Maintenance of Remission Among Patients With Crohn's Disease on Antimetabolite Therapy After Infliximab Therapy Is Stopped

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This article has an accompanying continuing medical education activity on page e31. Learning Objective: Upon completion of this exercise, successful learners will be able to assess the risk of relapse and the response to potential re-treatment in Crohn's disease patients in whom infliximab treatment would be stopped after prolonged stable remission under combined therapy with antimetabolite and infliximab.

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes; see Siegel CA et al on page 46 in *CGH*; see Covering the Cover synopsis on page 1.

BACKGROUND & AIMS: It is important to determine whether infliximab therapy can be safely interrupted in patients with Crohn's disease who have undergone a period of prolonged remission. We assessed the risk of relapse after infliximab therapy was discontinued in patients on combined maintenance therapy with antimetabolites and identified factors associated with relapse. **METHODS:** We performed a prospective study of 115 patients with Crohn's disease who were treated for at least 1 year with scheduled infliximab and an antimetabolite and had been in corticosteroid-free remission for at least 6 months. Infliximab was stopped, and patients were followed up for at least 1 year. We associated demographic, clinical, and biologic factors with time to relapse using a Cox model. **RESULTS:** After a median follow-up period of 28 months, 52 of the 115 patients experienced a relapse; the 1-year relapse rate was 43.9% ± 5.0%. Based on multivariable analysis, risk factors for relapse included male sex, the absence of surgical resection, leukocyte counts $>6.0 \times 10^9$/L, and levels of hemoglobin ≤145 g/L, C-reactive protein ≥5.0 mg/L, and fecal calprotectin ≥300 μg/g. Patients with no more than 2 of these risk factors (approximately 29% of the study population) had a 15% risk of relapse within 1 year. Re-treatment with infliximab was effective and well tolerated in 88% of patients who experienced a relapse. **CONCLUSIONS: Approximately 50% of patients with Crohn's disease who were treated for at least 1 year with infliximab and an antimetabolite agent experienced a relapse within 1 year after discontinuation of infliximab. However, patients with a low risk of relapse can be identified using a combination of clinical and biologic markers.**

Keywords: Inflammatory Bowel Disease; IBD; Clinical TrialStopping Therapy Factors That Contribute to Relapse.

The advent of tumor necrosis factor (TNF) antagonists has dramatically changed our concept of treating patients with inflammatory bowel disease. Infliximab and other monoclonal antibodies targeting TNF have shown efficacy in inducing and maintaining remission of Crohn's disease.[1–3] However, despite more than a decade of clinical experience, optimal treatment strategies are still debated. Ongoing controversies concern relevant timing for starting, management of loss of response, and need for combined therapy with an antimetabolite. Another important issue is whether and when to stop treatment with infliximab in patients with long-standing remission. Cessation of infliximab therapy may be considered for various reasons, including cost, concerns about long-term safety, or other circumstances, including pregnancy. The cost-effectiveness of maintenance treatment with infliximab has been questioned.[4] Although recent Markov model analyses have suggested cost-effectiveness for maintenance treatment for up to 4 years, longer therapy may not be cost-effective.[5] As far as safety, the increased risk of

Abbreviations used in this paper: CDEIS, Crohn's Disease Endoscopic Index of Severity; GETAID, Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives; hsCRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor.

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opportunistic infections and lymphoma remains a concern.[6,7] Finally, during pregnancy, transplacental active transport of immunoglobulin G1 from the 20th week potentially exposes the fetus to unwanted anti-TNF effects.[8] Data identifying candidates for TNF antagonist withdrawal are therefore strongly needed.

The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID) designed a study to assess the risk of relapse following withdrawal of infliximab therapy in patients with Crohn's disease in long-standing remission and to identify factors associated with a low risk of relapse.

Patients and Methods

Study Design and Patients

The study of infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors (STORI) was a prospective multicenter cohort study conducted at 20 centers in France and Belgium between March 2006 and December 2009. The study protocol and documents were approved by the Ethics Committee of the Saint-Louis Hospital in Paris on May 26, 2005. The investigational review board at each of the participating centers approved the protocol. All patients gave their written informed consent before screening.

Eligible patients were at least 17 years of age and had received at least 1 year of therapy with scheduled infliximab and an antimetabolite agent (azathioprine, 6-mercaptopurine, or methotrexate) for active luminal Crohn's disease. At least 2 infusions of infliximab had to have been administered during the past 6 months. The dose of the antimetabolite agent (azathioprine >2 mg/kg, 6-mercaptopurine >1.5 mg/kg, methotrexate >15 mg weekly subcutaneously or intramuscularly) had to have been stable since at least 3 months and to have been kept stable throughout the study period. The patients had to have been in corticosteroid-free remission over the past 6 months before inclusion. This stable remission and all other eligibility criteria were assessed retrospectively from patients' medical records; at inclusion, the prospective Crohn's Disease Activity Index (CDAI)[9] had to be <150.

Exclusion criteria included a history of severe acute or delayed infusion reaction to infliximab, initial indication for infliximab being predominantly fistulizing perianal disease without significant luminal disease, persistence of active fistulizing disease, predominant jejunal or proximal ileal lesions, an ostomy, severe extraintestinal manifestations, and pregnancy or lactation.

Inclusion and Follow-up After Treatment Cessation

The patients were prospectively included and followed up from the time of the last infliximab infusion. This had to be performed within 7 to 14 days after inclusion. Follow-up visits were performed at 14 days and every 2 months after the last infliximab infusion (or earlier in case of relapse or suspicion of relapse) up to 30 months, relapse, study withdrawal, or closing date (December 31, 2009).

Clinical and demographic data were collected and CDAI was prospectively calculated at baseline. An ileocolonoscopy was performed between screening and last infliximab infusion, and Crohn's Disease Endoscopic Index of Severity (CDEIS)[10] was calculated. The CDAI was evaluated at each scheduled visit or at the time of relapse. A relapse was defined by a CDAI above 250 points or between 150 points and 250 points with a 70-point increase from baseline over 2 consecutive weeks. Hemoglobin, hematocrit, white blood cell count, platelet count, and erythrocyte 6-thioguanine nucleotides (in patients treated with purine analogues) were measured by routine procedures. Serum and stool samples were also collected at baseline and just before the last infliximab infusion for central measurement of high-sensitivity C-reactive protein (hsCRP), infliximab trough, anti-infliximab antibody, and fecal calprotectin levels.

Follow-up After Relapse and Re-treatment

In case of relapse, the patients were re-treated with infliximab, resuming the previous scheduled treatment at the same dose and frequency as during the last 6 months before inclusion. The first re-treatment with infliximab had to be performed within 20 days of the relapse. This infusion was preceded by an infusion of 200 mg of hydrocortisone. Patients experiencing a relapse were assessed for response to treatment 30 days (±10 days) after the first infliximab re-treatment up to the third re-treatment infusion. Clinical response was defined by a decrease in CDAI of at least 70 points and 25% from CDAI at relapse. Remission was defined by a CDAI <150. Follow-up ended after the third re-treatment infusion. Blood samples were collected just before the first and second re-treatment infusions for central measurement of anti-infliximab antibodies and just before the third re-treatment infusion for central measurement of infliximab trough levels.

In addition, for patients who experienced a relapse and were re-treated, information about infliximab treatment, new treatment initiation, and surgery was retrospectively collected from patient records or direct contact up to the closing date. These retrospective data are presented in the supplementary material.

Adverse Events

During the study, serious adverse events were reported according to standard clinical practice. The investigators also systematically recorded all adverse events occurring after infliximab infusions in case of clinical relapse and re-treatment.

Central Measurements of Biologic Indicators

The sera were stored at −80°C and then analyzed for hsCRP, infliximab trough, and anti-infliximab antibody levels. The turbidimetric technique for hsCRP, involving latex sensitized beads, was performed on an AU 640 from Olympus (Rungis, France). This technique allows full-range quantification of C-reactive protein with detection of hsCRP (0.06–160 mg/L). Infliximab serum concentrations were measured using an enzyme-linked immunosorbent assay as previously described.[11] The limit of detection was 0.014 mg/L, and the lower limit of quantification was 0.04 mg/L. Serum concentrations of anti-infliximab antibodies were analyzed using a double-antigen enzyme-linked immunosorbent assay based on their capture by infliximab-coated microplates and their detection by peroxidase-coupled infliximab.[12] On account of the interference of circulating infliximab, anti-infliximab antibodies could not be detected if infliximab concentrations were too high. Anti-infliximab antibodies were therefore reported as inconclusive when the serum infliximab level was ≥1 mg/L, as negative when the concentration was <0.07 mg/L and the serum infliximab level was <1 mg/L, and as positive when the concentration of anti-infliximab antibodies was ≥0.07 mg/L.

Stool samples were collected and then stored at −80°C until measurement of calprotectin levels. Quantification of calprotectin was performed using the PhiCal test (Calpro S.A., Lysaker, Norway), an enzyme-linked immunosorbent assay. The PhiCal test is based on preparation of a feces extract of 0.1 g. After

centrifugation of the extract, the enzyme-linked immunosorbent assay was performed on 20 μL of the supernatant. Enzyme-linked immunosorbent assay was performed by following the manufacturer's instructions.

End Points

The primary end point was time to relapse after withdrawal of infliximab and identification of factors associated with a low risk of relapse. Secondary end points were tolerance, safety, and efficacy of re-treatment with infliximab in patients who experienced a relapse.

Statistical Analysis

Assuming that 100 patients could be included in the study by the GETAID centers, if 50% relapse was observed during the study, it would be possible with an 80% chance to detect a factor associated with relapse through a hazard ratio of 3.75 if the proportion of patients in the risk group represented 10 or 90% of the population (or a hazard ratio of 2.20 if this proportion was 50%).[13] If more relapses were observed (ie, 70%), the detectable hazard ratios would become 3.00 and 2.00 with the same proportions of patients in the risk group. No correction was made to sample size calculation to take into account the multiple correlations relating the coefficient of a given factor to the coefficients of all other factors.

Qualitative variables are described as n and percentage and quantitative variables as median and interquartile range. As described in Figure 1*A*, follow-up was censored in patients with ignored suspicion of relapse, unconfirmed relapse, or 2 successive missed visits. When studying time to relapse, patients who missed 2 successive visits had their follow-up censored at the time of their previous visit, patients with suspected relapse not confirmed over 2 consecutive weeks had their follow-up censored at the time of the preceding visit, patients who were wrongly considered in relapse had their follow-up censored at the time of their last visit, patients withdrawn from the study had their follow-up censored at the date of withdrawal, and patients not in relapse were censored at their last visit or at the closing date. In addition, all patients who fulfilled

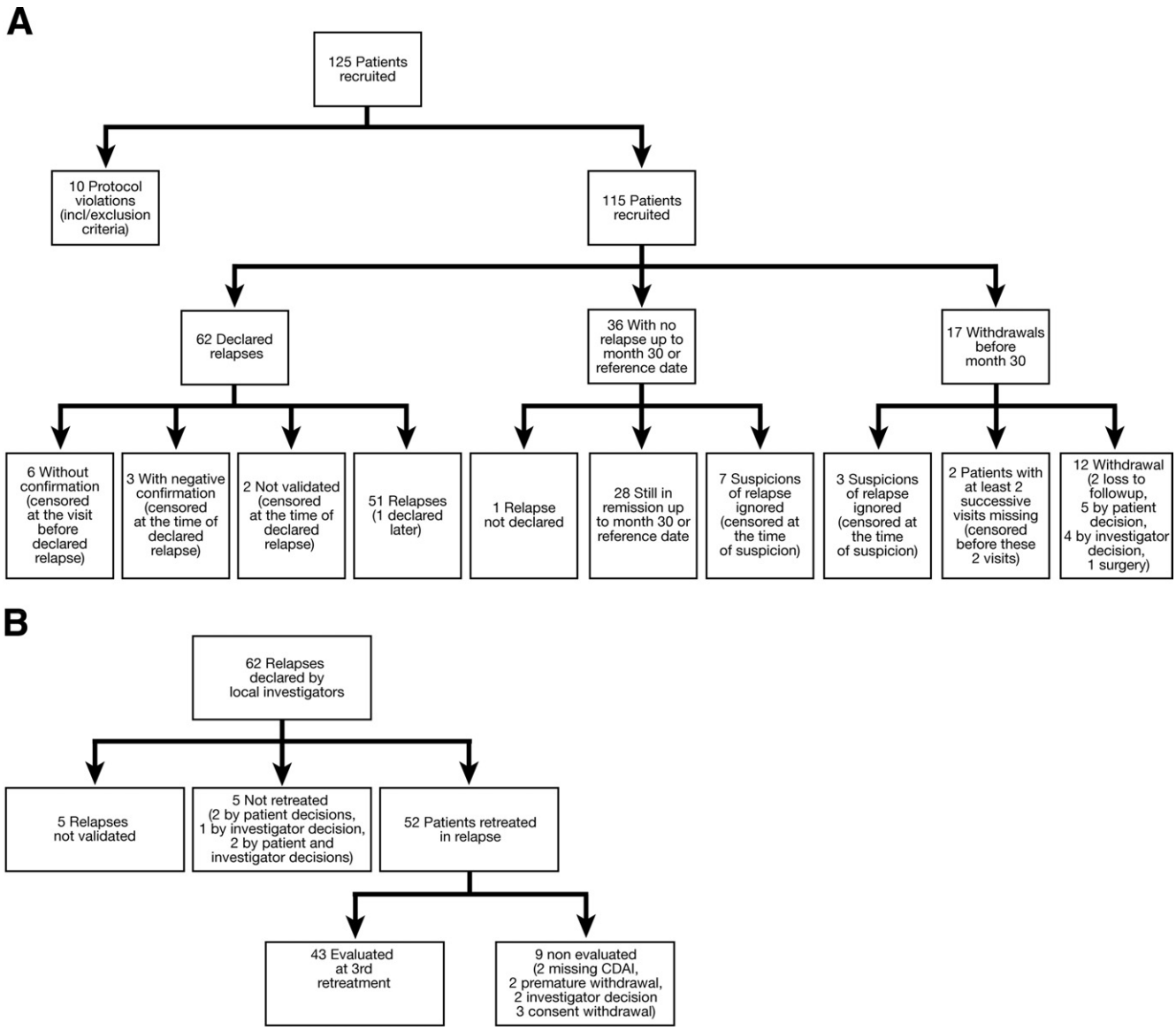

Figure 1. Flowchart of the patients in the study. (*A*) Disposal of all included patients up to relapse, withdrawal, 30 months, or closing date. (*B*) Disposal of relapsing patients up to third infliximab re-treatment infusion.

predefined criteria for relapse at a given time point were analyzed as relapsers, even if they were still followed up as nonrelapsers in their center. Proportions of nonrelapsers as a function of time after cessation of infliximab therapy were estimated by the Kaplan–Meier method.[14]

Factors related to time to relapse were studied through univariable and multivariable proportional hazards models.[15] Continuous variables were categorized into 2 or 3 classes following a systematic method described in the supplementary material. After univariable analysis, all variables with a *P* value of less than .30 were proposed in the multivariable analysis. Missing data (hsCRP in 6 cases, infliximab trough level in 2 cases, fecal calprotectin level in 30 cases) were handled through the multiple imputation method, taking into account baseline hazard curve and qualitative and categorized baseline variables.[16] Variables used to impute missing data through the logistic regression model were not limited, and 10 independent imputations were performed. Two different relapse-predicting models were developed: a complete model from all items recorded at inclusion, and a simplified model excluding infliximab trough level, a dosage that cannot be performed routinely in every center, and CDEIS evaluation that requires ileocolonoscopy. From each final model, an integer score was defined as the number of pejorative factors. Time-to-relapse curves were again estimated for each category of the score defined after grouping adjacent values of score using the same rule as the one used to categorize prognostic factors related to time to relapse. Time-to-relapse curves for each category of a score were drawn for the 10 imputations as a picture of uncertainty due to missing data in predicting time to relapse. The proportionality assumption was tested using the Grambsch and Therneau method based on Schoenfeld residuals[17] for the complete and simplified models, expressed in 4 risk group strata. The concordance probability, as proposed by Gönen and Heller,[18] was calculated from the 10 imputations (estimate ± SD) to evaluate the discriminatory power of the complete and simplified models when expressed in 4 risk group strata. Briefly, it measures the probability of observing a longer time to relapse for a patient in the low-risk group stratum compared with a patient in a higher-risk group stratum. A probability of 1 indicates a perfect discrimination between strata, whereas 0.5 indicates no discrimination at all. In an attempt to validate the complete and simplified models, when expressed in risk group strata, 2000 bootstrap samples were derived from the original sample (random selection of 115 individuals in the original sample using uniform distribution and replacement).[19] Following bootstrapping rationale, the distribution of the concordance probability was derived to evaluate the discriminatory power of the 2 models across these 2000 samples.

As far as the study of relapsing patients, those who were not in relapse according to protocol definition were excluded, even if re-treated. All other re-treated patients were analyzed, even in the absence of relapse confirmation over the 2 following weeks, due to the lack of a second CDAI calculation after a first CDAI showing a value between 150 and 250 points with a 70-point increase from baseline. For response, the last CDAI before re-treatment (either at relapse or at positive confirmation of relapse) was used as baseline. Response and remission were evaluated at 30 days (±10 days) and just before the third infliximab re-treatment infusion. The comparison of median infliximab trough level at baseline (just before the last infusion of infliximab preceding withdrawal) and just before the third re-treatment following relapse was performed through matched-pairs signed rank test.[20]

Results

Study Population

Between March 2006 and January 2008, 125 patients were prospectively recruited in 20 GETAID centers. The patients' flow diagram is shown in Figure 1. Ten patients with protocol violations as far as inclusion and/or exclusion criteria were not included in the analysis (detailed reasons for noninclusion are presented in the supplementary material). The demographic, clinical, biologic, and endoscopic characteristics of the 115 included patients at baseline are described in Table 1. Most patients had minimal symptoms before their last infliximab infusion with low CDAI values (median, 37; range, 19–61).

Relapse Rate and Predictive Factors of Relapse

Sixty-two relapses were declared by the investigators. Eleven of the 62 were not in relapse according to protocol definition, and one relapse was not declared by the investigator (Figure 1*A*). Therefore, 52 confirmed relapses were identified in these 115 patients. The time-to relapse curve is shown in Figure 2. The median follow-up time ± SE was 28 ± 2 months. Forty-four relapses occurred over the first year and 7 during the second year, with an estimated proportion ± SE of relapse over 1 year and 2 years of 43.9% ± 5.0% and 52.2% ± 5.2%, respectively.

Variables associated with time to relapse in univariable analysis are presented in the supplementary material. Multivariable analyses generated several models significantly associated with time to relapse. Both the most efficient complete model and a simplified model without infliximab trough levels and CDEIS are presented (Table 2).

Using the score based on the number of risk factors for each of these 2 models, 4 groups of patients with different risks of relapse over time were derived as shown by the time-to-relapse curves in Figure 3, with the various curves corresponding to a group arising from the 10 imputations. Detailed characteristics of the 4 risk groups with the 2 models are presented in the supplementary material. According to the score derived from the complete model, the low-risk group could be defined by the presence of no more than 3 of 9 deleterious risk factors representing across the 10 imputations 19% to 22% (mean ± SD, 20.4% ± 0.7%) of the study population and a 0% to 6% (mean, 5.0%; 95% confidence interval, 0.5% to 29.3%) risk of relapse over 1 year. According to the score derived from the simplified model without infliximab trough level and CDEIS value, the low-risk group was defined by the presence of no more than 2 of 6 deleterious risk factors, representing 28% to 30% (mean ± SD, 29.0% ± 0.8%) of the study population with a 14% to 16% (mean, 15.2%; 95% confidence interval, 5.9% to 35.7%) risk of relapse over 1 year. For the complete and simplified models expressed in 4 risk group strata, deviation to the proportionality assumption was never evidenced in any imputed sample. The concordance probability was estimated to be 0.74 ± 0.03 for the complete model and 0.71 ± 0.03 for the simplified model when defined as 4 risk group strata.

Table 1. Characteristics of the Included Population

Demographic and clinical characteristics	
Male, n (%)	49 (43)
Age (*y*)	32 (26–39)
Disease duration (*y*)	7.8 (4.5–11.9)
Active smoker, n (%)	45 (39)
Disease site (n = 114) (*y*)	
Ileal	14 (12)
Colonic	36 (31)
Ileocolonic	64 (56)
Anoperineal lesions at infliximab initiation, n (%)	40 (35)
Enterocutaneous fistula at infliximab initiation, n (%)	3 (3)
Intestinal stricture before infliximab initiation, n (%) (n = 114)	11 (10)
Intestinal stricture at infliximab initiation or during treatment, n (%) (n = 114)	5 (4)
Previous surgical resection, n (%)	25 (22)
CDAI	37 (19–61)
Treatment history	
Antimetabolite treatment	
Methotrexate, n (%)	19 (17)
Azathioprine/6-mercaptopurine, n (%)	96 (83)
Antimetabolite naïve[a] at infliximab initiation, n (%)	51 (44)
Duration of antimetabolite treatment (*y*)	2.8 (2.0–4.6)
Erythrocyte 6-thioguanine (pmol/10^8 red cells) (n = 64)	194 (124–280)
Corticosteroids between 12 and 6 mo before baseline, n (%)	8 (7)
Infliximab treatment	
Infliximab scheduled therapy from the start, n (%)	109 (95)
Relapse with infliximab before the past 6 months, n (%)	1 (1)
Duration of infliximab treatment (*y*)	2.2 (1.5–3.1)
No. of infliximab infusions	13 (10–16)
Dose of infliximab at inclusion (*mg/kg*), n (%)	
5	112 (97)
7.5	1 (1)
10	2 (2)
No. of infusions over past 6 months, n (%)	
≤2	14 (12)
3	74 (64)
≥4	27 (23)
Systematic corticosteroid preinfusion prophylaxis, n (%)	108 (94)
Previous nonsevere infusion reaction, n (%)	3 (3)
Infliximab trough level at baseline (n = 113)	
Median (mg/L)	3.7 (1.7–8.0)
Patients with trough level <1 mg/L (%)	15 (13)
Anti-infliximab antibody at baseline (n = 112), n (%)	
Positive	1 (1)
Negative	48 (43)
Inconclusive	63 (56)
Biologic variables	
Hemoglobin level (g/L)	135 (128–144)
Hematocrit	0.40 (0.37–0.43)
Leukocyte count (10^9/L)	6.1 (4.9–7.5)
Platelet count (10^9/L)	272 (233–314)
hsCRP level (*mg/L*) (n = 109)	2.0 (0.9–4.8)
Patients with hsCRP level ≤5 mg/L, n (%)	85 (78)
Fecal calprotectin level (*μg/g*) (n = 85)	51 (30–318)
Patients with calprotectin level ≤50 μg/g, n (%)	41 (48)
Endoscopy	
CDEIS	0.7 (0.0–3.0)
Patients with a CDEIS of 0, n (%)	39 (34)
Patients with a CDEIS of 0–3, n (%)	50 (43)
Patients with a CDEIS >3, n (%)	26 (23)
Patients with remaining ulcers, n (%)	39 (34)
Patients with remaining deep ulcers, n (%)	4 (3)

NOTE. N = 115, presented as n (%) or median (interquartile range).
[a]Antimetabolite naïve was defined as receiving the first infliximab infusion within 3 months after the start of the antimetabolite.

From the 2000 bootstrapped samples, the mean (95% confidence interval) of the concordance probability was 0.74 (0.67–0.76) and 0.71 (0.66–0.77) for the complete and simplified models, expressed in risk group strata, respectively. The distributions of the concordance probability derived from the bootstrapped samples are described in the supplementary material.

The profiles of patients associated with a low risk of relapse in the simplified model are shown in Figure 4.

Outcome of Re-treatment With Infliximab in Relapsers

Overall, 52 patients were re-treated (Figure 1*B*). Forty patients were adequately assessed at 30 days and 43 just before the third re-treatment infusion. Thirty days after re-treatment with infliximab, 37 of 40 patients (93%) were in remission and 39 of 40 (98%) had a clinical response. Among the 12 patients not evaluable at 30 days, there were one consent withdrawal just after the first infusion and 11 patients assessed earlier and/or later than 30 days, 9 being in remission and response, one in response only, and one neither in remission nor in response. Just before the third infliximab re-treatment infusion, 38 of 43 patients (88%) were in remission and 42 of 43 (98%) in clinical response. Among patients not assessed before the third infusion (Figure 1*B*), there were 2 patients with insufficient data and 7 study withdrawals for reasons other than treatment failure.

Median infliximab trough levels were not significantly different between baseline and before the third re-treatment infusion

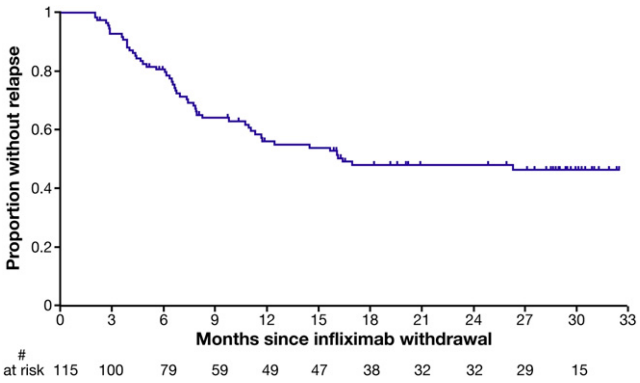

Figure 2. Kaplan–Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.

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Table 2. Factors Measured at Inclusion Independently Associated With Time to Relapse

	Complete multivariable model		Simplified multivariable model without infliximab trough level and CDEIS	
Risk factor	Hazard ratio[a] estimate (95% CI)	*P* value[b]	Hazard ratio estimate (95% CI)	*P* value
Corticosteroid use between 12 and 6 mo before baseline	3.5 (1.1–10.7)	.03		
No previous surgical resection	4.0 (1.4–11.4)	.01	4.2 (1.5–11.6)	.005
Male sex	3.7 (1.9–7.4)	<.001	3.5 (1.7–7.0)	<.001
Hemoglobin level ≤145 g/L	6.0 (2.2–16.5)	<.001	5.5 (2.0–15.5)	.001
Leukocyte count >6 × 10^9/L	2.4 (1.2–4.7)	.01	1.9 (1.0–3.5)	.05
CDEIS >0	2.3 (1.1–4.9)	.04		
hsCRP level ≥5 mg/L	3.2 (1.6–6.4)	<.001	2.7 (1.3–5.3)	.005
Infliximab trough level ≥2 mg/L	2.5 (1.1–5.4)	.02		
Fecal calprotectin level ≥300 μg/g	2.5 (1.1–5.8)	.04	3.1 (1.3–7.2)	.01

CI, confidence interval.
[a]Hazard ratio for each risk factor in Cox model (estimate and 95% CI from the 10 imputations).
[b]Significance level (mean from the 10 imputations).

(n = 35; 4.3 mg/L [interquartile range, 2.2–8.2] vs. 4.0 mg/L [interquartile range, 1.5–8.5]; *P* = .99). Before re-treatment with infliximab, the 39 available serum samples were negative for anti-infliximab antibody testing. Just before the second re-treatment infusion, among the 41 available serum samples, 11 (27%) were negative and 30 inconclusive.

Adverse Events

No infusion reaction or significant delayed reaction was reported in the re-treated patients up to the third re-treatment, despite a median drug holiday of 6.6 months (interquartile range, 4.0–10.8). No other serious adverse event was reported during the study.

Discussion

In this study, about one-half of patients with Crohn's disease who were in corticosteroid-free remission with infliximab therapy over the last 6 months and with a combined antimetabolite agent for at least 1 year experienced a relapse within 1 to 2 years after discontinuation of infliximab. Several factors associated with a low risk of relapse were identified. Re-treatment of relapsing patients with infliximab was effective and well tolerated, at least in the short-term.

Stopping treatment with infliximab is generally not a successful strategy. Indeed, while it is estimated that the loss of response to infliximab may reach approximately 13% per year with uninterrupted scheduled maintenance therapy,[21] we here observed a ~50% rate of relapse within 1 to 2 years after stopping the drug in a selected group of patients, with the vast majority in deep clinical, biologic, and endoscopic remission. These patients also had therapeutic trough levels of infliximab, which have been associated with a higher rate of sustained remission under infliximab maintenance therapy.[22] Nonetheless, in clinical practice, stopping infliximab may still be considered for various reasons, including cost, fear of long-term side effects, and concerns about pregnancy. Predictors of a low risk of relapse when stopping the drug would thus be useful. This study allowed us to build a model stratifying the patients in 4 groups with different risk of relapse when stopping infliximab therapy based on 6 simple demographic, clinical, and laboratory

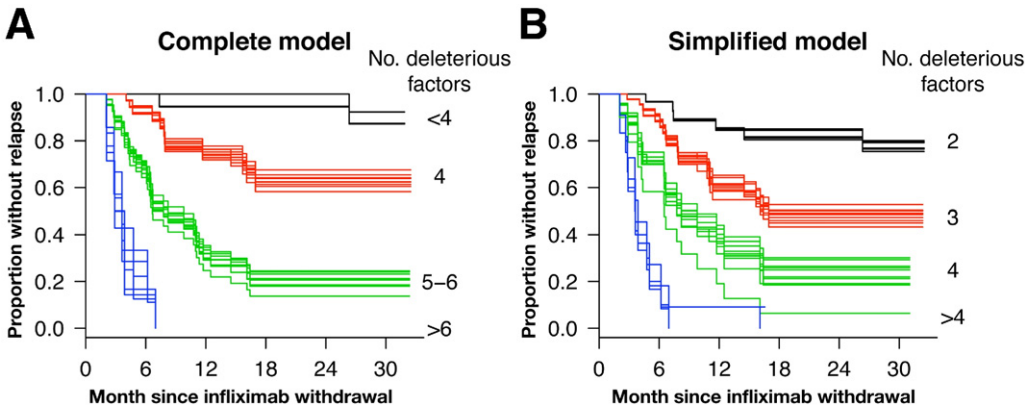

Figure 3. Kaplan–Meier time-to-relapse curves according to multivariable models and scores generated through the Cox model using the multiple imputation method. (*A*) According to a complete model: with this model (Table 2), the subgroup of patients presenting 3 deleterious prognostic factors or less corresponded to zero to one relapse over 1 year among 22 to 25 patients, depending on imputations. (*B*) According to a simplified model without infliximab trough levels and endoscopic data: with this model (Table 2), the subgroup presenting 2 deleterious prognostic factors or less corresponded to 4 relapses over 1 year among 32 to 35 patients, depending on imputations.

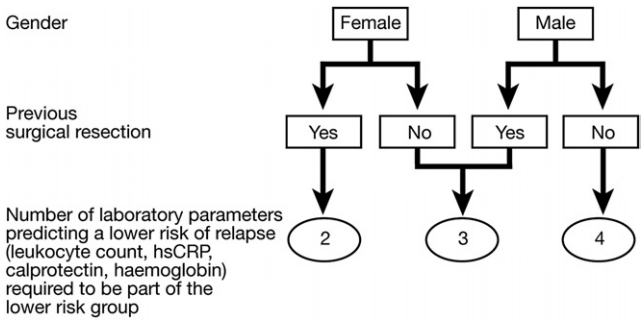

Figure 4. Profiles of the patients corresponding to the lower risk stratum defined according to the simplified multivariable model. Depending on the gender and the previous surgical history, a variable number of laboratory parameters associated with a lower risk of relapse are requested to be part of the lower risk stratum. For these laboratory parameters, the thresholds for a lower risk of relapse are as follows: leukocyte count $\leq 6 \times 10^9$/L, hemoglobin level $>$ 145 g/L, hsCRP level $<$5 mg/L, and fecal calprotectin level $<$300 μg/g.

elements. More specifically, the selected laboratory elements with their cutoff levels, including hemoglobin level >145 g/L, white blood cell count $\leq 6.0 \times 10^9$/L, hsCRP <5 mg/L, and fecal calprotectin <300 μg/g, could be used before contemplating cessation of infliximab therapy. The stability of our risk group model was confirmed using bootstrapping analysis. However, one of the main limitations of bootstrapping, which is patient selection within the original sample, has to be acknowledged. The size of the cohort was also relatively small when considering the number of predictors that were evaluated. Therefore, our results would need to be validated in an independent cohort before being applied to clinical practice.

An important question when considering cessation of infliximab therapy is whether or not the drug will still be effective if it has to be restarted in case of relapse. A drug "holiday" has indeed been associated with a risk of immunization resulting in hypersensitivity reactions to infliximab and loss of effect.[23] Overall, 52 patients in relapse following drug cessation were re-treated with infliximab. Almost all were in remission 1 month after a single infliximab re-treatment infusion and none experienced a significant acute or delayed infusion reaction, despite a drug holiday longer than 6 months for half of them. No significant infusion reaction was observed either after a second or third re-treatment. This observation contrasts with what was reported in the early days of infliximab, when a single infusion induction was not systematically followed by 2 other induction infusions and scheduled maintenance.[23] The high remission rate was sustained at least up to the third re-treatment infusion with no significant decrease in infliximab trough levels as compared with baseline and no formation of anti-infliximab antibodies. Administration of combination therapy with an antimetabolite in all patients as well as a corticosteroid preinfusion prophylaxis in almost all of them may partly explain these good results. Such a good outcome following re-treatment of relapsing patients after transient discontinuation of maintenance therapy with anti-TNF was already suggested in retrospective studies in rheumatoid arthritis,[24] ankylosing spondylitis,[25] and Crohn's disease.[26,27] More recently, a prospective multicenter study in rheumatoid arthritis also showed similar results; a low disease activity was maintained in about half of the patients over 1 year after discontinuation of infliximab therapy, and infliximab re-treatment was effective and well tolerated in the vast majority of the patients experiencing a relapse.[28]

There are several limitations to our study. First, there was no control group in which infliximab would have been continued; our primary objectives were indeed to assess relapse rate after discontinuation of infliximab therapy in Crohn's disease and to identify predictors of a low risk of relapse. Thus, no recommendation regarding withdrawal of infliximab should be made. Second, our patients were highly selected and can be considered as the best responders to infliximab therapy, being in deep remission when the drug was stopped. Third, 11 patients declared in relapse by the investigators were not considered as such in the analysis because they did not fulfill the predefined CDAI-based definition of relapse, possibly leading to a slight underestimation of the relapse rate, as shown in the supplementary material. Fourth, the follow-up of re-treated patients was relatively short and their good long-term outcome has to be confirmed. Finally, median disease duration was 7.8 years in our patients, and whether these data apply or not to patients with early Crohn's disease is uncertain.

In conclusion, in patients with Crohn's disease in stable remission with combined therapy with infliximab and an antimetabolite, cessation of infliximab is associated with an approximately 50% risk of relapse within 1 to 2 years. However, simple parameters may be used to identify a subgroup of patients with a low risk of relapse and in whom withdrawal of infliximab may be considered. When patients experienced a relapse, re-treatment with infliximab was effective and well tolerated in the vast majority. A controlled study comparing de-escalation strategies in this low-risk subgroup is warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.09.034.

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Conflicts of interest

The authors disclose the following: E.L. has received consultancy fees from Schering-Plough, Abbott Laboratories, MSD, Ferring Pharmaceuticals, Shire, Millennium Pharmaceuticals, and UCB; research or educational grants from MSD, Schering-Plough, AstraZeneca, and Abbott Laboratories; and lecture fees from Abbott Laboratories, AstraZeneca, Ferring Pharmaceuticals, MSD, Schering-Plough, Falk, Menarini, Chiesi, and Nycomed. Y.B. has received consultancy fees and lecture fees from Norgine, Abbott Laboratories, Schering-Plough, and Ferring Pharmaceuticals. D.L. has received consultancy fees from Norgine and Ferring Pharmaceuticals and has received lecture fees from Norgine, Ferring Pharmaceuticals, Abbott Laboratories, and Schering-Plough. G.S. has received lecture fees from Abbott Laboratories and Schering-Plough. M.D. has received an educational grant from Schering-Plough. G.P. has received consultancy fees from Roche and LFB and has received lecture fees from Janssen-Cilag. J.-F.C. has received consulting fees from Abbott Laboratories, ActogeniX, Albireo Pharma, Amgen, AstraZeneca, Bayer AG, Biogen Idec, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cellerix, Centocor, ChemoCentryx, Cosmo Technologies, Danone Research, Elan Pharmaceuticals, Genentech, Giuliani SpA, Given Imaging, GlaxoSmithKline, Hutchison MediPharma, Merck Sharp & Dohme Corp, Millennium Pharmaceuticals (now Takeda), Neovacs, Ocera Therapeutics, Pfizer, Shire Pharmaceuticals, Prometheus Laboratories, Sanofi-Aventis, Schering-Plough, Synta Pharmaceuticals Corp, Teva, Therakos, UCB Pharma, and Wyeth; has served on advisory committees for Abbott Laboratories, Centocor, Danone Research, Elan Pharmaceuticals, Merck Sharp & Dohme, Millennium Pharmaceuticals (now Takeda), Schering-Plough, and UCB Pharma; has received speaking fees from Abbott Laboratories, Centocor, Elan Pharmaceuticals, Given Imaging, Merck Sharp & Dohme Corp, Otsuka America Pharmaceutical, Schering-Plough, Shire Pharmaceuticals, Tillotts Pharma, and UCB Pharma; and has received grant support from Abbott Laboratories, AstraZeneca, Ferring Pharmaceuticals, Merck Sharp & Dohme Corp, Schering-Plough, and UCB Pharma. The remaining authors disclose no conflicts.

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Supplementary Patients and Methods

Patients and Methods

Ten of the 125 included patients were excluded for the following reasons: 3 for a CDAI >150, one for a CDAI without hematocrit, 2 having received corticosteroids within the past 6 months, 2 treated with an antimetabolite for less than 1 year, one having stopped treatment with an antimetabolite 15 days before inclusion, and one not being treated with an antimetabolite (mycophenolate mofetil).

Retrospective Follow-up in Re-treated Patients After the End of the Study

The following retrospective data were also collected concerning the period between last protocol visit (third infliximab retreatment infusion) and closing date (December 31, 2009): number of infusions and maximum dose of infliximab, reason for discontinuation if applicable, new corticosteroid treatment, new immunosuppressive or antimetabolite agent, new experimental treatment, and resection surgery with date and length of resection.

Statistical Analysis

Continuous variables were first divided in 4 categories at roughly the 25th, 50th, and 75th percentiles. If the relative relapse rates (ratio of the observed relapse rate in each category to the expected relapse rate assuming no variation of relapse rate across categories) in 2 or more adjacent categories were not substantially different, these categories were collapsed.[1,2] If no clear pattern was observed, the median was used as the cutoff point. Usual limits were also used, such as 3.0 for CDEIS. As a result, 2 or rarely 3 or 4 categories were used for each continuous variable.

In the long-term follow-up, time to loss of response was studied through the Kaplan–Meier method. Patients who stopped treatment for another reason than loss of response had their follow-up censored at that time.

Supplementary Results

The time-to-relapse curve using investigator decisions, in the case of a suspected relapse with CDAI between 150 and 250 with a missing confirmation in the 2 following weeks (but not if investigator decision was in contradiction to observed CDAI), is presented in Supplementary Figure 1. This time-to-relapse curve, which appears to be rather similar to the curve presented in the paper, was not further studied because investigator decision of relapse is known to be subject to interinvestigator variation.

Predictive Factors of Relapse

Association of the different variables at inclusion with time to relapse is shown in Supplementary Table 1 for univariable analysis (P value according to log-rank test,[3] hazard ratio estimated through Cox model[4]). Variables significantly associated ($P < .05$) with time to relapse were active smoking, CDAI >20, hemoglobin level ≤145 g/L, hsCRP level ≥5 mg/L, fecal calprotectin level ≥300 μg/g, and CDEIS ≥2. Borderline association ($.05 < P < .10$) was observed with previous surgical resection, anoperineal lesions at initiation of infliximab therapy, use of corticosteroids between 6 to 12 months before inclusion, and CDEIS >0.

Risk Group Strata

The 4 risk group strata obtained with the complete and simplified models are described in Supplementary Table 2.

Model Validation

Distributions of concordance probability[5] estimates of the complete and simplified models, expressed in risk group strata, arising from the 2000 bootstrapped samples[6] are described in Supplementary Figure 2, with the estimate and its 95% confidence interval derived from the original sample. The discriminatory power of these models appeared to be rather satisfactory. The estimate on the original sample was a little overestimated for the complete model, but not for the simplified model.

Outcome of Long-term Treatment With Infliximab in Relapsers

After a median follow-up time from first re-treatment of 2 years, only 12 of 52 patients had stopped infliximab due to loss of response (n = 6), adverse event (n = 1), impossibility of perfusion (n = 1), pregnancy (n = 2), patient's decision (n = 1), and loss to follow-up (n = 1). The proportion ± SE of patients experiencing loss of response after re-treatment was estimated to be 12% ± 5% at 2 years. The patients who had stopped infliximab therapy were still well either on infliximab again, on adalimumab or certolizumab, or untreated. None had surgery.

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Supplementary Table 1. Factors Associated With Time to Relapse in Univariable Analysis

	Relapses/total	*P* value (log-rank)	Hazard ratio estimate	95% confidence interval
Demographic and clinical characteristics				
Sex (n = 115)				
Female	26/66	.2752	1	
Male	26/49		1.35	0.78–2.33
Age (*y*) (n = 115)				
Older than 25	36/89	.2857	1	
25 or younger	16/26		1.38	0.76–2.49
Disease duration (*y*) (n = 115)				
≤4	14/26	.8997	1	
4–8	16/33		1.05	
8–12	12/28		0.85	
>12	10/28		0.82	
Active smoker (n = 115)				
No	28/70	.0358	1	
Yes	24/45		1.78	1.03–3.08
Disease site (n = 114)				
Ileal	6/14	.7233	1	
Colonic	27/64		0.97	
Ileocolonic	19/36		1.23	
Anoperineal lesions at infliximab initiation (n = 115)				
No	29/75	.0840	1	
Yes	23/40		1.61	0.93–2.79
Internal or enterocutaneous fistula at infliximab initiation (n = 115)				
No	52/112	.1230	NA	
Yes	0/3			
Intestinal stricture before infliximab initiation (n = 114)				
Yes	3/11	.2750	1	
No	48/103		1.89	0.59–6.08
Intestinal stricture at infliximab initiation or during treatment (n = 114)				
No	51/109	.1448	NA	
Yes	0/5			
Previous surgical resection (n = 115)				
Yes	6/26	.0722	1	
No	46/90		2.14	0.91–5.03
CDAI (n = 115)				
≤20	11/29	.0345	1	
>20	41/86		2.03	1.04–3.96
Treatment history				
Type of antimetabolite treatment (n = 115)				
Azathioprine/6-mercaptopurine	40/96	.1326	1	
Methotrexate	12/19		1.63	0.86–3.11
Antimetabolite naïve[a] at infliximab initiation (n = 115)				
Yes	24/51	.8789	1	
No	28/64		1.04	0.60–1.80
Duration of antimetabolite treatment (*y*) (n = 115)				
>5	7/24	.1978	1	
≤5	45/91		1.68	0.76–3.72
Erythrocyte 6-thioguanine (pmol/10^8 red cells) (n = 64)				
≤250	22/46	.9978	1	
>250	7/18		1.00	0.43–2.35
Corticosteroids between 12 and 6 mo before baseline (n = 115)				
No	46/107	.0553	1	
Yes	6/8		2.25	0.96–5.29
Infliximab treatment				
Infliximab scheduled therapy from the start (n = 115)				
No	2/6	.5954	1	
Yes	50/109		1.46	0.36–6.02

Supplementary Table 1. Continued

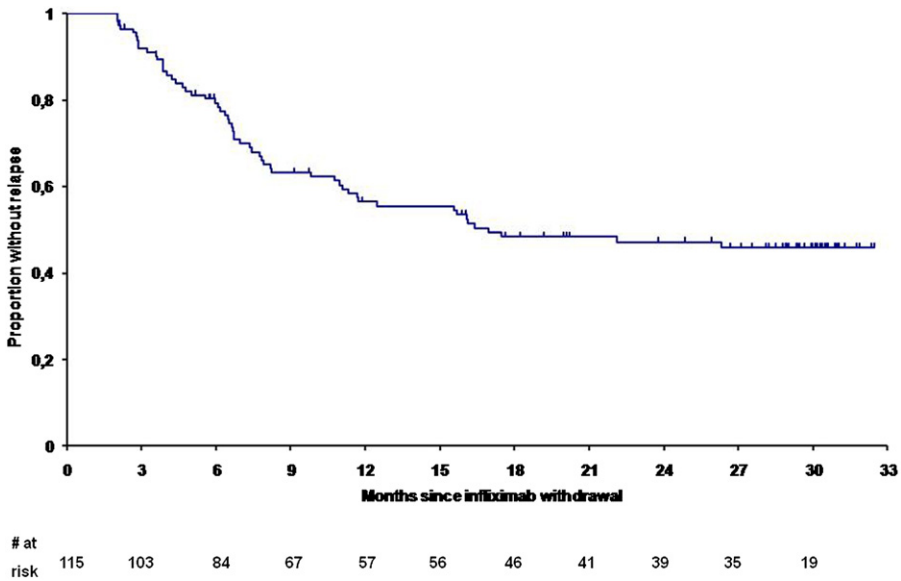
	Relapses/total	*P* value (log-rank)	Hazard ratio Estimate	95% confidence interval
Duration of infliximab treatment (*y*) (n = 115)				
>1.5	36/86	.1705	1	
≤1.5	16/29		1.51	0.83–2.72
No. of infliximab infusions over past 6 months (n = 115)				
<4	42/88	.5278	1	
≥4	10/27		0.80	0.40–1.60
Infliximab trough level at baseline (mg/L) (n = 113)				
<2	12/34	.2408	1	
≥2	40/79		1.47	0.77–2.80
Anti-infliximab antibody at baseline (n = 112)				
Inconclusive	33/63	.3701	NA	
Negative	19/48			
Positive	0/1			
Biologic variables				
Hemoglobin level (g/L) (n = 115)				
>145	6/23	.0391	1	
≤145	46/92		2.39	1.02–5.59
Hematocrit (n = 115)				
≤0.37	10/26	.7062	1	
0.37–0.40	17/35		1.23	
0.40–0.43	15/28		1.33	
>0.43	10/26		0.87	
Leukocyte count (10^9/L) (n = 115)				
≤6	21/55	.0714	1	
>6	31/60		1.66	0.95–2.89
Platelet count (10^9/L) (n = 115)				
≤230	14/28	.9383	1	
230–270	11/29		0.87	
270–310	13/28		1.12	
>310	14/30		0.94	
hsCRP level (mg/L) (n = 109)				
<5	32/83	.0008	1	
≥5	17/26		2.49	1.41–4.39
Fecal calprotectin level (μg/g) (n = 85)				
<300	25/64	.0002	1	
≥300	15/21		3.22	1.68–6.15
Endoscopy				
CDEIS (n = 115)				
0	14/39	.0581	1	
>0	38/76		1.79	0.97–3.31
Remaining segments with ulcer (n = 115)				
0	32/76	.2861	1	
>0	20/39		1.35	0.77–2.37
Remaining segments with deep ulcer (n = 115)				
>0	2/4	.8394	1	
0	50/111		1.16	0.28–4.76

NA, not available.

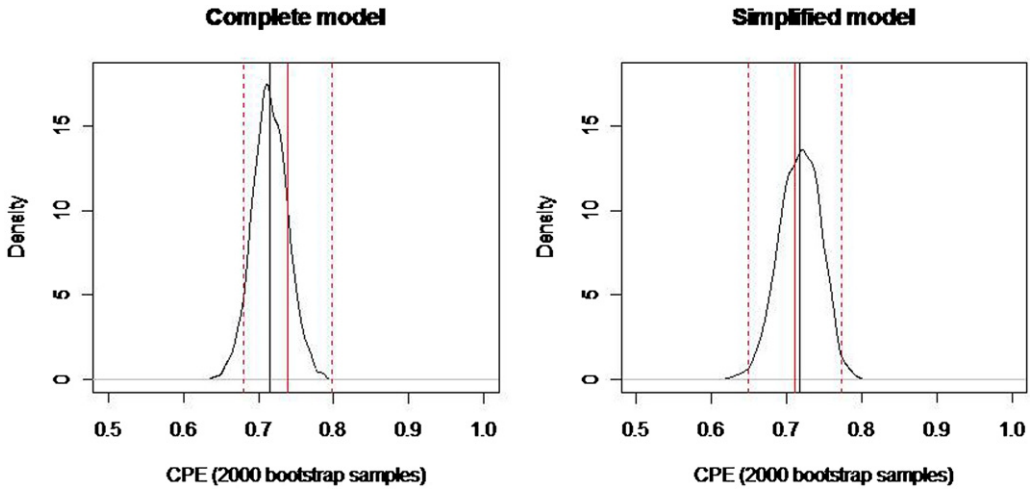
[a]Antimetabolite naïve was defined as receiving the first infliximab infusion within 3 months after the start of the antimetabolite.

Supplementary Table 2. One-Year Survival Rate and Number of Patients Within Each Stratum Obtained With the Complete and Simplified Models

Model instead	Stratum A	Stratum B	Stratum C	Stratum D
Complete model				
One-year relapse rate (%)				
Estimate	5.0	25.5	68.9	0
95% confidence interval	0.5–29.3	13.6–44.8	53.1–83.6	—
No. of patients				
Mean ± SD	23.5 ± 0.9	40.6 ± 2.1	44.0 ± 1.8	6.9 ± 1.0
Simplified model				
One-year relapse rate (%)				
Estimate	15.2	39.3	63.9	96.4
95% confidence interval	5.9–35.7	25.1–57.9	40.3–86.6	48.1–100
No. of patients				
Mean ± SD	33.3 ± 0.9	47.4 ± 1.8	23.0 ± 1.7	11.3 ± 0.7



Supplementary Figure 1. Kaplan–Meier time-to relapse curve of the 115 included patients when using investigators' declaration of relapse, even in the absence of relapse confirmation.



Supplementary Figure 2. Distribution of the concordance probability estimate (CPE) obtained from 2000 bootstrapped samples for the complete and simplified models when expressed as 4 risk group strata. CPE estimate and 95% confidence interval on the original sample are displayed in *red*.