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# Evolution and predictive factors of relapse in ulcerative colitis patients treated with mesalazine after a first course of corticosteroids

C. Bello, J. Belaiche, E. Louis, C. Reenaers*

*Gastroenterology Department, CHU Sart-Tilman, University of Liège, 4000 Liège, Belgium*

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**KEYWORDS**
Ulcerative colitis;
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**Abstract**

*Introduction:* Mesalazine remains the first line treatment for the induction and the maintenance of remission in mild to moderate ulcerative colitis (UC). Its efficacy as a maintenance treatment after a first flare treated with corticosteroids has not been specifically studied. The aims of our work were to study a cohort of UC patients treated with mesalazine after a course of oral systemic corticosteroids and to identify predictive factors of relapse and of colectomy.
*Material and method:* We studied retrospectively a cohort of 143 UC patients, who never received immunosuppressive drugs, and treated for the first time with oral corticosteroids for a flare. Among patients responding to corticosteroids, we studied the group treated by mesalazine after the flare.
*Results:* Fifty% (n=52) achieved a complete clinical remission with steroid weaning. In this group, 67% (n=35) received oral mesalazine. Seventy-five % of patients treated by mesalazine relapsed (median 29 months, range: 1–156). Fourteen % required a colectomy (median 11 months, range: 1–24). Kaplan Meier curve showed a relapse rate and a colectomy rate over one year of 26% and 11% respectively. In multivariate analysis, male gender and short duration of disease were predictive factors of the time-to-relapse. No factor was predictive of time-to-colectomy.
*Conclusion:* Maintenance efficacy of mesalazine over one year after a first course of corticosteroids for a disease flare is reasonably high. The longer-term relapse rate becomes higher in male patients with a short disease duration. An immunosuppressive treatment could be discussed in case of further relapse despite improved medication-adherence. Medication-adherence should first be assessed and promoted. An immunosuppressive treatment could be discussed in case of further relapse despite improved medication-adherence.


* Corresponding author. Tel.: +32 4 366 72 56; fax: +32 4 36678 89.
*E-mail address:* catherinereenaers@hotmail.com (C. Reenaers).

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## 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease affecting the rectum and the colon to a variable extent. The primary therapeutic goals in UC are: corticosteroid-free remission, avoidance of surgery, and the prevention of colorectal cancer. Treatment of UC depends on the anatomical extent, severity, and chronicity of the disease, as well as the development of complications.[1,2] Mesalazine still remains the first line treatment for induction and maintenance of remission in mild to moderate UC.[3–5] However, a large majority of patients will require oral corticosteroid therapy for a relapse.[6,7] While requiring corticosteroid treatment for a flare in Crohn's diseases (CD) it is now broadly considered as an indication for immunosuppressive drug or anti-TNF therapy,[8,9] the need for immunosuppressive treatment after a first successful steroid course in UC is less well established. Efficacy of mesalazine as a maintenance treatment after a first course of corticosteroids has not been specifically studied. The primary endpoint of our work was to study the evolution of a cohort of UC patients treated with mesalazine after a first course of corticosteroids. The secondary aim was to identify predictive factors of relapse and of colectomy in these patients.

## 2. Patients and methods

A total of 143 patients with a firm diagnosis of UC (according to the criteria of Lennard-Jones)[10] who required a first oral systemic corticosteroid course, and who were regularly followed at our institution, were screened for inclusion. We retrospectively studied the group of patients responding to steroids, but without steroid-dependence, who were subsequently treated with mesalazine after the flare. For all these patients we recorded: age at diagnosis; disease duration at the flare; smoking habit; location of the disease at diagnosis and at relapse according to the Montreal classification[11]; and haemoglobin, platelet count and c-reactive protein (CRP). Patients were defined as smokers if they smoked at least seven cigarettes/week and non-smokers if they had never smoked or had stopped smoking before diagnosis. The flare was assessed retrospectively based on patient medical notes. A flare was considered to have occurred when the physician in charge of the patient documented it in the notes and changed the treatment accordingly. These flares were characterised by a combination of symptoms, including diarrhoea, abdominal pain, blood loss, fever, weight loss, and worsening of the general physical condition. Satisfactory clinical response was defined as a resolution of clinical symptoms. Steroid-dependence was defined as a recurrence of clinical symptoms during the steroid weaning or within the 3 months after steroid cessation. Mesalazine was taken at a minimum dose of 2.4 grams per day. Exclusion criteria were the previous use of systemic steroids or immunosuppressive drugs, or a severe flare requiring intravenous corticosteroids. Results are expressed in median (range). A Cox regression and a Kaplan Meier curve were used to study the time-to-relapse and the time-to-colectomy. We initially used univariate analysis to study the association between time-to-relapse or time-to-colectomy and each of the described factors, using either a $Chi^2$ or Kruskal–Wallis test, as required. A multivariate analysis was then performed using stepwise discriminant analysis. This multivariate analysis was performed on a subgroup of 26 patients for whom we had complete data. Haemoglobin, platelet count and CRP were excluded from the multivariate analysis due to an excess of missing values. A p value $<0.05$ was considered significant.

## 3. Results

### 3.1. Patients outcome

We identified 143 patients suffering from a mild to moderate flare of UC requiring a first course of oral corticosteroid, in whom 15% (n = 21) did not respond to the treatment whereas 85% (n = 122) achieved a satisfactory clinical response (Fig. 1). Among these patients, 42% (n = 51) developed a steroid-dependence and 43% did not relapse after having stopped treatment. Sixteen % (n = 19) had no follow-up. Looking at the subgroup in remission after full corticosteroids weaning, we identified 35 patients (67%) receiving mesalazine as maintenance therapy. One year after the first flare, 13 of 35 patients on mesalazine as monotherapy were still in remission. The median maximum follow-up was 118 months (16–322). At the maximum follow-up, 26 patients had relapsed, with a median delay of 39 months between the withdrawal of the corticosteroids and the flare (Fig. 2). The Kaplan Meier curve shows that about 50% of patients on mesalazine are in remission after two years, but there is a higher risk of relapse over longer follow-up. At 10 years, approximately 80% have relapsed (Fig. 3). Regarding the risk of colectomy, we identified 6 patients requiring a colectomy within a median of 18 months (Fig. 2). The Kaplan Meier curve showed a low risk of colectomy during the first years following a flare (about 5% at 2 years), which finally reached 20% after 5 years (Fig. 4).

Demographic and clinical characteristics in this subgroup are shown in Table 1. Disease location was stable over long-term follow-up. According to the Montreal classification, 24%, 48% and 28% of patients were E1, E2 and E3 at diagnosis, respectively. At the time of relapse, 80% of patients had no extension of the disease. Among the 5 patients with a disease extension, all of them had a pancolitis at the time of relapse, while at the time of diagnosis, 3 of them had proctitis and 2 of them had a left-sided colitis.

### 3.2. Association between UC evolution and demographic, clinical and biological characteristics

Demographic, clinical and biological characteristics of relapsers and non-relapsers at 1 year, are shown in Table 3. In univariate analysis, no demographic, clinical or biological factors were predictive of a relapse at one year. The univariate analysis of the same parameters for the prediction of time-to-relapse over the total follow-up (median = 118 months) was unable to identify predictive factors of time-to-relapse (Table 2). In multivariate analysis, biological parameters were not selected because of a lack of data in several patients. Two independent predictive factors of time-to-relapse after a first course of oral corticosteroids were identified. The male gender was a risk factor (p = 0.03,

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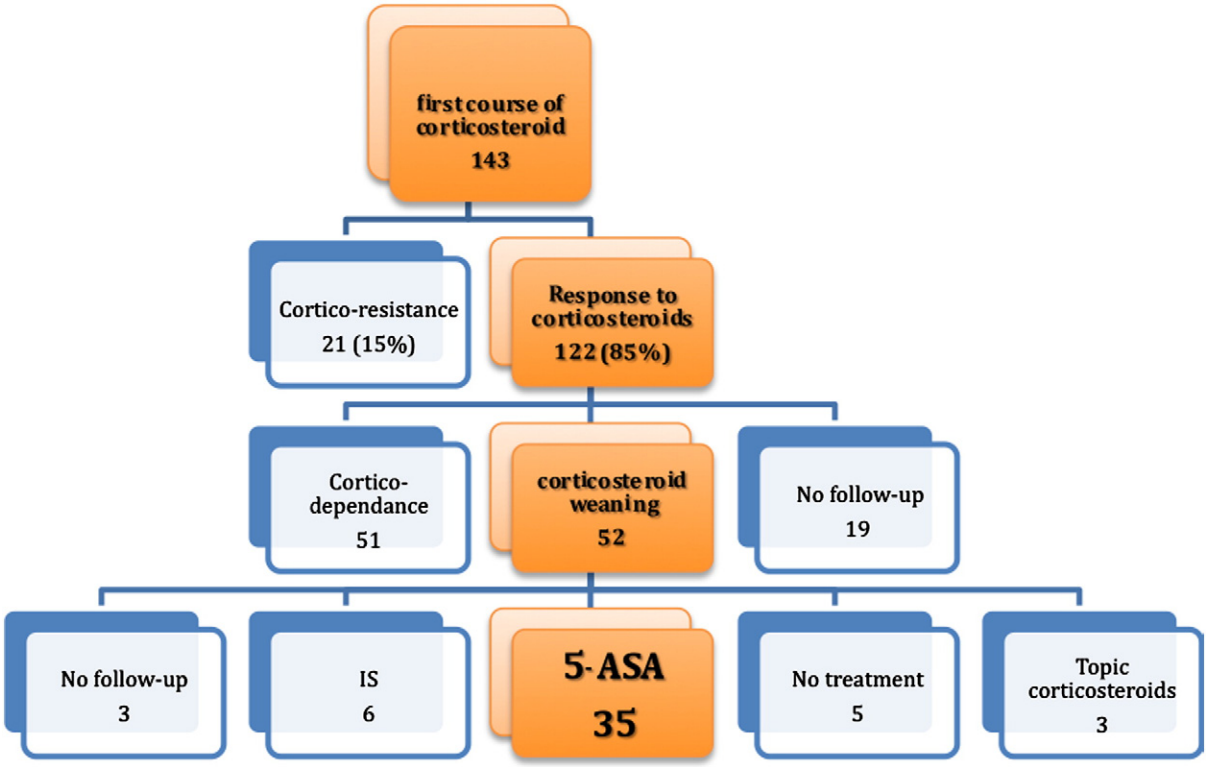


**Figure 1** Flowchart of a monocentre retrospective UC cohort after a first course of oral corticosteroids. 122 patients (85%) responded. Among 52 patients with corticosteroids weaning, 35 were treated with mesalazine and finally included in our study. The rates of steroid-resistance and steroid-dependence were 15% and 49% respectively.

HR=4, CI 95%: 1.46–11.5), whereas long disease duration was a protective factor of time-to relapse (p=0.03, HR 0.98, CI 95%: 0.97–0.99). No clinical or demographic factors were predictive of colectomy (Table 4).

## 4. Discussion

To date, no trial has specifically demonstrated the ability to maintain steroid-induced remission with mesalazine in UC after a first steroid course. An oral course of corticosteroids may be required in patients non-responding to oral mesalazine and/or rectal medication. Remission or partial response can be achieved in 55 to 80% of the patients. In our cohort, we obtained 85% complete clinical response after a first course of oral corticosteroid. In the subgroup of patients who could be withdrawn from steroids, the large majority (63%) were still in remission with mesalazine as monotherapy one

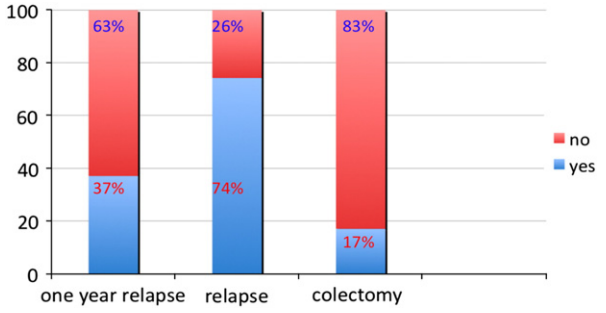


**Figure 2** Outcome of UC patients treated with mesalazine after a first course of oral corticosteroids.

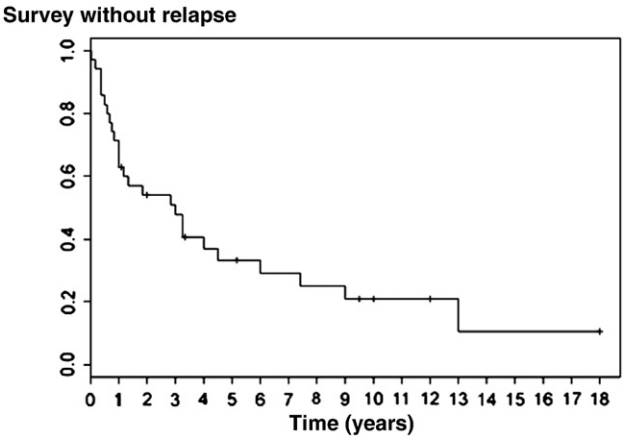


**Figure 3** Relapse-free Kaplan–Meier curve. The risk of relapse is low over the first year but increases importantly over longer follow-up.

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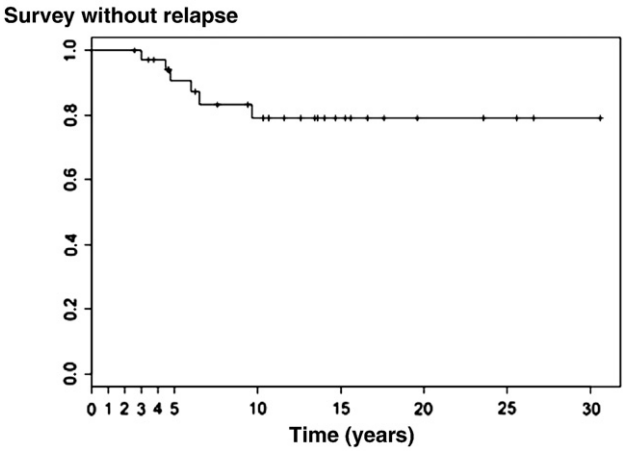


**Figure 4** Colectomy-free Kaplan–Meier curve. The risk of colectomy was very low during the first year after corticosteroid treatment but reached about 20% after 10 years.

year after the flare. When compared to the natural history of untreated UC following an initial flare, with a relapse rate of 73% over 1 year,[12,13] our study suggests that mesalazine can be considered as an effective drug for the maintenance of corticosteroid-free remission. However the relapse rate over the long term reaches more than 75%, suggesting that mesalazine may eventually become insufficient in most of these patients. These results must be qualified by the fact that our retrospective study may have focused on a subgroup of more severe patients. Coming from a large cohort of 143 patients, we were able to analyze only a subgroup of 35 patients. This was in part because of the high rate of steroid-dependence in our cohort, with a rate of 42% compared with an expected rate of about 20% at one year.[14] Although high rates of steroid-dependence have already been described in the literature in CD patients (45%)[15] and in UC paediatric population (45%),[16] such high rates have been less well reported in adult UC populations, with the highest at about 30%.[7] As this study was performed in a tertiary referral centre, our cohort may reflect a more severe UC population, and this could in partly explain why the results differ from those observed in population-based studies. Secondly, many patients (16%) were lost to follow-up, and it is possible that the majority of these had mild UC, well controlled under monotherapy or topical treatment, and who therefore did not return for hospital follow-up. This would have introduced a bias to more severe disease in the study population.

In UC, 50% of patients will eventually require maintenance therapy with immunosuppressive drugs, but the optimal timing to introduce them has not been extensively studied.[17] This is different in Crohn's disease where marginal efficacy of mesalazine and high frequency of complications and finally surgery has led to the search for predictive factors of poor outcome.[18,19] Among those, the need for steroids to treat the first flare of the disease has been repeatedly shown to be an independent predictor of the development of a disabling disease over the short term. Hence the need for such steroid treatment has become broadly considered as an indication for immunosuppressive and/or anti-TNF treatment to maintain disease remission. Our data indicates that this should not be extrapolated to ulcerative colitis.

The second aim of our work was to identify factors predictive of clinical relapse or colectomy in these patients. By identifying such factors, patients at high risk of relapse after a first course of corticosteroids may be offered treatment other than 5ASA to prevent future flares. As previously mentioned, only a small number of patients could be included in the univariate and multivariate analyses. Therefore, the results must be interpreted with caution. The multivariate analysis suggests that long disease duration was associated with a lower risk of relapse. These data have already been shown by one previous study. Langholz et al.[12] demonstrated that the risk of relapse became lower over time, while the risk of complications including colorectal cancer became higher in the presence of extensive disease. The probability of long-term relapse was higher in male patients in our cohort. There is no clear evidence in the literature that gender may influence the disease course, however non-adherence to medical therapy has been reported to be associated with a high rate of relapse and complication in UC.[20] Kane et al. showed prospectively that among UC patients with a 12 month-recurrence, 68% were non-adherent to 5ASA.[20] The overall non-adherence rate in Europe was about 29% where non-adherence was defined as taking less than 80% of prescribed medication.[21] Many studies[20,22] showed a correlation between poor adherence

**Table 1**

| Patients' features | N=35, * median (range) |
|---|---|
| Age at diagnosis (years) | 26 (10–76)* |
| Disease duration (months) | 19 (34–358)* |
| Sex (M/F) | 19/16 |
| Familial history (+/−) | 4/17 |
| Tobacco (+/−) | 4/29 |
| Disease location at diagnosis (Montreal) | 6 E1 14 E2 8 E3 |
| Disease location at relapse (Montreal) | 3 E1 10 E2 13 E3 |
| CRP at relapse (mg/L) | 430.8 (20.5–1220.4)* |
| Hb at relapse (g/dL) | 110.8 (8–14.6)* |
| Platelets at relapse ($10^3$/mm$^3$) | 415 (327–498)* |

* Median (range).

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**Table 2** Univariate analysis of predictive factors for maximum follow-up relapse. * Median (range).

| | | Relapse 0 | Relapse + | OR | P Value |
|---|---|---|---|---|---|
| Age at diagnosis (months)* | | 25 (14–45) | 29 (10–76) | 2.3 | 0.12 |
| Sex (n): | F | 6 (66.7%) | 10 (38.5%) | 2.04 | 0.15 |
| | M | 3 (33.3%) | 16 (61.5%) | | |
| Disease duration (months)* | | 36 (0–264) | 10.5 (0–168) | 2.8 | 0.09 |
| Tobacco (n): | + | 0 (0%) | 21 (84%) | 0.0018 | 0.96 |
| | 0 | 8 (100%) | 4 (16%) | | |
| Familial history (n): | + | 0 (0%) | 4 (26.7%) | 0.0022 | 0.96 |
| | 0 | 6 (100%) | 11 (73.3%) | | |
| Montreal at diagnosis (n): | E1 | 2 (25%) | 4 (20%) | 1.3 | 0.52 |
| | E2 | 5 (62.5%) | 9 (45%) | | |
| | E3 | 1 (12.5%) | 7 (35%) | | |
| Platelets (×l000/mm$^3$)* | | 380 (368–498) | 447 (327–485) | 0.66 | 0.46 |
| Hb (g%)* | | 12.4 (8.6–12.7) | 11.2 (8–14.6) | 0.0003 | 0.98 |
| CRP(mg/l)* | | 16.6 (6.6–47.7) | 99.4 (2.5–122.4) | 1.7 | 0.19 |

and the male gender. Lack of adherence linked to male gender could explain the higher risk of time-to-relapse of this subgroup in our study. Moreover, a recent diagnosis and disease duration shorter than 5 years were also associated with significantly worse adherence (24% of patients).[23] This suggests that poor adherence could also contribute to higher risk of relapse in the subgroup with shorter disease duration in our study. Despite the fact that adherence to medical therapy could not be assessed in the present retrospective study, these associations should support a good physician–patient relationship that achieves higher medication-adherent rates. Multiple studies have shown that smoking is a protective factor in UC, while ex or non-smokers have a higher risk of relapsing disease.[24] Our cohort, with only 4 active smokers, was too small to evaluate the effect of smoking. In UC, disease extension over time does occur. Pancolitis is observed at diagnosis in about 1/3 of patients, but observed in another third of patients 20 years after the diagnosis. Extensive disease is associated with a higher rate of complication.[25,26] In our study, disease extent was stable over time in 80% of patients and was not associated with time-to-relapse or colectomy. No other clinical or demographic factor was predictive of colectomy. This could be explained by the low absolute number of colectomies in our cohort despite the fact that the proportion of colectomy (17%) was within the range of previous studies. The risk of colectomy can reach 20 to 30% after 25 years of disease duration but some series also report lower rates. Hoie et al.[25,26] reported a 10-year cumulative risk of colectomy of 8.7%, which was associated with extensive colitis and geographic variations.

Our study has some limitations. First, it is retrospective. As previously discussed, we finally studied a rather small group of 35. Data coming from the Kaplan Meier curves can't be interpreted beyond 10 years because of the small number of remaining patients. The subgroups of smokers and patients undergoing colectomy were small which could explain why the statistical analysis was not significant in these patients. As expected in retrospective studies some data, such as CRP which has been associated with poor outcome in UC,[27,28] were missing and couldn't be included in the multivariable analysis. Likewise, mucosal healing, which has been associated with longer time-to-relapse[29] could not be assessed due to the lack of data on follow-up colonoscopies.

**Table 3** Univariate analysis of predictive factors for one-year relaspe. * Median (range).

| | | Relapse 0 | Relapse + | OR | P Value |
|---|---|---|---|---|---|
| Age at diagnosis (months)* | | 26 (10–66) | 30 (14–76) | 1.09 | 0.29 |
| Sex (n): | F | 12 (54.6%) | 4 (30.8%) | 1.8 | 0.17 |
| | M | 10 (45.4%) | 9 (69.2%) | | |
| Disease duration (months)* | | 31.5 (0–264) | 6 (0–55) | 2.3 | 0.12 |
| Tobacco (n): | + | 1 (5%) | 3 (23%) | 2.04 | 0.15 |
| | 0 | 19 (95%) | 10 (77%) | | |
| Familial history (n): | + | 2 (14%) | 2 (9.5%) | 0.59 | 0.44 |
| | 0 | 12 (86%) | 5 (71.5%) | | |
| Montreal at diagnosis (n): | E1 | 4 (23.5%) | 2 (18.2%) | 0.17 | 0.91 |
| | E2 | 8 (47.1%) | 6 (54.6%) | | |
| | E3 | 5 (29.4%) | 3 (27.3%) | | |
| Platelets (×l000/mm$^3$)* | | 428 (368–498) | 387 (327–447) | 0.75 | 0.39 |
| Hb (g%)* | | 10.5 (8–14.6) | 12.6 (11.2–13–9) | 0.71 | 0.4 |
| CRP (mg/l)* | | 43.8 (3.6–122.4) | 60 (2.5–99.4) | 0.04 | 0.84 |

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**Table 4** Univariate analysis of predictive factors for maximum follow-up colectomy. * Median (range).

| | | Colectomy 0 | Colectomy + | OR | P Value |
|---|---|---|---|---|---|
| Age at diagnosis (months)* | | 29 (14–76) | 22.5 (10–49) | 1.6 | 0.21 |
| Sex (n): | F | 14 (48.3%) | 2 (33.3%) | 0.43 | 0.5 |
| | M | 15 (51.7%) | 4 (66.7%) | | |
| Disease duration (months)* | | 19 (0–264) | 34 (0–60) | 0.24 | 0.62 |
| Tobacco (n): | + | 2 (7.4%) | 2 (33.3%) | 2.6 | 0.1 |
| | 0 | 25 (92.6%) | 4 (66.7%) | | |
| Familial history (n): | + | 3 (16.7%) | 1 (33.3%) | 0.44 | 0.51 |
| | 0 | 15 (83.3%) | 2 (66.7%) | | |
| Montreal at diagnosis (n): | E1 | 5 (20.8%) | 1 (25%) | | |
| | E2 | 12 (50%) | 2 (50%) | | |
| | E3 | 7 (29.2%) | 1 (25%) | | |
| Platelets ($\times$l000/mm$^3$)* | | 447 (327–498) | 384 | 0.38 | 0.54 |
| Hb (g%)* | | 11.2 (8–13.9) | 14.6 | 0.31 | 0.58 |
| CRP (mg/l)* | | 39.9 (2.5–122.4) | 122.4 | 0.0064 | 0.93 |

## 5. Conclusions

Only 1 in 3 patients treated with mesalazine after a first flare requiring oral corticosteroids relapsed over 1 year. However, over longer follow-up, three quarters of patients finally relapsed and 1 in 6 underwent colectomy. Mesalazine can thus be considered as an effective maintenance therapy over one year after a first flare treated with systemic steroids. Nevertheless, the relapse rate over longer follow-up becomes much higher particularly in male patients with short disease duration. As poor adherence to medication (leading to relapses and complications) has particularly been described in those categories of patients, adherence should first be assessed and promoted by effective patient–physician dialogue. Immunosuppressive treatment could then be discussed in the case of further relapse.

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