LONG-TERM CONSEQUENCES OF MUCOSAL HEALING AND NON-RECOVERY IN INFLAMMATORY BOWEL DISEASE

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Summary of Ph.D. THESIS

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LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS:

I. Kunovszki P¤, **Milassin Á**¤, Gimesi-Országh J, Takács P, Szántó K, Bálint A, Farkas K, Borsi A, Lakatos PL, Szamosi T, Molnár T. Epidemiology, mortality and prevalence of colorectal cancer in ulcerative colitis patients between 2010-2016 in Hungary – a population-based study. ¤*These authors contributed equally to this work.*
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CUMULATIVE IMPACT FACTOR: 79.263

LIST OF ABBREVIATIONS

CCR – continuous clinical response

CD – Crohn's disease

CDAI – Crohn's Disease Activity Index

CIs – confidence intervals

CRC – colorectal cancer

CRP – C-reactive protein

CS – corticosteroid

FC – faecal calprotectin

IBD – inflammatory bowel disease

IFX – infliximab

LOR – loss os response

MH – mucosal healing

NHIF – National Health Insurance Fund

UC – ulcerative colitis

1. INTRODUCTION

The term inflammatory bowel disease (IBD) primarily covers two chronic conditions: ulcerative colitis (UC) and Crohn's disease (CD). The course of the disease can vary from mild with prolonged periods of remission to severe often requiring therapy escalation, surgery and sometimes complicated with cancers. Historically, treatment was based on aminosalicylates, with the use of corticosteroids (CSs) for severe flares, and escalation to immunomodulators if needed. At the beginning of the 2000s, treatment options were revolutionised with the development of inhibitors of tumour necrosis factor (TNF). In the beginning, the therapeutic target was simply the control of the symptoms (clinical remission), which is now shifting towards a full control of the disease since even during clinical remission, laboratory or imaging tests can reveal persistent inflammation of the mucosa. It is assumed that this chronic inflammation leads to irreversible structural damage like strictures, fistulae and abscesses, and it even increases the risk of colitis-associated neoplasia. It has been suggested that deep remission (defined as clinical and endoscopic remission (endoscopic mucosal healing (endoscopic MH)) could prevent chronic inflammation. MH is associated with decreased hospitalisation rates, fewer surgeries and prolonged clinical remission. However, in some aspects, like in long-standing Crohn's disease, MH does not always go hand in hand with the healing of all layers, and in IBD with histological healing.

CT-P13, a biosimilar of infliximab (IFX), was the first monoclonal antibody biosimilar approved by the European Medicines Agency in 2013. Although highly effective, new therapeutic options are available, their ability to modify the natural course of the disease is still studied intensively. In Crohn's disease, the use of immunomodulators reduce the risk of surgery and hospitalisation; however, more than 70% of patients with CD require surgery during their lifetime. Surgical interventions are often required in case of bowel obstruction, abscess, fistula or refractory disease. To optimise treatment and surveillance programme after surgery, it is important to identify the potential risk factors of postoperative recurrence; like terminal ileal location, stricturing, and penetrating behaviour, age younger than 40 years at diagnosis. In 2006, *Ferrante et al.* found that the presence of myenteric plexitis in the proximal resection margins of ileocolonic resection specimens are highly associated with postoperative CD recurrence. Since then several studies have tried to identify myenteric or submucosal plexitis as a risk factor for postoperative recurrence; however, its predictive value is still controversial.

2. AIMS

2.1. To evaluate the long-term efficacy and safety of biosimilar CT-P13 therapy in Crohn's disease and ulcerative colitis and to identify the predictive factors of loss of response

2.2. To evaluate mucosal healing and safety in UC patients treated with biosimilar CT-P13

2.3. To evaluate the frequency of postoperative recurrence and to evaluate predictors of postoperative recurrence in Crohn's disease

2.4. To describe the mortality of the Hungarian UC population between 2010 and 2016 and to analyse the prevalence of malignancies

3. PATIENTS AND METHODS

3.1. To evaluate the long-term efficacy and safety of biosimilar CT-P13 therapy in Crohn's disease and ulcerative colitis

3.1.1. Study design and patients

Patients diagnosed with CD and UC and receiving biosimilar CT-P13 were eligible to participate in the study between June 2014 and September 2016 at the First Department of Medicine, University of Szeged. Medical records analysed included patients' demographic and clinical characteristics, previous surgeries, smoking and family history, previous history of originator IFX administration, concomitant medications, response to CT-P13, and adverse drug reactions.

3.1.2. Assessment of response to CT-P13 and end points

CT-P13 5 mg/kg was given as an intravenous infusion at weeks 0, 2 and 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. Clinical disease activity was assessed with the Crohn's Disease Activity Index (CDAI) in CD and the partial Mayo (pMayo) scoring system in UC. The primary end points were continuous clinical response (CCR) and clinical remission during the 54-week therapeutic period. The secondary end points were clinical and biochemical responses and safety evaluated at weeks 14 and 54. A further secondary end point was the identification of predictors of sustained clinical response during the 54-week study period.

3.1.3. Assessment of laboratory parameters, serum drug levels, and faecal calprotectin concentrations

CT-P13 trough levels as well as C-reactive protein (CRP) level, haematocrit, leukocyte, platelet count and serum albumin were determined at every visit. Faecal calprotectin (FC) was measured by lateral flow assay at weeks 2, 6 and 46. Enzyme-linked immunosorbent assay was applied to determine CT-P13 trough levels (LISA TRACKER, Theradiag, France).

3.1.4. Statistical analysis

Continuous variables are presented as mean±standard deviation; the groups were compared with Mann-Whitney U-test. Categorical variables are presented as frequency (percentage); the groups were compared using Fisher's exact test. Confidence intervals (CIs) for proportions were calculated with the Clopper-Pearson method. The changes from baseline in continuous variables were compared using paired-samples t-tests. For the multivariate modelling of response, logistic regression was used with L2-penalisation selected with Tsai's corrected AIC. Results are visualised as odds ratios (OR) on log scale with 90%, 95% and 99% CIs (using different shading). The significance was set at $p<0.05$.

3.1.5. Ethical approval

Ethical approval was acquired from the National Ethical Committee.

3.2. To evaluate mucosal healing and safety in UC patients treated with biosimilar CT-P13

3.2.1. Clinical assessment

This multicentre, prospective 'real life' study was conducted at four Hungarian and one Czech IBD centres between June 2014 and June 2017. Inclusion criterion was CT-P13 biosimilar therapy indicated by moderate or severe acute relapse (inpatients) or chronic, steroid-dependent and/or immunomodulatory-refractory disease (outpatients). Participants in the study were patients diagnosed with UC at least 3 months prior to the enrolment. CT-P13 infusions were administered to patients as monotherapy or together with immunomodulatory drugs. Disease activity was assessed by clinical data and endoscopy using Mayo Scoring System and by serum inflammatory markers at weeks 14 and 54.

3.2.2. Assessment of endoscopy

Based on total colonoscopy performed at inclusion, only patients with Mayo endoscopic subscores of at least 2 were enrolled in the study. Total colonoscopy or at least flexible sigmoidoscopy was performed at weeks 14 and 54 to evaluate MH. MH was defined as Mayo endoscopic subscore 0 or 1. Complete MH was defined as Mayo endoscopic subscore 0. Clinical response was characterised as a decrease in the total Mayo score by at least 30% and at least 3 points from baseline. Remission was defined as Mayo score ≤ 2, with no individual subscores >1. Primary non-response was defined as lack of response at week 14 after the induction phase.

3.2.3. Assessment of laboratory markers

Laboratory markers for assessing disease activity (CRP, leukocyte and thrombocyte, haematocrit, albumin, and FC levels), CT-P13 trough levels and antibody titers (anti-infliximab antibodies [ATIs]) were measured and evaluated at weeks 14 and 54.

3.2.4. Statistical analysis

The chi-square test, Fisher exact test, Wilcoxon ranksum test, Kruskal-Wallis test, and Student t-test were used in the statistical analyses. All analyses were carried out using STATA 9.1 statistical program package. The value of $p<0.05$ was considered statistically significant.

3.2.5. Ethical approval

The study was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of the University of Szeged. The study was carried out in accordance with the declaration of Helsinki.

3.3. To evaluate the frequency of postoperative recurrence and to evaluate predictors of postoperative recurrence in Crohn's disease

3.3.1. Patients and data collection

Patients were selected retrospectively from the database of the Department of Pathology, University of Szeged (Hungary). All patients who underwent CD-related surgery between 2004 and 2014 were included in the study. Diagnosis of Crohn's disease was based on clinical, endoscopic and histological findings. Demographic data, smoking habits, previous resection, treatment before and after surgery, resection margins, neural fiber hyperplasia, submucosal and myenteric plexitis were evaluated as possible predictors of postoperative recurrence. Patients were regularly followed up with colonoscopy after the surgery. Postoperative relapse was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection.

3.3.2. Pathological examination

Histological samples were analysed retrospectively by two expert pathologists, blinded to the postoperative outcome and the clinical history of the patient. Plexitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle. The severity of plexitis was graded according to the classification proposed by *Ferrante* et al. Evaluation was performed independently for each cellular type: mast cell, plasmocyte, lymphocyte, eosinophil and neutrophil cell counts.

3.3.3. Statistical analysis

The statistical analysis was performed by a biomedical statistician using SPSS. To identify predictors of postoperative recurrence (clinical or surgical recurrence) univariable

logistic regression analysis was used. Survival was examined with the Kaplan-Meier method. The value of $p<0.05$ was considered statistically significant.

3.3.4. Ethical approval

This study was reviewed and approved by the Ethics Committee of the University of Szeged.

3.4. To describe the mortality of the Hungarian UC population between 2010 and 2016 and to analyse the prevalence of malignancies

3.4.1. Data collection

This is an observational, non-interventional, retrospective, descriptive, epidemiological study based on the National Health Insurance Fund (NHIF) social security database. Data from 2010 to 2016 were analysed. All adult patients who had at least two events in outpatient care or at least two medication prescriptions, or at least one inpatient event with UC diagnosis were analysed. Malignancies and colorectal cancer (CRC) were defined using ICD-10 codes. Survival analysis was performed on a subgroup of patients who were newly diagnosed from the beginning of 2010. For comparison purposes, date of death data of a 3 to 1 matched reference population from the total Hungarian population was obtained.

3.4.2. Statistical analysis

Prevalence, incidence and mortality were described using patient counts. Demographic data was characterised using histograms and median age. To compare patient groups t-tests were used. Survival was examined with the Kaplan-Meier method. The survival curves were compared using log-rank tests. A Cox proportional hazards model was also used for comparison. The hazard ratio (HR) with 95% CI between the two groups was given as a result.

3.3.3. Ethical approval

The study was approved by the Medical Research Council – Research and Ethics Committee (TUKEB), Hungary. All data used in the study were held by NHIF, the researchers had access only to anonymised data. Data protection guidelines did not permit the reporting of patient level data even in anonymised form, only aggregate results could be reported.

4. RESULTS

4.1. To evaluate the long-term efficacy and safety of biosimilar CT-P13 therapy in Crohn's disease and ulcerative colitis

4.1.1. Patient population and disease activities

57 CD and 57 UC patients were included, of whom 55 CD and 49 UC patients completed the induction therapy and 50 CD and 46 UC patients completed the 54-week treatment period.

In CD, the indication of CT-P13 therapy was luminal disease in 38, fistulising disease in 12 cases, and both luminal and fistulising diseases in 7 cases. In UC, therapy was started due to either acute onset or severe flare-up in 32 and chronic refractory activity in 25 patients. Previous anti-TNF therapy was administered in 7 CD and 9 UC patients. In CD, previous anti-TNF therapy resulted in remission in two cases and in UC in six patients.

4.1.2. Response to CT-P13 therapy

4.1.2.1. Response to the induction phase, primary non-response

Of the 55 CD patients who completed induction phase, clinical response was achieved in 53 patients (96.4%) (95% CI 87.5-99.6) – remission in 36 and partial response in 17 patients. 2 patients showed primary non-response at week 14. In UC, clinical response was achieved in 48 patients (48/49, 97.9%) (95% CI 89.1-99.9) at week 14 – remission in 37 and partial response in 11 patients. 3 patients underwent colectomy before the end of induction therapy – two because of non-response and one because of the diagnosis of colonic dysplasia. At week 14, colectomy was required in one further patient due to non-response.

4.1.2.2. CCR during the maintenance phase, loss of response (LOR)

CCR was shown in 28 (28/55, 50.9%) (95% CI 22.2-48.6) CD patients at week 54. 50 CD patients completed week 54; 62% were in clinical remission, 18% showed partial response. 23 patients showed LOR between weeks 14 and 54. In UC CCR was detected in 25 (51%) (95% CI 23.4-51.7) patients at week 54. Of the 46 patients who completed the study period, 65.2% were in remission, 19.6% showed partial response at week 54. LOR occurred in 22 UC patients after the induction therapy.

4.1.3. Changes in activity scores and laboratory parameters

In CD, mean CDAI and perianal disease activity index scores, CRP levels at weeks 14 and 54 decreased significantly from the baseline value. Determination of FC was available in 18 patients. Mean level of FC did not decrease significantly at week 54 ($p=0.38$). In UC, mean pMayo scores at weeks 14 and 54 decreased significantly from the baseline value. CRP levels also dropped significantly in week 14 but not in week 54 compared to the baseline values (from 23.5 ± 7.4 to 10 ± 3.3 and to 9.5 ± 5.9, $p=0.05$ and $p=0.07$). Determination of FC was available in 17 patients. Mean level of FC decreased significantly from the baseline to week 54.

4.1.4. Predictors of outcome

None of the examined parameters were predictive to the clinical outcome either in CD, or in UC.

4.1.5. Adverse events

In CD, 2 patients stopped CT-P13 therapy before the third infusion because of the occurrence of infusion reaction. One patient had infusion reaction after the fourth infusion leading to therapy discontinuation. In UC, 4 patients discontinued CT-P13 therapy before week 14 because of the development of infusion reaction. One patient on combo therapy died after the second infusion (because of azathioprine-induced rapid and severe myelosuppression and fulminant colitis). One additional patient had to stop therapy because of infusion reaction after the induction phase.

4.2. To evaluate mucosal healing and safety in UC patients treated with biosimilar CT-P13

4.2.1. Patient characteristics and follow-up

75 UC patients were included in the study, of whom 74 patients completed the induction phase and 61 had already completed the 54-week treatment period. 13 patients stopped the therapy before week 30 due to allergy or LOR, 4 of them underwent colectomy. 55.7% of patients had moderate and 44.3% had severe UC according to Mayo score (the mean Mayo score was 9.1 (5-12) points). Extraintestinal manifestation was recorded in 22.9% of patients, where mostly the joints were affected. The indication for CT-P13 therapy was acute, severe relapse of UC in 22, and chronic, refractory disease in 39 cases. The concomitant use of CSs was significantly reduced from baseline to week 54 (63.9-9.8%, p=0.005); moreover, the daily dose decreased as well.

4.2.2. Characteristics of laboratory markers

Laboratory markers were recorded and compared at baseline and at week 54. We found that inflammatory markers showed improvement: CRP, leukocyte number, and platelet count significantly decreased, and serum albumin, haematocrit significantly increased from baseline to week 54. Serum albumin level differed significantly in endoscopically active versus inactive UC patients at week 54.

4.2.3. Mucosal healing and remission rates at week 54

Partial Mayo Score and Endoscopic Mayo Score points significantly decreased from baseline to week 54. Remission, response, and non-response rates at week 14 was 55.7%, 27.9%, and 16.4%, respectively. This proportion did not change significantly at week 54. 55.2% of the enrolled patients achieved corticosteroid-free mucosal healing, this means that corticosteroid-free mucosal healing was achieved in 88.8% of endoscopic remissions.

4.2.4. Therapeutic drug monitoring

We investigated associations of CT-P13 trough level and ATI positivity with MH. The median value of CT-P13 trough level were 4.0±5.03 μg/ml and 3.2±4.9 μg/ml at weeks 14 and

54, respectively (p=0.14). ATI positivity significantly increased during the study period: 4 patients and 12 patients were positive at week 14 and 54 (p=0.016). MH among patients with and without ATI positivity was 58.3% (6/12) and 62.2% (23/37) (p=0.99).

4.2.5. Safety

Infusion reaction occurred in 6.6% in all enrolled patients, and 3.3% in patients who had already completed the study period. CT-P13 treatment associated adverse events were the following: one patient with pneumonia, one patient with Clostridium difficile infection, and two cases with drug-induced systemic lupus erythematosus-like syndrome (serious joint and skin lesions).

4.3. To evaluate the frequency of postoperative recurrence and to evaluate predictors of postoperative recurrence in Crohn's disease

4.3.1. Patient characteristics

104 patients with CD were enrolled in the study. Mean age at index CD-related surgery was 34.8±13.24 years, mean disease duration at the time of index surgery was 6.25±6.12 years. Operations were performed for specific reasons: abscess (20.2%), fistulas (13.5%), perforation (4.8%), stenosis (67.3%) and other (1%). Ileocecal, colonic and small bowel resections were performed in 73.1%, 22.1% and 4.8% of the cases, respectively. Postoperative recurrence occurred in 61.5% of the patients; of them 39.1% had surgical recurrence. 92.2% of the recurrences developed within the first five years after the index surgery. Mean disease duration for postoperative relapse was 2.70±2.11 years.

4.3.2. Histological findings

Typical CD lesions were found in proximal resection margins (5.8%), distal resection margins (5.8%), and in both resection margins (16.3%). Median severity of submucosal plexitis was 1 and median severity of myenteric plexitis was 2. Submucosal plexitis was mainly constituted by lymphocytes (median: 2), while myenteric plexitis was mainly constituted by lymphocytes (median: 2) and plasmocytes (median: 2). Other cell types, such as mastocytes, eosinophils and neutrophil granulocytes were less frequently observed.

4.3.3. Risk factors for postoperative relapse

We found that perianal disease (OR=3.78, 95% CI 1.164-12.312, P=0.027) and female gender (OR 2.21, 95% CI 0.98-5.00, P=0.056) are risk factors for postoperative relapse. Stricturing disease behaviour (OR=3.584, 95% CI 1.344-9.559, P=0.011) and isolated ileal disease localisation (OR=2.671, 95% CI 1.033-6.910, P=0.043) increased the risk of second surgery. Stricturing disease behaviour (OR=6.417, 95% CI 0.999-41.212, P=0.050) and ileocecal disease (OR=6.00, 95% CI 0.832-43.293, P=0.076) also increased the risk of relapse

in previously operated CD patients. Higher lymphocyte cell count in the submucosal plexus was a risk factor for surgical or clinical relapse (OR=1.267, 95% CI 1.000-1.606, P=0.050). Moderate submucosal plexitis reduced the risk of second surgery by 85.4% compared to severe submucosal plexitis.

4.4. To describe the mortality of the Hungarian UC population between 2010 and 2016 and to analyse the prevalence of malignancies

4.4.1. Epidemiology, mortality of UC, demographics

The number of patients suffering from UC between 2010-2015 was 36 315. The annual prevalence increased during the examined period: in 2010 0.24%, while in 2015 0.34% of the total Hungarian population suffered from UC. The estimated incidence of UC from 2015 was 21.7/100 000 inhabitants.

The median age of patients at the time of the first diagnosis of UC was 51 years (males 49, females 53). The average and median age was higher for women ($p<0.001$).

The annual mortality rate between 2011 and 2015 was stable, varying between 18.7 and 23.3 per 1000 patients. The rate was considerably lower in 2010 (12.8/1000 patients), though. The median age at the time of death was 75.7 years in the whole UC population. Men died at a younger age (median 72.4) than women (median 78.7).

4.4.2. Malignancies of UC patients

Investigating all malignant neoplasms of this incident UC population, we found that CRC (1424 patients, 8.5%) was the most common cancer followed by non-melanotic skin cancer and prostate cancer. Among patients with CRC 470 (33%) have died, these deaths make up 25% of all deaths within the incident UC population. The median age of patients at the time of CRC diagnosis was 65.8 years (male: 64.7; female: 67.0). The median age of these patients at the time of death was 71.1 years (male: 68.9; female: 73.3).

4.4.3. Survival of UC and CRC patients

Overall survival of the incident UC patients from the time of diagnosis was examined. The 1-year survival rate was 97%, the 3-year survival rate was 91% and the 5-year survival rate was 86%. UC patients have significantly worse survival than their matched controls (HR=1.65, 95% CI: 1.56-1.75).

We also analysed the overall survival of CRC patients among the UC population from the diagnosis of CRC. 1-year survival rate was 88%, the 3-year survival rate was 75% and the 5-year survival rate was 65%. The median survival was 9.67 years.

5. DISCUSSION

The introduction of biological therapies and the favourable results of landmark studies have changed the traditional therapy algorithm of IBD. With the possibility of complete mucosal healing, new therapeutic goals have become available: endoscopic -, mucosal – and in some studies histological healing appeared as well. MH may be a major sign of effective therapy and a prognostic factor of long-term outcome. CT-P13, the first biosimilar was approved for the same indications as its originator IFX in 2013. The results of our prospective, observational study from our tertiary IBD centre revealed CCR in 51-51% of CD and UC patients at week 54. Primary non-response and loss of response occurred in about 40% of the patients. Before the publication of our study, most other studies have focused on the induction phase of the therapy, and the published data regarding the efficacy and safety of long-term CT-P13 use had been limited. Two randomised, clinical trials have been conducted: the one evaluating the safety and efficacy of biosimilar IFX in patients with CD or UC is still in progress, while the other one, a double-blind clinical trial (ended in 2017), demonstrated non-inferiority in efficacy and safety of CT-P13 in patients with active Crohn's disease who were naïve to biological therapy. The first long-term data have become available from a Korean study by *Jung et al* (54-week clinical response: CD: 87,5%, UC: 100%). Our results showed higher response rates in both CD and UC assessed at week 54 compared to the larger randomised, controlled trials of IFX, the ACCENT-1 (39%) and the ACT-1 trials (46%). Notably, in the PROSIT cohort, efficacy after one year was 71% for TNF-naïve patients.

Our study of mucosal healing adds a supplementary data to this topic, since we proved in an appropriate number of patients that long-term MH could be reached in 62.1% of the cases. Previous studies had assessed MH only in a small number of subjects and/or as a secondary endpoint without evaluating any influencing factors. A placebo-controlled, double-blind study with originator IFX included 728 moderate-to-severe UC patients confirmed that MH at weeks 8, 30, and 54 was significantly higher in UC patients treated with originator IFX than placebo. In this study, the rate of MH was approximately 50% at week 54. Based on a systematic review, the pooled rates of MH in naïve UC patients at week 54 was 0.63, 95% CI (0.50-0.73).

Factors predicting to worse outcome have high clinical importance. A nationwide prospective and observational Hungarian cohort study revealed that induction treatment with the biosimilar IFX was less effective in patients previously exposed to the originator compound. *Gönczi et al.* revealed that week 2 trough levels of CT-P13 were predictive for short- and medium-term clinical efficacy in UC but were associated only with short-term clinical

outcomes in CD. None of the examined parameters were predictive to clinical outcome or to MH, either in CD, or in UC in our studies.

Regarding safety, in our first study, therapy had to be discontinued as a consequence of infusion reaction in 5.3%, and 7.2% of CD and UC patients. In our second study the frequency of infusion reaction was 6.6% in all enrolled patients. Our data are in line with data published previously or later. In a randomised, double-blind study, 67% of the patients experienced at least one treatment-emergent adverse event. In the PROSIT Cohort the occurrence of infusion reactions was 8.7%. Based on a recent systematic review and meta-analysis, the overall rate of adverse events was 0.1 (95% CI 0.04-0.22) and 0.09 (95% CI 0.05-0.15) in naïve CD and naïve UC patients, while that of infusion reaction was 0.11 (95% CI 0.05-0.23) and 0.05 (95% CI 0.03-0.09).

Despite the available, highly effective, new therapeutic options postoperative relapse is still a major issue in CD. More than 70% of patients require surgery during their lifetime. In the third study we demonstrated that in CD the severity of submucosal plexitis in proximal resection margins, perianal manifestation and stricturing disease behaviour, as well as isolated ileal disease were all associated with postoperative recurrence. Studies have found myenteric plexitis in 42.5-88% of proximal surgical margins. We could evaluate myenteric and submucosal plexitis of different severity in every sample, in accordance with the findings of *Bressenot et al.*, while the rate of typical CD-lesions was low (5.7%) in proximal resection margins. A higher lymphocyte cell count in the submucosal plexus was a risk factor for surgical or clinical relapse ($p=0.050$), while moderate submucosal plexitis reduced the risk of a second surgery by 85.4% compared to severe submucosal plexitis ($p=0.020$), which is in accordance with other studies. Our data of surgical recurrence are in concordance with previously published ones (11-32% in 5 years). We could not confirm any association between postoperative recurrence and the presence of myenteric plexitis or the use of pre- or postoperative prophylactic treatment.

The fourth study was the first population-based study from Eastern Europe which simultaneously estimated mortality, morbidity, and the associated malignancy data in UC patients based on the Hungarian NHIF database. During our study, the prevalence of UC increased from 0.24% to 0.34%. Previous studies conducted between 2011 and 2013 found similar prevalence rates. The incidence of 21.7/100 000 inhabitants in 2015 found in our study is considerably higher than the one reported in 2006, but is in concordance with the increasing tendency published from industrialised countries. Most studies reported the peak incidence of UC in the early adulthood; however, in some studies a second modest rise in incidence in later decades of life has also been reported similarly to our findings.

It is still questionable whether UC-patients are at higher risk of death compared to the general population. Overall and cause-specific mortality was assessed with a meta-analysis of population-based inception cohort studies. They found that the overall mortality of UC patients was similar to the general population; however, the cause-of-death distribution seemed to be different, with a higher risk of gastrointestinal diseases. In our study only the overall mortality was assessed. In contrast to the above-mentioned meta-analysis, our study revealed a significant difference (HR=1.65) between the survival of patients with UC and that of the general population. The most common malignancies were CRC, malignant neoplasm of the skin and malignant neoplasm of the prostate.

6. CONCLUSION

To the best of our knowledge, at the time of publication, our study was the first prospective study that evaluated and confirmed long-term efficacy and safety of CT-P13 therapy in IBD. Response rates at week 54 were similar in CD and UC. The results of randomised being conducted presently may yield important data to confirm the expected safety and long-term efficacy of CT-P13, which would have a significant role in supporting the use of biosimilar drugs in IBD. Wider application and more clinical benefits may ensure that more patients will receive effective therapy in the future.

Our second study clearly demonstrated that mucosal healing can be achieved with CT-P13 therapy as well and it also had the same effectivity as the originator IFX in long-term treatment as.

The presence of severe submucosal plexitis with lymphocytes in the proximal resection margin is more likely to result in postoperative relapse. The postoperative assessment of plexitis could be performed routinely by every pathologist in every centre as proximal resection margins are systematically analysed. This requires no special immunostaining. The histological analysis of proximal resection margins may be useful when making a decision on early postoperative treatment without a postoperative follow-up colonoscopy, thus possibly modifying the natural course of CD. However, further studies with a prospective design and a longer follow-up period are needed.

Our nationwide, population-based study was the first to estimate the number of different malignancies and mortality rate among Hungarian ulcerative colitis patients, and it also updated previously available data of prevalence and incidence rates. Although the mortality trend of the Hungarian UC population corresponds to the trend observable in the general population of Hungary, our results revealed a significantly worse survival of UC patients than that of the

general population. These findings emphasize the importance of colorectal cancer surveillance program in the management of UC.

7. STATEMENTS

1. Our study was the first, prospective study that proved the long-term efficacy and safety of biosimilar CT-P13 therapy in both CD and UC patients.
2. Primary non response and loss of response in long term use of biosimilar CT-P13 was 43.9% in CD and 40.4% in UC patients.
3. Our study of mucosal healing proved that mucosal healing can be reached in UC patients with long-term CT-P13 therapy.
4. We demonstrated that in Crohn's disease the severity of submucosal plexitis in proximal resection margins, perianal manifestation and stricturing disease behaviour, isolated ileal disease, as well as female gender were all associated with postoperative recurrence.
5. We did not find any association between postoperative recurrence in Crohn's disease and preoperative or postoperative prophylactic treatment.
6. We could update prevalence and incidence rates in the Hungarian ulcerative colitis patient population. We found an increasing prevalence rate (2010: 0.24%, 2015: 0.34%) and an increasing incidence rate (21.7/100 000 inhabitants).
7. Two peaks were found in the onset of ulcerative colitis in the Hungarian UC population (30-39 years and over 50 years).
8. Investigating all malignant neoplasms of this incident UC population, we found that colorectal cancer was the most common cancer (1424 patients, 8.5% of the incident patient subpopulation) followed by non-melanotic skin cancer and prostate cancer.
9. Our study revealed that ulcerative colitis patients have a worse survival than that of the general population.

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