Biologic therapies for chronic inflammatory bowel disease

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ABSTRACT

Crohn’s disease (CD) and ulcerative colitis (UC) make up the so-called chronic inflammatory bowel disease (IBD). Advances in the understanding of IBD pathophysiologic mechanisms in the last few years have allowed the development of novel therapies such as biologic therapies, which at least theoretically represent a more specific management of this disease with fewer side effects. Currently, the only effective and widely accepted biologic therapy for the treatment of intraluminal, fistulizing CD, both for remission induction and maintenance, is infliximab. The role of other monoclonal antibodies such as adalimumab is not clearly established. It could be deemed an alternative for patients with allergic reactions to infliximab, and for those with lost response because of anti-infliximab antibody development. However, relevant issues such as dosage and administration regimen remain to be established. Anti-integrin α4 therapies, despite encouraging results in phase-3 studies, are still unavailable, as their marketing authorization was held back in view of a number of reports regarding progressive multifocal leukoencephalopathy cases. Immunostimulating therapy may be highly relevant in the near future, as it represents a novel strategy against disease with the inclusion of granulocyte-monocyte colony-stimulating factors.

Regarding ulcerative colitis, results from the ACT-1 and ACT-2 studies showed that infliximab is also useful for the management of serious UC flare-ups not responding to standard treatment, which will lead to a revision of therapeutic algorithms, where this drug should be given preference before intravenous cyclosporine. In the next few years, the role of anti-CD3 drugs (vilisilizumab), T-cell inhibiting therapies, and epithelial repair and healing stimulating factors will be established.

Key words: Inflammatory bowel disease. Crohn’s disease. Ulcerative colitis. Therapy.

INTRODUCTION

Crohn’s disease (CD) and ulcerative colitis (UC) make up the so-called inflammatory bowel disease (IBD). Advances in the knowledge of this condition’s etiopathogenesis have been correlated to the development of novel therapeutic agents. Medical treatment is currently the cornerstone for managing these conditions, and surgery is reserved for complications or treatment refractoriness (1). The available therapeutic armamentarium includes anti-inflammatory drugs (aminosalicylates and steroids), antibiotics, and immune modulators (azathioprine, 6-mercaptopurin, cyclosporin and methotrexate). All these drugs result in a nonspecific suppression of inflammatory processes, and their use during the past few years has determined a relevant advance in BDI control. However, their efficacy is limited and they are not exempt from side effects. Biologic therapies, at least theoretically, would be more therapeutically effective with fewer side effects, and thus would represent more specific means for the management of the disease. The efficacy and safety of infliximab in intraluminal, fistulizing Crohn’s disease (2-5), both for response induction and response maintenance, has resulted in research on new biologic therapies directed against specific mechanisms within the inflammatory process.

BIOLOGIC THERAPIES

Biologic therapies are made up of five agent classes (6):

1. Natural or modified preparations of biologic origin. These include blood products, hormones, and vaccines (with living, attenuated or dead organisms).
2. Recombinant peptides or proteins.
3. Antibody-based therapies.
4. Nucleic acid-based therapies.
5. Gene and cellular therapies.

Biologic preparations used in clinical practice or currently under assessment for the management of IBD mainly include recombinant proteins, antibodies and nucleic acids.

**FUNDAMENTALS OF BIOLOGIC THERAPIES**

IBD is presently considered the product of an abnormal immune response to harmless intraluminal antigens occurring in a genetically predisposed host and resulting in a chronic inflammation of the gastrointestinal tract in association with tissue damage (7).

Under normal conditions, the immune system can recognize harmless intraluminal antigens, versus which it will exert immune tolerance. In the presence of various pathogens, the immune system may initiate a number of downregulated responses, thereby preventing tissue lesions and allowing the elimination of causal agents. The fact that both CD and UC clinically manifest in a heterogeneous manner (site, severity, response to treatment) is believed to result from a number of changes in immunoregulatory pathways, which in turn would reflect the genetic variability of environmental influence (8). Thus, IBD would be a consequence of a complex interrelation between genetic, environmental, and microbial factors, which would induce a sustained inflammation of the bowel mucosa supported by mucosal barrier changes and immune system defects (9).

The first defense line in the gastrointestinal tract is the bowel epithelium, made up of a single cylindrical, epithelial cell layer with tight intercellular junctions to create a virtually impenetrable barrier for macromolecules (except for nutrients and invasive germs). Furthermore, all this is lined with mucus, which blocks the passage of pathogens and intraluminal antigens into the lamina propria (8). In addition, secretory IgA agglutinates bacteria and viruses into large complexes that are then included in the mucus and cleared with the feces with no contact with the epithelium (10,11). The mucosal barrier has been seen to be disturbed in IBD, with the presence of abnormal intercellular junctions and decreased mucus production, which allows antigens to freely enter the lamina propria (8). During inflammation, tissue damage can be repaired using cytoprotective factors such as the transforming growth factor (TGF-α and TGF-β), trophic factor, epidermal growth factor (EGF), keratinocyte growth factor (KGF), interleukin 11 (IL-11), and growth hormone, which upon secretion in the intestinal mucosa restore mucosal integrity (12). Therefore, a potential class of biologic therapies would include both trophic and growth factors, as these would be able of restoring mucosal integrity, thereby inhibiting the immune response.

Under normal conditions, the mucosa contains a number of epithelial cells devoted to antigen presentation. These include M cells, which transport intraluminal antigens to lymphoid follicles or Peyer plates, and dendritic cells, which through M cells or the sending out of prolongations among enterocytes can capture and present intraluminal antigens to naïve T cells in lymphoid follicles or Peyer plates (8). Activated lymphocytes then secrete interferon gamma (IFNγ) and IL-2, and non-differentiated T cells mature into effector T cells (Th1 or Th2) or regulator T cells (Th3 or Tr1) in response to stimuli received from antigen-presenting cells (8,10). Excessive effector T cell numbers leads to an excessive production of proinflammatory cytokines with the aim of eliminating the pathogenic agent. Once their goal is achieved, anti-inflammatory cytokines, including IL-10, Th3 cells, and trophic factors, arrest the inflammatory response. Defects in this slowing mechanism lead to severe inflammatory aggression to tissues, and the development of disease clinical manifestations. In contrast, regulator T cell abundance determines immune tolerance and anergy (13).

Classically, Crohn’s disease has a Th1-type cytokine profile resulting from immature T-cell exposure to IL-12, IL-18 or IL-23. Th1 cells produce IL-2 and IFN-γ. IFN-γ increases the expression of adhesion molecules in endothelial cells, which facilitates inflammatory cell recruitment and activates macrophages. The latter in turn generate free radicals and large numbers of proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, IL-12, IL-18). In patients with CD, intestinal mucosa T cells have been shown to be apoptosis-resistant, which leads to T-cell accumulation and a perpetuation of inflammatory response (9). This phenomenon seems to depend on IL-6, which may activate anti-apoptotic genes in intestinal T lymphocytes (14). Ulcerative colitis has a Th2-type cytokine profile characterized by IL-4, IL-5, and IL-10 production. Th2 response implicates natural killer T-cell (NKT) activation, and these cells may be responsible for inflammation through IL-13 production (15). It is currently accepted that ulcerative colitis entails a mixed, Th1 and Th2 immune response, which would account for the response elicited using anti-TNF therapy. It is also currently accepted that CD is characterized by high IFN-γ and low IL-13 production, whereas UC is characterized by high IL-13 production in intestinal lamina propria cells (15). Inflammation as induced in the intestinal mucosa is amplified by the recruitment of circulating “naïve” T cells, activated T cells, and polymorphonuclear cells into inflamed areas through an interaction between adhesion molecules expressed in the surface of lymphocytes and in endothelial cells. Thus, “naïve” T cells are captured by mesenteric nodes through an interaction of T-cell-associated L-selectins with their ICAM-1 ligand, whereas activated T cells travel to Peyer patches through an interaction between integrin α4β7 and its counterligand mucosal adressin, a molecular adherence molecule (MAdCAM-1) (16). Proinflammatory and anti-inflammatory...
cytokines, the various cells playing a role in the inflammatory cascade, and the mechanisms involved in lymphocyte recruitment in inflammation sites are all potential targets for biologic therapies.

It is currently considered that dendritic cells in charge of the immune response are responsible for inflammatory response tolerance or activation mechanisms, determine whether said response is to be of Th1 or Th2 type, and link both innate and adaptive immunity. In patients with Crohn’s disease it has been found that selected dendritic cells produce high TNF-α levels in response to polysaccharide LSP (endotoxin from gram-negative bacteria) (17), and the modulation of these cells’ activity has been suggested to have a potential therapeutic role.

It is long known that a genetic component plays a role in the pathogenesis of IBD, since the prevalence of this disease is much higher among members in one family. Genetic disturbances in relation to Crohn’s disease are best known. The first one is related to gene NOD2/CARD15 (C-terminal caspase recruitment domain) within chromosome 16; this gene codes for a protein that is essential in antigen recognition (bacterial polysaccharides), and for NFκB activation, the latter being a nuclear factor playing a role in the transcription of proinflammatory cytokines (18,19). Interestingly, mutations in this gene result in decreased NFκB activity, and a downregulation of inflammatory processes (9). To this moment three potential explanations have been suggested, which are based on experimental studies in mice with NOD2 gene mutations: a) in these mice bone marrow-derived macrophages respond excessively to the bacterial muramyl dipeptide, thus increasing IL-1β production, which would stimulate NFκB (20); b) loss of function in NOD2 mutation would affect epithelial cells in bowel crypts rather than macrophages (21); c) mouse cell lines expressing mutated or absent NOD2 together with TLR2 (type-2 toll-like receptor) after stimulation with muramyl dipeptide have been seen to induce increased NFκB activation via TLR2-dependent pathways; therefore, the function of NOD2/CARD15 may be inflammation control via TLR2 receptors. NOD2 mutations would increase proinflammatory cytokines through non-inhibited TLR2s (22). A second gene involved in Crohn’s disease is IBD5, sited in chromosome 5. This gene codes for two proteins (OCTN1 and OCTN2) that are present in epithelial cells, macrophages, and T but not B lymphocytes. Genetic defects may bring about a decrease in carnitine transportation in epithelial cells, and hence an interruption of β-oxidation. Alternatively, they may increase bacterial antigen transportation, and upregulate immune response (23). In UC, allelic variations of the MDR1 gene determine disease extension and susceptibility, as well as response to treatment (24). Genetic disorders are complex and manifold in inflammatory disease, and gene therapy is thus of little viability in this disease; however, knowing them allows to better understand etiopathogenic mechanisms, and the response to and toxicity of the various therapeutic agents (9).

Toll-like receptors (TLRs) were unveiled in 1990; these receptors recognize pathogen-associated molecular patterns (PAMPs) that are shared by many microbial agents. These receptors are located in epithelial cells, endothelial cells, macrophages, and other immune system cells. Their activation ultimately activates NFκB, which in turn results in the synthesis of proinflammatory cytokines responsible for specific Th responses (8). Polymorphism and the varying expression of these receptors have been associated with IBD (25,26), and may become potential therapy targets in the future. The mechanism of action of a number of probiotic agents may operate through the induction of or an interaction with these receptors. Tables I and III summarize the characteristics and major mechanisms of action of the main biologic therapies for Crohn’s disease and ulcerative colitis.

**BIOLOGIC THERAPIES IN CROHN’S DISEASE**

**Anti-tumor necrosis factor alpha (anti-TNF) therapies**

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine produced by intestinal mucosa macrophages, activated T lymphocytes, monocytes, and mastocytes. TNF levels are very high in the serum, urine and intestinal mucosa of patients with active CD. Several therapies are designed to neutralize TNFα (Table II).

**Infliximab**

Infliximab was the first anti-TNF agent to prove effective in CD, and to receive approval for its treatment by the European Agency for the Evaluation of Medicinal Products and the FDA. Infliximab is a chimeric monoclonal IgG1 antibody against soluble and cell-membrane TNF-α that binds the complement, favors antibody-mediated cytotoxicity, and induces T-cell apoptosis (Table II) (27). It is presently approved for remission induction in intraluminal, fistulizing, active CD (perianal and enterocutaneous) in corticoid-dependent patients or individuals unresponsive to standard treatment. It is used at doses of 5 mg/kg/i.v., administered on weeks 0, 2, and 6. Clinical remission maintenance may be achieved with sporadic or scheduled administration at doses of 5 mg/kg/i.v. every 8 weeks (3,4,28,29). The ACCENT I and ACCENT II trials demonstrated the drug’s efficacy, its safety profile, and the most appropriate dosage and administration scheme (3,4). While infliximab is a well-tolerated drug in most cases, severe side effects may develop, including severe infection (3,4), lupoid syndrome (30), acute infusional reactions and delayed hypersensitivity (5), de-myelinating conditions (31), heart failure (32), potential increased risk for lymphoma (33), and death (5). Among infections, reactivated latent tuberculosis should be high-
lighted in our setting, which requires a detailed history, chest x-rays, and a tuberculin test (with a booster in immunodepressed individuals) at baseline in all patents undergoing this therapy. Reactivated infection with hepatitis B virus has recently been reported in carrier patients, and thus this group of patients at risk needs detection (34). A patient subgroup develops antibodies against infliximab (ATI); these antibodies have been associated with the development of delayed and post-infusional acute reactions, and a loss or decrease in drug effectiveness. Infliximab regular administration every 8 weeks, together with concurrent immunosuppressant use, has been shown to reduce antibody development from 30 to 8%, and to increase therapeutic efficacy. However, we

### Table I. Biological therapies either approved or under assessment for the treatment of Crohn’s disease

<table>
<thead>
<tr>
<th>Drug &amp; Biologic target</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Research phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proinflammatory inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (chimeric monoclonal anti-TNF IgG1 antibody)</td>
<td>Centocor and Schering Plough</td>
<td>Crohn’s disease</td>
<td>Approved for therapeutic use by FDA</td>
</tr>
<tr>
<td>CDP571 (humanized monoclonal anti-TNF IgG4 antibody)</td>
<td>Celltech</td>
<td>Crohn’s disease</td>
<td>Failed phase 3/failed phase 4</td>
</tr>
<tr>
<td>CDP870 (humanized PEG-bound fragment of anti-TNF Fab)</td>
<td>Celltech</td>
<td>Crohn’s disease</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Etanercept (recombinant fusion protein made up of IgG1 Fc fragment bound to two human p75 TNF receptors)</td>
<td>Amgen</td>
<td>Crohn’s disease</td>
<td>Failed phase 2</td>
</tr>
<tr>
<td>Adalimumab (human monoclonal anti-TNF IgG1antibody)</td>
<td>Abbott</td>
<td>Crohn’s disease</td>
<td>Phase 3</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MRA (humanized anti-IL 6 receptor antibody)</td>
<td>Roche</td>
<td>Crohn’s disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Anti-inflammatory cytokines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 10</td>
<td>Schering Plough</td>
<td>Crohn’s disease</td>
<td>Failed phase 3/failed phase 2</td>
</tr>
<tr>
<td>Interleukin 11</td>
<td>Instituto Genético</td>
<td>Crohn’s disease</td>
<td>Failed phase 2</td>
</tr>
<tr>
<td><strong>Anti-leukocyte adhesion therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab (humanized monoclonal IgG4 antibody against integrin α 4)</td>
<td>Elan Farmaceuticos y Biogenicos</td>
<td>Crohn’s disease</td>
<td>Phase 3, marketing suspended</td>
</tr>
<tr>
<td>Antegrem MLN-02,LDP-02 (humanized monoclonal IgG1 antibody against integrin ε4-β7)</td>
<td>Millenium Pharmaceuticals</td>
<td>Crohn’s disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Alcaftor, lis 2302 (antisense oligonucleotide for ICAM)</td>
<td>Isis Pharmaceuticals</td>
<td>Crohn’s disease</td>
<td>Failed phase 3</td>
</tr>
<tr>
<td><strong>Th1 polarization inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-interleukin 12 antibody (humanized monoclonal IgG1 antibody against p40 IL-12 receptor)</td>
<td>Abbot</td>
<td>Crohn’s disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Fontolizumab (humanized anti-interferon gamma antibody)</td>
<td>Protein Design Labs</td>
<td>Crohn’s disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Scarring and epithelial replacement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatropin (human recombinant growth hormone)</td>
<td>Eli Lilly</td>
<td>Crohn’s disease</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Immunostimulation</strong></td>
<td></td>
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<tr>
<td>Filgrastim (human recombinant granulocyte colony stimulating factor)</td>
<td>Amgen</td>
<td>Crohn’s disease</td>
<td>Phase 2a</td>
</tr>
<tr>
<td>Sargamostim (human recombinant granulocyte-macrophage colony stimulating factor)</td>
<td>Berlex</td>
<td>Crohn’s disease</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
### Table II. Mechanism of action for the various anti-TNF agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Biologic structure</th>
<th>Binds soluble TNF</th>
<th>Binds transmembrane TNF</th>
<th>Binds complement</th>
<th>Mediates ADC</th>
<th>Causes T-cell apoptosis</th>
<th>Effective in non-selected patients</th>
<th>Effective only in patients with high CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Chimeric monoclonal IgG1 antibody</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Fusion protein made up of an IgG1 antibody bound to two humanized soluble p75 TNF receptors</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Fully humanized monoclonal anti-TNF antibody</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>CDP870</td>
<td>Humanized Fab fragment bound to PEG</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CDP571</td>
<td>Humanized monoclonal IgG4 antibody</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Onercept</td>
<td>Fully humanized, TNF-binding P55 TNF receptor</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>


### Table III. Main biologic therapies under assessment for the treatment of ulcerative colitis

<table>
<thead>
<tr>
<th>Drug and biologic target</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Research phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (chimeric monoclonal anti-TNF IgG1 antibody)</td>
<td>Centocor and Schering Plough Celloch</td>
<td>Ulcerative colitis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>CDP571 (humanized monoclonal anti-TNF IgG1 antibody)</td>
<td>Celltech</td>
<td>Ulcerative colitis</td>
<td>Failed phase 4</td>
</tr>
<tr>
<td>Anti-inflammatory cytokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 10</td>
<td>Schering Plough</td>
<td>Ulcerative colitis</td>
<td>Failed phase 2</td>
</tr>
<tr>
<td>Anti-leukocyte adhesion therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab (humanized monoclonal IgG4 antibody against integrin 4)</td>
<td>Elan Farmacéticos y Biogénicos</td>
<td>Ulcerative colitis</td>
<td>Phase 3, marketing suspended</td>
</tr>
<tr>
<td>Antegren MLN-02, LDP-02 (humanized monoclonal IgG1 antibody against integrin α4-β7)</td>
<td>Millenium Pharmaceuticals</td>
<td>Ulcerative colitis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Alicaforsen, Isi 2302 (antisense oligonucleotide for ICAM)</td>
<td>Isis Pharmaceuticals</td>
<td>Ulcerative colitis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>T-cell proliferation inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humanized daclizumab (antibody against interleukin 2 receptor)</td>
<td>Protein Design Labs</td>
<td>Ulcerative colitis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Basiliximab (chimeric antibody against interleukin 2 receptor)</td>
<td>Novartis</td>
<td>Ulcerative colitis</td>
<td>Phase 2a</td>
</tr>
<tr>
<td>Anti-CD3 therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visilizumab (anti-CD3 antibody)</td>
<td>Protein Design Labs</td>
<td>Ulcerative colitis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Epithelial replacement and repair</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Epidermal growth factor</td>
<td>Heber Biotec</td>
<td>Ulcerative colitis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Keratinocyte growth factor (repifermin)</td>
<td>Human Genome Sciences</td>
<td>Ulcerative colitis</td>
<td>Failed phase 2</td>
</tr>
</tbody>
</table>

must point out that the number of patients with a post-infusional reaction is relatively small (1-5%) (5), and only rarely IgE-mediated hypersensitivity develops, which precludes continued infliximab use (35). In general, reactions may be avoided or controlled with a previous or subsequent administration of acetaminophen, anti-histamines, or corticoids. Response attenuation or extinction regarding infliximab is a complex problem with several factors potentially implicated; one such factor would be ATI development, but otherwise results from other overexpressed proinflammatory cytokines or obstruction development (36,37).

These problems led to the development of new anti-TNF drugs, including CDP571 and CDP 870, etanercept and oncept, and adalimumab.

**CDP 571**

CDP 571 is a humanized, chimeric, monoclonal IgG4 antibody against TNF-α that is administered intravenously and whose mechanism of action is summarized in table II. Phase-2 studies failed to confirm the expected efficacy, and production stopped in Celltech (38,39).

**CDP 870 (certolizumab pegol)**

This is a Fab fragment of a humanized monoclonal antibody that is linked to a polyethylene glycol molecule in order to increase biologic half-life. It is administered subcutaneously. CDP 870 binds soluble and membrane-associated TNF, but being a Fab fragment induces no antibody-mediated cytotoxicity or apoptosis in T lymphocytes. A phase-2 study that randomized 292 patients with active CD to receive either placebo or CDP 870 subcutaneously at a dose of 100, 200, or 400 mg on weeks 0, 4, and 8 showed that 400 mg were more effective and induced earlier clinical responses at 2 weeks; however, no significant results were obtained after 12 weeks (40). When data were later analyzed by patient subgroup, those with C-reactive protein > 10 mg/dl showed significantly better responses at all doses versus placebo (41). A small phase-2 study where the drug was intravenously administered showed no significant results in association with placebo (42). Two large phase-3 studies have been currently performed in patients with active CD, but results have not been reported yet. In all studies the drug was well tolerated, both through the subcutaneous and the intravenous route.

**Etanercept and oncept**

TNF-α exerts its proinflammatory effect on binding membrane receptors p55 and p75. Etanercept is an anti-TNF-α agent approved for rheumatoid arthritis treatment. It is a human protein resulting from the binding together of an Fc fragment from a human IgG1 antibody and two human TNF p75 receptors. Oncept is a recombinant form of soluble TNF p55 receptor. Both drugs act by binding the soluble and transmembrane form of TNF-α. Phase-2 studies failed to prove it effective for CD treatment (43,44).

**Adalimumab**

This is a totally humanized recombinant monoclonal IgG1 antibody that specifically binds soluble and transmembrane TNF-α, binds complement, favors antibody-mediated toxicity, and induces T-cell apoptosis. Adalimumab is currently approved for use in the treatment of rheumatoid arthritis, psoriatic arthritis, and early-onset arthritis. In the last few years a number of studies (45-47) in patients not tolerating infliximab or having lost response to this agent were reported. These studies demonstrated no cross hypersensitivity reactions between both drugs, and showed that most patients responded clinically. A phase-3 study of 299 patients with CD to explore dose-response showed that blood therapeutic levels are superimposable to therapeutic concentrations in rheumatoid arthritis (48). We may currently conclude that this drug may be safely administered to patients intolerant to infliximab or who no longer respond to infliximab, is well tolerated, may be administered through the subcutaneous route, and has side effects, the most common including local reactions at administration sites. However, the appropriate dosage and administration regimen is unknown. Development of antibodies against adalimumab has been described in treated patients with rheumatoid arthritis (36), but their role in drug response and potential hypersensitivity reactions is currently unknown regarding patients with CD. Only 25% of patients with a loss of response to infliximab have positive antibodies against the latter drug, but we do not know whether this group of patients will indiscriminately respond to adalimumab.

Further studies are needed to reveal the role of this antibody in CD.

**Proinflammatory cytokine receptor inhibitors**

**Interleukin 6 (IL-6)**

IL-6 is a proinflammatory cytokine, and both its and its receptor (IL-6R) levels correlate with CD activity in humans and animal models. IL-6, upon binding its soluble receptor, stimulates an antiapoptotic gene cascade in T cells, which leads to T-cell accumulation in the bowel mucosa, and a perpetuation of inflammatory response (9).

A monoclonal antibody against IL-6R has been developed and used in 36 patients with active CD refractory to
conventional treatment. Early results are encouraging and the drug was well tolerated, but further use in a greater number of patients is still needed to reveal its real usefulness (49).

**Anti-inflammatory cytokines**

**Interleukin 10 (IL-10)**

IL-10 is an anti-inflammatory cytokine that inhibits IL-2 and IFNγ production in Th1 cells, and decreases IL-12 production by macrophages. The role of IL-10 in IBD was demonstrated by the fact that IL-10 knockout mice develop chronic enterocolitis (50), and the IL-10 administration to these mice prevents such development. If IL-10 is administered when the disease is already established, illness improvement but not a full cure ensues (51). An initial dose-response study (phase 2a) using IL-10 at 0.5, 1, 5, 10 or 25 µg/kg i.v. for 7 days showed results superior to those seen with placebo in 46 patients with active, treatment-refractory CD (52). However, three subsequent phase-3 studies in 797 patients showed no significant differences versus placebo, and IL-10 is currently of no use through the systemic route (53,54).

The discovery of IL-10 receptors in enteric cells has suggested the potential topical use of this cytokine, as this route would increase its concentration at the colonic mucosa thus improving efficacy. In experimental animals the oral administration of genetically-modified, IL-10-secreting lactobacilli, and the administration of IL-10 in an enema (using an adenoviral vector, or within jelly microspheres) have shown encouraging results (55-57). Encouraging results have also been reported in a small group of patients with CD who received genetically-modified, IL-10-producing lactobacilli (58).

**Interleukin 11 (IL-11)**

Interleukin 11 (IL-11) is a cytokine produced by mesenchymal cells with both thrombopoietic and anti-inflammatory actions through NFκB inhibition, and secondarily through proinflammatory cytokine inhibition. In addition, it has a protective effect on the intestinal mucosal barrier.

Based on these findings, Sand et al. (59,60) assessed the efficacy of recombinant IL-11 as administered through the subcutaneous route in the treatment of 224 patients with CD, and found no significant differences versus placebo. These authors witnessed the development of thrombocytosis, which was more common in patients receiving higher doses or in those with shorter dosage intervals, which may represent a serious side effect in an already thrombogenetic disease.

IL-11 has been seen to maintain its anti-inflammatory and repairing action when topically administered. When orally administered to healthy subjects, IL-11 has been seen to not be absorbed by the intestine, thereby decreasing its adverse effects. A phase-2 trial is ongoing, which results have not been reported yet.

**Therapies based on the inhibition of cell adhesion**

Lymphocyte migration and recruitment by the intestinal mucosa is an essential step for inflammation onset and perpetuation in IBD. The selective blockade of adhesion molecules involved in this process was achieved by using the monoclonal antibodies anti-integrin α4 (natalizumab) and anti-integrin α4β7 (MLN-02, LDP-02), as well as antisense oligonucleotides against the inter-cellular adhesion molecule 1 (ICAM-1).

**Natalizumab**

This is a chimeric recombinant human IgG4 antibody against the α4-integrin molecule. After the demonstration of efficacy and safety in preclinical and phase-2 studies (10,27), a phase-3 study (ENACT-1) was performed including 248 patients with moderate-severe CD. These subjects were randomized to receive the following four regimens: a) two placebo infusions; b) one natalizumab 3 mg/kg infusion followed by placebo; c) two 3 mg/kg infusions or; and d) two natalizumab 6 mg/kg infusions for four weeks. Patients receiving natalizumab showed better response and remission rates versus those in the placebo group, but never reaching statistical significant differences. Significant differences were only seen for quality of life and decreased C-reactive protein levels. Best results were obtained in patients receiving two natalizumab infusions at 3 and 6 mg/kg, respectively. Response was fast in those receiving two infusions, began at two weeks after the first infusion, and lasted for 12 weeks. The drug was well tolerated with no serious side effects, but 13 patients (7%) developed antibodies against the drug, and 2 of them had acute infusional reactions. These results were similar to those initially obtained with infliximab. The ideal dose is currently thought to consist of two 3 mg/kg i.v. infusions four weeks apart (61). The results of the ENACT-2 study were recently reported, with the study aiming at determining the drug’s capability to maintain clinical response/remission for 12 months in patients having responded to treatment in the ENACT-1 study. Overall results were as follows: natalizumab is a drug achieving clinical response/remission rates significantly superior to those of placebo, and is useful to induce clinical response/remission in patients not responding to infliximab and resistant to immunosuppressive therapy (azathioprine, 6-MP, methotrexate) (62-64). However, natalizumab was withdrawn following the report of three progressive multifocal leukoencephalopathy cases, two of them in patients with multiple sclerosis who
simultaneously received IFN-β, and one in a patient with CD (63).

MLN-02 (LDP-02)

MLN-02 is a recombinant human IgG1 antibody that is made up of the CDR regions of a murine antibody against human integrin α4β7, and a human IgG1 fragment. It blocks the interaction between lymphocyte integrin α4β7 and ligand MadCAM-1. Phase-2 studies (66) failed to show effectiveness in the treatment of active CD. However, following an analysis of results, doses employed are believed to be suboptimal, and patients where lymphocyte α4β7 receptors are ultimately saturated are thought to enter remission more likely. Further studies are needed to establish therapeutic utility.

ISIS 2302 (alicaforsen)

Integrin αLβ2 and its ligand ICAM-1 are essential for leukocyte recruitment to inflammation sites. Tissue ICAM-1 expression correlates to IBD activity. ISIS 2302 is a 20-base oligodeoxynucleotide phosphothioate that binds to the 3' untranslated region of human mRNA for ICAM-1. The dimer made up of ISIS 2302 and ICAM-1 mRNA is cleaved by a class of cellular RNAses, which results in diminished cellular ICAM-1 expression.

A placebo-controlled phase-2a pilot study showed encouraging results (67). However, two subsequent studies—one with 75 patients (phase 2), the other with 299 patients (phase 3)—failed to reveal this drug’s efficacy (10,27). When results were analyzed by subgroup, the subgroup including women with highest ISIS 2302 levels was seen to exhibit higher response rates, which suggests higher efficacy when administered at higher doses. The drug was well tolerated, and local reaction at the site of injection was most common among side effects. Three patients developed antibodies against the drug, and two of them lost clinical response. On examining the cytokine profile of the colonic mucosa lamina propria in patients showing improvement with anti-IL-12 agents, a decrease in IL-12, IFN-γ, and TNF-α secretion by mononuclear cells was seen. No definitive conclusions may be reached from available results, and further studies are needed (69).

Anti-interferon γ (fontolizumab, huzab)

IFN-γ production by Th1 cells facilitates immune response polarization towards the Th1 pathway, and inhibits Th2 cell proliferation. Fontolizumab is a human monoclonal antibody against IFN-γ. A phase-2 study where 196 patients received fontolizumab at doses of 1 mg/kg/s.c. or 4 mg/kg/s.c. showed no efficacy (70). A second phase-2, multicenter study where 133 patients received 4 or 10 mg/kg intravenously showed that, four weeks after the initial dose, 31% of patients had experienced clinical improvement, and 38% had experienced clinical remission; 96 of these patients received a second dose at 4 weeks after the initial dose, which induced clinical improvement in 53 and 59% at days 56 and 84 after the last perfusion, respectively (71). Further studies are needed to establish the role of fontolizumab for induction and maintenance in CD.

Anti-interleukin 18 (anti-IL 18)

IL-18 is a cytokine produced by activated macrophages and epithelial cells that, similar to IL-12, favors Th1 differentiation. A human anti-IL18 antibody has been synthesized that has been effective in mice to decrease inflammation in sodium sulphate-induced colitis (72); however, no studies have been performed in humans so far.

T-cell activation inhibitors

T-cell activation is a complex process depending upon other simultaneous processes, including the recognition of antigens presented by antigen-presenting cells (APCs),
the binding of co-stimulating molecules, and cytokine secretion by APCs. When T lymphocytes interact with an APC and the antigen is recognized, ligand CD40 is expressed on the surface of lymphocytes; this ligand binds APC CD40 receptor, which stimulates the expression of molecule B7 in APCs; this molecule in turn interacts with CD28 receptors in lymphocytes. A potential treatment could be based on the inhibition of T-cell activation by antibodies against these antigens. In this respect, a monoclonal antibody against CD40, IDEC-13, was developed, but phase-2 studies had to be abandoned because of thromboembolic disturbances (10).

**Anti-CD4 therapy**

Various observations have been reported showing a complete remission of Crohn’s disease in HIV-infected patients. Based on such observations a number of anti-CD antibodies have been developed, including CM-T412, Max-1645 and BF-5. Four phase-1 studies have been reported showing varying results in patients with CD and UC. The most relevant side effect was a decrease in CD4 lymphocytes, but this was not associated with opportunistic infection development. Further studies are needed to establish the therapeutic usefulness of these antibodies (10,73).

**Growth factors**

Growth factors are cytokines that stimulate tissue scarring and extracellular matrix synthesis, which contribute to tissue healing and, under abnormal conditions, pathologic fibrosis. In CD growth hormone has been used to reverse inflammation-related catabolic processes and to reduce mesenteric fat. A phase-2 study where 19 patients with moderate-to-severe CD received somatotropin (human recombinant granulocyte-colony stimulating factor, GM-CSF) and sargramostin (a human recombinant granulocyte-macrophage-colony stimulating factor). This therapy is aimed at stimulating the innate immune system, rather than suppressing the inflammatory response. Intestinal epithelium CD4+ lymphocytes and Paneth cells express GM-CSF receptors; these findings suggest that GM-CSF may play a key role in the maintenance of innate immunity at the intestinal barrier (76). Phase-2a studies have shown encouraging results (77,78). A randomized trial has been recently reported where 124 patients with moderate-severe active CD received either sargramostin 6 µg/kg subcutaneously or placebo for 56 days. Patients were allowed to continue with their aminosalicylates or antibiotics; however, immunosuppressing therapy (azathioprine, 6-MP or methotrexate) and infliximab were discontinued 4 and 12 weeks prior to onset, respectively. While the group receiving sargramostin had a greater number of patients in remission/response, differences reached no statistical significance. Overall, the drug was well tolerated, and most common side effects included local reactivity at injection sites, bone pain, and elevated WBC count with neutrophilia. Three patients had serious adverse events: a female patient developed serious migraine; another female subject had anorexia, weakness and lethargy, and a third one had a demyelinating illness. Regarding neutralizing antibody development, these became positive in one patient only (79).

**Immunomodulators**

Interferons are a group of cytokines naturally produced by virus-infected cells that have antiviral, immunomodulating, and anti-tumor properties. Cell response to interferons seems to be mediated by the JAK-STAT (Janus Kinase-Signal Transducers and Activators of Transcription) pathway. Non-controlled studies in patients with CD receiving INF-α2b have shown response rates ranging from 30 to 50%, and in patients treated with INF-α2a response rates of 50% (80,81). A pilot study in 8 patients with CD showed improvement in 80% of treated cases (82). Obviously, these are interim results that require confirmation from larger studies.

**BILOGIC THERAPIES IN ULCERATIVE COLITIS**

**Anti-TNF (tumor necrosis factor) therapy**

TNF-α, as in CD, seems to play a relevant role in UC. TNF-α levels have been shown to be highly elevated in the colonic mucosa of patients with UC; it has also been
seen that mononuclear cells in the lamina propria produce large amounts of TNF-α, and that this cytokine’s fecal and urine levels are very high in these patients.

To this day, results found in the literature regarding infliximab effectiveness in patients with UC are varying (83-88). Recently, however, the results from two multicenter, controlled, phase-3 studies—ACT-I and ACT-II—designed to assess infliximab effectiveness in UC—were reported. ACT-I (89) is a randomized clinical trial in 364 patients with moderate-severe UC unresponsive to corticoids, azathioprine, and 6-mercaptopurine. These patients were assigned to one of three groups: a) placebo, b) infliximab 5 mg/kg/i.v., and c) infliximab 10 mg/kg/i.v. at weeks 0, 2, and 6, and then every 8 weeks up to week 46. In both groups receiving infliximab clinical response, clinical remission, mucosal healing, and steroid discontinuation rates were significantly higher versus the placebo group. ACT-II was a multicenter, randomized study in 364 patients with UC resistant to at least one of the following therapies: 5-ASA, steroids, azathioprine or 6-mercaptopurine. Patients were divided up in three groups: a) placebo; b) infliximab 5 mg/kg/i.v.; and c) infliximab 10 mg/kg/i.v. at weeks 0, 2, 6, 14 and 22. Results obtained were superimposable to those seen in ACT-I (90). Safety profile was similar to that of infliximab in CD. Both studies concluded that infliximab is effective and safe for inducing clinical response and maintaining clinical remission in patients with moderate-to-severe ulcerative colitis resistant to other therapeutic options. Treatment results in mucosal healing and allows steroid discontinuation.

**RDP-58**

This is an anti-inflammatory decapeptide that blocks p38 and the p38 MAPK and JNK pathways, and that inhibits TNF-α, interferon γ, IL-2 and IL-12 production. In a phase-2 study, 127 patients with mild-moderate active UC were randomized to receive placebo or RDP 58 100, 200 or 300 mg/day in oral solution for 28 days (91). Patients receiving 200 and 300 mg achieved clinical remission in 72 and 70% of patients, respectively, versus 40% in the placebo group (p = 0.0006). Histological indices also improved in the groups receiving 200 and 300 mg (p = 0.0008). No significant differences in side effects were seen between groups. RDP 58 seems to be effective and safe at a dose of 200 mg/day, and side effects are few.

**Transcription factor inhibitors**

Transcription factor NFκB plays a very important role in the control of the intestinal immune system, and regulates gene transcription for various proinflammatory cytokines (IL-1β, IL-2, IL-12, and TNF-α), cell surface receptors, transcription factors, and adhesion molecules (ICAM-1). Sulfasalazine and mesalamine are non-selective NFκB inhibitors. NFκB overexpression has been demonstrated in the colon of patients with CD or UC. The enema administration of an antisense oligonucleotide phosphothioate against NFκB p65 subunit considerably reduces proinflammatory cytokine production in experimental animals (10). A small study has been reported as an abstract where 11 patients with CD or UC refractory to conventional therapy showed clinical, endoscopic and histological improvement following a single-dose enema administration of this antisense oligonucleotide with no infectious complications (92). Further studies are needed to assess the real usefulness of these oligonucleotides.

**Anti-leukocyte adhesion therapies**

MLN-02 is an already-mentioned humanized monoclonal antibody that specifically recognizes integrin α4β7 heterodimers, which provides it with tropism for gastrointestinal tract vessels. In a double-blind phase-2 study versus placebo, where 181 patients received two doses of either placebo or MLN-02 0.5 mg/kg/i.v. or 2 mg/kg/i.v. 4 weeks apart, remission rates of 15, 33 and 34% were seen at week 6, respectively (p = 0.03), with response rates of 33, 57 and 66%, respectively (p = 0.001) (93). A multicenter, randomized, double-blind study was recently reported, where 181 patients diagnosed with UC were divided into three groups: a) placebo; b) MLN-02 0.5 mg/kg/i.v.; and c) MLN-02 2 mg/kg/i.v. on days 1 and 29. In both groups the drug was more effective than placebo to induce clinical remission, and differences reached statistical significance. Endoscopic and histological improvement also occurred in treated patients. The drug was well tolerated. Three patients developed serious adverse events. One had an acute infusional reaction with angioedema; this female patient had antibodies against the drug (1: 3125 titers). Another patient developed cytomegalovirus infection, and yet another subject had lobar pneumonia. Overall, 44% of patients treated with MLN-02 develop antibodies against this drug, with titers above 1: 125 in 24% of cases. These patients show decreased α4β7 binding sites saturation, albeit clinical remission was not influenced by these antibodies. Interestingly, in contrast to natalizumab, no associated lymphocytosis develops. This fact would support the hypothesis that it selectively targets a small lymphocyte population involved in intestinal immunity, thereby lacking natalizumab's systemic effects (94).

Alicaforsen (ISIS 2302) administered in enema form may be useful in the management of left UC and antibiotic-resistant chronic pouchitis (95,96). A double-blind, placebo-controlled phase-2 study was recently reported where 120 patients with left active UC received alicaforsen...
en enemas at various doses. Maintenance was performed with placebo when UC was inactive. Final conclusions indicate that alicaforsen enemas at a dosage of 240 mg/qid for 6 weeks significantly reduces UC activity, with mean response duration being 6 months (97). This drug is well tolerated. Pharmacokinetic studies show minimal systemic absorption when the drug is administered in enema form (98).

**T-cell proliferation inhibitors**

**Antibodies against IL-2 receptor**

IL-2 is produced by Th1 cells. When this cytokine binds its specific receptor on T-cell membranes, it induces a clonal expansion of effector T cells. IL-2 seems to play a role in the induction of steroid resistance in T cells. Lymphocytes from corticoid-resistant patients have been seen to produce higher IL-2 levels, and steroid-sensitive lymphocytes become resistant when IL-2 is added to the culture medium (99,100). In addition, cell IL-2 activation pathways interfere with glucocorticoid pathways (10).

Intravenous cyclosporin, which inhibits IL-2 production through the calcineurin path, is effective in the management of serious corticoid-resistant UC flare-ups. This has led to the development of monoclonal antibodies to block IL-2 receptors. Two such anti-IL 2 antibodies are currently being investigated: daclizumab and basiliximab.

**Daclizumab**

This is a human recombinant monoclonal IgG1 antibody that binds with high affinity to the IL-2 receptor and prevents IL-2 from binding it.

In a phase-2a study 10 patients with refractory UC were administered two 1 mg/kg doses 4 weeks apart. Eight of 10 patients showed clinical improvement, and 5 of these achieved remission at week 4 after the last dose (101). Clinical improvement preceded endoscopic and histological improvement (102). A new phase-2 study is ongoing with a high number of patients (10,27).

**Basiliximab**

This is a human chimeric monoclonal antibody that also binds IL-2 receptor. In a phase-2 study including 10 patients with corticoid-resistant UC who were treated with a single dose of basiliximab 40 mg/i.v., clinical remission was achieved in 9 cases within the first week, albeit 8 relapsed at week 9. The results from this study led to consider its potential use as a “bridge” therapy in corticoid-resistant patients, in order to avoid colectomy and steroid-related side effects (103). Antibodies against this drug have been identified, and thus repeat infusions may be associated with hypersensitivity reactions and loss of effectiveness.

**Therapies against CD3**

**Visilizumab**

This is a humanized monoclonal IgG2 antibody against the CD3 region of T-cell receptors, which induces apoptosis in activated T cells. In a phase-1/2a study where 7 patients with serious, corticoid-resistant UC were included 5 patients achieved clinical and endoscopic remission after receiving 15 µg/kg/day i.v. for two days. The most relevant and common side effect (63%) was a cytokine release syndrome (nausea, headache, shivering, fever, joint pain), which develops a few hours after infusion, is transient and can be easily managed (104). A very significant elevation of TNFα, IL-6, IL-8, IL-10, MCP-1, IP-10 and VEGF has been seen to develop within two hours of visilizumab intravenous administration. Minor though significant elevations are seen in IFN-γ, IL-2 and FGF-β levels. Except for IL-10 and IP-10, all cytokine levels return to baseline at 24 hours, and do not rise again following a second dose. IL-10 rises anew with the second dose, and returns to normal on day 8. More relevant is the behavior of T-cell chemokine IP-10, whose levels inversely correlate to T-cell counts. Lymphocyte count will not recover until this chemokine levels are back to baseline, and this effect is thus thought to be a key element for visilizumab efficacy (105). This transient decrease in peripheral-blood T-cell count lasts for 2 to 6 weeks. Before visilizumab administration the presence of occult infection by the Epstein-Barr virus should be investigated, and serial screenings for this virus DNA will be performed during therapy. Treatment will not be administered or will be discontinued if DNA is positive or titers rise. A reverse correlation has been seen between decreased T-cell numbers, presence of Epstein-Barr virus, and lymphoproliferative disease development following bone marrow transplantation. Studies in patients with UC showed none of these side effects, but patient numbers are smaller (105,106). Further studies should be presently performed to establish this drug’s true role.

**Growth factors**

**Keratinocyte growth factor (repifermin)**

Fibroblastic factor 7, also called keratinocyte growth factor 1, is a potent stimulator of epithelial cell growth in the gastrointestinal tract. Repifermin (keratinocyte growth factor 2) is a homologous of factor 1. In a phase-2 study performed in patients with UC it failed to prove ef-
fective (107). Phase-1/2 studies with trefoil factor enemas in association with oral 5-ASA in patients with mild-moderate left UC have also failed to prove effectiveness (108).

**Epidermal growth factor**

This is a peptide produced by salivary and Brunner glands that stimulates cell proliferation in the gastrointestinal tract. A phase-2 study randomized 24 patients with left UC or proctitis in one of two groups: a) EGF enema (8 µg in 100 ml inert solution); or b) placebo for 14 days; patients simultaneously received concomitant therapy with mesalamine, corticoids or immunosuppressors. After 2 weeks, 10 of the 12 patients (83%) included in the EGF group were in remission, while this only happened in one subject (8%) in the placebo group (p < 0.001) (109). Further studies are needed to confirm these results and assess drug safety, as EGF induces the expression of protooncogenes such as c-fos and c-jun, and hence may increase the risk for tumor development (10).

**Immunomodulators**

The role of interferons α and β has already been assessed in the treatment of UC. In a study performed in 32 patients with mild-moderate left colitis, interferon α2a proved as effective as steroid enemas (110). A study with pegylated interferon α2b showed that this drug was poorly tolerated by patients (111).

Interferons β1a and β1b have also been assessed with encouraging results (112,113), but further studies are needed to establish their true role.

**CONCLUSIONS**

Currently, the only effective and widely accepted biologic therapy for the treatment of intraluminal, fistulizing CD, both for remission induction and maintenance, is infliximab. The role of other monoclonal antibodies such as adalimumab is not clearly established. It could be deemed an alternative for patients with allergic reactions to infliximab, and for those with lost response because of anti-infliximab antibody development. Anti-integrin c4 therapies, despite encouraging results in phase-3 studies, are still unavailable, as their marketing authorization was held back in view of a number of reports regarding progressive multifocal leukoencephalopathy cases. Immunostimulating therapy may be highly relevant in the near future, as it represents a novel strategy against disease with the inclusion of granulocyte-monocyte colony-stimulating factors.

Regarding ulcerative colitis, results from the ACT-1 and ACT-2 studies showed that infliximab is also useful for the management of serious UC flare-ups not responding to standard treatment, which will lead to a revision of therapeutic algorithms, where this drug should be given preference before intravenous cyclosporin. In the next few years, the role of anti-CD3 drugs (vilistilizumab), T-cell inhibiting therapies, and epithelial repair and healing stimulating factors will be established.

**REFERENCES**


66. Yacyshyn BR, Chey WY, Goff J, et al. Double blind, placebo controlled trial of the remission inducing and steroid sparing properties of...
88. Probert CS, Hearing SD, Schereiber S, et al. Infliximab in moderate-
87. Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not
86. Eldelwein AP, Cuffari C, Abadom V, et al. Infliximab efficacy in pedi-
84. Gornet JM, Couve S, Hassani Z, et al. Infliximab for refractory ulcer-
80. Hanauer S, Baert F, Robinson M. Interferon treatment in mild to mo-
78. Korzenik J, Dieckgraefe B. Immunostimulation in Crohn's disease:
75. Solis Herruzo JA, Fernández Baya B, Villalta Castel E, et al. Dimi-
74. Slonim AE, Bulone L, Damore MB, et al. A preliminary study of
73. Dieckgraef BK, Korzenik JR. Treatment of active Crohn's disease with
71. Korzenik J, Dieckgraef B. Immunostimulation in Crohn's disease: results of a pilot study of G-CSF (R-Methug-CSF) in mucosal and
70. Hanauer S, Baert F, Robinson M. Interferon treatment in mild to mo-
67. Protein design Lab reports progress on two humanized antibodies at International Organization of Inflammatory Bowel Disease. Internet Press Release, 2004 (http://www.pdl.com).
47. Sina H, Nightingale J, West KP, et al. Epidermal growth factor ene-
46. Sumer N, Palabiyikoglu M. Induction of remission by interferon-alpha in patients with chronic active ulcerative colitis. Eur J Gastroente-