REPORT

α_4 Integrin blockade in inflammatory bowel disease

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Inflammatory bowel disease comprises Crohn's disease (CD), a Th1 lymphocyte mediated chronic transmural inflammatory disease, and ulcerative colitis, resembling a Th2 lymphocyte mediated mucosal inflammation of the colon. Studies of patients with inflammatory bowel disease show that endothelial cells extracted from inflamed intestinal mucosa demonstrate increased α_4 integrin dependent adhesiveness to leucocytes in vitro.[1]

α_4 INTEGRIN

Integrins form a large family of transmembrane proteins required for cell adhesion, morphogenesis, migration, and differentiation, attach the cell to the extracellular matrix or to other cells, and anchor the cytoskeleton to the plasma membrane. Integrins consist of two non-covalently bound α and β subunits of 120–180 kDa and 90–120 kDa, respectively. The α_4 chain contains about 1000 amino acids and in association with the β_7 chain defines an integrin subfamily specifically involved in the interaction of lymphocytes with the intestinal mucosa. The $\alpha_4\beta_7$ integrin is widely expressed in the intestine and is present on most lamina propria T cells and IgA secreting B cells. The expression of $\alpha_4\beta_7$ on intraepithelial lymphocytes is lower. The main ligand for $\alpha_4\beta_7$ is mucosal vascular addressin cell adhesion molecule (MADCAM-1), a member of the immunoglobulin superfamily as mentioned below, but other ligands include fibronectin (an extracellular matrix protein), vascular cell adhesion molecule-1 (VCAM-1), and α_4 integrin itself. α_4 Integrin in the low affinity state, as well as L-selectin play a part in rolling of the lymphocytes in intestinal vascular epithelium, interacting with a number of ligands, including MADCAM-1. Activating signals to the lymphocytes, such as chemokines, result in expression of $\alpha_4\beta_7$ in a high affinity state and this leads to arrest and adhesion of lymphocytes to the vascular endothelium through interaction with MADCAM-1. Each of these steps is sequentially essential for lymphocyte trafficking into the lamina propria. α_4 Integrins are necessary not only for lymphocyte homing but also for lymphocyte activation and signalling as well as interaction with extracellular matrix protein such as fibronectin. Figure 1 illustrates these processes.

α_4 INTEGRIN ANTIBODIES

α_4 Integrin dimerises with β_1 integrin or with β_7 integrin to form molecules that are expressed by activated lymphocytes and monocytes. These molecules dictate the directed trafficking of lymphocytes from the circulation into tissues. $\alpha_4\beta_1$ Integrin recognises VCAM-1, which is up regulated on inflamed endothelium. $\alpha_4\beta_7$ Integrin binds MADCAM-1 and facilitates the entry of leucocytes into the inflamed intestinal tract. Interaction between MADCAM-1 and $\alpha_4\beta_7$ is most relevant to the pathogenesis of CD by accumulation of activated lymphocytes in inflamed intestinal wall.

Natalizumab is a recombinant IgG4 humanised monoclonal antibody against α_4 integrin. The proof of concept of effectiveness of α_4 integrin blockade was obtained in cotton-top tamarins who develop spontaneous colitis.[2 3] It improved diarrhoea and reduced leucocyte infiltration in mucosal biopsy specimens. An uncontrolled short term pilot study in 10 patients with active ulcerative colitis (UC) showed that a single 3

Abbreviations: CD, Crohn's disease; CDAI, CD activity index; IBDQ, inflammatory bowel disease quality of life; ICAM, intercellular adhesion molecule; MADCAM, mucosal vascular addressin cell adhesion molecule; UC, ulcerative colitis; VCAM, vascular cell adhesion molecule

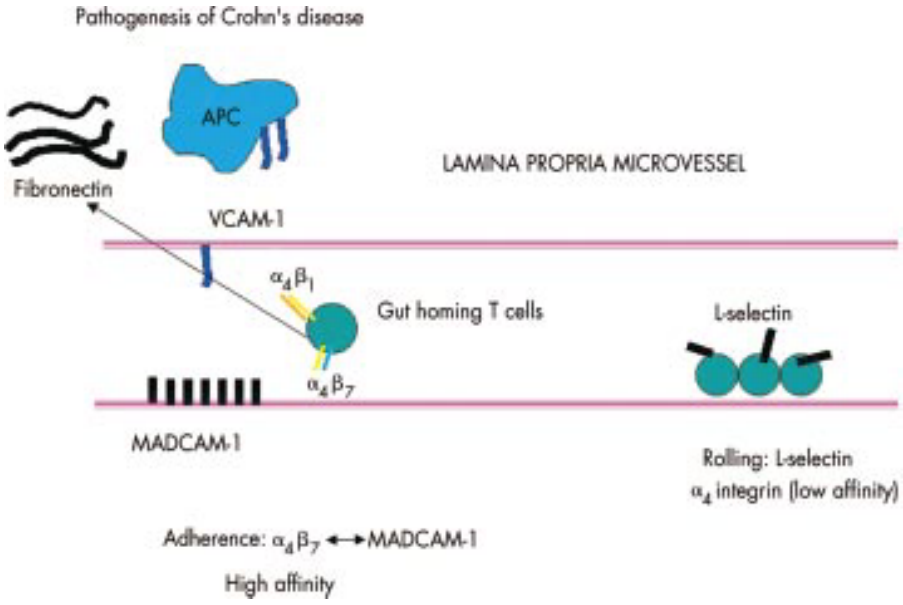

Figure 1 Lymphocyte trafficking to the intestine and key molecules involved.

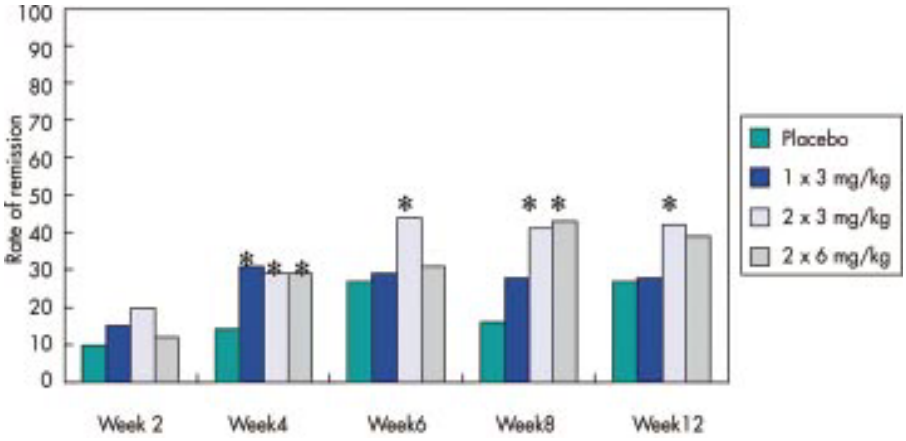

Figure 2 Rates of remission (CDAI<150) after different doses of natalizumab infusion compared with placebo. *Significant difference compared with placebo.[6]

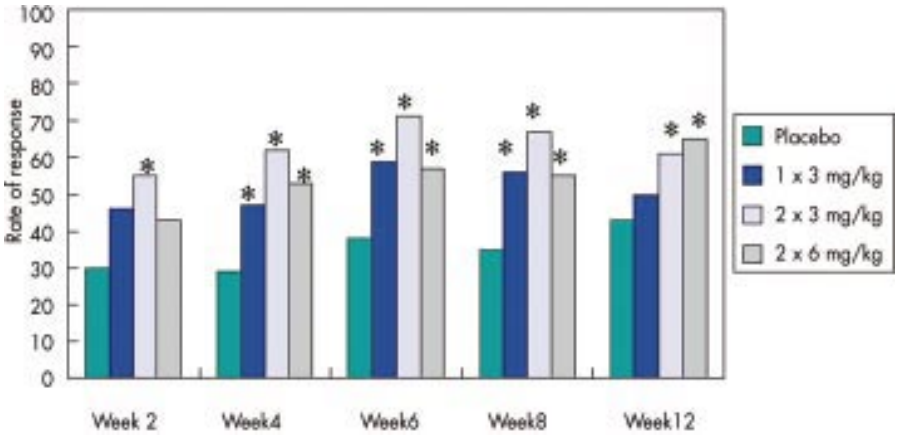

Figure 3 Rates of response (decrease in CDAI of at least 70 points from baseline) after different doses of natalizumab infusion compared with placebo. *Significant difference compared with placebo.[6]

mg/kg intravenous infusion of natalizumab may be beneficial.[4] Five of the 10 patients achieved a good clinical response at two weeks and one more patient by four weeks. The mean serum half life of natalizumab in this study was 3.8 days. The minimum serum natalizumab concentration of 5 µg/ml required to saturate at least 80% of circulating α_4 integrins was achieved in only a minority of patients at two weeks, suggesting that the dose was too low, explaining also the lack of mucosal healing. Both B and T lymphocyte counts rose after infusion of natalizumab. In CD, an initial small study on 30 patients with active CD showed that 3 mg/kg natalizumab was more effective than placebo in inducing remission at week 2 and the mean CD activity index (CDAI) was significantly less in the group receiving active treatment. Thirty nine per cent of natalizumab treated patients achieved remission at week 2 compared with 8% of those treated with placebo. Increase in circulating lymphocyte levels after administration of natalizumab was suggestive of blocking of lymphocyte trafficking into the intestine.[5] C reactive protein reduced significantly at weeks 2 and 4 in the patients treated with natalizumab compared with the controls. The mean plasma half life of natalizumab in this study was 4.8 days.

In a large placebo controlled randomised multicentre trial[6] of natalizumab in CD, 248 patients with moderate to severe CD were randomly allocated to two infusions of placebo, one infusion of 3 mg/kg of natalizumab followed by placebo, two infusions of 3 mg/kg of natalizumab, or two infusions of 6 mg/kg of natalizumab. The group given two infusions of 6 mg/kg (n=51) had significantly higher rates of remission at weeks 4 and 8 (29% and 39%) than the placebo group (14% and 16%). However, the remission at six weeks compared with placebo did not reach statistical significance (31% *v* 27%). The group given two infusions of natalizumab 3 mg/kg (n=66) had significantly higher rates of remission at weeks 4 (29% *v* 14%), 6 (44% *v* 27%), and 8 (41% *v* 16%) than the placebo group (fig 2). The rate of clinical response was significantly higher in all three natalizumab groups at weeks 4, 6, and 8 than in the placebo group, with the highest rate (71%) occurring at six weeks in the group given two infusions of 3 mg/kg (fig 3). All three groups receiving active treatment showed significant improvement in their inflammatory bowel disease quality of life (IBDQ) at week 6 compared with placebo (fig 4) and a significant decrease in C reactive protein concentrations. At week 12 both two dose regimens were significantly better than placebo.

Treatment with natalizumab was well tolerated. Antibodies to natalizumab were detected in 7% of patients. Only two patients had minor infusion reactions, one of whom had detectable antibody. During the study period 26 patients had serious adverse events—seven (11%) in the placebo group, six in the group given one infusion of 3 mg/kg (11%), six in the group given two infusions of 3 mg/kg (9%), and six in the group given two infusions of 6 mg/kg (12%). None of these serious adverse events were considered to be causally related to natalizumab infusion. There were no deaths.

Natalizumab is therefore an effective and well tolerated treatment for moderate to severe active CD.

OTHER ANTI-LEUCOCYTE TRAFFICKING STRATEGIES

Other strategies specifically designed to inhibit adhesion molecules include intercellular adhesion molecule-1 (ICAM-1), $\alpha_4\beta_7$ integrin, and the chemokine receptor CCR9 as target molecules. Clinical trials with antisense oligonucleotides to ICAM-1 (ISIS-2302) have been conducted in patients with active CD. In a pilot trial on 20 patients with chronically active

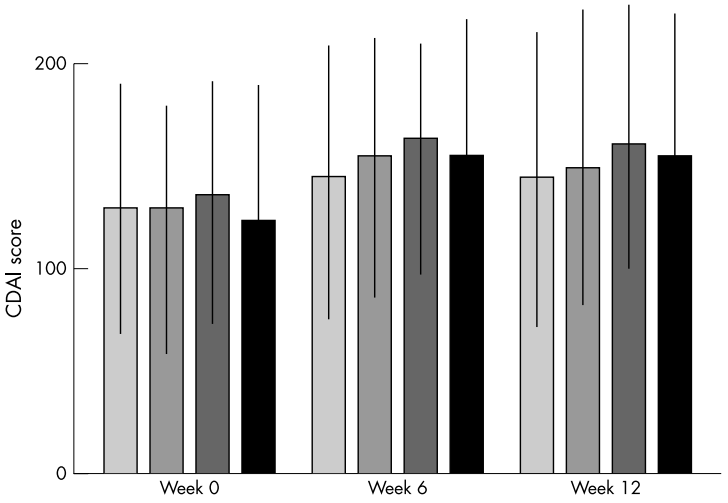

Figure 4 IBDQ scores in the four groups of patients.[6]

CD 47% treated with the active agent achieved remission after 26 days of treatment compared with 20% in the placebo group.[7] However the German multicentre study using subcutaneous ISIS-2302 at a dose of 0.5 mg/kg or placebo was terminated prematurely after interim analysis showed no evidence of efficacy.[8] Optimum dosing may not have been reached in this trial. A clinical trial with humanised anti-$\alpha_4\beta_7$ integrin antibody (LDP-02) has been carried out in UC (28 patients in four active treatment groups and a placebo group) and this dose finding safety study showed encouraging clinical response with a dose of 0.5 mg/kg intravenously.[9] This small study requires further larger studies to confirm the efficacy with a dose of 0.5 mg/kg or higher and such studies are continuing for CD and UC.

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