Mesalazime as a maintenance treatment in Crohn’s disease: is it the long awaited solution?

Crohn’s disease is characterised by alternating phases of quiescence and symptomatic relapses. Research for a maintenance treatment started in the late seventies. The National Co-operative Crohn’s Disease Study showed that neither prednisone, sulphalasalazine nor azathioprine was superior to placebo in prophylaxis among patients with quiescent disease.1 A few years later, the European Co-operative Crohn’s Disease Study did not find any significant benefit in quiescent patients receiving either sulphalasalazine, 6-methylprednisolone or their combination.2

The story with azathioprine, which is metabolised in the body to 6-mercaptopurine, in the maintenance setting is somewhat different. A small sized clinical trial concluded that azathioprine was effective compared with placebo in maintaining a prednisolone induced remission.3 Another small sized trial evaluated the effect of azathioprine discontinuation in patients who were in remission while taking the drug for at least six months and the authors reported that the relapse rate was less in the group of patients who continued the azathioprine.4 Both trials, plus others, agreed on the potential toxicity of azathioprine and concurred that it should be reserved for the treatment of the active phase in resistant cases. Recently, Bouhnik et al retrospectively analysed 199 patients who were in clinical remission (more than six months without corticosteroids) and were treated with either azathioprine or 6-mercaptopurine for more than six months with respect to time to relapse. The study confirmed the long term benefit of these drugs and suggested that withdrawal may be considered in patients who have been in remission for four years.5 This encouraged the Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID, France) to initiate a prospective randomised placebo controlled withdrawal trial aiming at confirmation of these results.

More recently, mesalazime has been reported to be an effective maintenance treatment in quiescent Crohn’s disease patients.6 7 In fact, the first trial showed that a tendency towards a beneficial effect of mesalazime was only observed in a subgroup of patients with ileocolitis and the authors, who did not report either the dose or the brand of mesalazime, mentioned that an additional two patients in the treatment arm relapsed but these relapses were not taken into account because of non-compliance.8 Also, the second trial concluded that mesalazime was effective after excluding 17% of the randomised patients.7

This new hope has been followed by conflicting results. Firstly a benefit was reported among patients who had a relapse free interval of more than three months.8 However, the GETAID group reported that mesalazime had no effect in this group of patients and was only effective among patients treated within three months after the achievement of remission.9 Their results led to the initiation of two randomised placebo controlled trials, one performed by the GETAID and the other by an Italian group.10 11 In both trials, patients with active Crohn’s disease were treated with corticosteroids (1 mg/kg/day) and those who achieved clinical remission within three to eight weeks were randomly assigned between mesalazime and a placebo. The GETAID trial showed a borderline significant benefit with respect to the percentage of patients who could successfully be weaned from corticosteroids (74% v 58% in the mesalazime and placebo arms respectively, p=0.054), but time to relapse curves after weaning did not suggest any beneficial effect for mesalazime.10 However, the authors reported that mesalazime turned out to be borderline significant in delaying relapses after weaning (p=0.042) if adjusted for three variables found to be of prognostic importance in their data: the CDAI level at weaning, the white blood cell count, and the use of mesalazime in the month before registration into the trial.10 Also, an interim analysis of the Italian data based on 106 patients followed up for 12 months (a total of 47 relapses) showed that the relapse rates were virtually identical in both groups and data concerning percentage of successful weaning were not reported.11 In view of these contradictory data, it remains unclear whether mesalazime is effective as a maintenance treatment and, if so, in which subgroups of quiescent Crohn’s disease patients. A few other trials investigated the efficacy of mesalazime in the prevention of postoperative recurrence but this particular question is outside the scope of this paper.

One reason for these contradictory results may lay in the between trial differences in the patient inclusion criteria, for example, the interval since the end of the previous relapse. We do not have a way, other than the visual examination of patient characteristics, of directly comparing these trials. Another reason may be the possible imbalances of prognostic factors between the two treatment arms in each trial. Although in most of these trials the authors mentioned that the distribution of patient characteristics was not significantly different between the two arms at randomisation, a slight statistically non-significant imbalance in an important prognostic factor may mask or exaggerate a treatment effect. For example, a beneficial effect of mesalazime was suggested only after adjustment for three other variables in the recent GETAID trial.10

In our opinion, the lack of a reliable, widely accepted method for identifying quiescent Crohn’s disease patients with a high risk of relapse leads to clinical trials being conducted on a heterogeneous group of patients. To our knowledge, there are only three published models for identifying patients with a high risk of relapse. The first model suggested that patients with a remarkable change in the baseline blood values of α1 glycoprotein, α2 globulin, and the erythrocyte sedimentation rate have a higher risk of relapse.12 More recently, the same group suggested a new index based on the same three variables and suggested that the use of this index would improve the clinical characteristics for identifying high risk patients.13 The third model suggested that young age (<25 years), a long interval since first symptoms (≥5 years), a short interval since last relapse (<6 months), and colonic involvement are factors associated with shorter time to relapse.14 These results were confirmed by the bootstrap resampling
technique. The authors reported that none of the biological variables studied were found to be of prognostic importance and suggested that the methods were questionable in the first two models published by the Italian group. None of these three models have yet been adopted in the design of clinical trials in this group of patients. Clinical trials based only on high risk patients will have a higher power in detecting treatment differences than the usual trials that mix both low and high risk patients. If limiting patient entry to this group of patients may cause a recruitment problem, then one should think about conducting multinational inter-group trials or at least stratify by risk group at randomisation.

This lack of consensus about the effectiveness of mesalazine for maintaining remission in patients with Crohn's disease encouraged a meta-analysis to be carried out, a technique of primary importance for such a situation. The authors analysed summary data from four clinical trials, published as full articles, and four published as abstracts. The negative results of the two more recent trials were not available at the time of performing this meta-analysis. This meta-analysis leaves little position in favour of the drug in terms of either efficacy or cost effectiveness. Nevertheless, we believe that these conclusions are not justified by the data and that the results should be interpreted with extreme caution for quite a few reasons.

Our first concern is that the lack of individual patient data may yield the following problems: (a) a bias in the estimation of the relapse rates and the calculation of the size of the treatment effect. Patients from individual trials who were excluded from the original analysis were also excluded from this meta-analysis, a pitfall which goes against the intent to treat principle. (c) Unacceptable generalisation from the data published in articles to those published only in abstracts. (d) The exclusion of one published trial. It was not possible to test the value of mesalazine while adjusting for prognostic factors. Concerning the last point, the GETAID trial showed a strong interaction between the treatment and the interval since the end of previous relapse. Secondly, as only published trials (whether as full articles or as abstracts) were included in this meta-analysis, a publication bias in favour of the drug may have been introduced. Thirdly, two of the trials were mainly investigating the prevention of postoperative endoscopic recurrences after intestinal resection considered to be 'curative' in one of the trials. Consequently the definition of quiescence in these two trials is different from the others. Fourthly, the forest plot, which is the standard way to report the results of meta-analyses, was not used and no statistical test for heterogeneity was performed. Fifthly, when the authors excluded half a trial 62 patients out of a total of 941 patients from eight trials (6-6%), the p value for the overall effect in the first six months jumped from <0.01 to almost 0.05. This is literally still significant but, in a meta-analysis context, this is not really convincing. This might even give an indication of statistical heterogeneity between the trials.

The authors also concluded that mesalazine was cost effective. They estimated the cost of a relapse to be somewhere between $700 and $170 000 with an expected average of $9000, figures only supported by unpublished findings. They also estimated the mesalazine cost for treating 100 patients for two years using 2 g/day to be $188 340. On the other hand, this price is overestimated because if one decides to treat 100 patients for two years, using their estimates only 91 patients will continue the drug after the first six months and only 71 after 12 months. On the other hand, recent trials testing mesalazine in this group of patients are using 3 g/day and 4 g/day. If these trials showed the efficacy of the treatment, which is not the case, this would have increased their estimates by 50–100%.

In conclusion, based on the available data in the medical literature, it is still too early to consider that mesalazine is effective as a maintenance monotherapy in quiescent Crohn's disease patients. A detailed cost effectiveness study is needed. A meta-analysis based on individual patient data for all published and unpublished trials is necessary before any definitive conclusions can be drawn.
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