Standard immunosuppression in IBD : current practice

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The use of immunosuppressive drug therapy in the treatment of IBD has a long history. Although preliminary experience with agents such as, azathioprine (AZA) and 6-mercaptopurine (6-MP) began in the 1960s, only in the past decade has the use of these drugs to treat patients with refractory Crohn's disease become a standard of care. Enthusiasm for the use of immunosuppression in ulcerative colitis has also increased but remains limited. This article reviews the current use of immunosuppressive therapy for both Crohn's disease and ulcerative colitis.

Crohn's disease

An important contributor to the acceptance of immunosuppressives in Crohn's disease was the growing awareness among clinicians of the high prevalence of steroid dependence. For example, Munkholm and colleagues (1) described the clinical course of patients following a disease acute exacerbation in a cohort of residents of Copenhagen County. One year after an initial course of glucocorticoid therapy the majority of patients (56%) were either therapy resistant (20%) or steroid dependent (36%). This issue and the recognition that chronic steroid therapy was associated with important morbidity led many clinicians to conclude that earlier and more aggressive treatment with immunosuppressives is warranted in selected patients with Crohn's disease.

Three classes of conventional immunosuppressive drugs have been extensively evaluated in Crohn's disease : the purine antimetabolites, cyclosporin, and methotrexate.

The purine antimetabolites

Early studies which evaluated these drugs were characterized by important methodological deficiencies and thus it is not surprising that inconsistent results were obtained. However over the past decade more rigorously designed controlled studies have confirmed the efficacy of these drugs.

One of the more important randomized controlled trials was conducted by Candy *et al.* (2), who assigned 63 patients with active Crohn's disease to receive a standard tapering induction regimen of prednisone (3 months) and either AZA 2.5 mg/kg daily or a placebo for 15 months. Although no early (12 week) benefit of AZA was identified for remission rates (CDAI < 150 and no prednisone), the proportion of patients who remained in remission over the entire follow-up time was greater in the AZA group (42% vs 7%, Absolute Risk Reduction (ARR) 35%, Number Needed to Treat = 3, P = 0.001). This result is consistent with earlier observational data that suggest that the purine antimetabolites require a minimum of 3 months to show a treatment effect. In an attempt to overcome this theoretical limitation Sandborn *et al.* performed an open study (3) in which patients with active disease received an intravenous 1800 mg loading dose of AZA. This strategy rapidly achieved stable erythrocyte concentrations of the thiol metabolites, which are believed responsible for the immunosuppressive effects of AZA. Despite this promising finding, a subsequent multicenter placebo controlled trial (n = 96) (4) showed equally low (8 week) remission rates in patients who received either loading or conventional AZA regimens (25% vs 24%) in spite of achieving steady state nucleotide levels by week 2. Furthermore, the proportion of patients entering remission did not increase after 8 weeks of treatment. The data from the trials which have evaluated the purine antimetabolites for the treatment of active Crohn's disease have been summarized in a meta-analysis (5) which the pooled ARR for AZA therapy induction of remission is approximately 20% (NNT = 5) (Fig. 1). A steroid sparing effect was also demonstrated. The NNT for steroid sparing (the number of patients needed to treat with AZA for one additional patient to reduce steroids to <10 mg/day) was estimated to be 3. However, these results should be interpreted with a fair degree of caution, since important clinical heterogeneity exists among the studies in their definitions of treatment response, duration, and the use of co-interventions.

More recently Markowitz and colleagues (6) evaluated the efficacy of 6-MP in children with newly diagnosed, steroid dependent Crohn's disease. All of their patients received a standard dose of prednisone which were subsequently tapered according to a defined schedule. Therapy with either 6-MP or placebo was continued for 18 months. A high rate of initial remission was obtained in both treatment groups however patients who were assigned to active therapy were much less

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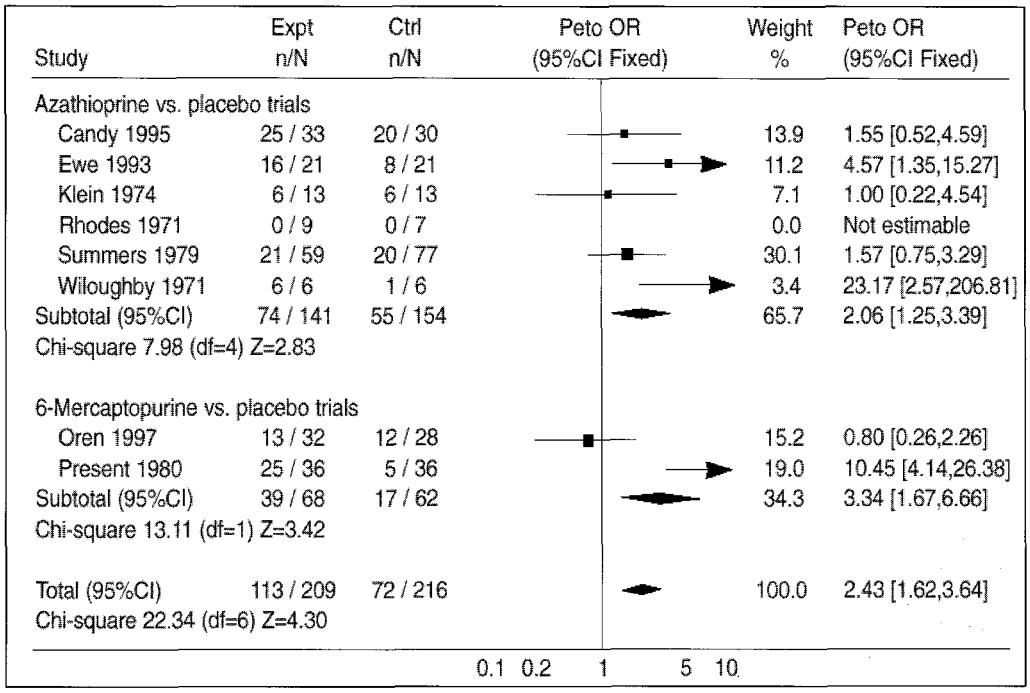

Fig. 1. — Azathioprine or 6-Mercaptopurine for inducing remission in Crohn's disease. Reprinted with permission (Sandborn W.J., Sutherland L., Pearson D. *et al.* Cochrane Review. In : The Cochrane Library, issue 2, 1999. Oxford : Update Software).

likely to relapse during the follow-up period (9% vs. 47% P = 0.007). Furthermore children who received 6-MP also were significantly less likely to receive steroid therapy. Apart from mild leukopenia and asymptomatic elevations of the serum transaminases no important toxicity was identified.

These studies suggest that AZA is a useful agent for maintenance of remission in selected high risk patients. This was also the conclusion of a systematic review which was performed by Pearson *et al.* (5,7). These authors analyzed the results of five randomized trials of AZA, of which two studied only patients with quiescent disease and three enrolled patients in a separate phase of a trial which also included patients with active disease. These trials were all relatively small, with a total of 319 patients included. The overall rate of maintenance of remission was 91/136 (67% ; CI 59–75%) for treatment compared to 96/183 (52% ; CI 45–60%) for placebo (Fig. 2). The analysis suggested that higher doses of AZA were more effective than a dose of 1 mg/kg. The Peto odds ratio for response to AZA in comparison to placebo was 2.16 (CI 1.35–3.47).

The NNT to prevent one recurrence was 7. There was some evidence of a steroid sparing effect, although this was based on the analysis of only 30 patients in two trials. Patients who received AZA were at greater risk of withdrawal from studies due to adverse events compared to those on placebo (Peto odds ratio 4.36 , CI1.63–11.67). The number needed to harm was estimated to be 19. Withdrawals due to adverse effects were noted in 5.8% of those patients receiving therapy, and 1.3% of the patients who were not. The authors concluded that AZA has a modest benefit for maintenance of remission, but there is strong evidence that a dose of 1 mg/kg is not effective.

Based on cumulative experience from the literature (8,9), minor toxicity (nausea, feeder, skin rash, leukopenia, increased liver enzymes) is relatively common with these drugs. Pancreatitis occurs in approximate 3% of patients. Although serious bacterial or viral infections are relatively rare, fatal cases have been reported. Whether use of these drugs is associated with an increased risk of neoplasia, specifically lymphoproliferative disease, remains controversial.

In summary most clinicians regard the purine metabolites drugs to be the treatment of choice for patients with Crohn's disease who fail to respond to or become depend upon glucocorticoids. Whether early treatment with these drugs should be considered for all patients with active Crohn's disease is currently unknown.

Cyclosporin

The emergence of cyclosporin as a standard therapy for organ transplantation led to several large scale evaluations for the treatment of chronically active Crohn's disease. The results of four RCTs have shown that the therapeutic index of cyclosporin is low (10-13), if there is any efficacy. The study of Brynskov (10), which demonstrated only a modest benefit, used a high drug dose (7.6 mg/kg per day), which cannot be recommend-

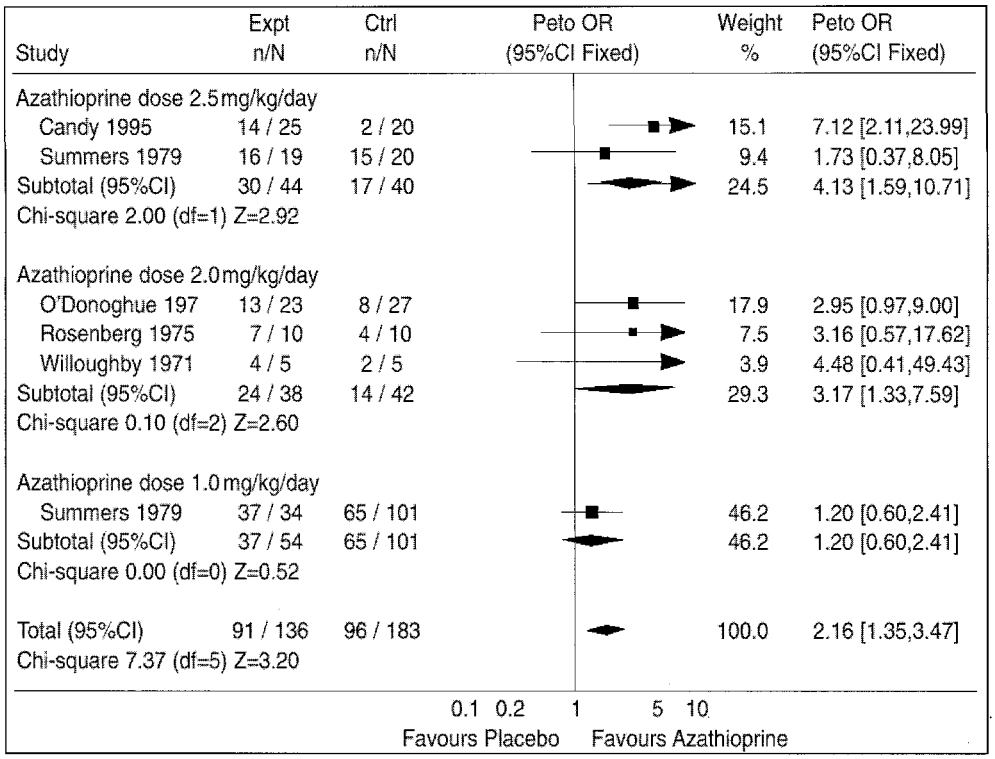

Fig. 2. — Azathioprine for maintaining remission of Crohn's disease. Reprinted with permission (Pearson D.C., May G.R., Fick G. *et al.* (Cochrane Review) In : The Cochrane Library, issue 2, 1999. Oxford : Update Software).

ed for chronic treatment, since the risk of nephrotoxicity is unacceptably high (14). Other well-documented adverse effects of cyclosporin include an increased risk of opportunistic infection, hypertension, seizures in patients with a low serum cholesterol concentration and lymphoma. The three trials (11-13) which assessed a dose of cyclosporin that is tolerable for chronic therapy (5 mg/kg per day) showed no benefit of treatment. Thus cyclosporin is neither effective or safe for the long term management of Crohn's disease. Although uncontrolled studies (15,16) have suggested that short duration, high dose intravenous therapy may be beneficial in patients with refractory disease, data from controlled trials are required before this intervention can be advocated for widespread use. Given the paucity of data to support efficacy and the well established toxicity of cyclosporin it is surprising that some opinion leaders and textbooks continue to suggest that it has a role in standard management the disease.

Methotrexate

The success of low dose (5–25 mg/weekly) methotrexate (MTX) as a treatment for rheumatoid arthritis led to its evaluation in patients with chronically active CD. In 1989 Kozarek and colleagues (17) first reported use of methotrexate for the treatment of IBD in 21 patients (14 with Crohn's disease, 7 with ulcerative colitis) with chronically active disease. MTX was administered intramuscularly at a dose of 25 mg once weekly with conversion to a maintenance dose of 15 mg orally in patients who responded to therapy. Approximately two thirds of patients had improvement in symptoms in this uncontrolled study and a steroid sparing effect was also demonstrated. Notably one third of the Crohn's patients demonstrated endoscopic improvement whereas no such beneficial effect was seen in the patients with ulcerative colitis. On the basis of these promising results further studies were initiated.

Four randomized, double blind, placebo controlled trials of MTX in chronic active, steroid dependent Crohn's disease have been reported. In the largest study, the North American Crohn's Study Group Study (NACSG) investigators (18) assigned 141 patients with chronically active steroid dependent disease to 25 mg of intramuscular MTX weekly or a placebo. Following 16 weeks of treatment, 39.4% of MTX treated patients were in remission without prednisone compared with 19.1% in the placebo arm ($p = 0.025$) (Fig. 3). Beneficial effects of methotrexate treatment were seen for disease activity, quality of life, and prednisone utilization. The effect of treatment was greatest in those patients who had required greater than 20 mg of prednisone per day to control their symptoms.

Although withdrawal from therapy for adverse events occurred more frequently in the methotrexate group (17% vs. 2%, $p = 0.012$) the majority of withdrawals were protocol-defined and were attributable to asymptomatic elevations of hepatic enzymes. On the basis of these results the investigators concluded that metho-

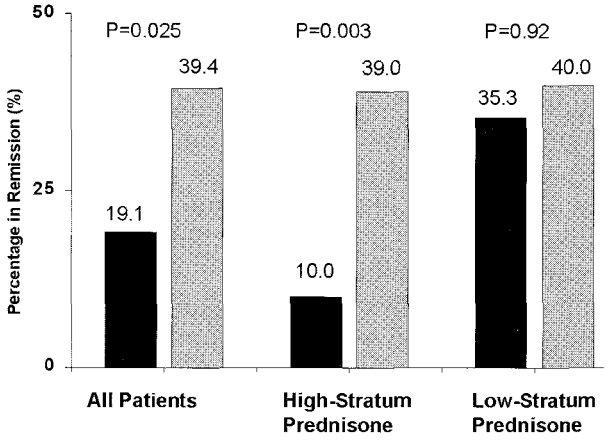

Fig. 3. — Percentages of patients in remission at week 16, according to study group and stratum of daily prednisone dose before entry into the study. Reprinted with permission (Feagan *et al.* Methotrexate for the treatment of Crohn's disease. *N. Engl. J. Med.*, 1995, **332** : 292-297).

trexate was an effective treatment for induction of remission in glucocorticoid dependent patients. A second trial performed by Oren and colleagues in Israel (19) compared oral methotrexate, (12.5 mg weekly), and 6-MP (50 mg once daily), to a placebo in 84 patients with chronically active steroid dependent disease. Patients were also allowed treatment with 5-aminosalicylates. Remission was defined as the occurrence of a Harvey-Bradshaw score of < 4 without steroid use at the end of 9 months of treatment. The proportion of patients who met this criterion in the three treatment groups was : 12/26 (46%) of patients who received placebo, 13/32 (41%) of patients assigned to 6-MP, and 10/26 (38%) of patients who received methotrexate ($p > 0.05$). Similarly, no significant differences were demonstrated among treatment groups in the time required to enter remission, mean Harvey-Bradshaw scores or the average monthly steroid dose. In subgroup analyses the methotrexate treated patients had a significant improvement in general well being and reduction in abdominal pain relative to the other two groups. This negative trial has been criticized because of the relatively low doses of 6 MP and methotrexate which were chosen for evaluation. A third trial recently published by Arora and colleagues (20) compared oral methotrexate 15-22.5 mg weekly to placebo in 33 Crohn's patients who were treated for one year. Fewer methotrexate treated patients experienced disease-related exacerbations during the follow-up period (46% vs. 80%) but this difference was not statistically significant. Similarly a non-significant trend toward an increased number of side effects in the MTX treated patients (33% vs. 0%, $p = 0.2$) was observed. Finally a study which was primarily concerned with evaluating the pharmacokinetics of subcutaneous MTX in patients with either refractory, steroid dependent Crohn's disease or ulcerative colitis showed equivalent complete remission rates (17%) irrespective of whether patients receive 15 mg/kg/week or 25 mg/kg/week of drug.

Data from a recently completed trial (21) shows that low dose MTX is effective as a maintenance therapy in patients with quiescent disease. In this study, 76 patients were randomly assigned to receive maintenance therapy with 15 mg weekly of intramuscular MTX or placebo. Prior to entry into the trial, all of the patients had been documented with chronically active steroid dependent disease and then had been successfully treated with a MTX induction regimen (16-24 weeks of 25 mg weekly by IM injection). Efficacy was evaluated by comparing the proportion of patients who remained free of a relapse (CDAI increase > 100 points or need for treatment of active Crohn's disease) over 40 weeks of follow-up. At the end of the study, 26 patients (65%) had remained in remission over the entire duration of follow-up in the MTX group, compared with 14 patients (38.9%) in the placebo group ($p = 0.015$).

Accordingly individuals who received MTX were less likely to require prednisone therapy (11 of 40, 27.5%, vs. 21 of 36, 58.3%, $P = 0.007$) and had lower disease activity (mean $\pm$ SE CDAI scores 135 ± 16 compared with 196 ± 18, $P = 0.001$). Moreover, over half of the patients who relapsed were successfully retreated with the induction regimen of MTX (25 mg weekly), were free of prednisone and in remission at the end of the study. An interesting observation was the relatively high rate of remission rate observed in the placebo group (38.9%) ; based on previous trials of AZA and/or glucocorticoids the investigators had predicted that a response rate of no greater than 20% was likely. One possible explanation is the possibility that the induction regimen of MTX which patients had received prior to randomization resulted in healing of mucosal ulceration and a durable clinical response. Although no serious adverse events were observed in this study, the participants were selected for tolerance of MTX. However, the adverse event profile of MTX is well described in other diseases. To minimize the possibility of hepatotoxicity patients with risk factors (obesity, diabetes mellitus, alcohol abuse, pre-existing liver disease) should not be treated. Patients should be monitored according to the American Rheumatological Association (ARA) criteria (22). In patients with rheumatoid arthritis the risk of serious liver disease is very low if these guidelines are followed. Nausea is the most common adverse event observed with MTX treatment, however it is uncommon for this problem to result in discontinuation of therapy. Hypersensitivity pneumonitis (23) usually presents with dyspnea and responds well to high dose glucocorticoid therapy. Women of childbearing potential should not received MTX because of the high risk of teratogenicity (24).

What conclusions can be drawn from this initial experience with MTX ? The largest studies have provided rigorous evidence, which supports the efficacy of MTX in both active disease and for maintenance therapy. However several points should be made regarding the

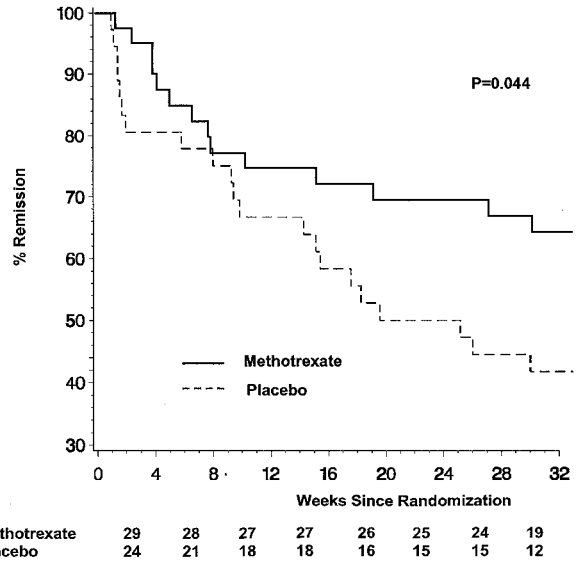

Fig. 4. — Kaplan-Meier estimates of the time to relapse in the methotrexate and the placebo group in the NACSG MTX maintenance trial. Reprinted with permission (Feagan *et al.* A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N. Engl. J. Med.*, 2000, **342** (22) : 1627-1632).

MTX regimens which were utilized. First, in the NACSG trial (25) MTX was used at a relatively high dose (25 mg/weekly) in conjunction with prednisone. Thus the efficacy of MTX monotherapy for induction of remission is unknown. Second, MTX was given by intramuscular injection. Using this route of administration 15 mg of MTX was also shown to be effective for maintenance therapy. In contrast, Oren and colleagues (26), who used a MTX dose of 12.5 mg orally for induction of remission, could not demonstrate a beneficial effect of MTX (or low dose 6-MP) in comparison to placebo. Finally, although the trial of Arora and colleagues (20) had limited statistical power, a beneficial response was suggested using a higher oral dose than that used in the Israeli study (15-22.5 mg/weekly). Collectively, these data may mean that the dose response curve for MTX therapy in Crohn's disease is shifted to the right in comparison to rheumatoid arthritis, where oral MTX doses as low as 7.5 mg/week are effective. If doses of more than 15 mg/week are required for efficacy then oral administration may be suboptimal due to incomplete drug absorption from the gastrointestinal tract. Intramuscular injection is inconvenient for patients and relatively costly if administration by health-care personnel is required. One potential solution to this problem is the use of subcutaneous administration of the drug. This approach has been utilized in rheumatoid arthritis with good results. Based on experience our center patients can easily be taught to self inject MTX subcutaneously and we perceive no loss of drug efficacy associated with this route of administration.

Important questions remain regarding the potential clinical applications of MTX in Crohn's disease. No data from controlled trials are currently available regarding the use of the drug for the treatment of fistulas. An initial uncontrolled experience suggested that MTX is effective for this indication in patients who are refractory to therapy with purine antimetabolites. Similarly, our anecdotal experience is that MTX is effective for some extraintestinal manifestations of the disease including arthralgias and arthritis, erythema nodosum and pyoderma gangrenosum. Additional experience with these syndromes is needed.

Current and future role of immunosuppressives in CD

In summary the purine antimetabolites are the most frequently prescribed drug for patients with Crohn's disease who are either refractory to or dependent upon glucocorticoids. This practice is based on the results of four relatively small, randomized controlled trials which utilized an adequate dose of either 6-MP or AZA and extensive clinical experience. However gastroenterologists should reflect upon the observation that in rheumatoid arthritis MTX has superseded AZA as a therapy due to superior efficacy and long-term tolerability. In the absence of good comparative data, clinicians must decide which of MTX or the purine antimetabolites is the preferred treatment for Crohn's disease (25,27). A great deal of long-term safety data is available for the purine antimetabolites whereas the risk of liver disease in patients with Crohn's disease treated with long-term MTX therapy remains an issue. However, significant hepatic toxicity in RA is rare and surveillance liver biopsy is no longer recommended. In the absence of biopsy data from patients with Crohn's disease, the ARA guidelines regarding surveillance for hepatic toxicity should be followed.

The emergence of infliximab as a new therapy for patients with refractory Crohn's disease (28,29) should also focus additional attention on the use of MTX as an alternative to the purine antimetabolites. In patients with rheumatoid arthritis concomitant treatment with MTX has been shown to enhance the response to infliximab therapy. Furthermore, patients who are receiving methotrexate are less likely to develop human antichimeric antibodies (30). These antibodies, which may block be beneficial action of infliximb or cause adverse effects, are a significant limitation to the long-term use of this form of treatment. Thus, a strong rationale exists to consider MTX-infliximab combination therapy in Crohn's disease.

Although controlled trials to compare the relative efficacy and safety of AZA and MTX in therapy resistant patients are desirable, these studies will be difficult to conduct because of the relatively small differences in potency and tolerability between these agents. A more

productive area for future investigation will be to explore the use of these drugs in combination with infliximab and other biological treatments.

Immunosuppression in ulcerative colitis

The majority of patients with ulcerative colitis are successfully managed with 5-ASA and brief courses of glucocorticoids. Patients with refractory disease, as defined by the need for chronic glucocorticoid therapy to control symptoms, often undergo colectomy since many clinicians are reluctant to consider the use of chronic immunosuppression in a disease which can be treated surgically and has a time-dependent, increased risk of colon cancer (31). Thus it is not surprising that far less data are available to assess the efficacy of immunosuppressive drugs in this condition as compared with Crohn's disease.

The purine antimetabolites

The data which support the use of this class of drugs in ulcerative colitis is far less compelling than in Crohn's disease. No randomized controlled trials have demonstrated efficacy for AZA in the induction of remission in patients with active colitis. However post hoc analysis of a trial by Jewell and Truelove (32), suggested a beneficial effect in maintaining remission in patients with an established diagnosis of the disease in distinction to those with a first attack (38% in remission vs. 12% after one year of treatment, P = 0.055). This finding is in keeping with data from Hawthorne and colleagues (33) who performed a withdrawal study which evaluated the efficacy of AZA in 79 patients who entered remission after receiving AZA therapy. Patients who were assigned to withdraw from AZA had a greater rate of relapse at one year compared to those who remained on drug therapy (59% vs. 35%, p = 0.04). Although this trial is encumbered by the presence of a "responder bias" which tends to inflate the estimate of efficacy it remains the most compelling evidence in support of a benefit of AZA. No randomized controlled trials have evaluated 6-MP treatment for colitis.

Not withstanding the limited data available many clinicians would prescribe AZA therapy in patients with chronic refractory colitis who decline the option of surgery. Clearly stronger evidence to support this practice would be welcome.

Cyclosporin

No controlled studies have evaluated the efficacy of oral cyclosporin therapy in ulcerative colitis. There have been numerous uncontrolled studies and one small controlled trial of high dose (4 mg/kg/day) intravenous cyclosporin in patients with severe colitis (34). The latter study evaluated 20 patients who had failed to respond to conventional therapy with intravenous steroids. This trial was stopped following randomization of 20 of a planned 48 patients. The investigators discontinued randomization because 9 of 11 cyclosporin treated patients (82%) experienced a treatment success compared with 0 of 9 (0%) assigned to the placebo group (P < 0.001). The mean time to respond was 7.1 days. Five of the 9 placebo treated patients responded following across over to open label cyclosporin. One cyclosporin treated patient develop a gran mal seizure which required withdrawal of therapy. Two of 11 patients (18%) developed hypertension which required treatment. On the basis of these results the investigators concluded that it was not ethical to continue to randomize patients to placebo and terminated the study.

Since publication of this study no further large-scale trials of cyclosporin have been performed. Although some experts have recommended combination therapy with azathioprine as a means of weaning patients from cyclosporin, strong evidence to support this position is lacking. Thus the long-term benefits of intravenous cyclosporin in this patient population are unclear. As noted previously nephropathy, opportunistic infection and neoplasm are important concerns. Clinicians who offer this form of therapy should clearly inform patients of these risks.

Methotrexate

Only one randomized, double blind, placebo controlled trial of MTX in chronic active ulcerative colitis has been performed. In this study, Oren and colleagues (26,35) compared oral MTX (12.5 mg weekly) to placebo for 9 months in 67 patients who had received steroids and/or immunosuppressive drugs for at least 4 of the 12 preceding months. No statistically significant differences were demonstrated among the treatment groups in the proportion of patients achieving remission, the time required to achieve remission, or the proportion of patients experiencing a relapse after a remission had been obtained.

Thus no good data from controlled trials exist to support the use of MTX as a therapy for ulcerative colitis. A research priority should be to evaluate the efficacy of a higher dose of MTX than 12.5 mg weekly in this disease.

Current and future role of immunosuppressives in ulcerative colitis

Important questions remain regarding the role of immunosuppressive drug therapy in ulcerative colitis. Although many clinicians prescribe AZA or 6-MP for the treatment of refractory patients the magnitude of benefit associated with this practice is unknown. Similarly although extensive anecdotal evidence and one small controlled trial indicate that intravenous cyclosporin is effective for induction of remission in patients with severe colitis the optimum long-term man-

agement strategy to be used in this group of patients has not been defined. Moreover, the toxicity of cyclosporin severely limits chronic use of this drug. Analysis of existing data suggests that the future of immunosuppression in ulcerative colitis may reside in the development of new agents rather than in refinement of our existing drug regimens.

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