Dosing interval and diagnosis predict infliximab levels in patients with inflammatory bowel disease on maintenance treatment

A. Krajcovicova[1], M. Batovsky[2], M. Gregus[1,3], M. Hlista[4], J. Durina[5], Z. Leskova[1], I. Sturdik[1], M. Gojdic[6], Y. Jalali[1] T. Koller[1], J. Toth[1], M. Huorka[1], T. Hlavaty[1]

(1) Comenius University, Faculty of Medicine, 5th department of Internal Medicine, University Hospital, Bratislava, Slovak republic ; (2) Clinic of Gastroenterology, University Hospital Bratislava, Slovak republic ; (3) Gastroenterology and Hepatology Centre, Nitra,Slovak republic ; (3) Centre of Gastroenterology, Department of Internal Medicine, Teaching Hospital, Trencin, Slovakia ; (4) Gastroenterology Centre, Department of Internal Medicine, Faculty Hospital Nove Zamky, Slovak Republic ; (5) Comenius University, Faculty of Medicine, Department of Urology, University Hospital, Bratislava, Slovak republic.

Abstract

Objective : **The aim of the study was to identify factors influencing infliximab (IFX) trough levels (TL) in patients with inflammatory bowel disease (IBD).**

Methods : **This was a multicentre cross-sectional study performed at 5 large IBD centres in Slovakia. The cohort consisted of IBD patients, treated either with original IFX or CT-P13 biosimilar, who were examined for the IFX TL and antidrug antibodies (ADA) in a central laboratory.**

Results : **The patient cohort consisted of 116 consecutive IBD patients, 68 with Crohn's disease (CD) and 48 with ulcerative colitis (UC). CD patients had significantly lower IFX TL compared to UC, 2.41 (0.998–5.56) mg/L vs. 4.49 (1.76–8.41) mg/L, p = 0.017. During maintenance treatment, significantly higher mean IFX TL were observed in patients with a 4 week dosing interval than in patients with a 6 or 8 (7.44±3.6 µg/mL vs. 4.19±4.2 vs. 3.30±3.1 µg/mL, p = 0.011 and p < 0.0001, respectively). There was no difference in median TL IFX between original IFX and biosimilar CT-P13 (3.25 (1.24–6.52) mg/L vs. 3.03 (1.30–7.10)). IFX TL correlated with ADA (p=0.005). Multiple regression analysis revealed two independent factors for IFX TL: dosing interval (p<0.0001) and diagnosis (p=0.02).**

Conclusion : **In the present study we observed that IBD patients assigned to an intensified dosing interval during maintenance therapy have significantly higher IFX TL than patients receiving conventional 8 week interval. Patients with UC had significantly higher IFX TL.** (Acta gastroenterol. belg., **2018,** 81, **465-470**).

Key words : Crohn's disease ; ulcerative colitis ; infliximab ; antidrug antibodies ; trough levels ; dosing interval.

Background

Infliximab (IFX) is a monoclonal IgG1 antibody biological drug that works against tumour necrosis factor alpha (TNF-α). IFX was the first anti-TNF-α therapy with proven effectiveness in the induction and maintenance of remission in patients with Crohn's disease (CD) (1) and ulcerative colitis (UC) (2,3). In July 2013, the European Medicines Agency licensed the first IFX biosimilar molecule, CT-P13, for the same indications as original IFX (4). To date, available studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CT-P13 and the original IFX treatment in IBD (5,6).

Research shows that the initial response to IFX is high, with up to 90% of patients with inflammatory bowel disease (IBD) responding to induction treatment (7,8). Data from the ACCENT I and ACT 1,2 studies indicate that the administration of 5 mg/kg IFX at 8 week intervals should be considered standard therapy for the maintenance of remission in both CD (9) and UC (2). However, in routine clinical practice, the present authors have encountered numerous patients in whom the therapeutic effect fails to be sustained across the 8 week dosing interval. Furthermore, loss of response has been reported in approximately 20–45% of primary responders (1,7,10,11). The annual risk for loss of response to IFX therapy is 13% per patient-year (12). To optimise IFX treatment, therapeutic drug monitoring has been introduced. Available data suggest the existence of a relationship between clinical efficacy and serum trough levels (TL) of IFX that is independent of ADA formation (13,14). Researchers from the TAXIT trial, which involved a combined pharmacokinetic and treat-to-target approach, have proposed an elective dose-escalation strategy in patients with IFX levels of <3 µg/mL (14).

The aim of the present multicentre cross-sectional study was to identify clinical factors influencing IFX TL in patients with IBD.

Subjects and Methods

Patient cohort

The study involved five large IBD centres in Slovakia (Bratislava-Ruzinov, Bratislava-Antolska, Nitra, Nove Zamky and Trencin). The data of consecutively admitted IBD patients (48 UC and 68 CD), who had been treated with IFX originator or CT-P13 biosimilar and assessed for IFX TL as a part of standard care, were analysed. Data concerning basic demographic and clinical characteristics (age, sex, weight, diagnosis, disease localisation and behaviour according to Montreal classification (15), concomitant immunosuppressive therapy) were collected from the participating centres .

Correspondence to : Anna Krajcovicova, MD, PhD, IBD Centre, Department of Internal Medicine V., Sub-department of Gastroenterology and Hepatology University Hospital Bratislava, Comenius University Bratislava Ruzinovska 6, 826 06 Bratislava, Slovakia.
E-mail: krajann@hotmail.com

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Ethical considerations

The study was approved by the respective local ethics committees. All subjects provided written informed consent to the use of their clinical data for research purposes.

Serum testing

Serum samples were collected within the context of routine clinical management immediately prior to IFX infusion. All samples were sent to a central laboratory for determination of IFX level. The therapeutic range for serum IFX level was defined as 3-7 mg/L, in accordance with the meta-analysis of Moore et al. (16). ADA levels were determined in patients with either a history of hypersensitivity to IFX or IFX levels below the therapeutic range (≤3 mg/L).

Serum levels of IFX and ADA were determined using the RIDASCREEN® IFX Monitoring kit and the RIDASCREEN® Anti-IFX Antibodies kit, respectively (R-biopharm, Germany). The RIDASCREEN® IFX Monitoring kit uses a highly specific monoclonal antibody (MA-IFX6B7) produced at KU Leuven. The lower and upper limits for quantification were as follows: 0.5-12 mg/L at a dilution of 1:100 for IFX; and 20–1000 µg/L at a dilution of 1:200 for ADA. The cut-off for ADA positivity was set at 400 µg/L, in accordance with the recommendations of the manufacturer.

Statistical analyses

All statistical analyses were performed using SPSS 19.0 software (IBM SPSS Inc., Chicago, Illinois, USA). The impact on IFX TL and ADA levels of the selected clinical characteristics was tested using non-parametric tests of qualitative data ($\chi 2$ test with Yates's correction or Fisher's exact test as appropriate). Parametric data were tested for normal distribution using the Kolmogorov-Smirnov test, followed by Student's t-test or ANOVA. Correlations were analysed using the Spearman correlation coefficient. Multiple regression analysis was performed to identify factors with an independent impact on the serum level of IFX and ADA. A two-tailed p-value <0.05 was considered statistically significant. Unless otherwise stated, the results are expressed as the median and interquartile range (IQR) or the mean and standard deviation (SD).

Results

Cohort characteristics

The cohort comprised 116 IBD patients (65 males (56%); 51 females (44%)). The mean age of the cohort was 41.13 ± 11.96 years. Fifty-five patients (47%) were treated with IFX originator, and 61 (53%) with biosimilar CT-P13. Out of 116 IBD patients, 52/68 (76.5%) of CD patients and 14/48 (29.2%) of UC patients were on concomitant immunosuppressive therapy with azathioprine. Two of the analysed serum samples were obtained from CD patients (n = 2) undergoing induction therapy. Both samples were obtained 6 weeks after the first infusion, i.e., immediately prior to the third and final infusion of induction therapy. Maintenance therapy dosing intervals in the present IBD cohort were as follows : 8 weeks, n = 84 (54 CD and 30 UC, 72%) ; 6 weeks, n = 11 (4 CD and 7 UC, 9%) ; and 4 weeks, n = 19 (8CD and 11 UC, 16%). The mean infused dose of IFX was 417 ± 95 mg. Basic demographic and clinical characteristics are shown in Table 1.

Table 1. **Demographic and clinical characteristics of the cohort**

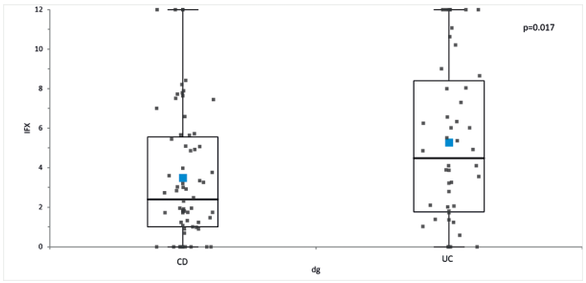
Characteristics	**IBD**	**UC**	**CD**
	(n=116)	**(n= 48)**	**(n= 68)**
Men/women (male %)	65/51 (56%)	25/23 (52%)	40/28 (58%)
Age (mean, range) / years/	41.13±11.96	42.89±11.75	39.89 ±11.95
Localisation	-	E1= 0	L1= 19 (27.9%)
	-	E2= 22 (45.8%)	L2= 25 (36.8%)
	-	E3= 26 (54.2%)	L3=22 (32.4%)
	-	-	L4=2 (2.9%)
Clinical behaviour of	-	-	B1= 26 (38.2%)
Crohn's disease			
	-	-	B2= 10 (14.7%)
	-	-	B3= 32 (47.1%)
Drug			
Infliximab originator	55 (47%)	28 (58%)	27 (40%)
CT-P13	61 (53%)	20 (42%)	41 (60%)
Concomitant		14 (29.2%)	52 (76.5%)
immunosuppressive	66 (56.9%)		
therapy*			
Interval			
Induction	2 (3%)	0	2 (3%)
Every 4 weeks	19 (16%)	11 (23%)	8 (12%)
Every 6 weeks	11 (9%)	7 (14.5%)	4 (6%)
Every 8 weeks	84 (72%)	30 (62.5%)	54 (79%)

*Concomitant immunosuppressive therapy = azathioprine ; UC= ulcerative colitis, CD= Crohn´s disease, IBD=Inflammatory Bowel Disease.

Infliximab serum trough levels

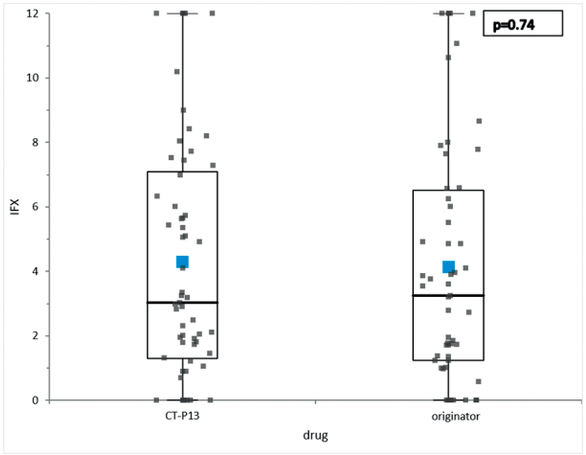
The median IFX TL for the IBD cohort was 3.21 (1.24–6.58) mg/L. IFX TL were significantly lower in CD patients than in patients with UC (2.41 (0.998-5.56) mg/L vs. 4.49 (1.76-8.41) mg/L, p = 0.017) (Fig. 1). No significant difference in mean IFX TL was observed between subgroups of CD patients according to localisation and disease behaviour as well as subgroups of UC patients. No significant difference in mean IFX TL was observed between males and females (4.160 ± 3.73 mg/L vs. 4.287 ± 3.81 mg/L).

Fig. 1. — Infliximab trough levels according to diagnosis.



IFX : infliximab ; dg: diagnosis ; UC : ulcerative colitis ; CD : Crohn's disease ; blue square : median value.

Fig. 2. — Infliximab trough levels in the infliximab originator and CT-P13 biosimilar groups



IFX : infliximab ; blue square : median value.

No significant difference in median serum IFX TL was found between the IFX originator and biosimilar CT-P13 groups (3.25 (1.24-6.52) mg/L vs. 3.03 (1.30-7.10) mg/L) (Fig. 2). Also, we did not find any significant difference in median serum IFX TL between patients with and without concomitant therapy of azathioprine neither in CD subgroups (2.41 (1.10-5.65) mg/L vs 2.43 (0.38-5.20) mg/L nor UC (4.49 (1.66-8.06) mg/L vs 4.52 (1.77-9.14) mg/L), respectively.

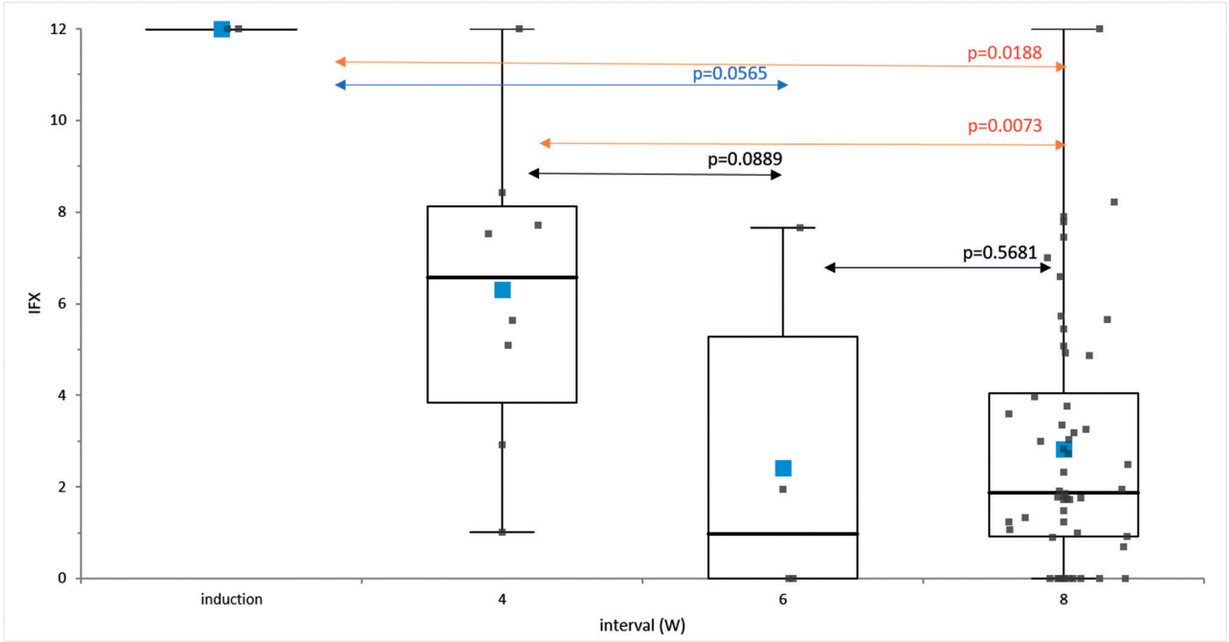
The highest IFX TL were observed in the two induction treatment patients (> 12 mg/L each). During maintenance treatment, significantly higher mean IFX TL were observed in patients with a 4 week dosing interval than in patients with a 6 or 8 week interval (7.44 ± 3.6 µg/mL vs. 4.19 ± 4.2 µg/mL vs. 3.30 ± 3.1 µg/mL, $p = 0.011$ and $p < 0.0001$, respectively) (Fig. 3). The same pattern was observed within the diagnostic subgroups CD (7.433 ± 3.86 µg/mL vs. 2.40 ± 3.619 µg/mL vs. 2.819 ± 2.68, $p = 0.0008$) and UC (8.276 ± 3.73 µg/mL vs.5.219 ± 4.359 µg/mL vs. 4.177 ± 3.71 µg/mL, $p = 0.005$). If divided according to Montreal classification, we did not find any significant difference of mean IFX TL between the subgroups of CD and UC patients.

Multiple regression analysis revealed two independent clinical factors influencing serum IFX TL: diagnosis ($p = 0.0173$); and dosing interval ($p < 0.0001$).

Serum antibodies to infliximab

ADA level was tested in 53/116 serum samples. Of these, 2/53 were obtained from subjects with a history

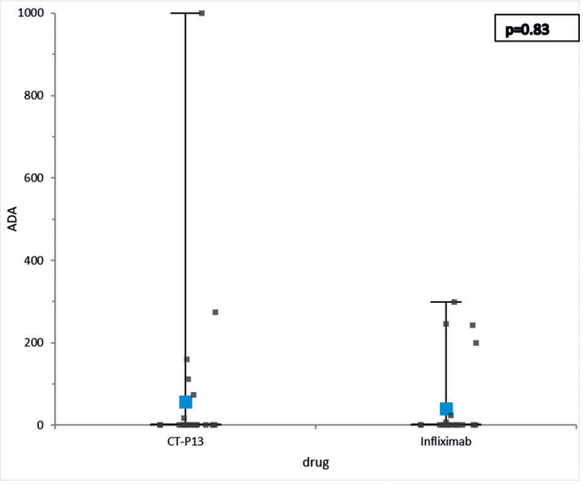
Fig. 3. — Serum infliximab trough levels of the entire cohort according to scheduled dosing interval. The mean value for each dosing interval is indicated by a horizontal line.



Interval (W) : interval in weeks ; IFX: infliximab ; blue square : median value.

of hypersensitivity to IFX (post-infusion dyspnoea, n = 1; anaphylactic reaction post-4th infusion, n = 1), and 51 were obtained from subjects with IFX TL of ≤3 mg/L. Serum IFX ADA were detected in 12/53 IBD patients (CD, n = 7; UC, n = 5). The minimal and maximal detected ADA level was 7.93 µg/L and >1000 µg/L, respectively. In total, 50% (6/12) of patients with detectable ADA were being treated with IFX originator. In 11/12 of the patients with detectable ADA, no serum IFX TL were detectable. The presence of both IFX levels and ADA was detected in one patient only. This patient was treated with IFX originator, had a diagnosis of UC and a dosing interval of 8 weeks. The IFX level was 2.8 µg/mL, and the ADA level was 7.93 µg/L. Most of the patients with detectable ADA (11/12 (92%)) received maintenance treatment every 8 weeks and all of them had immunomodulatory therapy of azathioprine. No difference in mean ADA level was observed between the IFX originator and biosimilar CT-P13 groups (Fig. 4). One patient with detectable ADA (242.68 µg/L) had a documented history of post-infusion dyspnoea. In the patient with a history of anaphylaxis after the 4th IFX originator infusion, no ADA were detectable despite repeated evaluation. Only one patient had a serum ADA level of >1000 µg/L. This patient had a diagnosis of UC and was receiving biosimilar CT-P13 every 8 weeks. Multiple regression analysis revealed that body weight was the only independent factor influencing ADA (p = 0.0348).

Fig. 4. — Comparison of ADA levels between infliximab originator and biosimilar CT-P13 groups.



Discussion

Since their introduction in 1998, anti-TNF-α agents have become widely used in the management of IBD. Recognition of TDM and the treat-to-target concept as the mainstay of individualised anti-TNF-α therapy for IBD is increasing (13,17).

The aims of the present cross-sectional multicentre study were to determine clinical factors influencing IFX TL in IBD patients. The main findings were, that UC patients displayed significantly higher serum IFX TL than patients with CD. The intensified 4 week dosing interval was a strong predictive factor for higher IFX serum levels. Since a drug sensitive ADA assay was used, in 11/12 of the patients with detectable ADA, no serum IFX TL were detectable.

The mean and median serum IFX TL were 4.22 ± 3.7 mg/L and 3.21 (1.24-6.58) mg/L, respectively. The highest IFX TL (>12 mg/L each) were observed in two CD patients at the 6 week time-point of induction therapy, i.e., following two infusions. In patients receiving maintenance treatment, subjects with the intensified 4 week dosing interval had significantly higher IFX TL than subjects with the 8 week interval (mean, 7.5 ± 3.6 mg/L vs. 2.4 ± 3.1 mg/L).

Previous authors have proposed various cut-off values for therapeutic serum IFX levels, ranging from 1 mg/L to >7 mg/L (18). In 2016, a meta-analysis of 22 studies by Moore *et al.* found that a >2 µg/mL IFX TL level during maintenance therapy was associated with a higher probability of clinical remission (risk ratio (RR), 2.9; 95% CI, 1.8 ± 4.7; p < 0.001), and mucosal healing (RR, 3.0; 95% CI, 1.4 ± 6.5; p = 0.004) (16). The algorithm proposed by Afif et al. suggests that patients with IFX TL below the therapeutic range (<1.4 µg/mL) and no detectable ADA require an intensification of IFX therapy, whereas patients with IFX TL within the therapeutic range (>1.4 µg/mL) and active disease should be switched to a non-anti-TNF agent (19). However, other authors have shown that intensification of anti-TNF-α agent therapy may also be effective in patients who develop ADA (20,21). The present results suggest that differing cut-off IFX TL are warranted for intensified regimens (4 to 6 weeks) and for regular maintenance treatment administered at 8 week intervals.

In the present study, significantly lower IFX TL were observed in patients with CD than in patients with UC (p = 0.017). Out of 68 CD, 54 (79%) had 8 week dosing interval compared to 30/48 (62.5%) of UC patients. Previous research has demonstrated differences in the pharmacokinetics of prescribed biological agents in the two types of IBD (22,23). Although IFX has been available for two decades, with the exception of the issue of neutralising antibodies, limited data are available concerning the factors that influence the pharmacokinetics of monoclonal antibodies (24). Uncontrolled studies have shown that IFX dosing intensification is beneficial in patients with severe acute UC, and results in a reduction of up to 80% in the rate of early colectomy (25). Yarur et al. demonstrated an association between higher median serum IFX levels and fistula closure in patients with CD (15.8 vs. 4.4 µg/mL, p < 0.0001) (26). Randomised controlled trials have been performed to compare anti-TNF-α drug efficacy between UC and CD patients. These have demonstrated relatively low rates of remission in UC following the administration of subcutaneous adalimumab induction therapy (27-29) at

doses that result in relatively high rates of remission in CD. A plausible assumption, therefore, is that different regimens are warranted according to IBD subtype and there is a requirement for higher IFX TL in patients with severe disease.

Research has shown that ADA formation occurs in a proportion of patients assigned to scheduled maintenance biological therapy (30). The development of antibodies has been associated with an increased risk of infusion reaction and a loss of response to treatment (31).In the present study, ADA formation was observed in 10.3% (12/116) of IBD patients. In 11/12 (92%) of these subjects, this was associated with undetectable levels of serum IFX. A meta-analysis of 13 studies and a total of 1378 IBD patients found that the presence of ADA increased the risk of a loss of response to IFX therapy. A comparison with the ADA-negative group revealed a RR of 3.2 (95% CI: 2.0-4.9, $p < 0.0001$) (32). Patients with high titers of anti-drug antibodies (levels of antibodies against IFX >9 µg/ml) do not respond well to dose escalation of the same drug, but switching within therapeutic class to another anti-TNF agent may restore clinical response ($P<0.03$) (33). According to our results, ADA positivity with a high sensitive assay led to undetectable IFX levels. Clinical management of IBD patients with clinical remission and positive ADA is controversial. Based on the controversial results of clinical studies and lack of controlled prospective studies, it is difficult to base the decision on discontinuation of IFX treatment solely on the presence of ADA. More complex approach including clinical, biochemical and endoscopic findings must be pursued.

The pharmacokinetics of infliximab, as of for all drugs administered intravenously, does not depend only on trough levels but also on post-infusion levels, distribution volume and clearance mechanisms. In our study we observed that body weight was an independent factor influencing ADA. There is no consensus on the influence of body weight and/or obesity on the response to IFX in IBD. However it has been shown that elevated BMI is associated with a poorer response to infliximab (34).

The present analyses revealed no difference in median IFX TL or ADA level between the IFX originator and biosimilar CT-P13 groups. These findings are consistent with the results of a recent study. This demonstrated that, in IBD patients, anti-IFX antibodies recognise and cross-react with CT-P13 and neutralise drug activity (35).

Present study had several limitations. First, the cohort was relatively small. Second, the analyses were restricted to characteristics detailed on the IFX TL laboratory request form. This precluded evaluation of clinical disease activity, and other laboratory findings such as CRP, calprotectin etc.

A strength of the present study was the use of the highly specific monoclonal antibody MA-IFX6B7. This method has been validated in clinical trials such as TAXIT (36). MA-IFX6B7 is equally suitable for measurement of the TL of Remicade®, Inflectra® and Remsima™ (37).

In conclusion, the present study demonstrated that IBD patients undergoing induction therapy show significantly higher IFX TL than patients on maintenance therapy, and that patients assigned an intensified dosing interval have significantly higher IFX TL than patients receiving conventional 8 week interval treatment. A further clinical factor leading to higher IFX TL was UC with ADA negativity. A reasonable assumption, therefore, is that a number of factors other than antibody formation modulate the pharmacokinetics of IFX, and thus IFX TL. The present data suggest that an adjustment in the therapeutic range of IFX TL may be required in accordance with specific clinical characteristics. Further research is required to re-evaluate conventional IFX therapy regimens.

Author's contribution

AK collected the data, performed the statistical analyses and drafted the manuscript. BM, GrM, HlM, DJ, ZL, SI, GoM, JY, KT, TJ, HuM contributed to the patients' recruitment, acquisition of the data and reviewed manuscript. TH designed the study, participated in the data collection, interpretation and analysis and revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest and source of funding

In the last 5 years, Anna Krajcovicova has served as a speaker for MSD, Egis and Takeda. Tibor Hlavaty has served as a speaker or advisory board members for either MSD, Abbvie, Hospira, Egis, Alfa Wasserman, Pfizer and Vifor. Tibor Hlavaty has received scientific grants and unrestricted educational grants from MSD, Hospira and Abbvie. Tomas Koller has served as an advisory board member for Hospira. Martin Huorka has served as a speaker and advisory board member for Abbvie, Hospira and Egis. Milos Gregus has served as a speaker for Abbvie, MSD, Pfizer, Takeda, Hospira, Ferring Pharmaceuticals, Alfa Wasserman. Milos Gregus has received payment for development of educational presentation including speaker's bureau for Takeda, Hospira, MSD, Egis, Alfa Wasserman, Vifor. For the remaining authors there are no conflicts of interests.

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