Review Article

MEDICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE (Part Two)

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Treatment of active Crohn's disease and ulcerative colitis

Alpha4 integrins are important mediators of leukocyte migration across vascular endothelium. The pilot placebo-controlled study aimed to assess the safety and efficacy of natalizumab, a recombinant humanized monoclonal antibody to alpha4 integrin, in patients with mild to moderately active CD. A single 3-mg/kg natalizumab infusion was well tolerated by CD patients, although the dose used may have been suboptimal by Gordon et al [22-25]. Elevated circulating lymphocyte levels after natalizumab suggest interrupted lymphocyte trafficking. Natalizumab therapy in active CD merits further investigation.

Until a cure for CD is found, strategies that prolong the time spent in remission offer the greatest hope for reducing the morbidity and significant social costs associated with the disease. Medical therapy to date has been disappointing, and the search for a safe, effective therapy that could be offered at low cost continues. The aminosalicylates, so effective in UC, have shown, at best, minimal efficacy in maintaining remission in CD. Conventional corticosteroids are not effective, and any reduction in time to relapse for budesonide-treated patients is measured in weeks not months. Azathioprine, 6-mercaptopurine, and methotrexate are effective in maintaining remission, but all three have significant side effects. Antibiotics may have a role to play. Biological therapy may be considered, but the issues of cost and long-term safety require evaluation. Future studies should segregate patients into two groups, those with a medically induced remission and patients whose concern is the prevention of postoperative recurrence [24].

The two variables determining the therapeutic approach in UC are disease extent and disease severity (Table 1). Effective medical treatment of UC is available. However, 20%-40% of patients remains refractory and become steroid dependent or chronic active. Azathioprine and its metabolite 6-mercaptopurine have been found effective in this setting, although duration of treatment and doses are not entirely clear. Methotrexate has no definitive part in the treatment of refractory colitis. CSA induces remission in a considerable number of patients; follow-up treatment is, however, not defined. This approach may be useful for elective surgery. A number of other treatments have been proposed including chloroquine, interferons and anti-cytokines. None of these can currently be recommended for clinical practice. Anti-inflammatory cytokines such as IL-10 may be good candidates [17,23]. There are no previous comparative studies of total abdominal colectomy by laparoscopic methods in CD and UC patients requiring urgent colectomy. To determine the safety and efficacy of laparoscopic colectomy in these patients compared with those undergoing conventional urgent colectomy has studied by Marcello et al [25]. Laparoscopic total colectomy is feasible and safe in patients with acute nonfulminant colitis and may lead to a faster recovery than conventional resection.

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Table 1 Treatment of active ulcerative colitis

Severity	Extent		
	Distal	**Left-sided**	**Extensive**
Mild	Topical GCS or 5-ASA	Topical GCS or 5-ASA + oral 5-ASA	Oral 5-ASA (+ topical therapy?)
Moderate/severe	Topical GCS or 5-ASA (+ Oral 5-ASA?)	Oral GCS	Oral or GCS iv
Refractory	Increase dose and duration Switch enemas Combine topical GCS and 5-ASA Oral GCS	GCS iv + CSA Surgery	GCS iv + CSA Surgery

Table 2 Major side effects of glucocorticosteroids

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	Short-term and long-term therapy	**Long-term therapy**
CNS	Pseudotumor cerebri Psychosis	
Musculoskeletal	Myopathy Aseptic necrosis	Osteoporosis
Ocular	Glaucoma	Cataracts
Gastrointestinal	Ulcer-pancreatitis	
Cardiovascular	Hypertension Fluid retention	
Endocrinological		Permanent suppression of HPA-axis Growth failure
Metabolic	Hyperglycemia Hyperosmolar state Hyperlipidemia	Fatty liver Hypokalemia
Skin	Acne, ecchymosis	Striae, atrophy, wound Infection Distribution Cushingoid fat

The side effects of CSA are multiple and opportunistic infections by pneumocystis and cytomegalovirus may be life-threatening. These complications were encountered especially in elderly patients treated with long-term CSA and GCS. Another serious side effect is epileptiform fits due to the CSA hydrophobia vehicle. Patients with lowered serum cholesterol or magnesium should not receive CSA. The side effects of CSA are following: paresthesias, miscellaneous, hypertrichosis, hypertension, tremor, gingival hyperplasia, seizure, nausea/vomiting, renal insufficiency, headache, seizure, anaphylaxis etc.

Side effects of drug therapy in patients with severe CD and UC result from cumulative toxicity of high-dose iv CSA and GCS. The exact role of CSA in the treatment of severe colitis needs to be defined and will very much depend on the long-term outcome of patients treated with this drug. The side effects associated with GCS therapy are important (Table 2). Short-term treatment carries mild side effects in the majority of patients but long-term therapy are associated with sometimes irreversible complications. In the past years, therefore, attempts have been made to develop GCS with high topical activity lacking the systemic activity of the drug and hence carrying fewer side effects.

Maintenance therapy of Crohn's disease and ulcerative colitis

As treatment of steroid-dependent patients with IBD is controversial, Mate-Jimenez et al [26] analyzed the efficacy and tolerance of 6-mercaptopurine (6-MP) and methotrexate (MTX) added to prednisone in increasing and maintaining the disease remission rate. Seventy-two steroid-dependent IBD patients, 34 with DC and 38 with CD receiving treatment with prednisone were randomly assigned in a 2:2:1 ratio to additionally receive, orally, over a period of 30 weeks 1.5 mg/kg/day of 6-MP (group A) or 15 mg/week of MTX (group B), or 3 g/day of 5-aminosalicylic acid (5-ASA) (group C). All patients who achieved remission were included in a maintaining remission study for 76 weeks. Remission was defined after stopping prednisone as a CD activity index of <150 and normal serum orosomucoid concentration for CD patients and a Mayo Clinic score < 7 for UC patients. With regard to achieved remission, asignificantly higher (P< 0.05) rate existed for UC patients in group A (78.6%) than in group C (25%), with no statistical differences in group B (58.3%) *vs C.* For CD patients, the rates were significantly higher (P< 0.001 and 0.01, respectively) in groups A (93.7%) and B (80%) vs C (14%). With regard to maintaining remission, UC patients in group a significantly higher (P< 0.05) rate existed for UC patients in group A (78.6%) than in group C (25%), with no statistical differences in group B (58.3%) *vs C.* For CD patients, the rates were significantly higher (P< 0.001 and 0.01, respectively) in groups A (93.7%) and B (80%) vs C (14%). With regard to maintaining remission, UC patients in group A (63.6%) presented significantly higher rates (P < 0.0015 and P < 0.001, respectively) versus 14.3% in group B and none in group C. For CD patients, statistical differences (P < 0.001) existed when comparing rates in groups A (53.3%) and B (66.6%) *vs* none in group C. Noticeable side effects appeared in 13.3% of patients from group A and 11.5% from group B. 6-MP or MTX added to prednisone could be effective in steroid sparing, as well as in achieving and maintaining remission in steroid-dependent IBD patients. MTX was less effective in maintaining remission in UC patients. Aminosalicylates are used as standard treatment for maintaining remission in UC [27,28]. As yet, there is no other existing alternative with proven efficacy. Immunosuppressives and Immunomo-dulation used in inflammatory bowel diseases (Table 3,4).

Since the beginning of the 1940s salazosulfapyridine (SASP) has been used in the treatment of chronic IBD. Almost 40 years later 5-aminosalicylic acid (5-ASA) that is split off by azo-reducing enzymes in the colon was identified as the therapeutically active moiety of SASP. Thus different 5-ASA containing drugs were produced from which 5-ASA is released in the small and large intestine in a pH-dependent manner. Since there is a firm clinical indication that the 5-ASA concentration in the gut lumen is decisive for the therapeutic effect, a method was developed to evaluate the 5-ASA concentration at different levels in the intestine. The method was subsequently used to clarify factors of importance for the release of 5-ASA from the preparations. Ileostomy patients and healthy volunteers were investigated during continuous treatment with the three 5-ASA containing drugs with pH-dependent 5-ASA release: Asacol, Mesacol (Salofalk, Claversal), and Pentasa. The study confirmed release of 5-ASA in the small intestine from all preparations, but at different levels and speeds. Despite similar peroral dosage, very different 5-ASA concentration profiles were found in the ileostomy effluents, reflecting not only the difference in the release pattern of the preparations, but also the influence of the gastric residence time for larger sized tablets. The 5-ASA concentrations increased in the faeces of healthy volunteers. Furthermore the systemically absorbed fraction of 5-

Table 3 Immunosuppressives used in inflammatory bowel diesases

Drugs	Mode of action	Mechanism of action
AZT/6 -MP	Inhibition of ribonucleotide sysnthesis	Inhibition of proliferation of T - cell clones
Methotrexate	Folic acid inhibitor	Inhibition of T - and B - cell Function decrease of IL - 1 and IL - 6
Cyclosporin A (CsA)	Inhibition of T- cell- receptor- stimulated	Inhibition of IL- 2 production and
Tacrolimus (FK 506)	Transcription of lymphokine genes	IL - 2 receptors; inhibition of Cyctokines (TNFα ,IFNγ)
Mycophenolate	Inhibition of guanosin nucleotide synthesis	

Table 4 Immunomodulation therapy in inflammatory bowel disease

	Cytokines	Anticytokines	Antisense nucleotides
Current studies	rhu IL - 10, rhu IL -11	TNF antibodies, inhibitors	ICAM -1
Future studies		IL - 1 antibodies IL - 1 ra	NFκB
		IFNγ antibodies	
		IL - 12 antibodies	

5-ASA concentration profiles were found in the ileostomy effluents, reflecting not only the difference in the release pattern of the preparations, but also the influence of the gastric residence time for larger sized tablets. The 5-ASA concentrations increased in the faeces of healthy volunteers. Furthermore the systemically absorbed fraction of 5-ASA was larger than previously found after SASP. The 5-ASA release from the preparation with the most proximal release, Pentasa, was less influenced by acceleration of the intestinal transit time than previously demonstrated after SASP in a similar study design. A comparative study of children given SASP and Pentasa showed similar results as in adults: a tendency for smaller 5-ASA concentration at rectal level after Pentasa than after SASP, and also larger systemic absorption. Despite higher 5-ASA dose per kg body weight, lower 5-ASA concentrations were seen in the faeces after both preparations, compared with adults. A peroral dose increase of Pentasa in healthy adults resulted in higher both preparations, compared with adults. A peroral dose increase of Pentasa in healthy adults resulted in higher intraluminal 5-ASA concentration in the gut lumen, but also in saturation of the local and probably also systemic acetylation capacity, demonstrated by higher plasma concentrations and larger urinary excretion of 5-ASA. Similar faecal water concentrations were found after Pentasa 4 g and the azo-bond preparation with colonic 5-ASA release, Dipentum (olsalazine) 2 g, confirming the substantial 5-ASA release from Pentasa in the small intestine. Investigation of pregnant patients treated with different 5-ASA containing drugs showed a similar pattern to SASP treatment: small amounts of 5-ASA cross the placenta, whereas the concentration of the metabolite Ac-5-ASA is similar in the maternal and fetal circulations. Only minute amounts of 5-ASA were found in milk from nursing mothers, while the concentrations of Ac-5-ASA were considerably higher. The decrease in the semen quality during SASP

-ASA were considerably higher. The decrease in the semen quality during SASP treatment was improved by changing to a controlled-release 5-ASA drug. The concentrations of 5-ASA in seminal plasma were similar during the two treatment periods, but higher of its metabolite Ac-5-ASA during treatment with the controlled-release preparation. That indicates that the toxic effect after SASP is not caused by the 5-ASA or Ac-5-ASA moiety. All the preparations have proved effective in the treatment of ulcerative colitis, but data concerning the 5-ASA treatment of CD are conflicting. Knowledge of the demonstrated differences in the release profiles of the 5-ASA containing drugs is therefore important when designing future clinical trial [28].

Prospects

1932-1933 defined the clinical diseases of CD and UC. After that, the major conceptual developments were the recognition that regional enteritis could clearly involve the colon, and that cancer and toxic megacolon could occur in both CD and UC. In the last half of the 20th century, the main thrust of gastroenterology has been in IBD with contributions to extra-intestinal manifestations, measurement of clinical activity in CD, the natural history of the placebo arm of controlled trials, complications and therapy with corticosteroids, 5-ASA, 6-mercaptopurine, immunomodulators and cyclosporine. Actuarial life tables were introduced for postoperative recurrence and re-operation rates, as well as for quality of life analysis. Two forms of CD were defined, perforating and non-perforating, and the role of the fecal stream was explored in light of the higher risk of recurrence after operations with anastomosis as compared with ileocolostomy [29].

The presence of disease heterogeneity, the relative low frequency in the population, the degree to which first-degree relatives are affected (approximately 10%), the presence of genes with minor genetic effects, and ethnic differences are some of the difficulties encountered when identifying disease susceptibility loci. Two major approaches to identify these genes are being followed at present. The first, family-based, consists of studying linkage analysis in sibling pairs and parental transmission in genome-wide screening using microsatellite markers. These studies are appropriate and helpful for finding genes of major or moderate effects but may be difficult when identifying genes with minor effects; and can be considered in the future in genome-wide screens with technologic advances. The second approach is based on conventional epidemiological designs, population-based studies, using candidate genes in the framework of a biologic hypothesis. Recent data using both approaches in both CD and UC are reviewed. The results of genome-wide linkage studies have not reached consensus, but suggest that these diseases are different and polygenic in nature. An abnormal immune dysbalance contributes to the biologic basis of the disease have studied. Therefore, polymorphisms in genes encoding proinflammatory and regulatory cytokines were studied. Preliminary data of these association studies suggest the importance of several genes with small effects in determining the severity and prognosis of these diseases. If the promised breakthrough of immunomodulation therapy occurs in IBD, one may anticipate quite dramatic changes in the treatment of IBD [20-25].

The etiology of IBD remains unknown. The understanding of the pathogenesis has expanded greatly over the last decade. The combination of genetic risk factors, abnormalities in the immune system, vascular and neural factors, and random environmental factors may all play an important role. Most treatments currently in use have multiple action. The choice of appropriate medical treatment is determined by the status (inductive or maintenance therapy) and severity of the disease and the potential for toxicity. Despite the variety of medical therapies available for the treatment of IBD, none is ideal. Ongoing research into the well-established drugs, as well as novel agents with more precise targets, may contribute to an optimal therapy of IBD in the near future. In this paper the current (5-aminosalicylates, glucocorticosteroids, thioguanine derivatives, methotrexate, cyclosporin and infliximab) as well as some of the new (mycophenolate mofetil and thalidomide) therapeutic options are reviewed [30].

CD and UC are idiopathic inflammatory bowel diseases characterized by dysregulated intestinal immune responses in genetically susceptible hosts. Conventional approaches to the medical therapy of CD and UC and can now be

directed at either induction or maintenance of remission to improve therapeutic efficacy while minimizing complications. Newer approaches have expanded the utility of conventional therapies by improving both safety and efficacy and highlight the importance of specific targets along the immunoinflammatory pathways. The combination of conventional and novel approaches now offers the potential of modifying the natural history of these diseases [31].

Conventional corticosteroids, although a mainstay of the acute treatment of IBD for many years, have many drawbacks, including a variety of side effects-particularly with chronic use. Budesonide appears to be relatively safe and at least moderately effective in inducing remission in active distal UC. Aminosalicylates, both oral and topical, have proven useful in managing mild-to-moderate active UC, as well as in maintaining remission. Data from recent trials suggest that higher doses of mesalamine are generally more efficacious than lower doses. In addition, a combination of oral and rectal formulations is successful, but is not when single route is used. The immunomodulatory agent's azathioprine, 6-mercaptopurine, and methotrexate have been shown to be effective in the treatment of IBD and are now widely accepted as valuable parts of the therapeutic armamentarium. CSA, although effective, is associated with much toxicity, and patients must be monitored closely in centers experienced with this agent. Clinical trials of IL-10, IL-11, and anti-TNFd have also shown promise. Antibiotics have been used empirically for many years in the treatment of IBD. Larger clinical trials are warranted to explore the potential efficacy of antibiotic therapy. The acemannan, heparin, and transdermal nicotine have also shown variable degrees of promise as possible therapies for IBD. Despite the variety of agents available for the treatment of IBD, none is ideal or universally accepted. Ongoing research into the well-established therapeutic agents, as well as novel drugs with more precise targets, may contribute to the design of a more optimal regimen for IBD in the not-too-distant future [32-36].

Both CD and UC are considered the result of an unrestrained inflammatory reaction, but an explanation for the aetiopathogenesis has still not understands [32]. Until the predisposing and trigger factors have been clearly defined, therapeutic and preventive strategies for these disorders must, therefore, rely on interrupting or inhibiting the immunopathogenic mechanisms involved. Current

understands [32]. Until the predisposing and trigger factors have been clearly defined, therapeutic and preventive strategies for these disorders must, therefore, rely on interrupting or inhibiting the immunopathogenic mechanisms involved. Current therapies, such as glucocor-ticoids and 5-ASA, inhibit raised concentrations of interdependent, soluble mediators of inflammation, which may amplify one another or have parallel effects. Future medical options for treatment of UC aim at removing perpetuating antigens, blocking entry of inflammatory cells by manipulating adhesion molecules, targeting soluble mediators of inflammation by blocking proinflammatory molecules or by preserving endogenous suppressive molecules, or correcting genetic defects. It remains; however, to be determined whether targeting multi-inflammatory actions or a single key pivotal process is the better therapeutic strategy and whether subgroups of UC with different clinical courses will require different treatment approaches [18,21-26,33-37].

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