



Original Article

Long-Term Outcome of Patients with Ulcerative Colitis and Primary Non-response to Infliximab

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Abstract

Background and Aims: We studied the long-term outcome of patients with ulcerative colitis [UC] and primary non response [PNR] to infliximab and searched for predictors of colectomy in these patients.

Methods: This retrospective, multi-centre study included UC patients from three European referral centres, with PNR to infliximab defined as a lack of clinical improvement after the induction therapy, leading to drug discontinuation. Relapse, for patients who continued on biologicals after PNR to infliximab, was defined as drug discontinuation for PNR, loss of response, or serious adverse event. Serum infliximab concentrations at Weeks 2 and 6 were evaluated using an enzyme-linked immunosorbent assay [ELISA] developed in house.

Results: The study population consisted of 99 anti-tumour necrosis factor [TNF]-naïve patients with UC and PNR to infliximab. At the end of follow-up (median: 3.2 [interquartile range 1–6.3] years), 55 [55.6%] of these patients underwent colectomy. Multiple Cox regression analysis identified acute severe UC (hazard ratio [HR]: 24; 95% confidence interval [CI]: 2.5–231; $p = 0.006$), baseline C-reactive protein [CRP] > 5 mg/l [HR: 11; 95% CI: 2.1–58.8; $p = 0.005$], baseline albumin < 40 g/l [HR: 9.5; 95% CI: 1.3–71.4; $p = 0.026$], and infliximab concentration at Week 2 < 16.5 µg/ml [HR: 5.6; 95% CI: 1.1–27.8; $p = 0.034$] as independent predictors of colectomy. Regarding patients who continued on biologicals after PNR to infliximab, there was a marginally higher cumulative probability for relapse in patients switching to another anti-TNF agent compared with those swapping to vedolizumab [p logrank = 0.08].

Conclusions: About half of UC patients with PNR to infliximab will undergo colectomy. Patients with severe inflammation and low serum infliximab concentrations during the induction phase are at greatest risk.

Key Words: Drug concentrations; infliximab; primary non-response; ulcerative colitis

1. Introduction

Anti-tumour necrosis factor [TNF] therapy is an effective treatment for patients with inflammatory bowel disease [IBD], namely Crohn's disease [CD] and ulcerative colitis [UC].¹ Nevertheless, 10–30% of IBD patients show no clinical benefit and are considered as primary non-responders.² The mechanisms underlying primary non-response [PNR] to anti-TNF therapy in IBD are not yet clearly defined.³ However, data suggest that some of the mechanisms are similar to those involved in secondary loss of response [SLR] including pharmacokinetic [PK] and/or pharmacodynamic [PD] issues.⁴ The former are characterised by undetectable or low serum drug concentrations due to an accelerated clearance of the drug in the systemic circulation and/or local tissue, whereas the latter are associated with adequate serum drug concentrations and a probable shift of the disease to a non TNF-driven inflammatory pathway.⁵

Currently, due to lack of relevant data, there are no clinical recommendations and/or guidelines on how to handle IBD patients with PNR to anti-TNF therapy and management remains therefore empirical. The only available data derive exclusively from small, observational, non-controlled studies that focus on the short-term efficacy of adalimumab in CD patients with PNR to infliximab.^{6,7,8,9} Besides surgical treatment, which still remains a valid therapeutic option when dealing with IBD, in real-life clinical practice most physicians, will often attempt a switch to another anti-TNF agent or to another drug class, such as anti-adhesion molecule therapy.^{10,11}

Preliminary data suggest that early measurement of drug and anti-drug antibody concentrations, known as therapeutic drug monitoring, could help to better understand the mechanisms of PNR and rationalise patient management.^{12,13,14,15,16,17,18} Nevertheless, in contrast to SLR,¹⁹ relevant data that could determine whether switching within the same drug class or swapping [switching out of the drug class] is preferable after PNR to the first biological agent, are largely missing.²⁰

The main goal of our study was to investigate the long-term outcome of UC patients with PNR to infliximab and search for predictors of colectomy including infliximab concentrations during the induction therapy.

2. Materials and Methods

2.1. Study design, definitions, and patient population

This was a retrospective, observational, multi-centre study including consecutive, anti-TNF naïve patients with UC and PNR to infliximab induction therapy, between 1999 and 2013, from three European tertiary referral IBD centres: University Hospitals Leuven, Belgium; Evangelismos Hospital, Athens, Greece; and University Hospital, Université de Lorraine, Nancy, France. All patients' data were reviewed from their paper and electronic medical records up to October 2014.

The decision or time to colectomy in all three hospitals was based on physician global assessment according to standard of care clinical practice criteria. Typically, surgery is recommended in patients who fail or cannot tolerate continued medical therapy [including rescue therapy with biologicals] characterised by severe toxic symptoms [such as > 10 stools/day, continuous bleeding, abdominal pain, and fever] or severe complications [such as colonic perforation, life-threatening gastrointestinal haemorrhage, and toxic megacolon] and/or have colorectal dysplasia or cancer.

Primary non-response to infliximab was defined as a lack of clinical improvement [based on physician global assessment] after induction therapy [Weeks 0-2-6, 5 or 10mg/kg, at least 2 infusions] leading to drug discontinuation.^{3,21} In the great majority of patients

Table 1. Baseline characteristics of the study population.

Patient characteristics	N = 99
Male, [%]	65 [66]
Age at start of infliximab, median [IQR], years	40 [29–57]
Disease duration, median [IQR], years ^a	3 [1.1–9.1]
UC extension, [%]	
Proctitis	2 [2]
Left-sided colitis	39 [39]
Pancolitis	58 [59]
Acute severe UC, ^b [%]	23 [23]
Smoking at baseline, [%]	6/73 [8]
Induction therapy with 10 mg/kg, [%]	13 [13]
Concomitant corticosteroids, ^c [%]	42 [42]
Concomitant immunomodulators, ^c [%]	37 [37]
Baseline BMI, median [IQR], kg/m ²	22.1 [20.5–25.3]
Baseline CRP > 5 mg/l, [%]	31/54 [57]
Baseline CRP, median [IQR], mg/l	9 [2–19]
Baseline albumin, median [IQR], g/l	40.8 [37.5–44]

^aFrom diagnosis to start of infliximab.

^bDefined as a serious, life-threatening clinical condition necessitating hospitalisation according to the Truelove and Witts criteria.⁴²

^cCombination treatment during induction therapy.

Ulcerative colitis; BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range.

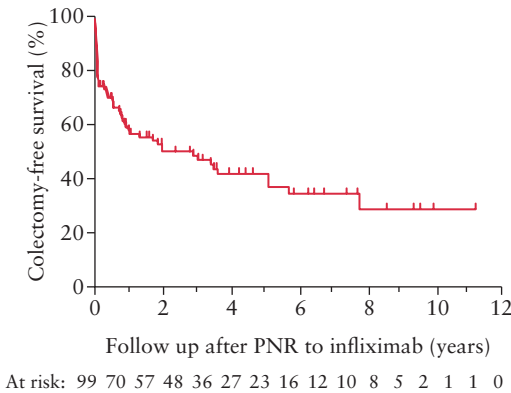


Figure 1. Kaplan-Meier colectomy-free survival curve of patients with ulcerative colitis and primary non-response to infliximab. PNR, primary non-response.

[*n* = 79/99, 80%], severe inflammation necessitating drug discontinuation was also confirmed by flexible sigmoidoscopy showing an endoscopic Mayo score of 2 or 3. Relapse for UC patients who continued on biologicals after PNR to infliximab, either by switching inside class [adalimumab, certolizumab pegol, and/or golimumab] or swapping [vedolizumab, etrolizumab, and/or other] was defined as drug discontinuation due to PNR, loss of response, or serious adverse event. For patients treated with investigational drugs only, open-label drug administrations were included in our analysis.

Serum samples from patients treated in the University Hospitals Leuven, Belgium, were prospectively collected just before an infliximab infusion at Weeks 2 [*n* = 42] and 6 [*n* = 37] and stored at -20°C. Patients gave written informed consent to participate in the institutional review board-approved Flemish Study for Research on IBD, VLECC registry B322201213950 / S53684.

2.2. Serology

Infliximab concentrations and antibodies to infliximab [ATI] were measured using an in-house developed and clinically validated enzyme-linked

Table 2. Variables associated with colectomy in patients with ulcerative colitis and primary non-response to infliximab.

Variables	Univariate analysis			Multivariate analysis						
	HR	95% CI	p [logrank]	HR	95% CI	p [logrank]	SN [%]	SP [%]	PPV [%]	NPV [%]
Male			0.997							
Age at start of infliximab < 60 years ^a			0.101							
Disease duration < 3.2 year ^a	2.6	1.5–4.5	< 0.001							
Smoking at baseline			0.113							
Pancolitis			0.165							
Acute severe UC [%]	6.6	2.8–15.1	< 0.001	24	2.5–231	0.006	74	50	31	86
Baseline albumin < 40 g/l ^a	5.7	2.3–14.2	< 0.001	9.5	1.3–71.4	0.026	71	67	62	75
Baseline CRP > 5 mg/l	4.2	2–9.2	< 0.001	11	2.1–58.8	0.005	71	78	81	67
Induction therapy with 10mg/kg			0.555							
Baseline BMI < 20.6 kg/m ^{2a}			0.093							
Concomitant corticosteroids	2.1	1.2–3.8	0.007							
Concomitant immunomodulators			0.728							
Infliximab concentration < 16.5 µg/ml at Week 2 ^a	5.4	2–14.6	0.001	5.6	1.1–27.8	0.034	80	70	60	86
Infliximab concentration < 5.3 µg/ml at Week 6 ^a	14.6	3.7–57.4	< 0.001							

UC, ulcerative colitis; BMI, body mass index; CI, confidence interval; NPV, negative predictive value; HR, hazard ratio; PPV, positive predictive value; SN, sensitivity; SP, specificity; CRP, C-reactive protein.
^aCut-off based on receiver operating curve analysis [Supplementary Figure 1, available as Supplementary data at ECCO-JCC online].

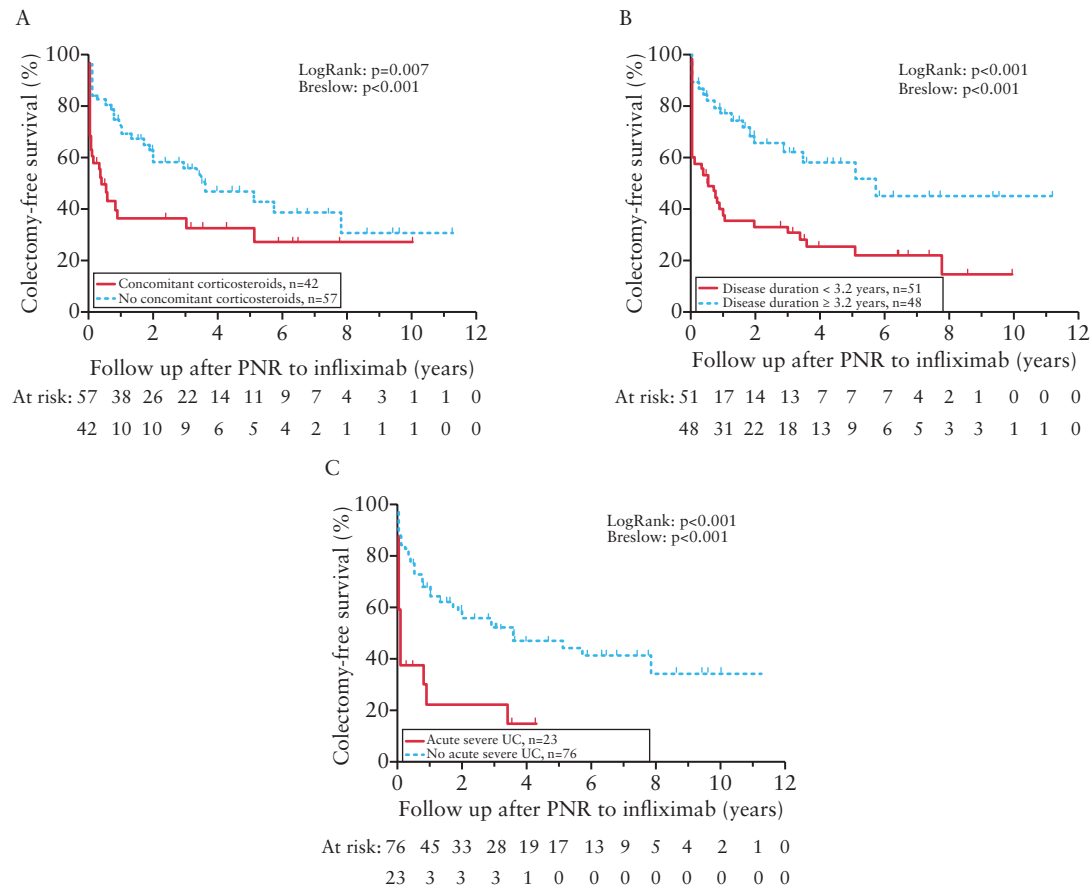


Figure 2. Kaplan-Meier curve demonstrating the cumulative probability for colectomy after primary non-response to infliximab stratified by concomitant corticosteroid treatment [A], disease duration [B], and acute severe ulcerative colitis [C]. UC, ulcerative colitis; PNR, primary non-response.

immunosorbent assay [ELISA] as previously described.²² The lower detection limits for infliximab concentrations and ATI were 0.3 µg/ml and 1 µg/ml equivalents, respectively. ATI were not detectable in serum if infliximab concentration was ≥ 0.3 µg/ml and were regarded as inconclusive

for ATI. The upper limit of quantification [ULOQ] using standard dilutions of 1/150 and 1/300 was 22.5 µg/ml. Samples with a drug concentration above the ULOQ were diluted up to 1/1200 until a result that fell within the linear phase of the standard curve of the assay was obtained.

Albumin and C-reactive protein [CRP] levels were measured at baseline and after the induction therapy by standard procedures. CRP ≤ 5 mg/l and albumin levels 35–50 g/l were considered as normal.

2.3. Statistical analysis

Descriptive statistics were provided with medians and interquartile ranges [IQRs] for continuous variables, and frequency and percentages for categorical variables.

A receiver-operating characteristic [ROC] analysis was performed for age at start of infliximab, disease duration, baseline body mass index [BMI], serum albumin, and infliximab concentration at Weeks 2 and 6 during the induction therapy, in order to trace thresholds associated with colectomy in UC patients following PNR to infliximab [Supplementary Figure 1, available as Supplementary data at ECCO-JCC online]. Optimal thresholds were chosen using the Youden index, which maximises the sum of the specificity and sensitivity of the ROC curve as previously described.¹² Sensitivity [SN], specificity [SP], positive predictive value [PPV], and negative predictive value [NPV] were also calculated.

Infliximab concentrations at Weeks 2 and 6 were compared between groups, using the Mann-Whitney U test. Serum infliximab concentrations were also categorised into quartiles. Rates of colectomy were compared across baseline albumin and CRP levels and serum infliximab concentrations at Week 2 and 6 quartiles, using the chi-square test [linear-by-linear association].

The Kaplan-Meier method was used to estimate the proportion of patients undergoing colectomy and the median time to colectomy. Univariate analysis using the logrank test was performed to identify variables predicting a colectomy in UC patients after PNR to infliximab. To determine the independent effects of variables, multiple Cox proportional hazards regression analysis was then performed, including variables with a p -value of < 0.1 based on the Wald Backward selection method. The results were expressed as hazard ratios [HRs] with 95% confidence intervals [95% CI] followed by the corresponding p -value. Multicollinearity between infliximab concentrations at Weeks 2 and 6 was assessed based on linear regression analysis and the variance inflation factor [VIF].

Relapse and PNR of an alternative anti-TNF drug treatment course was compared with those of a non-TNF agent in patients who continued on biologicals after PNR to infliximab, using the logrank test.

Results were considered statistically significant when $p < 0.05$. All statistical analyses were performed using the SPSS 23.0 software [SPSS, Chicago, IL, USA] and GraphPad Prism version 5.03 for Windows [GraphPad Software, San Diego, CA, USA].

3. Results

3.1. Study population

The study population consisted of 99 anti-TNF naïve patients with UC and PNR to infliximab. The majority of patients were male

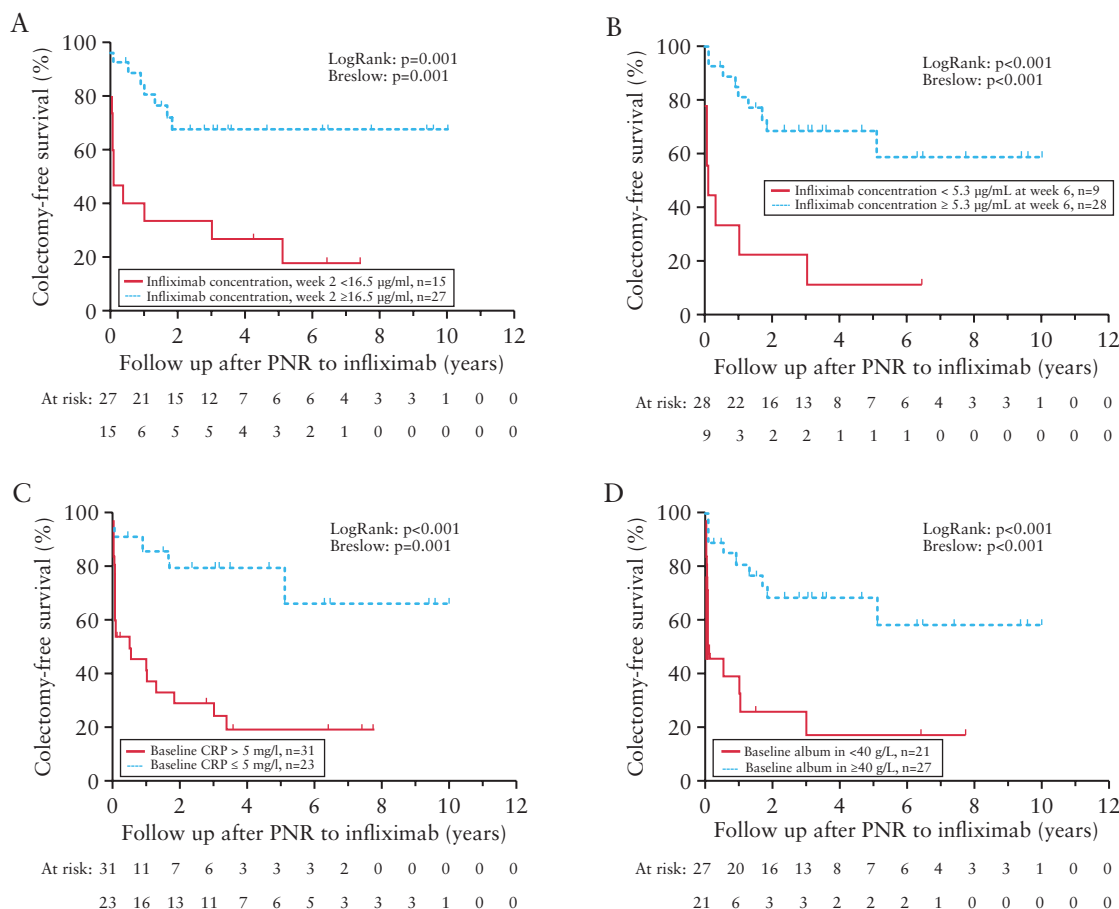


Figure 3. Kaplan-Meier curve demonstrating the cumulative probability for colectomy after primary non-response to infliximab stratified by infliximab concentration at Week 2 [A], Week 6 [B], baseline CRP [C], and baseline albumin [D]. CRP, C-reactive protein; PNR, primary non-response; UC, ulcerative colitis.

[*n* = 65] and had pancolitis [*n* = 58], and 23 had acute severe UC. Baseline characteristics of the patients are depicted in Table 1.

3.2. Long-term outcome of patients with UC and primary non-response to infliximab

After a median follow-up of 3.2 [IQR 1–6.3] years, 55 [55.6%] patients underwent colectomy. The 1st and the 5th year cumulative probabilities [standard error, SE] for colectomy after PNR to infliximab were 42.8 [0.052] and 62.4% [0.058], respectively. The median [95% CI] time to colectomy was 2 [0–4] years [Figure 1].

3.3. Factors associated with colectomy

Univariate [logrank test] analysis identified disease duration < 3.2 years [*p* < 0.001], acute severe UC [*p* < 0.001], concomitant corticosteroid treatment [*p* = 0.007], baseline CRP > 5 mg/l [*p* < 0.001], baseline albumin < 40 g/l [*p* < 0.001], infliximab concentration at Week 2 < 16.5 µg/ml [*p* = 0.001], and infliximab concentration < 5.3 µg/ml at Week 6 [*p* < 0.001] as variables associated with colectomy [Table 2, Figures 2 and 3]. No multicollinearity between infliximab concentrations at Week 2 or 6 was observed [VIF = 1 < 3]. Multiple Cox regression analysis

retained acute severe UC [*p* = 0.006], baseline albumin < 40 g/l [*p* = 0.026], baseline CRP > 5mg/l [*p* = 0.005], and infliximab concentration at Week 2 < 16.5 µg/ml [*p* = 0.034] as independent factors predicting colectomy [Table 2]. The relationship between baseline serum CRP and albumin with colectomy was further analysed by dividing baseline CRP levels and albumin into quartiles. The higher baseline serum CRP and lower albumin quartiles were associated with higher rates of colectomy [Figure 4 A and B].

3.4. Infliximab concentrations and ATI associated with colectomy

Serum infliximab concentrations at Weeks 2 and 6 were lower in UC patients with colectomy compared with those without [Figure 4C]. A ROC analysis identified infliximab concentration thresholds of 16.5 and 5.3 µg/ml at Weeks 2 and 6, respectively, associated with colectomy [Supplementary Figure 1A, B]. The relationship between serum infliximab concentrations at Weeks 2 and 6 and colectomy was further analysed by dividing serum infliximab concentrations into quartiles. The lower infliximab serum concentration quartiles at Weeks 2 and 6 were generally associated with higher rates of

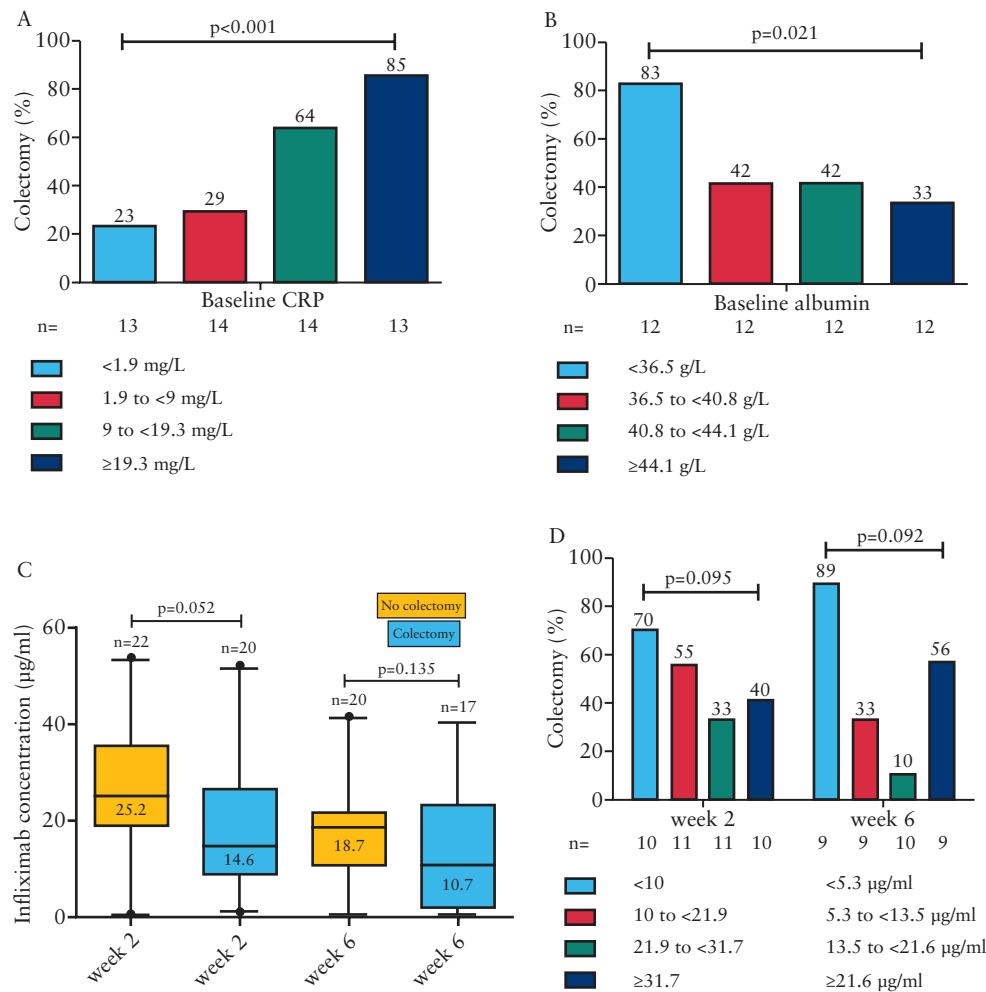


Figure 4. Rates of colectomy by baseline CRP levels [A] and albumin [B] quartiles. Distribution of infliximab serum concentrations at Weeks 2 and 6 based on colectomy rate. Grey boxes represent the infliximab serum concentrations of patients with colectomy, and white boxes represent the infliximab serum concentrations of patients without. Box plots [5–95%] show the median [solid line within box], interquartile range [upper and lower box boundaries], standard deviation [whiskers], and outliers [black dots] [C]. Rates of colectomy by infliximab serum concentrations quartiles at Weeks 2 and 6 [D]. CRP: C-reactive protein.

colectomy [Figure 4D]. Infliximab concentrations were not statistically significant different in patients on concomitant immunomodulators compared with those without, both at Week 2 (median [IQR], 21.4 [9.8–33.2] vs 21.9 [13.2–32], $p = 0.960$) and at Week 6 (18.3 [6.4–25] vs 13.1 [3.8–20.7], $p = 0.345$, respectively).

Measurements of ATI were available in 44 patients during the induction therapy [either at Week 2 or at Week 6]; none of these patients had positive ATI. In one patient with undetectable infliximab concentration ATI were negative, and in the remaining 43 patients were considered inconclusive.

3.5. Long-term outcome of UC patients who continued on biologicals after PNR to infliximab

Following PNR to infliximab, 41 UC patients received 51 courses of biological therapy and were followed for a median of 2.5 [IQR 1.2–3.9] years [Figure 5]. The median [95% CI] time for relapse was 8.8 [1–16.5] months. For patients who failed to respond to IFX but subsequently responded to an alternative anti-TNF agent, the interval [median, IQR] was 30 [7–63] weeks. There was no statistically significant difference between switching to another anti-TNF agent and swapping to an out of anti-TNF class biological drug in terms of relapse [p logrank = 0.136, Figure 6A], although there was a marginally higher cumulative probability of relapse in patients switching to another anti-TNF agent compared with those swapping to vedolizumab only [p logrank = 0.080, Figure 6B]. Moreover, the cumulative probability for PNR was higher in patients who switched to another anti-TNF agent compared with those swapping either to an out of anti-TNF class biological drug [p logrank = 0.022, HR = 5.3, 95% CI: 1.3–21.7], Figure 6C] or to vedolizumab only [p logrank = 0.037 Figure 6D].

4. Discussion

Although anti-TNF therapy is effective for IBD, 10–30% of patients show PNR.⁵ The management of PNR to anti-TNF therapy is still empirical. Therapeutic options include surgery, switch to another

anti-TNF agent and/or swapping to an out of class biological treatment, such as vedolizumab which recently reached the pharmaceutical market. Even after 20 years of use, little is known about the long-term outcome of patients with PNR to anti-TNF therapy.

We demonstrated that more than half of UC patients with PNR to infliximab will eventually undergo colectomy, especially those with acute severe UC, elevated baseline CRP levels, and lower baseline albumin levels and infliximab concentrations during the induction phase, probably due to the high inflammatory burden at the start of infliximab therapy. Signs of severe baseline inflammation such as high CRP [> 5 mg/l] and low albumin levels [< 35 g/l] were previously shown to be independent predictors of colectomy in UC patients treated with infliximab.¹⁷ These factors negatively influence the pharmacokinetic profile of infliximab by inducing a higher non-immune clearance in IBD patients.^{12,16,23,24,25} Consequently, severely active disease in these patients may not be controlled by a standard induction regimen of infliximab [5 mg/kg, 0–2–6 week] or adalimumab [160/80 mg, 0–2 week] and may require higher doses to avoid PNR.^{15,26,27,28,29,30,31,32} However, based on analysis of infliximab serum concentration quartiles, 40–50% of patients needed a colectomy despite adequate drug concentrations. These patients may be characterised by a non TNF-driven disease, as previously described.^{33,34,35,36}

Moreover, we showed that swapping to an out of class drug, such as vedolizumab, is probably better than switching to another anti-TNF agent for the long-term management of UC patients with PNR to infliximab, as the latter therapeutic strategy is associated with a higher likelihood of relapse and PNR. A recent meta-analysis showed a remission rate of 30% in CD patients switching to another anti-TNF agent,¹¹ and a durable response to adalimumab in some UC patients with PNR to infliximab was also observed.¹⁴ Furthermore, the efficacy of adalimumab in patients with CD and PNR to infliximab was 33–72% and 11–50% in terms of clinical response and remission, respectively, for up to 1 year of follow-up.⁵ These data demonstrate that some patients may still benefit from switching to

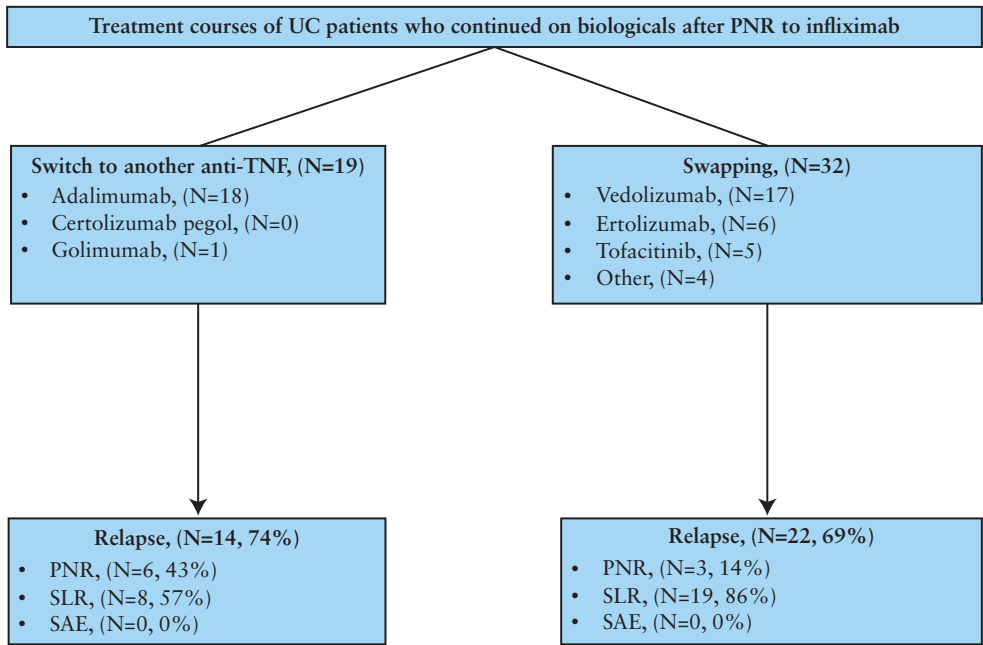


Figure 5. Long-term outcome of UC patients who continued on biologicals after primary non-response to infliximab. PNR, primary non response; SAE, serious adverse event; SLR, secondary loss of response; TNF, tumour necrosis factor; UC, ulcerative colitis.

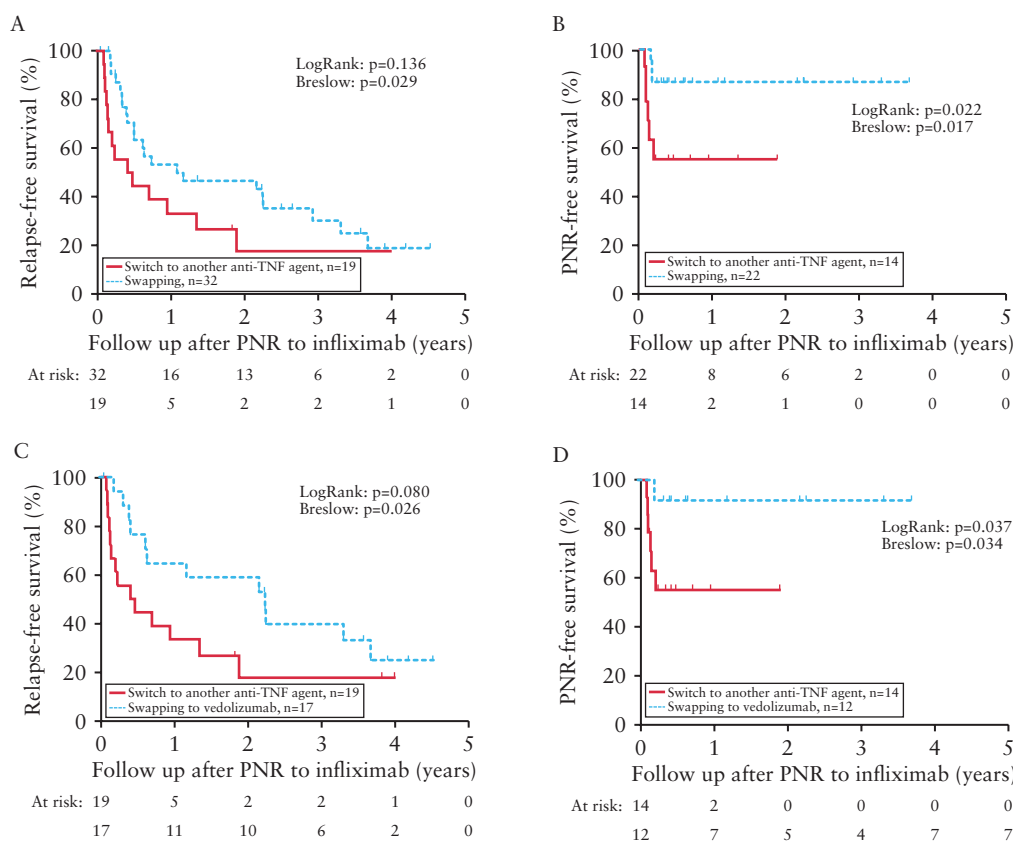


Figure 6. Kaplan-Meier curves demonstrating the cumulative probability for drug discontinuation [A] and primary non-response as a reason for drug discontinuation [B], stratified by the type of biological therapy in UC patients who continued on biologicals after primary non-response to infliximab. Kaplan-Meier curves demonstrating the cumulative probability for drug discontinuation [C] and primary non-response as a reason for drug discontinuation [D], stratified by the type of biological therapy in UC patients who continued on biologicals after primary non-response to infliximab, including those swapping only to vedolizumab. UC, ulcerative colitis.

another anti-TNF agent, suggesting that PNR to anti-TNF therapy may not be a class-effect phenomenon.^{4,37,38} However, swapping to an out of class drug rather than switching to another anti-TNF would be a more rational therapeutic approach for patients with adequate drug concentrations during the induction phase, suggesting a non-TNF-driven inflammation.⁵ Vedolizumab was previously shown to be efficacious in UC patients with PNR to anti-TNF therapy, although data regarding severe fulminant colitis are missing.³⁹ Additionally, studies from rheumatoid arthritis have demonstrated that patients with PNR to anti-TNF therapy had significantly higher drug retention for biological agents with a different mode of action compared with alternative anti-TNF agents, implying that these patients may have a non-TNF-mediated disease.^{39,40}

The main limitations of this study are its retrospective nature and the fact that infliximab concentrations were not available for all the patients. As a result, due to the small sample size, a robust, consistent analysis on the influence of infliximab drug concentrations on the efficacy of either swapping to a different anti-TNF or switching to another anti-TNF following PNR to infliximab, although of great significance, was not feasible. Another limitation was the use of a drug-sensitive assay to measure ATI leading probably to an underestimation of the positive ATI patients.

In conclusion, this large, multi-centre study, reflecting real-life clinical practice, indicates that more than half of UC patients with PNR to infliximab will eventually undergo colectomy, especially those with severe inflammation and low serum infliximab concentrations. The

colectomy rate may be under-estimated and could be even higher in non-referral hospitals, since our study contacted three tertiary referral IBD centres with relatively large therapeutic armamentaria and alternative treatment options [ertroliumab, tofacitinib, other], used as rescue therapy, before a surgical intervention is applied. Prospective, large therapeutic drug monitoring [TDM] studies to clearly define the therapeutic window of infliximab induction therapy, and drug concentration thresholds for prediction of response following pharmacological interventions after PNR to anti-TNF therapy, progressing towards individual, personalised medicine, are certainly warranted.^{20,41}

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Conflict of Interest

KP received a consultancy fee from MSD Hellas. NVC received consultancy fees from Janssen Biologics, MSD, UCB, Takeda, and Pfizer, and speaker fees from Abbvie. AG received speaker fees from Pfizer, Abbvie, Janssen Biologics, and MSD, and financial support for research from Pfizer. GVA received financial support for research from Abbott, and

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Author Contributions

KP: study concept and design, data acquisition, analysis and interpretation, statistical analysis, and manuscript writing. NVC, TB, OR: data acquisition and interpretation and manuscript critical revision. AG, PR, GVA, MF, GJM: data interpretation and manuscript critical revision. SV, LP-B: study concept and design, data interpretation, and manuscript critical revision.

References

- Billiet T, Rutgeerts P, Ferrante M, *et al.* Targeting TNF- α for the treatment of inflammatory bowel disease. *Expert Opin Biol Ther* 2014;14:75–101.
- Ben-Horin S, Chowers Y. Tailoring anti-TNF therapy in IBD: drug levels and disease activity. *Nat Rev Gastroenterol Hepatol* 2014;11:243–55.
- Allez M, Karmiris K, Louis E, *et al.* Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. *J Crohns Colitis* 2010;4:355–66.
- Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014;13:24–30.
- Papamichael K, Gils A, Rutgeerts P, *et al.* Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary non response. *Inflamm Bowel Dis* 2015;21:182–97.
- Seiderer J, Brand S, Dambacher J, *et al.* Adalimumab in patients with Crohn's disease safety and efficacy in an open-label single centre study. *Aliment Pharmacol Ther* 2007;25:787–96.
- Chaparro M, Andreu M, Barreiro-de Acosta M, *et al.* Effectiveness of infliximab after adalimumab failure in Crohn's disease. *World J Gastroenterol* 2012;18:5219–24.
- Ho GT, Mowat A, Potts L, *et al.* Efficacy and complications of adalimumab treatment for medically-refractory Crohn's disease: analysis of

nationwide experience in Scotland [2004–2008]. *Aliment Pharmacol Ther* 2009;29:527–34.

- Danese S, Mocchiari F, Guidi L, *et al.* Successful induction of clinical response and remission with certolizumab pegol in Crohn's disease patients refractory or intolerant to infliximab: a real-life multicentre experience of compassionate use. *Inflamm Bowel Dis* 2008;14:1168–70.
- Gisbert JP, Chaparro M. Use of a third anti-TNF after failure of two previous anti-TNFs in patients with inflammatory bowel disease: is it worth it? *Scand J Gastroenterol* 2015;50:379–86.
- Gisbert JP, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015;41:613–23.
- Adedokun OJ, Sandborn WJ, Feagan BG, *et al.* Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology* 2014;147:1296–307.
- Cornillie F, Hanauer SB, Diamond RH, *et al.* Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014;63:1721–7.
- Baert F, Vande Casteele N, Tops S, *et al.* Prior response to infliximab and early serum drug concentrations predict effects of adalimumab in ulcerative colitis. *Aliment Pharmacol Ther* 2014;40:1324–32.
- Brandse JF, van den Brink GR, Wildenberg ME, *et al.* Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology* 2015;149:350–5.
- Papamichael K, Van Stappen T, Vande Casteele N. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2016;14:5439.
- Arias MT, Vande Casteele N, Vermeire S, *et al.* A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2015;13:531–8.
- Bortlik M, Duricova D, Malickova K, *et al.* Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis* 2013;7:736–43.
- Yanai H, Lichtenstein L, Assa A, *et al.* Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015;13:522–30.
- Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015;12:537–45.
- Schnitzler F, Fidler 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.
- Vande Casteele N, Buurman DJ, Sturkenboom MG, *et al.* Detection of infliximab concentrations and anti-infliximab antibodies: a comparison of three different assays. *Aliment Pharmacol Ther* 2012;36:765–71.
- Ordas I, Mould DR, Feagan BG, *et al.* Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012;91: 635–46.
- Fasanmade AA, Adedokun OJ, Olson A, *et al.* Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010;48:297–308.
- Dotan I, Ron Y, Yanai H, *et al.* Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014;20:2247–59.
- Seow CH, Newman A, Irwin SP, *et al.* Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010;59:49–54.
- Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2015;21:1709–18.
- Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2015;41:1094–103.

29. Gibson DJ, Heetun ZS, Redmond CE, *et al.* An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2015;**13**:330–5.
30. Hendler SA, Cohen BL, Colombel JF, *et al.* High-dose infliximab therapy in Crohn's disease: clinical experience, safety, and efficacy. *J Crohns Colitis* 2015;**9**:266–75.
31. Yarur AJ, Jain A, Sussman DA, *et al.* The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut* 2016;**65**:249–55.
32. Brandse JF, Mathôt RA, van der Kleij D, *et al.* Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2016;**14**:251–8.
33. Leal RF, Planell N, Kajekar R, *et al.* Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNF α therapy. *Gut* 2015;**64**:233–42.
34. Arijis I, Quintens R, Van Lommel L, *et al.* Predictive value of epithelial gene expression profiles for response to infliximab in Crohn's disease. *Inflamm Bowel Dis* 2010;**16**:2090–8.
35. Arijis I, Li K, Toedter G, *et al.* Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis. *Gut* 2009;**58**:1612–9.
36. Feagan BG, Rutgeerts P, Sands BE, *et al.* Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;**369**:699–710.
37. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol Suppl.* 2005;**74**:13–8.
38. Slevin SM, Egan LJ. New insights into the mechanisms of action of anti-tumor necrosis factor- α monoclonal antibodies in inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**: 2909–20.
39. Du Pan SM, Scherer A, Gabay C, Finckh A. Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. *Ann Rheum Dis* 2012;**71**:997–9.
40. Finckh A, Ciurea A, Brulhart L, *et al.* Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor [TNF] agents after previous failure of an anti-TNF agent? *Ann Rheum Dis* 2010;**69**:387–93.
41. Bryant RV, Sandborn WJ, Travis SP. Introducing vedolizumab to clinical practice: who, when, and how? *J Crohns Colitis* 2015;**9**:356–66.
42. Dignass A, Eliakim R, Magro F, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohn's Colitis* 2012;**6**:695–90.