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Immunomodulator therapy of IBD

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MEDICAL therapy may help control the disease and improve the patient's quality of life in IBD. The conventional therapeutic armamentarium includes aminosalicylates, antibiotics, and corticosteroids. Unfortunately, many patients are either refractory or intolerant to these medications and for these patients surgery is often considered. The introduction of immunomodulator therapy has provided an alternative therapeutic option in the management of patients with IBD.

As shown in Table 1, the cellular arms of the inflammatory process, triggered by interleukin-1 (IL-1), offer many potential pathways for therapeutic intervention particularly in the treatment of patients with refractory IBD (1-2). In particular, the central role that T-cells and associated cytokines play in the pathogenesis of IBD is becoming well established. Activated mucosal T-cells can induce epithelial changes of IBD, probably related to release of T-cell-associated proinflammatory cytokines (IL-1,2,4,6,8 and 10), tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) that are capable of immune destruction (2-3). These and similar other steps can be inhibited by using immunomodular agents. For example, antimetabolites like azathioprine, 6-mercaptopurine, and methotrexate may inhibit nucleic acid synthesis in many inflammatory cells, especially T-cells. Cyclosporine and FK 506 more specifically inhibit mostly IL-2 mediated activation of T-helper cells, leaving T-suppressor cell function intact. These steps can now be selectively inhibited using agents such as specific monoclonal antibodies directed at molecules necessary in the activation of T-cells, synthetic peptides and antibodies targeted to block the action of cytokines (2).

ANTI-METABOLITES

Azathioprine and 6-mercaptopurine (6-MP) are purine analogs that inhibit the biosynthesis of purine ribonucleotides. Azathioprine is metabolized in vivo into 6-MP and subsequently converted to inactive 6-thiouric acid by xanthine oxidase. These agents have selective effects on T-cells and T-cell dependent responses. They also possess anti-inflammatory effects. The studies showed the effectiveness of these agents in the induction of remission, closure of fistula, and reduction of steroid requirement in refractory Crohn's disease (4-6). In addition, these agents were found to be beneficial at sustaining remission in patients with Crohn's disease (7-8). Similarly, they have been shown to be efficacious in the induction and maintenance of remission in patients with ulcerative colitis (9-10). These agents are slow-acting drugs that may require up to 3-6 months of treatment before clinical efficacy becomes apparent (4-6). The usual starting dose is 0.5-1.5 mg/kg/day. Reversible side-effects are leukopenia, hepatitis, pancreatitis and hypersensitivity reaction. Although a definite increase in risk for neoplasm has not been established, it would be prudent to avoid using these drugs in patients who are pregnant or are at an increased risk for developing neoplasms.

Methotrexate (MTX) is an inhibitor of dihydrofolate reductase important in the synthesis of DNA. It may also interfere with the activity of IL-1. Studies indicate that MTX given weekly as an intramuscular injection may be useful (25 mg once weekly) in improving symptoms and reducing requirements for prednisone in patients with IBD (11-12). Additional randomized trials and long-term prospective experience with MTX in IBD will enable us to assess its efficacy and risks (bone marrow depression, hepatotoxicity, interstitial pneumonitis and teratogenicity) and help determine its place in therapy.

CYCLOSPORINE and FK 506

Cyclosporine inhibits production of cytokines including 1L-2, 1L-3, 1L-4 and IFN-γ. Cyclosporine has a rapid onset of action and is useful for the induction of remission in refractory cases with Crohn's disease (13,14) and ulcerative colitis (15) in high dose i.v. regimen. Low dose oral regimen had no benefit in patients with Crohn's disease

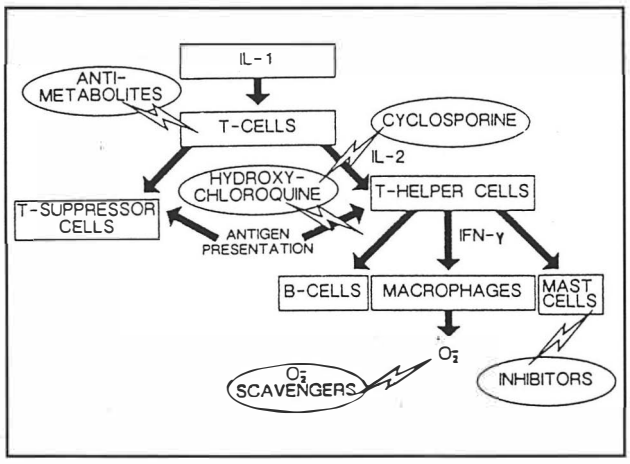

Figure 1. Cellular immune mechanisms in IBD and immunomodulator agents.

(16). The usual starting dose is 2-4 mg/kg/day i.v. and 8 mg/kg/day orally. Because of slow, incomplete, and variable intestinal absorption, particularly in patients with short bowel syndrome and active intestinal disease, a careful monitoring of blood levels is essential with oral administration. Moreover, patients with Crohn's disease relapse promptly when cyclosporine is discontinued that could perhaps be diminished by substituting other immunomodulator drugs. The value of cyclosporine therapy in patients with ulcerative colitis is also unclear at the present time. Appropriate candidates for i.v. cyclosporine may be patients with recently diagnosed ulcerative colitis who are not psychologically prepared for colectomy, those with left-sided colitis that has previously been easily controlled, ant those who are poor surgical risks. Side effects associated with the use of cyclosporine are significant, including nephrotoxicity, hypertension, paresthesia, grand mal seizure, hepatitis, hirsutism, colonic perforation and opportunistic infections (pneumocystic pneumonia, lung abscess, herpetic esophagitis and others). Toxic effects clearly limit the use of this drug. However, high dose cyclosporine therapy may be used in selected refractory IBD cases with other immunomodulators such as 6-MP, and MTX to maintain long-term remission and reduce drug induced toxicity.

FK 506 is a macrolide that has a potent immunosuppression effect and probably less toxicity than cyclosporine. Preliminary results suggest that FK 506 may have application in the treatment of pyoderma gangrenosum and chronic draining fistula in patients with IBD (17). Other studies are in progress with this promising agent in the medical management of IBD cases.

T-CELL APHERESIS

T-cell apheresis represents an alternative method of immunomodulator by a "non-specific" global reduction of circulating T-cells. This therapy resulted in long-term remission in up to 88% of patients with refractory Crohn's disease(18). Although the procedure is relatively safe, because of the high cost and labor-intensive nature of the therapy, it is unlikely to have a major role in the treatment of IBD.

BLOCKADE of T-CELLS ACTIVATION

Blockade of cellular infiltration has been achieved in several experimental models of GI disorders using monoclonal antibodies directed against molecules important in the activation of T-cells. Potential sites of blockade include T-cell receptors, CD_4 molecules on T-cells and major histocompatibility complex molecules of antigen-presenting cells. Preliminary studies using chimeric anti-CD_4 antibodies demonstrated clinical remission in over 80% of patients with minimal side effects (19-21). In addition, steroid reduction or discontinuation was achieved in two thirds of patients. However, clinical remission was limited to several months for most patients following treatment. Larger and controlled trials are needed in better defining the long-term efficacy and safety of this immunomodulator therapy.

CYTOKINE ANTAGONISTS

Increased gene expression of several cytokines, including 1L-1, 1L-2 and TNF has been found in surgical specimens, biopsies and cell preparations obtained from patients with either ulcerative colitis or Crohn's disease (22-24). Almost every drug used in the medical management of IBD is effective in inhibiting cytokine production. Corticosteroids have been shown to suppress the production of 1L-1, 1L-6, 1L-8 and TNF by macrophages, and 1L-2 and IFN secretion by activated T-lymphocytes. Sulfasalazine and 5-ASA have been shown to diminish the production of 1L-1, 1L-8 and TNF, as well as inhibit the upregulation of adhesion molecules induced by 1L-1 and TNF. Cyclosporine blocks 1L-2, 1L-3, 1L-4, 1L-5 and TNF production by mononuclear cells. These agents are non-specific cytokine antagonists (22-24).

Recent research has focused on developing specific target strategies designed to block inflammatory and lethal effects of cytokines. Specific blockade of 1L-1, 1L-2 and TNF can be effective in active IBD and can be used for preventing relapses.

A specific 1L-1 receptor antagonist (Antril) has been recently developed and tested in patients with septic shock, leukemia, psoriasis and rheumatoid arthritis. Studies with 1L-1, and 1L-2 receptor antagonists are currently at the stage of phase II trials in patients with IBD.

TNF is an important mediator of mucosal injury in Crohn's disease. The serum and stool TNF levels were elevated in patients with active Crohn's disease (25). A preliminary report on the use of monoclonal antibodies directed against TNF-α suggests a rapid and dramatic response in refractory Crohn's disease (26). Further studies are needed with these exciting and promising immunomodulator agents in patients with IBD.

OTHERS

Other immunomodulator agents may have a role in the treatment of patients with IBD are rapamycin, brequinar sodium, mycophenolic acid, discodermolide, ceflunomide and deoxyspergualin (2).

Multicenter, randomized, double-blind, placebo-controlled, crossover trial with fish oil in patients with ulcerative colitis resulted in reduction in rectal dialysate leukotriene B4 levels, improvements in histologic findings, and weight gain (27).

The availability of various immunomodulator agents should allow development of a combination drug regimen, similar to therapies already in use in the treatment of cancer, infectious disease and organ transplantation. Such "multiple-hit" strategy, designed to interrupt different stages in the inflammatory cascade simultaneously, should allow more effective immune modulation with less toxicity. Recent exciting advances suggest that immunomodulator agents with improved efficacy, reduced toxicity, and wider application will soon be widely available for medical management of patients with IBD.

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