Physiological Basis for Novel Drug Therapies Used to Treat the Inflammatory Bowel Diseases

I. Immunology and therapeutic potential of antiadhesion molecule therapy in inflammatory bowel disease

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Assche, Gert Van, and Paul Rutgeerts. Physiological Basis for Novel Drug Therapies Used to Treat the Inflammatory Bowel Diseases. I. Immunology and therapeutic potential of antiadhesion molecule therapy in inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol 288: G169–G174, 2005; doi:10.1152/ajpgi.00423.2004.—Adhesion molecules regulate the influx of leukocytes in normal and inflamed gut. They are also involved in local lymphocyte stimulation and antigen presentation within the intestinal mucosa. In intestinal inflammation, many adhesion molecules are upregulated, but α4-integrins most likely hold a key position in directing leukocytes into the inflamed bowel wall. Therapeutic compounds directed against trafficking of leukocytes have been designed and are being developed as a novel class of drugs in the treatment of Crohn’s disease and ulcerative colitis. This review deals with the immunological aspects of leukocyte trafficking focused on gut homing of T cells. Second, the changes in adhesion molecules and T cell trafficking during intestinal inflammation are discussed. Finally, we review the clinical data that have been gathered with respect to the therapeutic potential and the safety of antiadhesion molecule treatment. Antegren, or natalizumab, a humanized anti-α4 integrin IgG4 antibody, has been most extensively evaluated and may be close to registration. A more specific humanized α4β7-integrin MLN-02 has shown preliminary clinical efficacy in ulcerative colitis, and both antergren and MLN-02 appear to be very safe. Trials with the anti-ICAM-1 antisense oligonucleotide ISIS-2302 in steroid refractory Crohn’s disease have provided conflicting efficacy data. In the near future, some of these novel biological agents may prove valuable therapeutic tools in the management of refractory inflammatory bowel disease, although it is too early to define the patient population that will benefit most from these agents.

A proportion of Crohn’s disease (CD) and ulcerative colitis (UC) patients becomes refractory to standard treatment during disease progression. Refractory CD impairs quality of life and eventually results in debilitating complications often necessitating bowel resections. In UC, refractory patients end up with colectomy. The long-term outcome of the ileoanal pouch is far from optimal. Moreover, inflammatory bowel disease (IBD) therapies, such as corticosteroids, carry a heavy burden of undesired side effects that often offset their therapeutic benefit in the long term. In the last decade, the management of refractory IBD has changed dramatically by the increasing use of immunosuppressive drugs and the advent of biological therapies. The majority of refractory patients is now taking azathioprine/6-mercaptopurine or methotrexate as maintenance therapy. The novel biological therapies, created with genetic technology and directed against a specific inflammatory mediator, have found some of their first real clinical applications in the management of IBD (24). The chimeric anti-tumor necrosis factor antibody infliximab has proven very efficacious in patients with both active refractory and fistulizing CD failing standard therapy. This compound has set the standard for future development of IBD therapies, and several second generation anti-TNF drugs are being tested including some small-molecule compounds for oral administration. Still, 30–40% of patients with refractory CD do not respond to infliximab treatment. Moreover, the long-term use of this drug is hampered by immunogenicity and by the risk for infectious complications. Therefore, biological therapies based on alternative pathways in the inflammatory cascade would be valuable for the future. Lymphocytes are crucial in the pathogenesis of IBD and are important targets for drug development. T lymphocytes are very mobile cells involved in a continuous journey from the blood into the gut mucosa and back into the blood and primary lymphoid organs. T cell trafficking is regulated by adhesion molecules. Modulating T cell adhesion may therefore alter the course of the local inflammatory reaction in the intestinal wall, and this offers therapeutic potential for the management of IBD.

T CELL MIGRATION TO THE INTESTINE

Even if the pathogenesis of both CD and UC is still incompletely understood, the crucial role of T cells in the pathogenesis of IBD is beyond discussion. T cells originate in the bone marrow and mature in the primary lymphoid organs. For patrolling antigens in the gut lumen and for assisting in intestinal inflammatory reactions, they need to be directed toward the gastrointestinal tract. The journey of T cells from the blood to antigen-rich organs such as the gut or the lungs is, however, guided by an elaborate system of traffic signals or adhesion molecules. To encounter antigen and to engage in tissue inflammation, T cells must leave the blood stream. On average, they do not stay in the blood >30 min. Leukocytes engage with the endothelium of postcapillary vessels, the high endothelial venules, before they migrate into the tissue (27a). This interaction is hindered by the high relative speed at which T cells travel, creating an important shear stress in the blood stream. A highly effective and sequential adhesion system has emerged to overcome these physical forces. Initially, tethering occurs through the interaction between selectins (L-, P-, and E-selectins) and oligosaccharide moieties acting as ligands (27).
L-selectins are expressed leukocytes, whereas P- and E-selectins are found on the endothelium. Selectin bonds provide a high tensile strength but are short-lived, and the T cell rolls over the endothelium from one selectin bond to the next. Secondary adhesion molecules, all members of the integrin family, will definitively stop the lymphocytes to allow migration. Integrins important in T cell migration are leukocyte function-associated antigen 1 (LFA-1 or \( \alpha_L \beta_2 \)-integrin) and the two \( \alpha_4 \)-integrins: \( \alpha_4 \beta_1 \)-integrin and \( \alpha_4 \beta_7 \)-integrin (3) (Fig. 1; Table 1). In contrast to selectins, which are constitutively expressed, integrins must be activated before they can engage in rolling. This integrin activation is mediated by chemokines that appear at the endothelial surface and bind to G protein-coupled receptors on the lymphocyte. The integrins interact with specific ligands, the adressins, on the endothelium. LFA-1 or \( \alpha_3 \beta_2 \)-integrin, expressed on neutrophils, interacts with ICAM-1 and -2. \( \alpha_4 \)-Integrins are predominantly expressed on lymphocytes and interact with adressins expressed on the endothelium. \( \alpha_4 \beta_1 \)-integrin binds to VCAM-1, and \( \alpha_4 \beta_7 \)-integrin binds with mucosal adressin-cell adhesion molecule 1 (MAdCAM-1) (13). MAdCAM-1 is typically associated with murine Peyer’s patches and also with human gut-associated lymphoid tissue (6). \( \beta_7 \)-Integrin knockout mice do not form real Peyer’s patches and have lower densities of lamina propria CD4+ cells (28). Because there is a certain specificity to adressin distribution, adhesion molecules do not only serve to facilitate lymphocyte migration but also contribute to tissue-specific lymphocyte trafficking. For example, in lymph nodes, naïve T cells will start the slow rolling process when L-selectin engages with peripheral node adressin, whereas in intestinal Peyer’s patches, additional interaction of \( \alpha_4 \beta_7 \)-integrin with MAdCAM-1 is required for rolling (19). Moreover, in intestinal high endothelial venules, naïve T cells will first use L-selectin to engage with the endothelium, whereas T effector cells and T memory cells with a high density of membrane-bound \( \alpha_4 \beta_7 \)-integrin, so called gut-homing cells, directly engage with MAdCAM-1. Naïve

**Fig. 1.** Schematic depiction of the different stages in leukocyte adhesion occurring in the intestinal wall. The principal interactions occurring in the high endothelial venules of Peyer’s patches are represented. The leukocytes escape from the shear stresses in the blood flow to adhere and, after activation, to squeeze through the endothelial layer. MAdCAM-1, mucosal adressin-cell adhesion molecule-1.

<p>| Table 1. Adhesion molecules involved in leukocyte trafficking |
|---------------------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Selectins and Selectin Ligands</th>
<th>Leukocyte adhesion molecules</th>
<th>Vascular adhesion molecules</th>
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<tbody>
<tr>
<td>L-selectin</td>
<td>most leukocytes</td>
<td>peripheral node addressin</td>
</tr>
<tr>
<td>Unknown (sialyl-Lewisx ?)</td>
<td>leukocytes</td>
<td>E-selectin</td>
</tr>
<tr>
<td>P-selectin glycoprotein ligand 1</td>
<td>most leukocytes</td>
<td>P-selectin</td>
</tr>
<tr>
<td>( \beta_2 )-Integrins</td>
<td></td>
<td>ICAM-1</td>
</tr>
<tr>
<td>( \alpha_L \beta_2 ) (LFA-1)</td>
<td>all leukocytes</td>
<td>ICAM-2</td>
</tr>
<tr>
<td>( \alpha_3 \beta_2 ) (Mac-1)</td>
<td>myeloid lineage</td>
<td></td>
</tr>
<tr>
<td>( \alpha_4 \beta_2 )</td>
<td>dendritic cells</td>
<td></td>
</tr>
<tr>
<td>( \alpha_5 \beta_2 )</td>
<td>monocytes, eosinophils</td>
<td></td>
</tr>
<tr>
<td>( \alpha_6 \beta_2 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \alpha_7 \beta_2 ) (VLA-4)</td>
<td>most leukocytes</td>
<td>VCAM-1</td>
</tr>
<tr>
<td>( \alpha_8 \beta_7 )</td>
<td>not on neutrophils</td>
<td></td>
</tr>
<tr>
<td>( \alpha_9 \beta_7 )</td>
<td>lymphocytes, NK-cells, monocytes</td>
<td>MAdCAM-1, fibronectin, osteopontin, ADAM28</td>
</tr>
<tr>
<td>( \alpha_1 \beta_7 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L-selectins are found on the leukocyte membrane, whereas P- and E-selectins are expressed on the endothelial cells (see also Fig. 1). HEV, high endothelial venules. LFA1, leukocyte function-associated antigen-1.
T cells and T effector cells can also engage their \( \alpha_4\beta_2 \)-integrin to connect with ICAM-1, but this interaction is not gut specific.

**ADHESION MOLECULES IN IBD**

Recruitment of T effector and T memory cells that recognize antigens encountered in the gut lumen is crucial in disease states such as in acute intestinal inflammation due to luminal pathogens. Endothelial alterations in tissues that contain potential pathogens allow leukocyte adhesion and migration, whereas their microcirculation prevents leukocyte diapedesis in basal conditions. Inflammatory cytokines such as TNF and IL-1 induce the presence of ICAM-1, of E-selectin, and probably also of MAdCAM-1 on endothelium in inflamed tissue (4). Upregulation of MAdCAM-1 can be deduced from the observation that intestinal endothelium from IBD patients has a higher adhesiveness for \( \alpha_4\)-integrins (21). VCAM-1, the other ligand of \( \alpha_4\)-integrins, does not account for this observation because it is very sparsely expressed in the gut microcirculation (4). Also chemokines secreted by inflammatory cells in the diseased tissue will activate integrins expressed on membranes of T cells rolling over the endothelium. In surgical resection specimens from CD and UC patients, ICAM-1 and -2 expression is increased on the endothelium. Also, the ligands for ICAM, the \( \beta_2\)-integrins, are upregulated in both CD and UC. Intravital microscopy studies in rat intestinal inflammation induced by serosal application of Escherichia coli lipopolysaccharides have shown that in an early phase of the inflammation, leukocyte rolling is mediated by P-selectin, whereas in a more advanced phase, L-selectin and \( \alpha_4\)-integrins mediate this process (16). Interestingly, clinical response to anti-TNF therapy in CD patients is associated with a marked decrease in ICAM-1 expression in the intestinal endothelium (1). The same observation was made in the endothelium of infliximab-treated rheumatoid arthritis patients.

T cell migration into the inflamed bowel segments is probably of paramount importance in IBD pathogenesis. However, a decreased exit of lymphocytes from the mucosa and an increased local activation and/or proliferation could also contribute to the perpetuation of inflammatory reactions in IBD. There is some evidence to support a role for adhesion molecules in interactions between T cells and resident dendritic cells or mesenchymal cells in the intestinal mucosa and submucosa. The extracellular matrix protein, fibronectin for instance, is an \( \alpha_4\beta_2\)-integrin ligand (18), and this interaction may influence the function of stromal cells, such as antigen-presenting dendritic cells or fibroblasts. Other extravascular ligands for \( \alpha_4\)-integrins include matrix molecules, such as osteopontin and thrombospondin, and ADAM28, a metalloprotease domain constitutively expressed on lymphocytes (5). ICAM-1 and \( \alpha_4\)-integrin binding to their respective adrenergic mediators induce a costimulatory signal in antigen presentation to T cells inducing lymphocyte proliferation and cytokine production (18). Moreover, expression of ICAM-1 in CD is not only increased in the intestinal mucosa but also in the submucosa and in the muscle layers. Intestinal smooth muscle expresses ICAM-1 when stimulated by proinflammatory cytokines in vitro, and this may contribute to local interactions with lymphocytes that have penetrated in the deeper layers of the intestinal wall (15). Therefore, a therapeutic benefit of antiadhesion molecule therapy could be explained by a decrease of T cell recruitment at the endothelial surface, by an inhibition of costimulatory effects of adhesion molecules in local leukocyte activation within the mucosa, or by a combination of both mechanisms.

Extraintestinal inflammatory events, such as reactive arthritis and erythema nodosum, are frequent in both CD and UC. It is amenable to hypothesize that activated gut-homing lymphocytes also travel to synovial microvasculature to contribute to IBD-associated arthritis. Salmi and Jalkanen (25) have convincingly shown that several leukocyte populations originating from the inflamed gut adhere to synovial vessels. However, these cells engage CD44 to interact with vascular adhesion protein in the synovial venules, whereas \( \alpha_4\beta_7\)-integrin-MAdCAM-1 interactions dominate in the intestine.

**ANTIADHESION MOLECULE STRATEGIES IN IBD**

The crucial role of adhesion molecules in inflammatory disorders makes them interesting targets for drug development. Pioneering studies with antiadhesion strategies have been undertaken in asthma where antagonists of \( \alpha_4\beta_7\) helper 2-specific chemokines and inhibitors of \( \alpha_4\beta_1\)-integrins have been shown to induce profound anti-inflammatory effects.

In IBD, antiadhesion therapy has focused on two pathways: the \( \alpha_4\)-integrin/MAdCAM-1 and the \( \beta_2\)-integrin/ICAM-1 interaction.

**ANTI-\( \alpha_4\)-INTEGRIN THERAPY**

Two monoclonal antibodies have been selected for drug development and subsequently studied in a primate model and in clinical trials. Millennium Pharmaceuticals developed a specific humanized \( \alpha_4\beta_7\)-integrin monoclonal antibody, MLN-02, formerly LPD-02. Elan Pharmaceuticals introduced a humanized monoclonal \( \alpha_4\)-integrin IgG4 antibody, natalizumab. The only conceptual difference between the two compounds lies in the specificity of MLN-02 for blocking the \( \alpha_4\beta_7\)-MAdCAM-1 interaction, whereas natalizumab also inhibits the \( \alpha_4\beta_1\)-VCAM-1 binding (Fig. 2). Both compounds were first tested in the cotton-top tamarin. This South American primate develops chronic colitis when kept in captivity. The colitis in the primates resembles human IBD in that it is a spontaneously
developing disease with clear architectural alterations in surface and crypt epithelium. Anti-\(\alpha_4\beta_7\)-integrin antibodies were first evaluated in cotton-top tamarin colitis (22). Administration of this antibody markedly improved the clinical and histological scores in the colitic animals. In contrast, antibodies directed against E-selectin were not effective.

Antibodies to \(\alpha_4\beta_7\)-integrin (ACT-1, leukocyte) were also tested in cotton-top tamarins. The antibodies were administered intravenously and subsequently intramuscularly for 1 wk in four chronically colitic animals. Four other animals were treated with irrelevant antibodies (14). A striking improvement was observed in all anti-\(\alpha_4\beta_7\) antibody-treated animals within 24–72 h. This clinical response was mirrored by improvement of histological changes and by a reduction of mucosal T cells and neutrophils.

**NATALIZUMAB, HUMANIZED ANTI-\(\alpha_4\)-INTEGRIN IgG4 ANTIBODY**

Natalizumab, humanized anti-\(\alpha_4\)-integrin IgG4 antibody, Antegren, is developed in parallel for IBD and for multiple sclerosis. Indeed, whereas \(\alpha_4\beta_7\)-MadCAM-1 interaction is pivotal in gut lymphocyte homing, \(\alpha_4\beta_7\)-VCAM-1 binding appears to be a crucial step in experimental encephalomyelitis (31).

A first phase II randomized placebo-controlled trial included 30 patients. This study was not powered to really assess the therapeutic potential of natalizumab and the primary end point, the change in CD activity index (CDAI) at week 2 was not different between actively treated and control patients (10). However, at week 2, 39% (\(n = 7\)) of the natalizumab-treated patients vs. 8% (\(n = 1\)) of placebo-treated patients had achieved clinical remission (CDAI of <150). The effect of natalizumab was short-lived, because rescue therapy was initiated in most of the patients at week 4. A larger trial was consecutively conducted including 248 patients with moderately to severely active Crohn’s disease (11). Patients were treated twice at 4-wk intervals with 3 or 6 mg/kg iv of natalizumab or placebo. The primary end point was the number of patients in remission (CDAI of <150) at week 6. A significantly higher number of patients achieved remission at 6 wk in the 3 + 3 mg/kg group only [44 (29/66) vs. 27% (17/63) in the placebo group (\(P < 0.05\))]. Clinical response, as defined by a \(\geq 70\%\) drop in CDAI, was observed at week 6 in all treatment groups in a higher number compared with placebo [placebo 38%, 3 + 0 mg/kg; 59% (\(P < 0.03\)), 3 + 3 mg/kg; 71% (\(P < 0.001\)), 6 + 6 mg/kg; 57% (\(P < 0.05\))].

The combined safety data in the three trials were excellent, and only 8% of patients developed anti-Antegren antibodies, and the proportion of patients experiencing a severe infusion reaction was \(<1\%\). Interestingly, a transient increase in circulating lymphocytes was consistently observed in Antegren-treated patients across all clinical trials, indicating that the antibody really prevents the diapedesis of these cells through the vascular wall. The experience with Antegren in UC has been more limited. Ten patients with moderately active UC were treated in a small open-label trial. The results of the trial suggest therapeutic potential of Antegren in UC, but controlled evidence is needed.

**MLN-02**

LDP-02, the humanized anti-\(\alpha_4\beta_7\)-integrin antibody, has been most extensively studied in UC. Feagan et al. (9) reported on a randomized placebo-controlled trial in 28 patients with moderate UC. Patients received increasing doses of (humanized anti-\(\alpha_4\beta_7\)-integrin antibody) MLN-02 or placebo. The trial was designed to evaluate tolerability and not efficacy. Nevertheless, it should be noted that a complete endoscopic and clinical remission at day 30 was observed in three of five patients receiving the highest dose of 0.5 mg/kg iv. This dose saturated \(\alpha_4\beta_7\)-binding for up to 30 days. In a follow-up phase II trial that was recently reported, 181 patients were included and received either 0.5 or 2.0 mg/kg of MLN-02 or placebo twice with a 28-day interval (8). Remission rates on day 43 were significantly higher in actively treated (33%, 0.5 mg/kg; 34%, 2.0 mg/kg) than in placebo-treated patients (15%, \(P = 0.03\)). The drug was generally well tolerated, and infusion reaction with angioedema was seen in only one patient. A placebo-controlled trial in 185 patients with mild to moderately active CD treated with either 0.5 or 2.0 mg/kg of MLN-02 or placebo twice with 28 days interval indicated that at 2 mo there was no difference between actively treated and placebo-treated patients for clinical response (20). At this moment no further trials have been planned to explore the therapeutic potential of MLN-02 in IBD.

**ANTI-ICAM-1 THERAPY**

In human disease, efficacy of anti-ICAM strategies was first demonstrated in rheumatoid arthritis, a T-H1-driven inflammatory disorder that carries striking similarities with CD. Neutralizing anti-ICAM-1 antibodies have been shown to induce sustained improvement in symptoms even after a short treatment course of 2 or 5 days (17). The proof of concept for the use of anti-ICAM strategies in human IBD was found in animal models. Both blocking anti-ICAM1 antibodies and ICAM-1 antisense oligonucleotides have been successfully used in animal models of IBD. In dextran sulphate sodium-induced murine colitis and in SAMP-1/Yit adoptive transfer-induced murine ileitis, anti-ICAM antibodies were effective at reducing inflammation (7, 12). Interestingly inhibition of VCAM-1 proved at least as effective as anti-ICAM-1 therapy atameliorating experimental colitis. The relevance of VCAM-1 inhibi-
tion for human IBD can, however, be questioned in view of the observation that VCAM-1 is hardly expressed in human intestinal epithelium even in inflammatory conditions. In the mouse SAMp-1/Yit ileitis model, however, ICAM-1 antibodies were effective when administered in combination with anti-VCAM-1 or anti-α₄-integrin-blocking antibodies, suggesting a redundancy in the adhesion pathway during acute inflammation (7). Furthermore, only the acute component of the ileitis was affected, and the antiadhesion molecule therapy did not influence signs of chronic inflammation, such as architectural changes in the mucosa or muscle hypertrophy. Chronic inflammation was only ameliorated by corticosteroid treatment.

Clinical trials investigating the therapeutic potential of anti-ICAM agents have been exclusively conducted with antisense oligonucleotides to ICAM-1 (Table 2). Antisense oligonucleotides hybridize to a specific RNA molecule, most often mRNA, and consecutively prevent the translation of the protein encoded by the RNA (Fig. 2). The concept is appealing, because a disease-causing pathway can be targeted before translation that has produced numerous proteins starting from a limited number of mRNA molecules. However, the selection of the correct site in the target mRNA to obtain an optimal inhibition of translation is a complex process. Moreover, stability and resistance against enzyme degradation are crucial for application of an antisense compound in vivo. ISIS pharmaceuticals have provided several clinically applicable antisense oligonucleotides. ICAM-1 was chosen early on in the development of antisense compounds as an important target, more specifically for the treatment of IBD and rheumatoid arthritis. Several placebo-controlled randomized trials with an ICAM antisense oligonucleotide (ISIS-2302; alicaforsen) have been performed in active steroid-treated CD but have produced conflicting results. Alicaforesn binds to the 3' untranslated region of the mRNA and prevents further translation. A pilot trial including 15 patients with mild to moderate CD were treated with ISIS-2302 vs. five patients with placebo, suggested therapeutic potential for ICAM-1 antisense oligonucleotides in chronically active CD (29). Two larger multicenter trials were designed starting from these initial results: one in Germany with a novel subcutaneous formula and one in centers in the United States and Europe with intravenous ISIS-2302 (26, 30). In the German trial, corticoid-dependent patients with moderately active CD were treated subcutaneously with a dose of 0.5 mg/kg or placebo SC. However, enrollment was terminated after 78 subjects (75 with ≥1 treatment dose). Because only 3% of the patients actually achieved clinical remission with complete steroid taper and even for clinical remission regardless of steroid dose, there was no benefit of the active drug. The authors therefore concluded that there was no therapeutic benefit of ISIS-2302 in steroid refractory CD. The other large multicenter (US and Europe) study was also conducted in moderately active steroid-dependent CD patients. Patients received an intensified regimen of 2 mg/kg iv three times per week for 2 or 4 wk or placebo for 4 wk. After a 1-mo interval without dosing, the same treatment schedule was repeated. Pharmacokinetic studies were performed in this study, and the area under the curve (AUC) of plasma concentration over time was used to assess total drug exposure in an individual subject. Two hundred ninety-nine patients were included in this trial, and similar end points were used as in the German ISIS-2302 trial. Again there were no differences in remission rates between the placebo and any of the treatment groups. Steroid-free remission at week 14 was achieved in 20% of the patients in both the 2- and 4-wk ISIS-2302 groups and in 18% of placebo-treated patients. However, when patients were regrouped using the AUC of ISIS-2302 plasma concentration, the highest AUC group (AUC of >65 μg·h⁻¹·ml⁻¹, 9 patients) showed a consistent, increased improvement rate for most of the clinical end points (remission, median CDAI and IBDQ scores). Taken together, these studies do not convincingly show efficiency of anti-ICAM oligonucleotides. Therefore, the question of whether ISIS-2302 should be used at higher doses in CD remains unsolved. High dose exposure was reported in a small open-label trial including 20 patients, suggesting clinical efficacy (41% remission rate). Of these 20 patients receiving 250–350 mg alicaforsen, five withdrew from the trial due to infusion-related symptoms. Alternatively, the lack of efficacy of ISIS-2302 could be caused by the inability of the compound to penetrate in the inflamed bowel. However, the downregulation of ICAM-1 expression observed in the pilot trial does not support this hypothesis. A redundancy of adhesion pathways in the inflamed gut, providing alternative routes for leukocyte infiltration and activation, is a more appealing explanation that will need to be tested in additional studies also comparing antisense-based strategies with anti-ICAM antibodies. Recal enema treatment with alicaforsen in UC is being evaluated in clinical trials, and preliminary data should be available later in 2004.

The consistently described side effects of alicaforsen in all clinical trials were: injection site reactions or infusion reactions (23 and 2%, respectively) and moderate increases in activated partial thromboplastin time (aPTT). The increase in aPTT to ~50 s is probably clinically not relevant and is considered to be a class effect of anti-ICAM treatments, because it has been observed in most animal and human studies.

Table 2. Anti-adhesion molecules in development for IBD treatment

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Molecular Structure</th>
<th>Efficacy In Crohn’s Disease</th>
<th>Efficacy in Ulcerative Colitis</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab Antegren</td>
<td>Humanized mouse anti-human α₄ integrin monoclonal antibody (IgG4)</td>
<td>Efficacious in phase II/III trials</td>
<td>Efficacious in open label pilot study</td>
<td>More phase III trials underway. Registration pending</td>
</tr>
<tr>
<td>MLN-02 (formerly LDP-02; Millennium Pharmaceuticals, Genemech)</td>
<td>Humanized mouse anti-human α₄β₃-integrin monoclonal antibody</td>
<td>Not efficacious in phase II trial</td>
<td>Efficacious in phase II/III trials</td>
<td>Development temporarily halted</td>
</tr>
<tr>
<td>Alicaforesn (ISIS 2303; ISIS Pharmaceuticals)</td>
<td>Antisense oligonucleotide to ICAM-1 mRNA</td>
<td>Conflicting results in phase II/III trials</td>
<td>Efficacious in phase II trial</td>
<td>Phase II/III trials in ulcerative colitis ongoing</td>
</tr>
</tbody>
</table>
FUTURE PERSPECTIVES AND EXPERT OPINION

Antiadhesion molecule therapy for IBD is an appealing concept with a sound immunological background. Anti-α4 integrin therapy is theoretically the most gut-selective strategy, and the first clinical trials look promising. More specifically, the recent phase III trial with Antegren suggests that antiadhesion molecule therapy is efficacious even in patients failing to respond to anti-TNF antibodies. Also, combined antiadhesion molecule therapy with anti-TNF strategies or with immunosuppressants should be explored. Although Antegren appears to be slower acting than the anti-TNF agent infliximab, it appears to be devoid of clinically significant immunogenicity. Therefore, maintenance therapy after induction of remission with other agents might be an important therapeutic niche for anti-integrin antibodies. Anti-ICAM strategies need to be reconsidered in view of the two recent negative trials. On the basis of the immunology of IBDs, interesting candidate targets for future research concerning antiadhesion molecule treatment include chemokines and their receptors. The chemokine receptor CCR9 appears to be selectively involved in the migration of T cells to the gut and may become the subject of future drug development. Also, several small molecule antagonists of the chemokine receptors are already available. Finally, adhesion molecules could be used to direct genetically modified counterregulatory human T cells into the gut mucosa where they could have anti-inflammatory effects.

REFERENCES


