Preventing relapse in Crohn's disease

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J-P GENDRE. Preventing relapse in Crohn's disease. *Can J Gastroenterol* 1993;7(2):237-240. Preventing relapse remains a main challenge in Crohn's disease. Three different clinical situations should be considered separately. First, in patients in clinical remission, the most useful drugs might be sulphasalazine and its derivatives. Only 5-aminosalicylic acid (5-ASA) has been shown to be effective in such patients. It is likely that 5-ASA, at a dose from 2 to 3 g per day, reduces the relapse rate, particularly when used early after achieving remission. What is the proper dosage? How long must the treatment last? Must patients with a long-standing remission be treated? The three questions remain unanswered. Second, in patients clinically and macroscopically in remission seen immediately after surgery, there is no evidence of any drug efficacy to prevent clinical and/or endoscopic recurrence, but there is a slight trend in favour of 5-ASA. Third, in patients with chronic, mildly active disease, when surgery must be avoided because of anticipated disabling consequences, immuno-suppressants such as azathioprine and/or 6-mercaptopurine seem the most appropriate and effective drugs. Usefulness of methotrexate and/or cyclosporine needs evaluation.

Key Words: 5-Aminosalicylic acid, Crohn's disease, Immunosuppressives, Maintenance treatment, Pharmacotherapy

Prévention des redits de la maladie de Crohns

RÉSUMÉ: La prévention des rechutes de la maladie de Crohn demeure un problème mal résolu. Trois situations cliniques différentes doivent être envisagées. 1/Chez les malades en rémission clinique, qu'ils aient été ou non opérés auparavant, les produits les plus utiles sont la sulfapyridine et ses dérivés. Seul le 5-ASA s'est avéré efficace chez de tels malades. Il semble établi qu'à une posologie de 2 à 3 g/j, le 5-ASA est capable de réduire la fréquence des rechutes, en particulier chez les malades qui viennent d'être mis en rémission. Quelle est la meilleure posologie? Combien de temps faut-il prolonger le traitement? Faut-il traiter les malades en rémission depuis longtemps? Ces trois questions restent pour l'instant sans réponse. 2/Chez les malades en rémission clinique et macroscopique au décours d'une intervention chirurgicale, aucun traitement n'a fait

IN ULCERATIVE COLITIS, MAINTENANCE treatment has been well established for a long time. In contrast, preventing relapse in Crohn's disease remains an important therapeutic challenge and should be discussed according to some of its relevant aspects, the most important of which is the disease's natural history. The data collected from the placebo groups in maintenance therapeutic trials are very interesting in this respect. Clinical relapses occur at a rate of 40 to 65% over a 12- to 24-month period (1-3). Results of maintenance treatment trials are difficult to interpret in patients with quiescent Crohn's disease because the patients are not homogeneous with respect to their relapse risk. The easiest way to analyze the results and/or stratify the patients in clinical trials is probably to take into account their previous clinical history. The type of remission is also of great value. Therefore, three different clinical scenarios will be discussed separately: patients in complete clinical remission, patients clinically and macroscopically in remission immediately after surgery and patients with a chronic, mildly active disease.

Patients in complete clinical remission: In patients with complete clinical remission, the aim of treatment obviously is to maintain a long-standing

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preuve d'activité sauf une légère tendance en faveur du 5-ASA. 3/Chez les malades avec une forme chronique modérément active, lorsque la chirurgie doit être évitée du fait de ses conséquences invalidantes prévisibles, l'azathioprine et/ou la 6-mercaptopurine constituent les produits les plus appropriés et les plus efficaces. L'intérêt du métho-trexate et/ou de la cyclosporine reste à établir.

remission with a well-tolerated and easy-to-take drug.

The treatment of the acute phase of Crohn's disease may influence the further clinical course; thus, remission induced by an elemental diet has been shown to be shorter than remission induced by steroids (4,5). In fact, sustained treatment usually is advised.

Miscellaneous drugs such as oral BCG (6), levamisole (3) or rifampicin and ethambutol (7) have not been found to be effective in clinical trials.

The most commonly used drugs are corticosteroids, and sulphasalazine and its derivatives. All controlled therapeutic trials (1,8-11) but one (2) have failed to show any benefit from either low dose steroid or sulphasalazine (and even in that study (2), steroids alone or in combination with sulphasalazine were only effective in patients who responded initially to treatment of active disease; these drugs were not significantly beneficial when used in inactive disease).

It has been suggested that sulphasalazine efficacy was limited by its side effects and therefore 5-aminosalicylic acid (5-ASA) might be useful when used at equivalent or higher dosage. In accordance with clinical results in acute phases, five controlled trials (12-16) have been conducted to test the effectiveness of 5-ASA as maintenance treatment. The results of these studies are somewhat contradictory. Two of them (12,16) showed negative results. In both groups, the dose was low (Pentasa [Brocades Pharma] 1 or 2 g per day, respectively) and the trial was of short duration (four months). In the first (12), the number of patients included was only 46. Despite a greater number of patients (101 in each group) and a higher dose (Pentasa 3 g per day) in the second study (16), the cumulative percentage of relapses over 18 months was the same (29%) in the 5-ASA and the placebo groups, but the duration of

remission before entry was not taken into account. The three other trials found results in favour of 5-ASA.

In an international multicentre trial (13) (209 patients), the cumulative percentage of relapses over 12 months was 22.2% on Claversal (SmithKline French) (1.5 g per day) versus 42.8% on placebo ($P < 0.05$), with the difference more significant in patients with ileal disease location (13). In the French trial conducted by the Groupe d'Étude Thérapeutiques des Affections Inflammatoires du tube digestif (GETAID) (14), 161 patients were included in a controlled trial of Pentasa (2 g per day) versus placebo over two years. They were stratified into two strata, presumed to have a different relapse risk: a low relapse risk stratum (LRRS) for patients in remission from three to 24 months and a high relapse risk stratum (HRRS) for patients in remission for less than three months. Lifetable analysis showed no significant difference between treatment groups in the LRRS, but noted a significant difference in the HRRS ($P < 0.003$); in this stratum, the cumulative percentage of relapse in the Pentasa group was 28 and 55 at one and two years, respectively versus 68 and 71 in the placebo group. This difference between the two strata was not confirmed by the Italian study (15); in that trial, Asacol (Giuliani and Bracco) (2.4 g per day) was significantly better than placebo in a group of patients in remission for more than three months; the cumulative relapse rates were 34% versus 55%, respectively, at 12 months ($P = 0.02$).

Despite these trials, a number of questions about 5-ASA as maintenance treatment Crohn's disease remain without answer. What dose of 5-ASA should be recommended, even if a dose of 2 or 3 g per day is used widely in practice? Maintenance treatment must probably be started as soon as possible after achieving remission, but does

5-ASA facilitate steroid weaning in patients achieving remission on steroids? How long should the treatment last? One or two years? For the patient's life? Or, can treatment be stopped after two or three years without relapse? Is 5-ASA completely safe over a prolonged period? Further trials are warranted to help answer these questions.

Patients clinically and macroscopically in remission immediately after surgery: If all macroscopically pathological tissue has been removed surgically, then the risk of anatomical recurrence has been shown to reach 80% over the first year (17). Therefore, this group of patients provides a very accurate model to test the efficacy of different drugs, especially if the surgical procedure allows endoscopic control of the anastomosis. No study has demonstrated definite efficacy of any drug tested (9,11,18-20). Nevertheless, in one trial (20) there was a slight trend in favour of 5-ASA to prevent endoscopic recurrence in a three-month period after surgery: 50% on Claversal (3 g per day) versus 63% on placebo ($P = 0.16$). Other trials are needed to confirm these preliminary results.

Patients with chronic, mildly active disease: Patients with chronic mildly active disease are usually steroid-dependent, but despite steroid therapy they are not totally symptom-free, and they relapse as soon as steroids are decreased below the threshold of steroid dependence.

If the level of steroid dependence is low (about 10 mg per day), it is likely acceptable to continue the same dose, especially if the patient has only a few symptoms. On the contrary, if it is higher than 10 to 15 mg per day, the aim of treatment is not only to achieve a complete remission, but also to allow steroid sparing and/or weaning.

Bowel rest has been proven to be effective either as total parenteral nutrition or as a total elemental diet, but the results are often short-lived (21,22).

Lymphocyte apheresis remains controversial. It has been suggested to be of great promise in preliminary uncontrol-

led studies (23), but in one controlled trial it did not prevent early relapse (24). Immunosuppressants have probably their best indication in steroid-dependent patients, when anticipated consequences of surgery, such as extensive small bowel resection resulting in severe short bowel syndrome or proctocolectomy with permanent ileostomy, are likely to be disabling.

Methotrexate is likely to be a useful drug (25) but there is no controlled trial of its efficacy and cyclosporine has no proven efficacy as maintenance treatment (26,27). So the most often used immunosuppressant drugs are aza-

thioprine and 6-mercaptopurine. When used at the right dose (2 mg/kg per day for azathioprine, 1.5 mg/kg per day for 6-mercaptopurine), the results are very encouraging, even if they are delayed, with a median time to an effective response of three months (15 days to nine months) (28). As a whole, total remission (including steroid weaning) is observed in about 50% of the patients, with a partial response (improvement with reduction of steroid dosage) in 25% additional cases (28-31). When treatment is continued, the percentage of maintenance in remission reaches 85% over one year

(29). On the other hand, in the only published controlled trial (31), the relapse rate over one year after randomized withdrawal of azathioprine was 41% on placebo versus 5% in patients continuing azathioprine. The results could be different for patients in remission on azathioprine for a longer period (two or three years). At present, there are no data available to recommend how long the treatment must be continued. The therapeutic value of azathioprine and/or 6-mercaptopurine must be balanced against a 10% rate of potential adverse effects.

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