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Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy

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SUMMARY

Background
Some of the most important questions relating to the use of biological therapy in inflammatory bowel diseases concern the duration of maintenance therapy.

Aim
To assess the disease course and frequency of relapse of Crohn's disease (CD) following discontinuation of biological therapy, and to determine predictive factors for relapse.

Methods
One hundred twenty-one CD patients who had achieved clinical remission following 1 year of biological therapy and for whom biological therapy was then discontinued participated in this prospective observational study. Eighty-seven CD patients had received infliximab and 34 adalimumab. The definition of relapse was an increase of >100 points in CDAI to at least a CDAI of 150 points.

Results
Biological therapy was restarted within 1 year of treatment cessation in 45% of patients. Logistic regression analysis revealed that previous biological therapy ($P = 0.011$) and dose intensification during the 1-year course of biological therapy ($P = 0.024$) were associated with the need for and the time to the restarting of biological therapy. Smoking was observed to have an effect that was not statistically significant ($P = 0.053$).

Conclusions
Biological therapy was restarted a median of 6 months after discontinuation in almost half of Crohn's disease patients in who had been in clinical remission following 1 year of biological therapy. These results suggest that, in the event of the presence of certain predictive factors, biological therapy should probably be continued for more than 1 year by most patients.

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INTRODUCTION

Antitumour necrosis factor (TNF) therapy (infliximab or adalimumab) has proven effective in the treatment of Crohn's disease (CD) and ulcerative colitis, both in trials and in clinical practice.[1–3] Some of the most important questions relating to the use of biologicals include when therapy should be stopped and whether these drugs are still effective if they must be restarted in the event of a clinical relapse.

Data suggest that similar to other lifelong diseases, inflammatory bowel diseases (IBD) should be treated continuously. However, the clinical benefit of maintenance therapy in symptom-free periods is less well established. The World Congress of Gastroenterology's (WCOG) statement[4] indicates that withdrawal of therapy is possible in patients with CD who exhibit both complete mucosal healing and no biological evidence of inflammation [Evidence Level (EL): 2b]. For each patient, disease history and response to therapy should be taken into consideration. Data are currently available from the STORI study[5] and some single-centre studies concerning the risk factors of disease recurrence after discontinuation of successful biological therapy in CD. In the STORI study, infliximab therapy was terminated in 115 patients in clinical remission after treatment with combined scheduled infliximab and a stable dose of immunosuppressant for at least 1 year. Forty-five per cent of patients relapsed following withdrawal of infliximab. Factors predicting time-to-relapse included: male gender, previous steroid treatment, haemoglobin level, elevated white blood cell count, higher-than-normal levels of C-reactive protein (CRP) or faecal calprotectin, and the observation of mucosal lesions on endoscopy.

The Hungarian National Health Insurance Fund Administration reimbursement regulations specify that biological therapy must be discontinued after a 1-year treatment period in patients with luminal CD who have achieved remission.

The identification of factors predictive of the need to restart biological therapy, including demographic-, clinical-, laboratory- and treatment-related variables, would be helpful when determining the optimum duration of therapy. The aims of the present study were therefore to assess the disease course and the frequency of relapse in the year following mandated discontinuation of infliximab or adalimumab administration in CD patients who had achieved clinical remission, and to determine possible predicting factors.

PATIENTS AND METHODS

Study design and patients

The study, Relapse After Stopping biologicals in Hungary (RASH), was a prospective observational study conducted at five Hungarian tertiary referral centres, and was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics. Analysis focused on patients who attained a state of clinical remission (assessed via the Crohn's Disease Activity Index [CDAI]) after a 1-year period of biological therapy at which time biological therapy was discontinued. One hundred twenty-one consecutive CD patients were followed. After responding to induction therapy, all patients received maintenance infliximab or adalimumab therapy for 1 year, in accordance with Hungarian regulations, and achieved a CDAI of ≤ 150 points by the end of the 1-year treatment period. Each centre followed patients closely both during and after biological therapy, in accordance with national guidelines (see details below).

Diagnosis was based on the Lennard-Jones criteria,[6] while CD phenotype was determined in accordance with the Montreal Classification.[7] The clinical characteristics of these patients are presented in Table 1. In cases of perianal CD, only patients with luminal disease activity, but an inactive perianal fistula were enrolled in the study. Data on patients with active perianal disease (either initially, or during the study period) were not included in the analysis. Data relating to patients' smoking habits, previous appendectomy, perianal involvement, the presence of extraintestinal manifestation (EIM), magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) procedures, concomitant medication and previous surgical procedures (resections, perianal procedures, or colectomy) were collected from each centre.

Types of biological therapy and concomitant immunosuppression

Eighty-seven CD patients received infliximab and 34 adalimumab. Ninety-six patients (79%) were naive to biological therapy. Eleven infliximab- and 14 adalimumab-treated patients had received biological therapy previously; that is, they were treated with a biological agent before the 1-year period of biological therapy analysed in the present study. It should be reiterated that in Hungary biological therapy must be discontinued after a 1-year treatment period in patients with luminal disease who have achieved remission, but can be restarted upon relapse, regardless of the time between discontinuation and relapse. Previous

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Table 1 | Clinical characteristics of enrolled patients

Characteristics	CD patients (n = 121)	Retreated CD patients (n = 55)	Not retreated CD patients (n = 66)
Gender (female/male)	64/57	23/32	41/25
Mean age at diagnosis (years)	25.4 (8–67)	24.1 (10–51)	26.4 (8–67)
Mean age at the beginning of biological therapy (years)	30.7 (17–63)	30 (17–63)	31.3 (18–60)
Montreal classification			
Age at diagnosis			
<16 years (A1)	18 (14.9%)	10 (18.2%)	8 (12.1%)
17–40 years (A2)	89 (73.6%)	41 (74.5%)	48 (72.7%)
>40 years (A3)	14 (11.5%)	4 (7.3%)	10 (15.2%)
Location			
Ileal (L1)	8 (6.6%)	2 (3.6%)	6 (9.1%)
Colonic (L2)	46 (38%)	21 (38.2%)	25 (37.9%)
Ileocolonic (L3)	66 (54.5%)	32 (58.2%)	34 (51.5%)
Upper GI (L4)	1 (0.9%)	0	1 (1.5%)
Behaviour			
Inflammatory (B1)	46 (38%)	22 (40%)	24 (36.4%)
Stricturing (B2)	17 (14%)	7 (12.7%)	10 (15.2%)
Penetrating (B3)*	58 (48%)	26 (47.3%)	32 (48.5%)
Extraintestinal manifestation	70 (57.9%)	34 (61.8%)	36 (54.5%)
Concomitant medications			
Corticosteroids	72 (59.5%)	39 (70.9%)	33 (50%)
Thiopurines	103 (85.1%)	46 (83.6%)	57 (86.4%)
Surgery before the biological therapy	54 (44.6%)	23 (41.8%)	31 (47%)
Previous biological therapy†	25 (20.7%)	15 (27.3%)	10 (15.2%)
Median CDAI at the start of biological therapy	340	307	300
Median CRP level at the start of biological therapy	9.8	12.5	7.9
Current smokers (%)	33 (30.3%)‡	22 (40.7%)¶	11 (20%)††
Appendectomy (%)	16 (22.2%)§	5 (10.9%)**	11 (22.9%)‡‡

* Perianal fistula in the patient's history.

† Previous refers to treatment with biological agent before the 1-year period of biological therapy analysed in the study.

‡ Data of 12 patients were missing.

§ Data of 57 patients were missing.

¶ Data of 1 patients were missing.

** Data of 9 patients were missing.

†† Data of 11 patients were missing.

‡‡ Data of 48 patients were missing.

switching to adalimumab was due to the loss of response or intolerance to infliximab. In cases involving infliximab retreatment, only episodic infliximab had been administered previously. Concomitant immunosuppression during induction was achieved with steroids in 59.5% and with thiopurines in 85.1% of the patients. Of the steroid-treated patients, 33% demonstrated steroid dependence.

Assessment of response to biological therapy and follow-up after treatment discontinuation

Clinical activity scores, determined by CDAI,[8] were documented before the start of biological therapy, after 2, 6 and 12 weeks of therapy, every 2 months thereafter, at the end of the year, and when resumption of biological therapy was needed. The initial response to treatment was assessed 12 weeks after therapy commenced. A clinical response was defined as a decrease of >70 points in CDAI. Clinical remission was defined as a CDAI $\leq$150 points. Patients who responded or achieved remission by week 12 were offered a 1-year course of maintenance therapy, after which the biological therapy was discontinued. The definition of a relapse and an indication for restarting biologicals was an increase of >100 points in CDAI together with a CDAI of >150 points. Among patients with perianal CD, relapses were due to luminal

disease in every case. Mucosal healing was defined as the absence of mucosal lesions and no signs of active inflammation. Health authority regulations require mandatory follow-up appointments at least every 3 months. These visits involve a clinical assessment, a review of patient diaries, CDAI determination, a laboratory assessment (including CRP), and, every 6 months, a chest x-ray. CRP level was regarded as elevated if it exceeded 10 mg/dL. Specific details relating to patient selection and follow-up were standardised and uniform in all participating specialised centres. All participating centres were monitored for quality of care and compliance with regulations by the Hungarian National Health Insurance Fund Administration in June 2011.

End points

Data collection and analysis were performed at the 1st Department of Medicine at the University of Szeged and the 1st Department of Medicine Semmelweis University. The primary end points were time to clinical relapse after discontinuation of infliximab or adalimumab, and the identification of factors associated with the risk of a relapse. The secondary end points were the safety and efficacy of retreatment with biologicals in patients who relapsed. Colonoscopy was offered to all of the patients at the end of the therapy.

Statistical analysis

Variables were tested for normality with Shapiro Wilk's W test. The Chi-squared test and Chi-squared test with Yates correction and logistic regression analysis were used to assess the association between categorical clinical variables and the clinical or endoscopic outcome. Kaplan–Meier survival curves were plotted for analysis with the Log-Rank and Breslow tests. In addition, Cox-regression analysis was utilised to assess the association between categorical clinical variables (gender, smoking, steroid therapy, previous use of biological therapy, and CRP level at 52 weeks) and the probability of a clinical relapse leading to the resumption of biologicals. Variables with $P < 0.1$ were included in the multivariate testing. A P value <0.05 was considered significant. For statistical analysis, SPSS version 15.0 (IBM, Chicago, IL, USA) was used.

RESULTS

Clinical efficacy after weeks 12 and 52 of the 1-year course of biological therapy

The median CDAI at the start of induction therapy was 340 (IQR: 320-354) while the median CRP level was 9.8 mg/L (IQR: 5–27.2). Of the patients enrolled, 2.7% achieved remission at week 2, and 47.3% at week 6. Of patients that initially responded to induction, 70.6% achieved clinical remission at week 12, with a median CDAI of 119 and a median CRP level of 4.3 mg/L. At week 52, the median CDAI was 100 (IQR: 50–149), while the median CRP level was 2.2 mg/L (IQR: 1–5.75). Seventy-two patients had received steroids at the beginning of the 1-year course of biological therapy. Corticosteroids were discontinued in 82% of patients after a median of 8 weeks (IQR: 6–12). Of patients on thiopurines ($n = 103$), 8.8% had stopped the immunomodulators a median of 18 weeks (IQR: 14–25) after initiation of biological therapy. The main reasons for withdrawing thiopurines were the potential for infectious side-effects in cases of combined immunosuppression with biologicals, medication cost or intolerance to the drug. Patients at a high risk of relapse continued to be treated with combined therapy. Forty-three patients agreed to colonoscopy when biological therapy was discontinued, and mucosal healing was demonstrated in 35% of these patients. Dose intensification of the biological drug was needed in 10.4% of patients after a median period of 6 months (IQR: 4–8.25).

Predictors of need to restart of biological therapy

Within 1 year of discontinuation of biological therapy, resumption of therapy was necessary in 45% of patients who had achieved remission, with a median time to resumption of 6 months (IQR: 3.75–12 months). In each case, retreatment was necessitated by a clinical relapse. The clinical characteristics of patients who restarted biological therapy are presented in Table 1. The median CDAI at the time of resumption of biological therapy was 307 (IQR: 253–359) while the median CRP level was 12.5 (IQR: 7–32.6) mg/L. Clinical remission was again achieved in 54.7% of those who restarted biological therapy, whereas 9.1% of the patients underwent surgery. During further follow-up, 43% of the remaining patients needed retreatment within 18–24 months.

In univariate analysis, smoking ($P = 0.027$, OR: 2.34, 95% CI: 1.09–5.01), the use of corticosteroids at the start of the biological therapy ($P = 0.005$, OR: 3.43, 95% CI: 1.4–8.4), previous biological therapy ($P = 0.013$, OR: 3.05, 95% CI: 1.23–7.52), an elevated CRP level at the start of the biological therapy ($P = 0.025$, OR: 2.44, 95% CI: 1.11–5.36) and a dose intensification during the 1-year course of biological therapy ($P = 0.001$, OR: 15.4, 95% CI: 1.83–129.9) all proved to be associated with the need to restart biological therapy. Variables without a

significant association are detailed in Table 2. Gender and CRP levels were included in the multivariate analysis (Table 2). No differences were shown regarding the type on anti-TNF therapy.

In a logistic regression analysis, previous biological therapy ($P = 0.011$, OR: 4.23, 95% CI: 1.39–12.84), and dose intensification ($P = 0.024$, OR: 12.96, 95% CI: 1.39–120.5) were associated with the need to restart biological therapy in these CD patients. Smoking had a noticeable effect that failed, however, to meet statistical significance ($P = 0.053$). Steroid use ($P = 0.06$, OR: 1.67, 95% CI: 0.97–2.83) and elevated CRP ($P = 0.08$, OR: 2.38, 95% CI: 0.92–6.19) at the start of the 1-year biological therapy, and also female gender ($P = 0.15$, OR: 0.49, 95% CI: 0.19–1.28) also appeared to have an effect that was, however, not statistically significant. Predictive factors of restarting biological therapy in CD are listed in Table 3. Analyses were also performed ($n = 108$) after exclusion of steroid-dependent patients ($n = 13$) to assess the predictive factors for patients in remission not receiving steroids. This, however, changed the outcome only slightly: the effects of smoking, previous biological therapy, dose intensification and steroid use at the start of the 1-year course of biological therapy were significant. Moreover, the CRP level at the start of therapy appeared to have a potential role as predictive factor, although in this study the association was not statistically significant.

Table 2 | Univariate regression analysis of need for retreatment with biologicals (significant and insignificant variables)

Factor	*P*-value	OR	95% CI
Dose intensification during 1-year biological therapy	0.001	15.4	1.83–129.9
Corticosteroids at start of biological therapy	0.005	3.43	1.4–8.4
Previous biological therapy	0.013	3.05	1.23–7.52
Elevated CRP at start of 1-year biological therapy	0.025	2.44	1.11–5.36
Smoking	0.027	2.34	1.09–5.01
Elevated CRP at week 52*	0.37	1.69	0.53–5.4
Steroid dependency	0.31	1.67	0.62–4.48
Elevated CRP at week 12*	0.27	1.63	0.68–3.91
Remission at week 12	0.39	1.44	0.62–3.31
Appendectomy	0.6	1.34	0.45–4.03
Refractory to steroid therapy	0.53	1.32	0.56–3.11
Short disease duration	0.5	1.23	0.61–2.74
Type of TNF blocker	0.88	0.94	0.39–2.25
Extraintestinal manifestation	0.80	0.91	0.43–1.94
Concomitant thiopurine therapy	0.81	0.88	0.32–2.45
Previous surgery	0.60	0.82	0.38–1.75
Perianal manifestation	0.50	0.77	0.36–1.64
Male gender*	0.12	0.55	0.26–1.16
Behaviour	0.75	–	–
Location	0.67	–	–

*Included in the multivariate analysis.

Table 3 | Multivariate logistic regression: predictive factors for restarting biological therapy in Crohn's disease

Factor	*P*-value	OR	95% CI
Dose intensification	0.024	12.96	1.39–120.5
Previous biological therapy	0.011	4.23	1.39–12.84
Smoking	0.053	2.74	0.99–7.59
Elevated CRP at start of 1-year biological therapy	0.08	2.38	0.92–6.19
Corticosteroid use at start of 1-year biological therapy	0.06	1.67	0.97–2.83
Female gender	0.15	0.49	0.19–1.28

In a subsequent sensitivity analysis, patients who had undergone dose intensification were excluded. In this multivariable logistic regression analysis, previous biological therapy ($P = 0.035$, OR: 3.50, 95% CI: 1.10–11.1) and male gender ($P = 0.038$, OR: 2.92, 95% CI: 1.06–8.2) were identified as independent predictors of a need to restart biologicals. It was noteworthy that among anti-TNF-naive patients (96/121, 79%) the need for dose intensification (OR: 15.8) during the 1-year period of biological therapy was the only independent predictor of the need to restart biologicals. However, the analysis of this subgroup was underpowered to detect differences, with an OR ranging from 1.5–4.

In a Kaplan–Meier analysis with the Log-Rank and Breslow tests, smoking, concomitant steroids, previous biological therapy, elevated CRP level at week 52 when biological therapy was discontinued, and dose intensification were significantly associated with the time to the restarting of biological therapy (Figure 1). In a subsequent Cox-regression analysis, previous biological therapy ($P = 0.001$, HR: 2.77, 95% CI: 1.53–5.0) and elevated CRP level at week 52 ($P = 0.005$, HR: 2.44, 95% CI: 1.31–4.54) were independently associated with the time to reinitiation of infliximab therapy, with smoking being borderline-significant.

Disease location and behaviour, the presence of the perianal disease, the occurrence of extraintestinal manifestations, and previous surgery were not associated with the reinitiation of biological therapy. No correlation was found between mucosal healing and the frequency of, nor time to, clinical relapse.

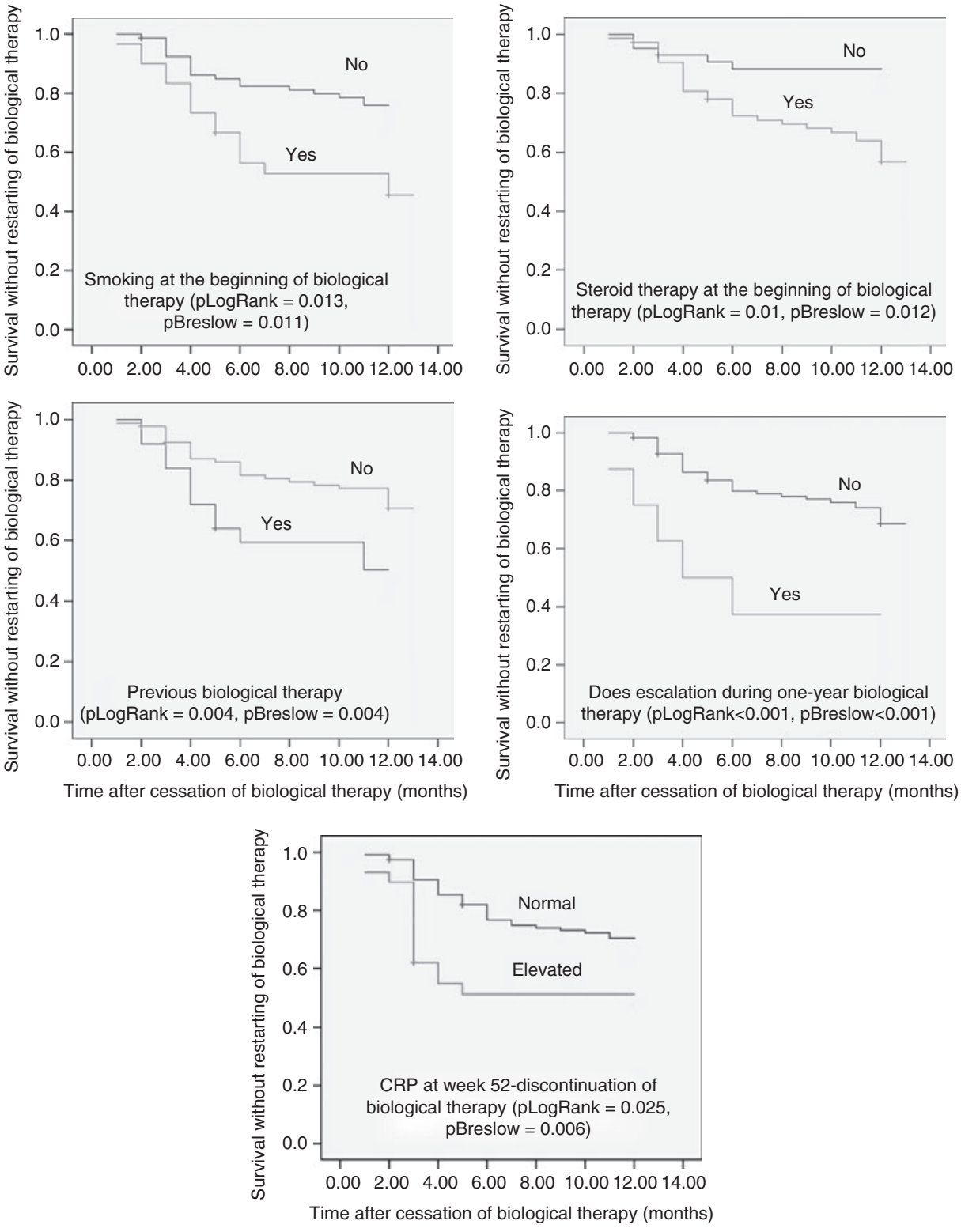

Figure 1 | In a Kaplan–Meier analysis with the Log-Rank and Breslow tests, smoking (pLogRank = 0.013, pBreslow = 0.011), concomitant steroids (pLogRank = 0.01, pBreslow = 0.012), previous biological therapy (pLogRank = 0.004, pBreslow = 0.004), an elevated CRP level at week 52, when the biological therapy was discontinued (pLogRank = 0.025, pBreslow = 0.006), and dose intensification (pLogRank < 0.001, pBreslow < 0.001) were associated with the time to the restarting of biological therapy.

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Adverse events

Adverse events occurred in 10.9% of patients during the 1-year treatment period. None were serious and none led to withdrawal of biological therapy. Steroid premedication was used in 51.2% of patients. Within the follow-up period after reinitiation of biological therapy, 4% of patients developed mild side-effects and 6% displayed an infusion reaction.

DISCUSSION

A major finding of this prospective follow-up study is that a high rate of clinical relapse exists within one year of discontinuing of biological therapy in patients in clinical remission. It was possible to identify clinically relevant predictors of the need to restart biological therapy due to clinical relapse. In univariate analysis, corticosteroid use at induction, smoking, previous biological therapy, elevated CRP level at discontinuation of biological therapy, and dose intensification during the 1-year course of biological therapy were associated with the need for and time to the restarting of biological therapy. Mucosal healing was not associated with the need for biological therapy to be restarted. However, a clear limitation of the present study is that the number of patients assessed by colonoscopy was low, which prevents a firm conclusion. To date, there are no established guidelines as to whether and when biological therapy can be discontinued. Kamm *et al.* [9] proposed that biological therapy should not be stopped in high-risk patients (those who have undergone multiple previous operations, demonstrated intolerance to multiple drugs or in whom the disease is difficult to control). Moreover, subgroups of patients may remain in longstanding clinical remission. In the longitudinal cohort study by Waugh *et al.*, 50% of patients relapsed within 477 days, while 35% remained in sustained clinical remission for nearly 7 years.[10] A recently published review[11] indicates that the average one- and five-year relapse rates after discontinuation of infliximab in CD in the studies reported to date were 45% and 75%. Thus, it is of the utmost clinical importance to identify factors predictive of relapse.

The only prospective clinical trial so far, STORI, identified male sex, the absence of previous surgical resection, steroid treatment in the previous 6-12 months, a CDEIS score >0, leucocyte count >$6.0x10^9$/L, haemoglobin $\leq$ 145 g/L, a CRP level $\geq$ 5.0 mg/L, and faecal calprotectin $\geq$ 300 μg/g as predictors of relapse after the cessation of biological therapy in patients in steroid-free clinical remission.[5] In the present prospective follow-up study, we examined the predictors of clinical relapse in both infliximab and adalimumab-treated CD patients. Dose intensification, previous biological therapy, smoking and steroid therapy at the time of induction, CRP >10 mg/L at the beginning and end of therapy were identified as predictors of the need for the restarting of biological therapy. A similar trend was observed as regards male gender. Retreatment of patients with biologicals was effective and well tolerated in 50% of patients. The overall relapse rates after the discontinuation of biological therapy proved to be similar in both the STORI study and the present study; however, the rates of success of the retreatment differed. Because there were substantial differences in the patient phenotype and management, the studies are difficult to compare. The mean duration of infliximab therapy was more than 2 years in the STORI trial, whereas it was 1 year in the present study. Another important difference was that the patients in the STORI study had been in corticosteroid-free remission for the 6 months prior to inclusion, while in this study treatment was stopped even if steroids could not be tapered off. In the STORI study, eligible patients were those treated with either a thiopurine or methotrexate, whereas in this study 85% of patients received combined immunomodulatory therapy. Lastly, in the present study data revealed that the previous use of biological therapy before the 1-year treatment period may predict the risk of relapse after the termination of anti-TNF therapy, while in the STORI study, the effects of previous biological therapy were not examined.

C-reactive protein is one of the most frequently studied laboratory parameters when predicting disease course in IBD. Schnitzler *et al.*[12] reported in 2009 that CRP normalised in 186 of 309 patients who responded to infliximab, and dropped by more than 50% in 123 additional patients. In the present study, we used a different cut-off for the CRP level (<10 mg/L) as suggested by previous randomised clinical trials with adalimumab[3] and certolizumab[13, 14] and previous findings from this research group.[15, 16] A phase 2 study[14] indicated greater differences in response and remission rates between the certolizumab and placebo groups with a baseline CRP level >10 mg/L. Kiss *et al.*[15] more recently reported that a normal/normalised CRP level at week 12, but not the baseline CRP level (>10 mg/L) was associated with a medium-term clinical benefit. The present study revealed that an elevated CRP level at the start of biological therapy and at week 52 was associated with need for, and time to, reinitiating biological therapy. This group has evaluated the predictive potential of CRP in a further

follow-up study.[16] The accuracy of CRP in identifying patients with active disease during prospective follow-up was good overall (AUC: 0.82). In addition, in Kaplan–Meier and Cox-regression analyses, CRP was an independent predictor of 3- ($P = 0.007$) or 12-month ($P = 0.001$) clinical relapses for patients in remission who had an elevated hsCRP at diagnosis. The cut-off values for both the static comparison (separation of active disease and clinical remission) and the prediction of clinical relapses were calculated by ROC analysis and the cut-off values identified were 10.7 and 10.1 mg/L respectively.

The authors are aware of the limitations of this study. Endoscopic activity was assessed in only a minority of the patients, and therefore it was not possible to determine whether mucosal healing is a predictor of sustained remission after discontinuation of biological therapy. Previous data demonstrated that patients who displayed complete mucosal healing remained in sustained remission when therapy was continuous.[17, 19] Drug trough levels, antibody status[18] and faecal calprotectin were not assessed. In contrast, one of the strengths of the present study is that the study cohort consisted of well-characterised CD patients representing the nationwide clinical practice in Hungary, it employed standardised patient selection and follow-up, as regulated by the Hungarian National Health Insurance Fund Administration, which monitored all participating centres for quality of care and compliance with regulations as of June 2011.

In conclusion, biological therapy was restarted a median of 6 months after discontinuation of biological therapy in almost 50% of CD patients who had achieved clinical remission following a 1-year course of biological therapy. Our findings indicated that previous biological therapy, steroid use and high CRP level at the start of the 1-year period of biological therapy, dose intensification and smoking may predict the need to restart biological therapy in patients with CD. Although the optimal duration of biological therapy is still to be determined, these results suggest that, in the presence of the above predictors, biological therapy should probably be continued for more than one year.

AUTHORSHIP

Guarantor of the article: T. Molnár.

Author contributions: Tamas Molnár, Peter Laszlo Lakatos and Klaudia Farkas contributed to study design, data collection, data analysis, supervising the collection and validation of patients and manuscript preparation. Other authors contributed to data collection and validation of patients and manuscript preparation. All authors have approved the final version of the manuscript.

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