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Review Article

Discontinuation of Anti-Tumour Necrosis Factor Therapy in Patients with Perianal Fistulizing Crohn's Disease: Individual Participant Data Meta-Analysis of 309 Patients from 12 Studies

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Abstract

Background: The risk of relapse after anti-tumour necrosis factor [TNF] therapy discontinuation in Crohn's disease patients with perianal fistulas [pCD] is unclear. We aimed to assess this risk.

Methods: A systematic literature search was conducted to identify cohort studies on the incidence of relapse following anti-TNF discontinuation in pCD patients. Individual participant data were requested from the original study cohorts. Inclusion criteria were age ≥16 years, pCD as a (co) indication for start of anti-TNF therapy, more than three doses, and remission of luminal and pCD at anti-TNF discontinuation. The primary outcome was the cumulative incidence of CD relapse using Kaplan–Meier estimates. Secondary outcomes included response to re-treatment and risk factors associated with relapse as assessed by Cox regression analysis.

Results: In total, 309 patients from 12 studies in ten countries were included. The median duration of anti-TNF treatment was 14 months [interquartile range 5.8–32.5]. Most patients were treated for pCD without active luminal disease [89%], received first-line anti-TNF therapy [87%], and continued immunomodulatory therapy following anti-TNF discontinuation [78%]. The overall cumulative incidence of relapse was 36% (95% confidence interval [CI] 25–48%) and 42% [95% CI 32–53%] at 1 and 2 years after anti-TNF discontinuation, respectively. Risk factors for relapse included smoking (hazard ratio [HR] 1.5 [1.0, 2.1]) and history of proctitis (HR 1.7 [1.1, 2.5]). The overall re-treatment response rate was 82%.

Conclusions: This individual participant data meta-analysis, on predominantly patients with pCD without active luminal disease and first-line anti-TNF therapy, shows that over half of patients remain in remission 2 years after anti-TNF discontinuation. Therefore, anti-TNF discontinuation may be considered in this subgroup.

Key Words: Crohn's disease; perianal fistulizing disease; anti-TNF therapy; discontinuation

1. Introduction

Perianal fistulas are associated with considerable morbidity and affect up to half of Crohn's disease [CD] patients during the disease course.[1] Treatment of perianal fistulizing CD [pCD] has evolved considerably over the last few decades. Anti-tumour necrosis factor [TNF] agents in combination with surgery are the mainstay of treatment.[2,3] However, despite their efficacy, safety profiles are concerns of long-term exposure to anti-TNF agents, and include infusion reactions, infections, skin diseases and possibly increased risk of melanoma.[4] In addition, treatment with anti-TNF drugs is associated with work productivity loss and chronic fatigue. Direct and indirect healthcare costs remain considerable despite the advent of biosimilars.[5] Altogether, the decision on discontinuation of anti-TNF therapy remains a dilemma.

In routine practice, anti-TNF therapy is infrequently withdrawn in patients with pCD for several reasons including risk of relapse, possible lower response rates after re-treatment with anti-TNF therapy and limited remaining treatment options. Available studies have reported inconsistent results on the relapse rates following anti-TNF discontinuation in patients with pCD. Some previous studies showed that pCD was associated with an increased risk of relapse as compared to luminal CD. Other studies did not report a difference between the two phenotypes.[6–9] Important drawbacks for interpretation of the available literature includes small sample size, varying endpoints, and combined analysis of perianal and other [entero-enteric] fistulas.

Therefore, the risk of relapse following anti-TNF discontinuation in patients with pCD is still debated. In this study we performed a meta-analysis of individual participant data [IPD-MA] and aimed to assess the risk of relapse after anti-TNF therapy discontinuation in patients with pCD in remission. The secondary aim was to evaluate response after re-treatment and to identify risk factors for relapse.

2. Methods

An IPD-MA of published studies was conducted using the Meta-analysis Of Observational Studies in Epidemiology [MOOSE] checklist including specifications for the reporting of a meta-analysis of observational studies.[10] Additionally, the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis [PRISMA] were followed.[11] The study protocol was approved by the Medical Ethical Review Committee of Erasmus MC—University Medical Center Rotterdam [number: MEC-2019-0359].

2.1 Search strategy

A comprehensive systematic literature search was conducted until July 2022 in Medline, Embase, the Cochrane database, Google Scholar and Web of Science in collaboration with the Medical School Library of the Erasmus University Rotterdam, the Netherlands. The literature search was conducted using controlled vocabulary supplemented with key words [Supplementary Figure 1]. Studies reporting on the effect of anti-TNF therapy discontinuation in CD patients with perianal fistulas were considered eligible. The retrieved studies were screened and selected by three independent reviewers [STBH, MC and LJ].

2.2 Study selection and IPD database

Studies reporting on the incidence of relapse after discontinuation of anti-TNF therapy in patients with CD were selected. Studies were included if full text was available in English. Abstracts published on international congresses were included as well. In case of incomplete data in abstracts, corresponding authors were contacted and requested for the complete data. Editorials and [systematic or narrative] reviews were excluded. For each selected study, the corresponding authors of the eligible cohort studies were contacted to request IPD.

After obtaining the IPD, inclusion criteria for further analyses comprised patients aged ≥16 years, perianal fistulizing disease as the (co)indication for start of anti-TNF therapy, three or more infusions of anti-TNF therapy, and remission of both luminal and pCD at the time of discontinuation of anti-TNF therapy. Patients with rectovaginal fistulas, non-fistulizing perianal lesions or fistulas unrelated to CD were excluded. In addition, patients who discontinued anti-TNF therapy for other reasons, i.e. primary or secondary non-response, were excluded. If IPD reported only perianal disease, the authors were asked to specify for perianal fistulas.

CD luminal remission was defined as clinical, biochemical or endoscopic/radiological disease remission at baseline, i.e. Crohn's Disease Activity Index [CDAI] < 150/Physicians' Global Assessment [PGA] 0/Harvey Bradshaw Index [HBI] < 5; and/or faecal calprotectin [FC] < 150 µg/g/C-reactive protein [CRP] < 10 mg/L; and/or endoscopic remission defined as a simple endoscopic score for Crohn's disease [SES-CD] 0–2/Rutgeerts' score 0–1/no ulcerations or mucosal healing Crohn's disease index of severity [CDEIS] < 3.

Remission of perianal fistula was defined as complete fistula closure at clinical examination, i.e. absence of anal pain and draining fistula despite gentle compression [Fistula Drainage Assessment score[12]] of the track by the examiner's finger without a new fistulizing episode, no further discharge from the fistula on firm finger pressure nor signs of perianal inflammation.

Radiological remission of perianal fistula was defined as complete resolution of a previous high signal tract or a subtle, narrow-calibre intermediate signal residual tract, or if pelvic magnetic resonance imaging demonstrated that the perianal fistula tracts showed no signs of activity and were without local complications.

Eventually, patients were subdivided into two groups with regard to disease activity at the start of anti-TNF therapy: [1] patients with parallel luminal disease activity and [2] without luminal disease activity at the start of anti-TNF therapy.

2.3 Data collection

Patient characteristics and disease-specific demographics [including gender, age, disease characteristics according to the Montreal classification, smoking status, treatment history, maintenance of immunosuppressive therapy after anti-TNF discontinuation and history of IBD-related surgery] and fistula characteristics (including type of perianal fistula [simple or complex], number of fistulae, prior antibiotics as treatment for perianal fistulas, perianal surgery [incision and drainage of perianal abscess, examination under anaesthesia, seton insertion, fistuolotomy, defunctioning surgery and proctectomy/proctocolectomy], prior abscess, seton or proctitis) were collected. Indication to start anti-TNF therapy was collected including both active luminal and perianal fistulizing disease or only perianal fistulizing disease without active luminal disease. Simple fistula was defined as a fistula

with only a single external opening without pain or fluctuation suggestive of perianal abscess, and was low in position (superficial, low inter-sphincteric or low trans-sphincteric origin) and had no evidence of anorectal stricture. Complex fistulas were defined as fistula[s] with multiple external openings with associated perianal abscess and were high in position [high inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra-sphincteric origin of the fistula tract] according to the American Gastroenterological Association (AGA).[13]

2.4 Outcomes and definitions

The primary outcome was perianal or luminal relapse. As a secondary outcome, perianal and luminal relapses were assessed separately. Perianal fistulizing relapse was defined as recurrence of a draining perianal fistula related to previous or the development of new fistula tracks, or an abscess. Luminal relapse was defined as a clinical, biochemical, endoscopic and/or radiological relapse requiring treatment or dose optimization of inflammatory bowel disease [IBD] medication or surgery. Other secondary outcomes included success of re-treatment with anti-TNF therapy and predictors of relapse. Success of re-treatment was defined as the absence of clinical symptoms [HBI < 5 or CDAI < 150 points], biochemical remission [FC < 250 µg/g and CRP < 5 mg/L], endoscopic/radiological remission [no sign of active inflammation] or complete fistula closure [no further discharge from the fistulas after manual pressure] during follow-up.

2.5 IPD integrity

Data were checked on inconsistency, invalid, missing or out-or-range values and these were queried and resolved with the corresponding authors. Data management was performed following published guidelines supported by the Amsterdam University Medical Centre directive for data management and incorporation of new European legislation on privacy protection.[14]

2.6 Quality of evidence assessment and risk of bias

Quality of evidence assessment and risk of bias were assessed by three investigators [STBH, MC and LJ] using the prediction model risk of bias assessment tool [PROBAST][15] and the Newcastle–Ottawa Quality Assessment Form for Cohort Studies [NOS].[16]

2.7 Statistical analyses

Descriptive statistics were used for baseline characteristics. Continuous variables were summarized with medians and interquartile ranges [IQRs] and categorical data were summarized with frequencies and percentages. Missing values were assumed to be missing at random and were imputed using the mice algorithm,[17] exploiting the correlations between variables. As some of the data were interval-censored, the Turnbull estimator was used to estimate the cumulative incidence of relapse within each cohort. Subsequently, the 1- and 2-year relapse rates were pooled across cohorts in a random effects meta-analysis. The heterogeneity between cohorts was quantified using the I^2-statistic.[18] In an exploratory secondary analysis, we estimated the cumulative incidence of each type of relapse in the pooled cohorts with available relapse type data, using a Fine and Gray model to account for competing risks.[19] To identify predictors for relapse after discontinuation of anti-TNF therapy, univariable hazard ratios [HRs] with 95% confidence intervals [CIs] were estimated. A stratified Cox proportional hazards model was used that accounted for interval censored data.[20] Predictors whose univariable HR had a p-value <0.2 were included in a multivariable stratified Cox model to estimate multivariable (adjusted) HRs. Small cohorts with fewer than 18 patients were merged in Cox regression analyses. Finally, we investigated the association between individual fistula characteristics and time to relapse in the subgroup of patients with active perianal fistula and in luminal remission at the start of anti-TNF. To this end, we again used a stratified Cox model to estimate univariable HRs, in cohorts where fistula characteristics were available. A p-value of <0.05 was considered statistically significant, without correction for multiple comparisons. Data analyses were performed using IBM SPSS Statistics for Windows, version 25.0 and R version 4.0.3.[21]

3. Results

3.1 Identification of studies

The electronic search retrieved a total of 418 publications, of which 113 articles were excluded due to duplication [Supplementary Figure 2]. In total, 305 articles were selected for a more thorough review. Sixteen studies fulfilled the eligible criteria after screening of titles and abstracts. After contacting the corresponding authors, the IPD were obtained from 12 studies [Supplementary Figure 2]. Four studies were excluded due to unavailability of IPD, no response or no database received [Supplementary Table 1, Supplementary Figure 2]. The cohorts were from Europe (ten studies) and Asia (two studies) [Supplementary Table 2]. Two studies were considered prospective and ten retrospective. Finally, IPD were obtained from 366 patients, of whom 309 were included [Supplementary Figure 3]. With regard to the methodological quality, studies scored between 6 and 7 stars (maximum of 9) according to the NOS [Supplementary Table 3].

3.2 Patient characteristics

A minority of patients [n = 34/307, 11%] had active luminal disease at the start of anti-TNF treatment. The median follow-up time after discontinuation was 29 months (interquartile range [IQR] 12–62) [Table 1]. For further analyses, percentages are mentioned on patients with available data. In total, 129/287 [45%] patients were male. Median age at anti-TNF discontinuation was 34 years [IQR 26–44] and the median disease duration was 6 years [IQR 3–11] [Table 1]. Thirty-seven of 281 [13%] patients were previously exposed to anti-TNF therapy [second or third line of anti-TNF therapy]. The median duration of anti-TNF exposure before discontinuation was 14 months [IQR 6.0–33]. Regarding anti-TNF agent use prior discontinuation, 259/309 [84%] patients discontinued infliximab and 49/309 [16%] adalimumab. Concomitant therapy with an immunomodulatory was continued in a majority of patients [234/300, 78%] following anti-TNF discontinuation [Table 1]. Based on the available data, complex fistulas were reported in 85/133 [64%] patients. In the past medical history, 56/96 [58%] patients had been diagnosed with proctitis, 69/101 [68%] had a seton and 75/140 [54%] had an abscess in the past [Table 2].

Table 1. Baseline patient characteristics

Parameter		*N* = 309
Age	Median [IQR]	33.6 [26.4–43.9]
Sex, female, *n* = 287	*n* [%]	129 [45]
Smoking, *n* = 293	*n* [%]	97 [33]
Disease duration, years	Median [IQR]	6.0 [2.80–11.3]
Follow-up time, months	Median [IQR]	29.0 [12.0–621.5]
Age, Montreal classification		
<16 years [A1]	*n* [%]	36 [12]
16–39 years [A2]	*n* [%]	229 [74]
≥ 40 years [A3]	*n* [%]	44 [14]
Disease location, *n* = 298		
Ileum [L1]	*n* [%]	44 [15]
Colon [L2]	*n* [%]	121 [41]
Ileocolonic [L3]	*n* [%]	133 [45]
+ upper GI involvement [L4]	*n* [%]	14 [5]
Disease behaviour, *n* = 269		
Non-stricturing, non-penetrating [B1]	*n* [%]	150 [56]
Stricturing [B2]	*n* [%]	37 [14]
Penetrating [B3]	*n* [%]	82 [31]
Only perianal fistulizing disease	*n* [%]	11 [4]
Previous intestinal resections[a], *n* = 286	*n* [%]	139 [49]
Duration anti-TNF therapy, months	Median [IQR]	13.5 [5.8–32.5]
Use of anti-TNF agent prior cessation, *n* = 308		
Adalimumab	*n* [%]	49 [16]
Infliximab	*n* [%]	259 [84]
Previous anti-TNF exposure, *n* = 279	*n* [%]	37 [13]
Concomitant medication continued after anti-TNF cessation, *n* = 300	*n* [%]	234 [78]
Thiopurines	*n* [%]	215 [92]
MTX	*n* [%]	11 [5]
Unknown	*n* [%]	8 [3]

n, Number of patients; CD, Crohn's disease; L, location; B, behaviour; E, extent; TNFα, tumour necrosis factor alpha.
[a]Including surgery for perianal diseases [i.e. incision and drainage of perianal abscess, examination under anaesthesia, seton insertion, fistuolotomy, defunctioning surgery and proctectomy/proctocolectomy].

Table 2. Fistula characteristics

Parameter		*n* = 309
Type, *n* = 133		
Simple	*n* [%]	48 [36]
Complex	*n* [%]	85 [64]
Missing	*n* [%]	176 [57]
Previous use of antibiotics, yes, *n* = 122	*n* [%]	82 [67]
Missing	*n* [%]	187 [61]
Number of fistulas, *n* = 87	Median [IQR]	1 [1–2]
Missing	*n* [%]	222 [72]
Previous surgery for fistulizing disease, yes, *n* = 128	*n* [%]	79 [62]
Missing	*n* [%]	181 [59]
Abscess in past, *n* = 140	*n* [%]	75 [54]
Missing	*n* [%]	169 [55]
Seton in past, *n* = 101	*n* [%]	69 [68]
Missing	*n* [%]	208 [67]
Proctitis in past, yes, *n* = 96	*n* [%]	56 [58]
Missing	*n* [%]	213 [69]

3.3 Outcomes after discontinuation of anti-TNF therapy

A total of 168/309 [54%] CD patients relapsed after discontinuation of anti-TNF therapy with a median time to relapse of 11.0 months [IQR 5.0–26.9]. The non-stratified cumulative incidence of relapse was estimated at 0.31 [0.28, 0.35] and 0.43 [0.40, 0.47], respectively, at 1 and 2 years after treatment discontinuation [Figure 1]. A meta-analysis of the pooled cohorts resulted in overall cumulative incidence estimates of 0.36 [0.25, 0.48] and 0.42 [0.32, 0.53] at 1 and 2 years, respectively [Figure 2]. The heterogeneity in observed relapse rates was high between studies (I^2 = 91% and 90% respectively).

3.4 Relapse of perianal and luminal CD

Regarding type of relapse, 75/168 [45%] patients developed a relapse of pCD after discontinuation of anti-TNF therapy after a median follow-up of 11 months [IQR 2.8–24.3]. Among these patients, 58/75 [77%] experienced perianal fistulizing relapse, 16/75 [21%] had both perianal fistulizing relapse and anal abscess whereas 1/75 [1%] had an anal abscess only. In total, 25/168 [15%] patients experienced relapse of pCD in combination with relapse of luminal CD after discontinuation of anti-TNF therapy. In the pooled cohorts where relapse type was recorded, cumulative incidences for relapse of perianal disease were 25% [21–34%] and 36% [30–46%] at 1 and 2 years, respectively [Figure 3].

Regarding luminal relapses, 32/168 [19%] patients developed a relapse of only luminal CD after discontinuation of anti-TNF therapy with a median time to relapse of 13.1 months [IQR 5.1–41.4]. Estimated cumulative incidences for luminal relapse were 7% [4–12%] and 11% [6–14%] at 1 and 2 years, respectively, after discontinuation of anti-TNF therapy, in the cohorts where relapse type was known [Figure 3].

Sensitivity analyses were performed including all patients in whom the type of relapse was unknown. During follow-up, 60 patients [19%] experienced a relapse, but without data specifying type of relapse. We examined two scenarios. In the first, we analysed all cohorts, assuming that all patients with unknown type of relapse experienced a relapse of perianal fistulizing CD. This resulted in estimated cumulative incidences of relapse with perianal disease of 22% and 31% at 1 and 2 years, respectively. The cumulative incidence of exclusively luminal relapses was 5% at 1 year and 7% at 2 years in this scenario.

Second, we investigated the scenario where all patients with unknown type of relapse did not experience perianal disease. These patients are assumed to have experienced only luminal relapses. In this case, the cumulative incidence of relapse with perianal disease was 15% at 1 year and 21% at 2 years. For luminal relapse without perianal disease, the cumulative incidence was estimated to be 15% at 1 year and 22% at 2 years.

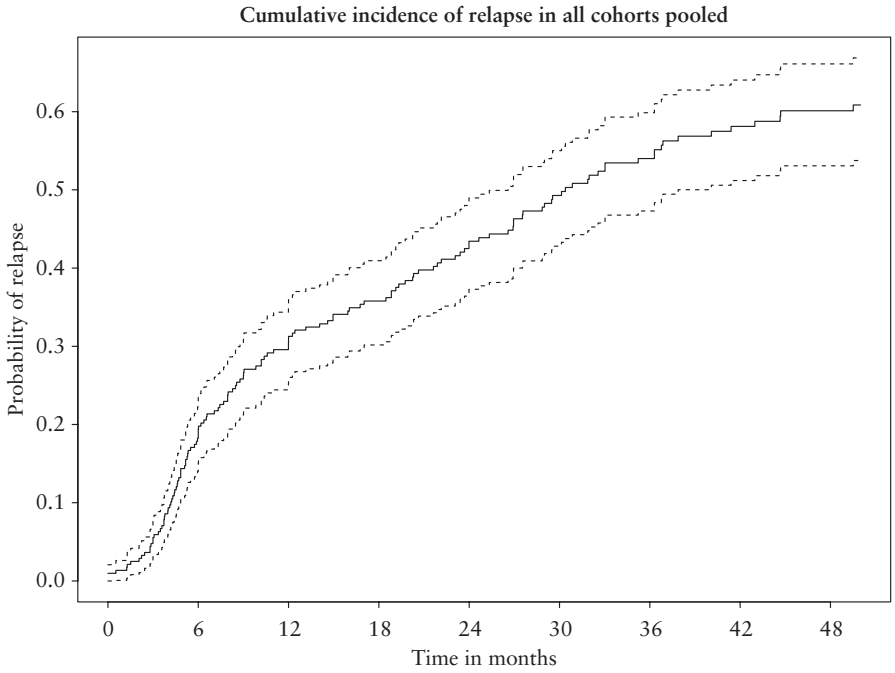

Figure 1. Cumulative probability of relapse after discontinuation of anti-TNF therapy in perianal fistulizing CD patients [all cohorts pooled].

3.5 Factors associated with relapse

The association between baseline characteristics and the rate of relapse was evaluated in a univariable analysis [Figure 4, Supplementary Table 4]. Our multivariable analysis included age at diagnosis, the duration of anti-TNF therapy in months, gender, smoking, disease behaviour, disease location and upper gastrointestinal involvement (L4). By using multivariable analysis, smoking was significantly associated with relapse (HR 1.48 [1.04, 2.10]) [Figure 4, Supplementary Table 4]. Maintenance therapy with immunomodulators and prior surgery were not associated with the risk of relapse.

The association between fistula characteristics and relapse risk was assessed in a univariable analysis of the cohorts where at least one fistula characteristic had been recorded (n = 166) [Figure 5a, Supplementary Table 5a]. The number of fistulas (HR 1.11 [0.96, 1.28] per additional fistula), a history of perianal abscess (HR 1.50 [0.99, 2.28]) and a history of proctitis (HR 1.65 [1.09, 2.48]) were associated ($p < 0.2$) with relapse. In a subgroup of patients with only perianal fistulizing disease and in luminal remission at the time of start of anti-TNF therapy [n = 144], a history of abscesses (HR 1.39 [0.89, 2.16]) and a history of proctitis (HR 1.62 [1.02, 2.59]) were associated with an increased risk of relapse [Figure 5b, Supplementary Table 5b]. A history of proctitis significantly increased the risk of relapse in both analyses.

3.6 Re-treatment with anti-TNF therapy

Among the patients with either fistulizing or luminal relapse after discontinuation of anti-TNF therapy, 109 were re-treated with an anti-TNF agent. Infliximab was used in 77/109 [71%] patients and adalimumab in 32/109 patients [29%]. The median duration of follow-up after re-treatment with anti-TNF therapy was 3.5 years [IQR 0.73–7.22]. Overall, anti-TNF re-treatment was effective in 82% of the patients [79/96] [Supplementary Table 6]. In total, 90/109 [83%] patients were re-treated with the same anti-TNF agent. Re-treatment was effective in 67/79 [85%] and 12/17 [71%] for patients treated with the same anti-TNF agent and patients treated with another agent, respectively [p = 0.174].

4. Discussion

Since perianal fistulizing CD is associated with a high disease burden, withdrawal of anti-TNF therapy following disease remission remains a clinical dilemma. According to this IPD-MA, approximately half of the patients with perianal fistulizing disease experience a relapse of either luminal or pCD within 2 years following anti-TNF discontinuation. Re-treatment with anti-TNF agents in patients who experienced a relapse following anti-TNF discontinuation was effective in the vast majority of patients. Risk factors for disease relapse comprised smoking and a history of proctitis. Since the data presented are mostly from patients in remission with perianal fistula without active luminal disease at the start of anti-TNF therapy and after receiving a first-line anti-TNF treatment, a strategy of anti-TNF discontinuation may be considered for this selected sub-group of patients. To further assess this strategy, more data on the comparison of discontinuation of anti-TNF therapy with continuation of therapy are required.

The majority of the included patients in this IPD-MA may have had a favourable prognostic phenotype of pCD at baseline, which is illustrated by, for instance, the relatively short duration of anti-TNF therapy, the first line of anti-TNF therapy and in a subgroup of patients a median number of fistula tracts of one. A higher rate of sustained remission after anti-TNF discontinuation in this subgroup of patients, as compared to the total population of pCD patients, seems likely, since the fistula complexity (both the number of fistula tracts as well as the anatomical location, classified into simple vs complex fistula tracts) determines the effectiveness of anti-TNF therapy on pCD.[29] Therefore, it must be acknowledged that the findings in this study refer to a selected patient population and cannot be generalized to all pCD patients.

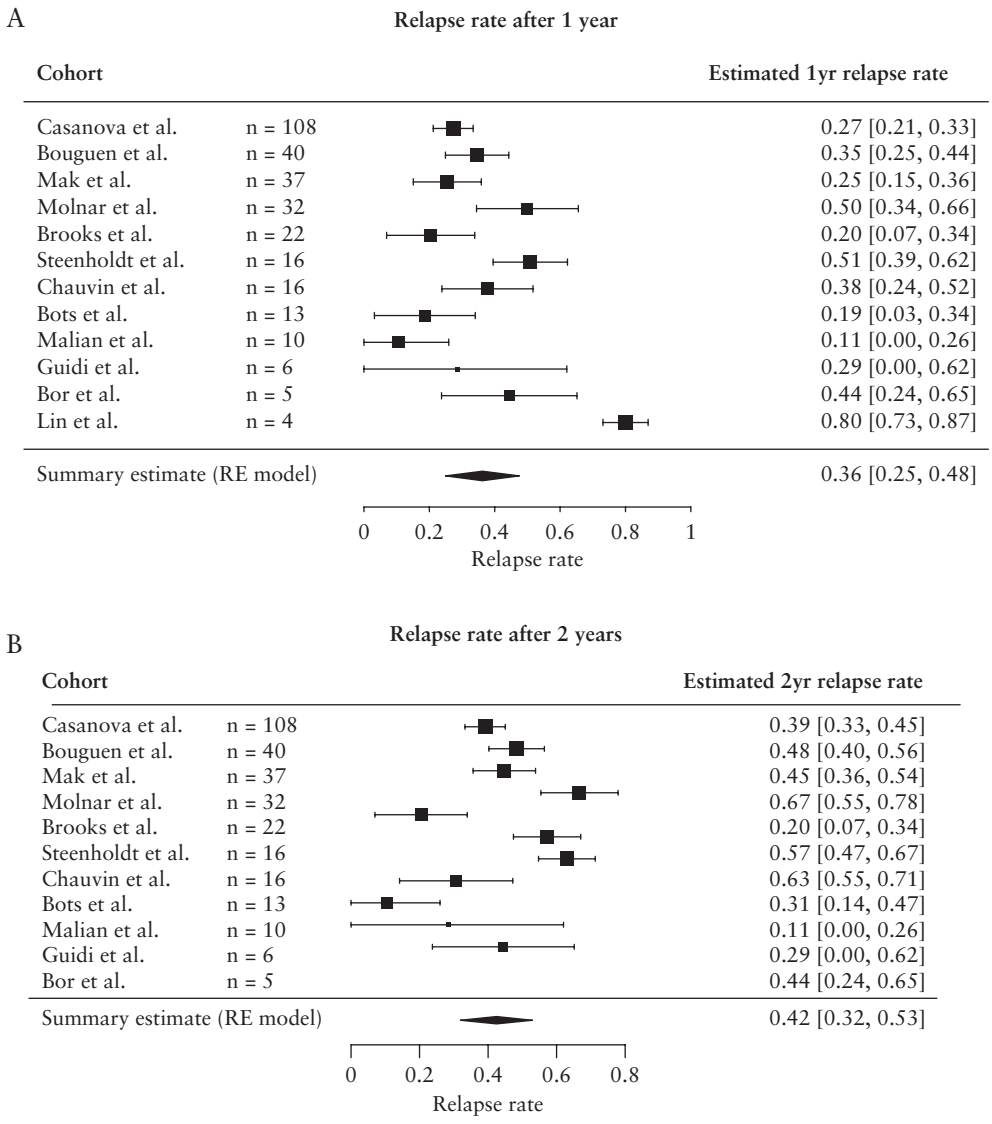

Figure 2. Stratified meta-analysis of relapse rates at 1 year [a] and 2 years [b] after cessation of anti-TNF therapy.

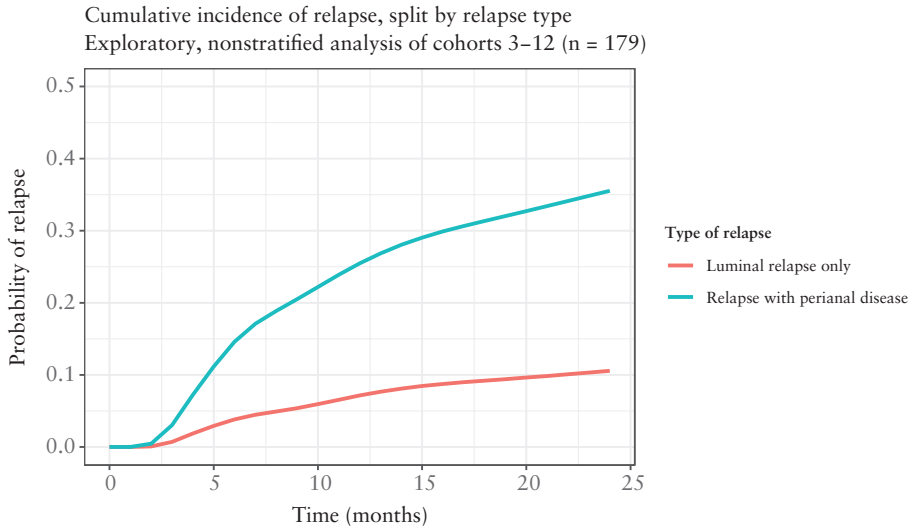

Figure 3. Cumulative probability of relapse after discontinuation of anti-TNF therapy in perianal fistulizing CD patients split by relapse type.

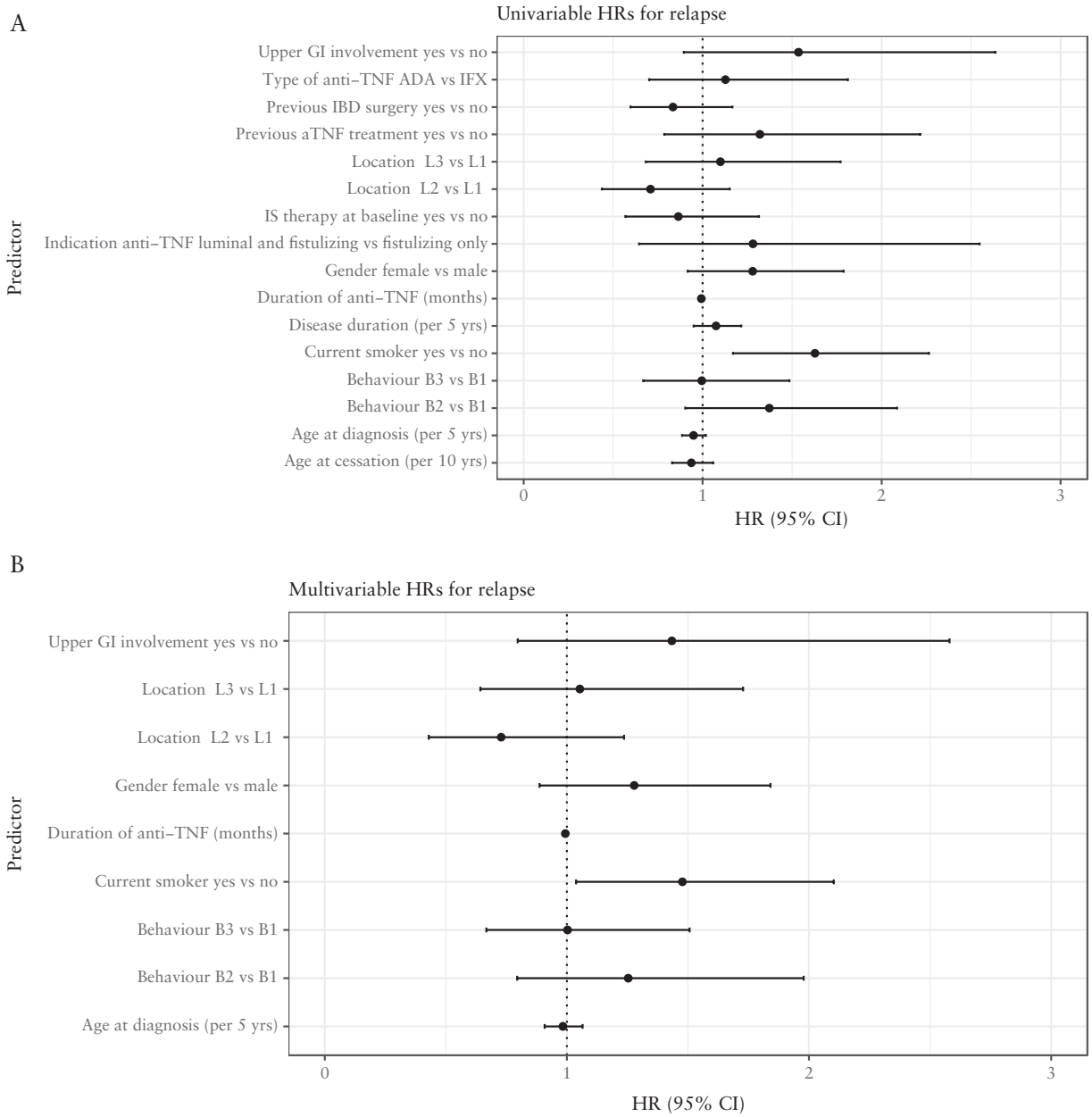

Figure 4. Forest plot of the predictors and their hazard ratios [HRs] for relapse resulting from univariable [a] and multivariable [b] stratified Cox-regression analysis of all included cohorts [*n* = 311].

Previous studies have shown that patients with a higher number of fistula tracts were less likely to achieve clinical remission following anti-TNF treatment and that complex fistulas were associated with a decreased change of long-term healing as compared to simple fistulas.[22,23] Since this IPD-MA also included patients with only one fistula tract at baseline, these results may not be extrapolated to the population with perianal fistulizing CD as a whole since in patients with multiple fistula tracts, anti-TNF therapy is less likely to be discontinued. Further data on patients with more complex perianal fistulizing CD with details on the fistula tracts are required to enhance risk stratification as a prerequisite for clinical decision-making on anti-TNF therapy discontinuation.

Healing of the skin but prior complete closure of the internal fistula tract is a relevant clinical issue in treating perianal fistulas. Further discrimination of patients with pCD for anti-TNF discontinuation may, therefore, be guided by the finding of closure of the fistula tract at imaging, with either anal endosonography [AE] or magnetic resonance imaging [MRI]. A previous study showed that radiological healing is slower than clinical healing with a time lag of 1 year.[22] After 1 year of follow-up, low disappearance of fistula tracts on adequate AE or MRI despite clinical remission on therapeutic response to anti-TNF agents was reported. In addition, patients with persistent fistula tracts showed higher fistula recurrence rates than patients with disappearance at imaging. In addition, a small prospective study showed that once internal fistula healing was observed on MRI, the fistulas remain healed after anti-TNF discontinuation.[24] Since both AE and MRI are sensitive methods to assess this deep tissue healing, use of these imaging techniques rather than clinical remission

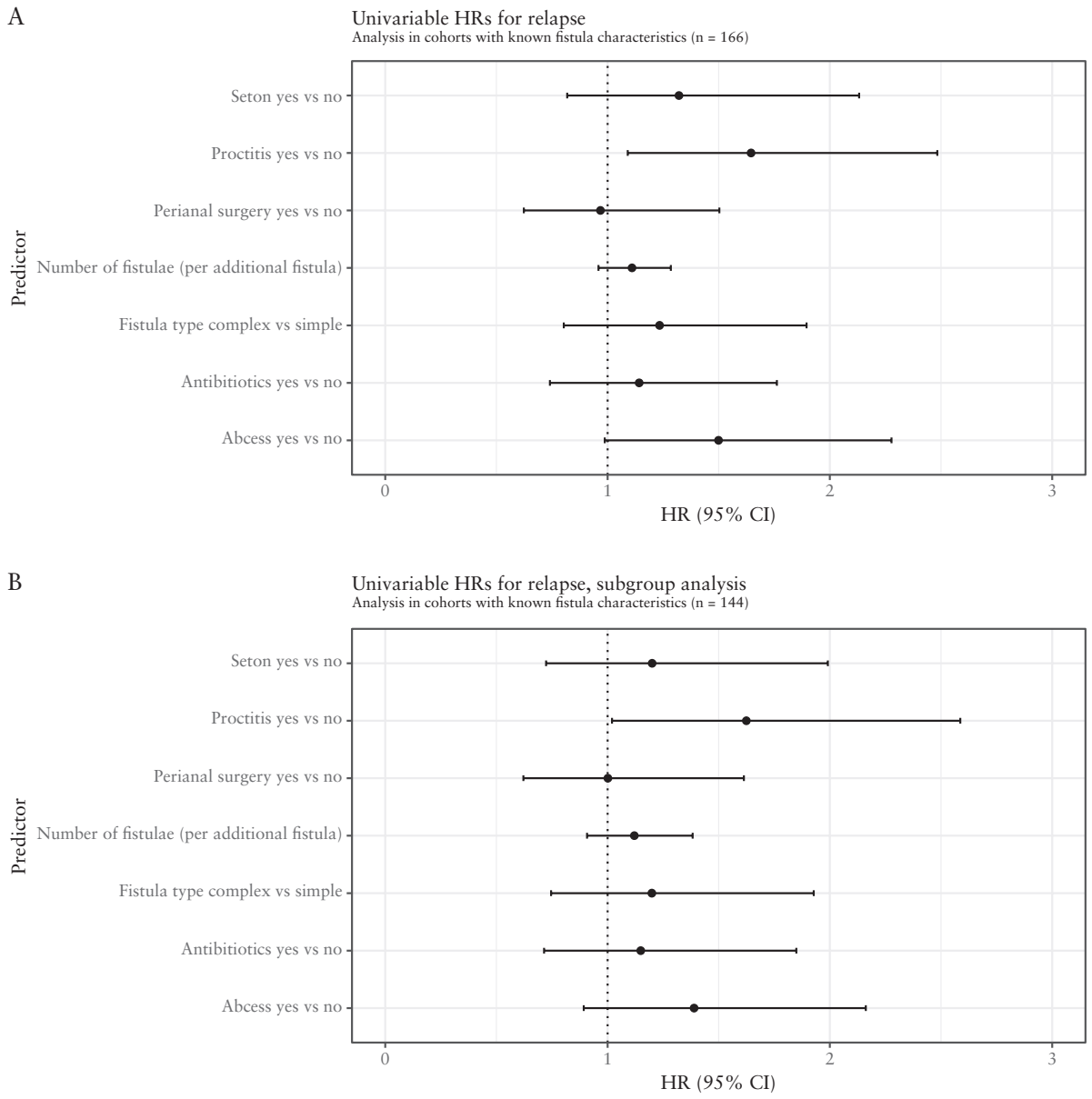

Figure 5. [a] Forest plot of fistula characteristics and their hazard ratios [HRs] for relapse in all cohorts where fistula characteristics were recorded [*n* = 166]. [b] Forest plot of fistula characteristics and their hazard ratios [HRs] for relapse in all cohorts where fistula characteristics were recorded, in the subgroup of patients with perianal fistulizing disease and in luminal remission at the time of start anti-TNF therapy [*n* = 144].

and/or physical examination alone has been suggested prior to anti-TNF discontinuation.[22,25] Unfortunately, this IPD-MA is hampered by the lack of MRI data. It may well be that patients in clinical remission without radiological remission are at an increased risk of relapse. The predictive value of fistula closure on MRI prior to anti-TNF discontinuation requires further study.

In this IPD-MA, smoking was associated with a higher risk of relapses of perianal or luminal disease activity in patients with CD after anti-TNF discontinuation. Our results again underline the importance of emphasizing the negative consequences of smoking. This is in line with observations on a more complicated disease course of CD in smokers, including a higher rate of relapse, need for biological therapy and hospitalization.[26] In addition, active proctitis in the presence of perianal disease might indicate a more severe disease phenotype that decreases the chance of sustained remission after anti-TNF therapy discontinuation, according to this IPD-MA. Finally, most patients continued concomitant immunotherapy when anti-TNF therapy was ceased in this IPD-MA. Relapse rates may be expected to be higher after discontinuation of anti-TNF monotherapy. However, we could not demonstrate a beneficial effect of concomitant therapy with an immunomodulator for the total pCD cohort in this IPD-MA. This finding is in line with the ECCO guideline, which states insufficient evidence for fistula healing induced by immunomodulators or adding immunomodulators to anti-TNF therapy on fistula healing.[27]

Re-treatment with anti-TNF agents in patients who experienced a relapse following anti-TNF discontinuation was effective in over 80% of the patients. This response rate is similar to that of luminal disease only, which was around 80% in a previous report.[28] These data seem reassuring for a decision on anti-TNF discontinuation. In addition, new

therapeutic strategies for pCD have been introduced in recent years, including a possible beneficial effect of ustekinumab on pCD and local stem cell therapy which have been shown to be an effective and safe treatment for perianal fistulas.[29,30] These therapeutic options could be an alternative for patients in whom no response to re-treatment with anti-TNF therapy is achieved.

In light of a recently published new classification system for perianal fistulizing CD which suggests a treatment strategy per class, anti-TNF discontinuation might be considered as an active treatment strategy for patients in class 1 [minimal symptoms and anorectal disease burden, requiring minimal intervention over time] and possibly class 2a [symptomatic fistulae suitable for combined medical and surgical closure or repair with fistula closure as the main goal] over time. However, further discrimination of patients in class 2 is required, guided by radiological healing, into those likely to suffer from relapse and those less at risk, which would allow rational treatment choices.

To our knowledge, this is the first IPD-MA evaluating the risk of relapse after anti-TNF discontinuation in patients with pCD. In addition, this IPD-MA comprises a large patient cohort from different countries. However, some limitations need to be considered when interpreting our data. Due to the retrospective design of most of the included cohorts and the variety of original study aims, some databases of the original study cohorts did not include fistula characteristics. It is most likely that these patients had complex fistulas at the time of anti-TNF introduction since anti-TNF agents are generally indicated for complex perianal fistulas. As mentioned above, data on radiological healing at the time of anti-TNF discontinuation were lacking in most studies. This has limited the evaluation of predictors of a relapse. In addition, given the high rate of immunomodulator continuation following anti-TNF discontinuation, data regarding allergic reactions or immunogenicity would be of interest for further decision-making on treatment discontinuation. Second, the type of relapse was not recorded in most available cohorts. In these cases, it was not possible to distinguish between perianal fistulizing and luminal relapse. To provide insight into the impact of these missing data, we chose to perform a worst case/best case scenario analysis. Finally, the studies included in this IPD-MA encompassed patients over a period of 11 years, probably leading to differences in treatment strategies over time. This may have influenced the varying relapse rates between the included cohorts.

In conclusion, half of patients with perianal fistulizing CD without active luminal disease at the start of anti-TNF therapy and who achieve remission after the first line of anti-TNF therapy remain in remission 2 years after discontinuation of anti-TNF therapy. In addition, the majority of these patients respond to re-treatment with anti-TNF therapy after relapse. Therefore, discontinuation of anti-TNF therapy may be considered in this subgroup of patients with perianal fistulizing CD. Individualized estimation of relapse risk for all other patients with perianal fistulizing CD requires further investigation, with a specific focus on healing of fistula tracts on imaging.

Conference

21st European Crohn's and Colitis Organisation (ECCO), viritual congress, 2021. Digestive disease days, Velthoven, 2021.

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Conflict of Interests

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Author Contributions

Study concept and design: ACV, STBH. Acquisition of individual participant data: STBH, RWMP. Offering the individual participant data: MJC, GB, JM, TM, AL, JS, AA, GDH, PR, LG, RB, WL, LPB. Statistical analysis and interpretation of data: DT, ES. Drafting of the manuscript: STBH, DT. Critical revision of the manuscript for important intellectual content: all authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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** Data from a *post-hoc* analysis of diary data from the double-blind, randomised, placebo-controlled 58-week SELECTION trial. Achievement of stool frequency subscore of ≤1 by Day 3 in biologic-naïve patients, and rectal bleeding subscore of 0 by Day 5 in biologic-experienced patients.[2]
† Interim analysis of SELECTIONLTE assessing the efficacy and safety of open-label JYSELECA 200 mg through LTE Week 144 in completers and LTE Week 192 in non-responders, respectively, representing a total of 3.9 years of treatment each (completers: 58 + 144 weeks; non-responders 10 + 192 weeks).[3]
†† Determined in a *post-hoc* exploratory analysis of the SELECTION trial assessing HRQoL and the comprehensive disease control multi-component endpoint, which comprises both clinical and QoL outcomes, in individuals receiving JYSELECA (n=786).[4] Each patient has their own definition of normal life.

▼ This medicine is subject to additional monitoring.

HRQoL, Health-related quality of life; LTE, Long term extension; QoL, Quality of life; UC, Ulcerative colitis.

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