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Efficacy of Infliximab Biosimilar CT-P13 Induction Therapy on Mucosal Healing in Ulcerative Colitis

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Abstract

Introduction: CT-P13 is the first biosimilar to infliximab that has been approved for the same indications as its originator infliximab. No data are available on the effect of infliximab biosimilar on mucosal healing. The aim of this study was to evaluate the efficacy of CT-P13 induction therapy on mucosal healing in patients with ulcerative colitis [UC].

Patients and methods: UC patients, who received CT-P13 therapy from its local introduction at three Hungarian and one Czech inflammatory bowel disease centres, were prospectively enrolled. Sigmoidoscopy was performed after the end of the induction therapy at week 14. Mucosal healing was defined as Mayo endoscopic subscore 0 or 1. Complete mucosal healing was defined as Mayo endoscopic subscore 0. Trough level of CT-P13 was measured at week 14.

Results: Sixty-three UC patients who underwent CT-P13 induction therapy were enrolled in the study. Indication for the therapy was acute, severe flare up and chronic, refractory activity in 24 and 39 patients, respectively. Cumulative clinical response and steroid-free remission at week 14 were achieved in 82.5% and 47.6% of the patients, respectively. Sigmoidoscopy revealed steroid-free mucosal healing in 47.6% of the patients, and complete mucosal healing was present in 27%. Mayo endoscopic subscore decreased significantly at week 14 compared to baseline. Trough levels of infliximab correlated with mucosal healing.

Conclusion: This is, to our knowledge, the first study examining the efficacy of CT-P13 induction therapy on mucosal healing in UC. The results indicate that mucosal healing is achieved in two-thirds of UC patients by the end of the induction treatment with CT-P13.

Key Words: Ulcerative colitis; infliximab; biosimilar; CT-P13; mucosal healing

1. Introduction

CT-P13 is the first biosimilar monoclonal antibody of reference infliximab that has been approved for use in all indications in which reference infliximab is approved but with the major advantage of reduced cost of therapy. CT-P13 is produced in the same type of cell line and has an identical amino acid sequence to infliximab. CT-P13 and infliximab show comparable binding affinities to monomeric and trimeric forms of human tumour necrosis factor [TNF]-α, and comparable TNF-α neutralizing and cytotoxic activities.[1] The approval of CT-P13 was based on two studies, one in rheumatoid arthritis evaluating its efficacy and safety and one pharmacokinetic study in ankylosing spondylitis.[2,3] Although pre-clinical comparative studies and analyses have demonstrated a high degree of similarity among originator and biosimilar infliximab, concerns have been expressed regarding extrapolation without direct clinical evidence in inflammatory bowel disease [IBD]. The review by Feagan *et al.* addressed factors such as clinical sensitivity, mechanism of action, immunogenicity, safety, pharmacokinetics, sites of action and pathophysiology of disease to consider when evaluating indications for extrapolation for biosimilars.[4]

Recently, favourable retrospective clinical data became available on the efficacy of CT-P13 in IBD. However, none of these studies evaluated the effect of infliximab biosimilar on mucosal healing defined by endoscopic Mayo subscore 0 or 1.[5,6,7] The traditional ulcerative colitis [UC] management goals to improve clinical symptoms have changed to achieve complete mucosal healing with the absence of all inflammatory and ulcerative lesions. Therefore, most of the clinical trials have incorporated mucosal healing as the most important outcome measure. The lack of endoscopic data on the efficacy of CT-P13 in UC leads to confusion among clinicians, which can decrease the use of CT-P13. To fulfil an unmet need, this study aimed to prospectively evaluate the efficacy of CT-P13 induction therapy on mucosal healing in patients with UC.

2. Patients and methods

This was a prospective, multicentre study carried out in three Hungarian and one Czech IBD tertiary centres. Adult patients diagnosed with UC, who were administered at least three CT-P13 infusions between June 2014 and April 2015 in the Hungarian centres and between September 2014 and May 2015 in the Czech centre, were enrolled in the study. Inpatients with acute relapse and outpatients with chronic, steroid-dependent and/or immunomodulatory-refractory disease were enrolled in the study. Previous biological therapy and corticosteroid treatment were also allowed at inclusion. Patients' demographic data, clinical characteristics, smoking history, previous surgery, history of previous anti-TNF-α administration, concomitant medications, indications for CT-P13 therapy, and clinical and endoscopic response to CT-P13 were analysed. Disease phenotype was determined in accordance with the Montreal Classification.[8]

CT-P13 5 mg/kg was given as an intravenous infusion at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks except for one Czech patient receiving 10 mg/kg induction dose for acute, severe disease. Although, disease activity was assessed at every appointment, at baseline, week 2, week 6, and then week 14 by using the Mayo Scoring System[9], response to therapy was evaluated and activity data were compared with baseline on week 14. Total colonoscopy was performed at inclusion. Only patients with Mayo endoscopic subscore of at least 2 were enrolled in the study. For control endoscopy, flexible sigmoidoscopy was performed at week 14 to evaluate mucosal healing. Mucosal healing was defined as Mayo endoscopic subscore 0 or 1. Complete mucosal healing was defined as Mayo endoscopic subscore 0 without the use of steroids. Clinical response was defined as at least 30% and 3 points decrease in the total Mayo score from baseline in addition to a decrease in rectal bleeding subscore of at least 1 or a rectal bleeding subscore of 0 or 1.[10] Remission was defined as Mayo score ≤2, with no individual subscores >1. Primary non-response was defined as a lack of response at week 14 after the induction phase. Previous anti-TNF therapy was allowed at inclusion but had to be stopped at least one year prior to CT-P13 therapy. According to Hungarian central regulations, only CT-P13 was allowed to be reintroduced if the patient received originator infliximab previously. In the case of adalimumab, the decision was made by the patient and the physician. Inflammatory laboratory parameters (C-reactive protein [CRP], leukocyte and thrombocyte levels), CT-P13 trough levels and antibody titres (anti-infliximab antibodies [ATIs]) were assessed at week 14 by quantitative enzyme-linked immunosorbent assay [ELISA] [LISA TRACKER, Theradiag, France, in Hungary; and SHIKARI Q-Inflixi, Q-ATI, Matriks Biotek, Turkey, in the Czech Republic]. With the LISA TRACKER, detectable trough level was 0.1 μg/ml for CT-P13. The measurement range was 10–200 ng/ml for antibodies [> 10 ng/ml considered positive]. With the SHIKARI kits, the lowest detectable level that can be distinguished from the zero standard was 30 ng/ml. ATIs were positive, when positivity index exceeded 3. These patients are also included in the Hungarian multicentre nationwide cohort evaluating the efficacy, safety and immunogenicity of CT-P13 in IBD.

2.1. Statistics

Categorical data were analysed using Pearson's chi-squared test or Fisher's exact test. The effects of drug therapy on Mayo score were examined with repeated-measures analysis of variance [ANOVA]. The changes from baseline in continuous variables [partial and endoscopic Mayo scores, trough levels] were compared using paired sample t-tests. Cut-off levels, specificity and sensitivity were calculated using the receiver operating characteristic [ROC] analysis. Statistical tests were performed using R statistical software [R version 3.1.2]; values of $p < 0.05$ were considered significant.

3. Results

Sixty-three UC patients completed the three-dose induction therapy with CT-P13. Male/female ratio was 32:31. Mean age at diagnosis was 30.5 years [range 14–65] and mean disease duration was 5.7 years [range 0.6–22]. Baseline characteristics of patients treated

with CT-P13 are summarized in Table 1. Indications for CT-P13 therapy were acute, severe flare up and chronic, refractory activity in 24 and 39 patients, respectively. The mean total Mayo score was 9.2 with mean endoscopic subscore [eMayo] of 2.7 points at the beginning of the CT-P13 therapy [21 patients with eMayo subscore of 2 and 42 patients with eMayo subscore of 3]. Cumulative clinical response at week 14 was achieved in 52 patients [82.5%]; the number of patients with steroid-free clinical remission was 30 [47.6%] [Figure 1]. At inclusion, concomitant corticosteroids were given for 11 of the 14 partial responder patients. At week 14, four were able to stop steroid therapy. Primary non-response occurred in 11 patients [17.5%]. Three of the patients with primary non-response received anti-TNF therapy previously: two received originator infliximab and one received adalimumab. None of the patients with primary non-response developed ATI.

One patient underwent colectomy; three patients needed dose intensification throughout the induction phase of CT-P13 therapy. Sigmoidoscopy revealed mucosal healing in 38 patients [60.3%], and steroid-free mucosal healing was shown in 30 patients [47.6%]. Complete mucosal healing was achieved in 17 [27%] patients at week 14. The mean total Mayo score was 3.4 with endoscopic subscore of 1.1 points at week 14. Figure 2 shows the number of patients with eMayo scores. Both the Mayo score and the eMayo score decreased significantly in responders at week 14 compared to baseline [$p < 0.001$ and $p < 0.001$] [Figures 3 and 4].

Subgroup analysis did not reveal a significant difference in disease outcome at week 14 between acute, steroid refractory inpatients and outpatients with chronic activity regarding steroid-free remission [48% vs. 51%, pMayo score: 0.44 vs. 0.45, $p = 0.49$], and cumulative clinical response [83% vs. 82.1%, tMayo score: 3.54 vs. 3.28, $p = 0.38$]. However, steroid-free mucosal healing proved to be more common in acute, steroid refractory inpatients than in outpatients with chronic activity [41.7% vs. 51.3%, eMayo: 0.3 vs. 0.65, $p = 0.04$]. None of the examined clinical demographical data [gender, smoking status, disease extent, and previous and current concomitant medications] or the laboratory parameters determined at inclusion [CRP, leukocyte count, haematocrit, and thrombocyte and serum albumin levels] predicted the outcome of therapy on mucosal healing at week 14. Trough levels of CT-P13 were significantly higher in patients who achieved mucosal healing or steroid-free mucosal healing than in patients who did not achieve endoscopic remission [mean values: 5.72, 6.35 and 2.85 µg/ml, respectively, $p = 0.02$ and $p = 0.008$] [Figure 5]. Mean CT-P13 trough levels were 3.18 µg/ml in responders and 6.15 µg/ml in patients in steroid-free remission [$p = 0.02$]. We also compared serum CT-P13 levels between the Hungarian and Czech patient population regarding mucosal healing. No statistical difference was found between the two groups [serum CT-P13 levels in Hungarian and Czech patients who achieved steroid-free mucosal healing were 6.01 µg/ml and 7.21 µg/ml, respectively, $p = 0.35$].

ATI was detectable in seven patients at week 14. ATI-positive patients presented with undetectable trough levels. None of these patients received anti-TNF-α therapy previously.

Overall, five patients had received anti-TNF-α before starting on CT-P13 therapy – adalimumab was given for two patients and originator infliximab for three patients. Notably, at least one year elapsed between stopping previous anti-TNF-α therapy and

Table 1. Baseline characteristics of patients treated with CT-P13

	Number of UC patients [$n = 63$]
Gender [male/female]	32/31 [50.8/49.2%]
Mean age at diagnosis [years, range]	30.5 [14–65]
Mean disease duration at CT-P13 therapy [years, range]	5.7 [0.6–22]
Disease extent [Montreal classification]	
Proctitis	5 [7.9%]
Left-sided colitis	23 [36.5%]
Extent colitis	35 [55.6%]
Previous anti-TNF-α	5 [7.9%]
Smoking status	
Current smoker	6 [9.5%]
Previous smoker	11 [17.5%]
Never smoked	35 [55.6%]
No data	11 [17.5%]
Mean total Mayo score at inclusion	9.2
Mean endoscopic Mayo score at inclusion	2.7
Indication for CT-P13 therapy	
Acute, severe flare-up	24 [38.1%]
Chronic activity, steroid refractoriness	39 [61.9%]
Previous medications	
5-Aminosalicylic acid [5-ASA]	53 [84.1%]
Corticosteroid	54 [85.7%]
Azathioprine	39 [61.9%]
Concomitant medications at inclusion	
5-ASA	47 [74.6%]
Corticosteroid	32 [50.8%]
Azathioprine	27 [42.9%]

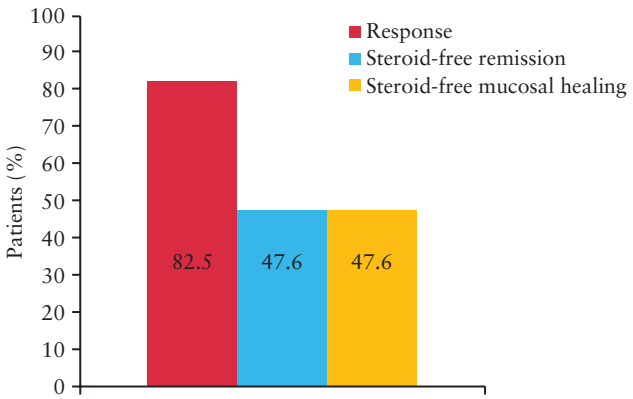

Figure 1. Proportion of patients with clinical response, steroid-free remission and steroid-free mucosal healing at week 14.

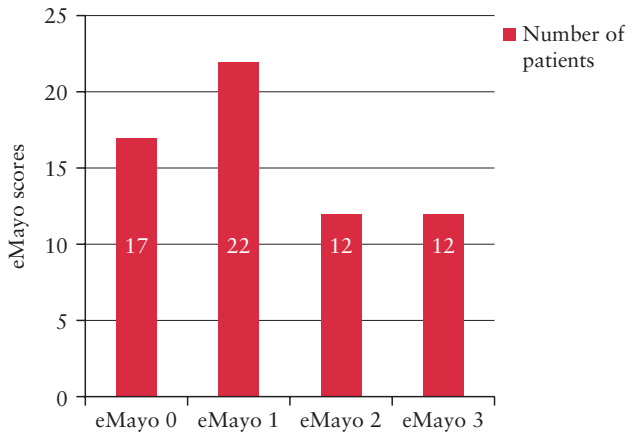

Figure 2. Number of patients with eMayo scores at week 14.

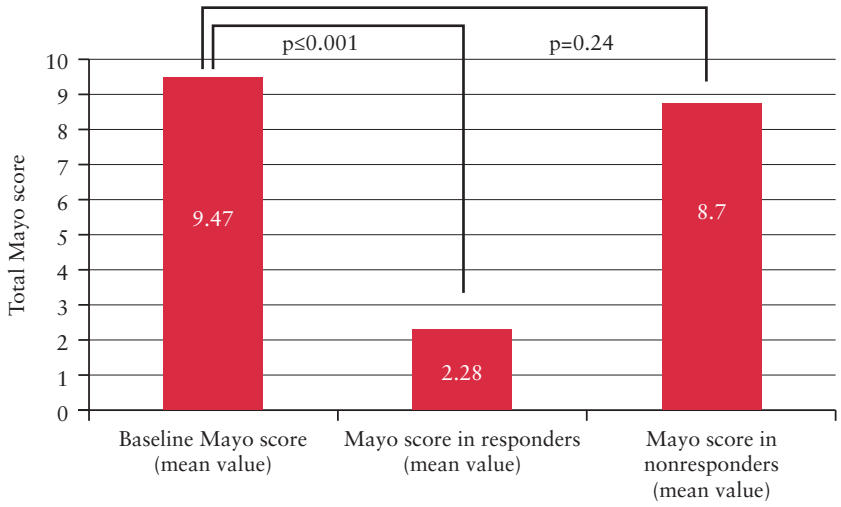

Figure 3. Change in the total Mayo score in responders vs. non-responders at week 14 compared to baseline.

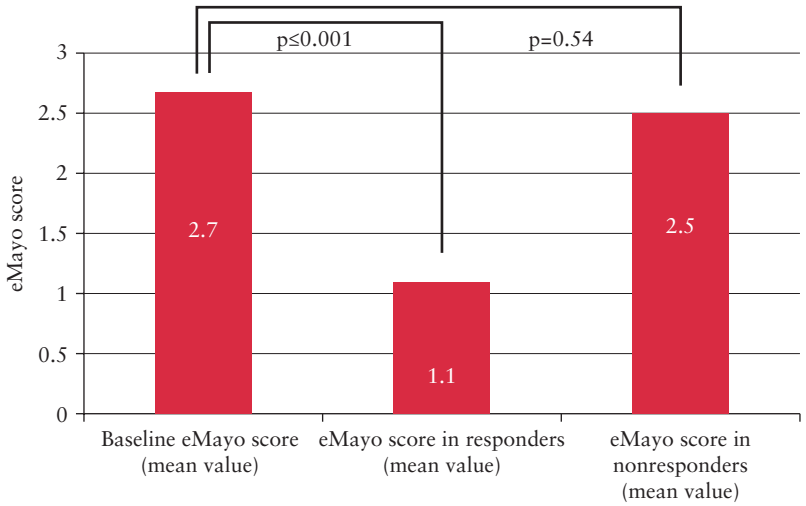

Figure 4. Change in the endoscopic Mayo subscore in responders vs. non-responders at week 14 compared to baseline.

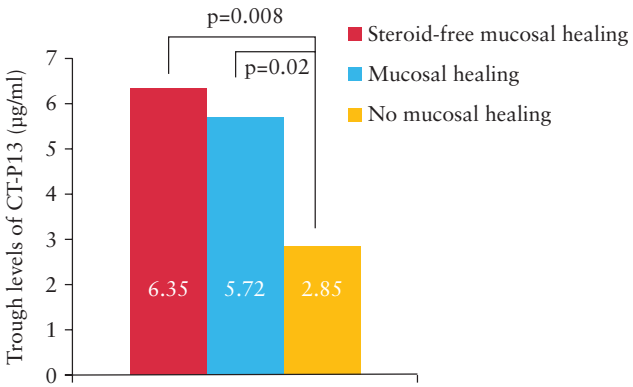

Figure 5. Trough levels of CT-P13 in patients who achieved mucosal healing and steroid-free mucosal healing vs. patients who did not achieve endoscopic remission.

restarting biological therapy. Previous anti-TNF therapy was discontinued because of a central regulation in Hungary. According to the central authorities' decision, for financial reasons, after a successful one-year treatment period of anti-TNF therapy resulting in clinical and endoscopic remission, biological therapy is recommended to be stopped. However, use of previous anti-TNF therapy did not prove to be statistically predictive of a loss of response in this cohort. Two of the patients achieved mucosal healing [eMayo of 1] and three patients had moderate disease activity on control sigmoidoscopy despite the clinical response to CT-P13 therapy. According to the ROC analyses, the cut-off value was 3.15 µg/ml both for steroid-free clinical remission and for mucosal healing [AUC = 0.65 and 0.69, respectively] with a sensitivity and specificity of 71% and 64%, respectively, for clinical remission and with a sensitivity and specificity of 66% and 61%, respectively, for mucosal healing [Figure 6].

4. Discussion

This multicentre, prospective study examined the outcome of induction therapy with the infliximab biosimilar CT-P13 focusing on endoscopic healing in active UC patients. CT-P13 induction therapy resulted in an 82.5% clinical response and 47.6% steroid-free clinical remission. Steroids could be tapered and stopped in 60% of the patients receiving systemic corticosteroids at inclusion. Mucosal healing was achieved in 60.3% by week 14; the rate of steroid-free mucosal healing was 47.6%. Moreover, almost half of these patients

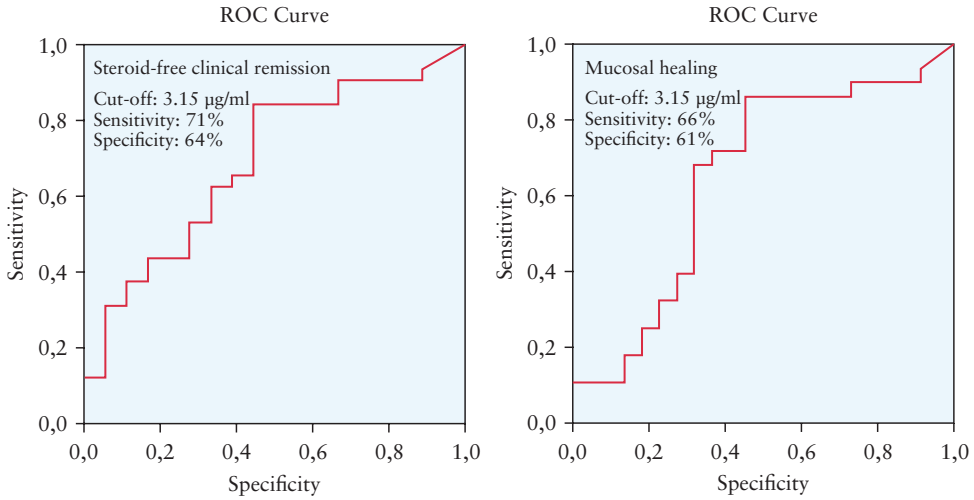

Figure 6. Receiver operating characteristic [ROC] of CT-P13 trough levels associated with steroid-free remission and mucosal healing.

showed complete mucosal healing with an eMayo score 0 at the time of control endoscopy.

As the approval for CT-P13 was based on randomized clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis,[2,3] it is unknown whether CT-P13 has a similar efficacy on mucosal healing in UC as the originator infliximab. In a recently published Korean study, CT-P13 showed comparable efficacy and safety relative to its originator in the treatment of moderate to severe Crohn's disease and UC.[5] This multicentre study retrospectively evaluated the efficacy, safety and interchangeability of CT-P13 in IBD patients; however, its ability to assess mucosal healing was limited.[5] In the study of Kang *et al.*, including case series, only two of the enrolled nine UC patients underwent control colonoscopy at week 8 of CT-P13 therapy. The endoscopic findings showed significant improvement in both cases as early as at week 8.[6] The originator drug, Active Ulcerative Colitis trial [ACT-1] revealed clinical response, remission, and mucosal healing rates of infliximab to be 69%, 39%, and 62%, respectively, at week 8, while in ACT-2 they were 65%, 34%, and 60% at week 8. Note that although this is not a comparison study, evaluation of the efficacy of biosimilar biologics in clinical practice is important. Response and remission rates of our cohort proved to be higher than those in the ACT trials; however, our observation that real life data represent better outcomes than clinical studies is not a new one. Although randomized controlled trials are considered the gold standard for the evaluation of the efficacy of a drug, real-life data provide more insight into factors that might influence therapy outcomes. In the retrospective analysis of Lee *et al.*, the rates of clinical response and remission were 87% and 45%, respectively, at week 8.[11] Zhou *et al.* revealed clinical response and remission rates of 91.3% and 73.9%, respectively, at week 6.[12] In paediatric patients, infliximab induced a response in 73.3% at week 8.[13]

Results regarding endoscopic healing in the ACT trials were highly similar to our findings assessed at week 14. A subanalysis of ACT trials showed that patients who had a week 8 endoscopic subscore of 0 or 1 had much lower rates of hospitalization or surgery and higher rates of steroid-free remission over the next 6–12 months. On the other hand, patients who did not achieve mucosal healing during the induction period had considerably higher rates of subsequent colectomy.[14] Additionally, steroid-free remission rates were higher in patients who achieved complete mucosal healing compared to patients with a subscore of 1 at week 8.[14] Furthermore, ACT-1 and ACT-2 trials showed a direct correlation with serum infliximab concentration both for clinical response and for mucosal healing.[10] Our results also revealed a significant association between higher infliximab trough levels, steroid-free mucosal healing and clinical remission.

The study has some limitations, including the relatively small patient number, the heterogeneous patient population including acute, severe UC patients and patients with chronic disease activity, use of corticosteroid therapy at inclusion, and different types of assays used for the detection of serum CT-P13 levels. Although corticosteroids may influence assessment of the outcome of biological therapy, in most the cases such as these, steroids cannot be avoided for use as an adjunctive therapy in clinical practice. Moreover, in the ACT studies, 50–60% of the patients were on steroid therapy at inclusion.

In this study LISA TRACKER and Matriks Biotek kits were used to measure infliximab biosimilar trough levels and anti-drug antibody. In Hungary, ELISA measurements were centralized and performed at the Department of Laboratory Medicine, Semmelweis University, Budapest. The LISA TRACKER assay, developed to reduce low-affinity binding of immune complexes or interfering molecules, was used in the study of Paul *et al.*[15] This type of ELISA is able to assess antibody levels independently from infliximab trough concentrations. Paul *et al.* revealed an association between antibody levels and loss of response to infliximab. When examining the impact of therapeutic drug monitoring on dose intensification, they found that patients with antibody levels >200 ng/ml did not respond to infliximab optimization, whereas all patients with infliximab trough levels <2 mg/ml and antibody levels <200 ng/ml responded to infliximab dose intensification. Cross-immunogenicity between the originator and biosimilar infliximab was an interesting topic when assessing the value of drug monitoring in CT-P13 therapy. The study by Ben-Horin *et al.*[16] revealed that antibodies to the originator infliximab in IBD patients similarly recognize and cross-react with CT-P13, supporting a similar immunogenic profile for originator and biosimilar infliximab. A recently published Czech study compared three ELISAs (Matriks Biotek [Turkey], Theradiag [France] and R-Biopharm [Germany]) for infliximab detection in the measurement of CT-P13 trough levels and revealed a perfect agreement in qualitative and quantitative results for the majority of the samples. These observations suggest that substitution between the assay methods evaluated in the study

may be possible.[17] Notably, a slight but statistically significant difference was also shown during the subanalysis between acute, steroid refractory inpatients and outpatients with chronic activity in steroid-free mucosal healing but not in clinical outcome, showing that the rate of mucosal healing is more common in acute, severe UC than in chronic disease activity.

Today, mucosal healing should be considered as the main goal of therapy in IBD. UC patients may be recommended to be re-evaluated with sigmoidoscopy at the end of induction therapy to ascertain whether they have achieved mucosal healing and, if not, the therapy may be escalated.[18] Achieving early mucosal healing is even more important given that mucosal healing itself does not predict sustained clinical remission in UC patients in whom infliximab therapy had stopped after achieving endoscopic remission.[19,20]

In conclusion, this is the first multicentre study to prospectively evaluate mucosal healing in UC in response to CT-P13 induction therapy. In this cohort, two-thirds of the patients achieved mucosal healing and almost half of the patients achieved steroid-free mucosal healing at week 14. Infliximab biosimilar CT-P13 represents a promising treatment option for patients with UC not only regarding clinical activity, but also in achieving mucosal healing.

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Conflict of Interest

No conflict of interest exists.

Author Contributions

Study design, data collection, supervision of patient selection and manuscript preparation: TM, KF, MR; data collection: PAG, ZV, BDL, KF, ZS, FN, MK, MB, DD, NM, VH, ML, KM, KM; data collection and manuscript preparation: KF, AB, RB, AM, PLL, KBG, MK; statistical analysis: TN. All authors have approved the final draft submitted.

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