Identifying patients with a high risk of relapse in quiescent Crohn’s disease

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Abstract

No reliable identification of quiescent Crohn’s disease (CD) patients with a high risk of relapse is available. The aim of this study was to develop a prognostic index to identify those patients. Untreated adult patients with quiescent disease (not induced by surgery) included in three phase III clinical trials were analysed retrospectively with respect to time to relapse. Nineteen factors related to biology, disease history, and topography were investigated. A relapse was defined as either a CD Activity Index (CDAI) >200, a CDAI >150 but over the baseline value by more than 100, or acute complications requiring surgery. The inclusion criteria were fulfilled by 178 patients. The median follow up was 23 months. The Cox model retained the following bad prognostic factors: age >25 years, interval since first symptoms >5 years, interval since previous relapse <6 months, and colonic involvement (p<0.001). Bootstrapping confirmed the variable selection. Patients were classified into three groups with an increasing risk of relapse (p<0.001). The worst risk group was composed of patients presenting at least three of the four bad prognostic factors. These results make possible the design of clinical trials in quiescent CD patients with a high risk of relapse.

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Crohn’s disease (CD) is characterised by alternating phases of quiescence and unpredictable clinical activity. A reliable identification of quiescent CD patients with a high risk of relapse would be of great interest. Firstly, early treatment of high risk patients may prevent relapses and the eventual side effects of the treatments currently used. Secondly it will be possible to design clinical trials in a homogenous group of patients with a high risk of relapse, trials that will be more effective in demonstrating treatment efficacy than the usual trials where both high risk and low risk patients are included.

Up till now, the results of research for a maintenance treatment in quiescent CD patients are contradictory and may depend on patient characteristics. Although mesalamine has recently been reported to be an effective maintenance treatment in quiescent CD patients, this result is still equivocal. The only confirmation was reported among patients who had a relapse-free interval of more than three months. However, Gendre et al reported that mesalamine had no effect in this group of patients and was only effective among patients treated within three months after the achievement of remission. Again, a recent interim analysis disagreed with this last viewpoint. Because of these contradictory data, it remains unclear whether mesalamine is effective as a maintenance treatment and, if so, in which subgroups of quiescent CD patients.

Risk factors of relapse in quiescent CD patients are poorly known. Many studies have investigated the possible correlation between the CDAI and certain biological factors measured at the same time. However, even a high correlation does not provide any information concerning the prediction of a future relapse. Although some investigators suggested that certain laboratory parameters might predict the course of the disease, their results were based on non-comparative studies with a small number of patients. Only a few clinical trials have considered this issue by looking for factors related to relapse: the National Co-operative Crohn’s Disease Study (NCCDS), the European Co-operative Crohn’s Disease Study (ECCDS), and an Italian co-operative trial. Only one prognostic index for CD based on a small number of patients has been published but not yet validated.

The purpose of this work is to study the natural history of CD among quiescent, untreated patients by evaluating the prognostic value of disease topography and history and the demographic and laboratory data to identify those patients who have a high risk of relapse.

Methods

Patients

Patients with quiescent disease who were randomised to the no treatment arm or to placebo in three controlled clinical trials performed by the Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) were considered as possible candidates for this study. The first trial was open to patient entry between March 1978 and May 1979 and was designed to test the efficacy of levamisole versus placebo in preventing relapse in quiescent CD patients. Patients were followed up for two years after randomisation. In the second trial, the usefulness of prednisolone prolongation was...
evaluated in patients in clinical – but not endoscopic – remission following prednisolone treatment of an acute episode of CD. Patient accrual for this trial lasted from June 1983 to September 1987 with a further follow up of 18 months. The third trial tested the efficacy and safety of mesalamine versus placebo in maintaining remission in quiescent CD patients. This trial was open to patient entry between December 1985 and December 1987 with a follow up period of 18 months after the accrual period. In this study, we will refer to these three trials as the levasolose, corticotherapy, and mesalamine trials respectively. Patient characteristics were collected at randomisation in the levasolose and mesalamine trials and at weaning in the corticotherapy trial.

Patient selection criteria for this study were:

- age > 16 years, diagnostic score \( \geq 6 \) and a CDAI < 150. If a patient was entered in more than one trial, only the data of the most recent trial were retained.

**Study design**

A relapse was defined either as a CDAI > 200, a CDAI > 150 but over the baseline value by more than 100 points, or severe complications requiring immediate surgery for CD.

The following factors were studied: age, age at first symptoms, age at diagnosis, sex, diagnostic score, time intervals since previous relapse, first symptoms and diagnosis, disease topography, presence of anoperineal lesions, previous medical treatment or intestinal resection, CDAI, haemoglobin, packed cell volume, erythrocyte sedimentation rate, albumin, white blood cell count, and percentage of weight loss relative to usual weight. The haemoglobin concentration was expressed as the absolute difference relative to 16 g/dl in men and to 14 g/dl in women. The packed cell volume percentage was expressed as the absolute difference relative to 47% in men and 42% in women.

Continuous variables were categorised into two or three groups. Apart from the CDAI, which was divided into three categories (< 50, 51–100, and > 100), each variable was first divided into five categories at approximately the 20th, 40th, 60th, and 80th percentiles. If the relative relapse rates (ratio of the estimates of the hazard of relapse – that is, observed number of relapses to the expected number of relapses in each category) in two or more adjacent categories were not substantially different, these categories were grouped together. If no clear pattern was seen, the median was taken as a cut off point.

The proportional hazards regression model was used for the clinical trial was used for both univariate and multivariate analyses of the time to relapse starting from entry to the study. A two sided test was used at the 5% level of significance. After categorisation, age and time intervals since previous relapse, first symptoms and diagnosis were tested as time dependent factors. In both the univariate and multivariate analyses to take into account their variation during the follow up. A step down (backward) variable selection procedure was used for building the multivariate model. The proportionality assumption for each of the variables retained in the final model was checked by testing the dependency of their relative risk estimate (RR) over time. After obtaining the final model, non-multivariate analyses was performed where the effect of the initial clinical trial – represented by two binary variables – was tested for possible interaction with any of the variables retained in the final model.

Another multivariate model was fitted taking as end point the time to relapse using the date of the end of previous relapse as a starting point (instead of the date of entry to the study). Age and intervals since first symptoms and diagnosis were recalculated. This model was based upon all the variables mentioned above except the ones that may have had different values at the end of the previous relapse: CDAI, percentage of weight loss relative to usual weight and all the biological variables.

The importance of a prognostic factor was expressed by the percentage of patients who relapsed and the median relapse free duration in each group of patients defined by a certain value of the prognostic factor, the p value of the Wald \( \chi^2 \) statistic, the relapse RR (risk of relapse in a group of patients in a given category compared with the reference one), and its 95% confidence intervals (95% CI).

To investigate the stability of variable selection in the final multivariate model, 1000 bootstrap samples, each of the same size as the original data set, were drawn by selecting patients at random with replacement from the original data set. The basic idea behind this technique is that the stability of the results based on the original data set can be assessed by studying their variability across a large number of bootstrap samples (or replications). In each replication the variables that have a prognostic influence on time to progression are identified using the same method that was used to identify these factors in the original data set. Thus, Cox regression analyses with a step down variable selection procedure was performed on each of the 1000 bootstrap samples to identify the most frequently selected variables. Age at first symptoms and age at diagnosis were not included in the bootstrap investigation because of their linear dependence, in the presence of age at inclusion, with the interval since first symptoms and the interval since diagnosis, respectively.

A simple Crohn’s disease prognostic score (PS) based on the prognostic factors retained in the multivariate model was derived. Using the same technique described above for categorising continuous variables, patients were classified into three risk groups according to the value of their PS. The three groups were compared for time to relapse using the proportional hazards regression model. Time to relapse curves, based on the group to which the patient belonged at entry, were estimated using the Kaplan–Meier technique.

The Statistical Package for Social Scientists (SPSS) was used for data management and analysis.
Identifying patients with a high risk of relapse in quiescent Crohn’s disease

the Statistical Analysis Software (SAS) was used for the data analysis.

**Results**

The total number of patients reported in the levamisole trial was 167. Data were not available for 12 patients excluded from the original analysis, 78 were treated by levamisole, 38 had a CDAI >150, two patients were included in a more recent trial and one patient was included twice. For the last patient, only the data of the first randomisation were retained. There remained 36 patients who met the criteria for inclusion in this study. Of the 150 patients in the corticotherapy trial, three patients were lost to follow up before clinical remission, 11 had a primary corticosteroid failure to respond to corticosteroid within seven weeks, 50 patients who were in clinical but not endoscopic remission were randomised for continuation of corticotherapy, four were lost to follow up before weaning, 12 had a secondary corticosteroid (during tapering), two had a CDAI >150 at corticotherapy discontinuation, the CDAI was missing for one patient, and three patients were included in the mesalamine trial. Consequently, 64 patients met the selection criteria. In the mesalamine trial, 161 patients were randomised. Eighty patients were treated by mesalamine, two were lost to follow up just after randomisation, and one patient was randomised twice in the same trial. Again, for the last patient, only the data of the first randomisation were retained. There remained 78 patients who were included in this study. Thus, this analysis is based on a total of 178 patients.

The median duration of follow up was 23 months with a maximum of 27 months. The median time to relapse from entry to the study was 21 months (Fig 1). The relapse free probabilities at 12 and 18 months were 60% (95% CI: 53 to 67%) and 53% (95% CI: 45 to 61%), respectively. The corresponding one year probabilities per trial were 72% (95% CI: 57 to 87%), 52% (95% CI: 40 to 64%), and 62% (95% CI: 50 to 74%) for the levamisole, corticotherapy, and mesalamine trial, respectively. The corresponding 18 month relapse free probabilities were 63% (95% CI: 55 to 71%), 42% (95% CI: 30 to 54%), and 59% (95% CI: 47 to 71%), respectively. The three trials differed with respect to the distribution of most of the variables under study. The level of disease activity as judged by the CDAI was not different in the three trials.

**Univariate analysis**

Table I presents the univariate time to relapse analyses as well as a brief description for each of the variables under study. Details of patient characteristics by clinical trial may be provided by request from the corresponding author. Poor prognosis was associated with young age, whether at first symptoms, at diagnosis, or at entry to the study, a short interval since last relapse, and colonic involvement. The relative risk varied between two and three (Table I). Estimates of the hazard of relapse in patients with only ileitis, patients with only colitis, and in patients with ileocolitis were 0.33, 1.14, and

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**Table I**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Median relapse free duration (months)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) &gt; 25*</td>
<td>≥ 25</td>
<td>&gt; 24-0</td>
<td>1-0</td>
</tr>
<tr>
<td>Age at first symptoms (y) &gt; 20*</td>
<td>≥ 20</td>
<td>&gt; 24-0</td>
<td>1-0</td>
</tr>
<tr>
<td>Age at diagnosis (y) &gt; 10*</td>
<td>≥ 10</td>
<td>0-10</td>
<td>0-1</td>
</tr>
<tr>
<td>Interval since last relapse (months) &gt; 6*</td>
<td>≤ 6</td>
<td>0-10</td>
<td>0-1</td>
</tr>
<tr>
<td>Disease topography</td>
<td>Beum only*</td>
<td>&gt; 24-0</td>
<td>1-0</td>
</tr>
<tr>
<td>Sex</td>
<td>Male*</td>
<td>15-0</td>
<td>0-1</td>
</tr>
<tr>
<td>Interval since first symptoms (y) &gt; 5*</td>
<td>≤ 5</td>
<td>19-3</td>
<td>0-10</td>
</tr>
<tr>
<td>Interval since diagnosis (y) &gt; 5*</td>
<td>≤ 5</td>
<td>19-3</td>
<td>0-10</td>
</tr>
<tr>
<td>CDAI ≤ 50*</td>
<td>&gt; 24-0</td>
<td>0-10</td>
<td>0-1</td>
</tr>
<tr>
<td>First relapse No*</td>
<td>23/36</td>
<td>22-6</td>
<td>0-1</td>
</tr>
<tr>
<td>Diarrhoeic score &gt; 16*</td>
<td>≤ 16</td>
<td>20-6</td>
<td>0-1</td>
</tr>
<tr>
<td>Ano-perianal lesions No*</td>
<td>20</td>
<td>0-1</td>
<td>0-0-01</td>
</tr>
<tr>
<td>Previous intestinal resection</td>
<td>No*</td>
<td>1-0</td>
<td>0-1</td>
</tr>
<tr>
<td>Previous medical treatment</td>
<td>Yes</td>
<td>1-0</td>
<td>0-1</td>
</tr>
<tr>
<td>Haemoglobin difference (g/dl) ≤ 3*</td>
<td>≥ 3</td>
<td>21-0</td>
<td>0-1</td>
</tr>
<tr>
<td>Packed cell volume difference (%/l) ≤ 3*</td>
<td>≥ 3</td>
<td>18-8</td>
<td>0-1</td>
</tr>
<tr>
<td>Albumin (g/dl) ≤ 35*</td>
<td>&gt; 3</td>
<td>24-6</td>
<td>0-1</td>
</tr>
<tr>
<td>Sedimentation rate (mm, first hour) ≤ 10*</td>
<td>&gt; 10</td>
<td>36-7</td>
<td>0-1</td>
</tr>
<tr>
<td>Weight loss relative to usual weight (%) ≤ 10*</td>
<td>&gt; 20</td>
<td>50/101</td>
<td>0-1</td>
</tr>
<tr>
<td>White blood cell count (×10³/μl) ≤ 9*</td>
<td>&gt; 9</td>
<td>28-8</td>
<td>0-1</td>
</tr>
</tbody>
</table>

*Reference category; O/N: observed relapse/number of patients; relative risk and its 95% confidence intervals; the difference relative to 16 g/dl in men and 14 g/dl in women; the difference relative to 47% in men and 42% in women.

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**Figure 1**

Time to relapse from entry on study among quiescent Crohn's disease patients.
TABLE II  Factors related to time to relapse using the multivariate Cox model

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Conditional RR (95% CD†)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>1-0</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>3.5 (2.0-6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interval since first symptoms (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>1-0</td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>0-4 (0-2-0-7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Interval since last relapse (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6*</td>
<td>1-0</td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>2-4 (1-0-5-7)</td>
<td>0.042</td>
</tr>
<tr>
<td>Disease topography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum only</td>
<td>1-0</td>
<td></td>
</tr>
<tr>
<td>Colonic involvement</td>
<td>2-9 (1-0-8-3)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

*Reference category; relative risk and its 95% confidence intervals, each variable adjusted for the others.

1-07, respectively. Thus, the last two categories were grouped together in one category (colonic involvement). Neither the disease activity at inclusion as measured by the CDAI nor any of the biological factors were predictive of clinical relapse.

Multivariate analysis

The Cox proportional hazards model was based on all the variables presented in Table I except for the white blood cell count, the albumin and the packed cell volume as their values were missing for a large number of patients (36, 87, and 86 respectively). The multivariate model retained the following prognostic factors: age, interval since first symptoms, interval since last relapse (all as time dependent covariates), and colonic involvement (Table II). The final model was based on 172 patients. No interaction could be detected between the original trial and any of these variables and no violation of the proportionality assumptions could be detected.

When considering time to relapse from the end of the previous relapse, the multivariate model retained age, interval since first symptoms, and colonic involvement, which confirms the results of the main multivariate analysis.

Model stability

The Cox regression analysis with a step down variable selection of 1000 bootstrap samples showed that the most frequently selected variables were those selected in the original model: age (98-7%), interval since first symptoms (93-9%), colonic involvement (52-2%), and interval since last relapse (47-9%). None of the other variables were selected in more than 35% of the models. Age and interval since first symptoms were selected together in 93-6% of the cases.

Risk groups

For each patient, a Crohn’s disease PS based on the maximum likelihood parameter estimates for these four prognostic factors was calculated as follows:

PS = -0.89 + 1.24 (if ≤25 years old) + 0-89 (if interval since first symptoms >5 years) + 0.89 (if interval since last relapse ≤6 months) + 1-06 (if colonic involvement)

This PS has 16 possible values (16 possible combinations of these four prognostic factors) ranging between -0-89 and 3-19. According to their PS value at entry to the study, patients were classified into three groups: a good prognosis group had a score ≤0-5, which corresponds to patients having none or only one of the four bad prognostic factors, an intermediate group had a score between 0-5 and 1-5 (patients having two bad prognostic factors), and a poor prognosis group had a score ≥1-5 (three or four bad prognostic factors). Table III provides further information about these three groups according to patient characteristics at entry in the study and Fig 2 presents the corresponding time to relapse curves.

Discussion

The prediction of relapse of Crohn’s disease is a persistent dream of both clinicians and patients. If achieved, this would allow the design of clinical trials aiming at an early treatment of the forthcoming relapse.

Time to relapse

Our study showed that the relapse free probability after two years from entry to the study was 46%. This estimate was 63% for the levasilone trial, 50% for the mesalamine trial, and could not be estimated separately for the corticotherapy trial because the follow up was limited to 18 months. Noteworthy, the relapse free probability in this trial was estimated to be only 42% at 18 months. These differences resulted from the fact that the distribution of patients in the three prognostic groups was different in the three trials. The levasilone trial had 10 (32%), 13 (42%), and eight (26%) patients in the good, intermediate, and bad prognosis groups, respectively. The corresponding figures in the corticotherapy trial were 0 (0%) 21 (33%), and 43 (67%) and for the mesalamine trial they were 13 (17%), 31 (40%), and 33 (43%).

The two year relapse free probability in the NCCDS was about 60%. The ECCDS reported that 68% of the patients who entered the study with quiescent disease (CDAI <150) maintained their remission at the end of the second year. More recently, an Italian study...
reported a relapse free probability after one year in the placebo group of about 46% and no estimate for two years was available because of insufficient follow up. In our opinion, this apparent disagreement between different clinical trials may be due to two reasons: either a time trend for hospital recruited patients toward more severe cases as recent trials tend to find more pessimistic estimates or intertrial differences in the starting point. A more meaningful estimate of the relapse free probabilities would be based on the end of the previous relapse and not the date of randomisation into the new trial as the starting point.

Statistical methods
Prognostic factor analyses with respect to the time to an event (relapse in our case) requires appropriate statistical methodology. Two widely used statistical techniques are appropriate as they take the event as well as the time to event into account: the log rank test and the Cox proportional hazards regression model. The multiple linear regression and the correlation analyses used in the NCCDS and the linear discriminant analysis used by Brignola et al. do not take the time to relapse into account. Mekhjian et al. mentioned the use of Cox model but no corresponding results were presented and the log rank test was not used for comparisons.

Although the continuous variables under study could have been analysed as such, it is more useful clinically to group the values into a few categories permitting the estimation of the relative risk of relapse as the variable changes from one level to another. The essential question then becomes whether these categories differ with respect to the outcome of interest. There is no unequivocal method for the choice of cut off points. The one used here is recommended and described in detail by Byar. Some statisticians may prefer the median value as a cut off point but usually it is the patients with extreme values who behave differently with respect to the end point of interest. Others may like what they call the ‘optimal cut off point’ – that is, the cut off point that leads to the smallest p value. But in that case the ‘optimal’ cut off point will probably not be optimal for another data set.

Biological factors
Six biological factors regarded to be of potential prognostic value were studied. Other possible prognostic factors such as C reactive protein, orosomucoid, α1 antitrypsin, serum iron, etc. were not available in our trials. Some of these parameters were reported to be predictors of further disease activity by other investigators: the C reactive protein, orosomucoid, and α1 antitrypsin. Both publications were based on a small number of patients (five and 33 respectively), however, and were non-comparative – that is, the variation of these biological parameters in the group of patients who did not relapse was not provided. Also, Wright et al. reported that some patients were included more than once in their study. In the NCCDS a favourable outcome as measured by a change in CDAI had a positive correlation with the leucocyte count and a negative correlation with albumin, both measured at randomisation amongst quiescent CD patients receiving placebo. The investigators were aware, however, that statistical significance was probably achieved because of the large number of variables tested, rather than because of any profound biological implications. Recently, Prantera et al. mentioned that only the presence of laboratory signs of inflammation was significantly correlated with relapse without detailing these signs. Our results showed that the packed cell volume and weight loss did not show any prognostic value, which confirms the NCCDS results amongst patients receiving placebo.

Sachar stated that ‘the list of tests proposed as either predictors or markers of disease activity is growing longer every day. The length of the list is, unfortunately, inversely proportional to the adequacy of any of its components’. Our results showed that none of the biological factors were significant in either the univariate or multivariate analyses. This is reasonable as the median time to relapse is probably too long to be affected by biological parameters measured at entry. In other words, it is difficult to consider that a trans-sectional biological measurement might affect an event that has a median free duration of more than 20 months. Few investigators were aware of this pitfall and analysed biological data measured one to three months before the relapse. A definitive answer may be provided by collecting repeatedly laboratory measures every one to two months during the course of the disease. The analysis of these data should be performed using appropriate techniques, for example, as time dependent covariates in the Cox proportional hazards regression model.
This was taken into account in the design of the current GETAID double blind randomised trial comparing 5-aminosalicylic acid (4 g/day) with placebo. This trial will be analysed towards the end of 1994.

**Disease topography**

Although patients with colonic involvement had three times the risk of relapse relative to patients with ileitis only, it is necessary to take into consideration the small number of patients with disease confined to the ileum and the small number of relapses in this group. This is reflected in the wide 95% confidence intervals for the relative risk (1.0 to 8.7). Our results disagree with those of Basilisco et al., but their end point was the time to first surgical operation for CD irrespective of the clinical relapse. The NCCDS showed that there is little evidence to suggest a correlation between clinical and radiographic findings. This result could be the consequence of the radiographic techniques used in the late 'seventies and left an unanswered question of whether an improved technique would improve prediction of the clinical outcome of CD. Mekhjian et al. tested the possible predictive value of the maximal extent of both small bowel and colon involvement in the NCCDS. Neither of these two continuous variables showed any significant results, but the authors did not report testing only ileum involvement (yes/no) and colon involvement (yes/no). In our work, the presence of anoperineal lesions was not of prognostic value. The NCCDS showed that this group of patients ranked significantly poorer in outcome than the others but that was among patients who had active Crohn's disease at randomisation.

**Age related factors**

Our results showed that younger CD patients, either at first symptoms, at diagnosis, or at entry to the trial tended to have a higher risk of relapse than older patients. Although these results confirm those of other investigators, others reported that none of these three variables were of prognostic value. However, their results were among patients randomised in part I of the NCCDS, which included patients with active disease and nothing was mentioned concerning the prognostic value of these variables among quiescent patients who were included in part II of the trial. Weterman et al. reported that patients whose disease started before the age of 20 years had an excess mortality compared with older patients.

It was shown that a short interval since first symptoms was positively correlated to the outcome after adjusting for age but not alone. This was confirmed by the results of bootstrapping and also by the results of the second multivariate model using the time calculated from the end of the last relapse. In our opinion, the effect of the interval since first symptoms in a univariate analysis was completely masked by the effect of age. Stratification for age to take into account its effect shows that patients with a short interval since first symptoms had a significantly better prognosis (RR=0.5, 95% CI: 0.3 to 0.9, p=0.018). This means that age corrects the effect of the interval since first symptoms. In other words, the importance of interval since first symptoms becomes evident only once age is taken into account. This also emphasises the importance of multivariate analysis as an essential element of the data analysis. Although the ECCDS reported a favourable prognosis for patients with a long duration of symptoms, its prognostic value when taking age into account was not tested. We should also keep in mind that age, whether at first symptoms, at diagnosis, or at consultation, and intervals since first symptoms and diagnosis are highly correlated with each other. Further investigation on another set of data is necessary for a better understanding of the prognostic value of these variables.

**Interval since the end of the previous relapse**

A prolonged pre-study remission was positively correlated to a prolonged time to relapse. Similar results were reported by other investigators. This finding reflects a clinical finding that has led the GETAID to introduce the pre-study duration of remission as an element in the definition of risk groups in two recent randomised clinical trials (Gendre et al. and a current clinical trial). The choice of cut off points in these two trials was somewhat arbitrary, however, and based only on clinical experience, even if this variable has been shown to be an important prognostic factor.

Previous surgery or treatment for CD

We did not find any prognostic value for previous intestinal resection. The ECCDS reported that patients with a previous bowel resection had a less favourable outcome, whereas other investigators reported the opposite. The NCCDS results showed that patients who entered the trial with recurrent disease after complete resection ranked significantly better in outcome than patients who entered with no prior history of surgery or after an incomplete resection. Our results confirm the ECCDS findings, which showed no prognostic difference between previously untreated and treated patients. The drug(s) used in the previous relapse to achieve remission were not investigated in this study. To our knowledge, however, it has never been shown or even claimed in the context of a randomised clinical trial for active Crohn's disease, that a specific drug used to achieve remission has any influence of the duration of this remission.

**CDAI**

We found no statistically significant prognostic value for the CDAI. The NCCDS showed that a CDAI <200 was associated with a favourable outcome in placebo treated patients. Again that was among patients with active disease at randomisation. Wright and coauthors reported that the CDAI increases in the three
months preceding the attack but no comparisons were provided of the CDAI variation in the group of patients who did not relapse. This result has not been confirmed by other investigators despite the fact that the CDAI is the most frequently used index in clinical trials of CD.

**Multivariate results**

Model validation is a necessary but often neglected task. Up to now, in the field of CD, only one index has been validated using an independent data set. To assure the validity of the conclusions based on any suggested model, investigating its stability should be an important step in the analysis. The bootstrap technique is a useful and simple tool to investigate the variation in the variable constituting the model. Our results showed that the proposed model is stable, that is, the most frequently selected variables using the bootstrap technique were those selected in the original model. Nevertheless, validation on an independent data set is foreseen.

**Risk groups**

The identification of risk groups will improve the design of clinical trials among quiescent CD patients. Patients entered in clinical trials tend to be quite heterogeneous. In clinical trials that mix high and low risk patients, a possible bias when assessing treatment efficacy may occur because of an imbalance of the percentage of high risk patients in each treatment arm. Stratification by risk group at randomisation would highly minimise the possibility of such a bias. Nevertheless, even if such an imbalance does not exist, a lack of power in detecting treatment differences may result from the inclusion of low and intermediate risk patients as all treatments may show roughly the same efficacy in these patients. In other words, clinical trials based on a homogenous group of high risk patients are more powerful in detecting a difference in treatment efficacy. The trial conducted by our group provides a clear example, as patients were stratified at randomisation by the pre-trial remission period (<3 months versus 3–24 months). The treatment (mesalamine 2 g/day) was only effective among patients who had a short pre-trial remission. Identifying risk groups also allows different trials to be carried out in quiescent CD patients with good or poor prognoses.

Based on our findings the following conclusions may be made: (a) a young age whether at first symptoms, at diagnosis, or at consultation is related to a high risk of clinical relapse in quiescent (not induced by surgery) CD patients; (b) the prognostic value of the interval since first symptoms and the interval since diagnosis and their relation with age needs further investigation on an independent group of patients; (c) a short interval since the previous relapse is associated with a poor prognosis; (d) colonic involvement is associated with a bad prognosis. This study provides the possibility for the design of powerful clinical trials in quiescent CD patients with a high risk of relapse.

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