Prevention of relapse by mesalazine (Pentasa®) in pediatric Crohn’s disease: A multicenter, double-blind, randomized, placebo-controlled trial

Prévention des rechutes par la mésalazine (Pentasa®) dans la maladie de Crohn de l’enfant. Étude multicentrique randomisée, en double insu


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Available online 31 December 2008

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Summary

Aim. — This study aimed to test the efficacy of mesalazine in maintaining remission in pediatric Crohn’s disease (CD) following successful flare-up treatment.

Methods. — In this double-blind, randomized, placebo-controlled trial, 122 patients received either mesalazine 50 mg/kg per day (n = 60) or placebo (n = 62) for one year. Treatment allocation was stratified according to flare-up treatment (nutrition or medication alone). Recruitment was carried out over two periods, as the first period’s results showed a trend favoring mesalazine. Relapse was defined as a Harvey—Bradshaw score more than or equal to 5. Time to relapse was analyzed using the Cox model.

Results. — The one-year relapse rate was 57% (n = 29) and 63% (n = 35) in the mesalazine and placebo groups, respectively. We demonstrated a twofold lower relapse risk (P < 0.02) in patients taking mesalazine in the medication stratum (first recruitment period), and a twofold higher risk in patients taking mesalazine in the nutrition stratum (second recruitment period), compared with the other groups. None of the children’s characteristics, which differed across the two recruitment periods, accounted for the between-period variation in mesalazine efficacy. One serious adverse event was reported in each treatment group.

Conclusion. — Overall, mesalazine does not appear to be an effective maintenance treatment in pediatric CD.

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Résumé

Objectifs. — Tester l’efficacité et la tolérance de la mésalazine dans la prévention des rechutes de la maladie de Crohn de l’enfant.

Méthodes. — Cent vingt-deux patients ont reçu de façon randomisée, en double insu soit de la Mésalazine (50 mg/kg par jour) (n = 60) ou du placebo (n = 62) pendant un an. Le recrutement a eu lieu sur deux périodes (1990—1993 et 1996—1999) du fait d’une tendance positive en faveur de la mésalazine pour la première période et suivant les modalités thérapeutiques (médicament seul [M] ou nutrition entérale [NE]) du traitement de la poussée de la maladie. La rechute a été définie par un score de Harvey-Bradshaw supérieur ou égal à 5. L’analyse statistique a été réalisée par le modèle de Cox.

Résultats. — Le taux de rechutes à un an a été de 57 % (29) et 63 % (35) dans le groupe mésalazine et le groupe placebo (N.S.). Une réduction significative a été retrouvée en faveur des patients traités par M (p < 0.02) dans la première période et une augmentation en faveur des patients traités par NE dans la seconde période. Aucune différence dans les deux périodes d’étude n’a permis de retrouver un facteur prédictif de ces résultats.

Conclusion. — La mésalazine ne paraît pas être efficace dans la prévention des rechutes de la MC de l’enfant.

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Introduction

Crohn’s disease (CD) is a chronic inflammatory intestinal disorder diagnosed during childhood (before the age of 16) in 10—20% of patients [1]. The symptomatic relapse rate is high in both adults and children with CD, ranging from 40 to 70% over a period of one to two years [2,3]. Prevention of symptomatic relapses remains a major issue in the long-term management of pediatric CD, including the prevention of complications specific to that age group such as growth failure, pubertal retardation and bone demineralization [4—7].

Controlled clinical trials in adults [8] and, more recently, in children [9] have demonstrated the efficacy of azathioprine and 6-mercaptopurine in maintaining CD patients in remission. Also, trials published at the time that our study was completed have shown that methotrexate [10] and infliximab [11] are also effective in adult CD. However, these treatments are usually reserved for chronic active or steroid-dependent CD because of their potential toxicity. In children, continuous or intermittent maintenance of enteral nutrition [12,13] appears to prevent relapses, but is more likely to be rejected by patients due to its adverse effects on quality of life [14].

Clinical trials using mesalazine to treat active, mild-to-moderate adult CD have shown that the agent is somewhat effective and well-tolerated [15—17]. Before our study began, a multicenter placebo-controlled study demonstrated the efficacy of oral mesalazine in adult CD patients when given within three months of achieving remission, following the successful treatment of a flare-up with steroids [18]. Consequently, it appeared of interest to assess the safety of mesalazine in children and to compare its efficacy with placebo in maintaining remission in children following the successful treatment of a clinical relapse, despite the fact that a meta-analysis [19] of mesalazine efficacy in adults found contradictory results and that a recent review [20] claimed to find no positive effect with mesalazine in adult CD.
Prevention of relapse by mesalazine (Pentasa®) in pediatric Crohn's disease

For this reason, a multicenter, double-blind, randomized, placebo-controlled trial was designed to determine the efficacy of mesalazine in maintaining remission in pediatric CD patients following the successful treatment of a relapse. Following the recruitment of 57 children from 1991 to 1993 [21], trial results showed a favorable trend with mesalazine. Recruitment was thus resumed from 1996 to 1999. The final results are presented according to these two different patient-recruitment periods.

Material and methods

The trial's primary objective was to compare the efficacy of mesalazine (Pentasa®, Ferring) vs. placebo in maintaining remission in pediatric CD patients when used after the successful treatment of an acute episode by either medication alone or parenteral/enteral nutritional techniques with or without medication. The trial schedule is shown in Fig. 1.

Patients

Patients were recruited from 17 centers—16 in France and one in Switzerland. Patients had to be less than 18 years old and diagnosed with CD before the age of 16, according to clinical, radiological, endoscopic and histological data, as previously defined [1]. Patients had to be in an active phase of disease as defined by a Harvey—Bradshaw score (HB) [22] over or equal to 5 and an erythrocyte sedimentation rate (ESR) over or equal to 25 mm at hour 1. All lesion localizations, except an exclusively anorectal localization, were included, provided that extension of the patients' lesions had been assessed within two years of inclusion in the study. Patients were excluded if a flare-up had been treated with mesalazine or immunosuppressants, or if they had a known hypersensitivity to salicylate. After flare-up treatment, inclusion criteria were as follows: patients in clinical remission within six months of flare-up treatment started prior to inclusion, with an HB score inferior to 5, an ESR superior to 25 mm, and normal hepatic and renal function. Informed written consent was requested from both parents and children on inclusion. The ethics committee of Paris-VII approved the trial protocol on 10 January 1991 covering all participating centers. The trial registry number is ISRCTN 84003996.

Treatment

Two strata were defined based on the flare-up treatment: the nutrition stratum comprised patients treated with parenteral or enteral nutritional techniques with or without drugs; the medication stratum included patients treated with drugs alone (steroids, sulfasalazine or metronidazole).

On inclusion, patients were randomized by stratum within each center, using randomized blocks of two to four (no center was aware of the size of its block), and received either 50 mg/kg per day of mesalazine or a placebo (identical tablets) over a one-year period. The randomization lists—one per center and per stratum—were generated by the randomization center. At randomization, a chronological treatment number was assigned to each patient and, accordingly, the treatment allocated to each patient was given to the physician in charge of that patient in numbered bottles, labeled with the protocol identification, center and stratum, patient's initials, treatment number, batch number and expiry date. Each allocated treatment was sent to the physician in charge of that patient in an individual sealed envelope, labeled with the treatment number, center, stratum and patient's initials. The sealed envelope was only to be opened in case of severe intolerance, in which case, the study monitor had to be informed immediately. The envelopes were retrieved at the end of the study.

The study treatment was initiated either one week after the interruption of parenteral or enteral nutrition, or at the end of sulfasalazine or metronidazole treatment, or if the prednisone dose during the steroid-weaning period was less than 0.2 mg/kg. After the study treatment began, only antispasmodic and antidiarrheal agents as well as sedatives were allowed as possible additional medications.

Data collection and follow-up

Upon study entry, each patient's complete history was taken, an HB score was calculated according to the patient's diary card, and clinical variables were measured (full blood count, ESR, serum albumin and creatinine levels, and hepatic and pancreatic function). Patients were monitored every three months over a one-year period or until the study endpoint. At each clinical visit, the patient's HB score and biological variables were evaluated, and the patient questioned regarding side-effects. Electrocardiographic monitoring was performed at study inclusion, at month 3 and at the end of the study.

The trial's primary endpoint was clinical relapse (HB score ≥ 5, confirmed within two weeks) or surgery for an acute complication of CD. The secondary endpoint was treatment failure, defined as a relapse, failure of steroid withdrawal (weaning failure), side-effect intolerance requiring treatment discontinuation, worsening or aggravation of patient's status requiring treatment interruption or initiation of a new treatment as decided upon by the clinician.

Sample-size determination

The initial sample size (n = 60) was calculated by taking into account a 70% relapse rate in the placebo group at year 1, a 35% absolute decrease in the one-year relapse rate in the mesalazine group vs. controls (placebo group) and a 20% withdrawal rate, and by using a one-sided test with a 0.05 type I error level, ensuring a power of 80%. At the end of 1993, as 57 patients had been enrolled and a low patient withdrawal rate was expected, recruitment was stopped. At the end of 1994, when all patients had been followed-up for at least a year after the withdrawal of their flare-up treatment, data monitoring—with extensive data-cleaning procedures—was performed, followed by data analysis according to the protocol. This analysis, initially planned as the final analysis, showed a trend toward mesalazine efficacy in preventing relapse [21]. It was then decided, following a meeting at the end of 1995 where these promising results were presented to all trial investigators, to resume recruitment at the beginning of 1996, using each period of recruitment (pre-1994 and post-1995) as an additional stratification factor. Sample size was recalculated according to a lower relapse rate in the controls and a lower estimate of the mesalazine effect. Assuming a 65% relapse rate in the control group, a 25% absolute decrease in the relapse rate in the mesalazine group vs. the placebo group and a 15% rate of withdrawal, the sample size was increased to 132 patients.

Statistical methods

Comparison of baseline characteristics between groups (defined by treatment and/or stratum) was performed using a chi-square and Fisher's exact tests, when necessary, for qualitative items, and using the Mann–Whitney test for quantitative items.

Comparisons between maintenance-treatment groups were performed on an intention-to-treat basis (in all eligible patients). Time to relapse or time to failure was estimated using the Kaplan–Meier method [23], and the curves compared using log-rank tests and the proportional-hazards model [24]. In addition to the initial flare-up treatment, defined as a stratification factor in the protocol...
design, it was decided, at the end of 1995, to establish the recruitment period (pre-1994 and post-1995) as an additional stratification factor. This approach appeared logical as the patient recruitment periods were separated by an interval of around two years.

The primary endpoint—that is, the time to relapse—was analyzed in two ways, taking into account the treatment group (mesalazine or placebo) and the two stratification factors: the flare-up treatment (medications alone, or nutrition with or without medications); and the recruitment period (pre-1994 and post-1995). The time to relapse was analyzed according to treatment effect, stratification-factor effects and possible variation in treatment effect across stratification factors (interaction). This was done with
the Cox model, using the following dummy variables: maintenance treatment (mesalazine vs. placebo); flare-up treatment (nutrition vs. medication); recruitment period (pre-1994 vs. post-1995); and the two-by-two interactions, using backward selection through a likelihood ratio test [25]. The time to relapse was then analyzed in three successive steps to first assess the effect of each stratification factor in the placebo group (step 1), then to assess their effect in the mesalazine treatment group (step 2) and, finally, to assess any treatment effect (step 3) after having collapsed the stratification-factor groups with similar times to relapse in the first two steps. In this second approach, the Cox model was used to:

Figure 2  Flow chart of the trial. Suivi de l’essai clinique.
compare the four placebo groups according to flare-up treatment and recruitment period, and collapse groups if no difference was seen;

- similarly compare the four mesalazine groups;

- and further analyze the mesalazine groups if there was any evidence of a clear difference between these groups vs. placebo groups, and to collapse groups with similar relative risks of relapse.

In an attempt to explain the difference in mesalazine efficacy observed between the two recruitment periods, the baseline characteristics across the two groups—according to recruitment period—were compared, as described above. The prognostic role of each putative factor, evaluated prior to or at inclusion, was then tested by the proportional-hazards model, which included variables such as flare-up treatment, recruitment period, putative factor and their interactions, followed by backward selection using a likelihood ratio test [24]. This enabled us to determine whether or not a factor influencing relapse risk in a different way in patients treated with mesalazine compared with placebo could suppress the recruitment-period effect on treatment efficacy (with mesalazine vs. placebo). Finally, as differences according to recruitment period were observed only in patients treated with mesalazine, we analyzed the (potential) prognostic role of each factor using the Cox model—taking into account the effect of flare-up treatment, recruitment period, and each factor and their interactions—separately in patients treated with mesalazine and with placebo. This analysis enabled us to search for a factor accounting for the difference in mesalazine efficacy observed between the two recruitment periods, despite the absence of any change in placebo efficacy.

**Funding source**

Material support was given by Ferring S.A., and included providing the mesalazine and placebo randomization, and patients’ charts. Data were collected at each center by Mrs. J. Crand, a research assistant employed by Ferring S.A. The fund provider (Ferring S.A.) played no role in the study design, data analysis or manuscript preparation and submission, all of which were carried out independently by the present study investigators.

**Results**

Fig. 2 presents the trial flow chart. To summarize, 137 patients were included in the trial. Of these 132 patients, 10 were withdrawn from the study because of failure to satisfy the inclusion criteria. Thus, 122 eligible patients had their outcomes evaluated.

A total of 60 patients were treated with mesalazine (39 and 21 in the medication and nutrition strata, respectively), and 62 with a placebo (42 and 20 in the medication and nutrition strata, respectively). Recruitment was well balanced over the two recruitment periods (27 and 29 in the first period, and 33 and 33 in the second period in the mesalazine and placebo groups, respectively). Table 1 presents the

<table>
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<th>Table 1 Characteristics of the studied population per treatment group.</th>
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<td>Harvey—Bradshaw score</td>
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<td>Serum creatinine (µmol/L)</td>
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*a Significance level (chi-square test).

**b Significance level (Fisher’s exact test).

*n (%) .

Mean ± S.D. (n, if different from column heading).
study population’s clinical characteristics. In general, our study could find no significant differences between the mesalazine and placebo groups, or between the medication and nutrition strata in terms of age, gender, disease localization, duration and history, HB score and biological variables before and after inclusion.

Among our 122 patients, there were four failures reported during steroid withdrawal after inclusion—two due to weaning failures (one in each treatment group), and two due to intolerance (one in each treatment group). This left 58 and 60 patients for the time-to-relapse analysis in the mesalazine and placebo groups, respectively. After flare-up treatment withdrawal, 29 and 35 relapses were observed within a year in the mesalazine and placebo groups, respectively. During follow-up, 11 and five patients were withdrawn from the trial in the mesalazine and placebo groups, respectively (Fig. 2). At year 1, 18 and 20 patients were still taking the study treatment and in remission in the mesalazine and placebo groups, respectively.

The proportion of patients still in remission is shown in Fig. 3 according to the time since withdrawal of flare-up treatment and by maintenance-treatment group. At year 1, relapse rates (means ± S.E.) were 57 ± 7 and 63 ± 7% in the mesalazine and placebo groups, respectively. Time without relapse (means ± S.E.) was 8.6 ± 0.6 and 7.9 ± 0.7 months in the mesalazine and placebo groups, respectively. Failure rates at year 1, were 60 ± 7 and 66 ± 6% in the mesalazine and placebo groups, respectively.

The separate analyses of time to relapse in the mesalazine and placebo groups showed comparable results in the four groups treated with the placebo (P > 0.90) (Fig. 4A), but a significant difference among the four groups treated with mesalazine (P = 0.017) (Fig. 4B). Indeed, in the placebo-treated patients, the one-year relapse rates were 60 and 68% in the medication stratum, and 62 and 56% in the nutrition stratum, in the first and second recruitment periods, respectively. In the mesalazine-treated patients, the corresponding figures were 42 and 60%, and 42 and 86%, respectively. With placebo, the times to relapse (means ± S.E.) were 8.1 ± 1.2 and 7.2 ± 1.0 months in the medication stratum, and 6.6 ± 2.3 and 8.2 ± 1.2 months in the nutrition stratum, during the first and second recruitment periods, respectively. With mesalazine, the corresponding figures were 10.4 ± 0.8 and 8.4 ± 0.9, and 9.4 ± 1.6 and 5.5 ± 1.2 months, respectively.

The analysis of time to relapse, using the Cox model and including the four mesalazine and four placebo groups, enabled us to determine three different prognostic groups.
The number of patients necessary to treat to prevent one relapse during the one-year follow-up was approximately six for both the medication and nutrition flare-up treatment strata in the first recruitment period, 13 in the medication stratum and not evaluable in the nutrition stratum in the second recruitment period.

As there were differences in mesalazine efficacy between the two recruitment periods, an analysis of factors to account for these differences was carried out. No error was detected in the medication conditioning. A second independent data collection established only minor differences (7%) with no consequences on data analysis. No difference was established between the two recruitment periods in terms of gender, age at inclusion, disease localization and history, flare-up duration, HB score, ESR and serum creatinine levels before and after inclusion. The only significant differences observed between patients from the first compared with the second recruitment period involved: duration of disease since the initial symptoms (means ± S.D.), 1.9 ± 2.3 vs. 1.2 ± 2.2 years (P = 0.04); flare-up treatment with mesalazine, 30% vs. 6% (P = 0.001), and with metronidazole, 50% vs. 21% (P < 0.001); duration of the metronidazole flare-up treatment, 136 ± 64 days (P = 0.02); albuminemia prior to inclusion, 32.4 ± 5.9 vs. 29.7 ± 6.8 g/L (P = 0.04); and hemoglobin levels at inclusion, 129± 13 vs. 123 ± 13 g/L (P = 0.04). However, none of the methods used in this trial was able to reveal any factors to account for the observed variation in mesalazine efficacy between the two recruitment periods.

Most of the reported adverse drug events were not considered to be serious, and there was no difference between the mesalazine and placebo groups (Table 2). However, two serious adverse events were found: one was a case of interstitial pneumopathy in the placebo group. The other was a case of interstitial nephritis in the mesalazine group, and the other was serious, adverse events were found: one was a case of interstitial pneumopathy in the placebo group. The other was a case of interstitial nephritis in the mesalazine group, and the other was a case of interstitial pneumopathy in the placebo group.

Discussion
This was the first randomized, placebo-controlled trial of the prevention of symptomatic relapse in pediatric CD and it demonstrated that mesalazine is well tolerated. Twelve months after flare-up treatment withdrawal, the relapse rate was similar with mesalazine (57%) and placebo (63%). However, the analysis of time to relapse, taking into account the recruitment period and flare-up treatment stratification factors, revealed a significant twofold lower relapse risk in the patients treated with mesalazine whose flare-up had been medically treated during the first recruitment period, compared with the intermediate group comprising all placebo-treated patients and those treated with treatment period and their two-by-two interaction, enabled us to define three prognostic groups (P = 0.017) (Fig. 5B). Compared with that of the intermediate prognostic group, both the low- and high-risk groups’ relative risks of relapse were similar to those established in the first prognostic classification; the only difference was that the mesalazine nutrition group in the first recruitment period was part of the intermediate group instead of being part of the low-risk group. As for the time to failure analyses, these also showed similar results.


The group showing the most favorable responses was the mesalazine nutrition and medication groups from the first recruitment period, whereas the group with the highest relapse risk was the mesalazine nutrition group from the second recruitment period. The intermediate-risk group included all placebo groups and the mesalazine medication group from the second recruitment period. Compared with that of the intermediate prognostic group, the low-risk group’s relapse risk was 2.1 times lower (95% CI: 1.0—4.3) and that of the high-risk group was 1.9 times greater (95% CI: 1.0—3.9). Similarly, the analysis of time to relapse, using the Cox model and taking into account the treatment, flare-up treatment, recruit-
mesalazine whose flare-up had been medically treated during the second recruitment period. A twofold higher risk of relapse was observed in patients treated with mesalazine whose flare-up had been treated with nutritional techniques during the second recruitment period compared with those treated with medications during the first recruitment period. Our data analyses did not enable us to classify those mesalazine-treated patients whose flare-up had been nutritionally treated during the first recruitment period into either the low- or intermediate-risk group. This is clearly the consequence of the limited sample size of this group of patients (nine patients and three relapses). It should be noted that the analysis of time to relapse according to treatment and stratification factors could not be considered a subgroup analysis as these stratification factors were defined either a priori in the protocol or during the trial, when patient recruitment was halted and then resumed. Moreover, any variation in treatment efficacy across strata, as observed in our study, renders the interpretation of overall results difficult, as the results depend on the proportion of patients within each stratum.

Patient recruitment for this study took place in two successive periods (1991—1993 and 1996—1999). In fact, recruitment of the patients into the trial was interrupted at the end of 1993, as planned in the protocol, to perform a final analysis. This analysis showed a positive trend towards mesalazine efficacy in preventing relapse [21]. Following the presentation of these results during a general meeting of trial investigators, it was decided to resume patient recruitment and to use the additional recruitment period as another stratification factor, and to recalculate the necessary sample size according to a lower estimate of mesalazine efficacy compared with placebo (a 25% vs. 35% drop in the one-year relapse rate). The results observed in 1995 were confirmed in the final analysis of patients enrolled during the first period as a one-year relapse rate of 41 ± 11 and 61 ± 10%, but not in patients enrolled during the second period with a one-year relapse rate of 69 ± 9 and 65 ± 9%, in the mesalazine and placebo groups, respectively. Unfortunately, we were unable to explain this difference, given the differences in patients’ characteristics at inclusion between the two recruitment periods.

Our study confirmed the previously reported good tolerability of mesalazine. A prospective study [26] comparing the tolerability of mesalazine and sulfasalazine in pediatric patients showed that a majority of patients maintained in remission had fewer side-effects with mesalazine. A retrospective study of 153 pediatric CD patients confirmed this finding [27], and also suggested that mesalazine may be more effective for maintaining remission in such CD patients compared with adult cases.

Mesalazine as a maintenance treatment [15—20,28] has been extensively studied in mild-to-moderate adult CD. Our study results are similar to those of a number of others carried out in adults. Out of 15 randomized, controlled trials, 13 showed results favoring mesalazine. In general, the meta-analysis by Camma et al. [19] established a significantly reduced relapse risk with mesalazine. However, this result was not related to the medical setting, but was mainly due to good results in ileal disease, post-surgically induced remission and prolonged disease duration. The flare-up treatment (with either medication or nutrition), one of the pre-inclusion criteria in our study, probably accounts for the negative results observed in the whole studied population. The significant effect of mesalazine in the group treated with medications during the first recruitment period and the absence of any effect in the second recruitment period remain unexplained despite the differences established between the two recruitment periods, especially in terms of duration of disease, a factor known to be related to mesalazine efficacy in adults with CD [18]. In conclusion, the long-term use of mesalazine in pediatric CD is safe. However, in the present study overall, mesalazine did not appear to be an effective maintenance treatment in pediatric CD, despite some success as revealed by small, within-strata analyses.

There is no conflict of interest between the study authors and Ferring S.A.

References


