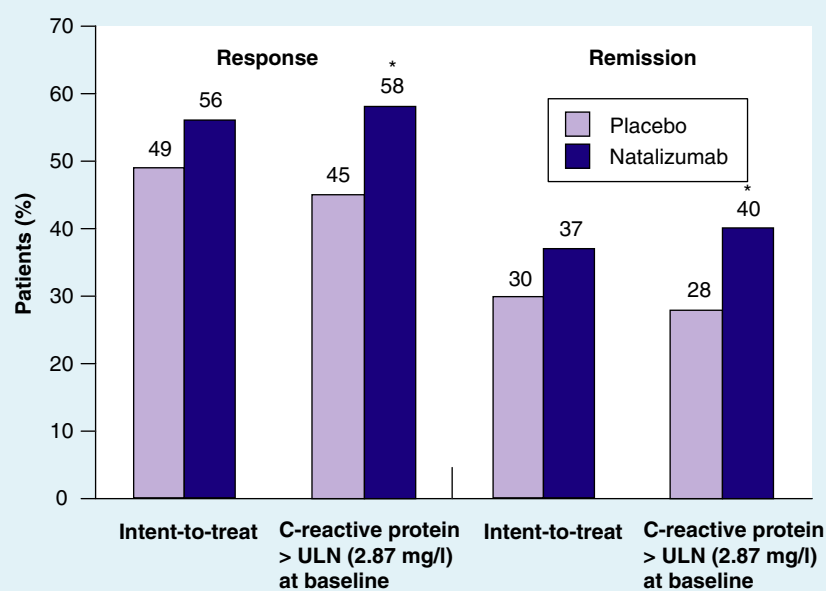


Figure 3. Response and remission at week 10 in ENACT-1: comparison of intent-to-treat population with patients with elevated C-reactive protein.

ENACT-1: Efficacy of Natalizumab as Active Crohn's Therapy; ULN: Upper limit of normal.

response at both weeks 8 and 12 compared with patients in the placebo group (48% [124/259] vs 32% [81/250]; $p < 0.001$). A clinical response was observed as early as week 4 (following the first infusion) (51% [133/259] for natalizumab vs 37% [92/250] for placebo; $p = 0.001$) and remained significantly higher in the natalizumab group at all subsequent assessments ($p < 0.001$ for all comparisons with placebo). Remission at both weeks 8 and 12 was also achieved by a higher proportion of patients in the natalizumab group compared with placebo (26% [68/259] vs 16% [40/250]; $p = 0.002$) [45].

Phase III data on the efficacy of natalizumab maintenance therapy have also been reported and are the longest controlled data to date on any biological maintenance treatment for moderately-to-severely active CD [38]. Evaluation of Natalizumab As Continuous Therapy (ENACT-2) examined the ability of natalizumab 300 mg to maintain a sustained response (primary end point; at least a 70-point decrease in baseline CDAI score) and remission (contingent primary end point; CDAI ≤ 150) at every assessment throughout 36 weeks in natalizumab-treated patients who had achieved clinical response or remission at both weeks 10 and 12 during ENACT-1. Additional prespecified end points included the proportion of patients who did not lose

response or remission achieved during the induction trial though a total of 60 weeks and the proportion of patients who were in response or remission at 36 and 60 weeks.

In ENACT-2, 354 patients who had initially responded to natalizumab in ENACT-1 were re-randomized to receive maintenance therapy with either placebo or natalizumab 300 mg every 4 weeks. Both primary end points of the ENACT-2 trial were met with statistical significance ($p < 0.001$) and natalizumab maintenance therapy continued to provide statistically superior sustained response and remission rates at every assessment throughout a total of 60 weeks (FIGURES 4 & 5). As previous clinical trials in CD have traditionally examined the ability of therapies to affect response or remission at particular time points (i.e., at 36 weeks) rather than require sustained response and remission at every timepoint through to the end point for analysis (i.e., through to 36 weeks), response and remission at the

prespecified time points of 36 and 60 weeks were also examined. At week 36, 67% of patients in the natalizumab group met the criteria for response and 55% were in remission compared with 37 and 24% in the placebo group ($p < 0.05$ for both comparisons with placebo). Similarly, at week 60, 59% of the patients in the natalizumab group met the criteria for response and 55% were in remission compared with 30 and 22% in the placebo group ($p < 0.05$ for both comparisons with placebo).

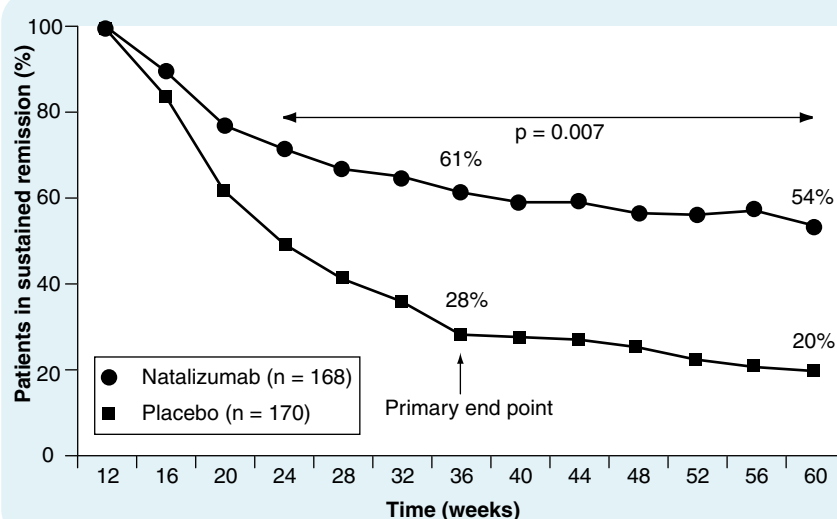


Figure 4. Maintenance of response in Evaluation of Natalizumab As Continuous Therapy (ENACT-2): natalizumab responder population.

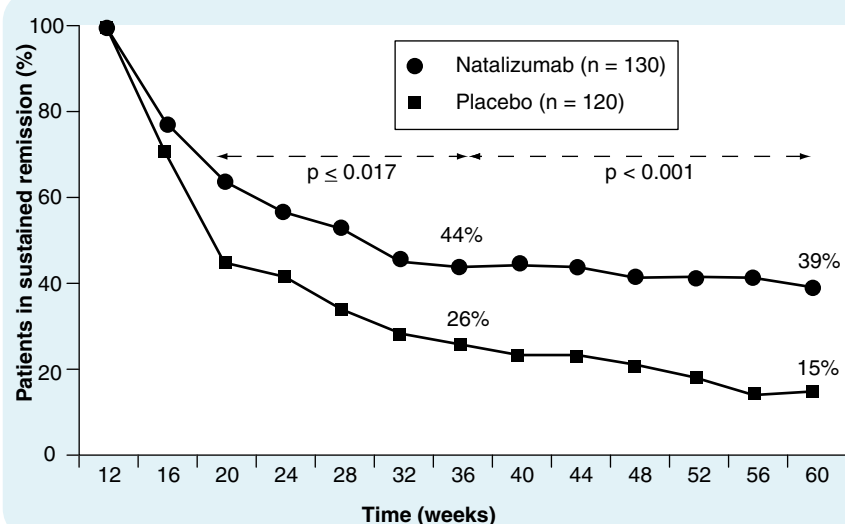


Figure 5. Maintenance of remission in Evaluation of Natalizumab As Continuous Therapy (ENACT-2): natalizumab remission population.

Although concomitant immunosuppressants are required to reduce immunogenicity and prolong response rates to infliximab [8], the clinical benefit of natalizumab maintenance therapy in the ENACT-2 trial was the same regardless of whether or not patients were taking concomitant immunosuppressives at baseline of the ENACT-1 induction trial. A total of 52% of patients who were on baseline immunosuppressants had a sustained response throughout 60 weeks compared with 55% who were not receiving immunosuppressants at baseline. Similarly, 37% of patients on baseline immunosuppressants and 41% of patients not on baseline immunosuppressants maintained sustained remission through to week 60 [47].

The ability to maintain response and remission and allow for the elimination or reduction of steroids is one of the largest unmet needs and primary goals of new therapies for CD. Maintenance therapy with natalizumab for an additional 48 weeks in patients who responded to a 12-week induction regimen allowed for complete elimination of steroids in a significant number of patients, while sustaining response and remission [48]. Throughout 60 weeks in ENACT-2, 49% of patients re-randomized to natalizumab were steroid-free compared with 20% re-randomized to placebo ($p < 0.001$) (FIGURE 6). In addition, 45% of patients re-randomized to natalizumab were steroid-free and maintained clinical response compared with 17% of patients re-randomized to placebo ($p = 0.001$). A total of 42% of patients re-randomized to natalizumab were steroid-free and maintained clinical remission

compared with 15% of patients re-randomized to placebo ($p = 0.001$) throughout 60 weeks.

Health-related QoL (HRQoL) end points in clinical trials provide additional insight into the impact of treatment on health status and well-being. Results from ENACT-1 and -2 indicated that patients who responded to natalizumab induction therapy in ENACT-1 achieved rapid HRQoL improvements during the induction phase that were sustained over time with natalizumab maintenance therapy [49–51]. In the ENACT-2 trial, HRQoL was measured both by the disease-specific IBD Questionnaire (IBDQ) and the generic Short Form-36 (SF-36) and Euro-QoL 5D (EQ-5D) instruments. A Total IBDQ score of more than 170 has been identified as typical of a patient in clinical remission. Mean total

IBDQ scores of the patients randomized to maintenance therapy with natalizumab exceeded 170 at each assessment during the ENACT-2 trial, while the total IBDQ score in the placebo group fell below this threshold by the week 12 assessment and continued to decrease over time [49].

Endoscopic healing

Natalizumab appears to induce endoscopic and histological healing in patients with active CD [52]. A total of 53 patients (natalizumab = 38; placebo = 15) were evaluated in a small, exploratory, colonoscopy substudy in the ENACT-1 trial. Week 0 (baseline) and week 10 colonoscopies were performed and video-recorded. Endoscopic lesions were scored using the

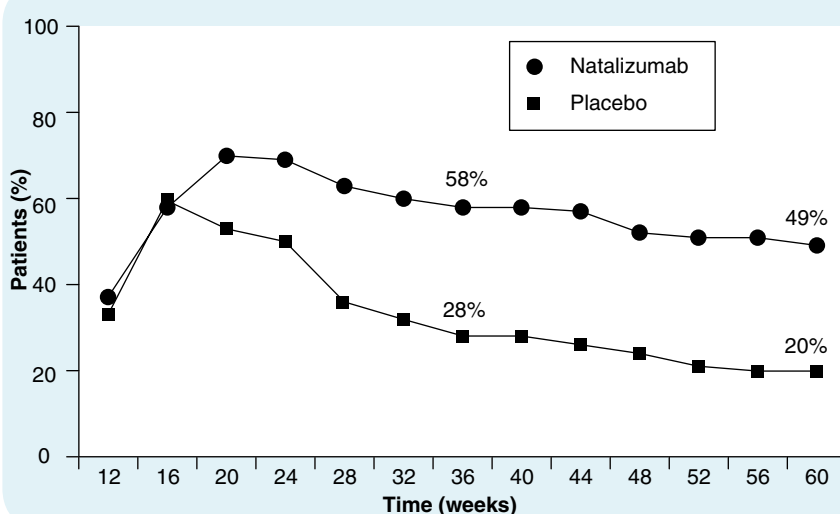


Figure 6. Evaluation of Natalizumab As Continuous Therapy (ENACT-2): patients withdrawn from concurrent steroids.

CD Endoscopic Index of Severity (CDEIS). The proportion of patients with ulcers at week 0 who were ulcer-free at week 10 was also assessed through review of the videos. Biopsies from an area of inflamed mucosa within the terminal ileum and colon were obtained during colonoscopy and histological analysis of biopsies was performed using the global histological activity score (GHAS). In evaluable natalizumab-treated patients (those with both a baseline and a week 10 endoscopic assessment; $n = 33$), median CDEIS scores decreased by nearly 50% from week 0 to week 10 (median of 18, range of 5–43 vs median of 10, range of 0–41, respectively). In evaluable placebo-treated patients ($n = 12$), median CDEIS scores decreased by 7% from week 0 to week 10 (median of 22, range of 6–67 vs median of 18, range of 0–41, respectively). Additionally, 22% of natalizumab-treated patients with ulcers at week 0 ($n = 37$) were ulcer-free by week 10. Only 8% of the placebo-treated patients ($n = 13$) were ulcer-free at the same time point. A greater proportion of patients in the natalizumab group achieved histological remission ($\text{GHAS} \leq 3$) or healing ($\text{GHAS} \leq 2$) compared with those in the placebo group (80 vs 57% and 64 vs 29%, respectively). There was a strong correlation between the endoscopic and histological findings in the natalizumab group (i.e., every natalizumab patient that was ulcer-free was also in histological remission).

This substudy also assessed the ability of natalizumab to inhibit the accumulation of leukocytes within inflamed colonic lamina propria [53]. Biopsies were examined from a total of 40 patients treated with natalizumab ($n = 30$) or placebo ($n = 10$). At week 10, natalizumab decreased the number of mononuclear cells in biopsy samples ($n = 30$) by 60% from baseline compared with 30% from baseline in the placebo samples ($p = 0.052$). A 50% reduction in the number of macrophages compared with baseline values was observed in 53% of the natalizumab samples compared with 30% observed in placebo samples. A greater proportion of natalizumab samples also had 50% reductions in T- and B-cell counts from baseline compared with placebo samples (30 vs 10% and 20 vs 0%, respectively) [53]. The decrease in leukocytes observed within the lamina propria supports the proposed mechanism of action of natalizumab, specifically the inhibition of migration and activation of leukocytes or a combination of these events. Based on these preliminary results, further investigation of the effect of natalizumab on gut healing is warranted.

Safety & tolerability

Natalizumab is well tolerated in a majority of patients and has demonstrated a consistent safety profile in controlled clinical trials of moderately-to-severely active CD [35,37,38,54,55]. In the Phase III ENACT-1 and -2 trials, the rates of all adverse and serious and severe adverse events (AEs) were similar between placebo- and natalizumab-treated patients [38]. No hematological cancers occurred during either study. Side effects in ENACT-1 occurred equally between groups and consisted most frequently of headache, nausea and abdominal pain. Serious AEs were reported in 7% of both placebo- and

natalizumab-treated patients. This percentage is broadly similar to those reported with various anti-TNF agents in CD [7,56,57]. No opportunistic infections or lymphomas were reported during ENACT-1. Acute infusion reactions (any AE occurring within 120 min of the initiation of an infusion) occurred in 11% of patients in the natalizumab group and 8% of patients in the placebo group. Hypersensitivity-like reactions occurred in 5% of patients in the natalizumab group and 2% of patients in the placebo group.

In ENACT-2, the accompanying long-term maintenance trial, natalizumab demonstrated a similar safety profile [38]. Influenza and influenza-like illness were more frequent in the natalizumab group than in the placebo group. During the trial, there was one report each of varicella pneumonia (after exposure to a child who had Varicella-Zoster virus) and Cytomegalovirus hepatitis (judged not to be serious by the investigator), both in patients receiving natalizumab. Both cases resolved with appropriate treatment with no sequelae. Acute infusion reactions occurred in 7% of patients in the natalizumab group and 8% of patients in the placebo group. Hypersensitivity-like reactions occurred in 3% of patients in the natalizumab group and 1% of patients in the placebo group.

The incidence of adverse and serious AEs was also similar between treatment groups in the Phase II study of patients concurrently receiving infliximab [40]. Results indicated that natalizumab was well tolerated, with similar incidence and severity of AEs between treatment groups. The most frequently reported AEs for both treatment groups were headache, CD exacerbation, nausea and nasopharyngitis. No patient had a hypersensitivity-like reaction to natalizumab, while four patients (5%) experienced a reaction to an infliximab infusion. Notably, no patient had a hypersensitivity-like reaction to both agents and patients who developed antibodies to infliximab did not demonstrate an increased probability of developing antinatalizumab antibodies.

In a small, short-term, open-label safety study, natalizumab was also shown to be well tolerated by adolescent CD patients [55,56]. The most common AEs considered to be related to natalizumab were headache (13%) and pyrexia (11%). There were eight serious AEs, none of which were considered to be related to natalizumab. No clinically-significant changes were noted in physical examinations, vital signs or lab values. Although the study was small and not powered to detect the occurrence of rare AEs, no opportunistic infections or lymphomas were noted.

Immunogenicity to natalizumab has been consistently low in both short- and longer-term Phase II and Phase III CD studies [35,37–40,54]. A total of 8% (53/650) of patients in ENACT-1 and 9% (36/390) of patients in ENACT-2 had detectable levels of anti-natalizumab antibodies [38]. In ENACT-2, patients were further classified as having 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) or transient antibodies (defined as antibody-positive but not meeting the definition of persistent antibodies). A total of 6% (23/390) of patients were

persistently positive for antibodies against natalizumab and 3% (13/390) were transiently positive. Occurrences of acute infusion reactions and hypersensitivity-like reactions were more frequent among patients with persistent, rather than transient, antibodies against natalizumab. Although none of the patients with persistent antibodies against natalizumab maintained a response through to week 60, transient antibodies did not have an effect on efficacy; 75% of patients with transient antibodies continued to maintain a response through to week 60.

Although natalizumab has demonstrated a consistent safety profile in clinical trials, concerns have arisen as a result of reports of three cases of progressive multifocal leukoencephalopathy (PML), which occurred in natalizumab-treated patients, two of which were fatal [58–60]. Two of these cases occurred in MS patients receiving concomitant interferon (IFN)- β_{1a} treatment and one of the two fatal cases occurred in a CD patient receiving natalizumab as part of an open-label trial. This patient had been treated with multiple therapies, including long-term daily azathioprine and had suffered from severe intermittent lymphopenia for approximately 6 years. Complete details of this case have been reported elsewhere [58]. Results of extensive safety analyses of more than 3000 CD, MS, and rheumatoid arthritis (RA) patients who had participated in natalizumab clinical trials have been completed recently and have not identified any additional confirmed cases of PML beyond the three cases mentioned previously. This study suggested a risk of development of PML of roughly one in 1000 patients (95% confidence interval: 0.2–2.8 per 1000) treated with natalizumab for a mean of 17.9 months [61]. The risk associated with longer treatment is not known currently, although any therapy affecting immune balance also has the potential to affect rates of opportunistic infections. Longer-term data is needed to define these potential rates with natalizumab accurately.

Regulatory affairs

Natalizumab received initial approval for the treatment of relapsing MS after accelerated review by the US FDA in November 2004. However, Elan and Biogen Idec, USA voluntarily suspended the marketing and clinical trials on February 28, 2005. This decision was based on two serious AEs of PML that occurred in MS patients treated with natalizumab in combination with IFN- β_{1a} in clinical trials. On March 30, 2005, Elan and Biogen Idec, USA announced that their ongoing safety evaluation of TYSABRI[®] led to a previously diagnosed fatal case of malignant astrocytoma being reassessed as PML, in a patient in an open-label CD clinical trial. Safety evaluations of TYSABRI in MS, CD and RA have been completed and resulted in no new confirmed cases of PML [55]. On September 26, 2005, a supplemental Biologics License Application (sBLA) for natalizumab was submitted to the FDA for the treatment of MS. The FDA granted priority review for the sBLA on November 17, 2005 and the Advisory Committee meeting that convened on March 7th and 8th, 2006 voted unanimously to recommend reintroduction of natalizumab for relapsing forms of MS. The FDA approved natalizumab for commercial availability in June

2006. Natalizumab was also approved for use in Europe for the treatment of MS in June 2006 and is currently under review for CD. Approval in both jurisdictions is accompanied by enhanced pharmacovigilance or risk management plans to better evaluate the actual risk of serious infections, as well as ensuring that patients and physicians are fully informed of the risks of therapy. At present, clinical vigilance is the best method for early detection of symptoms suggestive of PML. Detection of JC polyomavirus DNA in plasma by PCR testing has shown low sensitivity and specificity making its use as a monitoring tool uncertain. This is being further explored in studies in MS patients.

Conclusions

Biological therapy has rapidly gained a central role in CD treatment. While the efficacy of infliximab in inducing and maintaining remission is proven, it is clear that, for some patients, such treatment remains ineffective. Furthermore, significant hurdles to the long-term use of infliximab, including immunogenicity and long-term safety risks, have emerged. Fortunately, an expanding armamentarium is poised to further advance patient care.

Natalizumab offers significant promise. It appears to disrupt leukocyte recruitment and disrupt activation of key components of the inflammatory cascade. Long-term benefits have been observed in clinical trials, including high steroid-free remission rates and maintenance of a level of QoL for patients with CD that approaches that of a cross-section of the general population. The long-term efficacy of natalizumab has been demonstrated in a number of patient types, including patients with biological evidence of active inflammation, patients who are steroid-dependent or refractory to steroids and patients with active disease, despite a prior history of anti-TNF or immunosuppressive therapy. Natalizumab may eventually play an important alternative role in the treatment of patients unresponsive to or intolerant of TNF-targeted agents and may not incur the same long-term immunogenic risks. Although natalizumab has been shown to be well tolerated by most patients, longer-term data and continued research are required in order to weigh the clinical benefit of natalizumab therapy against the potential risk of rare but serious AEs. Encouraging results of the amended safety assessment of natalizumab in MS, CD and RA patients suggest that the occurrence of PML may be a rare (~0.1%) event [61]. Larger, long-term studies will elucidate the ultimate role of natalizumab in the treatment of CD.

PML has been associated previously with patients with chronically depressed immune systems (e.g., HIV patients and organ transplant recipients). The potential relationship between inhibition of α_4 integrin-mediated events and the development of PML is unclear and remains an important area of concern [62,63].

Expert commentary

Natalizumab has demonstrated efficacy among some of the most difficult-to-treat patients with CD and may offer advantages over existing traditional and biological therapy. Early data

suggest it provides true disease modulation through inhibition of leukocyte trafficking and effects on underlying inflammation, rather than merely symptomatic control. Immunogenicity data suggest low rates of antibody development. This may herald better long-term efficacy and fewer immunologically mediated side effects.

If approved for CD, groups of patients who might benefit particularly from the use of natalizumab therapy include patients with active disease, despite the use of conventional therapies, those who do not respond to, have lost response to or can no longer tolerate infliximab, patients with refractory disease on steroids and, with further study, possibly pediatric and adolescent patients. In addition, the low rates of immunogenicity, strong maintenance data and steroid-sparing effects of the drug make it a potential option for use prior to conventional immunosuppressants.

Of special interest is the ability of natalizumab to eliminate long-term steroid use. This may ultimately be of significant importance for young patients in whom steroid use is of particular concern. While the short-term, open-label study in adolescent patients demonstrated that natalizumab was well tolerated, longer-term data and further studies on dosing in the adolescent population are warranted, as is caution in the use of natalizumab in adolescent or pediatric patients until the overall risk:benefit ratio is defined.

α_4 -integrin antibodies also show great promise in the treatment of UC. MLN02 has been shown to be effective for the treatment of patients with UC and early data suggest that natalizumab may

also be effective. In a study of ten patients with UC and Powell–Tuck scores greater than 4, a single intravenous infusion of natalizumab 3 mg/kg resulted in a significantly improved Powell–Tuck score at 1, 2, and 4 weeks post-treatment [36].

The use of natalizumab as postoperative maintenance may also merit further study. Treatments, including corticosteroids, mesalamine, AZA and 6-MP have been investigated for the delay of postoperative recurrence of CD but, to date, there is no standard of postoperative therapy [64].

Another CD treatment aim is healing of the bowel mucosa. Current treatments that promote mucosal healing are limited; corticosteroids are not effective at healing mucosal lesions, while some data has shown that immunosuppressants (i.e., AZA) or biologics (i.e., infliximab) may be effective [65,66]. Natalizumab appears to induce endoscopic and histologic healing in patients with active CD and further studies are warranted [52].

Natalizumab may ultimately be an important addition to the armamentarium of therapies for the treatment of IBD in general and CD specifically. Its mechanism of action, which targets the underlying pathology of CD, may offer an alternative to conventional therapies, which have traditionally only afforded symptomatic disease control.

At the present time, longer-term safety data are still required to help define the overall risk:benefit profile of natalizumab and to position this potential therapy among the mainstays of maintenance treatment of moderate to severe CD currently available.

Key issues

- Crohn's disease (CD) is a chronic, progressive disease that often requires surgery.
- Standard treatment does not alter the natural disease course and available treatment has significant side effects.
- Biological therapies show significant promise in altering the natural disease course.
- Immunogenicity and carcinogenic potential may threaten long-term benefits of some biological therapies.
- Emerging agents, such as anti- α_4 integrin antibodies, have demonstrated significant efficacy in the CD management.
- Short- and long-term immunogenicity is low (<10%) in Phase II and III trials.
- The presence of persistent but not transient antibodies is not associated with an increase in infusion reactions, hypersensitivity-like reactions and reduced efficacy.
- Future therapy will incorporate earlier use of disease-altering biological therapy to attempt to avoid complications of chronic CD.
- Regimens of alternating biological therapies will become increasingly common.
- Use of combined biological therapies may be considered but must be approached cautiously because of potential additive or synergistic safety risks.
- The report of three cases of progressive multifocal leukoencephalopathy (two in multiple sclerosis patients and one in a CD patient) that were attributed to the drug warrants caution.
- Data from a thorough review of a large cohort of multiple sclerosis, CD and rheumatoid arthritis patients treated with the drug suggest that the overall risk may be low.
- Longer-term safety data are needed.
- Clinical guidelines should include strategies for surveillance and risk management.

Five-year view

In the next 5 years, the 'therapeutic pyramid' on which CD care is currently based will change significantly. The future paradigm of CD care will probably be a top-down approach based on earlier, more aggressive, use of biological therapies, in the hopes of changing the disease's course substantially. New and existing biological therapies will be used more widely in alternating, combined and cyclic regimens to both induce and maintain remission, and other novel therapeutic agents will join TNF inhibitors as cornerstones of CD management. Ongoing research will elucidate the specific regimens and identify patients for whom they are suited over the coming years, which may reduce the prevalence of, and reliance on, surgical treatment.

Significant advances in our understanding of the genetic and immunological basis of IBD have been made in past decades; however, our understanding of its pharmacogenetics and genotype/phenotype relationships is in its infancy. It is probable that, in the coming years, biological therapies will play an

increasing and more standard role in CD care, based on genetically defined cytokine profiles in CD and other immune-mediated inflammatory diseases. An increasing awareness of the relationship between genotype and phenotype in IBD will probably affect future CD management [67].

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References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 126, 1504–1517 (2004).
- 2 Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am. J. Gastroenterol.* 96, 635–643 (2001).
- 3 Travis SP, Stange EF, Lemann M *et al.* European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 55(Suppl. 1), 6–35 (2006).
- 4 Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 50, 485–489 (2002).
- 5 Lemann M, Mary JY, Colombel JF *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 128(7), 1812–1818 (2005).
- 6 Kandiel A, Fraser AG, Korelitz BI *et al.* Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 54(8), 1121–1125 (2005).
- 7 Hanauer SB, Feagan BG, Lichtenstein GR *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 359, 1541–1549 (2002).
- 8 Baert F, Norman M, Vermeire S *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N. Engl. J. Med.* 348, 601–608 (2003).
- 9 Bongartz T, Sutton AJ, Sweeting MJ *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 17, 2275–2285 (2006).
- 10 Sandborn WJ. Treatment of Crohn's disease. In: *Kirsner's Inflammatory Bowel Disease, 6th Edition*. Sartor R, Sandborn WJ (Eds). Elsevier Science, FL, USA (2004).
- 11 Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 54, 237–241 (2005).
- 12 Rutgeerts P. A critical assessment of new therapies in inflammatory bowel disease. *J. Gastroenterol. Hepatol.* 17, 176–185 (2002).
- 13 Cosnes J, Cattani S, Blain A *et al.* Long-term evolution of disease behavior of Crohn's disease. *Inflamm. Bowel Dis.* 8, 244–250 (2002).
- 14 Hay AR, Hay JW. Inflammatory bowel disease: Medical cost algorithms. *J. Clin. Gastroenterol.* 14, 318–327 (1992).
- 15 Vermeire S, Rutgeerts P. Novel biologic strategies in inflammatory bowel diseases. *Inflamm. Bowel Dis.* 10, 44–51 (2004).
- 16 Hemler ME, Elices MJ, Parker C, Takada Y. Structure of the integrin VLA-4 and its cell–cell and cell–matrix adhesion functions. *Immunol. Rev.* 114, 45–65 (1990).
- 17 Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 69, 11–25 (1992).
- 18 Lobb RR, Hemler ME. The patho-physiologic role of $\alpha 4$ integrins *in vivo*. *J. Clin. Invest.* 94, 1722–1728 (1994).
- 19 Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 76, 301–314 (1994).
- 20 Bevilacqua MP. Endothelial-leukocyte adhesion molecules. *Ann. Rev. Immunol.* 11, 767–804 (1993).
- 21 Postigo AA, Teixido J, Sanchez-Madrid F. The $\alpha 4 \beta 1$ /VCAM-1 adhesion pathway in physiology and disease. *Res. Immunol.* 144, 723–735 (1993).
- 22 Sandborn WJ, Yednock TA. Novel approaches to treating inflammatory bowel disease: targeting $\alpha 4$ integrin. *Am. J. Gastroenterol.* 98, 2372–2382 (2003).
- Nice review that highlights the relevance of targeting antiadhesion molecules in inflammatory bowel disease.
- 23 Lindenboom K, Brazier G. *Millennium Pharmaceuticals Announces Phase II Data for MLN02 in Crohn's Disease*. Millennium Pharmaceuticals, MA, USA (2002).
- 24 Feagan B, Greenberg G, Wild G *et al.* Treatment of ulcerative colitis with a humanized antibody to $\alpha 4 \beta 7$ integrin. *New. Engl. J. Med.* 352, 2499–2507 (2005).
- Controlled trial demonstrating that MLN02 ($\alpha 4 \beta 7$ integrin) is able to induce remission in ulcerative colitis.
- 25 Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L *et al.* A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. *Gastroenterology* 114, 1133–1142 (1998).

- 26 Schreiber S, Nikolaus S, Malchow H *et al.* Absence of efficacy of subcutaneous antisense ICAM-1 treatment of chronic active Crohn's disease. *Gastroenterology* 120, 1339–4136 (2001).
- 27 van Deventer SJ, Tami JA, Wedel MK. A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis. *Gut*. 53, 1646–1651 (2004).
- 28 van Deventer SJ, Wedel MK, Baker BF *et al.* A phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis. *Ailment Pharmacol. Ther.* 23, 1415–1425 (2006).
- 29 Leger OJ, Yednock TA, Tanner L *et al.* Humanization of a mouse antibody against human α -4 integrin: a potential therapeutic for the treatment of *Mult. Scler. Hum. Antibodies* 8, 3–16 (1997).
- 30 Mountain A, Adair JR. Engineering antibodies for therapy. *Biotechnol. Genet. Eng. Rev.* 10, 1–142 (1992).
- 31 Kent SJ, Karlik SJ, Cannon C *et al.* A monoclonal antibody to α 4 integrin suppresses and reverses active experimental allergic encephalomyelitis. *J. Neuroimmunol.* 58, 1–10 (1995).
- 32 Podolsky DK, Lobb R, King N *et al.* Attenuation of colitis in the cotton-top tamarin by anti- α 4 integrin monoclonal antibody. *J. Clin. Invest.* 92, 372–380 (1993).
- **First experimental evidence of the efficacy of anti- α 4-integrin antibodies in treating intestinal inflammation.**
- 33 Hesterberg PE, Winsor-Hines D, Briskin MJ *et al.* Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin α 4 β 7. *Gastroenterology* 111, 1373–1380 (1996).
- 34 Gordon FH, Pounder RE, Amlot PL *et al.* The effect of natalizumab, a humanized monoclonal antibody to the α 4 integrin on circulating activated leucocytes in active inflammatory bowel disease (IBD). *Gastroenterology* 122, A434 (2002).
- 35 Gordon FH, Lai CW, Hamilton MI *et al.* A randomized placebo-controlled trial of a humanized monoclonal antibody to α 4 integrin in active Crohn's disease. *Gastroenterology* 121, 268–274 (2001).
- 36 Gordon FH, Hamilton MI, Donoghue S *et al.* A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to α -4 integrin. *Ailment Pharmacol. Ther.* 16, 699–705 (2002).
- 37 Ghosh S, Goldin E, Gordon FH *et al.* Natalizumab for active Crohn's disease. *N. Engl. J. Med.* 348, 24–32 (2003).
- 38 Sandborn WJ, Colombel J-F, Enns R *et al.* Natalizumab induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* 353, 1912–1925 (2005).
- **Pivotal controlled trial demonstrating the efficacy of natalizumab in maintaining remission in Crohn's disease.**
- 39 Grundy J, Pan W, Kugathasan S *et al.* Pharmacokinetics and pharmacodynamics of natalizumab in a Phase 2 study of adolescent patients with Crohn's disease. *Proceedings of the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition, 2004.* Salt Lake City, UT, USA (2005).
- 40 Sands B, Kozarek R, Spainhour J *et al.* Safety and efficacy of natalizumab in patients concurrently receiving infliximab in a phase 2 study of active Crohn's disease. *Am. J. Gastroenterol.* 99, 526 (2004).
- 41 Sheremata WA, Vollmer TL, Stone LA *et al.* A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. *Neurology* 52(5), 1072–1074 (1999).
- 42 van Deventer S, Rutgeerts P, Rask-Madsen J *et al.* Pharmacokinetics (PK) and pharmacodynamics (PD) of natalizumab in active Crohn's disease patients. *Gastroenterology* 122, 433 (2002).
- 43 Bennett D, Ludden T, Shah J *et al.* The use of pharmacokinetic (PK) modeling and efficacy data to establish optimal dosing of natalizumab (Antegren). *Mult. Scler.* 8, 130 (2002).
- 44 Panaccione R, Colombel JF, Enns R *et al.* Comparability of natalizumab pharmacokinetics (PK), α 4 integrin receptor saturation, and clinical response in patients with Crohn's disease (CD) treated once monthly IV with either a fixed dose of 300 mg (ENACT-1) or doses of 3 or 6 mg/kg. *Gastroenterology* 126, A584 (2003).
- 45 Targan S, Feagan B, Fedorak B *et al.* Natalizumab induces durable response in patients with active Crohn's disease: results from the ENCORE trial. *Gastroenterology* 130, A108 (2006).
- **Controlled trial demonstrating that natalizumab is able to induce clinical remission in Crohn's disease.**
- 46 Poullis AP, Zar S, Sundaram KK *et al.* A new, highly sensitive assay for C-reactive protein can aid the differentiation of inflammatory bowel disorders from constipation- and diarrhoea-predominant functional bowel disorders. *Eur. J. Gastroenterol. Hepatol.* 14, 409–412 (2002).
- 47 Sandborn WJ, Colombel JF, Enns R *et al.* Maintenance therapy with natalizumab does not require use of concomitant immunosuppressants for sustained efficacy in patients with active Crohn's disease: results from the ENACT-2 study. *Gastroenterology* 130, A482 (2006).
- 48 Colombel J, Enns R, Feagan B *et al.* 12-month steroid-sparing results of natalizumab in a controlled study of patients with Crohn's disease. *Gastroenterology* 128, A576 (2005).
- 49 Feagan B, Colombel JF, Enns R *et al.* Maintenance treatment with natalizumab improves the health related quality of life (HRQOL) in Crohn's disease patients. *Gastroenterology* 130, A48 (2006).
- 50 Feagan B, Enns R, Colombel JF *et al.* Natalizumab improves the health related quality of life (HRQOL) in Crohn's disease patients. *Am. J. Gastroenterol.* 100, 310 (2005).
- 51 Feagan B, Enns R, Colombel JF *et al.* Maintenance natalizumab results in greater quality of life in Crohn's disease patients. *Gut*. 54, A18 (2005).
- 52 Rutgeerts P, Allison MC, Cortot A *et al.* Effects of natalizumab on gut healing in a phase 3 study of active Crohn's disease therapy (ENACT-I). *Gastroenterology* 126, A208 (2004).
- 53 Geboes K, Allison MC, Cortot A *et al.* Natalizumab decreases inflammatory cells within the colonic lamina propria of patients with active Crohn's disease: results from ENACT-I. *Gastroenterology* 126, A213 (2004).
- 54 Wilson DC, Thomas AG, Mitchell B *et al.* Safety, tolerability, immunogenicity and efficacy of natalizumab in adolescents with moderately to severely active Crohn's disease: an open-label study. *Gut*. 53, A48 (2004).
- 55 Hyams J, Wilson D, Thomas A *et al.* An open-label safety, tolerability, and efficacy study of natalizumab in adolescents with moderately to severely active Crohn's disease. *Am. J. Gastroenterol.* 99, 256 (2004).
- 56 Sandborn WJ, Hanauer SB, Lucas M *et al.* Maintenance of remission over 1 year in patients with active Crohn's disease treated with adalimumab: results of CLASSIC II, a blinded, placebo-controlled study. *Gut* 54, A81 (2005).
- 57 Colombel JF, Sandborn WJ, Rutgeerts R *et al.* Adalimumab induces and maintains clinical response and remission in patients with active Crohn's disease: results of the CHARM trial. *Presented at Digestive Diseases Week, Los Angeles, CA, USA.* Late Breaking Abstract 686d (2006).

- 58 Van Assche G, Van Ranst M, Sciot R *et al.* Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N. Engl. J. Med.* 353, 362–368 (2005).
- 59 Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon β -1a for multiple sclerosis. *N. Engl. J. Med.* 353, 369–374 (2005).
- 60 Langer-Gould A, Atlas SW, Green AJ *et al.* Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N. Engl. J. Med.* 353, 375–381 (2005).
- 61 Yousry TA, Major E, Ryschkewitsch C *et al.* Evaluation for progressive multifocal leukoencephalopathy in natalizumab treated patients. *N. Engl. J. Med.* 354, 924–33 (2006).
- 62 Podolsky DK. Selective adhesion-molecule therapy and inflammatory bowel disease – a tale of Janus? *N. Engl. J. Med.* 353, 1965–1968 (2005).
- 63 Ropper AH. Selective treatment of multiple sclerosis. *N. Engl. J. Med.* 354, 965–967 (2006).
- 64 Hanauer SB, Korelitz BI, Rutgeerts P *et al.* Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 127, 723–729 (2004).
- 65 Rutgeerts PJ. An historical overview of the treatment of Crohn's disease: why do we need biological therapies? *Rev. Gastroenterol. Disorders.* 4, 3–9 (2004).
- 66 D'Haens G, van Deventer S, van Hogeand R *et al.* Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 116, 1029–1034 (1999).
- 67 Ahmad T, Tamboli CP, Jewell D, Colombel JF. Clinical relevance of advances in genetics and pharmacogenetics of IBD. *Gastroenterology* 126, 1533–1549 (2004).

Affiliations

- Jean Frédéric Colombel, MD
Hôpital Huriez, Service d'Hépatogastro-Entérologie Rue Polonovski
59037 Lille Cedex, France
Tél.: +33 320 444 714
Fax: +33 320 444 713
jfcolumbel@chru-lille.fr
- Laurent Peyrin-Biroulet, MD
Hôpital Braboiz, Service d'Hépatogastro-Entérologie Allée du Morvan
54511 Vandoeuvre, France
peyrin-biroulet@netcourier.com