Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-year follow-up study

O. A. PAOLUZI, F. IACOPINI, R. PICA, P. CRISPINO, A. MARCHEGGIANO, A. CONSOLAZIO, M. RIVERA & P. PAOLUZI

Gastroenterology Unit, Department of Clinical Science, 'La Sapienza' University, Rome, Italy

SUMMARY

Background: Mesalazine as maintenance therapy in ulcerative colitis is used worldwide and has been proven to be effective. However, the optimal dosage remains to be defined.

Aim: To establish whether daily treatment with 2.4 g of oral mesalazine is more effective than 1.2 g in preventing disease relapse.

Methods: A total of 156 patients with ulcerative colitis in remission were randomly treated for 1 year with 2.4 ($n = 80$) or 1.2 ($n = 76$) g/day of mesalazine. Activity of disease was assessed by periodical clinical, endoscopic and histological examinations.

Results: After 12 months, 24 of 80 patients (30%) on 2.4 g and 20 of 76 patients (26%) on 1.2 g were still in remission (P = N.S.). Patients in 2.4 g group remained in remission for a longer time than those in 1.2 g group ($P < 0.001$). Among clinical variables considered in the study, course of disease prior to enrolment ($\leq 3/>3$ relapses/year) was found to influence response to therapy.

Conclusions: A daily dosage of 2.4 g of oral mesalazine seems to better at preventing and delaying relapses of ulcerative colitis than 1.2 g. The course of disease seems to be crucial in choosing the optimal dosage of mesalazine in a maintenance regimen.

INTRODUCTION

The administration of sulfasalazine (sulphasalazine; SASP) and its derivative 5-aminosalicylic acid (5-ASA) is used throughout the world in the treatment of ulcerative colitis (UC).[1–4] Besides findings in active disease, several studies have demonstrated that 5-ASA is more effective than placebo[5–10] and equally as effective as SASP[11–14] in the maintenance of remission in UC patients. In a recent review by Sutherland *et al.*,[13] results of all double-blind randomized studies published on the efficacy of 5-ASA in the maintenance of remission in UC patients were evaluated and the efficacy of 5-ASA in the prevention of disease relapse was confirmed. Whilst these results deal with the widespread use of 5-ASA, the daily dosage of this drug administered in the different studies, on the other hand, varied considerably, ranging from 0.75[11] to 4.4 g.[14] In a recent report,[15] daily administration of 2 g of 5-ASA has been proposed as the optimal dosage in order to reach a good balance between side-effects and therapeutic efficacy. As yet, however, the efficacy and tolerability of the different daily dosages of 5-ASA in the prevention of UC relapse have rarely been compared with non-conclusive results as far as concerns the superiority of doubling the dosage of mesalazine.[6, 8, 16]

Correspondence to: Prof. P. Paoluzi, Cattedra di Gastroenterologia, Dipartimento di Scienze Cliniche, Viale del Policlinico 157, 00161 Roma, Italy.
E-mail: paolo.paoluzi@uniroma1.it

Aim of the present study was to establish whether a daily dosage of 2.4 g of oral mesalazine is more effective than and as well-tolerated as 1.2 g in the maintenance of remission in UC patients.

PATIENTS AND METHODS

Selection and recruitment of patients

Patients over 18 years of age with UC involving more than 20 cm from the anus and in a phase of clinical, endoscopic and histological remission, were considered as eligible for the study. The diagnosis of UC, as well as the staging of activity, were established on the basis of standard clinical, endoscopic and histological criteria.[17–19] All subjects were out-patients, attending our Gastroenterology Unit, who presented recent disease relapse (within the last 3 months) prior to the study who have been appropriately treated until clinical, endoscopic and histological remission had been achieved. In all patients activity prior to entry into the study was mild-to-moderate and the treatment consisted in oral and topical mesalazine. A condition of steroid dependence, renal impairment, pregnancy, lactation or established low compliance were considered as exclusion criteria. Also considered as a condition of non-eligibility was absence of relapse within the 5 years prior to the study. Patients fulfilling entry criteria were enrolled after written informed consent was obtained.

Design of the study and sample size calculation

The investigation was designed as a randomized single-blind open-label study with a duration of 12 months. Hypothesizing a minimal difference of 20% in the results obtained from the two groups, and fixing the probability of an α- and β-error <5%, the minimal number of patients to be enrolled in each group was 76.

Study drugs and follow-up

After enrolment, patients were randomized into two groups to receive mesalazine at 1.2 g/day or 2.4 g/day, respectively, for the entire study period of 12 months. Mesalazine was administered in the form of open-label marketed packages (400 or 800 mg tablets; Asacol, Giuliani SpA, Milan, Italy), one tablet to be taken three times per day, in both groups of patients. The use of other drugs, such as rectal mesalazine or steroids preparations, was not allowed during investigation.

During the study period, patients were periodically submitted to clinical (every 3 months), endoscopic and histological examinations (every 6 months). In the event of clinical relapse, colonoscopy and histological studies were performed in order to confirm the activity of the disease. Medical staff performing these controls were unaware as far as concerns the patient's treatment. Patients were free to leave the study at any time (withdrawal of consent). Other reasons for withdrawal from the investigation were: lack of adherence to the therapeutic schedule or programmed controls (<85%, poor compliance); onset of symptoms of relapse, confirmed by instrumental procedures (therapeutic failure); endoscopic and/or histological findings of disease activity in the absence of symptoms (asymptomatic relapse); onset of drug-related adverse events requiring interruption of treatment.

Assessment of disease activity and evaluation of drug tolerability

Clinical examination. At each visit, the course of disease, from the previous control to that day, was assessed evaluating the presence of symptoms indicating relapse of the disease (number of bowel movements per day, consistency of faeces, presence of rectal bleeding, abdominal pain, tenesmus and urgency at defecation). Blood tests, including inflammatory parameters (erythrocyte sedimentation rate, C-reactive protein, α-1 glycoprotein), full blood count, renal (creatininaemia, urea) and liver function (transaminases) parameters, albumin, electrolytes, lipase and amylase, were investigated at each follow-up control. At the end of each visit, disease activity was graded as absent (remission), mild, moderate or severe according to the criteria of Truelove and Witts.[17]

Colonoscopy. The endoscopic appearance of inflammatory changes of colonic mucosa was evaluated by full colonoscopy and graded as mild, moderate or severe, while the absence of mucosal inflammatory changes was considered as endoscopic remission according to the criteria of Baron *et al.*[18] During colonoscopy, at least two biopsies were collected from each colonic tract affected by the disease in order to confirm the extent of disease and to evaluate the presence of inflammatory changes at histology.

Histology. Biopsy specimens were fixed in formalin, embedded in paraffin, stained with haematoxylin-eosin and examined at light microscopy. Specimens were assessed for inflammatory changes, which were classified as mild, moderate or severe according to the criteria of Truelove and Richard.[19] Remission was defined as the absence of inflammatory changes in the mucosa.

Tolerability of drugs and compliance with the therapy. Upon assignment of the treatment, each patient was informed about the possible clinical side-effects or laboratory adverse events related to the study drugs. All patients received a predefined chart, on which to record the time of onset, the type and severity of symptoms. Recovery from side-effects, after reduction or discontinuation of the study drug, or the need for specific therapy were also recorded and all data were stored in a computerized patient file. The side-effect was defined as serious when life-threatening or causing a permanent disability or requiring hospitalization; as moderate when limiting normal daily activity and disappearing after reduction of dosage or withdrawal from therapy; and as mild when not interfering with normal daily activity and disappearing after reduction of dosage or withdrawal.

Compliance was defined by interviewing the patient to assess the adherence to the treatment, evaluating the number of tablets taken per day, and was considered as good when a patient took >85% of the drug prescribed per week (i.e. <3 tablets forgotten per week).

Elaboration and statistical analysis of results

The maintenance of clinical and anatomical (endoscopic and histological) remission was defined as the primary end-point of the study. Remission was considered as the absence of symptoms and endoscopic/histological changes typical of active UC. Tolerability of the study drugs, evaluated on the basis of incidence, as well as type and severity of side-effects occurring during the entire study period, was the secondary end-point. In order to avoid possible bias related to different features of the disease, data were also analysed following stratification of the patient population according to duration (≤10 vs. >10 years), extent (left-sided vs. diffuse/total colitis) and course (≤3 relapses vs. >3 relapses/year during the 3 years prior to the study) of the disease. Results were also stratified according to demographic features of patients, namely age (≤40 vs. >40 years) and sex.

Differences between the patients treated with 1.2 g/day and those treated with 2.4 g/day of mesalazine were analysed using the chi-square test and Fisher's exact test, as appropriate, for the comparison of proportions, and Student's *t*-test for comparison of mean ± s.d.. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS/PC+ Advanced Statistics V2.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient population

From April 2001 to November 2002, a total of 156 patients were enrolled in the study, 80 were randomized to the 2.4 g group and 76 to the 1.2 g group. As far as concerns data regarding the course of the disease prior to the study, 132 patients (84%) were treated with 5-ASA and 24 (16%) with SASP, 104 patients (66%) experienced >3 relapses of disease and 52 (34%) ≤3 relapses of disease per year. None of the patients in either group required oral steroids or immunosuppressants during the course of the disease. Distribution of patients was well balanced according to age, sex, smoking habit, extent and duration of disease, whilst according to activity of the disease prior to the study entry, patients in the 2.4 g group were found to have a more active disease than patients in the 1.2 g group (Table 1). This difference between the two groups was taken into account in the analysis of results comparing data according to disease activity and other patient features.

Of the 156 patients, 16 (10%), eight in the 2.4 g group and eight in the 1.2 g group, dropped out because of side-effects (skin rash in one patient in the 2.4 g group) or because they were lost to follow-up (15 patients), as scheduled. These drop outs were included in the analysis of results which, therefore, were evaluated according to intention-to-treat (ITT) criteria.

Maintenance of remission

After 12-month of follow-up, 24 of 80 patients (30%) in the 2.4 g group and 20 of 76 (26%) in the 1.2 g group were found to be still in remission (Table 2), the difference being not statistically significant. All these patients were free from symptoms of UC and showed no inflammatory changes either at endoscopy or histology.

Table 1. Baseline characteristics of 156 ulcerative colitis patients randomized to the 2.4 g (*n* = 80) or 1.2 g group (*n* = 76)

Features	2.4 g group (*n* = 80)	1.2 g group (*n* = 76)	*P*-value
Sex			
Female/male	32/48	32/44	N.S.
Age (years)			
Mean ± s.d.	47.7 ± 14.2	46.9 ± 11.1	N.S.
Smoking habit			
Smokers	15	18	
Ex-smokers	28	17	N.S.
No smokers	37	45	
Disease			
Duration (years)			
Median	10.0	9.7	
Range	4–26	3–27	N.S.
Extent			
Left-sided	56	64	N.S.
Diffuse/total	24	12	
Activity prior to the study			
≤3 relapses/year	16	36	
>3 relapses/year	64	40	<0.001

N.S., not significant.

Table 2. Patients in remission after 12 months oral maintenance therapy with 2.4 g or 1.2 g of mesalazine

Patients groups (g)	N	Remission, *n* (%)	Relapse, *n* (%)	Drop-outs, *n* (%)	*P*-value
2.4	80	24 (30)	48 (60)	8 (10)	N.S.
1.2	76	20 (26)	48 (63)	8 (11)	

N.S., not significant.

Data regarding outcome of disease at 12 months after stratification of the population according to patient and disease features are shown in Table 3. Comparison of data, according to activity of disease, in the 3 years prior to entry into the study showed that the number of patients with ≤3 relapses/year who remained in remission in the 2.4 g group (12 of 16, 75%) was greater than that of patients with >3 relapses/year in the same group (12 of 64, 19%; *P* < 0.0001, Fisher's exact test; 95% CI: 2.232–7.168) and than those of patients in the 1.2 g group with ≤3 relapses/year (12 of 36, 33%; *P* < 0.008; Fisher's exact test; 95% CI: 1.309–3.868) and with >3 relapses (eight of 40, 20%; *P* < 0.0005; Fisher's exact test; 95% CI: 1.897–7.413). The number of patients with >3 relapses/year in the 2.4 g group who were still in remission at the end of the study was similar to that with >3 relapses/year in the 1.2 g/group (12 of 64, 19%, vs. eight of 40, 20%; *P* = N.S.).

No difference was found when patients were compared according to age, sex, extent and duration of disease.

Features and time to relapse

Of the 96 patients who relapsed during the study period, 48 were in the 2.4 g group and 48 in the 1.2 g group. Clinical relapse, associated with the finding of inflammatory changes at endoscopy and histology, occurred in 84 patients (87.5%). In the remaining 12 patients (12.5%), six in the 2.4 g group and six in the 1.2 g group, all with left-sided colitis, the asymptomatic flare up (presence of inflammatory changes at endoscopic and histological controls in the absence of symptoms) was detected, at 6 months' control in the six patients in the 1.2 g group, and at 12 months in the six patients in the 2.4 g group.

No reasons for flare up of the disease were identified in either patient group. Albeit, one patient in the 2.4 g group, who stopped smoking after enrolment in the study, relapsed within the first 3 months of treatment.

Comparing duration of remission in those patients who relapsed in the two treatment groups, patients in the 2.4 g group were found to relapse later than patients in the 1.2 g group (Figure 1), the difference between the mean number of days prior to the flare up being statistically significant (175 ± 126.0 vs. 129 ± 95.3, respectively; *P* < 0.001, Student's *t*-test). Once the population was stratified according to extent of the disease, the difference between the number of days prior to relapse in the two groups remained statistically significant both comparing patients with left-sided colitis (191 ± 144.0 vs. 145 ± 95.1, respectively; *P* < 0.009, Student's *t*-test) and with diffuse/total colitis (143.0 ± 71.6 vs. 47.3 ± 37.2, respectively; *P* < 0.05, Student's *t*-test).

Compliance and tolerability

All patients took the drugs as prescribed, the compliance being good in both treatment groups.

One of 156 patients (0.6%) experienced side-effects. This patient, previously treated with SASP, presented an idiosyncratic manifestation (skin rash) which occurred few days after mesalazine intake. The eruption disappeared 4 days after treatment withdrawal. No other symptoms, or laboratory adverse event were recorded in the remaining patients.

Table 3. Outcome of disease at 12 months stratifying patients according to age, sex and disease features

Features	N	2.4 g group (n = 80)			1.2 g group (n = 76)			P-value
		R	A	DO	R	A	DO	
Age (years)								
≤ 40	60	8 (25)	20 (63)	4 (12)	8 (29)	16 (57)	4 (14)	N.S.
>40	96	16 (33)	28 (58)	4 (9)	12 (25)	32 (66)	4 (9)	
Sex								
Male	92	16 (33)	28 (58)	4 (9)	16 (36)	28 (64)	–	N.S.
Female	64	8 (25)	20 (63)	4 (12)	4 (12)	20 (64)	8 (24)	
Disease								
Extent								
Left-sided	120	16 (29)	32 (57)	8 (14)	16 (25)	40 (63)	8 (12)	N.S.
Diffuse/total	36	8 (33)	16 (67)	–	4 (33)	8 (67)	–	
Duration (years)								
≤ 10	104	12 (25)	32 (66)	4 (9)	16 (29)	32 (57)	8 (14)	N.S.
>10	52	12 (37)	16 (50)	4 (13)	4 (20)	16 (60)	–	
Relapses in the last 3 years								
≤ 3	52	12 (75)	–	4 (25)	12 (33)	16 (45)	8 (22)	<0.01
>3	104	12 (19)	48 (75)	4 (6)	8 (20)	32 (80)	–	

R, remission; A, activity; DO, drop outs; N.S., not significant.
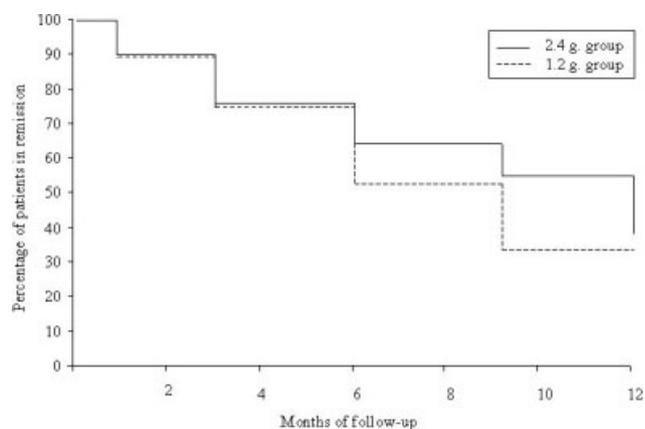Numbers in parentheses are percentages.

Figure 1. Patients (%) in 2.4 g group and 1.2 g group who remained in remission during 12-month' follow-up. Majority of patients in 2.4 g group relapsed later than patients in 1.2 g group.

DISCUSSION

The present report outlines the results emerging from a monocentric open-label study aimed at evaluating whether doubling a 1.2 g daily dosage of oral mesalazine may better prevent a flare up in patients with UC. The rationale for this comparative investigation was the empirical finding, in a preliminary evaluation, that a daily dosage of 2.4 g was more effective than 1.2 g, considered a standard maintenance regimen in our Unit, and the lack of conclusive data in the literature regarding the optimal dosage of oral mesalazine in maintenance therapy of UC. Furthermore, a dose–response effect, a property already demonstrated for SASP,[20] has been hypothesized but not yet confirmed for 5-ASA.[3, 21] The need to better establish which may be the optimal dosage of this drug in the maintenance of UC, especially in patients with frequent relapses, has been stressed by several authors over the last few years[22–24] but, up to now, only a few studies, and with conflicting results, have attempted to elucidate whether an increase in the daily dosage of oral mesalazine corresponds to a rise of probability to remain in remission. Fockens et al.[16] compared 1.5 vs. 3.0 g of mesalazine, as maintenance therapy, and 54% vs. 66% of patients were found to be still in remission at the end of the study, the difference being not statistically significant. Hanauer et al.,[8] in a 6-month comparative placebo controlled trial, failed to demonstrate a superiority of 1.6 g compared with 0.8 g of mesalazine per day in the prevention of flare up in UC patients (patients remained in remission: 70.1 and 63.3%, respectively). These data are in agreement with results emerging from the present study, which indicate that a dosage of 2.4 g of mesalazine per day is equally as effective and well-tolerated as 1.2 g but does not significantly increase the rates of remission in UC patients. In fact, no statistically significant difference was found comparing remission rates in the two treatment groups at the end of the study

period. These findings appear to suggest that the effect of oral mesalazine is not dose-related. However, in favour of a possible dose–response effect is the evidence that patients on 2.4 g/day dosage remained in remission for a longer period than patients who took 1.2 g/day, a difference which remained evident following stratification according to extent of disease. On the other hand, during analysis of results, stratification of patients according to activity of disease prior entry into the study revealed that the proportion of patients with more active disease (>3 relapses/year) in the 2.4 g group was significantly greater than that in the 1.2 g group (80 vs. 49%, respectively). It is possible, therefore, that this unbalanced distribution of more active disease in the study arms could account for the lack of a difference in the remission rates achieved by the two drug dosages. In order to better evaluate the impact of the different disease activity on efficacy of the two regimens, results were analysed stratifying patients according to number of relapses per year. A larger proportion of patients treated with 2.4 g/day of mesalazine and with ≤3 relapses/year in the 3 years prior entry into the study remained in remission compared with those patients treated with 1.2 g, whilst no statistical significant difference was found when patients with >3 relapses/year were compared. These findings, although their power could be decreased due to stratification of population according to clinical variables, suggest that a dosage of 2.4 g/day of mesalazine may reduce the incidence of relapses in patients affected by a disease with a low active course (≤3 relapses/year). Conversely, patients showing a trend to frequently relapse (>3 relapses/year) seem to require a higher dosage (>2.4 g/day) of oral mesalazine to better maintain remission. This hypothesis is in agreement with the opinion of several authors[22, 23, 25] who have suggested that patients who more frequently relapse probably need to be treated with higher doses of 5-ASA.

It is worthwhile pointing out that in the present investigation about 30% of patients were in remission at the end of the study period. This figure is lower than that reported by several authors, which ranges from 44[8] to 60%,[9] and could lead to possible criticism regarding the dosages compared in the present study. However, as stressed in a recent review,[26] the optimal dosage of oral mesalazine in the treatment of active UC ranges from 2 to 4 g/day, and it is a widely held that a lower dosage of the drug should be administered for maintenance purposes. Moreover, no previous study aimed to com-

pare 2.4 g with 1.2 g of mesalazine up to now. Several factors, all disease-related, could account for the discrepancy between remission rates observed in the present and previous studies. First of all, the type of patients enrolled in the various studies. UC runs a variable course with some patients enjoying prolonged remission and others relapsing frequently. Bearing in mind the observation of Bitton *et al.*[27] that a greater number of relapses is a predictor of a shorter time to flare up, it is reasonable to speculate that previous trials on maintenance therapy in UC patients, in remission for long time, may have led to biased high remission rates. This hypothesis is supported by the finding, in the present study, that the proportion of patients with a previous history of ≤3 relapses/year and still in remission at the end of the study was more than twofold greater than that of patients with >3 relapses/year. This evidence is in keeping with a study by Ardizzone *et al.*,[10] who found that patients with a longer duration of remission had less risk of relapse compared to patients with a shorter duration and do not appear to require maintenance treatment if the disease remains in remission for more than 2 years. To note, in the present study, we enrolled only patients suffering from a recent relapse, whilst those without relapse, within the last 5 years, were excluded in order to avoid a possible bias because of a different activity of disease. Indeed, the majority (66%) of patients enrolled in the present investigation had a course of disease characterized by >3 relapses/year and the remaining 34% had ≤3 but at least 1 relapse/year. Thus, our study population could represent a selected group of patients who regularly relapse, and, taking into account this characteristic, we expected lower remission rates than those reported in previous studies on unselected patients. Secondly, the strict criteria adopted in the present study to define remission, which included histology as well as endoscopy to confirm the absence of inflammatory changes of the mucosa. It is noteworthy that 12.5% of patients who relapsed were judged as having active disease on the basis of the histological evidence of mild inflammatory changes in the mucosa in the absence of symptoms and endoscopic signs of activity. If patients with only clinical and/or endoscopic activity were taken into account, we would obtain remission rates similar to those emerging from other studies. Taking into account these methodological differences, it is not possible to exclude an overestimation of patients in remission, in other studies in which absence of inflammation was assessed only by clinical

and/or endoscopic assessments but not by histology. Histological absence of inflammatory changes could be considered as a not relevant goal in a clinical study aimed to evaluate the efficacy of 5-ASA therapies in maintenance of remission in UC patients. However, the presence of microscopic inflammatory changes of the mucosa, in patients with quiescent UC, has been considered a predictor of early relapse[27] and seems to strongly influence the long-term outcome of disease, as we already observed in our previous investigation.[28] In our opinion, histological assessment has to be considered as crucial before starting a maintenance regimen, both in trials and in clinical practice, in order to achieve a more scrupulous assessment of the remission. Furthermore, during a maintenance therapy histology may increase the possibility to early detect mild inflammatory changes which may be promptly treated, avoiding the recurrence of symptoms. Thirdly, in the present investigation, patients were monitored for 12 months, a longer follow-up period than that reported in other studies,[8, 9] showing higher remission rates, in which patients were followed up for 6 months. It is possible that remission rates in those previous studies, would become similar to the results emerging from the present investigation if the period of follow-up were extended to 12 months.

As far as concerns tolerability, mesalazine is generally considered to be well-tolerated. The most common adverse events associated with mesalazine are headaches, abdominal pain, diarrhoea and nausea/vomiting, most of these symptoms being mild-to-moderate in severity.[29–31] Excluding patients previously intolerant/allergic to SASP or other salicylates, the incidence of side-effects to mesalazine is very rare, accounting, in our experience, for only 1.5%.[32] Despite these reassuring data, the occurrence of interstitial nephritis or nephrotic syndrome in UC patients during treatment with mesalazine has been reported in the literature,[33–35] and the possible relationship of the renal impairment with the 5-ASA[30] or with the basic disease still remains a controversial issue.[36] Furthermore, it has not been completely clarified whether an increase of the daily dosage of mesalazine may favour the occurrence of adverse events, especially in long-term regimens. In the present study, doubling the daily dosage of mesalazine from 1.2 to 2.4 g was well-tolerated over a study period of 1 year, with no cases of severe side-effects and/or changes in laboratory parameters being found. Only one patient experienced a side-effect, namely a skin rash. Because this event is due to an allergic mechanism, the increase in the daily mesalazine dosage could not, therefore, influence the occurrence of this untoward event. Taking into account the findings regarding tolerability emerging from the present and previous investigations, mesalazine seems to be a safe and well-tolerated drug. However, administration of increasing dosages of oral mesalazine gives rise to concern regarding a progressive decrease in drug tolerability. Although preliminary data on patients treated with doses even as high as 7.2 g/day, over a mean period of 53 weeks, showed good tolerability of this agent,[37, 38] further data from studies on large populations are necessary to establish whether higher dosages (>2.4 g/day), for long periods, might increase the risk of renal impairment or other adverse events.

The present study has several strengths and limitations. One possible limitation could be addressed to the lack of a placebo control group. Indeed, we did not include a placebo arm because previous studies had clearly demonstrated the greater efficacy of mesalazine in comparison with placebo. On the contrary, the present trial was a dose-ranging investigation on a selected group of patients who showed a tendency to regularly relapse. These characteristics of our study population, would, in our opinion, further stress the relevance of the present findings which could be useful when maintenance therapy has to be administered in those UC patients frequently presenting relapse.

In conclusion, a daily dosage of 2.4 g of mesalazine did not appear to reduce the incidence of relapse of UC in comparison with 1.2 g over a period of 1 year, but it certainly delayed the occurrence of a flare up. The course of disease is probably an useful parameter to be considered during the administration of a maintenance therapy. Further studies using higher dosages (>2.4 g/day) of mesalazine are necessary, especially in patients with frequent relapse of disease.

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