

# Immunosuppressive agents in inflammatory bowel disease: Current status and future prospects

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F SHANAHAN, GC O'SULLIVAN, JK COLLINS. *Immunosuppressive agents in inflammatory bowel disease: Current status and future prospects.* *Can J Gastroenterol* 1994;8(6):383-387. Inflammatory bowel disease involves an interaction between genetic susceptibility factors and environmental triggers, and the intestinal injury is mediated by the host immunoinflammatory response. Identification of the mechanisms and mediators that contribute to the tissue injury has provided a sound rationale for the therapeutic use of immunosuppressive and immunomodulatory agents. The efficacy of traditional immunosuppressive drugs, such as the purine analogues in both Crohn's disease and ulcerative colitis, is well established. The major limitation of the use of these drugs is the delayed clinical response associated with their use. This has prompted an evaluation of other immunosuppressives, such as cyclosporine and related drugs, that have a more rapid onset of action. Convincing data indicate a distinct role for cyclosporine in certain patients with acute severe ulcerative colitis. However, despite early promising results with cyclosporine in Crohn's disease, recent results have been less encouraging. There is also uncertainty about the exact clinical role of cyclosporine because of concerns regarding long term toxicity. At present, many investigators regard cyclosporine as an interim measure for acutely ill patients. The challenge that remains is the development of novel immunomodulatory strategies that are specific for the mucosal immune system and that are based on recent advances in our understanding of the pathogenesis of mucosal inflammation. (Pour résumé, voir page 384)

**Key Words:** Crohn's disease, Cyclosporine, Immunosuppression, Purine analogues, Ulcerative colitis

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**I**NFLAMMATORY BOWEL DISEASE (IBD) has become an exciting area for both the clinician investigator and the basic researcher. Because of improvements in our understanding of the mechanisms and mediators involved in immune-mediated tissue injury, new and exciting forms of immunotherapy are emerging (1-3). The interacting elements that contribute to the pathogenesis of Crohn's disease and ulcerative colitis are summarized in Figure 1. Central to this schema is the concept that tissue damage is mediated by the mucosal immunoinflammatory response (4,5), and therein lies the rationale for the therapeutic use of immunomodulatory agents in these conditions. The various immunomodulatory strategies that have been reported in patients with IBD have been comprehensively reviewed elsewhere (2). What follows is a brief overview of the current status of immunosuppressive therapy in these disorders and a commentary on future prospects.

## PURINE ANALOGUES

The efficacy of the immunosuppressive purine analogues, azathioprine and its active metabolite, 6-mercaptopurine, is generally accepted in both

## Agents immunosuppresseurs dans la maladie inflammatoire de l'intestin

**RÉSUMÉ :** La maladie inflammatoire de l'intestin suppose une interaction entre facteurs génétiques prédisposants et déclencheurs environnementaux, et l'atteinte intestinale est modulée par les réponses immuno-inflammatoires de l'hôte. L'identification des mécanismes et des éléments modulateurs impliqués dans les lésions tissulaires justifient le recours à des agents immunosuppresseurs et immunomodulateurs. L'efficacité des agents immunosuppresseurs classiques, comme les antipurines, est bien établie, tant dans la maladie de Crohn que dans la colite ulcéreuse. La principale restriction touchant ces médicaments est la lenteur de la réponse clinique qui leur est associée. Cette lacune a conduit à l'évaluation d'autres immunosuppresseurs, comme la cyclosporine et d'autres médicaments apparentés, qui ont un début d'action plus rapide. Des résultats probants indiquent que la cyclosporine jouerait un rôle distinct chez certains patients atteints de colite ulcéreuse grave et aiguë. Les résultats prometteurs obtenus au début avec la cyclosporine dans la maladie de Crohn n'ont toutefois pas semblé se confirmer récemment. On ignore aussi quel rôle clinique précis peut jouer la cyclosporine, compte tenu sa toxicité à long terme. À l'heure actuelle, de nombreux chercheurs considèrent la cyclosporine comme une solution transitoire lors d'épisodes aigus. Le défi consiste à mettre au point de nouvelles stratégies immunomodulatrices spécifiques au système immunitaire des muqueuses et fondées sur les plus récents progrès accomplis au chapitre de notre compréhension de la pathogenèse de l'inflammation des muqueuses.

Crohn's disease and ulcerative colitis. Although a statistically significant benefit was not obtained in early studies including the National Cooperative Crohn's Disease Study, this can be attributed, in large part, to the relatively short duration of the trials (6). The latency or delayed onset of clinical efficacy of the purine analogues is now recognized. For both Crohn's disease and ulcerative colitis, the role of purine analogues in the treatment of active disease (7,8) and maintenance of remission (9,10) has been convincingly demonstrated in well designed controlled trials.

In practice, these drugs are particularly useful in chronically active Crohn's disease that is uncontrolled by corticosteroids and in patients requiring persistently high doses of steroids for control of disease activity (8). The chief limitation to their use is that they are slow acting, having a mean response time of approximately three months. Because of this, they have no role in the management of acutely ill patients. Also, when these drugs are prescribed it is necessary to continue steroid therapy until sufficient time has elapsed for the immunosuppressant effect to become established.

Although doses up to 2 mg/kg/day were initially used, most clinicians now use a single daily dose of 50 to 100 mg/day 6-mercaptopurine or 100 mg/day azathioprine. At these low doses, the purine analogues are remarkably well tolerated by patients with IBD, and bone marrow suppression is uncommon (11,12). Indeed, a very low frequency of adverse effects was found in a study of 396 patients with IBD followed for up to 18 years with a mean follow-up of five years (13). Pancreatitis occurs in approximately 3% of patients. This is probably a hypersensitivity event and precludes further use of either form of purine analogue. Occasionally these drugs produce a debilitating 'flu-like' illness that also appears to be a hypersensitivity phenomenon. The most important potential drug interaction may occur if purine analogues are given to patients taking the xanthine oxidase inhibitor, allopurinol. Purine analogues are metabolized by this enzyme and the concomitant use of allopurinol leads to dangerously high drug levels.

While opportunistic infections are uncommon in patients taking low dose 6-mercaptopurine, the most worrisome potential hazard of long term use of purine analogues is the possibility of

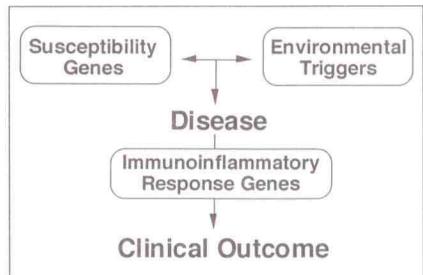


Figure 1) Factors contributing to the pathogenesis of inflammatory bowel disease

opportunistic neoplasia. Whether this is a real or theoretical risk is unclear. It may not be a significant problem with the low doses currently used (13). Many clinicians feel that it is wise to provide patients with a pamphlet that attempts to place in perspective the theoretical risks associated with these drugs in addition to their well established benefits.

### METHOTREXATE

The folic acid antagonist methotrexate has been found to have clinical efficacy in a variety of immunologically mediated disorders. The molecular mechanism by which methotrexate suppresses inflammation has recently been clarified (14). Its action involves a series of biochemical steps that promote the local release of adenosine. Adenosine has a variety of receptor-mediated immunomodulatory properties and inhibits the generation of toxic oxygen metabolites from neutrophils (14).

In an open study of patients with IBD, methotrexate was found to have a marked beneficial effect in some patients, particularly those with Crohn's colitis (15). Some of these patients were refractory to other treatments including steroids and 6-mercaptopurine, and responded to high dose methotrexate 25 mg intramuscularly over a 12-week period. Lower doses of methotrexate may also have a steroid-sparing effect (16). However, the clinical usefulness of methotrexate is limited by adverse effects which include leukopenia, gastrointestinal toxicity, hypersensitivity pneumonitis and hepatic dysfunction. For this reason, methotrexate is probably best reserved for pa-

tients who are refractory to or are intolerant of purine analogues.

### CYCLOSPORINE

The delayed induction of clinical response associated with purine analogues and methotrexate prompted an investigation of other immunomodulatory agents that might have a more rapid onset of clinical efficacy in acutely ill patients with IBD (17,18). Cyclosporine has a rapid onset of action, and is thought to suppress the induction and amplification of the immune response by inhibiting cytokine gene activation, particularly interleukin-2 (2,18,19). More recently, evidence for an additional mode of action has emerged that may have particular relevance in IBD. The cyclosporine binding protein cyclophilin, which had been considered to be an intracellular protein, has recently been shown to be a secretory product of activated macrophages. Furthermore, it has cytokine-like, preinflammatory activity with chemotactic effects on neutrophils and eosinophils (19-21). It has been proposed that this, rather than inhibition of cytokine production, may be the primary immunomodulatory mechanism of action of cyclosporine (22).

One placebo controlled study of oral cyclosporine in patients with Crohn's disease who were intolerant of or resistant to corticosteroids has been published (24). Of 37 patients, 22 (59%) improved on cyclosporine (5 to 7.5 mg/kg/day for three months) compared with 11 of 34 (32%) receiving placebo. The improvement was evident after only two weeks. However, the preliminary results of a second placebo-controlled trial that have been reported in abstract form suggest a cautious approach to the use of cyclosporine in Crohn's disease (24). This large ongoing Canadian study found that cyclosporine 4.8 mg/kg is ineffective as therapy for Crohn's disease, and may even have an adverse effect on disease activity in patients in remission.

Several factors limit the long term use of cyclosporine. These include its wide range of serious toxic side effects, the need for close monitoring of blood levels, the variable bioavailability

when given by the oral route and the frequency of drug interactions (2). Many clinicians regard the role of cyclosporine in acute Crohn's disease as a short term measure, at best. Whether it has an interim role before more slow-acting drugs such as 6-mercaptopurine take full effect needs to be assessed.

In contrast to Crohn's disease, cyclosporine appears to have a rapid and dramatic beneficial effect in patients with acute severe ulcerative colitis (25,26). In a preliminary open study of patients with severe ulcerative colitis who had failed to respond to intravenous steroids over 10 days, treatment was supplemented with intravenous cyclosporine 4 mg/kg/day. Remission was achieved in about 80% of the patients and surgery was avoided (25). Similar results were found in a subsequent double-blind trial. In fact, the trial was halted after 82% of the patients on cyclosporine responded whereas none of those on placebo improved (26). For patients with severe colitis who have not responded to traditional treatment with steroids and who are either not suited or not psychologically ready for colectomy, cyclosporine offers a welcome new option.

Topical enema preparations of cyclosporine have also been used in patients with resistant proctitis (27,28). However, although several open studies have been encouraging, a recent controlled trial of cyclosporine enemas in patients with mild to moderate ulcerative colitis failed to show a significant therapeutic benefit (29).

### OTHER IMMUNOMODULATORY STRATEGIES

The introduction of newer immunosuppressive drugs, such as the macrolides, rapamycin and FK506, may eclipse cyclosporine in clinical use during the next decade (2,30). Studies of FK506 in IBD are already underway (31). Its mode of action is similar to that of cyclosporine but it is approximately 100-fold more potent. Its toxicity is also likely to be similar, although early data have suggested that it occurs with a lower frequency than with cyclosporine. Its efficacy in intestinal transplantation has been particularly

impressive but whether this implies a greater specificity for the intestinal mucosal immune system than occurs with cyclosporine is not clear (32).

Intravenous immunoglobulin therapy appears to have a beneficial effect in a variety of immunologically mediated disorders although its mechanism of action is uncertain. In a recent open study of patients with IBD, some patients appeared to benefit (33). This is a cumbersome and expensive form of therapy and is unlikely to eclipse other therapeutic strategies. The same limitations apply to the use of T cell apheresis even though its efficacy in Crohn's disease appears impressive from the results of a recent open study (34). A similar outcome can now be achieved with monoclonal antibodies to specific T cell subsets (35).

Cytokine modulation and antagonism is perhaps one of the more exciting recent approaches to therapeutic immunomodulation. Cytokines are the regulatory and effector intercellular messenger molecules of the immune response. They are, thus, ideal targets for selective immunotherapy (36). Encouraging preliminary results of cytokine antagonism directed against interleukin-1 in animal models of intestinal inflammation (37,38) and against tumour necrosis factor in humans with IBD (39), have already been reported.

### PROSPECTS AND PREDICTIONS

It is likely that the pharmaceutical industry will continue to introduce modifications that improve either the biological activity or the delivery systems for most of the traditional immunosuppressive drugs. For example, newer purine analogues are already in use for certain leukemias (40). Whether these agents will have a role in the management of chronic inflammatory disease is unknown. There is also the potential and rationale for developing another generation of cyclosporine-like drugs. As discussed earlier, cyclosporine and related drugs may act primarily by inhibiting the chemotactic activity of secreted cyclophilin. It has been proposed that this mecha-

nism, rather than inhibition of interleukin-synthesis, is responsible for the therapeutic effect in both organ graft survival and chronic inflammatory disorders (23). If this is true, it would be desirable to develop novel agents, including cyclosporine derivatives, that are potent inhibitors of chemotaxis with less effect on cytokine synthesis by T cells. The potential for selectively removing subsets of T cells by monoclonal antibodies has been facilitated by the ability to engineer 'humanized' antibodies (41) and by the identification of several new receptor/ligand interactions on the T cell surface that influence activation and physiological cell death (35,42). For example, rather than targeting an entire CD4 subpopu-

lation, it may be more appropriate to use monoclonal antibodies directed to molecules on the T cell surface that are responsible for physiological cell death and termination of autoreactive lymphocytes during development. Thus, an antibody directed toward the Apo-I/Fas antigen may selectively eliminate a subset of activated T cells by apoptosis (43,44). Thus, it may be possible to exploit endogenous mechanisms for lymphocyte cell death for beneficial effect in chronic inflammatory disorders with minimal collateral damage or toxicity.

From a clinical perspective, immunosuppressive strategies are likely to be used widely. The traditional use of drugs on an empiric basis has been re-

placed by approaches that have a sound rationale and are based on improved understanding of the pathogenesis of IBD. Because of the remarkable reserve of mediators within the inflammatory cascade, it is likely that combination therapy should be used rather than a step-wise approach. Unlike rheumatologists, gastroenterologists have been slow to adopt this concept and may have much to benefit by earlier use of disease-modifying drugs such as immunosuppressives for chronic inflammatory disease. Finally, future immunomodulatory strategies should target the mucosal immune system rather than the systemic immune response and should focus on maintenance of disease remission rather than treatment of relapse.

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