

## Leading article

# New forms of treatment for inflammatory bowel disease

Until the aetiology of inflammatory bowel disease is established the development of new forms of treatment is limited. Induction of remission is associated with inhibition or a decrease in the formation of the inflammatory mediators or, alternatively, may be achieved by blocking their specific receptors. Prostanoids, leukotrienes, platelet activating factor, cytokines, and free oxygen radicals may all contribute to the pathogenesis of the inflammatory response. The drugs that effectively modulate the disease process – such as steroids, sulphasalazine, and 5-aminosalicylic acid – affect most or all of the inflammatory mediators. Current efforts, however, are directed to the development of new drugs with selective inhibition or receptor blockade of a single mediator. In addition, new therapeutic approaches include manipulation of eicosanoid formation by dietary fatty acids, development of topically active new steroid components, and the blockade of neuroimmune interactions.

In view of the raised leukotriene concentrations in rectal mucosa and rectal dialysates of patients with active inflammatory bowel disease – concentrations that also reflect the disease severity – treatment with selective 5-lipoxygenase inhibitors and with leukotriene receptor antagonists is a logical new therapeutic approach. The results of a double blind study of an oral specific 5-lipoxygenase inhibitor, Zileuton (Abbott Labs) are disappointing. In this study,<sup>1</sup> statistically significant improvement was achieved only in patients with mild to moderately active ulcerative colitis who were not receiving concurrent treatment with sulphasalazine: no significant improvement was shown in patients receiving sulphasalazine. More potent inhibition of 5-lipoxygenase activity using higher doses of the drug have been suggested since unless a high level of inhibition is achieved, endogenous leukotrienes may still be present in sufficient amounts to exert their effects. A specific leukotriene receptor antagonist awaits development.

Platelet activating factor may be involved in the pathogenesis of ulcerative colitis<sup>2</sup> as well as in experimental colitis.<sup>3</sup> However, the effect of specific inhibition of platelet activating factor by a specific receptor antagonist has so far been evaluated in models of experimental colitis only. The results obtained indicate that inhibition of its action induced a significant reduction of colonic inflammation in the chronic model of colitis induced by trinitrobenzene sulphonic acid.<sup>3</sup> The possible therapeutic effect of a specific receptor antagonist in inflammatory bowel disease remains to be evaluated.

The recent interest in the role of cytokines, such as interleukin-1 and interleukin-6 in the pathogenesis of inflammatory bowel disease has prompted a search for drugs that may inhibit their formation or, alternatively, block their receptors. The recent modulation of immune colitis in rabbits given interleukin-1 receptor antagonists<sup>4</sup> is encouraging and their use in human inflammatory bowel disease may follow.

Prolonged dietary supplementation with large quantities of fish oil has been tried in ulcerative colitis patients but the results are not encouraging and, at best, may be considered as an adjunctive treatment in chronic ulcerative colitis.<sup>5</sup> The hypothesis is based on the observation that fish oil contains large quantities of eicosapentanoic acid (EPA) that is structurally similar to arachidonic acid, but metabolised by

5-lipoxygenase to leukotriene B<sub>5</sub>, which lacks most of the proinflammatory properties of leukotriene B<sub>4</sub>. The reduction in leukotriene B<sub>4</sub> values induced by fish oil supplementation does not seem to be large enough to modulate active inflammatory bowel disease.

Pronounced changes have been found in gut neuropeptides in patients with inflammatory bowel disease. These changes include the participation of the enteric nervous system, hyperplasia of the mucosal adrenergic innervation, and the possible role of substance P and vasoactive intestinal peptide in the pathogenesis of ulcerative colitis. A preliminary study<sup>6</sup> in which topical treatment with the local anaesthetic lidocaine was evaluated is therefore of interest but further controlled studies are needed.

Corticosteroids are still the most effective treatment for active inflammatory bowel disease, but side effects are common and dose related. New corticosteroid compounds with high topical and little systemic activity seem to offer great benefit to inflammatory bowel disease patients. Studies with enemas of budesonide, a new corticosteroid drug with high topical anti-inflammatory activity and extensive first pass hepatic metabolism to biologically inactive metabolites, have shown efficacy in patients with proctitis and proctosigmoiditis.<sup>7</sup> Moreover, preliminary data also suggest that oral budesonide is effective in active ileocaecal Crohn's disease.<sup>8</sup> Recently an open pilot study showed that fluticasone propionate, a topically active corticosteroid of low systemic bioavailability after oral administration, helped patients with mild to moderately active Crohn's disease.<sup>9</sup>

In both ulcerative colitis and Crohn's disease, immunological mechanisms seem to play a role in either perpetuating or increasing the inflammatory response. Several studies have shown the efficacy of 6-mercaptopurine and azathioprine in the treatment of both ulcerative colitis and Crohn's disease. New immunosuppressive agents have been used recently and are claimed to be beneficial in the treatment of inflammatory bowel disease. Twelve weeks' treatment with intramuscular methotrexate induced clinical remission in 16 of 21 patients with refractory inflammatory bowel disease.<sup>10</sup> However, when the drug was administered orally for 18 weeks its effect was less pronounced.<sup>11</sup> Methotrexate works more quickly than mercaptopurine and azathioprine, and steroid sparing has been shown to be one of its advantages. When administered for short periods its toxicity seems low but may cause nausea, abdominal cramps, and abnormal liver function tests.

Cyclosporine is an immunosuppressive drug that was found to be of benefit in a recent double blind study in Crohn's disease<sup>12</sup> and in an open study conducted in ulcerative colitis.<sup>13</sup> One of the advantages of cyclosporine is its rapid onset of action (about two weeks) compared with the mean response time of about three months with 6-mercaptopurine and azathioprine. The side effects of this treatment include paraesthesias, hypertrichosis, and increased plasma creatinine concentrations. Until more data become available, however, the use of cyclosporine should be restricted to formal clinical trials.

Controlled trials have shown that topical 4-aminosalicylic acid enemas are effective in patients with proctitis and left sided colitis.<sup>14</sup> The place of 4-aminosalicylic acid in the

treatment of ulcerative colitis is not clear, especially since its mechanism of action is not known. 4-Aminosalicylic acid, though similar in structure to 5-aminosalicylic acid, does not inhibit eicosanoid generation and is not an effective free radical scavenger.<sup>15</sup>

Ketotifen has recently been suggested as a new treatment for maintaining remission and preventing relapse. Ketotifen, a drug used for the prevention of asthma, was found to decrease significantly the extent and severity of experimental colitis in two rat models.<sup>16</sup> Ketotifen may prevent the release of the inflammatory mediators from mast cells as well as from other inflammatory cells. Its potential use in inflammatory bowel disease deserves clinical trials.

In recent years the physician's armamentarium for the treatment of inflammatory bowel disease has increased significantly. However, it is also clear that since inflammatory bowel disease is a process that involves several agonists, only drugs which affect most or all of the agonists are likely to be of proven benefit. Drugs which affect one single mediator and/or block one single receptor are unlikely to be helpful. Unless the sequence of events in which the various inflammatory mediators act is established there is little chance that a specific receptor antagonist or inhibitor of the synthesis of a single mediator will be of important therapeutic benefit.

DANIEL RACHMILEWITZ

Department of Medicine,  
Hadassah University Hospital,  
Mount Scopus,  
PO Box 24035,  
Jerusalem 91240, Israel

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