
EDITORIAL

Cyclosporine: Is there a role in inflammatory bowel disease?

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THE IDIOPATHIC INFLAMMATORY BOWEL DISEASES (IBD) are a spectrum of disorders characterized by chronic inflammation of the gastrointestinal tract. Genetic (1-5), environmental (6), dietary (7) and infectious agents (7,8-15) have been implicated in the cause of IBD; however, much more evidence is required before any is considered proven.

Because the exact etiology of IBD has thus far been difficult to establish many investigators consider that the basis of the disease lies in an endogenous immunological defect. Thirty years ago Broberger and Pearlmann (16) first demonstrated that IBD was associated with anti-epithelial cell antibodies in both blood and draining lymph nodes in patients with ulcerative colitis. Since then a large body of evidence has grown to support the immunologic hypothesis of IBD pathogenesis.

Prior to examining the concept that IBD is a consequence of an immunologic process it is important to review the function of the mucosal immune system in normal individuals. The gastrointestinal luminal environment contains numerous substances capable of activating the immune system. However, the fact that this does not occur can be attributed to the mucosal immune systems 'programmed' un-

responsiveness. For example, during antigen-specific reactions, protein antigens entering the gastrointestinal tract via the oral route produce antigen-specific suppressor T cells with negative effects on the immune system rather than helper T cells with their stimulatory effects (17-19). With antigen-nonspecific reactions the mucosal immune response is again influenced by antigen-nonspecific suppressor T cell mechanisms (20,21). The one exception to mucosal unresponsiveness is that of per oral immunization evoking a positive IgA immune response, while at the same time causing a negative suppressor T cell response. Because IgA antibodies provide a 'scavenger' function to eliminate 'foreign' antigens which inadvertently gain entry via the mucosal surface, a positive IgA response is, in the end, reducing the immune system response as a whole.

The earlier lesions of Crohn's disease, and likely ulcerative colitis, do not begin within the enterocyte but rather as an accumulation of plasma cells and lymphocytes adjacent to mucosal crypts (22). This is followed by an influx of macrophages and subsequent inflammatory processes within the lamina propria. Damage to the enterocyte is, therefore, a by-product of this underlying inflammatory process.

The mature inflammatory lesions in IBD contain a three-fold enhancement in lymphocytes (both T cells and B cells increased to a similar extent) compared to normal mucosa (23). The increased B cell population in IBD tends to be

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located in superficial areas of the mucosa and is composed of both nonimmunoglobulin and immunoglobulin producing B cells. Within the immunoglobulin producing population IgM and IgG predominate over IgA and IgE plasma cells, reversing the normal gastrointestinal mucosal IgA predominance (24-27). The increased T cell population in IBD is located in deeper regions of the mucosa and muscle layers and is composed of both T4 (helper) cells and T8 (suppressor) cells in the same 2:1 ratio as normal mucosa (28). In addition to the lymphocytes, increased numbers of inflammatory cells are also present in IBD (29). Neutrophils (particularly in ulcerative colitis), eosinophils and macrophages (particularly in Crohn's disease) and mast cells are localized to the submucosa where they release vasoactive amines which further alter vascular permeability and facilitate the influx of additional inflammatory elements into the IBD lesion (29,30).

Not only are the B and T cell systems increased in number but also in immune functional activity. B cell activity can be demonstrated by an increased antibody response to the B cell mitogen lipopolysaccharide and the enterobacterial common antigen of Kunin, a bacterial cell wall constituent of many enterobacteria (31,32). Increased suppressor T cell activity can be demonstrated by the fact that peripheral T cells obtained from patients with IBD produce migration inhibition factor when exposed to the enterobacterial common antigen of Kunin (33,34). Ultimately, however, the T cell population from which the suppressor T cells originate is depleted or perhaps suppressed. At this point one sees reduced rather than increased suppressor T cell activity and it is at this point that the immune defect of IBD becomes manifest.

These changes in B and T cell number and function may simply be due to mucosal inflammation and the consequent increase in exposure of the immune system to mucosal antigens. However, it is more likely to be a primary mucosal immunoregulatory defect; specifically, a fault in the 'programmed' unresponsiveness of the gastrointestinal mucosa.

SEQUENCE OF EVENTS

In summary, one can propose the following sequence of pathologic events leading to IBD. The gastrointestinal immune system becomes exposed to a mucosal antigen, perhaps even an antigen normally present within the lumen, ie, a bacterial constituent of normal flora. However, on this occasion the antigen does not evoke the typical antigen-specific suppressor T cell activity, ie, mucosal unresponsiveness, but, because of an antigen-specific immunoregulatory defect, it evokes helper T cell activity and sets into play an ongoing immune response. This immune response as an epiphenomenon leads eventually to the development of self antigens and appearance of autoantibodies. Subsequently, in an attempt to down regulate the antigen-specific response, antigen-nonspecific suppressor T cells appear. Initially these antigen-nonspecific suppressor T cells may prevent disease progression; however, they are

gradually depleted leaving the unregulated antigen-specific helper T cell activity to predominate. This unregulated antigen-specific immune response leads to the production of lymphokines which stimulate migration of inflammatory and cytolytic cells to the region. Through this process the microscopic and gross morphological changes of IBD are manifest.

Therapy for Crohn's disease has up to now consisted of corticosteroids, immunosuppressive agents and, to a lesser extent, 5-ASA and metronidazole (35,36). Efficacy of therapy in acute disease, however, has for the most part been suboptimal, while a definite absence of therapy exists for preventing relapses. With the hypothesis that IBD may indeed be related to an immune regulatory dysfunction, potent immunosuppressive agents may be useful where other therapy has failed.

Cyclosporine A is a unique fungal metabolite which possesses potent specific immunosuppressive properties (37). Cyclosporine interferes with helper T cell activity by binding to specific membrane receptors, subsequently inhibiting cell growth and interleukin-2 lymphokine release. This depletion of interleukin-2 interferes with B cell and helper T cell proliferation while allowing the expansion of the suppressor T cell population. In this way cyclosporine may return the immunoregulatory defect of the gastrointestinal immune response seen in IBD to the normal state of 'programmed' unresponsiveness.

CLINICAL TRIALS

Cyclosporine has now been used in treating over 100 patients with Crohn's disease worldwide. Many of these are anecdotal experiences or open trials with small numbers of subjects (38-43). Often the cyclosporine was utilized only after conventional therapy failed. Nevertheless, in this difficult patient population the initial overall response rate while on cyclosporine was approximately 70% (44). Allison and Pounder (40,41) in an open trial treated eight patients with uncomplicated Crohn's disease who were resistant to conventional therapy. All the patients were able to tolerate the mean cyclosporine dose rate of 8.2 mg/kg/day (range 2.5 to 10 mg/kg/day) for the six-week duration of the study. Seven of the eight patients responded to cyclosporine with symptomatic improvement, a fall in the Crohn's Disease Activity Index and return of the C-reactive protein concentration to normal. Nevertheless, all patients relapsed within the first week of stopping cyclosporine treatment.

Brynskov and colleagues (42), in an open multicentre study in Denmark, examined the use of cyclosporine over three months in 11 patients with therapy-resistant active Crohn's disease. One patient, unable to absorb the cyclosporine, was excluded from the study at two weeks. The remainder of the subjects tolerated a dose rate of 5 to 7.5 mg/kg/day with minimal side effects. After three months of therapy, two of 11 patients (18%) failed to respond. Eight of 11 patients (72%) improved, however, only three of these eight patients (38%) remained in remission once the cyclosporine was withdrawn.

In this issue of *The Canadian Journal of Gastroenterology* Peltekian and colleagues (p5) examined the use of cyclosporine in 15 patients with active Crohn's disease refractory to conventional therapy. Similar to the earlier studies, cyclosporine doses were monitored to maintain serum trough levels of cyclosporine between 100 and 200 ng/mL. Nevertheless, five of 15 patients withdrew early from the study (three because of side effects; one because of poor absorption; one because of noncompliance). Although the trial was open and the study population small it is encouraging to see that four weeks after beginning cyclosporine, all 10 patients able to tolerate the drug demonstrated improvement as documented by a fall in the Crohn's Disease Activity Index, Simple Index of Crohn's Activity, and reduction in corticosteroid requirements. However, by 16 weeks of therapy only seven of these 10 patients remained improved and once the cyclosporine was stopped only three of them (30%) remained in remission at 75 ± 2 weeks of follow-up.

These results of an early clinical response to cyclosporine therapy, followed by frequent and often rapid relapses once the cyclosporine is stopped, are similar to those of earlier trials with cyclosporine (41,42). This contrasts, however, with the use of prednisone and 6-mercaptopurine where the mean onset of response is longer and the relapse rate following withdrawal is not as high as that seen with cyclosporine (45). It is interesting to note that, in the present study as well as in earlier reports, corticosteroids were aggressively tapered or discontinued following the cyclosporine response. Perhaps a more liberal use of corticosteroids may

have altered the high relapse rate encountered when cyclosporine was withdrawn.

SIDE EFFECTS

Cyclosporine is known to predictably reduce glomerular filtration rate and cause mild hypertension, hypertrichosis, mild liver function abnormalities, gingival hyperplasia and a fall in hemoglobin (46). Despite these adverse events, patient withdrawal because of side effects remains relatively low with careful therapeutic drug monitoring. Specific to inflammatory bowel disease will be the considerations of: (i) the effect of enteritis and diarrhea on an already slow and unpredictable cyclosporine absorption; (ii) the effect of associated liver disease on cyclosporine metabolism as cyclosporine is primarily eliminated by hepatic metabolism; (iii) and the interaction between cyclosporine, corticosteroids and nonsteroidal anti-inflammatory agents.

Certainly from our present immunological understanding of inflammatory bowel disease, cyclosporine appears to have great potential in our therapeutic armament. Nevertheless, whether lifelong therapy will be required to maintain remission, whether side effects of therapy will be more serious than the disease itself and whether low dose cyclosporine will be effective and improve patient tolerance can only be confirmed by placebo controlled double blind clinical trials. We await, with some excitement, the results of two separate multicentre double blind Canadian studies examining the role of cyclosporine in active refractory Crohn's disease and in maintaining Crohn's disease remission.

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Clinical Quiz

Please note, there may be more answers than asked for in the question.

SMALL INTESTINE

1. List six causes of vitamin B₁₂ deficiency. What are the pathogenic processes induced by each cause?
2. Name four causes of the intestinal pseudo-obstruction syndrome and give the pathogenesis of each.
3. Give four renal and urinary complications of Crohn's disease and the mechanisms of these complications.
(Answers page 30)

ESOPHAGUS

1. What are six indications for surgery in reflux esophagitis?
2. List four features of the typical motility pattern you may expect to see in a patient with well established achalasia of the stomach.
3. Name six complications of endoscopic sclerotherapy of esophageal varices.
(Answers page 44)



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