

Natalizumab in Crohn's disease: past and future areas of applicability

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The treatment of moderate-to-severe Crohn's disease (CD) has been changing over the last decades. Several studies on the pathophysiological mechanisms of tissue damage in inflammatory bowel diseases (IBD) have led to development of new drugs directed against specific molecular targets. Anti-tumor necrosis factor (TNF)- α monoclonal antibodies were demonstrated to be efficacious in inducing and maintaining clinical remission and are recommended in patients refractory or intolerant to other conventional immunosuppressive agents [1-3]. However, a considerable percentage of patients primarily do not respond to anti-TNF- α or lose response over time, mainly due to immunogenicity or probably because of the activation of alternative pathways of inflammation that do not involve TNF- α [4]. In this context, the need for new therapeutic strategies is emerging, considering that patients with refractory CD are often doomed to surgery or chronically active disease, with consequent disability and elevated healthcare costs.

Natalizumab (Tysabri[®]) is a recombinant humanized monoclonal antibody directed against the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins and inhibits migration of T cells to different tissues avoiding their interaction with specific ligands VCAM-1 (vascular cell adhesion molecule-1) and MadCAM-1 (mucosal addressin cell adhesion molecule-1), respectively. Thus, its mechanism of action leads to reduction in lymphocyte infiltrate into the intestinal mucosa and finally improves chronic inflammation [5].

Several studies have already demonstrated its efficacy in moderate-to-severe CD, although initial results were not so impressive. In the ENACT-1 study, after 10 weeks of treatment, no statistically significant differences were found in response and remission rates among patients who received placebo or natalizumab (49% versus 56% and 30% versus 37%, respectively) [6]. However, a *post-hoc* analysis of specific subpopulations of patients showed significantly better outcomes in subjects with elevated C-reactive protein (CRP) concentration (>2.87 mg/L), active disease despite the use of immunosuppressants and prior use of anti-TNF- α . Based on these results, the following ENCORE trial included only

patients with clinically active moderate-to-severe CD and elevated CRP levels: natalizumab was superior to placebo as induction therapy for both response and remission rates (48% versus 32% $P<0.001$ and 26% versus 16% $P=0.002$, respectively, at week 12) [7]. No studies have been performed in the specific subpopulation of patients already treated with at least one anti-TNF- α , but their percentage in these randomized trials was around 50% [6,7].

Better outcomes were achieved in the maintenance of clinical remission. In the ENACT-2 study the percentage of response was 61% at week 36, whereas remission was maintained in 44% of patients treated with natalizumab, compared to 28% and 26% in the placebo group ($P<0.001$ and $P=0.003$, respectively). The open-label long-term extension of this trial up to an overall period of 27 months of treatment showed that 86% of patients who initially achieved clinical remission maintained it over time [8].

Despite these results, natalizumab was reapproved for the treatment of CD in 2008 only in the United States (US), after a temporary suspension from the market because of warnings about severe adverse events [9]. In particular, its use was associated to progressive multifocal leukoencephalopathy (PML), an opportunistic often fatal infection due to reactivation of JC virus, initially developed in two patients with CD and in one patient with multiple sclerosis (MS), the other disease in which natalizumab showed high percentages of therapeutic success. In Europe, natalizumab is now approved only for the treatment of MS.

Data about the "real-life" use of natalizumab are recently emerging from US tertiary IBD centers [10-12], where patients who received this drug were monitored in a specific surveillance prescribing program (Tysabri Outreach: Unified Commitment to Health, TOUCH). Percentages of clinical response or remission were similar to those reported in previous studies: 42% (17/40 patients) were in clinical response at 12 months of treatment at Chicago [10]; the cumulative probability of achieving a complete response with natalizumab at one year was 56% at Mayo Clinic [11]; finally, Chen *et al* reported that more than 50% of patients had partial or complete clinical response after 3 infusions of natalizumab [12]. However, these results should be read considering some important differences between these real-life reports and randomized clinical trials. In particular, in US natalizumab has been approved for CD only as monotherapy in patients who have failed or are intolerant to conventional treatments: thus, almost all subjects analyzed in these real-life studies have already been treated with at least one anti-TNF- α and immunomodulators were never administered in combination with natalizumab.

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An improvement in endoscopic and radiologic findings [11] and a reduction in the need for surgery [10] were also described in patients who continued natalizumab treatment over time in comparison to those who discontinued it. No specific data about the efficacy on perianal disease were reported, with the exception of only one patient who achieved complete fistula healing during therapy with natalizumab [12]. Satisfactory results were also obtained in a younger population of CD patients (ages 12-17 years), considering that percentages of clinical response and remission after 3 infusions of natalizumab were 55% and 29%, respectively [13].

With respect to natalizumab safety in CD, no cases of PML were reported in real-life studies. The most frequent side effect was headache. Lower rates of infusion reactions (11%) and incidence of antibodies against natalizumab (9%) were described [6], in comparison with those in patients receiving anti-TNF- α [4]. Two patients were treated with natalizumab during the last months of pregnancy: one of them presented preeclampsia, with a premature induced vaginal delivery at 37 weeks and neonatal complications [12].

In summary, more data are needed to validate the efficacy and safety of natalizumab in specific categories of CD patients, based on encouraging results obtained so far and the emerging necessity for biological treatments alternative to anti-TNF- α . The main concern of further investigation on natalizumab is the risk of PML related to this drug. With the exception of the two cases initially described in CD patients, all other reports concerned subjects with MS: in particular, among 99,571 MS patients treated with natalizumab until February 2012, 212 confirmed cases of PML were reported, with an incidence of 2.1/1000 patients and a mortality of 22% [14]. The incidence of PML decreases to 0.09/1000 in subjects negative for anti-JC virus antibodies, whereas it increases up to 11.1/1000 in those who present specific risk factors for the development of PML, such as positive anti-JC virus antibodies, immunosuppressive treatment before starting natalizumab and duration of therapy of more than 25 months [14].

Hypothesizing the extension of natalizumab use to CD in Europe, a prescribing surveillance program should be mandatory; moreover, only patients tested negative for anti-JC virus antibody should be considered eligible for this treatment and the therapy should not exceed 24 consecutive months to reduce the risk of PML. Unfortunately, it should be more difficult to exclude patients who previously received immunomodulators, especially if natalizumab continues to be reserved for subjects refractory or intolerant to conventional therapies.

One more obstacle to its approval in Europe could be the possible future use of vedolizumab, another humanized monoclonal antibody, directed against the $\alpha 4\beta 7$ integrin that interacts with MadCam-1 specifically on the intestinal mucosa. Because of its selective target, vedolizumab does not have any effect on lymphocyte migration into the central nervous system and it is hypothetically without risk of PML. Considering the similar mechanism of action, efficacy rates similar to natalizumab should be expected. Analysis of results from the GEMINI III study showed that percentages of remission at week 6 (19.1%) and week 10 (28.7%) were superior in

CD patients treated with vedolizumab compared to placebo (12.1% and 13%, respectively) [15]. In the GEMINI II trial, after 54 weeks of scheduled treatment with vedolizumab, clinical remission was maintained in 39% of patients compared with 21.6% of those treated with placebo [16].

In conclusion, the correct treatment of moderate-to-severe refractory CD is still far from being found, but it should never be forgotten that selected patients should have the possibility to choose a potentially efficient therapy, considering all the benefits and risks.

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