Current medical therapy for ulcerative colitis

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INTRODUCTION

In recent years, the advances in therapy of ulcerative colitis (UC) have been characterized mainly by the more extensive use of immunosuppression. Cyclosporin (CSA) may become a drug of choice to treat severe UC, but its long-term effect is insufficient. Topically, glucocorticosteroids (GCS) are hopeful in right ileocolonic UC, but no action for maintenance therapy[1-3]. The most significant development in recent years is the introduction of immunomodulatory treatments using cytokines and anticytokines. Immunomodulation therapy creates great expectations since early reset of the immunosystem might be able to control inflammation in a long term. Current treatment strategies are anti-inflammatory and to modulate the immune response. Standard therapies with sulphasalazine (SAS) or 5-aminosalicylic acids (5-ASA, mesalazine or mesalamine), GCS and antibiotics yield a fair immediate success, but long-term response to these therapies is poor. The greatest advance has been the introduction of immunosuppressive strategies. The indexes like the clinical activity index (CAI) proposed by Rachmilewitz[1], although useful, have not received general acknowledgement.

Patients with an inflammatory bowel disease (IBD), such as UC or Crohn’s disease, have recurrent symptoms with high morbidity. Mild disease requires only symptomatic relief and dietary manipulation. Mild to moderate disease can be managed with 5-ASA, including olsalazine and mesalamine. Mesalamine enemas and suppositories are useful in treating proctosigmoiditis. Corticosteroids are beneficial in patients with more severe symptoms, but side effects limit their use, particularly for chronic therapy. Immunosuppressant therapy may be considered in patients with refractory disease that is not amenable to surgery. IBD in pregnant women can be managed with 5-ASA and corticosteroids[2]. Since longstanding IBD is associated with an increased risk of colon cancer, periodic colonoscopy is warranted.

Since lesions in UC are quite diffuse and uniform endoscopic indexes used are quite straightforward, clinical activity, endoscopic activity and histology show a reasonable correlation and it is useful to monitor disease activity also with flexible proctosigmoidoscopy. The persistence of active inflammatory lesions at histology in the presence of endoscopic remission predicts relapse. Bresci G et al[3] reported that the activity of the disease was evaluated by a Clinical Activity Index and an Endoscopic Index. Of 112 cases of UC observed, 95 showed no change in extent and were studied as examples of non-progressive UC, and in this group the extension of the disease was: pancolitis in 19%, left sided colitis in 39%, proctosigmoiditis in 17% and proctitis in 25%. A colectomy had to be performed in 5%. None of the enrolled cases developed a cancer during the follow up. The patients with ulcerative pancolitis or left-sided colitis were treated with 5-ASA 1.6g/d in a delayed-release formulation, while the patients with proctosigmoiditis or proctitis were treated with 5-ASA enemas 4g/d. The patients with more than one relapse/year accounted for 39%. The proportion of patients with only one relapse/year was 53%. The patients with steady remission for all the seven years of the trial were only 8%, but with a statistically significant difference between the groups with initial diagnosis of proctosigmoiditis or proctitis and the group with initial diagnosis of pancolitis or left-sided colitis (12% vs 5%). Among the patients with continuous remission, 37% showed colonic alterations, with an endoscopic score higher than 4 but a clinical score less than 6. Side effects were observed in 6% of patients but without treatment withdrawal. Non-progressive UC throughout the colon has a relatively good prognosis, which seems to be independent of the location of the disease, even if Bresci G et al[8] have found a statistically significant higher percentage of patients with steady remission among the patients with more distal diseases.

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CURRENT TREATMENT OF ULCEARATIVE COLITIS

Ulcerative colitis is a mucosal disease and therefore well suited for treatment in most instances with topically acting drugs at the level of the colonic mucosa. UC is controlled mainly using GCS and 5-ASA.

Ardizzone et al[4] had reviewed the role of corticosteroids, ASA and mesalazine (5-ASA, mesalamine), immunosuppressive agents and alternative nove 1 drugs for the treatment of distal UC. Short cycles of traditional, rectally administered corticosteroids (methylprednisolone, betamethasone, and hydrocortisone) are effective for the treatment of mild to moderately active distal UC. In this context, their systemic administration is limited to patients who are refractory to either oral 5-ASA, topical mesalazine or topical corticosteroids. Of no value in maintaining remission, the long-term use of either systemic or topical corticosteroids may be hazardous. A new class of topically acting corticosteroids [budesonide, fluticasone, beclomethasone dipropionate, prednisolone -21- methasulphobenzoate, tixocortol (tixocortol pivalate)] represents a valid alternative for the treatment of active UC, and may be useful for refractory distal UC. Although there is controversy concerning dosage or duration of therapy, oral and topical mesalazine is effective in the treatment of mild to moderately active distal UC. Evidence shows a trend to a higher remission rate with higher doses of oral mesalazine. Topical mesalazine (suppositories or enemas) is also effective in maintenance treatment. For patients with chronically active or corticosteroid-dependent disease, azathioprine and mercap topurine are effective in reducing either the need for corticosteroids or clinical relapses. Moreover, they are effective for long-term maintenance remission. CSA may be useful in inducing remission in patients with acutely severe disease that does not achieve remission with an intensive intravenous regimen. Existing data suggest that azathioprine and mercaptopurine may be effective in prolonging remission in these patients. The role of alternative drugs in the treatment of distal UC and its different forms are reviewed. In particular data are reported concerning the effectiveness of 5-lipoxygenase inhibitors, topical use of short chain fatty acids, nicotine, local anesthetics, bismuth subsalicylate enema, sulphate, clonidine, free radical scavengers, heparin and hydroxychloroquine. The management of patients with acute severe UC requires careful in-hospital assessment of the patient and the coordinated treatment of a team of experienced gastroenterologists and surgeons. Complete understanding of the potential complications and their management, especially toxic megacolon, is essential.

The current medical arsenal advocates a standardized approach to management that includes continuous, high dose iv hydrocortisone, more aggressive use of topical steroids as well as feeding the patients and continuing (but not initiating) oral 5-ASA agents was reviewed[5]. For those patients whose disease proves refractory to iv steroids, iv. CSA (with an acute response rate of 82%) is an essential component in the medical management of these patients. Antibiotics should be used only when specifically indicated. Total parental nutrition has not been shown to be helpful in the acute setting. Air contrast barium enema and colonscopy have been used to predict response but may be dangerous diagnostic modalities in these acutely ill patients and are not better than good clinical judgement. Marion et al[5] review and advocate long-term management of acute response using 6-mercaptopurine or azathioprine. The surgical experience and the postoperative complications of the ileal pouch anal anastomosis, which include acute pouchitis in 50% - 60%, chronic pouchitis in 5%-10% and recent reports of dysphasia among patients with chronic pouchitis, must be considered before colectomy is advised. Over 80% of patients with acute severe colitis can be spared colectomy using the current arsenal of medical therapies.

The inhibited release of 5-lipoxygenase products may account for some of the anti-inflammatory effects of ropivacaine seen in the treatment of UC[6]. Prompt diagnosis and exclusion of infection require a minimum of rigid sigmoidoscopy, rectal mucosal biopsy and stool culture. Admission to hospital is mandatory for patients with features of severe disease, or who are in their first attack of UC and have bloody diarrhea, even if the criteria for severe disease are not met. Once admitted, plain abdominal X-ray, full blood count, and serum albumin and C reactive protein should be used to monitor the patients on alternate days; temperature and pulse rate should be recorded four times per day. Treatment should be instituted as soon as the diagnosis is made with an intravenous corticosteroid (hydrocortisone 100mg iv. four times daily or equivalent). Antibiotics may be included if infection cannot be confidently excluded. Free diet is allowed but attention should be given to nutritional, fluid and electrolyte status with intravenous replacement if necessary. Any evidence of colonic dilatation occurring despite maximal therapy should be regarded as an absolute indication for colectomy. The patient should be kept fully informed from an early stage about the
likely natural history of the condition and about the possible therapeutic options including surgery. CSA therapy should be reserved for patients who have a poor response to the first 3d-4d of corticosteroid therapy, particularly those with serum C reactive protein >45mg/L and who do not yet have absolute indications for colectomy. Most patients who have not convincingly responded within 10 days of starting medical therapy should undergo colectomy, although some responders who are febrile may reasonably continue for up to 14 days before a final decision. Approximately 30%-40% of patients with severe colitis will need colectomy within the first 6 months. With optimal management, mortality can be zero, but better medical therapies are urgently needed to reduce the colectomy rate[7].

Finnie et al[8] speculated that corticosteroids might cause beneficial stimulation of mucus synthesis, since this is a known action of carbenoxolone, a corticosteroid itself, and has also been proposed as a possible mechanism for the protective effect of smoking on UC. We have therefore compared the effects of corticosteroids including carbenoxolone, and nicotine on mucin synthesis, assessed by incorporation of N-[3H] acetylglucosamine into mucin by colonic epithelial biopsies in culture. In histologically normal biopsies from the left colon, hydrocortisone and prednisolone caused a very marked concentration-dependent increase in mucin synthesis, with maximal effect at 6 nmol/L (P < 0.001) and 1.5 nmol/L (P<0.001) respectively. The maximal effect of hydrocortisone was significantly greater than that of prednisolone (P < 0.05). Carbenoxolone, 0.17 nmol/L, also increased mucin synthesis in the left colon [P < 0.05, n = 15 (three patients)]. In contrast, these corticosteroids caused only a small, non-significant increase in mucin synthesis in the histologically normal right colon; fluocortisone, 2 nmol/L and 20 nmol/L, and aldosterone, 0.1 nmol/L - 10 nmol/L had no effect. Nicotine significantly increased mucin synthesis between 62.5 nmol/L and 6.25 nmol/L (P < 0.05 at all concentrations) in both the right and left colon. In biopsies from the relatively uninvolved right colon of patients with UC, corticosteroids and nicotine caused relatively smaller increases in mucin synthesis. The marked stimulation of mucin synthesis by corticosteroids suggests that this may account, at least in part, for their therapeutic effect in UC.

GCS act by binding to the GCS-R (glucocorticosteroid receptor). The activated receptor assembles to a dimer that is transported in the nucleus of the cell where it binds to DNA and acts via enhanced or reduced transcription, reduced translation and breakdown of DNA. GCS have a very extensive anti-inflammatory and immunosuppressive action. Since the receptor is the same for all body cells, GCS in the circulation have many systemic effects. Many actions have been described for the aminosalicylates[9]. SAS and 5-ASA inhibit the production of cyclooxygenase, thromboxane synthetase, platelet-activating-factor synthetase, and IL-1 by macrophages and can decrease immunoglobulin production by plasma cells. Both SAS and 5-ASA inhibit the production of reactive oxygen species and scavenge reactive oxygen metabolites. 5-ASA lacks the antibacterial effect of SAS.

### TREATMENT OF ACTIVE ULCERATIVE COLITIS

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. iv. 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[5,10].

In the presence of proctitis or distal colitis, a topical approach should always be the first choice. To control active distal disease rectal 5-ASA is at least as effective as rectal GCS[11]. In patients with left-sided colitis, enemas are the best choice because of the retrograde spread up to the splenicflexure. GCS enemas have been used for a long time in the treatment of distal UC. Prednisolone (20 mg - 30 mg), hydrocortisone (100 mg-125 mg ), and bethamethasone (5 mg) have all been shown to be effective. To minimize side effects, poorly absorbable GCS have been used for enema therapy including hydrocortisone foam and prednisolone metasulphobenzoate or molecules with increased first-pass metabolisation in the liver, e.g., betamethasone dipropionate and tixocortol pivalate. Budesonide enemas carry almost no systemic effects because of a very high first-pass effect. Doses of 2 mg are as effective as 20 mg - 30 mg of prednisone. Repeated therapy courses with budesonide enemas have been found safe without suppression of the HPA axis[5,12].
CSA has been proposed in the management of patients with acute UC in whom standard therapy failed and who were candidates for colectomy\textsuperscript{13}. Seven academic hospitals contributed to this retrospective study which included 29 patients (median age: 33 years, 12 females and 17 males). The median duration of the disease was 4 years. For the responders, maintenance therapy included tapering dose of steroids ($n = 12$), azathioprine ($n = 12$), 5-ASA or salazopyrine ($n = 10$), methotrexate ($n = 1$) or oral CSA ($n = 11$). The median duration of follow-up was 12 months (4 to 48 months). Among the 20 respondents, 7 were subsequently referred for colectomy either selectively ($n = 3$) or because of recurrence of the disease ($n = 4$). Among the 12 patients treated by azathioprine as a maintenance therapy, only 3 (25%) had to be referred for surgery. Among the 8 patients who did not receive azathioprine, 4 (50%) were subsequently subject to a colectomy (NS). In patients with acute refractory UC who received CSA, the short-term efficacy (avoidance of immediate colectomy) was obtained in 20 (69%) out of 29 patients. However, after a median follow-up of 12 months, only 13 (45%) patients were colectomy free.

Refractory distal colitis is a difficult medical problem and is defined as active distal inflammation unresponsive within 4 wk - 6 wk to a topical treatment with 5-ASA or corticosteroids associated with oral salicylates or sulphasalazine\textsuperscript{6,7}. Although there is little controlled evidence, it is logical to increase the dose of the topically administered drug or to continue the drug for a longer time. A further step is to switch drugs. All clinicians have experience with patients in whom proctitis not responsive to 5-ASA responded to GCS enemas and vice versa. Another valuable approach seems to combine 5-ASA and GCS in one enema. Frequently, patients with refractory distal disease do not respond even to oral therapy with GCS and a rectal drip of GCS over several hours together with administration of antidiarrheals in hospital may be necessary or iv administration of high doses of GCS. Active disease extending beyond the rectum necessitates oral therapy. In mild-to-moderate disease oral SAS or 5-ASA formulations in high doses can be used or a combined approach of oral 5-ASA and topical 5-ASA. Many physicians prefer this approach because of the low incidence of side effects and the reluctance of the patients to take GCS\textsuperscript{4,6}.

Oral salicylates at doses of over 2g have been shown to be more effective than placebo to control mild-to-moderate attacks of UC\textsuperscript{14}. There probably is a dose-response effect with doses up to 3.8g being increasingly more effective, but this was not demonstrated in all studies. 5-ASA was not more effective than SAS and was beneficial especially to the SAS-sensitive patient. Recent data\textsuperscript{15} have shown that balsalazide is more effective and better tolerated than mesalamine in the treatment of active UC. Patients taking balsalazide not only experienced more asymptomatic days and achieved the first asymptomatic day more rapidly but with side effects. Differences were highly significant.

Improvement of symptoms of UC with 5-ASA may be slow and overall 5-ASA or sulphasalazine are certainly less effective to control active UC than GCS. There is a dose effect for oral GCS, 40 mg prednisolone daily being more effective than 20 mg; while 60 mg offers little extra benefit but is associated with a considerable increase in side effects\textsuperscript{3,4}.

Severe UC is defined using the criteria of Nielove and Witts\textsuperscript{16} as six or more bloody stools in a patient with fever, tachycardia, hypoalbuminemia and raised ESR. These patients will mostly be admitted to hospital to receive a continuous iv infusion of GCS. In severe left-sided or extensive disease GCS are mandatory and combined therapy with 5-ASA is probably not more efficacious than GCS alone. As soon as symptoms are controlled, tapering of the GCS can be started but proctoscopic monitoring of disease activity is valuable.

Recently parameters predictive of outcome of severe colitis under 3 days of intravenous glucocorticosteroids have been revised\textsuperscript{17}. The need for colectomy was predicted in 85% of the patients on the basis of the presence of eight or more stools per 24 h or 4-5 stools per 24 h together with C-reactive protein >45mg/L. Based on these criteria one could make the decision to introduce intravenous CSA or to decide for colectomy. In patients who deteriorate or are admitted with toxic colonic dilatation, immediate colectomy has to be performed. If a pouch-anal anastomosis is constructed, a temporary diversion ileostomy is indicated. Many surgeons’ three-step procedures, i.e. first colectomy with closure of a short rectal stump, subsequent construction of an ileoanal pouch with temporary ileostomy and finally closure of the stoma. The side effects of CSA are multiple (Table 2) 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 hydrophobic vehicle. Patients with lowered serum cholesterol or magnesium should not receive CSA.
### Table 1  Treatment of active ulcerative colitis

| Extent       | Severity   | Distal | Left-sided | Extensive                        |
|--------------|------------|--------|------------|----------------------------------|
|              | Mild       | Topical GCS or 5-ASA | Topical GCS or 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 | GCS iv+CSA | GCS iv+CSA                      |
|              |            | Switch enemas | Surgery | Surgery                         |
|              |            | Combine topical GCS and 5-ASA | Oral GCS | Others                          |

### Table 2  Adverse events reported with use of cyclosporin (iv+oral) in IBD

| Type of side effect | %       | Type of side effect | %       |
|---------------------|---------|---------------------|---------|
| Paresthesias        | 26      | Headache            | 5       |
| Miscellaneous       | 13      | Infection           | 3       |
| Hypertrichosis      | 13      | Hepatotoxicity      | 3       |
| Hypertension        | 11      | Gingival hyperplasia| 2       |
| Tremor              | 7       | Seizure             | 1       |
| Nausea/vomiting     | 6       | Anaphylaxis         | 0.3     |
| Renal insufficiency | 6       | Side effects/patient| 0.94   |

### Table 3  Major side effects of glucocorticosteroids

| Type of side effect         | Short-term and long-term therapy | Long-term therapy                      |
|-----------------------------|----------------------------------|----------------------------------------|
| CNS                         | Pseudotumor cerebri              | Psychosis                              |
| Musculoskeletal             | Myopathy                         | Aseptic necrosis                       |
| Ocular                      | Glaucma                          | Cataracts                              |
| Gastrointestinal            | Ulcer-pancreatitis               |                                        |
| Cardiovascular              | Hypertension                     |                                        |
| Endocrinological            | Fluid retention                  |                                        |
| Metabolic                   | Hyperglycemia                    | Fatty liver                            |
| Metabolic                   | Hyperosmolar state               | Hypokalemia                            |
| Skin                        | Acne, ecchymosis                 | Striae, atrophy, wound                 |
|                             |                                  | Cushingoid fat                         |
|                             |                                  | Distribution                           |

### Table 4  Immunosuppressives used in inflammatory bowel diseases

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

### Table 5  Immunomodulation therapy in inflammatory bowel disease

| Cytokines | Anticytokines | Antisense nucleotides |
|-----------|---------------|------------------------|
| Current studies | rhu IL-10, rhu IL-11 | TNF antibodies, inhibitors IL-1 antibodies IL-1 ra IFN-γ antibodies IL-12 antibodies | ICAM-1 NFκB |
| Future studies  |               |                        |                                      |             |
Side effects of drug therapy in patients with refractory colitis 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 greatly depend on the long-term outcome of patients treated with this drug. The side effects associated with GCS therapy are important (Table 3).

Short-term treatment carries mild side effects in the majority of patients but long-term therapy are sometimes associated with 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.

Other approaches to therapy of UC are currently under investigation. Transdermal nicotine in doses of 15 mg - 25 mg daily added to conventional therapy was effective against placebo to control acute exacerbations of UC. The rationale to use this therapy is smoking may have a beneficial effect. Another recent trial confirmed the moderate efficacy of nicotine in the treatment of UC. The use of nicotine as a treatment, however, remains highly controversial. The use of oral ridogrel, a thromboxane synthase inhibitor in UC is currently investigated. A study suggests that there is no benefit of adding azathioprine in patients with chronic stable colitis, whereas the drug is efficacious to maintain UC in remission. The evidence for the use of methotrexate in the treatment of chronic active UC is largely negative. It should be emphasized that UC is a curable disease. Colectomy with ileo-anal pouch anastomosis is a valuable treatment alternative in chronically active or intractable disease.

Rectal treatment with mesalazine enemas is the first-line therapy for distal UC. In order to improve the benefits of rectal therapy, a new 60 mL-5-ASA rectal gel enema preparation has been developed using a device that excludes direct contact of the inert propellant gas with the active drug. Twelve patients with active UC administered 4 g of the mesalazine rectal enema labelled with 100MBq technetium sulfur colloid (99mTc-SC). Anterior scans of the abdomen were acquired at intervals of 4 hours. Scans were analyzed to evaluate the extent of retrograde flow and homogeneity of distribution of the radiolabeled enema in the rectum, sigmoid, descending and transverse colon. In addition, plasma levels of 5-ASA and Ac-5-ASA were measured for 6 hours. All patients retained the entire rectal gel throughout the course of the study without adverse events. In 11 (92%) out of 12 patients, the gel had spread homogeneously beyond the sigmoid colon and had reached the upper limit of disease in all cases. The maximum spread (splenic flexure) was observed in 6 (50%) out of 12 patients within the first 2 hours. The systemic absorption of mesalazine and its metabolite Ac-5-ASA were low. The new mesalazine enema represents an adequate alternative and a further technological improvement in the topical treatment of distal UC.

The choice between sulfasalazine and 5-aminosalicylate (5-ASA) drugs in the management of UC patients often depends on idiosyncrasies of drug tolerance and control of the disease in individual patients. Walker et al. sought to evaluate whether there were population differences in the effect of 5-ASA and SAS on the occurrence of clinically recognized adverse events. We also attempted to determine whether there were differences in the use of concomitant steroids and in the rates of hospitalization. A large computerized database drawn from general practices in the United Kingdom was reviewed. The 2894 patients who were diagnosed having UC were receiving ongoing medical therapy specific to UC. The period of data availability ran from early 1990 to late 1993. The average duration of observation was 2.1 years per patient. Patient histories were categorized into distinct periods according to the dose of 5-ASA and SAS, steroids, and immunosuppressants, and were further divided based on the UC activity. Within these categories, they examined the initiation and discontinuation of steroids, rate of new hospitalizations for UC, and clinical complaint of adverse events. The results show new clinical mentions of hepatic, pancreatic, renal, and hematological events other than anemia were similar among the 5-ASAs and were very infrequent generally. Hospitalizations for UC occurred with similar frequency (about 15 hospitalizations per 100 patients per year) among users of those drugs. Patients receiving SAS had lower rates of initiation of prednisolone than patients receiving 5-ASA, but SAS was used proportionately less often in patients who had been recently hospitalized, and it may be that SAS patients were somewhat less sick than patients using 5-ASA. The choice of drug did not affect discontinuation rates for prednisolone among established users. In the United Kingdom, during the period of this study, serious adverse reactions to drugs were not an important aspect of the management of patients with UC. Renal and pancreatic complications of SAS and 5-ASA therapy were extremely rare. SAS and 5-ASA drugs have similar steroid-sparing properties. Disease-specific
hospitalizations are approximately 100 times more common in UC patients than serious adverse drug effects. Considerations of drug efficacy should therefore dominate the choice between the therapeutic agents.

The efficacy and safety of 5-ASA suspension enema were compared with oral SAS in patients with active mild to moderate distal UC\(^2\). Thirty-seven patients were randomly assigned to treatment with either rectal mesalamine, 4 g at night \((n = 19)\) or oral SAS, 1 g four times a day \((n = 18)\) in a 6 week, double blind, double-dummy, parallel-group, multicenter study. A physician-rated Disease Activity Index (DAI), which included symptom evaluations and sigmoidoscopic findings, assessed efficacy, by physician-rated Clinical Global Improvement (CGI) scores, and by Patient Global Improvement (PGI) scores. Adverse event reports, clinical laboratory tests, and physical examination assessed safety. Mean DAI scores indicated significant improvement from baseline in both treatment groups. CGI scores indicated that 94% of the 5-ASA patients were either “very much improved” or “much improved” at wk 6 vs 77% of the SAS patients. PGI ratings showed more improvement in the 5-ASA treatment group than in the SAS group at week 2 \(P = 0.02\) and at 4 week \(P = 0.04\). Adverse events, primarily headache and nausea, occurred significantly more frequently \(P = 0.02\) in the SAS than in the 5-ASA group \(83% vs 42\%\). Three patients were withdrawn from SAS treatment because of adverse events. Rectally administered 5-ASA is as effective as oral SAS in treatment of active distal UC but is associated with fewer and milder adverse events. Patients treated with 5-ASA reported improvement earlier than those treated with SAS.

Since transdermal nicotine is of value in the treatment of active UC but is often associated with side effects, an alternative in the form of topical therapy with nicotine enemas has been developed. In an open study\(^2\), 22 patients with active colitis, all non-smokers, were asked to take a 100mL enema containing 6mg of nicotine every night for 4 weeks. Pre-trial treatment using mesalazine \((n = 16)\), oral prednisolone \((8)\), cyclosporin \((1)\) and azathioprine \((1)\) was kept constant for the month prior to assessment and during the study period. Symptoms, with stool frequency, were recorded on a diary card and an endoscopy was performed with rectal biopsy at the beginning of the study and after 4 weeks. Seventeen of the 22 patients completed 1 month of treatment. Mean duration of relapse was 29 weeks. Sixteen of 17 improved their St Mark’s score. Urgency and stool frequency improved in 12 patients, sigmoidoscopic and histological scores in 10. Three patients had a full remission of symptoms with normal sigmoidoscopy. Six of 10 patients with a partial response continued with the enemas for the second month, and five showed further improvement with full remission in two. The enema appeared effective when added to conventional treatment and produced few side effects. Topical nicotine therapy for UC may have a place in future management, but case control studies are needed\(^3\). Immunomodulators used in IBD (Table 4), and immunomodulation therapy in IBD are directed toward suppressing the action of proinflammatory cytokines for enhancing the effects of antiinflammatory mediators (Table 5).

### Maintenance Therapy in Ulcerative Colitis

Aminosalicylates are used as standard treatment for maintaining remission in UC\(^4\). As yet, there is no other existing alternative with proven efficacy. In the light of the hypothesis that the intestinal environment may contribute to the pathophysiology of UC, a trial was conducted to test the effects of probiotic treatment with an oral preparation of non-pathogenic E. coli. A total of 120 patients with inactive UC were included in a double blind, double-dummy study comparing mesalazine 500mg three times daily. An oral preparation of viable E. coli strain Nissle (Serotype 06:K5:H1) for 12 weeks was studied with regard to their efficacy in preventing a relapse of the disease. Study objectives were to assess the equivalence of the clinical activity index (CAI) under the two treatment modalities and to compare relapse rates, relapse free times and global assessment. The start and end scores of the CAI demonstrated no significant difference between the two treatment groups. Relapse rates were 11.3% under mesalazine and 16.0% under E. coli Nissle 1917 (NS). Life table analysis showed a relapse-free time of 103 ± 4 d for mesalazine and 106 ± 5 d for E. coli Nissle 1917 (N.S.). Global assessment was similar for both groups. Tolerability to the treatment was excellent. No serious adverse events were reported. From the results of this preliminary study, probiotic treatment appears to offer another option for maintenance therapy of UC. Additional support is provided for the hypothesis of a pathophysiological role for the intestinal environment in UC.

Distal UC can be maintained with a topical approach. Regimens such as alternate-day enema administration has been shown to be effective, while for maintenance, the use of suppositories may be feasible as far as compliance is concerned, and the long-term use of enemas is difficult. The benefit of
maintenance treatment with oral 5-ASA of extensive UC is well established. SAS reduces the relapse rate by fourfold and all 5-ASA formulations have comparable efficacy with fewer side effects. The rate of GI side effects is especially decreased with 5-ASA. The optimal 5-ASA dose may be 2 g. A dose effect was not demonstrated for most 5-ASA formulations and SAS, except for olsalazine[27].

PROSPECTS

There is overwhelming evidence that genetic factors play a role in the predisposition to develop the chronic IBD[28-30]. The genetic analysis of complex diseases, such as UC, is difficult. 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 in 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 in 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 Crohn’s disease 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. We have started our studies with the hypothesis that an abnormal immune disbalance contributes to the biologic basis of the disease. 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 in immunomodulation therapy is achieved in IBD, one may anticipate quite dramatic changes in the treatment of IBD. GCS still are the mainstay of therapy of UC within 5-10 years.

This review[30] focuses on current developments in the major categories of the therapy used in the management of IBD. 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 been proved 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 so when single route is used. The immunomodulatory agents 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-TNF-α 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.

Both UC and Crohn’s disease are considered to be the result of an unrestrained inflammatory reaction, but an explanation for the aetiopathogenesis has still not emerged[30]. Until the predisposing and trigger factors are clearly defined, therapeutic and preventive strategies for these disorders must, therefore, rely on interrupting or inhibiting the immunopathogenic mechanisms involved. Current therapies, such as glucocorticoids 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[24,31].
