Journal of Crohn's and Colitis, 2018, 644–652
doi:10.1093/ecco-jcc/jjy021
Advance Access publication February 21, 2018
Original Article

Original Article

Subtherapeutic Infliximab Trough Levels and Complete Mucosal Healing Are Associated With Sustained Clinical Remission After Infliximab Cessation in Paediatric-onset Crohn's Disease Patients Treated With Combined Immunosuppressive Therapy

Ben Kang,[a,b,c] So Yoon Choi,[d] Young Ok Choi,[c] Min-ji Kim,[e] Kyunga Kim,[e] Ji-Hyuk Lee,[f] Yon Ho Choe[c]

[a]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, Korea [b]Crohn's and Colitis Association in Daegu-Gyeongbuk [CCAiD], Daegu, Korea [c]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea [d]Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea [e]Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea [f]Department of Pediatrics, Chungbuk National University College of Medicine, Cheongju, Korea

Corresponding author: Yon Ho Choe, MD, PhD, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Tel.: 82-2-3410-3527; fax: 82-2-3410-0043; email: i101016@skku.edu

Conference presentation: presented at the 12th Congress of the European Crohn's and Colitis Organisation [ECCO], 2017, as a digital oral presentation.

Abstract

Background and Aims: We aimed to investigate the outcome in paediatric-onset Crohn's disease patients who had discontinued infliximab after maintaining clinical remission with combined immunosuppression, and to determine factors associated with clinical relapse.

Methods: We conducted a retrospective observational study of 63 paediatric-onset Crohn's disease patients who had stopped scheduled infliximab during sustained corticosteroid-free clinical remission for at least 1 year with infliximab and azathioprine, and were followed up for at least 1 year thereafter. Cumulative relapse rates and the median time to relapse were estimated statistically. Factors at cessation were also evaluated for their association with clinical relapse.

Results: After a median follow-up period of 4.3 years [range, 1–7.5 years], 60.3% [38/63] of patients had experienced clinical relapse. According to Kaplan–Meier survival analysis, the estimated cumulative relapse rates at 1, 4, and 6 years were 19.0%, 62.2%, and 75.2%, respectively, and the median relapse time was 3.3 years from infliximab cessation. According to multivariate Cox proportional hazard regression analysis, infliximab trough levels of ≥2.5 μg/mL and incomplete mucosal healing were associated with clinical relapse (hazard ratio [HR] = 7.199, 95% confidence interval [CI] = 1.641–31.571, $p = 0.009$ and HR = 3.628, 95% CI = 1.608–8.185, $p = 0.002$, respectively). Although re-treatment with infliximab was effective in 90.9% [30/33] of patients, 7.9% [3/38] eventually underwent surgery within 1 year of relapse.

Conclusions: Considering the high cumulative relapse rates in the long term and cases of severe relapse requiring surgery, discontinuing infliximab in paediatric-onset Crohn's disease patients is currently inadvisable. However, there may be a subgroup of patients who are good candidates for infliximab withdrawal.

Key Words: Infliximab; pharmacokinetics; mucosal healing

1. Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] that can affect the entire gastrointestinal [GI] tract, leading to a disease course of irreversible bowel damage complicated by strictures and fistulas when inadequately treated.[1,2] However, with the introduction of anti-tumour necrosis factor [TNF] agents such as infliximab [IFX] and adalimumab [ADL], patients with CD in all age groups including children and adolescents, have benefited from the use of these agents.[3–6] Moreover, current treatment strategies have evolved to introduce biologics at an early stage of disease, in order to target a window of opportunity before irreversible intestinal damage occurs.[7,8]

A question that clinicians are increasingly faced with in this era of early treatment is related to the feasibility and timing of stopping biologics.[9] Factors such as the cost of medication, potential for serious adverse effects, and possibility that the patient could maintain durable remission off treatment have been stated as reasons to consider discontinuation of anti-TNF agents.[10] However, there are also concerns related to the discontinuation of anti-TNF therapy in CD patients, including the risk of disease relapse, possibility of insufficient effectiveness when the discontinued drug is re-started, risk of infusion reactions and other adverse events at re-treatment, and concerns about losing out on future medical treatment options.[11]

There are currently insufficient data to recommend when and in whom discontinuing anti-TNF treatment is suitable among patients with CD.[12,13] Therefore, in clinical practice, the decision of whether to continue or discontinue biologics is typically based on weighing the risks and benefits for each patient on an individual basis. Currently available data from previous observational studies in adults have indicated that a short duration of remission, endoscopically active disease, high levels of markers of inflammation, and a high IFX trough level [TL] are risk factors for relapse in patients with CD.[14–18]

Despite these studies in adults, there are limited data regarding the clinical course after cessation of scheduled long-term treatment with anti-TNF agents in the paediatric population of CD. Therefore, we aimed to investigate the clinical outcome in paediatric-onset CD patients who had discontinued IFX after maintaining corticosteroid-free clinical remission with combined immunosuppression with azathioprine [AZA], and to reveal risk factors for clinical relapse in these patients. We also aimed to evaluate the effectiveness and possible infusion reactions after re-treatment with anti-TNF agents in those who showed relapse.

2. Materials and Methods

2.1. Patients and data collection

This study was a retrospective observational study conducted at the Department of Pediatrics of Samsung Medical Center between January 2009 and June 2016. Subjects included in this study were paediatric-onset luminal CD patients who had discontinued scheduled IFX after maintaining corticosteroid-free clinical remission with combination treatment with AZA for at least 1 year. Patients with indeterminate-type IBD, those taking IFX indicated for the treatment of refractory perianal fistulas, those aged 18 years or more at IFX initiation, those who discontinued IFX owing to a loss of response, and those who had been lost to follow-up before 1 year, were excluded. CD was diagnosed in accordance with the revised Porto criteria of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.[19] Disease classification and behaviour were based on the Paris classification.[20] This study was approved by the Institutional Review Board of Samsung Medical Center and conducted in accordance with the Declaration of Helsinki.

Baseline clinicodemographic data at diagnosis, including sex, age, disease classification, and family history of IBD, and data at IFX initiation, including duration from diagnosis to IFX, corticosteroid use before IFX, CD-related GI tract surgery before IFX, Pediatric Crohn's Disease Activity Index [PCDAI] at IFX initiation, Simple Endoscopic Score for Crohn's Disease [SES-CD] at IFX initiation, and deep ulcers on ileocolonoscopy at IFX initiation, were collected from electronic medical records. At IFX cessation, data on IFX duration, PCDAI score, white blood cell count, erythrocyte sedimentation rate, C-reactive protein [CRP] level, 6-thioguanine nucleotide [6-TGN] level, IFX TL, presence of antibody to IFX [ATI], and SES-CD were collected. Serum IFX TL and ATI had been measured using an enzyme-linked immunosorbent assay kit [Matriks Biotek Laboratories, Ankara, Turkey]. Clinical remission was defined as PCDAI ≤10, and biochemical remission as CRP <0.5 mg/dL. Complete mucosal healing [MH] was defined as SES-CD = 0, partial MH as SES-CD = 1–2, and endoscopically active disease as SES-CD ≥3. Relapse was defined as clinical relapse corresponding to PCDAI >10 or Harvey–Bradshaw index >4.

2.2. Statistical analysis

Kaplan–Meier survival analysis was used to derive the estimated cumulative relapse rate after IFX cessation during the follow-up period. Univariate and multivariate Cox proportional hazard regression analyses were used to investigate factors associated with relapse after IFX cessation. Factors with p <0.1 on univariate analysis were included in the multivariate analysis. To simplify the model, further analysis was conducted after converting continuous and multiple categorical variables of p <0.1 on univariate analysis into binary categorical variables. A log-rank test was performed to derive the best cut-off value of the continuous variable that stratified patients into two groups. Further investigation was performed in a subgroup of patients who had complete MH at IFX cessation. The results were expressed as hazard ratios [HRs] with 95% confidence intervals [CIs]. The p-value for statistical significance was defined as p <0.05. Statistical analysis was performed using SAS version 9.4 [SAS Institute, Cary, NC, USA].

3. Results

3.1. Baseline characteristics

A total of 73 patients had stopped IFX after a minimum of 1 year of combination treatment with IFX and AZA. Among these patients,

six had stopped IFX owing to a loss of response, and 67 had stopped the medication because of sustained clinical remission after the initiation of combination therapy. Among these 67 patients, four were lost to follow-up before 1 year; thus, 63 patients were included in this retrospective observational study. Endoscopic data with SES-CD and histological data of mucosal biopsies at IFX cessation were available for 57 patients, IFX TL and ATI status at IFX cessation were available for 48 patients, and 6-TGN levels at IFX cessation were available for 42 patients. The baseline characteristics of the study patients are described in Table 1.

Table 1. Baseline characteristics [*n* = 63].

At diagnosis	*n*
Male sex, *n* [%]	47 [75%]
Age at diagnosis [years], median [IQR]	14.9 [13.5–15.4]
Lower GI tract involvement, *n* [%]	
L1	5 [8%]
L2	5 [8%]
L3	53 [84%]
Upper GI tract involvement, *n* [%]	
None	17 [27%]
L4a	12 [19%]
L4b	22 [35%]
L4a+b	12 [19%]
Disease behaviour, *n* [%]	
B1	56 [89%]
B2	5 [8%]
B3	2 [3%]
Perianal fistulas, *n* [%]	37[59%]
First-degree family history of IBD, *n* [%]	3 [5%]
At IFX initiation	
Duration from diagnosis to IFX [months], median [IQR]	1.3 [0.4–4.5]
IFX initiation within 1 month of diagnosis	32 [51%]
IFX initiation within 1 year of diagnosis	58 [92%]
Corticosteroid use before IFX, *n* [%]	12 [19%]
CD related GI surgery, *n* [%]	3 [5%]
PCDAI, mean ± SD	35.0 ± 9.4
SES-CD, mean ± SD	15.6 ± 5.2
Deep ulcers on colonoscopy, *n* [%]	37 [59%]
At IFX cessation	
IFX duration [months], median [IQR]	12 [12–14]
Dose intensification during maintenance IFX, *n* [%]	0 [0%]
PCDAI, median [IQR]	0 [0–2.5]
WBC [/μL], mean ± SD	5820 ± 1560
ESR [mm/hr], median [IQR]	10 [2–15]
CRP [mg/dL], median [IQR]	0.04 [0.03–0.15]
6-TGN [pmol/8 × 10^8 RBC], median [IQR], [*n* = 42]	280.6 [240.7–356.9]
IFX TL, [μg/mL], mean ± SD, [*n* = 48]	3.81 ± 1.84
ATI positive, *n* [%], [*n* = 48]	2 [3%]
Clinical remission, *n* [%]	63 [100%]
Biochemical remission, *n* [%]	58 [92%]
Mucosal healing, *n* [%], [*n* = 57]	
No [SES-CD ≥3]	12 [21%]
Partial [SES-CD = 1–2]	8 [14%]
Complete [SES-CD = 0]	37 [65%]
Histological remission, *n* [%], [*n* = 57]	18 [32%]

IQR, interquartile range; GI, gastrointestinal; L1, distal 1/3 ileum ± limited caecal disease; L2, colonic disease; L3, ileocolonic disease; L4a, upper disease proximal to ligament of Treitz; L4b, upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum; L4a+b, upper disease involvement in both L4a and L4b; B1, non-stricturing non-penetrating behaviour; B2, stricturing behaviour; B3, penetrating behaviour; IBD, inflammatory bowel disease; IFX, infliximab; CD, Crohn's disease; PCDAI, Paediatric Crohn's disease Activity Index; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; 6-TGN, 6-thioguanine nucleotides; TL, trough level; ATI, antibody to infliximab; RBC, red blood cells.

3.2. Relapse rate and factors associated with clinical relapse

After a median follow-up period of 4.3 years [range, 1–7.5 years], 60.3% [38/63] of patients had experienced clinical relapse. According to Kaplan–Meier survival analysis, the estimated cumulative relapse rates at 1, 2, 4, and 6 years were 19.0%, 36.4%, 62.2%, and 75.2%, respectively, and 81.4% at the maximum follow-up period of 7.5 years. The median time to relapse was 3.3 years from IFX cessation [Figure 1].

Univariate Cox proportional hazard regression analysis revealed that the duration from diagnosis to IFX initiation and IFX TL at IFX cessation was positively associated with clinical relapse, and complete MH was negatively associated with clinical relapse compared with partial MH and no MH [Table 2, Figure 2]. Factors that showed a *p*-value of <0.1 on univariate analysis, namely the duration from diagnosis to IFX initiation, IFX TL at IFX cessation, MH at IFX cessation, and histological remission at IFX cessation, were included in the multivariate analysis [Table 2]. According to the multivariate Cox proportional hazard regression analysis, IFX TL and the MH status at IFX cessation were the only factors associated with clinical relapse [Table 2].

According to the log-rank test, the best cut-off values for the continuous variables that showed statistical significance on univariate Cox proportional hazard regression analysis were 2.5 μg/mL for serum IFX TL at IFX cessation and 4.8 months for the duration from diagnosis to IFX initiation [Figure 3]. According to the multivariate Cox proportional hazard regression analysis using statistically significant variables converted into binary categorical variables, a serum IFX TL of ≥2.5 μg/mL at IFX cessation and incomplete MH status were positively associated with clinical relapse [HR = 7.199, 95% CI = 1.641–31.571, p = 0.009, and HR = 3.628, 95% CI = 1.608–8.185, p = 0.002, respectively] [Table 3].

3.3. Relapse rate and factors associated with clinical relapse among patients with complete MH

Further analysis was performed in 37 patients with complete MH at IFX cessation. After a median follow-up period of 3.4 years [range, 1–6.7 years], 37.8% [14/37] of the patients had experienced clinical relapse. According to the Kaplan–Meier survival analysis, the cumulative relapse rates at 1, 2, 4, and 6 years were 5.4%, 17.8%, 43.5%, and 55.5%, respectively, and the median time to relapse was 4.6 years from IFX cessation [Figure 2D]. According to the Cox proportional hazard regression analysis, IFX TL at IFX cessation was the only factor associated with clinical relapse [HR = 1.389, 95% CI = 1.059–1.822, p = 0.018].

3.4. Outcome in patients without clinical relapse

Among the 25 patients who did not experience relapse, complete MH was observed in 23 patients at IFX cessation, and partial MH and no MH were observed in one patient each. Follow-up ileocolonoscopies were conducted in 20 patients at a median of 2.6 years [range, 1.0–6.1 years], among whom 18 patients had complete MH at IFX cessation. Among the 18 patients with complete MH at IFX cessation, complete MH was continuously

observed in 55.6% [10/18], whereas 44.4% [8/18] showed deterioration, with a median SES-CD of 4 [range 3–6]. Among the 10 patients who showed complete MH on follow-up ileocolonoscopies, five had simultaneously undergone magnetic resonance enterography [MRE]. Four of five patients [80%] showed no demonstrable active inflammation on MRE, and one patient showed mild active inflammation. Among the five patients in whom follow-up ileocolonoscopies were not conducted, faecal calprotectin [FC] was measured in three patients, revealing levels of 33.3, 243.2, and 400.2 μg/g, respectively. Among the two patients in whom incomplete MH was observed at IFX cessation, complete MH was observed at follow-up in the patient who showed partial MH at IFX cessation, whereas ulcers were continuously observed in the patient who showed no MH at IFX cessation.

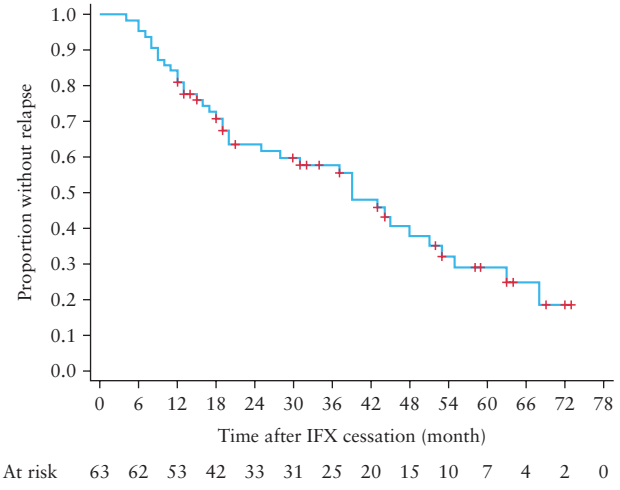

Figure 1. Relapse-free survival curve after infliximab cessation.

3.5. Outcome of re-treatment with IFX in patients with clinical relapse

Among the 38 patients who had experienced clinical relapse after IFX cessation, retreatment with biologics was applied in 36 patients [33 with IFX and 3 with ADL], whereas the AZA dose was increased in two patients. For all patients who were retreated with biologics, treatment was re-induced using scheduled regimens and doses. Re-treatment with IFX was effective in 90.9% of patients [30/33] when assessed post-induction, and in 82.1% [23/28] at 1 year [Figure 4]. A total of 7.9% [3/38] of patients eventually underwent surgery within 1 year of relapse, and one infusion reaction occurred in a patient who had re-started IFX [Figure 4].

4. Discussion

This is the first study to investigate the clinical course as well as the factors associated with clinical relapse after IFX cessation among paediatric-onset CD patients who had maintained corticosteroid-free clinical remission with scheduled IFX treatment and thiopurines for at least 1 year. The present study demonstrated that IFX TLs and complete MH status were the only factors significantly associated

Table 2. Factors Associated with clinical relapse after infliximab cessation.

	Univariate Cox analysis			Multivariate Cox analysis [*n* = 48]		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Sex [female vs male]	1.271	0.597–2.705	0.533			
Diagnosis age	0.945	0.802–1.114	0.503			
Lower GI tract involvement			0.629			
Any colonic involvement [yes vs no]	1.807	0.432–7.556	0.417			
Any terminal ileal involvement [yes vs no]	1.389	0.333–5.792	0.652			
Upper GI tract involvement [yes vs no]	1.199	0.581–2.474	0.624			
B1 disease behaviour [yes vs no]	0.884	0.344–2.273	0.798			
Perianal fistula [yes v no]	0.876	0.456–1.685	0.692			
Duration from diagnosis to IFX initiation	1.033	1.001–1.066	0.046	1.013	0.974–1.052	0.519
Corticosteroid use before IFX [yes vs no]	0.864	0.380–1.965	0.727			
PCDAI before IFX initiation	0.987	0.953–1.022	0.465			
CD-related GI surgery [yes vs no]	1.677	0.395–7.122	0.484			
SES-CD before IFX initiation	1.052	0.984–1.124	0.134			
Deep ulcers on colonoscopy [yes vs no]	1.219	0.628–2.367	0.559			
IFX duration	0.989	0.906–1.080	0.812			
PCDAI at IFX cessation	1.014	0.881–1.166	0.850			
WBC count at IFX cessation	1.057	0.855–1.306	0.611			
ESR at IFX cessation	1.006	0.980–1.033	0.645			
CRP at IFX cessation	1.992	0.477–8.327	0.345			
6-TGN at IFX cessation [*n* = 42]	0.999	0.996–1.002	0.511			
IFX TL at IFX cessation [*n* = 48]	1.319	1.077–1.615	0.008	1.514	1.173–1.955	0.002
MH at IFX cessation [*n* = 57]			<0.001			0.003
Partial vs no	0.696	0.230–2.106	0.4628	0.471	0.102–2.167	0.538
Complete v. no	0.180	0.071–0.460	<0.001	0.098	0.019–0.514	0.003
Histological remission at IFX cessation [yes vs no] [*n* = 57]	0.457	0.188–1.112	0.085	0.623	0.181–2.155	0.460

GI, gastrointestinal; B1, non-stricturing nonp-enetrating behaviour; IBD, inflammatory bowel disease; IFX, infliximab; CD, Crohn's disease; PCDAI, Paediatric Crohn's disease Activity Index; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; 6-TGN, 6-thioguanine nucleotides; MH, mucosal healing; HR, hazard ratio; CI, confidence interval.

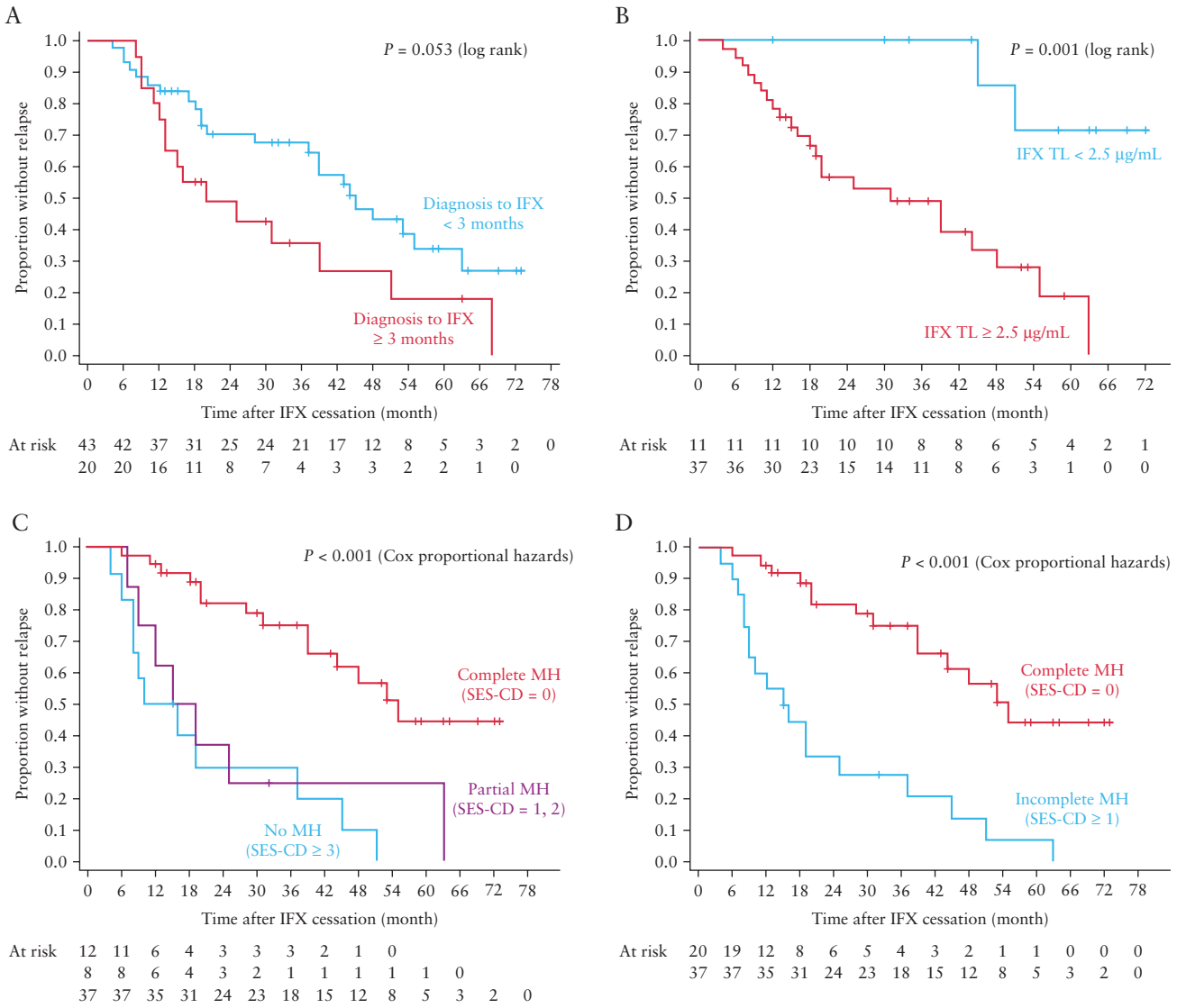

Figure 2. Relapse-free survival according to statistically significant factors on univariate Cox proportional hazard regression analysis.

with sustained clinical remission after IFX cessation in paediatric-onset CD patients.

In contrast to the many large-scale studies in the adult population, only a few small-scale studies to date have investigated the outcomes after cessation of biologics in paediatric-onset CD patients,[21,22] showing a wide variation in the relapse rates. The cumulative probability of relapse after a median of 125 months of follow-up in one study was 14.8% in 27 patients,[21] whereas the relapse rate at 12 months in another study was 61.5% in 13 patients.[22] Meanwhile, the 1- and 2-year relapse rates seem consistent in adult studies that have reported anti-TNF discontinuation with clinical remission, despite the heterogeneous study designs and patient populations and variable use of immunomodulators.[9] According to a recent systematic review, the relapse rates in adult studies were 21.1–39% and 37–55.7% at 1 year and 2 years, respectively, after stopping anti-TNF treatment with clinical remission.[9] The cumulative rates were 49–88% by the end of the follow-up period, and the median time to relapse was 4.8–16.4 months.[9] Although the relapse rate at 1 year in our study [19.0%] was lower than that reported in previous adult studies, the cumulative relapse rate at maximum follow-up [81.4% at 7.5 years] was similar to that in previous studies. The high proportion of patients with an endoscopic remission status in our study, among whom 79% had at least partial MH, may explain this low relapse rate during the first year after IFX cessation. Another potential factor that may have played a role is the short disease duration from diagnosis to IFX initiation [51% of patients had started IFX within 1 month from diagnosis and 92% within 1 year].

Therapeutic strategies in CD have recently evolved to introduce anti-TNF agents at earlier stages, before the development of irreversible and permanent bowel damage.[7,8,23,24] According to recent studies, a shorter interval between the diagnosis of CD and initiation of anti-TNF agents was associated with longer sustained clinical remission.[9,25] Our findings also correlate with these findings, although statistical significance between the duration from diagnosis to IFX initiation and relapse after IFX cessation was observed only in the univariate Cox analysis. However, considering that only those who had sustained corticosteroid-free clinical remission for 1 year were included in the present study, and our previous findings that the incidence of MH is significantly higher in those who had received early combined immunosuppression than in those who had received

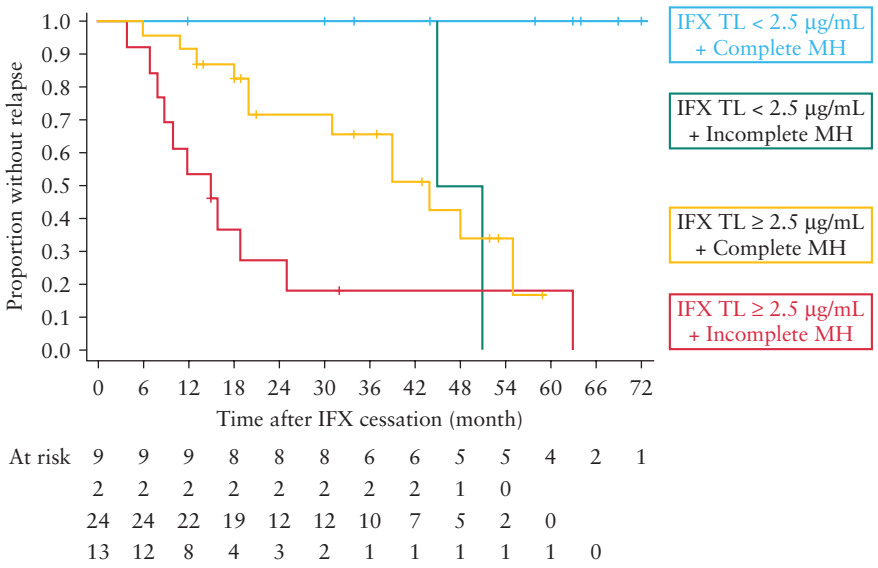

Figure 3. Relapse-free survival according to infliximab trough level and mucosal healing status.

Table 3. Final multivariate Cox model of factors associated with clinical relapse after infliximab cessation.

	HR	95% CI	*p*-Value
Duration from diagnosis to IFX initiation ≥3 months	2.415	0.972–6.004	0.058
IFX TL at IFX cessation ≥2.5 µg/mL	7.199	1.641–31.571	0.009
Incomplete MH at IFX cessation	3.628	1.608–8.185	0.002

IFX, infliximab; TL, trough level; MH, mucosal healing; HR, hazard ratio; CI, confidence interval.

combined immunosuppression through a step-up approach,[8] the effect of early IFX treatment at diagnosis may play a significant role in the clinical course after IFX cessation in patients with sustained clinical remission with combination treatment. This may be attributed to the concept that the early introduction of anti-TNF treatment is associated with the normalisation of dysregulated immunity, less intestinal tissue impairment, and restored mucosal immune homeostasis.[7,26]

Although some studies have failed to reveal an association between MH and relapse after cessation of biologics in CD patients,[27,28] results of a recent meta-analysis have indicated that the relapse rate at 1 year decreased from 42% in CD patients who had stopped anti-TNF treatment based on clinical remission to 26% in those who had discontinued biologics based on both clinical and endoscopic remission.[11] Moreover, recent position statements have advised that discontinuing anti-TNF agents can be attempted in CD patients with clinical and endoscopic remission.[29,30] Meanwhile, although the definition and target degree of MH vary across centres and studies, the currently suggested target in CD regarding MH or endoscopic remission is defined as the resolution of ulceration as seen on ileocolonoscopy, which correlates with an SES-CD of <3.[31] However, our findings demonstrate that partial MH may not be adequate in maintaining clinical remission after IFX cessation. Our findings are consistent with the results of the STORI trial and an observational study from Leuven, Belgium.[15,17] These findings suggest that the treatment goal for MH should aim at the complete amelioration of any active lesions when considering the cessation of biologics in CD patients with a prolonged period of clinical remission. Currently, there is no consensus on the optimal duration of sustained clinical remission required before endoscopic evaluation or de-escalating treatment during combined immunosuppression. Although an endoscopic examination is recommended at 6–9 months after treatment initiation,[31] a one-time identification of complete MH may not be adequate for IFX cessation considering that MH is a cross-sectional outcome. For example, whereas some patients may have had complete MH long before endoscopic evaluation, otherss may have achieved complete MH just before evaluation. Therefore, a two-time identification of endoscopic remission, or a composite remission end-point that incorporates continuous longitudinal biochemical remission in addition to the two endoscopic evaluations, could be a better target in order to maintain remission after de-escalating treatment.

During maintenance treatment with anti-TNF agents, high TLs and low antidrug antibodies are well known to be associated with superior endoscopic outcomes.[32] However, studies on IFX cessation have reported that higher TLs at cessation were associated with disease relapse.[15,17] According to the STORI trial, an IFX TL of ≥2 mg/L was associated with relapse after IFX cessation in a multivariate Cox model [HR = 2.5, 95% CI = 1.1–5.4, p = 0.02].[15] Meanwhile, Papamichael *et al.* reported that an IFX TL of <6 µg/mL was associated with sustained clinical remission after IFX cessation only in the univariate Cox analysis.[17] Another study by Ben-Horin *et al.* showed that detectable drug levels were associated with relapse [odds ratio = 8.4, 95% CI = 2.2–32, p = 0.002].[33] The present findings, which indicated that IFX TL ≥2.5 µg/mL was associated with clinical relapse in the final multivariate Cox model [HR = 7.199, 95% CI = 1.641–31.571, p = 0.009], correlate with the findings of previous studies. Likewise, therapeutic drug monitoring may aid in identifying a subgroup of patients in whom remission is independent from treatment with anti-TNF agents.

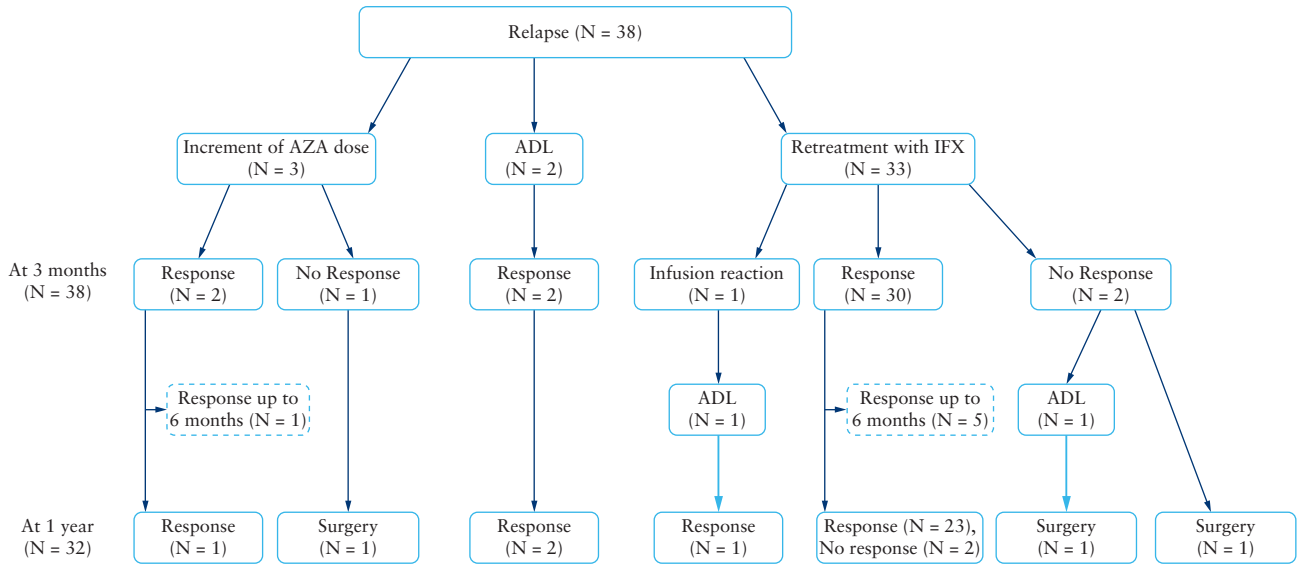

Figure 4. Outcome of retreatment with infliximab in subjects with clinical relapse.

Although data on the role of immunomodulators after IFX cessation are limited, a recent large-scale study demonstrated that treatment with immunomodulators after the discontinuation of anti-TNF agents was a protective factor for relapse [HR = 0.67, 95% CI = 0.51–0.87].[25] Meanwhile, recently published data from the global ALIGN study, which investigated the impact of treatment-related beliefs on medication adherence, suggest that the rate of self-reported adherence was <50% in patients with CD who were receiving conventional therapy.[34] The median 6-TGN level at IFX cessation of 194 pmol/8 × 10^8 red blood cells [RBCs] (interquartile range [IQR] = 124–280) in the STORI trial reflects this high proportion of non-adherence in real-life situations.[15] Meanwhile, the median 6-TGN level of 280.6 pmol/8 × 10^8 RBCs [IQR = 240.7–356.9] at IFX cessation in our study was relatively high compared with that in the STORI trial. One explanation for the relatively high proportion of patients with 6-TGN levels within the therapeutic range in our study is that, from 2011 to 2013, thiopurine metabolite monitoring was conducted on a regular basis with 1–3-month intervals at our centre. Consequently, doses were adjusted so that 6-TGN levels would be within the therapeutic range of 235–450 pmol/8 × 10^8 RBCs. Moreover, by regularly checking thiopurine metabolites, we could identify patients who were non-adherent to AZA and urge them to diligently comply with their medication routine. This may have influenced the relatively high proportion of patients with therapeutic levels of 6-TGN in our study. Although data of 6-TGN levels were available for only 42 patients at cessation, we could show that 6-TGN levels at IFX cessation were not associated with clinical relapse in the univariate Cox analysis, which correlates with findings from the STORI trial [HR = 1.00, 95% CI = 0.43–2.35]. However, owing to the small number of patients and the majority of them having levels within the therapeutic range, there are limitations in concluding that 6-TGN levels at cessation were not associated with clinical relapse. Further studies on this issue are warranted in the future.

IFX cessation in paediatric-onset CD patients remains inadvisable with respect to concerns of non-response to IFX re-introduction and the risk of severe relapse leading to surgery. Regarding the response to IFX re-introduction after relapse, clinical remission was reported in 78.3–100% of patients at short-term follow-up and in 80–92% of patients at 1 year.[9,16,25,27] Our observations that 90.9% [30/33] and 82.1% [23/28] of patients responded to IFX retreatment at 3 months and 1 year, respectively, correlate with the findings from these previous studies. Meanwhile, although severe relapse requiring surgery seems to be rare after IFX cessation, the aforementioned study by Ben-Horin *et al*. reported a surgery rate of up to 8% among the total patients.[33] Our study also showed that three patients [4.8% among the total patients] required surgery within 1 year after relapse. These findings may support the continuation of IFX rather than its cessation. Further large-scale studies including a controlled arm are required to better clarify whether severe relapse requiring surgery is actually associated with IFX cessation or is due to other factors during treatment.

Our study has some limitations. First, there was no control group to properly evaluate the outcome of IFX cessation in patients with clinical remission with combination therapy. As loss of response leading to an unintentional discontinuation of IFX is observed in approximately 13% of patients annually,[35] some patients could have experienced relapse despite continuously receiving IFX. Second, relapse was defined on a clinical basis. Therefore, despite the detection of biochemical and/or endoscopic relapse, re-treatment with IFX was started only when clinical relapse was obvious. This was because of the national insurance policy in Korea, which allows IFX treatment only when symptoms are definite. However, a recent study has reported a significant increase in CRP and FC levels during the 4 months before relapse in those who had experienced relapse,[36] and close monitoring of patients with CRP and FC has been suggested to detect early subclinical relapse and allow early re-treatment with biologics.[37] Cases of severe relapse and consequent surgery in our study could have been avoided if IFX was re-initiated at stages when active inflammation was detected before clinical relapse. Third, because of the retrospective design, endoscopic, laboratory, and pharmacokinetic data at cessation were not available for some patients. IFX TL or 6-TGN data were lacking for some of the patients from the early period of this study, as such tests were unavailable at that time. Because of these limitations, the results of our study should be cautiously interpreted. Further large-scale prospective studies are required in paediatric-onset CD patients to better assess the potential

advantages and disadvantages of discontinuing anti-TNF therapy in patients with corticosteroid-free clinical remission.

In conclusion, considering the high cumulative relapse rates in the long term, IFX cessation in paediatric-onset CD patients remains inadvisable. However, according to the present findings and extrapolation of data from adult studies, there may be a subgroup of paediatric-onset CD patients who are good candidates for IFX withdrawal. Those with subtherapeutic TLs and complete MH at IFX cessation have been identified as such candidates in the present study.

Funding

This work was conducted without any funding.

Conflict of Interest

All authors have no conflict of interest to declare.

Author Contributions

BK contributed to the conception and design of the study, acquisition, analysis and interpretation of data, drafting of the initial manuscript, and critical revision for important intellectual content. SYC contributed to the acquisition, analysis and interpretation of data, and drafting of the initial manuscript. YOC contributed to the acquisition, analysis and interpretation of data, and drafting of the initial manuscript. MK contributed to statistical analysis, and drafting of the initial manuscript. KK contributed to statistical analysis, and critical revision for important intellectual content. JL contributed to the analysis and interpretation of data, and critical revision for important intellectual content. YHC contributed to the conception and design of the study, analysis and interpretation of data, and critical revision for important intellectual content.

References

1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;**369**:1641–57.
2. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;**139**:1147–55.
3. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
4. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**:1232–9.
5. Hyams J, Crandall W, Kugathasan S, *et al.* REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;**132**:863–73; quiz 1165–6.
6. Hyams JS, Griffiths A, Markowitz J, *et al.* Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012;**143**:365–74.e2.
7. Danese S, Fiorino G, Fernandes C, Peyrin-Biroulet L. Catching the therapeutic window of opportunity in early Crohn's disease. *Curr Drug Targets* 2014;**15**:1056–63.
8. Kang B, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal healing in paediatric patients with moderate-to-severe luminal Crohn's disease under combined immunosuppression: escalation versus early treatment. *J Crohns Colitis* 2016;**10**:1279–86.
9. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology* 2015;**149**:1716–30.
10. Clarke K, Regueiro M. Stopping immunomodulators and biologics in inflammatory bowel disease patients in remission. *Inflamm Bowel Dis* 2012;**18**:174–9.
11. Gisbert JP, Marín 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**:632–47.
12. Dignass A, Van Assche G, Lindsay JO, *et al.* European Crohn's and Colitis Organisation [ECCO]. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010;**4**:28–62.
13. Ruemmele FM, Veres G, Kolho KL, *et al.* European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of paediatric Crohn's disease. *J Crohns Colitis* 2014;**8**:1179–207.
14. 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**:1129–34.
15. 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
16. Molander P, Färkkilä M, Salminen K, *et al.* Outcome after discontinuation of TNFα-blocking therapy in patients with inflammatory bowel disease in deep remission. *Inflamm Bowel Dis* 2014;**20**:1021–8.
17. Papamichael K, Vande Casteele N, Gils A, *et al.* Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission. *Clin Gastroenterol Hepatol* 2015;**13**:1103–10.
18. Kennedy NA, Warner B, Johnston EL, *et al.* UK Anti-TNF withdrawal study group. 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**:910–23.
19. Levine A, Koletzko S, Turner D, *et al.* European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;**58**:795–806.
20. Levine A, Griffiths A, Markowitz J, *et al.* Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;**17**:1314–21.
21. Crombé V, Salleron J, Savoye G, *et al.* Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease: a population-based study. *Inflamm Bowel Dis* 2011;**17**:2144–52.
22. Nuti F, Conte F, Cavallari N, *et al.* Long term efficacy of infliximab in inflammatory bowel disease at a single tertiary center. *Dig Liver Dis* 2010;**42**:S326–7.
23. Bouguen G, Levesque BG, Feagan BG, *et al.* Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol* 2015;**13**:1042–50.e2.
24. Kang B, Choe YH. Early biologic treatment in pediatric Crohn's disease: catching the therapeutic window of opportunity in early disease by treat-to-target. *Pediatr Gastroenterol Hepatol Nutr* 2018;**21**:1–11.
25. Casanova MJ, Chaparro M, García-Sánchez 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**:120–31.
26. Sorrentino D, Nash P, Viladomiu M, Hontecillas R, Bassaganya-Riera J. Stopping anti-TNF agents in patients with Crohn's disease in remission: is it a feasible long-term strategy? *Inflamm Bowel Dis* 2014;**20**:757–66.
27. 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**:1456–62.
28. Molnár 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**:225–33.
29. D'Haens GR, Panaccione R, Higgins PD, *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011;**106**:199–212; quiz 213.
30. Pittet V, Froehlich F, Maillard MH, *et al.* EPACT-II Update Panellists. When do we dare to stop biological or immunomodulatory therapy for

Crohn's disease? Results of a multidisciplinary European expert panel. *J Crohns Colitis* 2013;**7**:820–6.
31. 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**:1324–38.
32. Ungar B, Levy I, Yavne Y, *et al*. Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016;**14**:550–7.e2.
33. 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**:356–64.
34. Michetti P, Weinman J, Mrowietz U, *et al*. Impact of treatment-related beliefs on medication adherence in immune-mediated inflammatory diseases: results of the global ALIGN study. *Adv Ther* 2017;**34**:91–108.
35. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther* 2016;**43**:30–51.
36. Molander P, Färkkilä M, Ristimäki A, *et al*. Does fecal calprotectin predict short-term relapse after stopping TNFα-blocking agents in inflammatory bowel disease patients in deep remission? *J Crohns Colitis* 2015;**9**:33–40.
37. Papamichael K, Vermeire S. Withdrawal of anti-tumour necrosis factor α therapy in inflammatory bowel disease. *World J Gastroenterol* 2015;**21**:4773–8.