Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels/antidrug antibody levels or clinical/biochemical markers play a more important role?

Journal:	*Journal of Crohn's and Colitis*
Manuscript ID	ECCO-JCC-2016-0704.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	02-Nov-2016
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Subject:	Biomarkers

Classifications:	Biomarkers

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November 02, 2016

Prof. Laurence Egan, MD
Editor in Chief
Journal of Crohn's and Colitis

Prof. Shomron Ben-Horin, MD
Associate Editor

Dear Editor in Chief,
Dear Associate Editor,

Please find attached the revised version of our manuscript:

Article title: "Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels/antidrug antibody levels or clinical/biochemical markers play a more important role?"

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We thank the reviewers and associate editor for the detailed and helpful comments that helped in further clarifying the manuscript.

We are sending revised version as requested to the editorial office: **in red the new text** (and NOT SHOWING the text that was removed):

Associate Editor's comment:

Please consider to include in the manuscript itself the results you reported in the response letter, namely that "Week 14 or 30 drug cut-off levels were not associated with clinical outcomes at week 30 or 54 in a ROC analysis (AUC 0.47-0.60)". This is importatnt as it stands in contrast to Cornille et al findings reported in Gut 2014 (Ref 35), and is especially pertinent since you devoted a full paragraph in page 21 to discuss Cornille publication. Your findings are thus important message for clinicains to understand that w14 levels can not still be taken as holy grail to predict long term outcomes, so I think these week 14 drug levels analyses (for UC and CD) should be included in the manuscript Results section, and referred to in the Discussion when you discuss Cornille paper.

Thank you for the comment. We included these results and revised the Discussion in our manuscript as suggested.

Sincerely yours,

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TITLE PAGE

Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels and antidrug antibody levels or clinical and biochemical markers play a more important role?

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Short title: Prediction of clinical efficacy of biosimilar infliximab therapy

Non-standard abbreviations:

TL: trough level

ADA: antidrug antibody

AUC: area under the curve

OR: Odds ratio

CI: confidence interval

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Conference presentation: 11th Congress of ECCO, March 16-19, 2016, Amsterdam, The Netherlands (oral presentation), DDW 2016, May 21-24, 2016, San Diego, California, United States (poster presentation), UEG Week 2016, October 15-19, 2016, Vienna, Austria (the abstract has been accepted for poster presentation)

ABSTRACT

Background and Aims: Biosimilar infliximab CT-P13 received European Medicines Agency (EMA) approval in June 2013 for all indications of the originator product. In the present study we aimed to evaluate the predictors of short- and medium-term clinical outcome in patients treated with the biosimilar infliximab at the participating IBD centres in Hungary.

Methods: Demographic data were collected and a harmonized monitoring strategy was applied. Clinical and biochemical activity were evaluated at weeks 14, 30 and 54. Trough level (TL) and anti-drug antibody (ADA) concentration were measured by ELISA (LT-005, Theradiag, France) at baseline at 14, 30 and 54 weeks and in 2 centres at weeks 2 and 6.

Results: 291 consecutive IBD patients (184 CD/107 UC) were included. In UC, TLs at week 2 were predicting both clinical response and remission at week 14 and 30 (clinical response/remission at week 14: AUC=0.81, p<0.001, cut-off: 11.5µg/ml/AUC=0.79, p<0.001, cut-off: 15.3µg/ml; clinical response/remission at week 30: AUC=0.79, p=0.002, cut-off:11.5 µg/ml/AUC=0.74, p=0.006, cut-off: 14.5µg/ml), while ADA positivity at week 14 was inversely associated with clinical response at week 30 (58.3%vs.84.8%,p=0.04). Previous anti-TNF exposure was inversely associated with short-term clinical remission (week 2: 18.8% vs. 47.8%, p=0.03, at week 6: 38.9% vs. 69.7%, p=0.013, at week 14: 37.5% vs. 2.5%, p=0.06). In CD, TLs at week 2 were predicting short term- (week 14 response/remission, $AUC_{TLweek2}$=0.715/0.721, p=0.05/0.005) but not medium-term clinical efficacy. In addition, early ADA status by week 14 (p=0.04-0.05 for week 14 and 30), early clinical response (p<0.001 for week 30/54) and normal CRP at week 14 (p=0.005-0.0001) and previous anti-TNF exposure (p=0.03-0.0001 for week 14, 30 and 54) were associated with short-and medium-term clinical response and remission.

Conclusions: In UC, early TLs were predictive for short-and medium term clinical efficacy, while in CD, week 2 TLs were associated only with short-term clinical outcomes.

Key words: biosimilar infliximab, inflammatory bowel diseases

Introduction

Biosimilar infliximab CT-P13 was approved by the European Medicines Agency (EMA) in 2013 and by the Food and Drug Administration (FDA) in 2016 for the use in all indications of the originator infliximab[1,2]. The use of biosimilar infliximab is mandatory in Hungary since May 2014 in all new inflammatory bowel disease (IBD) patients, including anti-TNF naïve patients and in patients who were previously successfully treated with the originator product but were on drug holiday for at least 12 months. Data on the efficacy, safety and immunogenicity of the biosimilar IFX in IBD from real-life cohort studies published so far showed comparable outcomes to those of the originator product[3,4,5,6,7,8,9,10,11,12,13,14].

The efficacy of anti-TNF therapy in Crohn's disease (CD) has been reported to be associated with shorter disease duration, isolated colonic disease location, absence of previous surgery, young age and non-smoking status[15]. High C-reactive protein (CRP) level (≥0.8 mg/dl) at start of the infliximab (IFX) therapy was associated with corticosteroid-free clinical remission at week 26 in CD patients[16].

In the study by García-Bosch et al., higher albumin level was predicitve of clinical remission at week 8 (OR 1.4, CI 95 % 1.06–1.8; p= 0.017), while clinical remission at week 8 was the only independent predictor for maintained clinical remission at week 30 and 54 in ulcerative colitis (UC) patients treated with IFX. Previous cyclosporine therapy, absence of concomitant immunomodulator and absence of response at week 8 were associated with a higher colectomy rate at week 54[17].

The use of therapeutic drug monitoring (TDM) has become widespread in management of patients receiving biological therapy. CD patients with loss of response (LOR) to infliximab had significantly lower IFX trough levels (TLs) and higher anti-drug antibody (ADA) levels compared to responders (cut-off values for identifying LOR: <0.5 μg/ml for IFX TL and ≥10 U/ml for ADA)[18].The rate of clinical remission was higher in CD

patients with detectable IFX TLs compared to patients with undetectable serum IFX TLs after a median of 14 infusions (82% vs. 6%; $p<0.001$)[19]. In the TAXIT (Trough level Adapted infliXImab Treatment) trial IBD patients were assigned to groups either receiving infliximab based on their clinical activity or based on their TL after reaching the target infliximab concentration (3-7 µg/mL). No significant difference was found between the TDM-based strategy and clinically-based dosing in achieving clinical remission after one year. However, TDM-based dosing was associated with fewer flares during follow-up[20]. According to the findings of the Tailored Treatment With Infliximab for Active Crohn's Disease (TAILORIX) study, trough-level-based and symptom-driven dose adaptation did not differ in terms of the proportion of CD patients being in steroid-free clinical remission from week 22 to 54 and in endoscopic remission at week 54[21].

Until now, few data are available on the predictive potential of the IFX TL and ADA status in IBD patients treated with IFX. In a post-hoc analysis of a multicenter, prospective trial with the originator IFX, TLs at week 2 were significantly associated with week 14 and 30 clinical remission and mucosal healing at week 30 in UC[22].

Therefore, in the present study we aimed to prospectively identify the predictors of short- and medium-term clinical outcome in patients treated with the biosimilar infliximab CT-P13 in a nationwide cohort of IBD patients. In addition to clinical factors, the predictive potential of biochemical markers and serial TDM samples were also evaluated.

Materials and Methods

The inclusion period of this prospective, nationwide, multicenter, observational study started in May 2014 at 12 IBD centres in Hungary. Unselected, consecutive IBD patients starting on biosimilar infliximab were prospectively enrolled. No patient received originator infliximab 12 months prior to the initiation of biosimilar infliximab therapy. A harmonized monitoring strategy was applied as requested by the Hungarian National Health Fund (Table 1). Clinical (Crohn's Disease Activity Index (CDAI) in CD and partial Mayo Score (pMayo) in UC) and biochemical activity (including total blood count [TBC], serum C-reactive protein [CRP, normal cut-off: 5 mg/l], and albumin) were evaluated at baseline and at weeks 14, 30 and 54.

Disease location and disease behaviour in CD and disease extent in UC were classified according to the Montreal classification[23].

In CD, clinical remission was defined as a CDAI < 150 points or no fistula drainage as assessed by the Fistula Drainage Assessment, while clinical response was defined as a decrease in CDAI with more than 70 points or at least 50% reduction in the number of draining fistulas[24,25]. In UC, clinical remission was defined as a pMayo of less than 3 points and clinical response was defined as a decrease in the pMayo score with more than 3 points[26]. At Week 14, response was evaluated, which qualified patients for maintenance treatment.

Biosimilar IFX TLs and ADA levels were measured using the conventional and bridging enzyme-linked immunosorbent assay [ELISA, [LISA TRACKER, Theradiag, France]] at baseline, at weeks 14, 30 and 54 in all participating centres and additionally at weeks 2 and 6 in two centres (First Department of Medicine, Semmelweis University, Budapest and First Department of Medicine, University of Szeged, Szeged. The ELISA kit was validated for accuracy and reproducibility of TDM of the biosimilar IFX [Theradiag, France/Hospira, UK]. ELISA measurements were performed at the Department of Laboratory

Medicine, Semmelweis University, Budapest. A more detailed description of the case ascertainment and monitoring strategy of the present cohort was published earlier[6]. The detection cut-off value of biosimilar infliximab TL was 0.1 µg/ml, while 3-7 µg/ml was defined as therapeutic. At week 2 and 6, cut-off values of biosimilar infliximab TL were calculated by ROC analysis. The standard cut-off value of ADA level was 10 ng/ml. The cut-off value of CRP was 10 mg/l. Due to cohort size the predictive potential of clinical and biochemical factors at week 54 were calculated in CD, but not in UC.

Statistical considerations

For categorical data frequency distributions were performed, for continuous variables medians and interquartile ranges were calculated. Receiver operating characteristics (ROC) analysis was performed to identify cut-off values of TL at week 2 and 6 to identify patients in clinical response or remission at week 14, 30 and 54. Chi-squared test was used to evaluate differences within subgroups of patients with CD and UC. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) of week 2 TL values were calculated. Logistic regression analysis was used to test the association between disease characteristics, clinical and biochemical factors and clinical response or remission at week 2, 6, 14, 30 and 54, independent variables with a p value of <0.1 were selected for multivariate analysis. A p value of < 0.05 was considered as significant. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL).

Ethical statement

Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU [292/2014]). The study was registered at the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCEPP/SDPP/9053]. Written informed consent was signed by all participants.

Results

A total of 291 consecutive IBD patients - 184 patients with CD and 107 patients with UC - were enrolled in the study. Patient characteristics are shown in Table 2. Mean TLs were 20.1, 14.7 and 5.1 µg/ml at weeks 2, 6 and 14 (n=124, 86 and 158). Cumulative ADA positivity rates were 8.7%, 19.3%, and 28.0% in IBD patients at weeks 0, 14, and 30 (n_{total}= 229, 192 and 143).

Ulcerative colitis

Association between early trough levels and ADA status and clinical outcomes

TLs measured at week 2 in UC were predictive for both clinical response and remission at week 14 and 30 (clinical response at week 14: AUC=0.81, p<0.001, cut-off: 11.5 µg/ml, clinical remission at week 14: AUC=0.79, p<0.001, cut-off: 15.3 µg/ml; clinical response at week 30: AUC=0.79, p=0.002, cut-off: 11.5 µg/ml, clinical remission at week 30: AUC=0.74, p=0.006, cut-off: 14.5 µg/ml) (Figure 1A, 1B, 2A, 2B). Sensitivity, specificity, PPV, NPV were also calculated. (Table 3.)

TLs measured at week 6 were not associated with either clinical response or remission at week 14 or 30 (clinical response at week 14: AUC: 0.62, p=0.40, clinical remission at week 14: AUC: 0.63, p=0.19, clinical response at week 30: AUC: 0.76, p=0.08, AUC: 0.68, p=0.12). TLs measured at week 14 or 30 were also not associated with clinical outcomes at week 30 or 54 in a ROC analysis (AUC: 0,47-0,60).

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Cumulative ADA development at week 14 was inversely associated with clinical response at week 30 (58.3% vs. 84.8%, p=0.04, OR: 0.25, 95%CI: 0.06-1.02), but not with clinical response and remission at week 14 (75% vs. 88.7%, p=0.16, OR: 0.38, 95%CI: 0.10-1.52; 62.5% vs. 66.1%, p=0.79, OR: 0.85, 95%CI: 0.27-2.67) and clinical remission at week 30 (41.7% vs. 56.5%, p=0.36, OR: 0.55, 95%CI: 0.15-1.99). Concomitant steroid or AZA therapy was not associated with ADA positivity at week 2, 6, 14 and 30.

Predictive potential of clinical and biochemical factors

Previous anti-TNF exposure was inversely associated with clinical remission at week 2 (18.8% vs. 47.8%, p=0.03, OR: 3.97, 95%CI: 1.06-14.92), at week 6 (38.9% vs. 69.7%, p=0.013, OR: 0.28, 95%CI: 0.097-0.792), but not with clinical response at week 2 and week 6 (week 2: 43.8% vs. 59.3%, p=0.245, OR: 0.53, 95%CI: 0.18-1.56; week 6: 61.1% vs. 74.4%, p=0.252, OR: 0.54, 95%CI: 0.19-1.57) and there was a tendency for association with clinical remission at week 14 (p=0.06). No association was found between previous anti-TNF exposure and clinical response or remission at week 30 (p=0.12 and p=0.11). Previous anti-TNF exposure was associated with ADA development at week 0, 2 and 6 (p<0.001, p<0.001 and p=0.012), but was not associated with cumulative ADA development at week 14 and 30 (p=0.192, OR: 0.552, 95%CI: 0.235-1.30 and p=0.38, OR: 0.69, 95%CI: 0.31-1.53). Gender, disease extent, concomitant steroid or AZA therapy were not associated with clinical response or remission at weeks 2, 6, 14 and 30 (Tables 4 and 5).

Crohn's disease

Association between early trough levels and ADA status and clinical outcomes

Trough levels measured at week 2 in CD were associated both with clinical response and remission at week 14 (Figure 3A and 3B).

Trough levels measured at week 6 were not predictive for the clinical efficacy at weeks 14, 30 and 54 (clinical response at week 14: AUC=0.47, p=0.8, clinical remission at week 14: AUC=0.6, p=0.22, clinical response at week 30: AUC=0.5, p=0.98, clinical remission at week 30: AUC=0.6, p=0.31, clinical response at week 54: AUC=0.51, p=0.97, clinical remission at week 54: AUC=0.45, p=0.69). Week 14 or 30 cut-off levels were also not associated with clinical outcomes at week 30 or 54 (AUC: 0.50-0.54).

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ADA positivity was inversely associated with clinical remission at week 14 (48.5% vs. 66.9%, p=0.04, OR: 2.15, 95%CI: 0.996-4.63), but not with clinical response at week 14 (81.8% vs. 90.6%, p=0.15, OR: 0.46, 95%CI: 0.16-1.33), clinical response and remission at week 30 and 54 (clinical response at week 30: 69.2% vs. 85.3%, p=0.054, OR: 0.39, 95%CI: 0.14-1.04, clinical remission at week 30: 46.2% vs. 64.2%, p=0.09, OR: 0.48, 95%CI: 0.20-1.13, clinical response at week 54: 59.1% vs. 75.5%, p=0.16, OR: 0.47, 95%CI: 0.16-1.35, clinical remission at week 54: 45.5% vs. 60.4%, p=0.24, OR: 0.55, 95%CI: 0.2-1.49)

Predictive potential of clinical and biochemical factors

Normal CRP level at week 14 was associated with clinical response and remission at week 14 ($p<0.001$ and $p<0.001$) and at week 30 ($p<0.001$ and $p=0.005$) but not with clinical response and remission at week 54 ($p=0.10$ and $p=0.114$). Previous anti-TNF exposure was inversely associated with clinical response and remission at week 14 ($p=0.002$ and $p=0.002$), clinical response and remission at week 30 ($p=0.008$ and $p=0.03$) and at week 54 ($p<0.001$ and $p=0.004$). Previous anti-TNF exposure was associated with ADA development at week 0 and 2 ($p<0.001$ for both), but not at weeks 6, 14 or 30. Clinical response at week 14 was associated with clinical response and remission at week 30 ($p<0.001$ and $p<0.001$) and at week 54 ($p<0.001$ and $p<0.001$). Clinical remission at week 14 was associated with clinical

response and remission at week 30 (p<0.001 and p<0.001) and with clinical response and remission at week 54 (p<0.001 and p<0.001). Gender, disease location, disease behaviour, perianal disease, previous or concomitant steroid or AZA therapy was not associated with clinical response or remission at weeks 14, 30 and 54 (Tables 4, 5 and 6). Normal CRP and clinical response or remission at week 14 but not previous anti-TNF exposure was significantly associated with clinical response or remission rates at week 30 or 54 in multivariate analysis. Of note, previous anti-TNF exposure can not be assumed to be independent from week 14 clinical outcomes.

Discussion

This is the first report on the predictive value of TL levels and ADA status in IBD patients treated with biosimilar infliximab in a prospective, nationwide, multicentre IBD cohort. In UC, TLs measured at week 2 were associated with clinical response and remission at both week 14 and 30, while ADA development at week 14 was inversely associated with clinical response at week 30.

These results are in agreement with previous observations in UC patients treated with the originator IFX therapy, where TL ≥ 20.7 ug/l at week 2 was significantly associated with clinical remission week 14 and 30 [22]. A retrospective study from a tertiary referral center investigated the association between early TLs and short-term mucosal healing (STMH) at week 14. Patients with STMH had higher TLs at week 2, 6 and 14 compared to patients without STMH (ROC curve analysis: infliximab concentration thresholds of 28.3, 15.0, and 2.1 mg/mL)[27].

In a study involving 115 UC patients treated with IFX over a median period of 13.9 months, patients with detectable IFX TL had higher rates of clinical remission (69% vs. 15%; p<0.001), endoscopic improvement (76% vs. 28%; p<0.001), endoscopic remission (27% vs. 8%; p=0.021) and a lower rate of colectomy (7% vs. 55%; p<0.001) compared to patients

with undetectable serum IFX TL. Univariate analysis identified baseline Mayo score ≥10, antibodies to IFX and detectable IFX TL as predictors for clinical remission and colectomy (clinical remission: Mayo score≥10: OR: 0.36 (95%CI: 0.15-0.83) p=0.028, antibodies to IFX: OR: 0.15 (95%CI: 0.06-0.40) p<0.001, detectable IFX level: OR: 12.0 (95%CI: 4.76-30.26) p<0.001; colectomy: Mayo score≥10: OR: 3.42 (95%CI: 1.56-7.51) p=0.004, antibodies to IFX: OR: 2.71 (95% CI: 1.22-6.01), p=0.023, detectable IFX TL: OR: 0.13 (95%CI: 0.05-0.35) p<0.001). In addition, undetectable IFX TL was a strong predictor for the need for colectomy (OR 9.3, 95%CI: 2.9-29.9; p<0.001)[28]. According to the results of the post-hoc analysis of the ACT-1 and ACT-2 (Active Ulverative Colitis Trials) trials, serum IFX levels at weeks 8, 30 and 54 were significantly in higher in UC patients being in clinical response and/or remission or having mucosal healing compared to patients having lower IFX levels. Furthermore, patients with lower IFX levels were more likely to fail to maintain clinical efficacy compared to patients with higher IFX levels.[29]

In CD, week 2 TL was associated and ADA positivity was inversely associated with clinical remission at week 14. In contrast, TDM was not predicting medium-and long-term clinical efficacy. Other studies investigated the association of TL and ADA status of originator IFX with clinical outcomes. In the study by Maser et al., out of 105 CD patients 90 patients continued maintenance scheduled IFX treatment with a median follow-up of 23 months. The rate of clinical remission was higher in CD patients with detectable IFX TL (82% vs. 6%; p<0.001). In addition, detectable IFX TL was associated with lower CRP level (2.0 vs 11.8 mug/L; p< 0.001) and endoscopic improvement (88% vs 33%; p< 0.001)[30]. In a study with 125 consecutive CD patients starting IFX therapy, antibody concentration of ≥8.0 µg/ml was a predictive factor of a shorter duration of clinical response. The median duration of clinical response in patients with antibody concentrations ≤ 8.0 µg/ml was 71 days (95%CI: 57-88) compared to 35 days (95%CI: 28-42) in the group of patients with antibody

concentrations of ≥8.0 µg/ml (p<0.001). Antibodies against IFX were independently associated (p<0.001), whereas the use of immunosuppressive agents (p=0.58) and the infliximab concentrations (p=0.70) were not associated with shorter duration of clinical response in logistic-regression analysis[31].

In CD, normal CRP level at week 14 was associated with clinical remission at week 14 and at week 30. CRP is an accurate marker strongly correlating with disease activity and endoscopic inflammation in patients with CD[32,33]. High-sensitivity CRP (hs-CRP) positivity at diagnosis might be a helpful marker also for patient classification, as it was associated with colonic and ileocolonic disease location, non-inflammatory disease behaviour and with the need for azathioprine or biological therapy during the later disease course. In addition, in patients having elevated hs-CRP level at diagnosis, hs-CRP was an independent predictor for clinical relapse at 3 and 12 month [34]. In the post-hoc analysis of A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I (ACCENT I) trial, week 14 IFX TL with a cut-off point of ≥3.5 mg/mL and a CRP decrease ≥ 60% from baseline at week 14 (OR: 3.5, 95% CI: 1.1-11.4 and OR: 7.3, 95%CI: 1.4-36.7) were predictive factors for long-term sustained clinical response in CD patients with elevated baseline CRP level (>8.0 mg/L) given infliximab 5 mg/kg every 8 weeks. In contrast, in our study TLs measured at week 14 were not associated with medium-, long term (week 30 and week 54) clinical outcomes[35]. In another post-hoc analysis of the ACCENT I trial high baseline CRP level (cut- off points of 0.7– 2.5 mg/ dL) was associated with maintenance of clinical remission through 54 weeks of IFX therapy. Normal week-14 CRP levels with cut-off points of 0.5, 0.6, 0.7 and 0.9-mg/ dl were significantly associated with maintained clinical response, while the absolute reduction of CRP level between baseline and week 14 was significantly associated with the maintenance of clinical response and remission between weeks 14 and 54[36].

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We found no association between other investigated clinical factors, as gender, disease behaviour, disease extent, concomitant steroid/azathioprine therapy and the clinical outcomes in IBD patients on biosimilar infliximab therapy. Similarly, Seow et al. reported no effect of concurrent immunosuppressive therapy on clinical remission and colectomy rates in a cohort of 115 UC patients on IFX therapy[28]. In contrast, in the study by Papamichael et al., univariate analysis identified female gender (p=0.039), concomitant immunomodulators at start of infliximab (p=0.028) as variables associated with short-term mucosal healing in UC patients[27]. Of note, previous anti-TNF exposure was inversely associated with clinical remission at week 14, 30 and 54 in CD, while in UC, previous anti-TNF exposure was only associated with short-term clinical outcomes. In the previous study of our study group enrolling 210 IBD patients on biosimilar infliximab therapy, clinical remission rates were also influenced by previous exposure to the originator infliximab both in CD and UC at week 14 but not at week 30 (at week 14 clinical remission with no previous exposure vs. previous exposure to the originator infliximab: CD: 60.9% vs. 35.7% p<0.05, UC: 65.1% vs. 33.3%, p<0.05 and p<0.05, at week 30: CD: 60% vs. 38.9%, p=0.13, UC: 78.9% vs. 33.3%, p=0.06)[6].

The main strengths of the present study are the prospective data collection and the standardized, harmonized monitoring strategy. So far, the predictive value of TL and ADA level in IBD patients receiving biosimilar infliximab therapy was not studied. Limitations of our study are that TDM measurement at week 2 and 6 was not mandatory, only selected centres participated. Furthermore, endoscopic evaluation was not performed at weeks 14 or 30 and predictive potential was evaluated compared to clinical and biochemical remission criteria. Of note, the assay was not able to detect ADA in the presence of drug, which may have influenced the ADA clinical outcome associations as suggested in recent publications.[37]

In conclusion, TL measured at week 2 might be an important factor in the prediction of short-and medium-term clinical efficacy in UC and short-term clinical outcomes in CD

patients treated with biosimilar infliximab. Further prospective studies are needed to determine the role of TDM in the prognosis of the clinical efficacy of biosimilar infliximab therapy. In addition, previous anti-TNF exposure has been proven to be a relevant factor associated with clinical efficacy throughout the 54-week treatment period in CD, while it was associated only with short-term clinical outcomes in UC.

Funding

This work was supported by OTKA (Hungarian Scientific Research Fund) Research Grant 2015 (Grant ID: 115345).

Conflicts of interest

LG, ZK, MR, MP, LB, BG, TK, LL, AP, AS TGT, EB, SZ - none, ZV, PAG, BDL- have been a speaker: AbbVie, Ferring, and Takeda, RB, KF have been speaker for Abbvie and Ferring . KBG has been a speaker and/or advisory board member: Amgen, AbbVie, Ferring, Hospira, MSD, Pfizer, Sandoz, Tigenix and Takeda**.** PM, TM, KP, TSZ, AV have been a speaker and/or advisory board member: AbbVie, EGIS, Ferring, MSD and Takeda, PLL has been a speaker and/or advisory board member: AbbVie, EGIS, Falk Pharma GmbH, Ferring, Genetech, Hopsira, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka Pharma, Pharmacosmos, Pfizer, Roche and Takeda and has received unrestricted research grant: AbbVie, MSD and Hospira/Pfizer

Acknowledgements

LG performed data collection, and drafted the manuscript. ZV, PAG, MR, KBG, RB, KF, JB, LB, BG, TK, LL, PM, MJ, KP, MP, AP, LL, AS, TS, ZS, GTT, AV, BDL, ZK, ZS, TM

performed data collection. EB performed measurements for therapeutic drug level monitoring. PLL conceived the study and consulted the concept, performed data collection and validation, carried out statistical analysis, supervised the manuscript preparation. All authors read and approved the final manuscript.

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Figure legends

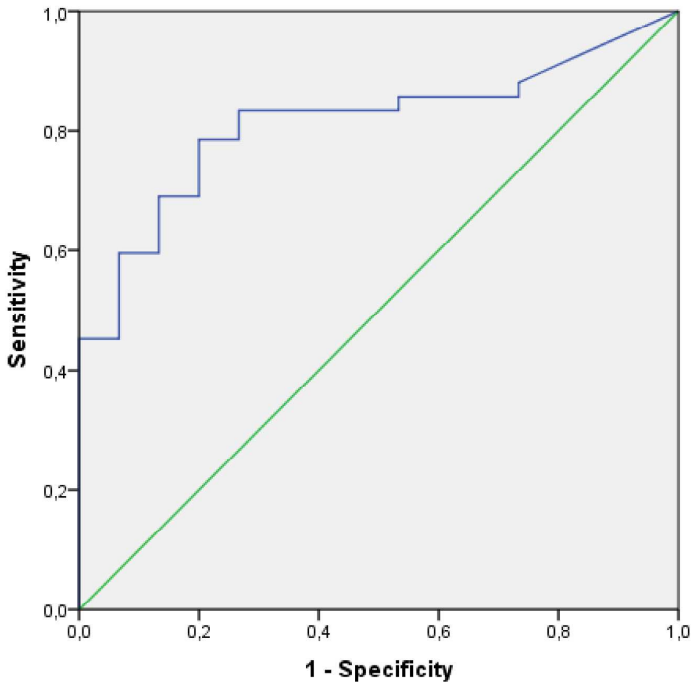

Figure 1A. Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 14 in patients with ulcerative colitis ($AUC_{TLweek2}$=0.81, p<0.001, cut-off: 11.5 µg/ml)

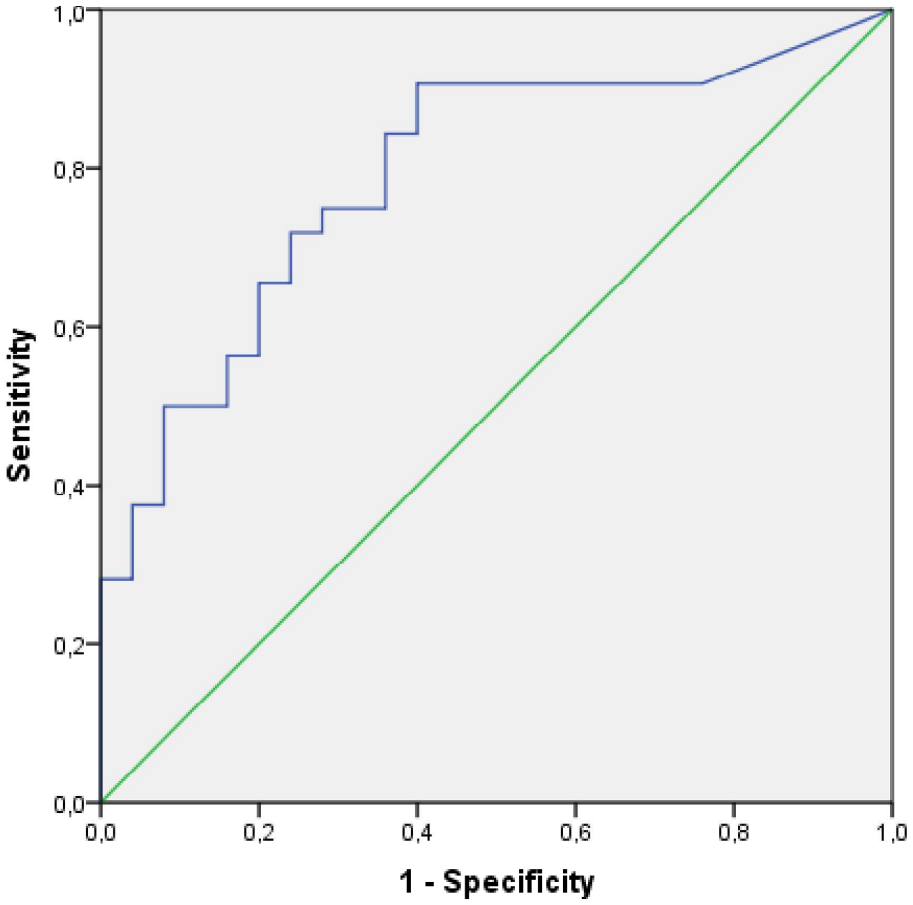

Figure 1B. Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 14 in patients with ulcerative colitis ($AUC_{TLweek2}$=0.79, p<0.001, cut-off: 15.3 µg/ml)

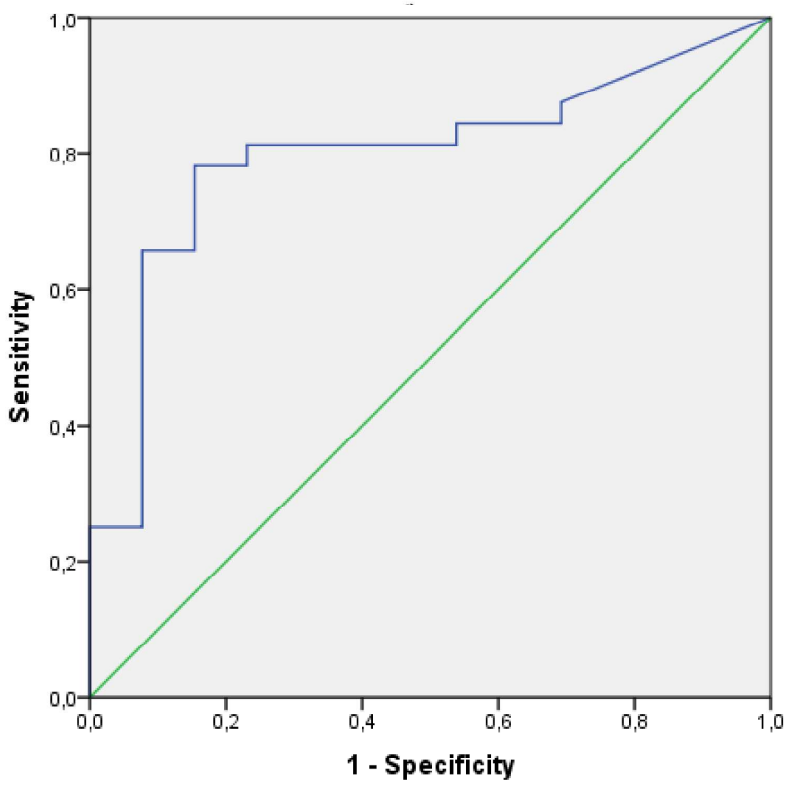

Figure 2A. Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 30 in patients with ulcerative colitis ($AUC_{TLweek2}$=0.79, p=0.002, cut-off: 11.5 µg/ml)

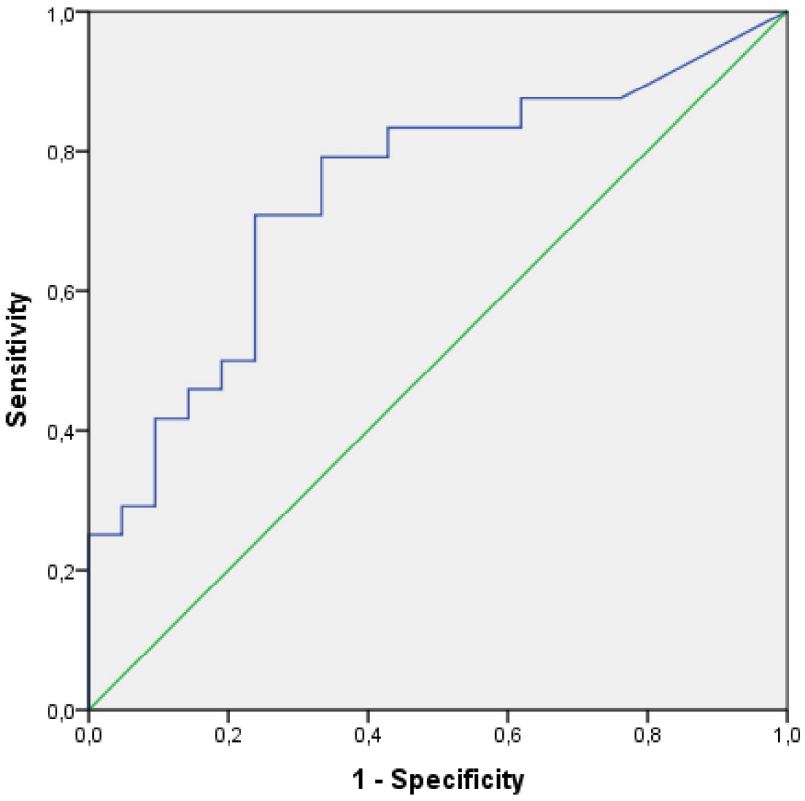

Figure 2B. Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 30 in patients with ulcerative colitis ($AUC_{TLweek2}$=0.74, p=0.006, cut-off: 14.5 µg/ml)

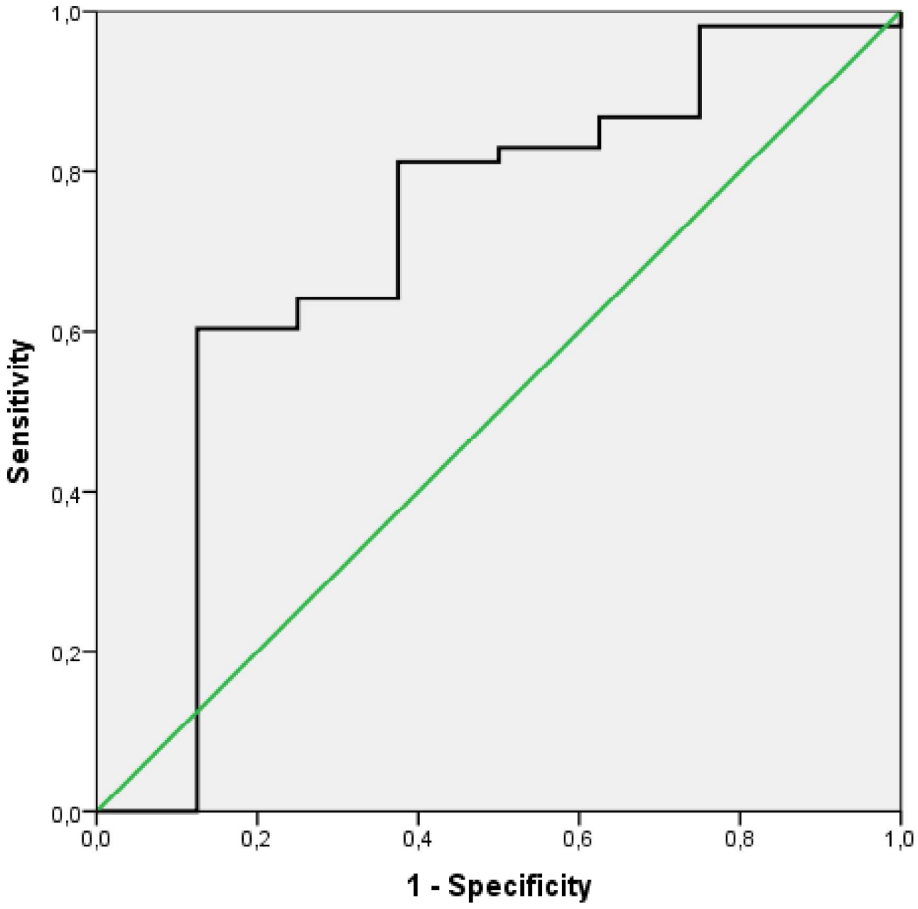

Figure 3A. Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 14 in patients with Crohn's disease ($AUC_{TLweek2}$=0.72, p=0.05, 95%CI: 0.496-0.933, cut-off: 16.9µg/ml)

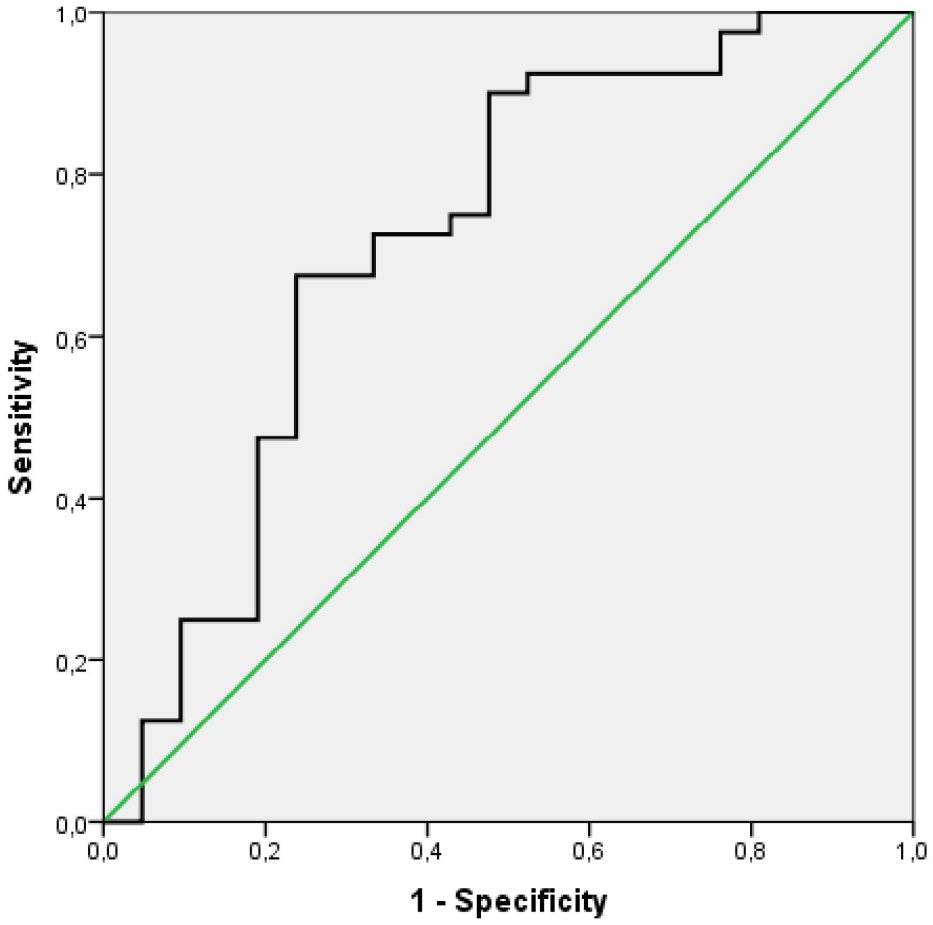

Figure 3B. Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 14 in patients with Crohn's disease ($AUC_{TLweek2}$=0.72, p=0.005, 95%CI: 0.575-0.868, cut-off: 20.4 µg/ml)

Tables

Table 1. Monitoring strategy of Hungarian patients with inflammatory bowel disease receiving biosimilar infliximab

	Baseline	Week 14	Week 30	Week 54
Demographic data	✔			
Medication history	✔	✔	✔	✔
Clinical activity CDAI/PDAI or pMayo[a]	✔	✔	✔	✔
Biochemical activity WBC, CRP, We, albumin[b]	✔	✔	✔	✔

[a] CDAI: Crohn's Disease Activity Index, PDAI: Perianal Disease Activity Index, pMayo: partial Mayo Score, [b] WBC: white blood cell, CRP: C-reactive protein

Table 2. Characteristics of patients with inflammatory bowel disease receiving biosimilar infliximab in the participating Hungarian centers

	Crohn's disease (N = 184)	**Ulcerative colitis (N= 107)**
Male/female	**82 / 102**	**62/45**
Age at onset, median (IQR)	**23 (19-34) yrs**	**28 (22-39) yrs**
Disease duration, median (IQR)	**5 (2-11) yrs**	**4 (2-11) yrs**
Baseline disease activity, median (IQR)	**CDAI:** 321 (301-352) n=145 **PDAI:** 10 (IQR: 6-11) n=56	**MAYO:** 9 (IQR: 7-11) n=107 **pMAYO:** 7 (IQR: 6-9) n=107
Disease location (L1/L2/L3/L4/all L4)[a]	**16.8%/32.4%/ 49.1%/1.7%/7.9%**	-
Disease extent (E1/E2/E3)[b]	-	**8.4% / 32.7% / 51.1%**
Disease behavior (B1/B2/B3)[c]	**58.7% / 21.2% / 20.1%**	-
Perianal disease	**35.0%**	-
Previous surgery	**22.5%**	-
Prior treatments		
5-ASA[d]	**84.6%**	**92.3%**
Steroids	**81.0%**	**90.9%**
AZA[e]	**87.4%**	**74.5%**

CSA[f]	**-**	**7.3%**
Anti-TNF (IFX/ADA)	**24.5% (21.8%/2.7%)**	**14.0% (9.4%/4.6%)**
Concomitant imunomodulators		
Steroids	**44.2%**	**66.4%**
AZA[e]	**60.3%**	**51.4%**

[a] L1: ileal, L2: colonic, L3: ileocolonic, L4: upper GI disease, [b] E1: proctitis, E2: left-sided colitis, E3: extensive colitis, [c] B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating, [d] 5-ASA: 5-aminosalicylic acid, [e] AZA: azathioprine, [f] CSA: cyclosporin A

Table 3. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) of week 2 TL values

	Sensitivity	Specificity	NPV [d]	PPV [e]
CD[a] week 2 TL[b] 14 response	71%	50%	19%	91%
CD[a] week 2 TL[b] 14 remission	68%	59%	59%	68%
UC[c] week 2 TL[b] 14 response	79%	80%	57%	92%
UC[c] week 2 TL[b] 14 remission	72%	76%	68%	80%
UC[c] week 2 TL[b] 30 response	78%	85%	61%	93%
UC[c] week 2 TL[b] 30 remission	70%	76%	70%	76%

[a] CD: Crohn's disease, [b] TL: trough level, [c] UC: ulcerative colitis, [d] NPV: negative predictive value, [e] PPV: positive predictive value

Table 4. Clinical and biochemical factors associated with clinical response and remission at week 14 in patients with inflammatory bowel disease on biosimilar infliximab therapy

	Clinical response at week 14			*Clinical remission at week 14*		
	OR	**CI (95%)**	***p***	**OR**	**CI (95%)**	***p***
Ulcerative colitis						
Previous anti-TNF exposure	0.77	0.22-2.68	0.68	0.36	0.12-1.08	0.06
Gender	0.89	0.34-2.29	0.80	0.86	0.39-1.92	0.72
Disease extent	-	-	0.37	-	-	0.44
Concomitant steroid therapy	0.77	0.28-2.10	0.60	1.05	0.47-2.36	0.90
Concomitant AZA therapy[a]	0.66	0.25-1.71	0.39	0.61	0.28-1.34	0.22
Crohn's disease						
Normal CRP level at week 14[b]	5.59	2.21-14.08	***<0.001***	4.57	2.22-9.43	***<0.001***
Previous anti-TNF exposure	3.04	1.48-6.21	***0.002***	2.74	1.44-5.21	***0.002***
Gender	1.28	0.66-2.47	0.46	0.84	0.50-1.40	0.50
Disease location	-	-	0.22	-	-	0.10
Disease behavior	-	-	0.13	-	-	0.61
Perianal disease	1.16	0.42-3.2	0.78	0.85	0.40-1.79	0.66
Previous steroid therapy	1.65	0.68-3.99	0.27	1.47	0.68-3.18	0.32
Previous AZA therapy[a]	0.93	0.38-2.27	0.87	0.75	0.37-1.52	0.43
Concomitant steroid therapy	-	-	0.84	-	-	0.60
Concomitant AZA therapy[a]	1.15	0.59-2.24	0.68	0.80	0.47-1.36	0.41

[a] AZA: azathioprine, [b] CRP: C-reactive protein

Table 5. Clinical and biochemical factors associated with clinical response and remission at week 30 in patients with inflammatory bowel disease on biosimilar infliximab therapy

	Clinical response at week 30			***Clinical remission at week 30***		
	OR	**CI (95%)**	***p***	**OR**	**CI (95%)**	***p***
Ulcerative colitis						
Previous anti-TNF exposure	0.38	0.11-1.33	0.12	0.33	0.08-1.35	0.11
Gender	0.84	0.31-2.28	0.73	1.05	0.41-2.67	0.92
Disease extent	-	-	0.99	-	-	0.26
Concomitant steroid therapy	0.99	0.36-2.73	0.99	0.68	0.27-1.74	0.42
Concomitant AZA therapy[a]	0.80	0.30-2.15	0.66	0.53	0.21-1.33	0.17
Crohn's disease						
Normal CRP level at week 14[b]	7.81	3.07-20	***<0.001***	3.16	1.38-7.30	***0.005***
Previous anti-TNF exposure	2.7	1.28-5.71	***0.008***	2.21	1.07-4.57	***0.03***
Clinical response at week 14	42.81	15.20-120.54	***<0.001***	21.41	6.23-73.57	***<0.001***
Clinical remission at week 14	9.84	4.19-23.11	***<0.001***	9.41	4.64-19.08	***<0.001***
Gender	0.72	0.36-1.41	0.33	0.80	0.44-1.46	0.47
Disease location	-	-	0.49	-	-	***0.03***
Disease behavior	-	-	0.12	-	-	0.21
Perianal disease	0.57	0.22-1.52	0.26	0.54	0.23-1.27	0.16
Previous steroid therapy	0.66	0.17-2.55	0.54	0.75	0.32-1.80	0.52

Previous AZA therapy[a]	0.95	0.39-2.31	0.91	1.05	0.48-2.28	0.90
Concomitant steroid therapy	1.07	0.55-2.10	0.84	0.86	0.47-1.56	0.62
Concomitant AZA therapy[a]	1.22	0.61-2.42	0.58	1.13	0.61-2.08	0.70

[a] AZA: azathioprine, [b] CRP: C-reactive protein

Table 6. Clinical and biochemical factors associated with clinical response and remission at week 54 in patients with Crohn's disease on biosimilar infliximab therapy

	Clinical response at week 54			*Clinical remission at week 54*		
	OR	**CI (95%)**	***p***	**OR**	**CI (95%)**	***p***
Crohn's disease						
Normal CRP level at week 14[a]	0.42	0.14-1.20	0.10	0.45	0.16-1.23	0.11
Previous anti-TNF exposure	6.25	2.21-17.54	***<0.001***	4.57	1.54-13.51	***0.004***
Clinical response at week 14	15.25	4.94-47.14	***<0.001***	7.39	2.48-21.98	***<0.001***
Clinical remission at week 14	11.13	4.14-29.91	***<0.001***	4.61	1.93-11.05	***<0.001***
Gender	0.72	0.31-1.66	0.44	0.55	0.24-1.26	0.16
Disease location	-	-	0.30	-	-	0.31
Disease behavior	-	-	0.19	-	-	0.23
Perianal disease	0.62	0.20-1.88	0.39	0.88	0.29-2.67	0.82
Previous steroid therapy	1.29	0.47-3.54	0.62	1.31	0.47-3.60	0.60
Previous AZA therapy[b]	0.34	0.10-1.12	0.07	0.51	0.18-1.45	0.20
Concomitant steroid therapy	1.29	0.58-2.88	0.54	0.85	0.38-1.88	0.69
Concomitant AZA therapy[b]	0.85	0.37-1.96	0.70	1.02	0.45-2.31	0.97

[a] CRP: C-reactive protein, [b] AZA: azathioprine

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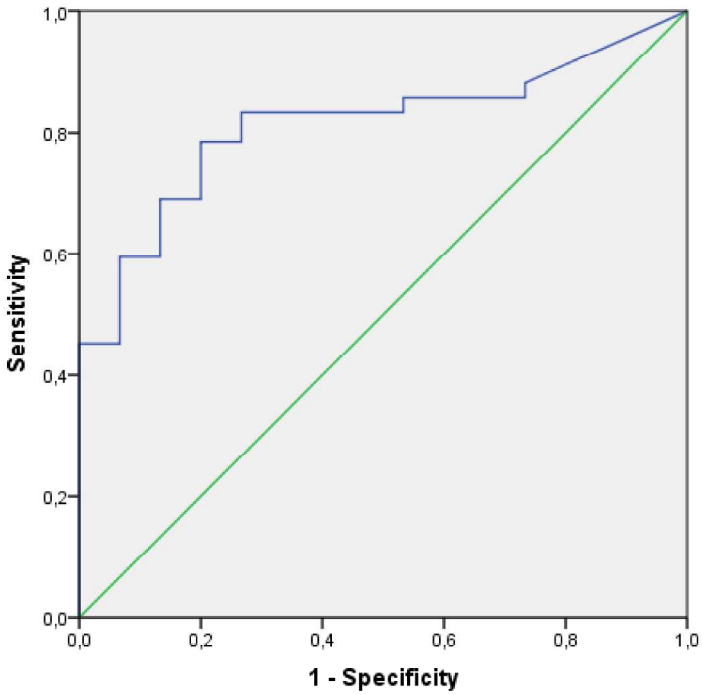
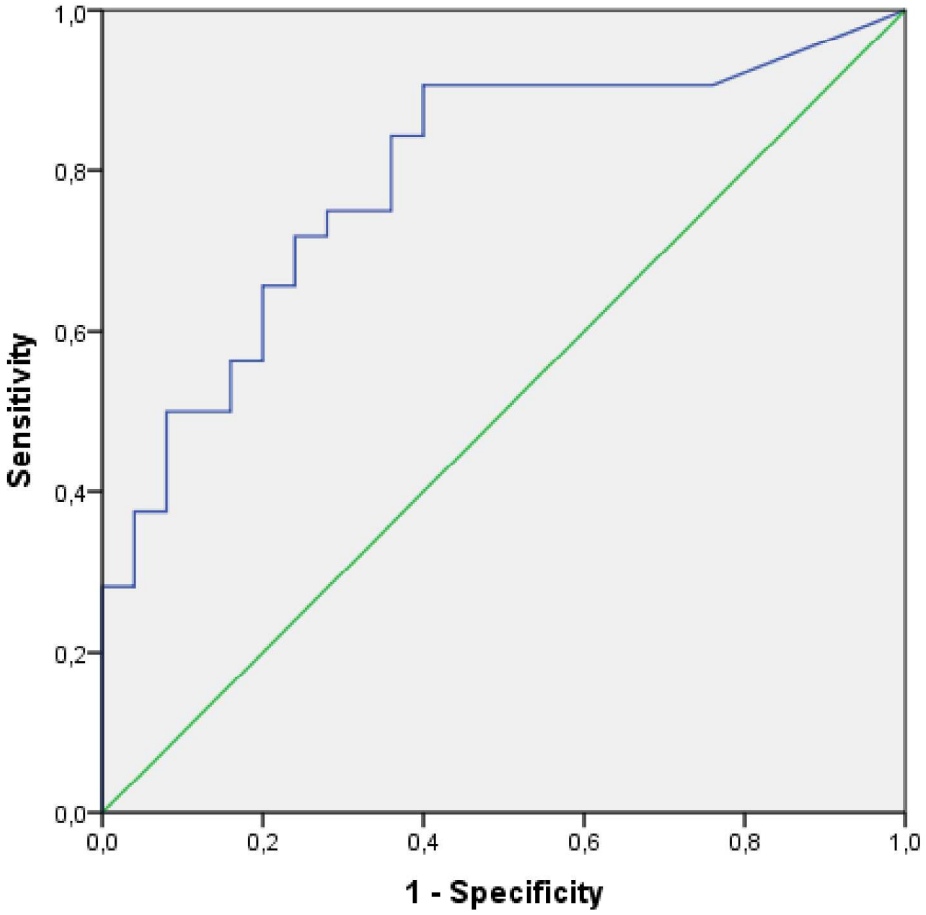
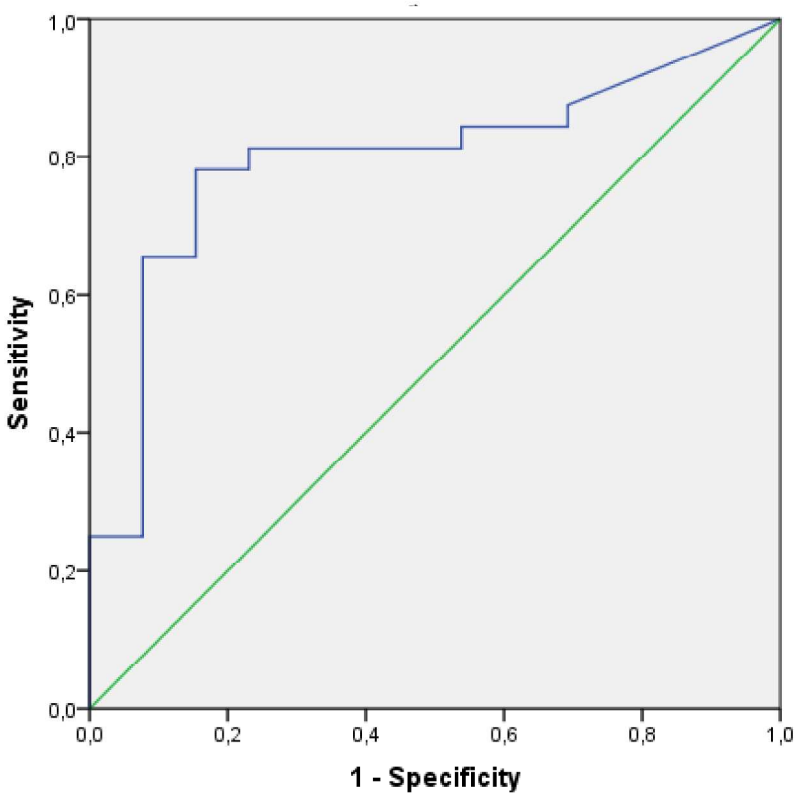


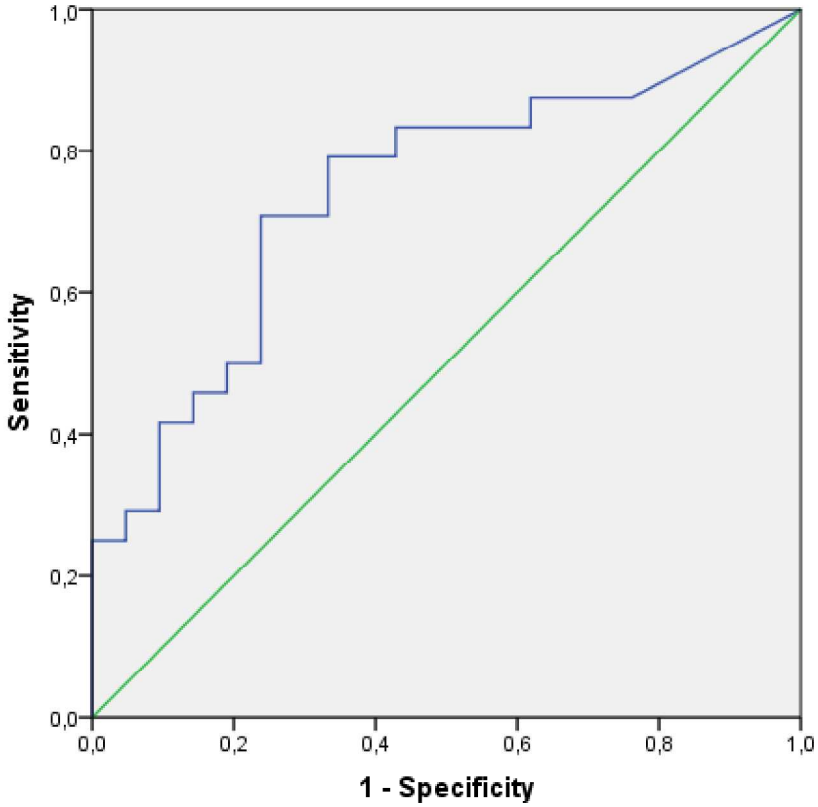
Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 14 in patients with ulcerative colitis (AUCTLweek2=0.81, p<0.001, cut-off: 11.5 µg/ml)
Figure 1A
423x339mm (300 x 300 DPI)



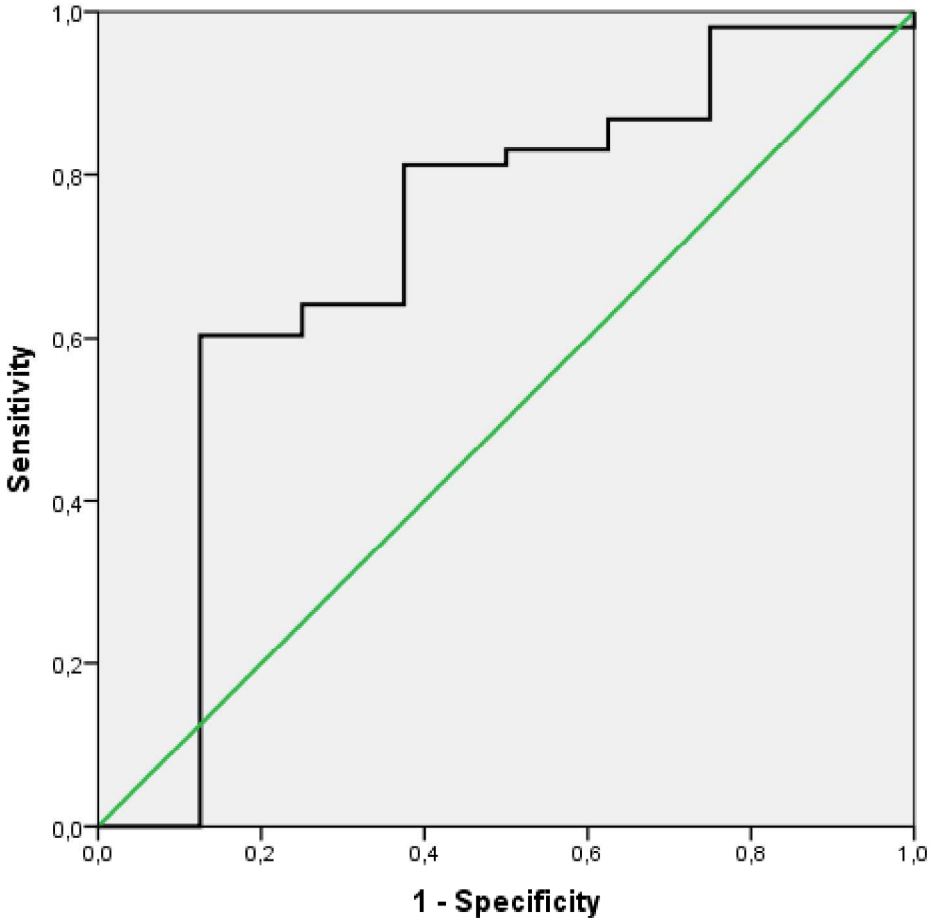
Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 14 in patients with ulcerative colitis (AUCTLweek2=0.79, p<0.001, cut-off: 15.3 µg/ml)
Figure 1B
481x509mm (300 x 300 DPI)



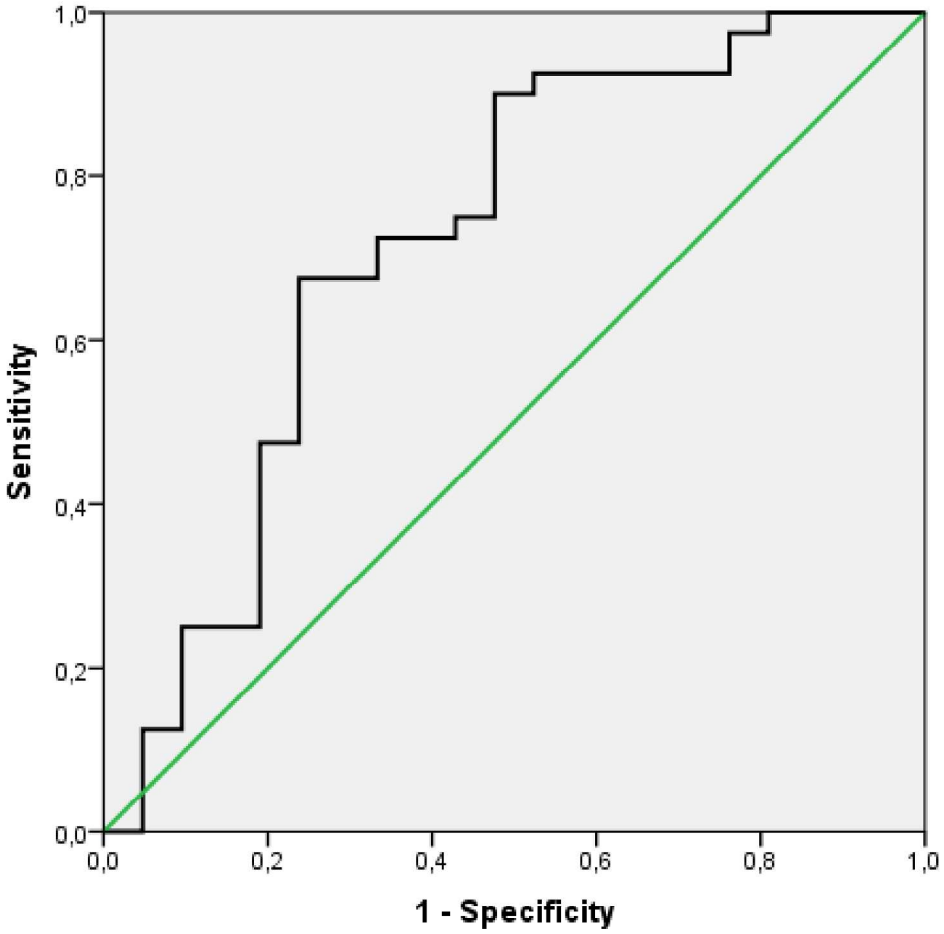
Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 30 in patients with ulcerative colitis (AUCTLweek2=0.79, p=0.002, cut-off: 11.5 µg/ml)
Figure 2A
560x509mm (300 x 300 DPI)



Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 30 in patients with ulcerative colitis (AUCTLweek2=0.74, p=0.006, cut-off: 14.5 µg/ml)
Figure 2B
546x509mm (300 x 300 DPI)



Predictive power of infliximab trough levels measured at week 2 for identifying clinical response at week 14 in patients with Crohn's disease (AUCTLweek2=0.72, p=0.05, 95%CI: 0.496-0.933, cut-off: 16.9µg/ml)
Figure 3A
436x439mm (300 x 300 DPI)



Predictive power of infliximab trough levels measured at week 2 for identifying clinical remission at week 14 in patients with Crohn's disease (AUCTLweek2=0.72, p=0.005, 95%CI: 0.575-0.868, cut-off: 20.4 µg/ml)
Figure 3B
436x467mm (300 x 300 DPI)