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Prediction of Relapse After Anti–Tumor Necrosis Factor Cessation in Crohn's Disease: Individual Participant Data Meta-analysis of 1317 Patients From 14 Studies

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BACKGROUND & AIMS: **Tools for stratification of relapse risk of Crohn's disease (CD) after anti–tumor necrosis factor (TNF) therapy cessation are needed. We aimed to validate a previously developed prediction model from the diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressants (STORI) trial, and to develop an updated model.**

METHODS: **Cohort studies were selected that reported on anti-TNF cessation in 30 or more CD patients in remission. Individual participant data were requested for luminal CD patients and anti-TNF treatment duration of 6 months or longer. The discriminative ability (concordance-statistic [C-statistic]) and calibration (agreement between observed and predicted risks) were explored for the STORI model. Next, an updated prognostic model was constructed, with performance assessment by cross-validation.**

RESULTS: **This individual participant data meta-analysis included 1317 patients from 14 studies in 11 countries. Relapses after anti-TNF cessation occurred in 632 of 1317 patients after a median of 13 months. The pooled 1-year relapse rate was 38%. The STORI prediction model showed poor discriminative ability (C-statistic, 0.51). The updated model reached a moderate discriminative ability (C-statistic, 0.59), and included clinical symptoms at cessation (hazard ratio [HR], 2.2; 95% CI, 1.2–4), younger age at diagnosis (HR, 1.5 for A1 (age at diagnosis ≤16 years) vs A2 (age**

Abbreviations used in this paper: C-statistic, concordance-statistic; CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; HR, hazard ratio; IPD-MA, individual participant data meta-analysis; IS, immunosuppressant; PGA, Physicians' Global Assessment; STORI, diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressants; TNF, tumor necrosis factor.

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at diagnosis 17 - 40 years); 95% CI, 1.11–1.89), no concomitant immunosuppressants (HR, 1.4; 95% CI, 1.18–172), smoking (HR, 1.4; 95% CI, 1.15–1.67), second line anti-TNF (HR, 1.3; 95% CI, 1.01–1.69), upper gastrointestinal tract involvement (HR, 1.3 for L4 vs non-L4; 95% CI, 0.96–1.79), adalimumab (HR, 1.22 vs infliximab; 95% CI, 0.99–1.50), age at cessation (HR, 1.2 per 10 years younger; 95% CI, 1–1.33), C-reactive protein (HR, 1.04 per doubling; 95% CI, 1.00–1.08), and longer disease duration (HR, 1.07 per 5 years; 95% CI, 0.98–1.17). In subanalysis, the discriminative ability of the model improved by adding fecal calprotectin (C-statistic, 0.63).

CONCLUSIONS: **This updated prediction model showed a reasonable discriminative ability, exceeding the performance of a previously published model. It might be useful to guide clinical decisions on anti-TNF therapy cessation in CD patients after further validation.**

Keywords: Crohn's Disease; Anti-TNF Cessation; Prediction.

Anti-tumor necrosis factor (TNF) therapy is a pivotal therapy for the induction and maintenance treatment of patients with moderate to severe Crohn's disease (CD).[1,2] After its launch, the biological exposure rate in CD patients has increased markedly from 3% to 41% over the past 2 decades.[3] Despite the expanding arsenal of medication options in CD, the use of anti-TNF therapy may increase further with the introduction of biosimilars and with changing treatment paradigms including top-down and treat-to-target strategies.[4,5] Notwithstanding its beneficial effect, important drawbacks of prolonged anti-TNF therapy are side effects and possibly an increased risk of malignancy. Malignancies associated with the use of anti-TNF therapy include nonmelanoma skin cancer, melanoma, and solid organ and lymphoproliferative malignancies.[6] However, a causal relationship is difficult to ascribe to the use of anti-TNF therapy, especially because of the sequential or concomitant use of thiopurines. Recently, chronic fatigue and work productivity loss have been associated with long-term anti-TNF therapy.[7] Finally, the direct health care costs of anti-TNF therapy remain high, even in the era of biosimilars.[8,9] Anti-TNF therapy cessation is a difficult decision in clinical practice because predictors of the risk of relapse after cessation can be insufficiently weighed on an individual patient level.[10] The overall risk of CD relapse within 1 year after anti-TNF therapy cessation is considerable, and estimated at approximately 40% in CD patients in clinical remission.[11] Although several publications have investigated risk factors of relapse after anti-TNF therapy cessation, most publications lack sufficient power for adequate risk assessment. In the diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressants (STORI) trial, risk factors of relapse after step-down from the combination of immunosuppressant (IS) and anti-TNF therapy to IS monotherapy were identified.[12] However, the STORI prediction model for anti-TNF cessation has not yet been adopted in guidelines or implemented in routine clinical care.

In this study, we aimed to validate the STORI prediction model and to update the model by pooling data from current literature in an individual participant data meta-analysis (IPD-MA). Second, we aimed to develop a patient stratification tool to allow for identification of CD patients in remission at low or high risk of relapse after anti-TNF therapy cessation.

Methods

An IPD-MA of published studies was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis.[13] In addition, the Meta-analysis Of Observational Studies in Epidemiology checklist was used, containing specifications for the reporting of a meta-analysis of observational studies[14] and reporting followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines.[15] The study protocol was approved by the Medical Ethical Review Committee of the Erasmus University Medical Center (MEC-2019-0359) and was registered in the International prospective register of systematic reviews (PROSPERO) register (CRD42019131607).

Search Strategy

A comprehensive systematic search was designed in collaboration with the Medical School Library of Erasmus University (Rotterdam, The Netherlands) and was conducted on February 26, 2020, in Embase, Medline, Web of Science, the Cochrane database, and Google scholar. Studies evaluating the incidence and risk factors of relapse after anti-TNF therapy cessation in CD patients in remission were selected. The search was conducted using controlled vocabulary supplemented with keywords (Supplementary Figure 1). In addition, abstracts were included. Abstracts published on international congresses additionally were found by a manual search in the abstract books of American Digestive Disease Week, United European Gastroenterology Week, and the Congresses of the European Crohn's and Colitis Organisation. In case of incomplete data in abstracts, authors were contacted to obtain complete data. The retrieved studies

What You Need to Know

Background

In this meta-analysis based on individual patient data of previous study cohorts, a prediction model was developed to prognosticate relapse risk after anti–tumor necrosis factor (TNF) therapy cessation in Crohn's disease (CD) patients in remission. Anti-TNF therapy cessation in CD patients in remission is a difficult decision in clinical practice because predictors of the risk of relapse after cessation can be insufficiently weighed on an individual patient level.

Findings

With meta-analysis data from 1317 individual patients from 14 studies, an updated prediction model with routinely available parameters was constructed.

Implications for patient care

The provided clinical score chart based on the updated prediction model might guide clinical decisions on anti-TNF cessation in CD patients.

were screened and selected based on the inclusion and exclusion criteria by 2 independent reviewers (R.W.M.P. and J.A.M.S. [CEASE Study Group]). Discrepancies were solved after consensus with a third party (A.C.d.V.).

Study and Patient Selection

Cohort studies evaluating the incidence and risk factors of relapse after anti-TNF therapy (infliximab or adalimumab) cessation in CD patients in remission were included according to the following criteria: (1) size of the study population of greater than 30 patients (2) duration of anti-TNF therapy of 6 months or longer; (3) concomitant therapy with IS was allowed; (4) luminal CD as indication for anti-TNF therapy; and (5) full-text or abstract availability in English language. The following studies were excluded: perianal disease as an indication for anti-TNF therapy and (systematic) reviews and editorial letters. After obtaining the IPD from the study cohorts, patients were included only when in documented remission at baseline, defined as steroid-free clinical, biochemical, or endoscopic disease remission, that is, Crohn's Disease Activity Index less than 150/Harvey Bradshaw Index less than 5/Physicians' Global Assessment (PGA) score of 0 (the PGA consists of a 4-point scale, divided as follows: remission, 0; mild, 1; moderate, 2; and severe disease, 3); or fecal calprotectin (FC) level of less than 150 μg/g or C-reactive protein (CRP) level of less than 10 mg/L; or endoscopic remission defined as a simple endoscopic score for CD of 0 to 2, Crohn's disease index of severity less than 3, Rutgeerts score of 0 to 1, or no ulcerations/mucosal healing. Patients were excluded as follows: (1) age younger than 16 years, (2) duration of anti-TNF therapy shorter than 6 months, and (3) perianal disease activity as indication for anti-TNF therapy.

Outcome Parameters

The primary outcome was a relapse of CD that necessitated (re)introduction of biologicals, glucocorticosteroids, IS, or surgery for CD luminal activity or complications.

Request of Individual Participant Data

For each selected study, the corresponding authors were contacted to request the IPD. Terms and conditions for transfer and use of the data were specified in a data transfer agreement, signed by both the data provider and receiver. The IPD were de-identified.

Individual Participant Data Integrity

All included IPD were checked on missing-, invalid-, or out-of-range data, and (in)-consistency. All biochemical markers were transformed to standardized and consistent units. Any inconsistency was queried and solved with the corresponding authors. Data management was executed following recently published guidelines supported by the Amsterdam University Medical Centre directive for data management and incorporation of new European legislation on privacy protection.[16]

Risk of Bias and Quality-of-Evidence Assessment

Risk of bias and quality of evidence were assessed by 2 investigators (R.W.M.P. and J.A.M.S. [CEASE Study Group]) using the Newcastle–Ottawa Quality Assessment Form for Cohort Studies and the prediction model risk of bias assessment tool.[17,18]

Statistical Analyses

Descriptive statistics were used for baseline characteristics. Continuous data were presented as median and first and third quartiles. Categoric data were presented in percentages. The chi-square test, Wilcoxon rank-sum test, or t tests were used to evaluate differences between patients in categoric or continuous (not) normally distributed data. A 2-sided P value of less than .05 was considered significant.

Kaplan–Meier survival analysis was used to assess the risk of relapse after anti-TNF cessation. Kaplan–Meier curves were constructed for each included study. Pooled relapse rates at 1 and 2 years were estimated in a random-effects meta-analysis. A multivariable Cox proportional hazard regression model with stratified

baseline hazards for study was used to evaluate factors related to time to relapse after anti-TNF cessation.

First, we validated the STORI model on all patients from studies measuring FC. For the second cohort, inclusion criteria of the STORI trial were used to select a subpopulation (ie, steroid-free clinical remission, age $\geq$17 y, $\geq$1 year infliximab therapy, and baseline IS use). Discrimination was quantified by a Harrell's concordance statistic (C-statistic).[19,20] Calibration was evaluated graphically using a calibration plot and quantified through calibration-in-the-large and the calibration slope. Second, updated IPD-MA prediction models were constructed considering potential risk factors for relapse. The risk factors for relapse were selected based on the literature.[10,11] These factors comprised the following: (1) demographics and disease characteristics: age, sex, smoking, disease duration, Montreal classification, history of intestinal resection, and clinical remission (based on the Crohn's Disease Activity Index, Harvey Bradshaw Index, and/or PGA score); (2) medication use: previous anti-TNF exposure, type of anti-TNF (infliximab or adalimumab), intensified anti-TNF dose or interval, duration of anti-TNF therapy, previous IS use, numbers of previous IS, concomitant use of IS, type of IS, and corticosteroid use before cessation of anti-TNF; (3) biochemical markers: hemoglobin level (mmol/L), leukocyte count (10^9/L), thrombocytes (10^9/L), serum albumin (g/L), CRP (mg/L), FC level (μg/g), anti-TNF serum concentration (μg/mL), and antidrug antibody concentrations (ng/mL); and (4) endoscopy and imaging: endoscopic remission (simple endoscopic score for CD/Crohn's disease index of severity), and radiologic remission (magnetic resonance imaging of the bowel; preferably by validated scores, otherwise by assessment by a local radiologist). The prediction models were developed according to modern statistical methods.[15,21–23] Three prediction models for relapse were constructed in a stepwise approach: (1) clinical model, including variables on demographics and disease characteristics; (2) biochemical model, including the predictors from the clinical model plus biochemical markers; and (3) endoscopic model, including clinical and biochemical predictors plus variables on endoscopy and imaging. For the assessment of the association of FC and relapse risk, separate models with the inclusion of the identified clinical, biochemical, and endoscopic risk factors were constructed based on the subpopulation from 8 of 14 studies (297 patients) that recorded FC.[3,7–10,12–14] For this analysis, FC was log-transformed. The selection criterion to incorporate a risk factor into the prediction model was a P value less than 0.2.[26] Possible nonlinear associations between continuous predictors and the probability of relapse were assessed using restricted cubic splines. If there was evidence of a nonlinear association the restricted cubic spline was approximated using a simpler function (eg, logarithmic/quadratic function). Missing data were imputed using the mice algorithm in R when the percentage of missing values was less than 50 for clinical parameters and less than 60 for continuous biochemical data.[24,27] Clustering at the study level was considered when missing data were imputed.

In addition, we included the cumulative hazard of the time until relapse and the relapse indicator in the imputation model. Missing values were imputed 5 times and statistical analyses were performed on each of the imputed data sets and results were pooled using Rubin rules. Validation of the developed model was performed using an internal–external validation procedure, which means that every study was left out once to validate the models developed in the remaining studies. The discriminative ability of each prediction model was assessed using the C-statistic.[19,20] A pooled C-statistic was estimated with a random-effects model to indicate the overall performance. The calibration of the prediction model was quantified using the calibration-in-the-large and the calibration slope. Heterogeneity in performance across studies was quantified by the I^2 statistic.[28] The 95% CIs and prediction intervals of the pooled performance measures were calculated.[29] Clinical usefulness of the developed model was assessed using decision curve analysis.[30] We assessed the ability of the prediction model to make a better selection of patients to stop anti-TNF treatment compared with the default strategies of continuing anti-TNF treatment in all patients or stopping anti-TNF treatment in all patients. In decision curve analysis, the net benefit of using a prediction model is calculated by summing the benefits (correctly identifying patients who would relapse within 1 year) and subtracting the harms (continuing anti-TNF treatment within patients who would not relapse within 1 year) using a weighting factor. This weighting factor is related to the number of patients the physician is willing to continue on anti-TNF treatment who will not relapse in 1 year to correctly identify 1 patient who will relapse within 1 year. The risk threshold (and corresponding weighting factor) is subjective to the preferences of patients and the physician, therefore we investigated the clinical usefulness across a range of thresholds. A score chart was constructed for the final presentation of the updated prediction model.

Results

Identification of Studies

From a total of 6561 studies identified after the electronic database search, 4364 studies were excluded after screening of titles and abstracts (Supplementary Figure 2). After full-text reading, 29 studies fulfilled the eligibility criteria. After contacting the corresponding authors, the IPD were obtained for 1777 patients from 14 studies (Supplementary Figure 3). The included studies comprised 8 retrospective and 6 prospective cohort studies, 12 studies from Europe, 1 study from Asia, and 1 study from North America (Table 1,

Table 1. Characteristics of the 14 Included Studies

Study	Type of study	Country	Publication year	Eligible participants, N	Relapse, N	Definition of remission	Definition of relapse
Lu et al[31]	Retrospective	Canada	2010	34	21	Steroid free clinical remission with CDAI <150	Physician or hospital visit for documented symptoms of disease activity and a therapeutic intervention with CD medication(s), or a hospitalization with complications related to active CD
Louis et al[12]	Prospective	France and Belgium	2012	115	52	Steroid-free clinical remission; CDAI <150	CDAI >250 or CDAI between 150 and 250 with >70 point increase from baseline over 2 weeks
Molnár et al[32]	Prospective	Hungary	2012	103	47	Clinical remission; CDAI ≤150	CDAI rise of >100 points and CDAI of >150 points
Steenholdt et al[33]	Retrospective	Denmark	2012	10	5	Steroid-free clinical remission; PGA: remission No clinical symptoms	Re-treatment with a biologic, systemic steroid or surgery Introduction or dose increase in an immunosuppressant
Chauvin et al[34]	Retrospective	France	2014	34	23	Clinical remission; HBI<4	HBI >4 or the need to introduce any specific treatment for CD
Farkas et al[35]	Prospective, multicenter	Hungary	2014	19	10	Clinical remission; CDAI <150	An increase of >100 points in CDAI and a CDAI of >150
Ben-Horin et al[36]	Retrospective, multicenter	France	2015	29	15	Clinical remission; HBI ≤4 or CDAI ≤150	Re-emergence of symptoms accompanied by objective evidence of IBD inflammation (increased CRP or FC, evidence of active inflammation on endoscopy or imaging, or appearance of a draining fistula)
Bortlik et al[37]	Prospective	Czech Republic	2015	48	27	Steroid free clinical and endoscopic (no ulcerations) remission	Defined as a clinical exacerbation of the disease confirmed by endoscopy and/or another imaging procedure) with or without laboratory (CRP or FC) or new onset of perianal disease (abscess or fistula) leading to a change in medical therapy or to surgery
Brooks et al[38]	Prospective, multicenter	United Kingdom	2015	62	28	Clinical remission; PGA: remission	Recurrent symptoms of Crohn's disease requiring an escalation in medical therapy or surgery

Table 1. Continued

Study	Type of study	Country	Publication year	Eligible participants, N	Relapse, N	Definition of remission	Definition of relapse
Kennedy et al[39]	Retrospective, multicenter	United Kingdom	2016	143	73	Steroid-free clinical remission	The requirement of a therapeutic intervention (steroids, immunosuppressants, anti-TNF, hospital admission, or surgical resection)
Casanova et al[40]	Retrospective, multicenter	Spain	2017	562	249	Clinical remission; HBI $\leq$4 points	The onset of documented clinical, biochemical, endoscopic, or radiologic activity leading to a therapeutic intervention
García-Ortíz et al[25]	Abstract, retrospective	Spain	2017	56	25	Endoscopic remission; mucosal healing	NR
Lin et al[41]	Retrospective, multicenter	Taiwan	2017	36	21	Clinical remission; CDAI $<$150	CDAI score of $\geq$70 points, or a CDAI score of $>$250
Bots et al[42]	Prospective	The Netherlands	2019	66	36	Clinical remission; PGA: remission and/or biochemical (FC $<$250 μg/g and CRP $<$5 mg/L) and/or endoscopic/ radiologic (no signs of inflammation)	The requirement for (re)treatment with IBD medication (ie, corticosteroids, immunosuppressants, biologicals, or experimental medication), dose increase of IBD medication or IBD-related surgical interventions

Study	Duration of anti-TNF use before cessation, median (Q1–Q3), *mo*	IFX/ADA, N (%)	Number of infusions/injections	Type immunosuppressant, N (%)	Dose antimetabolite	Continuation of antimetabolite at cessation, yes/no
Lu et al[31]	13 (11–24)	IFX, 34 (100)	Median, 8 (2–51)	Azathioprine, 14 (64) 6-Mercaptopurine, 1 (5) Methotrexate, 5 (23) Both azathioprine and methotrexate, 2 (9) (12 missing values)	NR	Yes
Louis et al[12]	26 (18–37)	IFX, 115 (100)	At least 2 $\leq$2 infusions 14 (12) 3 infusions 74 (64) $\geq$4 infusions 27 (23)	Azathioprine, 90 (78) 6-Mercaptopurine, 6 (5) Methotrexate, 19 (17)	$>$2 mg/kg $>$1.5 mg/kg $>$15 mg/wk SC/IM	Yes
Molnár et al[32]	12 (11–12)	IFX, 77 (75) ADA, 26 (25)	Median, 8 (8–8.5)/26 (26–26)	Azathioprine, 88 (100) (15 missing values)	NR	Yes

Table 1. Continued

Study	Duration of anti-TNF use before cessation, median (Q1–Q3), *mo*	IFX/ADA, N (%)	Number of infusions/injections	Type immunosuppressant, N (%)	Dose antimetabolite	Continuation of antimetabolite at cessation, yes/no
Steenholdt et al[33]	12 (9–18)	IFX, 10 (100)	9 (7–13)	Azathioprine, 7 (78) 6-Mercaptopurine, 1 (11) Methotrexate, 1 (11) (1 missing value)	NR	Yes
Chauvin et al[34]	15 (11–27)	IFX, 34 (100)	11 (8–16)	Azathioprine, 28 (82) 6-Mercaptopurine, 1 (3) 6-Thioguanine, 3 (9) Methotrexate, 2 (6)	>2 mg/kg >1.5 mg/kg 25 mg/wk SC/IM	Yes
Farkas et al[35]	12 (NR)	IFX, 14 (74) ADA, 5 (26)	NR	Azathioprine, 7 (100) (12 missing values)	NR	NR
Ben-Horin et al[36]	24 (14–30)	IFX, 23 (79) ADA, 6 (21)	NR	Azathioprine, 6 (76) 6-Mercaptopurine, 1 (12) Methotrexate, 1 (12) (21 missing values)	NR	Yes
Bortlik et al[37]	23 (NR)	IFX, 33 (69) ADA, 15 (31)	NR	NR; 77% on immunosuppressant	NR	Yes
Brooks et al[38]	22 (14–28)	IFX, 54 (87) ADA, 8 (13)	NR	Azathioprine, 54 (96) 6-Mercaptopurine, 1 (2) Methotrexate, 1 (2) (6 missing values)	NR	Yes
Kennedy et al[39]	29 (17–46)	IFX, 117 (80) ADA, 29 (20)	NR	Azathioprine, 66 (70) 6-Mercaptopurine, 9 (9) Methotrexate, 20 (21) (51 missing values)	NR	Yes
Casanova et al[40]	23 (14–40)	IFX, 358 (64) ADA, 204 (36)	NR	Azathioprine, 328 (89) 6-Mercaptopurine, 27 (7) Methotrexate, 14 (4) (193 missing values)	NR	Yes
García-Ortíz et al[25]	25 (14–40)	IFX, 34 (52) ADA, 31 (48)	NR	Azathioprine, 52 (95) Methotrexate, 3 (5) (10 missing values)	NR	Yes

Table 1. Continued

Study	Duration of anti-TNF use before cessation, median (Q1–Q3), *mo*	IFX/ADA, N (%)	Number of infusions/injections	Type immunosuppressant, N (%)	Dose antimetabolite	Continuation of antimetabolite at cessation, yes/no
Lin et al[41]	16 (10–21)	ADA, 37 (100)	NR	Azathioprine, 30 (94) Methotrexate, 2 (6) (5 missing values)	NR	Yes
Bots et al[42]	59 (29–95)	IFX, 33 (50) ADA, 33 (50)	NR	NR; 29% thiopurines, 5% methotrexate	NR	Yes

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's disease activity index (in points); CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IFX, infliximab; IM, intramuscular; NR, not reported; PGA, physician's global assessment; Q, quartile; SC, subcutaneous; TNF, tumor necrosis factor.

Supplementary Tables 1 and 2). On methodologic quality, studies scored between 5 and 8 stars (maximum, 9) according to the Newcastle–Ottawa Quality Assessment Form for Cohort Studies, and an overall unclear risk of bias according to the prediction model risk of bias assessment tool, which indicates a low-to-medium risk of bias for prognostic relations (Supplementary Tables 3 and 4).

Patient Characteristics

In accordance with the predefined inclusion and exclusion criteria, 1317 patients were included in the IPD-MA (567 [43%] males; median age, 35 years [28–45 y]) (Table 2). Anti-TNF therapy was infliximab in 927 patients (70%) and adalimumab in 390 patients (30%), and was discontinued after a median disease duration of 7.7 years (3.7–13.0 y) and a median anti-TNF treatment duration of 23 months (14–40 mo). In total, 933 (71%) patients used concomitant IS therapy at anti-TNF cessation. In 632 of 1317 patients a relapse occurred after a median follow-up period of 13 months (7–28 mo). The overall cumulative 1- and 2-year relapse rates were 38% (33%–42%) and 52% (46%–57%) (Supplementary Figure 4). The heterogeneity in observed relapse rates was moderate between studies (I^2 = 57% and 54%, respectively).

DiSconTinuation in CrOhn's Disease Patients in Stable Remission on Combined Therapy With Immunosuppressants Trial Model Validation

Validation of the STORI prediction model in the 14 cohorts showed a poor discriminative ability (cross-validated C-statistic, 0.51; 95% CI, 0.47–0.56) (Figure 1*A*). A second validation cohort included a subpopulation of the total study cohort, which consisted of 143 patients fulfilling the inclusion criteria of the STORI trial. Similar to the first cohort, the discriminative ability of the STORI prediction model was poor (C-statistic, 0.51; 95% CI, 0.17–0.84) (Figure 1*B* and *C*).

Clinical Model

In the clinical model, the combination of 9 predictors resulted in a somewhat better discriminative ability (C-statistic, 0.59; 95% CI, 0.56–0.61) (Table 3, Supplementary Table 5). Clinical remission was an important protective factor (hazard ratio [HR], 0.45; 95% CI, 0.24–0.84), as well as continuation of IS at the moment of anti-TNF cessation (HR, 0.70; 95% CI, 0.58–0.85). The type of anti-TNF used at the time of cessation and previous use were associated with a higher risk of relapse. This included adalimumab vs infliximab (HR, 1.21; 95% CI, 0.99–1.49) and second-line anti-TNF therapy (HR, 1.32; 95% CI, 1.01–1.72). CD-specific risk factors associated with relapse were younger age at CD diagnosis (A1 vs A2 [≤16 years vs 17 - 40 years]) (HR,

Table 2. Baseline Patient Characteristics

	N = 1317	Missing, n (%)
Male, n (%)	567/1269 (44.7)	48 (3.6)
Median age, *y* (Q1–Q3)	35.0 (27.7–45.0)	132 (10)
Smoking, n (%)	354/1234 (28.7)	83 (6.3)
Median disease duration, *y* (Q1–Q3)	7.7 (3.7–13.0)	210 (15.9)
Disease location, n (%)		
L1 ileal	296/1312 (22.6)	5 (0.38)
L2 colonic	341/1312 (26.0)	5 (0.38)
L3 ileocolonic	667/1312 (50.8)	5 (0.38)
L4 isolated	8/1312 (0.6)	5 (0.38)
+L4 upper GI disease	75/1255 (6.0)	62 (4.7)
Disease behavior, n (%)		
B1	765/1230 (62.2)	87 (6.6)
B2	213/1230 (17.3)	87 (6.6)
B3	252/1230 (20.5)	87 (6.6)
Perianal disease, n (%)	352/1265 (27.8)	52 (3.9)
Previous intestinal resection, n (%)	320/1254 (25.5)	63 (4.8)
Second-line anti-TNF therapy, n (%)	120/830 (14.5)	
Anti-TNF type, n (%)		
Infliximab	927/1317 (70.4)	0 (0)
Adalimumab	390/1317 (29.6)	0 (0)
Median duration of anti-TNF therapy, *mo* (Q1–Q3)	23.0 (14.0–40.0)	223 (16.9)
Median remission length, *mo* (Q1–Q3)	20.3 (12.8–30.5)	1223 (93)
Anti-TNF trough level, therapeutic,[a] n (%)	138/255 (54.1)	1062 (80.6)
Anti-TNF intensified[b]	50/1034 (4.8)	283 (21.5)
Median infliximab trough level, *μg/mL* (Q1–Q3)	3.0 (1.1–6.9)	1148 (87.2)
Median adalimumab trough level, *μg/mL* (Q1–Q3)	4.7 (0.0–8.8)	1278 (97)
Anti-TNF antibodies, n (%)	21/154 (13.6)	1163 (88.3)
Immunosuppressant at baseline, n (%)	933/1285 (72.6)	32 (2.4)
Azathioprine	761/883 (86.2)	434 (33)
6-Mercaptopurine	47/883 (5.3)	434 (33)
6-Thioguanine	3/883 (0.3)	434 (33)
Methotrexate	70/883 (7.9)	434 (33)
Azathioprine and methotrexate	2/883 (0.2)	434 (33)
Clinical remission,[c] n (%)	1221/1246 (98)	71 (5.4)
Median hemoglobin level, *mmol/L* (Q1–Q3)	8.5 (7.9–9.1)	738 (56)
Median leukocyte count, $10^9/L$ (Q1–Q3)	6.5 (5.2–8.0)	497 (37.7)
Median thrombocytes, $10^9/L$ (Q1–Q3)	256.0 (217.5–307.0)	495 (37.6)
Median albumin level, *g/L* (Q1–Q3)	43.0 (39.5–46.0)	1008 (76.5)
Median CRP level, *mg/L* (Q1–Q3)	2.0 (0.7–4.0)	665 (50.5)
Median FC level, *μg/g* (Q1–Q3)	56.0 (30.0–168.0)	1020 (77.4)
Endoscopic remission,[d] n (%)	581/671 (86.6)	646 (49.1)

B, behavior; CRP, C-reactive protein; FC, fecal calprotectin; GI, gastrointestinal; L, location; Q, quartile; TNF, tumor necrosis factor.
[a]IFX ≥3 μg/mL, adalimumab ≥2.83 μg/mL.
[b]Anti-TNF high/intensified dose or interval (IFX >5 mg/kg or adalimumab >40 mg; IFX interval <1×/8 wk or adalimumab interval <1×/2 wk).
[c]Defined as (steroid-free) Crohn's Disease Activity Index less than 150, Harvey Bradshaw Index less than 5, Physicians' Global Assessment of 0.
[d]Defined as a simple endoscopic score for CD of 0 to 2, Crohn's disease index of severity less than 3, Rutgeerts' score of 0 to 1, no ulcerations/mucosal healing.

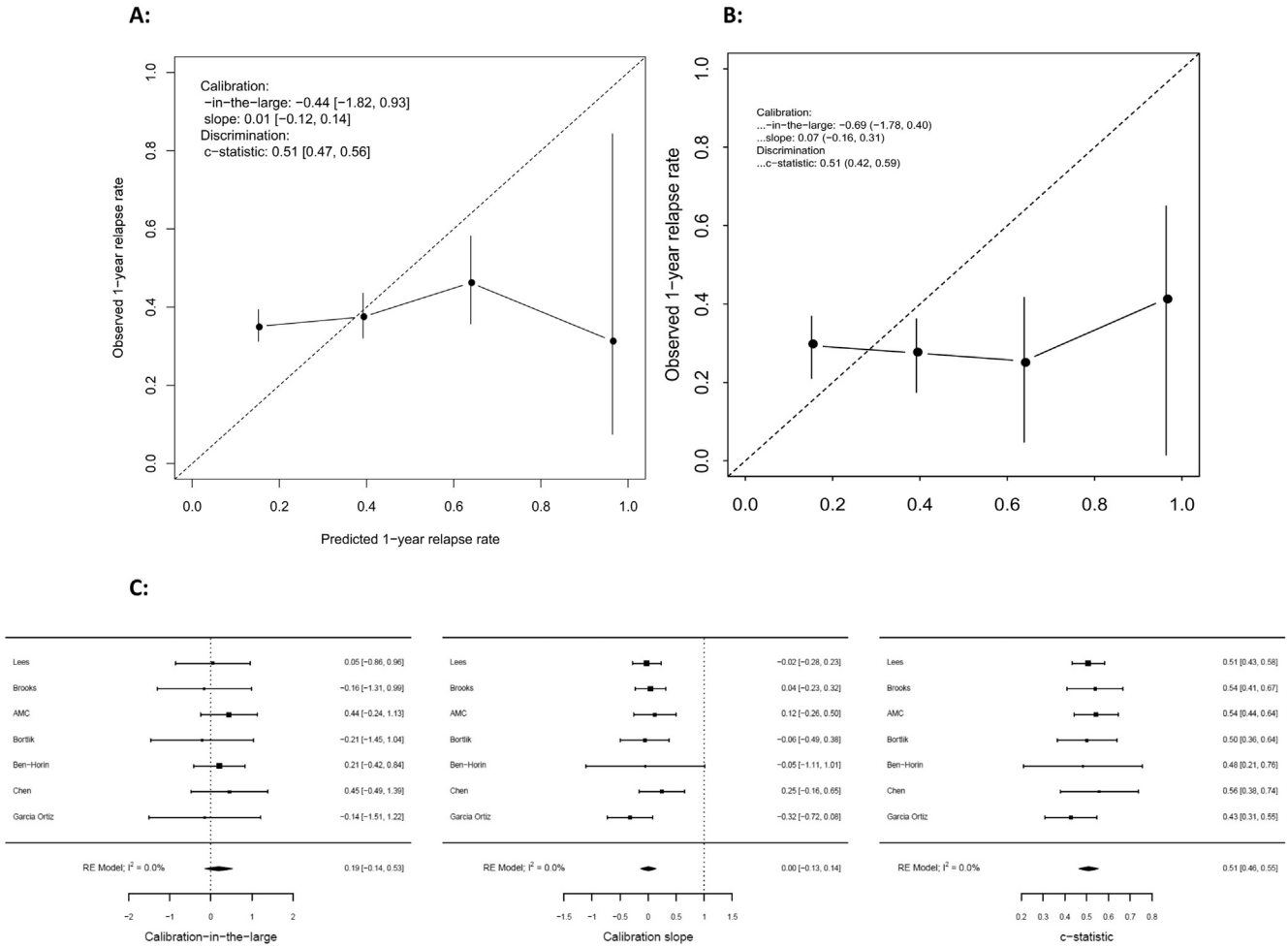

Figure 1. Performance of the discontinuation in Crohn's disease patients in stable Remission on combined therapy with Immunosuppressants (STORI) trial, validated on (*A*) the total individual participant data meta-analysis cohort (n = 1317), (*B*) patients who fulfilled the inclusion criteria of the STORI trial (n = 143), and (*C*) stratified per cohort.

1.47; 95% CI, 1.12–1.92), longer disease duration (HR, 1.07; 95% CI, 0.98–1.17 per 5 years), and involvement of the upper gastrointestinal tract (L4) (HR, 1.33; 95% CI, 0.97–1.82). Finally, smoking and younger age at anti-TNF cessation were identified as risk factors (HR, 1.39; 95% CI, 1.15–1.67; and HR, 1.16; 95% CI, 1.00–1.33 per decade).

Biochemical Model

In addition to the identified clinical factors associated with relapse, increased CRP was the only biochemical marker associated with an increased risk of relapse (HR, 1.04; 95% CI, 1.00–1.08 per doubling) (Table 3). Adding CRP to the clinical prediction model showed no increase in performance (C-statistic, 0.59; 95% CI, 0.56–0.62) (Figure 2*A*).

Endoscopic Model

Active inflammation at endoscopy was not associated significantly with relapse (HR, 1.14; 95% CI, 0.80–1.64) independent of the clinical and biochemical risk factors. Adding endoscopic findings to the prediction model showed no increase in discriminative ability of the model (C-statistic, 0.58; 95% CI, 0.55–0.61) (Table 3).

Individual Participant Data Meta-Analysis Prediction Models on Studies Including Fecal Calprotectin Levels

FC was associated with an increased risk of relapse in all 3 models (Table 3). Adding FC led to higher discriminative abilities in each of the 3 versions of the prediction models (Figure 2*B*).

Decision Curve Analysis and Support Tool

The decision curve analysis showed that using the biochemical model provided a net benefit in the threshold probability range of relapse between 25% and 50% compared with default strategies (Supplementary Figure 5). The biochemical model was transformed into a clinical decision support tool, in which points were

Table 3. Constructed Prediction Models

Predictor	Prediction models			Prediction models constructed on 8 of 14 IPD cohorts with FC		
	Clinical model C-statistic, 0.59; HR (95% CI)	Biochemical model C-statistic; 0.59; HR (95% CI)	Endoscopic model C-statistic, 0.58; HR (95% CI)	Clinical model + FC C-statistic, 0.63; HR (95% CI)	Biochemical model + FC C-statistic, 0.63; HR (95% CI)	Endoscopic model + FC C-statistic, 0.63; HR (95% CI)
Age, every 10 y	0.86 (0.75–1.00)	0.86 (0.75–1.00)	0.87 (0.75–1.00)	0.90 (0.71–1.14)	0.90 (0.71–1.14)	0.90 (0.71–1.14)
Smoking, yes	1.39 (1.15–1.67)	1.39 (1.15–1.67)	1.37 (1.15–1.64)	1.52 (1.10–2.08)	1.52 (1.10–2.08)	1.52 (1.10–2.08)
Age at diagnosis 17–40 y, A2 vs A1	0.68 (0.52–0.89)	0.69 (0.53–0.90)	0.69 (0.53–0.90)	0.46 (0.30–0.72)	0.46 (0.30–0.72)	0.46 (0.30–0.72)
Age at diagnosis >40 y, A3 vs A1	0.71 (0.40–1.25)	0.71 (0.40–1.25)	0.70 (0.40–1.25)	0.75 (0.29–1.91)	0.74 (0.29–1.92)	0.75 (0.29–1.98)
Any disease location, including L4	1.33 (0.97–1.82)	1.32 (0.96–1.79)	1.30 (0.95–1.79)	1.64 (0.98–2.78)	1.64 (0.98–2.70)	1.61 (0.98–2.63)
Disease duration, every 5 years	1.07 (0.98–1.17)	1.07 (0.98–1.17)	1.07 (0.98–1.17)	1.02 (0.90–1.16)	1.02 (0.90–1.16)	1.02 (0.90–1.16)
Immunosuppressant, yes	0.70 (0.58–0.85)	0.70 (0.58–0.85)	0.71 (0.58–0.86)	0.86 (0.61–1.22)	0.87 (0.61–1.23)	0.87 (0.62–1.23)
Adalimumab, vs IFX	1.21 (0.99–1.49)	1.22 (0.99–1.50)	1.22 (0.99–1.50)	1.04 (0.71–1.52)	1.04 (0.71–1.52)	1.02 (0.69–1.51)
Second-line anti-TNF[a]	1.32 (1.01–1.72)	1.32 (1.01–1.69)	1.30 (1.01–1.69)	1.72 (1.09–2.78)	1.72 (1.09–2.70)	1.72 (1.08–2.78)
Clinical remission,[b] yes	0.45 (0.24–0.84)	0.45 (0.25–0.83)	0.46 (0.25–0.83)	0.31 (0.16–0.58)	0.31 (0.16–0.58)	0.30 (0.16–0.57)
C-reactive protein, per doubling, *mg/L*		1.04 (1.00–1.08)	1.04 (1.00–1.08)		1.00 (0.94–1.08)	1.01 (0.94–1.08)
Fecal calprotectin, per doubling, *μg/g*				1.13 (1.02–1.27)	1.13 (1.02–1.27)	1.13 (1.01–1.27)
Endoscopic remission,[c] yes			0.88 (0.61–1.25)			0.86 (0.49–1.51)

A, age; C-statistic, concordance statistic; FC, fecal calprotectin; HR, hazard ratio; IFX, infliximab; IPD, individual participant data; L, location; TNF, tumor necrosis factor.
[a]One or more anti-TNF therapies in the patient's medical history.
[b]Defined as (steroid-free) Crohn's Disease Activity Index less than 150, Harvey Bradshaw Index less than 5, Physicians' Global Assessment of 0.
[c]Defined as a simple endoscopic score for CD of 0 to 2, Crohn's disease index of severity less than 3, Rutgeerts score of 0 to 1, no ulcerations/mucosal healing.

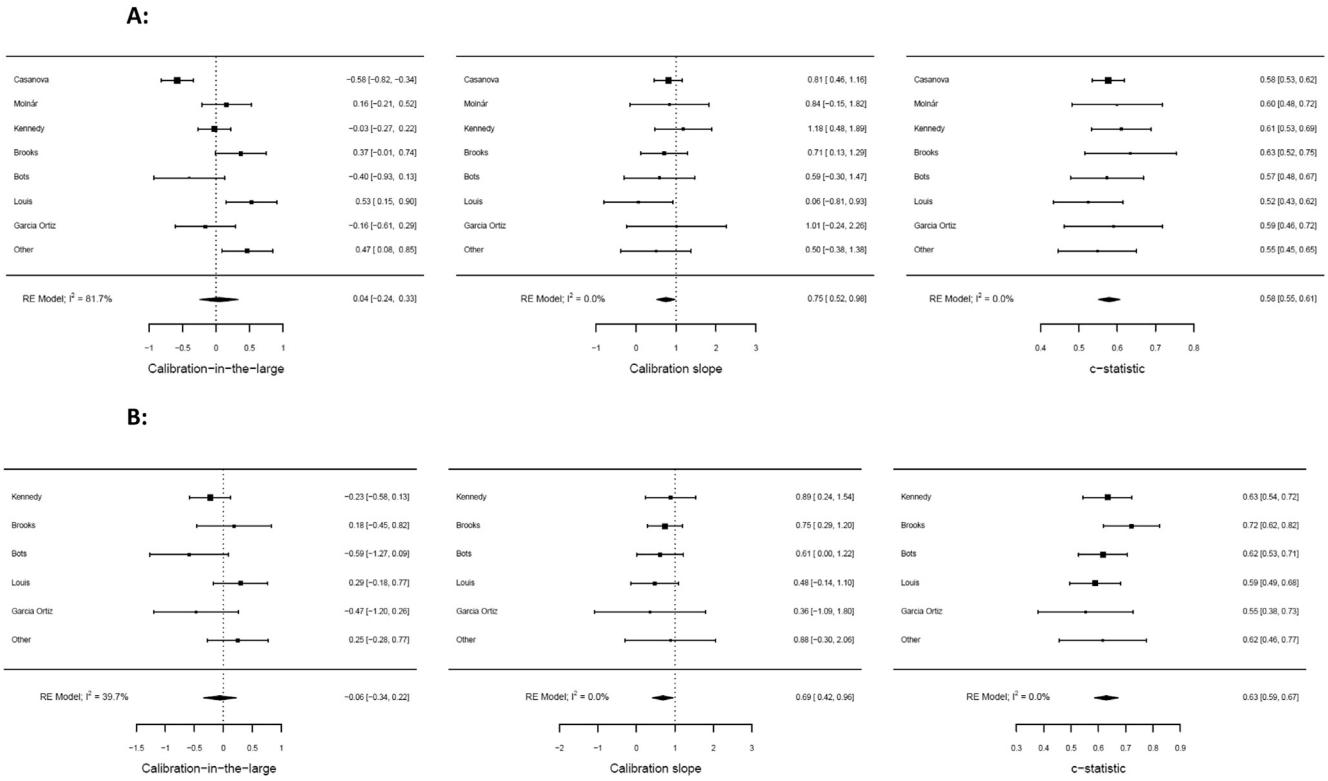

Figure 2. Internal–external validation of the (*A*) constructed biochemical model and the (*B*) biochemical model constructed on the cohorts with available and added FC with corresponding calibration-in-the-large, calibration slope, and predictive performance (C-statistic). Calibration-in-the-large measures whether predictions of the prediction model are on average too high or too low and should ideally be equal to zero. Values less than zero indicate overestimation of the probability of relapse and values greater than zero indicate underestimation of the probability of relapse. The calibration slope measures whether the average predictor effect is correct and ideally should be equal to 1. Values less than 1 indicate too extreme predictor effects, while values greater than 1 indicate too weak predictor effects. Small cohorts (<50 patients) were combined in the category of "other."

assigned to each variable, ranging from 0 to 28 points (Table 4). Patients with a low risk of relapse could be defined by the presence of 3 or fewer of the depicted points, with a 22% risk of relapse over 1 year (sensitivity, 79%; specificity, 39%). If high risk of relapse would be defined by the presence of 5 or more points, the risk of relapse would be more than 42% within 1 year (sensitivity, 37%; specificity, 78%) (Supplementary Tables 6 and 7).

Discussion

Personalized prediction of the risk of relapse after anti-TNF cessation in CD is an important unmet need. According to this IPD-MA of 1317 CD patients in remission, the overall risk of relapse after anti-TNF therapy cessation is 38% at 1 year and 52% at 2 years. By pooling all available data, a predictive diagnostic tool with an overall moderate discriminative ability to prognosticate relapse risk could be developed. The proposed score chart for prediction of the risk of relapse in an individual patient may serve as a shared decision-making tool for clinical practice. This chart has a modest diagnostic accuracy both in identifying patients at risk of relapse below 22% within a year (≤3 points on the diagnostic tool) (sensitivity, 79%; specificity, 39%), as well as in identifying patients at risk of relapse exceeding 42% within a year (sensitivity, 37%; specificity, 78%). According to the included IPD-MA study population, approximately one third of patients will be in each risk group. Therefore, an important implication of the model is that it may not only support the decision of anti-TNF cessation, but also will avoid detrimental anti-TNF cessation in a considerable subgroup of patients with significant risk of relapse.

The identified clinical risk factors in this IPD-MA are in line with previous studies. Although previous cohort studies have suggested a difference between ileal and colonic disease as a prognostic factor, this IPD-MA only confirmed upper gastrointestinal tract involvement as a consistent risk factor for relapse.[43] It may well be that previous series were too small for accurate multivariable analysis, and were not able to account for the correlation of disease location with other risk factors. Because the variance inflation factor for the clinical predictors was low, it was shown that the model was not influenced by collinearity, which also was true for factors that seem correlated such as age at diagnosis and age at anti-TNF cessation. In patients with a history of therapy-

Table 4. Score Chart for Prediction of the Individual Risk of Relapse Based on the Biochemical Model

Predictor	Points
Clinical symptoms[a]	4
Smoking	2
Age at cessation, *y*	
<40	3
40–60	2
61–80	1
>80	0
Age at diagnosis ≤16 y (A1)	2
No immunosuppressant	2
Steroid use 6–12 mo before cessation	2
Disease location including L4	1
Second-line anti-TNF	1
Adalimumab	1
Infliximab	0
Disease duration, *y*	
0–15	0
15–30	1
30–40	2
>40	3
CRP, *mg/L*	
≤5	0
>5	1

A, age; L, location; CRP, C-reactive protein; TNF, tumor necrosis factor.
[a]Defined as Crohn's Disease Activity Index of 150 or more, Harvey Bradshaw Index of 5 or more, Physicians' Global Assessment greater than 0.

refractory CD or combination therapy at the time of cessation, IS continuation at the moment of anti-TNF cessation may be considered because the use of IS protects against relapse. In the developed model, clinical remission was included as a predictor, which may be regarded as a condition for cessation of anti-TNF. By inclusion of these data, the model also is applicable to patients with bowel symptoms. To explore the effect of inclusion of this predictor, an additional subanalysis with construction of the prediction model was performed, restricted to patients in clinical remission, which showed no change in other identified predictors (Supplementary Table 8). With regard to the identified biochemical markers, a low CRP and FC level were associated with a favorable outcome after anti-TNF cessation in this IPD-MA, in accordance with available literature.[12,32,36] Endoscopy to confirm disease remission before anti-TNF cessation does not add to the risk estimation of CD relapse. This finding possibly could be explained by the selection of patients for anti-TNF cessation in available studies because 87% of patients with available endoscopic data were in endoscopic remission, and 99% of patients with endoscopic remission were also in clinical and/or biochemical remission. We presume that endoscopic remission is a predictor of relapse when considering all CD patients, but not anymore in the selected subgroup of patients for which one reasonably would consider anti-TNF cessation in clinical practice. It should be noted that the predictive value of histologic remission as a possible protective factor for relapse was not investigated in this IPD-MA; further studies are required to investigate this possible predictor.[11,44]

Remarkably, the STORI prediction model[12] could not be validated in this IPD-MA. We observed that the identified risk factors by this IPD-MA and in the STORI trial showed similarity in direction, pointing at a protective or increased risk of relapse. Despite this similarity, the predictive power of 0.51 was lower compared with the predictive performance of 0.71 in the initial publication, with overprediction of relapse risk in most cohorts. The disappointing performance of the STORI prediction model in this IPD-MA potentially may be explained by statistical overfitting in a relatively small population (115 patients, 52 relapses). In addition, dichotomization of predictors and categorization of variables in the analysis of the STORI trial may be seen as introducing an extreme form of rounding, with an inevitable loss of information and power.[45,46]

Even though the study size in this IPD-MA was rather large, it has resulted in a predictive diagnostic tool that requires further refinement. To this end, more data on FC and other biochemical, genetic, and/or histologic markers are needed. Because of the high numbers of missing values, serum albumin and anti-TNF serum concentrations could not be analyzed as risk factors for relapse. However, biomarkers closely related to the pathophysiology of CD might be most promising. Several potential DNA, messenger RNA, and protein markers were evaluated previously to predict response to anti-TNF treatment.[47] Interesting genetic associations include *IBD5* and *NOD2/CARD15* mutations, as well as *FCGR3A* 158V/V genotype polymorphisms.[31,48] In addition, mucosal cytokines need further exploration (eg, as mucosal TNF and/or interleukin 17a expression).[49] Microbial dysbiosis with decreased diversity warrants further exploration.[50]

In addition to the risk of exacerbation after cessation of anti-TNF, the efficacy of re-treatment of anti-TNF in case of a relapse is an important clinical issue, even in this era of expanding medical treatment options for CD. A period without anti-TNF therapy, or so-called drug holiday, has been associated with an increased risk of immunization potentially leading to a loss of treatment effect after re-introduction.[51] Pooled IPD-MA data analysis on the effect of re-treatment was not justified in the current data set because of considerable missing values. In Supplementary Table 9 an overview of the data on the efficacy of re-treatment was depicted and showed that response to reintroduction after relapse was considerably high (ie, up to > 80% in large cohorts).[39,40]

Although this IPD-MA was performed following the Transparent Reporting of a multivariable prediction

model for Individual Prognosis Or Diagnosis statement, a few limitations need to be addressed. First, 11 cohorts published in the literature were excluded owing to unavailability of IPD. In particular, the low number of included Asian cohorts may limit the external validity of this IPD-MA to Western countries. Second, the model predicts the risk of relapse 1 year after cessation of anti-TNF, and may not prognosticate the risk at long-term follow-up evaluation. Third, the model is only applicable to patients who started anti-TNF for the indication of luminal CD (not perianal CD). Third, heterogeneity may occur owing to the inclusion of different studies into the model development. In this IPD-MA, we developed the prediction model by adding a stratified baseline hazard for each study to ensure that the effects of predictors are based on within-study effects and not an artifact of between-study differences. In addition, interaction tests between predictors and retrospective or prospective study design were nonsignificant. These findings indicate that pooling of the data from these different studies is reasonable. Fourth, in this IPD-MA the developed model was validated by using an internal–external validation procedure. Nevertheless, further external validation is required. Finally, FC levels were available only in relatively small study populations. Therefore, the constructed prediction model including FC has to be validated in an external, independent, real-word patient cohort with available FC to enhance its predictive performance.

In conclusion, a clinically relevant predictive diagnostic tool to cease anti-TNF in CD has been developed based on multiple cohorts. The proposed simple score chart might be used to guide clinical decision making after further external validation. Future updating of the prediction model with FC and other potent biomarkers is desired to improve identification of CD patients at low and high risk of relapse after anti-TNF cessation. Furthermore, to determine the (cost-) effectiveness of the model, long-term follow-up studies are required. Eventually, anti-TNF cessation after individual risk estimation will improve the quality of care to CD patients by implementation of uniform treatment protocols.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.03.037.

References

1. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
2. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132:52–65.
3. Jeuring SF, van den Heuvel TR, Liu LY, et al. Improvements in the long-term outcome of Crohn's disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL cohort. Am J Gastroenterol 2017;112:325–336.
4. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–1338.
5. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2018; 390:2779–2789.
6. D'Haens G, Reinisch W, Colombel J-F, et al. Five-year safety data from ENCORE, a European observational safety registry for adults with Crohn's disease treated with infliximab [Remicade®] or conventional therapy. J Crohns Colitis 2016; 11:680–689.
7. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. J Crohns Colitis 2017;11:165–174.
8. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. Gut 2014;63:72–79.
9. Severs M, Oldenburg B, van Bodegraven AA, et al. The economic impact of the introduction of biosimilars in inflammatory bowel disease. J Crohns Colitis 2017;11:289–296.
10. Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. J Crohns Colitis 2018;12:17–31.
11. Gisbert JP, Marin AC, Chaparro M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2016; 111:632–647.
12. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63–70 e5, quiz e31.
13. Moher D, Altman DG, Liberati A, et al. PRISMA statement. Epidemiology 2011;22:128.
14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008–2012.
15. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–W73.
16. Publications Office of the EU, Regulation of (EU) 2016/679 the European Parliament and of the Council Regulation, 679; 2016:2016.
17. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford asp. 2001.
18. Wolff RF, Moons KGM, Riley RD, et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. Ann Intern Med 2019;170:51–58.

19. Debray TP, Vergouwe Y, Koffijberg H, et al. A new framework to enhance the interpretation of external validation studies of clinical prediction models. J Clin Epidemiol 2015;68:279–289.
20. Gönen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. Biometrika 2005;92:965–970.
21. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128–138.
22. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–1931.
23. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015;162:55–63.
24. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009;28:1982–1998.
25. García Ortíz JM, Sáenz Gallo M, Trigo Salado C, et al. P634 long term risk of relapse after anti-TNF discontinuation based on mucosal healing in inflammatory bowel disease. J Crohns Colitis 2017;11(Suppl 1):S404-S.
26. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19:1059–1079.
27. Moons KG, Donders RA, Stijnen T, et al. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006;59:1092–1101.
28. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
29. IntHout J, Ioannidis JP, Rovers MM, et al. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 2016;6:e010247.
30. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA 2015;313:409–410.
31. Lu C, Waugh A, Bailey RJ, et al. Crohn's disease genotypes of patients in remission vs relapses after infliximab discontinuation. World J Gastroenterol 2012;18:5058–5064.
32. Molnar T, Lakatos PL, Farkas K, et al. Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy. Aliment Pharmacol Ther 2013;37:225–233.
33. Steenholdt C, Molazahi A, Ainsworth MA, et al. Outcome after discontinuation of infliximab in patients with inflammatory bowel disease in clinical remission: an observational Danish single center study. Scand J Gastroenterol 2012;47:518–527.
34. Chauvin A, Le Thuaut A, Belhassan M, et al. Infliximab as a bridge to remission maintained by antimetabolite therapy in Crohn's disease: a retrospective study. Dig Liver Dis 2014;46:695–700.
35. Farkas K, Lakatos PL, Szucs M, et al. Frequency and prognostic role of mucosal healing in patients with Crohn's disease and ulcerative colitis after one-year of biological therapy. World J Gastroenterol 2014;20:2995–3001.
36. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. Aliment Pharmacol Ther 2015;42:356–364.
37. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. Inflamm Bowel Dis 2014;20:495–501.
38. Brooks AJ, Sebastian S, Cross SS, et al. Outcome of elective withdrawal of anti-tumour necrosis factor-alpha therapy in patients with Crohn's disease in established remission. J Crohns Colitis 2017;11:1456–1462.
39. Kennedy NA, Warner B, Johnston EL, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. Aliment Pharmacol Ther 2016;43:910–923.
40. Casanova MJ, Chaparro M, Garcia-Sanchez V, et al. Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease: a multicenter long-term follow-up study. Am J Gastroenterol 2017;112:120–131.
41. Lin W-C, Chou J-W, Yen H-H, et al. Outcomes of limited period of adalimumab treatment in moderate to severe Crohn's disease patients: Taiwan Society of Inflammatory Bowel Disease Study. Intest Res 2017;15:487–494.
42. Bots SJ, Kuin S, Ponsioen CY, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. Scand J Gastroenterol 2019;54:281–288.
43. Reenaers C, Mary JY, Nachury M, et al. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. Clin Gastroenterol Hepatol 2018;16:234–243 e2.
44. Bryant RV, Winer S, Travis SPL, et al. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. J Crohns Colitis 2014;8:1582–1597.
45. Steyerberg EW, Uno H, Ioannidis JPA, et al. Poor performance of clinical prediction models: the harm of commonly applied methods. J Clin Epidemiol 2018;98:133–143.
46. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;25:127–141.
47. Stevens TW, Matheeuwsen M, Lonnkvist MH, et al. Systematic review: predictive biomarkers of therapeutic response in inflammatory bowel disease-personalised medicine in its infancy. Aliment Pharmacol Ther 2018;48:1213–1231.
48. Ternant D, Berkane Z, Picon L, et al. Assessment of the influence of inflammation and FCGR3A genotype on infliximab pharmacokinetics and time to relapse in patients with Crohn's disease. Clin Pharmacokinet 2015;54:551–562.
49. Rismo R, Olsen T, Cui G, et al. Normalization of mucosal cytokine gene expression levels predicts long-term remission after discontinuation of anti-TNF therapy in Crohn's disease. Scand J Gastroenterol 2013;48:311–319.
50. Rajca S, Grondin V, Louis E, et al. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. Inflamm Bowel Dis 2014;20:978–986.
51. Farrell RJ, Alsahli M, Jeen YT, et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003;124:917–924.

Reprint requests
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Poster presentation at the 14th congress of ECCO–Inflammatory Bowel Diseases 2018 (March 6–9, 2018; Copenhagen, Denmark): P138 Prediction model to safely cease anti-TNF therapy in Crohn's disease: individual participant data meta-analysis (IPD-MA).

Oral presentation at the Dutch Digestive Days (Veldhoven, the Netherlands) 2019 (March 20–21, 2019): 53 Prediction model to safely cease anti-TNF therapy in Crohn's disease: individual participant data meta-analysis (IPD-MA).

The CEASE (Safe anti-TNF cessation in Crohn's disease) study group comprises the following members: Annemarie C. de Vries, Renske W. M. Pauwels, C. Janneke van der Woude, Daan Nieboer, Ewout W. Steyerberg, Jasmijn A.M. Sleutjes, Marjolijn Duijvestein, Geert R. D'Haens, María J. Casanova, Javier P. Gisbert, Nick A. Kennedy, Charlie W. Lees, Edouard Louis, Tamás Molnár, Kata Szántó, Eduardo Leo, J.M. García-Ortíz, Robert Downey, Alenka J. Brooks, Peter J. Hamlin, Shaji Sebastian, Alan J. Lobo, Milan Lukas, Wei C. Lin, Aurelien Amiot, Cathy Lu, Levinus (Leo) A. Dieleman, Xavier Roblin, Shomron Ben-Horin, Klaudia Farkas, Jakob B. Seidelin, Casper Steenholdt, and Steven Bots.

Conflicts of interest

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('inflammatory bowel disease'/de OR 'Crohn disease'/exp OR ((inflammat* NEAR/3 bowel NEAR/3 diseas*) OR crohn* OR ibd):ab,ti) AND ('drug withdrawal'/exp OR 'treatment withdrawal'/de OR (((drug* OR agent* OR medicat* OR tnf OR tumor-necrosis-factor OR therap* OR treat* OR infliximab* OR adalimumab* OR golimumab* OR mercaptopurin*) NEAR/6 (withdraw* OR cessat* OR abstinen* OR stop* OR discontinu*)) OR ((withdraw* OR stop) NEAR/3 (criteria* OR timing OR when))):ab,ti) AND ('tumor necrosis factor inhibitor'/de OR 'tumor necrosis factor alpha inhibitor'/de OR 'tumor necrosis factor antibody'/de OR 'tumor necrosis factor alpha antibody'/de OR 'biological therapy'/de OR 'infliximab'/mj OR adalimumab/mj OR golimumab/mj OR 'mercaptopurine'/mj OR (((tnf* OR necrosis-factor*) NEAR/6 (anti* OR inhibitor* OR block* OR antagon* OR target* OR against*)) OR biological* OR infliximab* OR adalimumab* OR golimumab* OR mercaptopurin*):ab,ti) AND [english]/lim

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("Inflammatory Bowel Diseases"/ OR "Crohn Disease"/ OR ((inflammat* ADJ3 bowel ADJ3 diseas*) OR crohn* OR ibd).ab,ti.) AND ("Withholding Treatment"/ OR "Substance Withdrawal Syndrome"/ OR (((drug* OR agent* OR medicat* OR tnf OR tumor-necrosis-factor OR therap* OR treat* OR infliximab* OR adalimumab* OR golimumab*) ADJ6 (withdraw* OR cessat* OR abstinen* OR stop* OR discontinu*)) OR ((withdraw* OR stop) ADJ3 (criteria* OR timing OR when))).ab,ti.) AND ("tumor necrosis factor"/ai OR "Biological Therapy"/ OR *"infliximab"/ OR *adalimumab/ OR *golimumab/ OR (((tnf* OR necrosis-factor*) ADJ6 (anti* OR inhibitor* OR block* OR antagon* OR target* OR against*)) OR biological* OR infliximab* OR adalimumab* OR golimumab*).ab,ti.) AND english.la.

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TS=((((inflammat* NEAR/2 bowel NEAR/2 diseas*) OR crohn* OR ibd)) AND ((((drug* OR agent* OR medicat* OR tnf OR tumor-necrosis-factor OR therap* OR treat* OR infliximab* OR adalimumab* OR

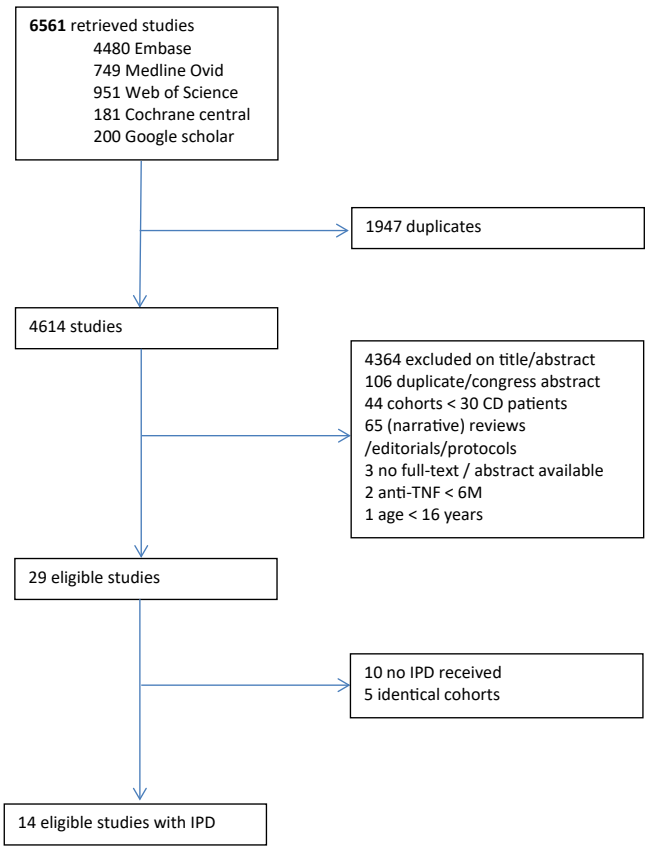
Supplementary Figure 1. Systematic search.

golimumab* OR methotrexat* OR "mtx") NEAR/5 (withdraw* OR cessat* OR abstinen* OR stop* OR discontinu*)) OR ((withdraw* OR stop) NEAR/2 (criteria* OR timing OR when)))) AND ((((tnf* OR necrosis-factor*) NEAR/5 (anti* OR inhibitor* OR block* OR antagon* OR target* OR against*)) OR biological* OR infliximab* OR adalimumab* OR golimumab*))) AND LA=(english)

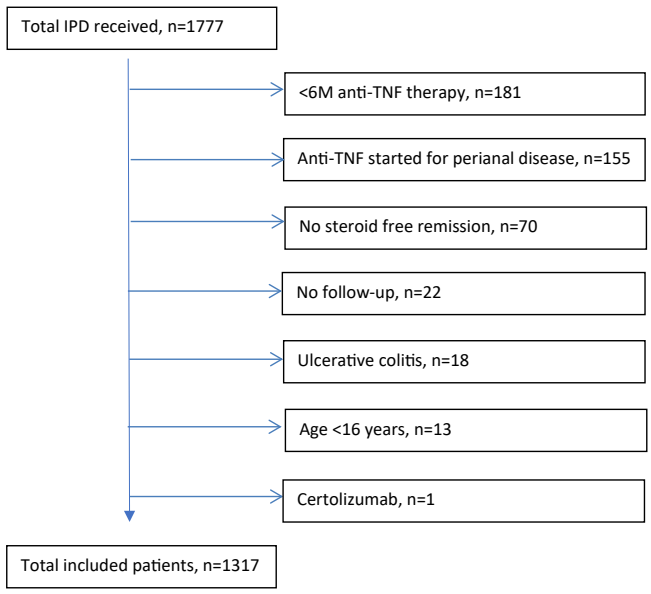
Google scholar

"inflammatory bowel diseases"|crohn|ibd
withdrawal|cessation|discontinuation|discontinuing|"stopping criteria" "anti tnf"|"anti tumor|tumour necrosis"|"tumor|tumour necrosis factor inhibitor|inhibitors|blocking|antagonist|antagonists"

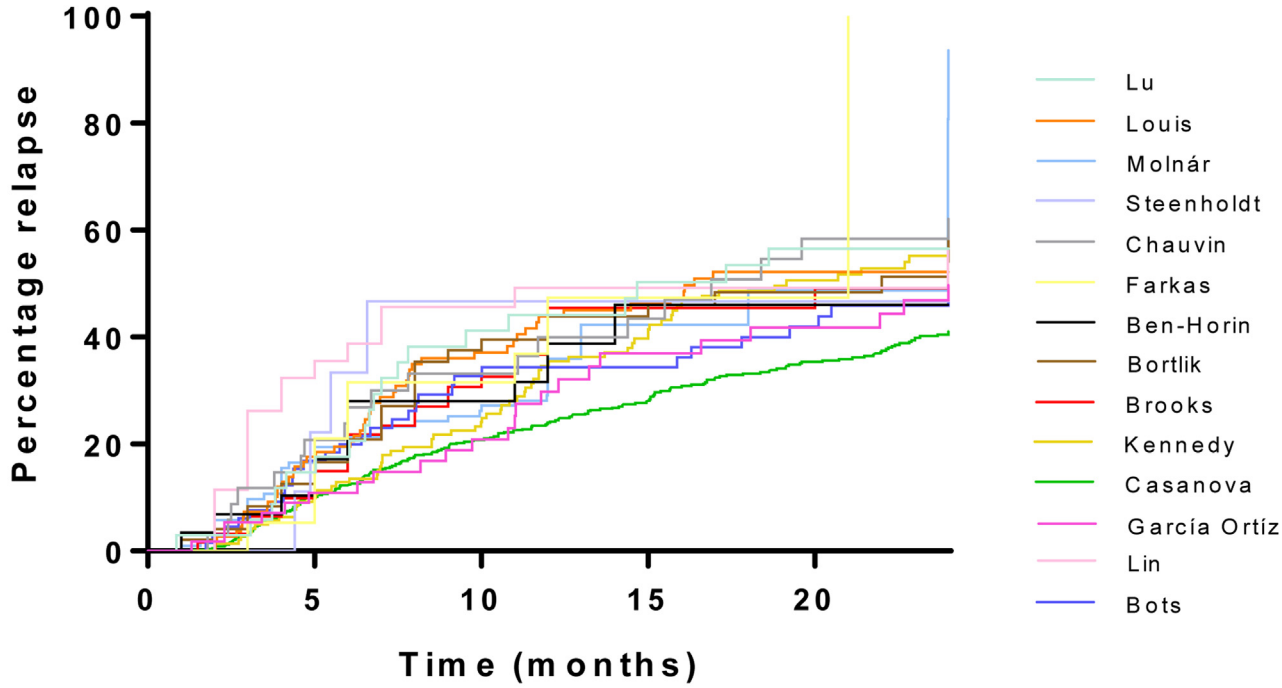
Supplementary Figure 1. Continued.

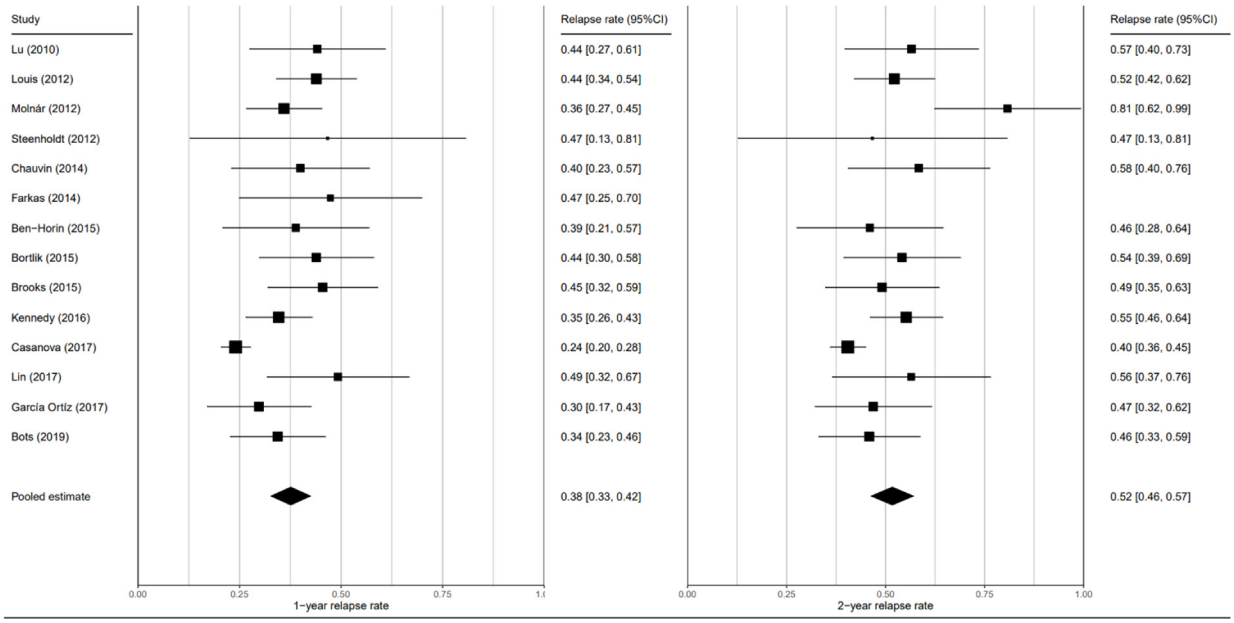


Supplementary Figure 2. Flow chart of study selection. CD, Crohn's disease; IPD, individual patient data; M, months; TNF, tumor necrosis factor.

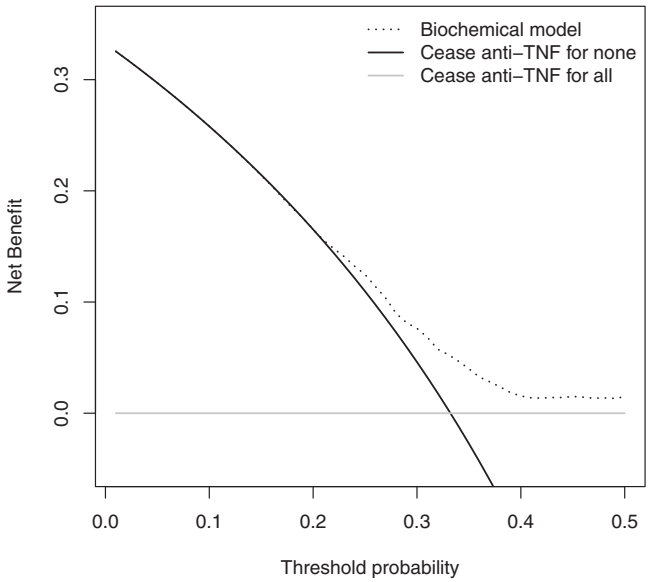


Supplementary Figure 3. Flowchart of individual participant data selection. IPD, individual participant data; M, months; TNF, tumor necrosis factor.





Supplementary Figure 4. Incidence of relapse, categorized by study.



Supplementary Figure 5. Decision curve analysis for the prediction of relapse using the biochemical model. *Solid black line* shows the assumption that patients continue anti–tumor necrosis factor (TNF) therapy. *Solid grey line* shows the assumption that all patients cease anti-TNF therapy. *Dotted line* depicts the net benefit using the biochemical model. The net benefit is the sum of benefit (ie, no relapse after anti-TNF cessation) minus harms (ie, relapse after anti-TNF cessation). Threshold probability is the accepted risk of relapse after anti-TNF cessation. The net benefit of the biochemical model is higher compared with anti-TNF cessation in all patients as applied by the included studies and with anti-TNF continuation in all patients, in the threshold probability range of 0.25 to 0.5. Because risk thresholds are subjective to patient and physician preferences, a range of risk thresholds needs to be investigated. In this figure, the net benefit was plotted for the total individual patient data meta-analysis cohort against a range of clinically relevant risk thresholds.

Supplementary Table 1. Study Characteristics of Excluded Studies as a Result of Unavailability of IPD

Study	Type of study	Country	Publication year	Eligible participants, N	Definition of remission	Definition of relapse
Schnitzler et al[16]	Prospective	Belgium	2008	110	Sustained clinical remission; a lasting control of disease activity during FU with persistent improvement of symptoms	NR
Armuzzi et al[17]	Abstract, retrospective	Italy	2010	69	Prolonged steroid-free remission	NR
Rismo et al[18]	Prospective	Norway	2013	37	Endoscopic remission; complete endoscopic healing (absence of ulceration and redness)	CDAI increase of >70 points from baseline and/or endoscopic findings qualifying for re-treatment with an anti-TNF agent or use of systemic steroids
Echarri et al[19]	Abstract, NR	Spain	2013	32	Deep remission, defined as steroid-free clinical remission, mucosal healing assessed by endoscopy or the absence of activity as confirmed by bowel MRI	NR
Dai et al[20]	Prospective, observational	China	2014	92	Clinical steroid-free remission; CDAI <150	Indication for restarting biologicals: An increase of >100 points in CDAI and a CDAI of >150 points
Ampuero et al[21]	Retrospective	Spain	2015	55	Steroid free clinical remission; CDAI <150	CDAI >250
Parisi et al[22]	Abstract, retrospective	United Kingdom	2016	42	Clinical remission; HBI <5	NR
Huiqin Hu et al[23]	Retrospective	China	2017	106	Clinical remission; CDAI <150	Clinical relapse was defined as retreatment with a biologic therapy or systemic steroid or CD-related surgery Endoscopic relapse was defined as SES-CD >2
Zheng et al[24]	Abstract, retrospective	China	2017	90	Steroid free clinical remission	NR
Bohn Thomsen et al[25]	Retrospective	Denmark	2018	33	Clinical and biochemical remission; HBI <5 and a FC level of <200 μg/g	Surgery, reinstitution of anti-TNF therapy, or start of steroids or other biological agents

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FC, fecal calprotectin; FU, follow-up; HBI, Harvey Bradshaw Index; IPD, individual participant data; MRI, magnetic resonance imaging; NR, not reported; SES, simple endoscopic score; TNF, tumor necrosis factor.

Supplementary Table 2. Identical Study Cohorts

Study	Year	Identical cohort
Waugh et al[26]	2010	Identical cohort to Lu et al[1]
de Suray et al[27]	2012	Subanalysis of the STORI cohort[3]
Rajca et al[28]	2014	Subanalysis of the STORI cohort[3]
Ternant et al[29]	2015	Subanalysis of the STORI cohort[3]
Reenaers et al[30]	2018	Long-term follow-up evaluation of the STORI cohort[3]

STORI, diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressants.

Supplementary Table 3. Risk of Bias Assessment With the Newcastle–Ottawa Scale

	Publication year	Selection (maximum, 4)	Comparability (maximum, 2)	Outcome (maximum, 3)	Total (maximum, 9)
Lu et al[1]	2010	***	*	*	*****
Molnar et al[2]	2012	***	*	**	******
Louis et al[3]	2012	***	**	***	********
Steenholdt et al[4]	2012	***	*	**	******
Chauvin et al[5]	2014	***	*	**	******
Farkas et al[6]	2014	***	*	**	******
Brooks et al[7]	2015	***	*	***	*******
Bortlik et al[8]	2015	***	*	**	******
Ben-Horin et al[9]	2015	***	*	***	*******
Kennedy et al[10]	2016	***	*	***	*******
Casanova et al[11]	2017	***	*	**	******
García Ortíz et al[12]	2017	***	*	*	*****
Lin et al[13]	2017	***	*	**	******
Bots et al[14]	2019	***	*	**	******

The Newcastle–Ottawa Scale scores the quality of the design of (cohort) studies. The Newcastle–Ottawa Quality Assessment Form for Cohort Studies system has been developed with stars, in which studies were scored on the following: (1) selection of study groups, (2) comparability of groups, and (3) the outcome of interest. The total score can range from 0 (low) to 9 (high) stars.

Supplementary Table 4. Risk of Bias Assessment After PROBAST

	ROB				Applicability			Overall	
Study	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Lu et al[1]	+	?	+	-	+	?	+	-	?
Molnar et al[2]	+	+	+	?	+	+	+	?	+
Louis et al[3]	+	+	+	+	+	+	+	+	+
Steenholdt et al[4]	+	?	+	?	-	+	+	?	-
Chauvin et al[5]	+	?	+	?	+	+	+	?	+
Farkas et al[6]	+	+	+	-	-	+	+	-	-
Brooks et al[7]	+	+	+	+	+	+	+	+	+
Bortlik et al[15]	+	?	+	?	+	+	+	?	+
Ben-Horin et al[9]	+	+	+	?	-	+	+	?	-
Kennedy et al[10]	+	+	+	+	+	+	+	+	+
Casanova et al[11]	+	+	+	?	+	+	+	?	+
García Ortíz et al[12]	+	?	-	-	+	+	+	-	+
Lin et al[13]	+	?	+	?	+	+	+	?	+
Bots et al[14]	+	?	+	+	+	+	+	?	+

PROBAST, prediction model risk of bias assessment tool; ROB, risk of bias; +, indicates low ROB/low concern regarding applicability; -, indicates high ROB/high concern regarding applicability; ?, indicates unclear ROB/unclear concern regarding applicability.

Supplementary Table 5. Univariable Analysis of Associations Between Clinical, Biochemical, and Endoscopic Parameters and Relapse After Anti-TNF Cessation

Predictor	HR (95% CI)
Clinical symptoms	3.85 (2.38–6.25)
Smoking, yes	1.28 (1.08–1.52)
Immunosuppressant, yes	0.75 (0.63–0.89)
Any disease location including L4 vs no L4	1.22 (0.91–1.67)
Second-line anti-TNF	1.33 (1.05–1.69)
Adalimumab vs infliximab	1.21 (1.02–1.44)
Disease duration, every 5 y	1.02 (0.97–1.08)
Age, every 10 y	0.87 (0.81–0.92)
Female sex	1.09 (0.93–1.28)
Age at diagnosis 17–40 y, A2 vs A1	0.61 (0.49–0.75)
Age at diagnosis >40 y, A3 vs A1	0.45 (0.32–0.63)
Colon localization, L2 vs L1	1.18 (0.93–1.49)
Ileocolic localization, L3 vs L1	1.33 (1.08–1.62)
Isolated upper GI involvement	1.97 (0.81–4.81)
Stricturing disease, B2 vs B1	1.03 (0.83–1.28)
Penetrating disease, B3 vs B1	0.95 (0.76–1.18)
Perianal (fistulizing) disease, yes	0.95 (0.79–1.14)
Previous intestinal resection, yes	1.09 (0.93–1.30)
Duration of anti-TNF therapy, every 12 mo	1.00 (0.95–1.04)
Escalated anti-TNF therapy,[a] yes	1.17 (0.80–1.72)
Previous IS use, yes	0.88 (0.60–1.28)
Two previous IS vs 1	1.12 (0.85–1.46)
Three previous IS vs 1	1.02 (0.60–1.73)
Type of previous IS, thiopurine, vs no	0.84 (0.61–1.16)
Type of previous IS, MTX, vs no	1.56 (0.94–2.58)
Type of previous IS, MTX, vs thiopurine	1.46 (0.96–2.21)
Type of previous IS, thiopurine and MTX, vs thiopurine	1.10 (0.83–1.46)
Platelet count,[b] per 100 *10^9 increase	1.07 (0.94–1.21)
Hemoglobin level, per 1-mmol/L increase	1.00 (0.89–1.13)
Leukocyte count, per 1-10^9/L increase	1.03 (0.99–1.08)
CRP, per doubling, *mg/L*	1.02 (0.97–1.06)
FC, per doubling, *μg/g*	1.03 (0.97–1.10)
Endoscopic remission, yes	0.85 (0.65–1.12)

A, age; B, behavior; CRP, C-reactive protein; FC, fecal calprotectin; GI, gastrointestinal; HR, hazard ratio; IS, immunosuppressant; L, location; MTX, methotrexate; TNF, tumor necrosis factor.

[a]Infliximab greater than 5 mg/kg or adalimumab greater than 40 mg, or infliximab interval <1×/8 wk or adalimumab interval <1×/2 wk.

[b]No further increase in risk was observed for platelet count of 300*10^9 or greater.

Supplementary Table 6. Relapse Rates Based on the Allocated Points From the Simple Score Chart to Each Patient (According to the Biochemical Model)

Allocated points from the score chart	Sensitivity, %	Specificity, %	Patients above, n (%)	Patients below, n (%)	Relapse rate above threshold, %	Relapse rate at and below threshold, %
1[a]	99	3	1292 (98)	25 (2)	33	13
2	95	11	1205 (91)	112 (9)	34	21
3	79	39	903 (69)	414 (31)	37	22
4	60	59	645 (49)	672 (51)	40	26
5	37	78	372 (28)	945 (72)	42	29
6	20	89	200 (15)	1117 (85)	43	31
7	11	96	100 (8)	1217 (92)	45	32
≥8	4	99	36 (3)	1281 (97)	53	32

[a]No patients with less than 1 point were identified in the individual participant data meta-analysis cohort.

Supplementary Table 7. Sensitivity and Specificity Values of Different Relapse Rate Thresholds According to the Biochemical Model

Relapse rate, %	Sensitivity, %	Specificity, %
20	96	9
21	94	11
22	93	15
23	90	20
24	88	25
25	84	30
26	80	35
27	76	39
28	71	44
29	67	48
30	64	52
31	61	56
32	56	59
33	53	63
34	48	67
35	44	70
36	40	73
37	37	76
38	34	78
39	31	80
40	29	82
41	27	84
42	25	86
43	23	88
44	21	89
45	19	91

Supplementary Table 8. Constructed Prediction Models Restricted to Patients in Clinical Remission (n = 1221)

	Prediction models			Prediction models constructed on 8/14 IPD cohorts with FC		
Predictor	Clinical model C-statistic, 0.60; HR (95% CI)	Biochemical model C-statistic, 0.61; HR (95% CI)	Endoscopic model C-statistic, 0.61; HR (95% CI)	Clinical model + FC C-statistic, 0.65; HR (95% CI)	Biochemical model + FC C-statistic, 0.65; HR, 95% CI	Endoscopic model + FC C-statistic, 0.65; HR, 95% CI
Age, every 10 y	0.84 (0.73–0.98)	0.85 (0.73–0.98)	0.85 (0.73–0.98)	0.86 (0.67–1.09)	0.85 (0.66–1.09)	0.84 (0.65–1.09)
Smoking, yes	1.42 (1.18–1.73)	1.42 (1.18–1.72)	1.41 (1.17–1.72)	1.52 (1.09–2.10)	1.53 (1.04–2.24)	1.52 (1.04–2.25)
Age at diagnosis 17–40 y, A2 vs A1	0.71 (0.53–0.95)	0.70 (0.52–0.94)	0.70 (0.52–0.94)	0.49 (0.31–0.76)	0.48 (0.30–0.77)	0.48 (0.31–0.77)
Age at diagnosis >40 year, A3 vs A1	0.76 (0.41–1.44)	0.74 (0.39–1.40)	0.74 (0.39–1.41)	0.70 (0.25–1.96)	0.69 (0.23–2.02)	0.70 (0.24–2.08)
Any disease location, including L4	1.32 (0.96–1.81)	1.31 (0.96–1.79)	1.29 (0.95–1.77)	1.75 (1.04–2.95)	1.58 (0.92–2.71)	1.55 (0.9–2.68)
Disease duration, every 5 years	1.07 (0.97–1.17)	1.06 (0.97–1.17)	1.06 (0.97–1.17)	1.03 (0.89–1.19)	1.03 (0.89–1.21)	1.03 (0.89–1.20)
Immunosuppressant, yes	0.70 (0.57–0.85)	0.70 (0.57–0.86)	0.71 (0.57–0.87)	0.83 (0.58–1.20)	0.88 (0.60–1.27)	0.88 (0.61–1.26)
Adalimumab, vs IFX	1.24 (0.99–1.55)	1.25 (1.00–1.55)	1.25 (0.99–1.57)	0.95 (0.66–1.37)	0.97 (0.63–1.50)	0.96 (0.62–1.50)
Second-line anti-TNF[a]	1.26 (0.88–1.80)	1.24 (0.87–1.77)	1.22 (0.82–1.83)	2.1 (1.31–3.36)	1.72 (1.09–2.70)	2.19 (1.18–4.07)
C-reactive protein, per doubling, *mg/L*		1.06 (0.97–1.16)	1.06 (0.97–1.16)		1.00 (0.93–1.08)	1.00 (0.93–1.08)
Endoscopic remission,[b] yes			0.90 (0.60–1.35)			0.88 (0.51–1.51)
FC, per doubling, *μg/g*				1.14 (1.03–1.25)	1.12 (1.0–1.26)	1.12 (1.0–1.25)

A, age; C-statistic, concordance statistic; FC, fecal calprotectin; HR, hazard ratio; IFX, infliximab; L, location; TNF, tumor necrosis factor.
[a]One or more anti-TNF therapies in the patient's medical history.
[b]Defined as a simple endoscopic score for CD of 0 to 2, Crohn's disease index of severity less than 3, Rutgeerts score of 0 to 1, no ulcerations/mucosal healing.

Supplementary Table 9. Response to Re-treatment in Patients With a Relapse After Anti-TNF Cessation

Study	Year of publication	Definition of response to retreatment	Week of assessment, median	Re-treated,[a] n (%)	(Same) anti-TNF, n (%)	Steroids, n (%)	IS therapy, n (%)	Hospitalization, n (%)	Surgery, n (%)	Efficacy	Side effects
Lu et al[1]	2010	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Louis et al[3]	2012	CDAI decrease of at least 70 points and 25% from CDAI at relapse or CDAI <150	Short term: 4 (±1.4) Long term: 335	48/52 (92%) (4 missing values)	Anti-TNF: 48/48 (100%) Same anti-TNF: 48/48 (100%)	NR	NR	3/48 (6%) (4 missing values) 1 patient underwent surgery and had cutaneous side effects, 2 patients were primary nonresponders	6/51 (12%) (1 missing value)	Short term: 39/40 (98%) (12 missing values) Long term: 30/52 (58%) Primary nonresponse, n = 2 Secondary loss of response, n = 2 Pregnancy, n = 3 Remission, n = 2	Cutaneous side effects, n = 2 Infection, n = 2 Cancer, n = 1 Other, n = 2
Molnár et al[2]	2012	CDAI decrease of >70 points or CDAI ≤150	13	47/47 (100%)	Anti-TNF: 47/47 (100%) Same anti-TNF: 39/47 (83%)	7/47 (15%)	NR	1/7 (14%) (40 missing values)	8/47 (17%)	7/7 (100%) (40 missing values)	NR

Supplementary Table 9. Continued

Study	Year of publication	Definition of response to retreatment	Week of assessment, median	Re-treated,[a] n (%)	(Same) anti-TNF, n (%)	Steroids, n (%)	IS therapy, n (%)	Hospitalization, n (%)	Surgery, n (%)	Efficacy	Side effects
Steenholdt et al[4]	2012	Complete response, defined as clinical remission with no symptoms or clinical findings indicating active disease or partial response, defined as all other and intermediate response type	6	5/5 (100%)	Anti-TNF: 5/5 (100%) Same anti-TNF: 5/5 (100%)	NR	NR	NR	NR	5/5 (100%)	NR
Chauvin et al[5]	2014	Clinical response by the physician	14	23/23 (100%)	Anti-TNF: 22/23 (96%) Same anti-TNF: 19/23 (83%)	6/23 (26%) 6 patients received steroids + anti-TNF	NR	6/23 (26%) 4 patients received anti-TNF, 1 underwent surgery and 1 patient received both	2/23 (9%)	19/22 (86%)	Delayed infusion reaction, n = 1
Farkas et al[6]	2014	NR	6	10/10 (100%)	Anti-TNF: 10/10 (100%) Same anti-TNF: 8/10 (80%)	NR	NR	NR	2/10 (20%)	5/10 (50%)	Infection, n = 1 Other (not specified), n = 1 (8 missing values)

Supplementary Table 9. Continued

Study	Year of publication	Definition of response to retreatment	Week of assessment, median	Re-treated,[a] n (%)	(Same) anti-TNF, n (%)	Steroids, n (%)	IS therapy, n (%)	Hospitalization, n (%)	Surgery, n (%)	Efficacy	Side effects
Brooks et al[7]	2015	Defined clinically by the supervising physician on the basis of significant and satisfactory improvement in symptoms	NR	28/28 (100%)	Anti-TNF: 24/27 (89%) (1 missing value) Same anti-TNF: 18/24 (75%)	NR	26/26 (100%) (2 missing values)	NR	NR	NR	NR
Bortlik et al[8]	2015	Efficacy was assessed	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ben-Horin et al[9]	2015	NR	NR	15/15 (100%)	Anti-TNF: 14/15 (93.3%) (1 missing value) Same anti-TNF: 8/14 (57%)	NR	2/2 (100%) (13 missing values)	NR	2/15 (13%)	4/5 (80%), where 1 patient responded after switching (10 missing values)	NR
Kennedy et al[10]	2016	NR	NR	66/73 (90%) (7 patients with a relapse were not re-treated)	Anti-TNF: 55/66 (83%) Same anti-TNF: 45/55 (82%)	33/65 (51%) (1 missing value)	NR	11/65 (17%) (1 missing value) 1 patient underwent surgery, 1 underwent surgery in combination with anti-TNF, 2 received steroids, 7 received anti-TNF	4/66 (6%) 3 patients additionally received postoperative anti-TNF	50/54 (93%) (12 missing values)	NR

Supplementary Table 9. Continued

Study	Year of publication	Definition of response to retreatment	Week of assessment, median	Re-treated,[a] n (%)	(Same) anti-TNF, n (%)	Steroids, n (%)	IS therapy, n (%)	Hospitalization, n (%)	Surgery, n (%)	Efficacy	Side effects
Casanova et al[11]	2017	HBI ≤4 points and a decrease of ≥3 points from baseline	14	238/238 (100%) (11 missing values)	Anti-TNF: 182/238 (77%) Same anti-TNF: 140/182 (77%)	NR	NR	NR	6/238 (3%) 6 patients underwent solely surgery	129/154 (84%) (84 missing values)	Infections, n = 4 Skin reactions, n = 5 Acute infusion reaction, n = 7 Injection site reaction, n = 1 Delayed infusion reaction, n = 1 (220 missing values)
García Ortíz et al[12]	2017	NR	NR	25/25 (100%)	Anti-TNF: 22/25 (88%) Same anti-TNF: 21/22 (95%)	25/25 (100%) 3 patients received solely steroids	NR	6/25 (24%) For clinically anti-TNF and/or steroids	0/25 (0%)	20/22 (91%) (3 missing values)	NR
Lin et al[13]	2017	Clinical response and remission	NR	21/21 (100%)	Anti-TNF: 21/21 (100%) Same anti-TNF: 21/21 (100%)	NR	NR	NR	NR	17/18 (94%) (3 missing values)	NR
Bots et al[14]	2019	Determined by PGA based on clinical, biochemical, endoscopic, and/or radiologic assessment	NR	36/36 (100%)	Anti-TNF: 27/32 (84%) (4 missing values) Same anti-TNF: 22/27 (82%)	8/28 (29%) (8 missing values) 5 patients received steroids + anti-TNF	6/6 (100%) (30 missing values)	NR	NR	24/28 (86%) (8 missing values)	Acute infusion reaction n = 1 (35 missing values)

CDAI, Crohn's Disease Activity Index; HBI, Harvey Bradshaw Index; IS, immunosuppressant; NR, not received; PGA, physician's global assessment; TNF, tumor necrosis factor.
[a]Included re-treatment with the (same) anti-TNF, the need for corticosteroids, immunosuppressants, other biologicals, hospitalization, and surgery.

Supplementary References

1. Lu C, Waugh A, Bailey RJ, et al. Crohn's disease genotypes of patients in remission vs relapses after infliximab discontinuation. World J Gastroenterol 2012;18:5058–5064.
2. Molnar T, Lakatos PL, Farkas K, et al. Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy. Aliment Pharmacol Ther 2013;37:225–233.
3. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63–70 e5, quiz e31.
4. Steenholdt C, Molazahi A, Ainsworth MA, et al. Outcome after discontinuation of infliximab in patients with inflammatory bowel disease in clinical remission: an observational Danish single center study. Scand J Gastroenterol 2012;47:518–527.
5. Chauvin A, Le Thuaut A, Belhassan M, et al. Infliximab as a bridge to remission maintained by antimetabolite therapy in Crohn's disease: a retrospective study. Dig Liver Dis 2014; 46:695–700.
6. Farkas K, Lakatos PL, Szucs M, et al. Frequency and prognostic role of mucosal healing in patients with Crohn's disease and ulcerative colitis after one-year of biological therapy. World J Gastroenterol 2014;20:2995–3001.
7. Brooks AJ, Sebastian S, Cross SS, et al. Outcome of elective withdrawal of anti-tumour necrosis factor-alpha therapy in patients with Crohn's disease in established remission. J Crohns Colitis 2017;11:1456–1462.
8. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. Inflamm Bowel Dis 2014;20:495–501.
9. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. Aliment Pharmacol Ther 2015; 42:356–364.
10. Kennedy NA, Warner B, Johnston EL, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. Aliment Pharmacol Ther 2016;43:910–923.
11. Casanova MJ, Chaparro M, Garcia-Sanchez V, et al. Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease: a multicenter long-term follow-up study. Am J Gastroenterol 2017;112:120–131.
12. García Ortíz JM, Sáenz Gallo M, Trigo Salado C, et al. P634 Long term risk of relapse after anti-TNF discontinuation based on mucosal healing in inflammatory bowel disease. J Crohns Colitis 2017;11(Suppl 1):S404, –S.
13. Lin W-C, Chou J-W, Yen H-H, et al. Outcomes of limited period of adalimumab treatment in moderate to severe Crohn's disease patients: Taiwan Society of Inflammatory Bowel Disease Study. Intest Res 2017;15:487–494.
14. Bots SJ, Kuin S, Ponsioen CY, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. Scand J Gastroenterol 2019;54:281–288.
15. Bortlik M, Duricova D, Machkova N, et al. Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. Scand J Gastroenterol 2016;51:196–202.
16. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492–500.
17. Armuzzi A, Rizzi M, Monterubbianesi R, et al. W1268 The course of infliximab discontinuation after long-term maintenance treatment in Crohn's disease. Gastroenterology 2010; 138:S-687.
18. Rismo R, Olsen T, Cui G, et al. Normalization of mucosal cytokine gene expression levels predicts long-term remission after discontinuation of anti-TNF therapy in Crohn's disease. Scand J Gastroenterol 2013;48:311–319.
19. Echarri A, Ollero V, Rodriguez JA, et al. P403 Predictors of relapse after discontinuing anti-TNF therapy in Crohn's disease patients on deep remission. J Crohns Colitis 2013; 7:S171.
20. Dai C, Liu WX, Jiang M, et al. Mucosal healing did not predict sustained clinical remission in patients with IBD after discontinuation of one-year infliximab therapy. PLoS One 2014;9: e110797.
21. Ampuero J, Rojas-Feria M, Castro-Fernández M, et al. Remission maintained by monotherapy after biological+ immunosuppressive combination for Crohn's disease in clinical practice. J Gastroenterol Hepatol 2016;31:112–118.
22. Parisi I, Vega R, McCartney S, et al. PWE-014 Anti-TNF withdrawal in IBD remission: relapse, restart and outcomes. Gut 2016;65:A144.
23. Hu H, Xiang C, Qiu C, et al. Discontinuation of scheduled infliximab in Crohn's patients with clinical remission: a retrospective single-center study. Gastroenterol Res 2017; 10:92–99.
24. Zheng D, Mao R, Chen B, et al. P402 Discontinuation of short-term infliximab maintenance therapy in patients with Crohn's disease: outcomes and risk factors associated with relapse. J Crohns Colitis 2017;11(Suppl 1):S281–S282.
25. Bohn Thomsen S, Kiszka-Kanowitz M, Theede K, et al. Optimized thiopurine therapy before withdrawal of anti-tumour necrosis factor-α in patients with Crohn's disease. Eur J Gastroenterol Hepatol 2018;30:1155–1158.
26. Waugh AW, Garg S, Matic K, et al. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. Aliment Pharmacol Ther 2010;32:1129–1134.
27. de Suray N, Salleron J, Vernier-Massouille G, et al. P274 Close monitoring of CRP and fecal calprotectin levels to predict relapse in Crohn's disease patients. A sub-analysis of the STORI study. J Crohns Colitis 2012;6(Suppl 1):S118–S119.
28. Rajca S, Grondin V, Louis E, et al. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. Inflamm Bowel Dis 2014; 20:978–986.
29. Ternant D, Berkane Z, Picon L, et al. Assessment of the influence of inflammation and FCGR3A genotype on infliximab pharmacokinetics and time to relapse in patients with Crohn's disease. Clin Pharmacokinet 2015;54:551–562.
30. Reenaers C, Mary JY, Nachury M, et al. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. Clin Gastroenterol Hepatol 2018; 16:234–243 e2.