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

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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

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LIST OF ABBREVIATIONS

5-ASA – 5-aminosalicylate

ADA – anti-drug antibody

ALB – albumin

ATI – antibody titer

CCR – continuous clinical response

CD – Crohn's disease

CDAI – Crohn's Disease Activity Index

CDEIS – Crohn's Disease Index of Severity

CIs – confidence intervals

CRC – colorectal cancer

CRP – C-reactive protein

CS - corticosteroid

ECCO – European Crohn's and Colitis Organization

ECCO EpiCom – European Crohn's and Colitis Organization – Epidemiological Committee

eMayo – endoscopic Mayo score

FC – faecal calprotectin

HR – hazard ratio

HTC – haematocrit

ICD-10 – International Classification of Diseases

IBD – inflammatory bowel disease

IBSEN study group – Inflammatory Bowel South-Eastern Norway study group

IFX – infliximab

LOR – loss of response

MH – mucosal healing

MM – multiple myeloma

MN – malignant neoplasm of

NHIF – National Health Insurance Fund

NHL – non-Hodgkin's lymphoma

OR – odds ratio

Other&unspec – other or unspecified part/type

PDAI – perianal disease activity index

PLT – platelet

pMayo score – partial Mayo score

Sec. MN – secondary malignant neoplasm of

SES-CD – Simple Endoscopic Score for Crohn’s Disease

TNF – tumour necrosis factor

UC – ulcerative colitis

WBC – white blood cell

1. INTRODUCTION

The term inflammatory bowel disease (IBD) primarily covers two chronic conditions: ulcerative colitis (UC) and Crohn's disease (CD). Both of them are chronic, relapsing, lifelong diseases with unknown aetiology, often requiring lifelong medical treatment and monitoring to keep the disease under control. 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 [1, 2]. 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) antagonists. Recently, with the newly developed drugs targeting inflammatory cytokines and leukocyte-trafficking molecules, a wide range of therapeutic options has become available paving the way for personalised treatment. 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 [3] since even during clinical remission, laboratory or imaging tests can reveal persistent inflammation of the mucosa [4]. 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 [1, 5, 6]. It has been suggested that deep remission (defined as clinical and endoscopic remission (endoscopic mucosal healing (endoscopic MH)) could prevent chronic inflammation [7]. In the biological era, MH has been suggested as a treatment target in most studies. Mucosal healing is defined by endoscopic assessment and generally it is accepted that in CD it refers to the absence of mucosal ulcerations and inflammatory lesions [SES-CD (Simple endoscopic score for Crohn's disease) 0, CDEIS (Crohn's disease index of severity) 0, while in UC it is defined as the absence of friability, blood, erosions and ulcers of the gut mucosa (Mayo score 0)]; however, a validated definition is still lacking [8, 9]. MH is associated with decreased hospitalisation rates, fewer surgeries and prolonged clinical remission [10–12]. 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 [13].

With the introduction of immunosuppressive and biological drugs, the need for corticosteroids to treat flares has decreased. The first biological agent approved for the treatment of CD and UC was infliximab (IFX) in 1997 and 2006, respectively. Later adalimumab was approved for CD in 2007 and for UC in 2012, and golimumab for UC in 2013. The ACCENT and ACT trials were the landmark randomised controlled trials demonstrating that the originator IFX can induce and maintain remission [14, 15]. CT-P13, a biosimilar of

IFX, was the first monoclonal antibody biosimilar approved by the European Medicines Agency in 2013. Its therapeutic indications, as well as the dosing regimen are the same as those of the originator infliximab, and they were based on data derived from two randomised, controlled, double-blind clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis [16, 17]. CT-P13 is an IgG1 chimeric human-murine monoclonal antibody biosimilar of infliximab produced in the same type of cell line (Sp2/0-AG1 purchased from ATCC). CT-P13 does not only have a structure (amino acid sequence) identical to infliximab, but its actions of mechanism are also comparable both in vitro and in vivo [18]. CT-P13 and its originator IFX showed comparable binding affinities to TNF-α, relative binding affinities to complement protein C1q and they have similar TNF-α neutralising activity, complement-dependent cytotoxicity and apoptotic effects [18]. In the beginning, many physicians and several national societies raised concerns regarding the use of biosimilars in extrapolated indications [19]. Later, real-life data confirmed the comparable efficacy and safety of CT-P13 and its originator in the treatment of IBD [20, 21, 30, 22–29].

Although highly effective, new therapeutic options are available, their ability to modify the natural course of the disease is still studied intensively [31, 32]. In Crohn's disease, the use of immunomodulators reduce the risk of surgery and hospitalisation [32]; however, more than 70% of patients with CD require surgery during their lifetime [33]. Surgical interventions are often required in case of bowel obstruction, abscess, fistula or refractory disease. The 10-year risk of surgical interventions after the diagnosis of CD is 46.6% [34]. The overall risk of a second surgery is 24.2%, and the majority of such complications occur in the first 5 years of the disease [35]. The highest recurrence rate has been observed in the ileocolonic disease location [33, 36]. To optimise treatment and surveillance programme after surgery, it is important to identify the potential risk factors of postoperative recurrence; however, the currently available data are conflicting. The Inflammatory Bowel South-Eastern Norway (IBSEN) study group revealed terminal ileal location, stricturing, penetrating behaviour and age younger than 40 years at diagnosis as independent risk factors of subsequent surgery [37]. Other studies found that smoking increases the risk of clinical and surgical recurrence [38], while steroid use [39] and the previous use of two or more anti-TNFα agents [40] increase the risk of endoscopic recurrence. Histological changes in the enteric nervous system are common in CD. Major structural abnormalities are irregular hypertrophy and hyperplasia of nerve fibres, as well as alterations of neuronal cell bodies and enteric glial cells in the ganglia of the submucosal and myenteric plexus [41]. 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 [42]. 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 [43–49].

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

Our prospective, observational study was conducted between June 2014 and September 2016 at the First Department of Medicine, University of Szeged. Patients over 18 years of age, diagnosed with CD or UC and receiving biosimilar CT-P13 were eligible to participate in the study. In case of CD, patients were eligible if they had moderate-to-severe therapy-refractory or steroid dependent luminal or therapy-refractory simple fistulising disease or if complex fistulas occurred. Patients with UC had therapy-refractory, steroid-dependent or moderate-to-severe acute steroid-refractory colitis. Clinical outcome was evaluated at fixed appointments throughout the 54-week treatment period. 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. According to the national regulation at the time of the study, none of the patients had received originator IFX treatment within 12 months before the initiation of the biosimilar IFX.

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 [50] and the partial Mayo (pMayo) scoring system in UC [51] at weeks 0, 2, 6, 14, 22, 30, 46 and 54. Continuous clinical response (CCR) was defined as a maintained response through week 54 without intermediate relapses. CD response was defined as a >100-point decrease in CDAI. UC response was defined as >30% decrease in the activity index and a decrease in rectal bleeding and endoscopy subscores. Remission was defined as CDAI below 150 for luminal CD, and for UC it was defined as a pMayo score ≤2, with no individual subscores over one. The severity of perianal CD was evaluated with the Perianal Disease Activity Index (PDAI) [52]. Clinical response was defined as a decrease of 50% or more in the amount of fistula discharge, and clinical remission was defined as a complete closure of fistulas. Fistula closure was defined as no drainage, either spontaneously or on gentle compression. Primary non-response was described as failure to achieve clinical response following the induction phase of CT-P13. Loss of response (LOR) was defined as an increase in CDAI of at least 70 points or an at least 2-point increase in pMayo

score with an absolute pMayo score of 4 or higher. The primary end points were 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 with 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). Cut-off values were 5 mg/l for CRP and 300 μg/g for faecal calprotectin. The detection cut-off value of CT-P13 trough level was 0.1 μg/ml, while 3-7 μg/ml was defined as therapeutic.

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. The examined variables in CD were CT-P13 trough levels at weeks 2, 6 and 14; CRP level at weeks 0, 2, 6, 14, 30 and 46; faecal calprotectin at weeks 2, 6 and 46, concomitant steroid and azathioprine use at the time of induction therapy and at week 30; previous use of anti- TNF drug; and the need for dose intensification. In UC, examined variables consisted of CT-P13 trough levels at weeks 2, 6, 14, 30 and 46; CRP level at weeks 0, 2, 6, 14, 30 and 46; faecal calprotectin at weeks 2, 6 and 46; concomitant steroid and azathioprine therapy at the time of induction therapy at week 30, previous use of anti-TNF drug; and the need for dose intensification.

Confidence intervals (CIs) for proportions were calculated with the Clopper-Pearson method. The changes from baseline in continuous variables (e.g. CRP, FC, CDAI and pMayo score) 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 [53]. Results are visualised as odds ratios (ORs) 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 929772-22014/EKU [292/2014]).

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 above 18 years, 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. The phenotype of UC was determined with Montreal classification [54]. CT-P13 was administered as an intravenous infusion at 0, 2 and 6 weeks in a dose of 5 mg/kg followed by a maintenance regimen of 5 mg/kg every 8 weeks except for one patient who was given 10 mg/kg for induction and maintenance treatment. Biological therapy-naïve patients and subjects with previous anti-TNF therapy were enrolled as well, but previous anti-TNF therapy had to have been stopped at least 1 year prior to the CT-P13 therapy. According to Hungarian central regulations, only CT-P13 was allowed to be reintroduced in the study period if the patient had received originator IFX previously. Disease activity was assessed with clinical data and endoscopy using the Mayo Scoring System and with 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 mucosal healing. MH was defined as a Mayo endoscopic subscore of 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. Change in rectal bleeding was specifically assessed (decrease of at least 1 point or a rectal bleeding subscore of 0 or 1). 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. CT-P13 trough levels and ATIs were measured with 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)]. Detectable trough level was 0.1 μg/ml for CT-P13, and the measurement range for ATIs was 10-200 ng/ml [>10 ng/ml considered positive] with the LISA TRACKER; with the SHIKARI kits, the lowest detectable level was 30 ng/ml. ATIs were considered positive when the positivity index exceeded 3. Faecal specimens were thawed and prepared for FC assay as described by the manufacturer, then they were assessed with a quantitative lateral flow assay (Quantum Blue, Bühlmann Laboratories, Switzerland).

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 the 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 (49/15-55/101,651, 36/2016-SZTE). The study was carried out in accordance with the declaration of Helsinki. All study participants or their legal guardians provided written informed consent prior to study enrolment.

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. The following data were extracted retrospectively from the medical chart of each patient: age, sex, year of diagnosis of Crohn's disease, phenotype of Crohn's disease according to the Montréal classification [55], smoking habits, date of the CD-related surgery, type of the anastomosis, CD-related therapy before and after surgery and the presence of postoperative relapse. Postoperative relapse was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection. Patients were regularly followed up with colonoscopy after the surgery. Postoperative endoscopy findings were classified on the basis of the Rutgeerts score in case of ileocolonic resection [56]; remission was defined as Rutgeerts endoscopic score i0-i1, and recurrence as a score of i2-i4 [56].

Postoperative recurrences were defined on the basis of the work of Ng et al. Clinical recurrence was defined as the presence of CD-related symptoms associated with radiological or endoscopic findings, considered severe enough to change the current therapy (need steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation (refractory to medical treatment or new complications developed) [44].

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. Both resection margins (ileal and colonic margins) were investigated for typical CD lesions (inflammatory infiltrates, granuloma, etc). Further investigations focused on the proximal resection margin. Special attention was given to the enteric nervous system, namely to the myenteric and submucosal plexuses. Plexitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle [46]. The severity of plexitis was graded according to the classification proposed by *Ferrante et al*. [42]: mild plexitis if the ganglion or nerve bundle contained 0-4 inflammatory cells (G1), moderate plexitis if it contained 4 to 9 cells (G2), or severe if containing ≥10 cells (G3). Evaluation was performed independently for each cellular type: mast cell, plasmocyte, lymphocyte, eosinophil and neutrophil cell counts were also evaluated [46]. Each sample was fixed in buffered formalin and analysed using haematoxylin-eosin staining. Some examples are demonstrated in Figure 1.

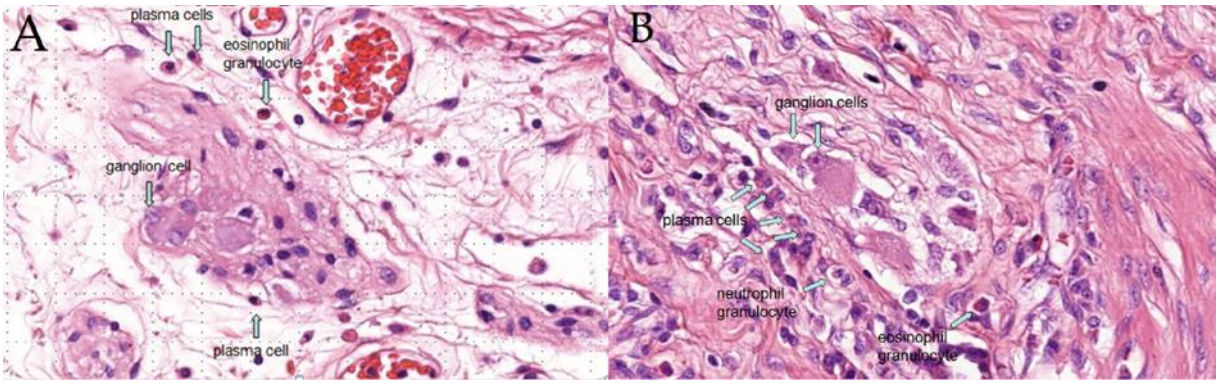

Figure 1 Submucosal plexitis (A) with plasma cells and eosinophil granulocyte surrounding the ganglion cell (haematoxylin-eosin staining); and myenteric plexitis (B) with plasma cells, neutrophil granulocyte, and eosinophil granulocyte surrounding the ganglion cell (haematoxylin-eosin staining) in a CD resection specimen.

3.3.3. Statistical analysis

The statistical analysis of the data was performed by a biomedical statistician using SPSS. To identify predictors of postoperative recurrence (clinical or surgical recurrence) univariable logistic regression analysis was used on patients' baseline characteristics and

histological findings, such as severity of myenteric and submucosal. P values <0.05 were considered statistically significant. Survival was examined with the Kaplan-Meier method.

3.3.4. Ethical approval

This study was reviewed and approved by the Ethics Committee of the University of Szeged (3594, 114/2015-SZTE)

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 NHIF social security database. This database contains financial claims data on all healthcare events (inpatient hospital stays, outpatient visits, pharmacy drug reimbursements and special drug reimbursements) of the whole population of Hungary. Medication prescriptions carry diagnosis information and demographic data (date of birth, gender, geographical region and date of death, where applicable), but non-finance-related information – such as laboratory test results – are not available. Data from 2010 to 2016 were analysed.

Differentiation between CD and UC was performed in the following way: as a first step, a background population consisting of patients with either CD or UC codes was created. Patients who had at least two events detected in all relevant health care services, or at least one inpatient event with the diagnosis of UC (based on the 10th revision of the International Classification of Diseases (ICD-10) code: K51*) or CD (ICD-10 code: K50*) during the study period were included. Back-data were available from the beginning of 2007. In patients who had both diagnoses the following algorithm was followed: if at least 80% of the diagnosis codes were UC related, the patient was classified as an UC patient. At that point, the patient group still contained subjects whose UC diagnosis could not be ascertained, so a further refining step, similar to the one outlined in the paper by Kurti et al, was necessary [57]. In this step, patients were excluded if they had none of the flowing: any record of biological therapy, any record of UC-related surgical interventions (based on diagnosis related group) or record of a sufficient number of drug prescriptions (defined as at least 2 dispensings of 5-aminosalicylates (5-ASA) or corticosteroids or immunosuppressants per year). This requirement focusing on the number of prescriptions causes patients with a short follow-up time – i.e. those who were incident in the second half of 2016 – to be easily excluded from the analysis. Therefore, the year of 2016 was excluded from the epidemiological analysis.

Survival analysis was performed on a subgroup of patients who were newly diagnosed (defined as having no UC diagnoses before) from the beginning of 2010. This means that all incident patients have at least a 3-year long diagnosis-free baseline period. For comparison purposes, date of death data of a 3 to 1 matched reference population from the total Hungarian population was obtained. Matching was based on age (year of birth), gender and permanent residency. Demographic data were also evaluated.

Malignant neoplasms were evaluated in the incident UC subpopulation. Malignancies were categorised based on 3-digit ICD10 codes. Presence of a certain malignancy was defined as having at least 2 diagnoses in the in- or outpatient care setting following the date of the UC diagnosis. Colorectal cancer (CRC) was analysed in detail. CRC was defined as ICD-10 codes C15*-C26*. The appearance of the first CRC code was considered as the date of the diagnosis of CRC. Proportion of patients with certain malignancies, yearly incidence and prevalence of CRC were evaluated. Survival data of the study population were assessed. Overall survival from the time of the diagnosis of UC and from the time of the diagnosis of CRC were evaluated. Overall survival data from the diagnosis of UC were compared with the data from the matched general population.

3.4.2. Statistical analysis

Prevalence, incidence and mortality were described using patient counts. Demographic data were characterised using histograms and median age. To compare the age of different patient groups t-tests were used. Survival analysis was performed to analyse overall survival and Kaplan-Meier estimators were used to characterize survival function. Comparison of survival of two groups was performed in two cases: for all UC patients versus controls and for the two different age groups for the CRC subpopulation. The survival curves were compared using log-rank tests. A Cox proportional hazards model – using a single binary predictor for the two groups – was also used for comparison. The hazard ratio (HR) with 95% confidence interval between the two groups was given as a result. The proportional hazards assumption was tested using plots of Schoenfeld residuals.

Due to the claims nature of the data, missing data are undiscoverable in most cases. If a certain intervention or diagnosis was not recorded, there is no chance that it could be imputed in any way. Therefore, no handling of missing data was performed.

Analyses was carried out using the statistical software R 3.5.1 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

3.4.3. Ethical approval

The study was approved by the Medical Research Council – Research and Ethics Committee (TUKEB), Hungary (Appr. no: 12288-3/2018/EKU).

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 the same number of 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 initiated 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 (3 originator IFX and 4 adalimumab) and 9 UC (6 originator IFX, 2 adalimumab, and one golimumab) patients. In CD, previous anti-TNF therapy resulted in remission in two cases and in UC in six patients. Demographic data and the clinical characteristics of the enrolled patients and that of those who completed week 54 are detailed in Table 1.

	Patients enrolled in the study		Patients who completed week 54	
	CD patients (n=57)	UC patients (n=57)	CD patients (n=50)	UC patients (n=46)
Mean age at diagnosis (years)	28 (10-55)	31(15-65)	28 (10-55)	30.5 (17-65)
Mean disease duration (years)	9 (0-27)	7 (0-22)	9 (0-27)	8 (0-22)
Male/female ratio	31/26	29/28	27/23	24/22
Smoking history				
- Ex-smoker	5	5	5	8
- Current smoker	13	1	13	1
- Never smoked	26	19	30	30
- No data	3	8	2	7
Family history of IBD	2	2	2	4
Surgical history				
- Bowel resection	17	0	15	0
- Fistula/abscess surgery	18	0	16	0
- Colectomy	1	1	1	1
Location/extent				
- Ileal	7	0	6	0
- Colonic	16	0	14	0
- Ileocolonic	26	0	23	0
- Upper GI	1	0	1	0
- Ileocolonic + Upper GI	7	0	6	0
- Extensive colitis	0	27	0	21
- Left-sided colitis	0	25	0	22
- Proctitis	0	5	0	3
Behaviour				
- Inflammatory	19	0	17	0
- Stricturing	17	0	15	0
- Penetrating	21	0	18	0
Extraintestinal manifestation				
- Arthralgia/arthritis	14	15	10	11
- Erythema nodosum/pyoderma gangrenosum	8 0	3 2	6 1	2 1
- Scleritis/episcleritis/uveitis				

Previous medications				
- 5-ASA	36	48	29	40
- Corticosteroids	43	48	37	41
- Thiopurines	51	42	44	35
- Cyclosporine	0	5	0	6
- Anti-TNF-alfa	7	9	5	7
Efficacy of previous anti-TNF alfa therapy				
- Remission	2	6	1	4
- Response	0	0	0	0
- No response/loss of response	5	2	4	2
- Allergy	0	1	0	1
Concomitant medications at induction				
- 5-ASA	17	37	16	29
- Corticosteroids	21	35	18	29
- Thiopurines	34	26	30	22

Table 1 Demographic data and clinical characteristics of patients. 5-ASA: 5-aminosalicylate

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 the induction phase, clinical response was achieved in 53 patients (96.4%) (95% CI, 87.5-99.6) – remission in 36 (65.5%) and partial response in 17 (30.9%) patients. 2 (3.6%) 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 (77.1%) and partial response in 11 (22.9%) patients. At week 14, colectomy was required in one further patient due to non-response. 3 patients underwent colectomy before the end of the induction therapy – two because of non-response and one because of the diagnosis of colonic dysplasia.

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

CD – CCR was shown in 28 (28/55, 50.9%) (95% I, 22.2-48.6) CD patients at week 54. 50 patients completed week 54; 31 of them (62%) (95% CI, 48.6-80.4) were in clinical remission, 9 (18%) showed partial response and 10 (20%) had an active disease (95% CI, 9.6-37.3). 23 patients showed LOR between weeks 14 and 54. The overall rate of primary non-response and LOR was 43.9% (95% CI, 26.0-52.4). Steroid was administered in 4 patients, dose escalation was necessary in 6 patients, and combination therapy was used in 4 patients with LOR. 5 patients required a surgical intervention: 2 of them underwent ileocecal resection, one patient had right hemicolectomy and 2 needed perianal abscess surgery. CT-P13 therapy was continued in 3 of the operated patients after the surgery. No intervention was applied in 3 patients with LOR. Considering patients who required CT-P13 therapy because of perianal fistulas and completed week 54, partial response was achieved in 5 patients and remission with complete closure of all fistulas was achieved in 4 patients. 3 patients showed LOR with

continuous fistula discharge. At week 54, 15 patients stopped CT-P13 therapy based on the decision of the physician.

UC – CCR was detected in 25 (51%) (95% CI, 23.4-51.7) UC patients at week 54. Of the 46 patients who completed the study period, 30 patients (65.2%) (95% CI, 40.6-76.3) were in remission, nine patients (19.6%) showed partial response, and seven patients (15.2%) had active disease (95% CI, 7.2-36.4) at week 54. LOR occurred in 22 patients after the induction therapy. Steroid was given in five, dose escalation was used in seven, and both were administered in six patients. No intervention was required in four patients. One of the patients did not respond to dose escalation and had to be operated on before achieving week 54. The overall rate of primary non-response and LOR was 40.4% (95% CI, 20.8-47.9). At week 54, the gastroenterologist decided to stop CT-P13 therapy in 24 patients.

In both diseases, CT-P13 therapy was stopped only in case of remission or CCR. Therapy discontinuation was always discussed with the patients since in some cases with the same outcome therapy was continued because of the patients' previous complicated disease course, surgeries, responses to other treatments, need of dose escalation etc.

4.1.3. Changes in activity scores and laboratory parameters

In CD, mean CDAI scores at weeks 14 and 54 decreased from the baseline value of 307.0±20.1 to 106.3±14.5 and 118±19.8 ($p<0.001$ in both cases) and mean PDAI scores from 10±0.58 to 2.4±1.3 and 3.3±0.9 ($p=0.001$ and $p=0.003$). However, the mean value of CDAI and PDAI scores did not change significantly in patients who completed the 54-week treatment period compared to the mean values of their CDAI and PDAI scores at week 14 ($p=0.38$ and $p=0.29$). CRP levels dropped significantly at weeks 14 and 54 compared to the baseline values (27.7±6.9 to 9.86±2.8 and to 13.7±4.3, $p=0.01$ and $p=0.05$). Determination of FC was available in 18 patients. The mean level of faecal calprotectin did not decrease significantly at week 54 (725.5-762.3 μg/g, $p=0.38$).

In UC, mean pMayo scores at weeks 14 and 54 decreased significantly from 7.57±0.2 to 2.33±0.5 and 1.15±0.39 ($p<0.001$ in both cases). Decrease in the mean value of pMayo scores from week 14 to 54 showed borderline significance ($p=0.055$). 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 faecal calprotectin was available in 17 UC patients. The mean level of faecal calprotectin decreased significantly from the baseline to week 54 (953.4 to 604.5 μg/g, $p\leq0.001$).

Serum CT-P13 levels measured at weeks 14 and 54 did not differ significantly between patients with CCR and secondary non-responders either in CD (7.34±5.93 vs. 4.85±5.05 μg/ml,

p=0.2, and 7.85±9.2 vs. 4.02±5.56 μg/ml, p=0.19) or in UC (6.1±5.4 vs 5.87±4.58 μg/ml, p=0.98, and 4.67±4.59 vs 4.9±6.1 μg/ml, p=0.74). Table 2 and 3 summarise the laboratory parameters throughout the treatment period.

	Anti-TNF drug level (μg/ml)		CRP (mg/l)		WBC (g/l)		HTC (%)		PLT (g/l)		ALB (g/l)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Week 0	0.00	0.00	10.6	31.2	7.6	3.0	40.0	9.0	31.0	134.0	44.0	7.0
Week 2	17.22	14.87	3.9	4.0	6.9	2.8	39.0	7.0	288.0	92.3	45.0	6.0
Week 6	8.904	17.23	3.55	5.4	6.1	2.4	40.0	7.0	276.0	67.0	44.0	5.0
Week 14	6.09	9.85	4.2	5.7	6.8	2.9	40.0	7.0	286.0	75.0	46.0	5.0
Week 30	2.39	6.99	6.4	10.4	6.2	2.6	40.0	6.0	256.0	133.0	45.0	5.0
Week 46	3.03	8.19	5.4	10.4	6.1	2.8	39.5	5.0	261.5	90.8	44.5	5.3

Table 2 Summary of the laboratory parameters throughout the treatment period in Crohn's disease. Anti-TNF: anti-tumour necrosis factor, CRP: C-reactive protein, WBC: white blood cell, HTC: haematocrit, PLT: platelet, ALB: albumin

	Anti-TNF drug level (μg/ml)		CRP (mg/l)		WBC (g/l)		HTC (%)		PLT (g/l)		ALB (g/l)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Week 0	0.00	0.00	14.0	35.0	9.5	5.0	37.0	10.3	343.5	153.8	44.0	6.5
Week 2	16.5	11.3	4.9	7.4	8.0	3.7	38.0	9.0	338.0	161.0	44.0	4.0
Week 6	12.2	15.5	3.8	3.6	7.7	3.7	37.0	10.0	292.0	156.0	46.0	5.5
Week 14	5.1	5.9	3.4	4.4	7.7	5.4	39.0	8.0	317.0	144.0	46.0	5.5
Week 30	5.5	7.4	3.0	3.8	6.1	3.1	39.0	7.0	282.0	98.0	48.0	7.0
Week 46	3.2	8.9	2.7	2.2	5.9	2.7	39.0	7.0	255.0	94.0	46.0	4.5

Table 3 Summary of the laboratory parameters throughout the treatment period in ulcerative colitis. Anti-TNF: anti-tumour necrosis factor, CRP: C-reactive protein, WBC: white blood cell, HTC: haematocrit, PLT: platelet, ALB: albumin

4.1.4. Predictors of outcome

According to univariate analysis, none of the examined parameters predicted LOR either in CD or in UC. Moreover, multivariate analysis with CRP level and CT-P13 trough level at week 14, earlier anti-TNF use, baseline steroid requirement and dose intensification did not identify any of the variables as a possible predictor of outcome in CD (Figure 2). In UC, CRP level, CT-P13 trough level and faecal calprotectin concentration at week 6, baseline steroid requirement and dose intensification did not predict disease outcome (Figure 3). No difference was observed regarding the clinical outcome at week 54 between anti-TNF-naïve patients and patients previously treated with an anti-TNF agent.

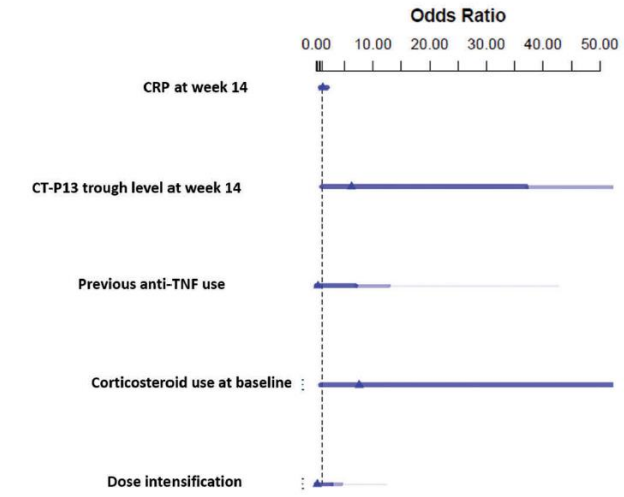

Figure 2 Multivariate analysis of patients to identify predictive factors of disease outcome in CD. CRP: C-reactive protein

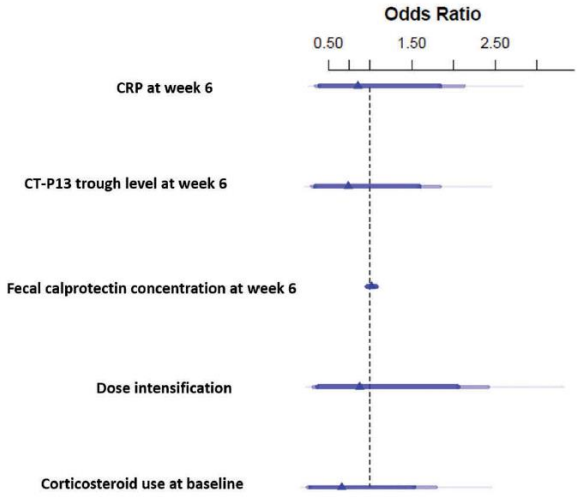

Figure 3 Multivariate analysis of patients to identify predictive factors of disease outcome in UC

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. Mild infusion reaction occurred in three patients during the 54-week period; however, CT-P13 therapy did not have to be discontinued. In UC, four 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: the azathioprine-induced rapid and severe myelosuppression and fulminant colitis required colectomy; however, after the successful surgical intervention, fatal fungal and bacterial sepsis with neutropenia occurred. One additional patient had to stop the therapy because of infusion reaction after the induction

phase. Infusion reaction occurred in four further UC patients after the induction phase; however, CT-P13 therapy had to be discontinued in only one of them.

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

4.2.1. Patient characteristics and follow-up

Seventy-five 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, four of them underwent colectomy.

Statistical analysis was performed with data from patients who finished the 54-week CT-P13 treatment period (61 patients). The male-female ratio was approximately equal. Patient characteristics are detailed in Table 4. 55.7% of patients had moderate and 44.3% had severe UC according to the 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. Most subjects (40 of 61) did not smoke; however, 11 of them were ex-smokers who quitted and 4 patients were smokers at the time of the study. Only 4 patients had a positive family history for IBD. Among the 61 UC patients, 57 were anti-TNF naïve and 4 had previous biological therapy (3 patients received originator infliximab, 1 patient received adalimumab). 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 corticosteroids was significantly reduced from baseline to week 54 (63.9-9.8%, p=0.005); moreover, the daily dose decreased as well (Table 5). Other concomitant medications were azathioprine/6-mercaptopurine, which must be highlighted due to their role in immunogenicity in biological therapy; in our group, the rate of use remained relatively stable during the study period (40.9-45.9%).

Patient characteristics	n=61
Male:female ratio n, (%)	32:29 (52.5:47.5%)
Age, years (median±SD, [min-max])	33.5±12.8 [19-68]
Age at diagnosis, years (median±SD, [min-max])	27±11.4 [14-65]
Disease duration, years (median±SD, [min-max])	3±6.3 [0-22]
UC extent Proctitis n (%) Left-sided colitis n (%) Pancolitis n (%)	 6 (9.8%) 24 (39.4%) 31 (50.8%)
Extra-intestinal manifestation n (%)	14 (22.9%)
Previous anti-TNF-α therapy n (%)	4 (6.6%)

Table 4 Characteristics of patients who completed the 54-week treatment period

	Week 0 (baseline)	Week 54
5-ASA, n (%)	43 (70.5)	32 (52.5)
Topical 5-ASA, n (%)	16 (26.3)	11 (18)
Systemic corticosteroid, n (%)	39 (63.9)	6 (9.8)
Dose of corticosteroid in mg/day (median±SD)	24±23.2	5±9.7

AZA/6-MP, n (%)	25 (40.9)	28 (45.9)
Dose of AZA/6-MP in mg/bwkg, median±SD	1.5 (0.75)	1.7 (0.5)
Other immunomodulatory (tacrolimus), n (%)	1 (1.6)	1 (1.6)

Table 5 Concomitant medications during CT-P13 therapy at baseline and at week 54. 5-ASA: 5-aminosalicylates, SD: standard deviation, AZA: azathioprine, 6-MP: 6-mercaptopurine

4.2.2. Characteristics of laboratory markers

Laboratory markers were recorded and compared at baseline and at week 54 (Table 6). We found that inflammatory markers showed improvement, which suggests treatment efficacy: 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 (mean 46.2/l vs. 45.4 g/l, p=0.036).

	Week 0	Week 54	Significance
CRP, mg/l, median±SD (min-max)	4.3±37.0 (0.3-235.9)	2.35±7.2 (0.3-33)	p=0.007
Leucocytes, G/l, median±SD (min-max)	9.8±3.6 (3.6-24.4)	6.3±2.5 (2.6-14.8)	P<0.0001
Haematocrit, l/l, median±SD (min-max)	0.38±0.06 (0.14-0.53)	0.39±0.04 (0.30-0.50)	P=0.0025
Thrombocytes, G/l, median±SD (min-max)	341.0±148.3 (106.0-992.0)	283.0±89.8 (169.0-656.0)	P=0.0009
Serum albumin, g/l, median±SD (min-max)	44.0±7.5 (25.0-53.0)	46.0±4.1 (36.1-53.0)	P=0.0029
Faecal calprotectin, µg/g, median±SD (min-max)	1000.0±1129.0 (124.0-4440.0)	468.8±996.1 (12.0-5481.0)	NS

Table 6 Laboratory markers of patients at baseline and at week 54

4.2.3. Mucosal healing and remission rates at week 54

The mean endoscopic Mayo Score points and the total Mayo score points at baseline, at week 14 and at week 54 were 2.6 (2-3), 1.2 (0-3), 1.2 (0-3), and 9.1 (5-12), 3.3 (0-11), 2.8 (0-11), respectively. Partial Mayo Score and Endoscopic Mayo Score points decreased significantly from baseline to week 54 (p=0.0001, p=0.0001). Remission, response and non-response rates at week 14 were 55.7%, 27.9%, and 16.4%, respectively. This proportion did not change significantly at week 54; the rates of remission, partial response, and non-response were 51.7%, 36.7%, and 11.6%, respectively.

The rate of MH was 65.5% at week 14, and this did not change significantly thereafter at week 54 (62.1%, p=0.3). No significant difference was detected between the rates of complete mucosal haling at week 14 and week 54 either (31% vs. 38, p=0.06). Only the serum albumin level was significantly higher in endoscopically inactive vs. active patients at week 54 (p=0.036), in other demographic, clinical and laboratory factors no association was revealed.

4.2.4. Steroid-free mucosal healing at week 54

Among patients with mucosal healing 2 patients were on oral, and 2 on topical corticosteroid. 55.2% of the enrolled patients achieved corticosteroid-free mucosal healing, which means that corticosteroid-free mucosal healing was achieved in 88.8% of endoscopic remissions (Figure 4).

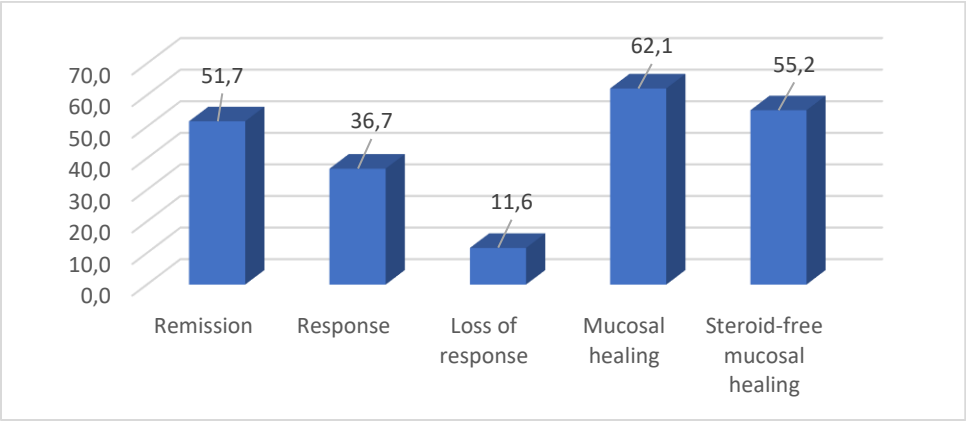

Figure 4 Rates of clinical remission, response, loss of response, mucosal healing and steroid-free mucosal healing with CT-O13 therapy at week 54

4.2.5. Therapeutic drug monitoring

We investigated associations of CT-P13 trough level and ATI positivity with MH. The median values 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).

4.2.6. Safety

Infusion reaction occurred in 6.6% of all enrolled patients (5/75), and 3.3% of patients who had already completed the study period (2/61). 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 Crohn's disease were enrolled in the study. Baseline patient characteristics are reported in Table 7. 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. 86.5% of the patients were on specific CD-related treatment at the time of the index surgery; 37.5% of patients were on aminosalicylates, 13.5% on anti-TNF-α therapy, 51% on corticosteroid, 12.5%

on budesonide, 43.3% on azathioprine, 6.7% on methotrexate, and 35.6% on antibiotics. 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. Twenty-six patients had undergone previous CD-related surgery. Postoperative treatment was the following: 43.2% of the patients received 5-aminosalicylate, 20% corticosteroid, 68.3% immunomodulant, and 4% anti-TNF-α. 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.

Baseline characteristics of patients	n=104
Gender (female:male) n(%)	50:54 (48%:52%)
Age at the time of index resection n(%)	
Younger than 40 years	64 (71.2%)
40 years or older	30 (28.8%)
Smoking history at index surgery	
Current smoker	32 (30.8%)
Never smoked	68 (65.4%)
Ex-smoker	4 (3.8%)
Montréal classification	
A1:A2:A3	15:71:18 (14.4%:58.3%:17.3%)
B1:B2:B3	12:52:40 (11.5%:50%:38.5%)
L1:L2:L3:L4	51:22:31:0 (49%:21.2%:29.8%)
P	14 (13.5%)
Type of index resection	
Ileocolonic resection	76 (73.1%)
Colonic resection	23 (22.1%)
Small bowel resection	5 (4.8%)
Previous resection before the index surgery	26 (25%)

Table 7 Baseline characteristics of Crohn's disease patients included in the study

4.3.2. Histological findings

Typical Crohn's lesions, such as inflammatory cell infiltration, architectural alterations, crypt abscesses, ulcers and granulomas were detected in both resection margins. Typical CD lesions were found in proximal resection margins (5.8%), distal resection margins (5.8%), and in both resection margins (16.3%). Neural fibre hyperplasia was present in 37.5% of proximal resection margins. The pathological examination focused on proximal resection margins with quantitative evaluation of myenteric and submucosal plexitis. Inflammatory cell count (mastocyte, plasmocyte, lymphocyte, eosinophil and neutrophil granulocyte) findings for myenteric and submucosal plexuses are summarised in Table 8. 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.

Myenteric plexus	Median	IQR, 25th to 75th	**Submucosal plexus**	Median	IQR, 25th to 75th
Eosinophils	0	0-1	Eosinophils	0	0-0
Lymphocytes	2	1-4	Lymphocytes	2	1-3
Neutrophils	0	0-0	Neutrophils	0	0-0
Plasmocytes	2	1-3	Plasmocytes	1	0-3
Mastocytes	0	0-0	Mastocytes	0	0-0

Table 8 Inflammatory cell count of histopathological findings (n=104)

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 (OR=0.146, 95% CI, 0.029-0.738, P=0.020). No association was revealed between postoperative recurrence and smoking status, postoperative prophylactic treatment and the presence of myenteric plexitis and relapse. Figure 5 shows survival probability without a second CD-related surgery and the probability without clinical recurrence.

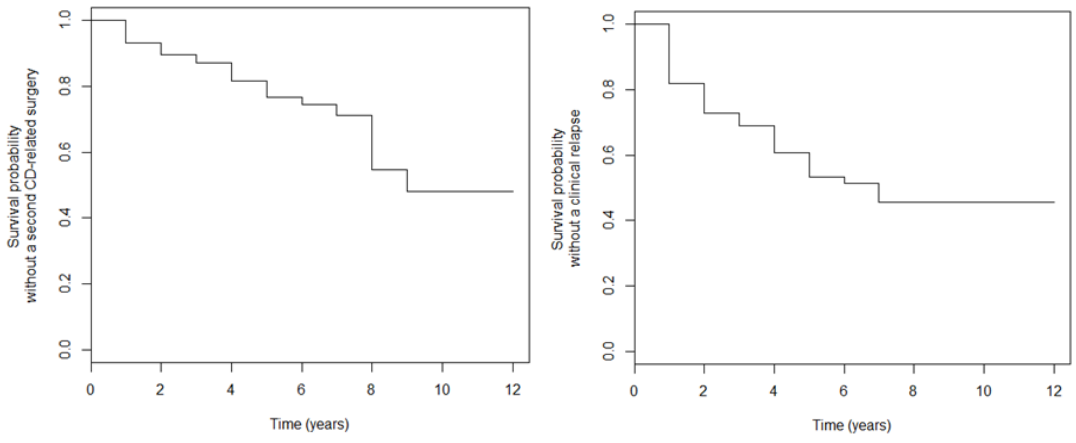

Figure 5 shows survival probability without a second CD-related surgery and the probability without clinical recurrence with the Kaplan-Meier method

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

For the reasons outlined in the 'Materials and methods' section, patients incident in 2016 were excluded from the epidemiological analysis. The number of patients suffering from UC between 2010-2015 was 36 315. The annual prevalence increased during the examined period (Figure 6). In 2010 0.24%, while in 2015 0.34% of the total Hungarian population suffered from UC. The estimated incidence of UC in 2015 was 21.7/100 000 inhabitants. The proportion of females amongst the prevalent population was 55%. 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, which is clearly demonstrated by the population pyramid (Figure 7). The difference is statistically significant at $p<0.001$.

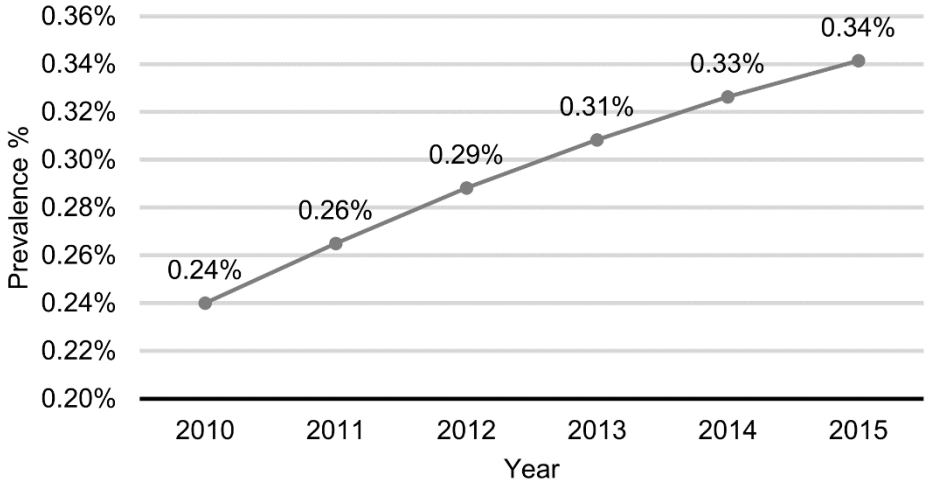

Figure 6 The annual prevalence of ulcerative colitis in Hungary

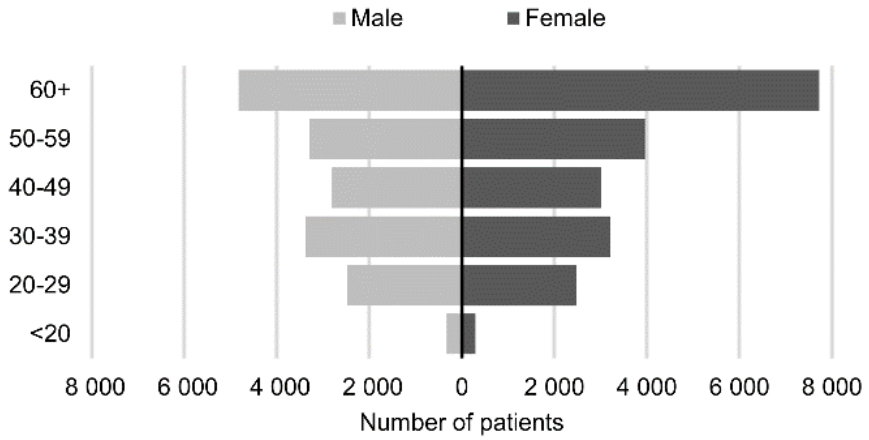

Figure 7 The population pyramid (distribution by age and gender) of the prevalent UC population at the time of diagnosis

In total, 3 188 prevalent patients died in the study period between 2010 and 2015. 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 (Figure 8).

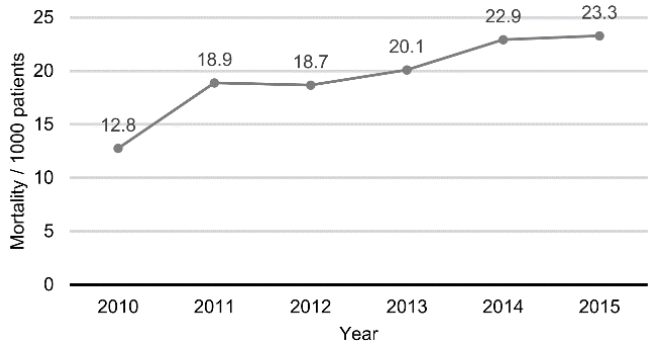

Figure 8 Mortality rate of UC patients between 2010 and 2015

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 years) than women (median 78.7 years), which corresponds to the trend observable in the general population of Hungary.

4.4.2. Malignancies of UC patients

15 232 patients received their first diagnosis during the observational period (incident population). Investigating all malignant neoplasms of this incident UC population, we found that CRC was the most common cancer followed by non-melanotic skin cancer and prostate cancer (Figure 9).

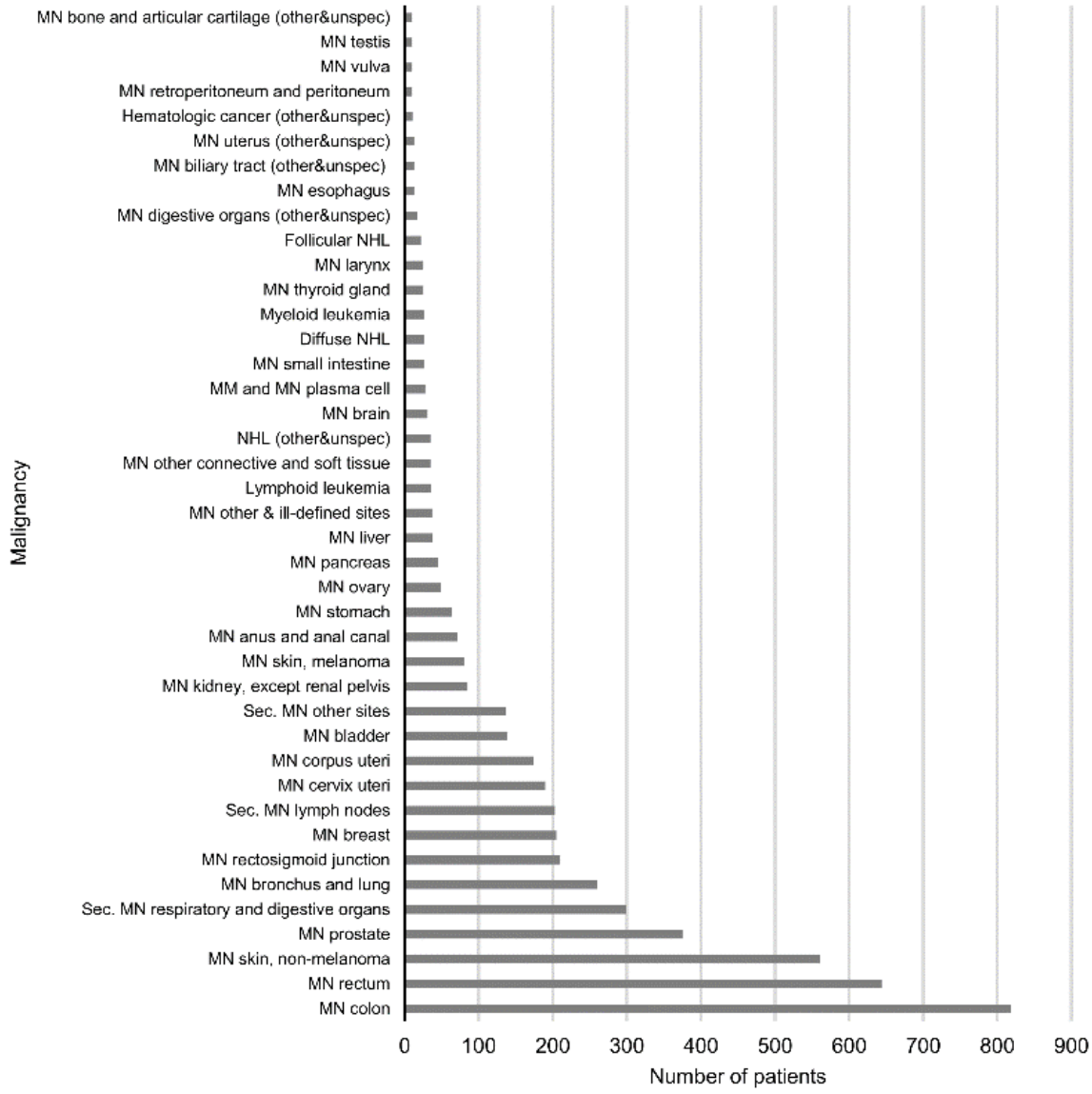

Figure 9 The number of patients diagnosed with certain types of malignant tumours. MN – malignant neoplasm of, Sec. MN – secondary malignant neoplasm of, (other&unspec) – other or unspecified part/type, NHL – non-Hodgkin's lymphoma, MM – multiple myeloma

As CRC was the most commonly appearing malignancy, and because it can be the consequence of long-term UC, it was analysed in detail. In total, 1424 patients (8.5%) were diagnosed with CRC in the incident patient subpopulation. The number of new diagnoses was stable within the study period with roughly 200 new cases every year. A small decrease in the numbers is observable in 2015 and 2016. These results may be biased due to the methodology where two diagnoses of CRC were required for a patient to be considered. With shorter follow-up times the probability of a second diagnosis would be lower.

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). These patients died at a younger age than the average patients with UC as the median age at the time of death within the incident UC population was 75.3 years (male: 71.9; female: 78.3).

4.4.3. Survival of UC and CRC patients

Overall survival of the incident UC patients from the time of diagnosis was examined (Figure 10). The survival probability decreased over time at a linear rate. 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).

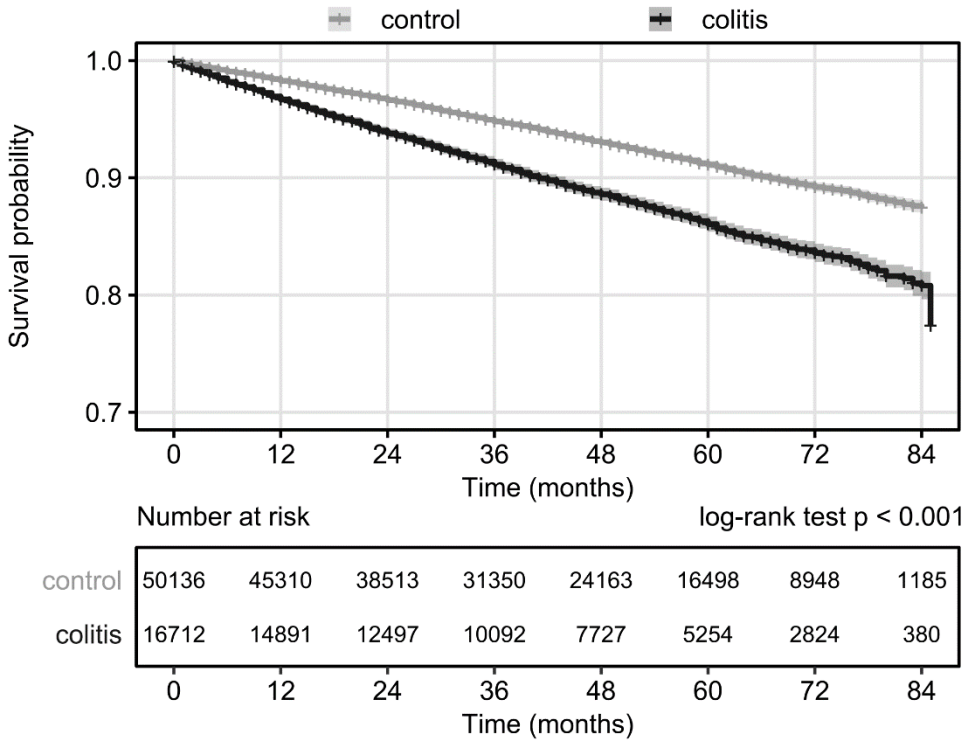

Figure 10 Overall survival of UC patients and matched controls from diagnosis. Start: UC diagnosis date for UC patients, UC diagnosis date of matched patients for controls. Event: death. Censoring: end of data availability (end of 2016). Shaded areas denote 95% confidence bands.

We also analysed the overall survival of CRC patients among the UC population from the diagnosis of CRC (Figure 11). Their survival probability also decreased over time at a linear rate. The 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.

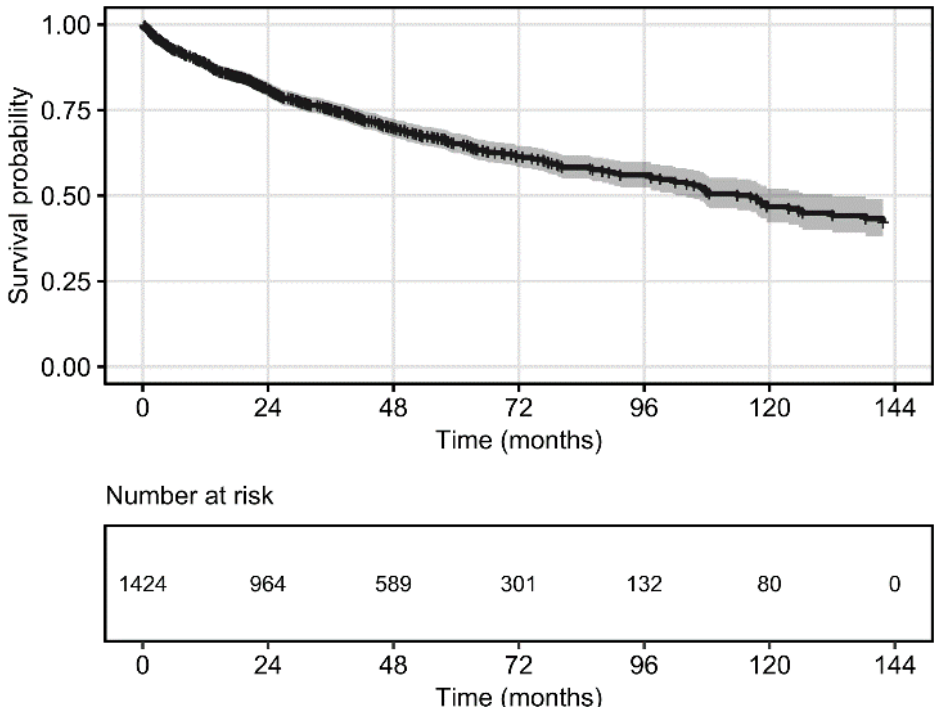

Figure 11 Overall survival of CRC patients among the UC population from the diagnosis of CRC. Start: CRC diagnosis date. Event: death. Censoring: end of data availability (end of 2016). Shaded area denotes 95% confidence band.

This analysis was also performed using a breakdown of patients based on age (over and under 60 years) (Figure 12). No significant difference could be found between the survival probabilities of these two age groups (HR=1.18, 95% CI, 0.94-1.46, p=0.147).

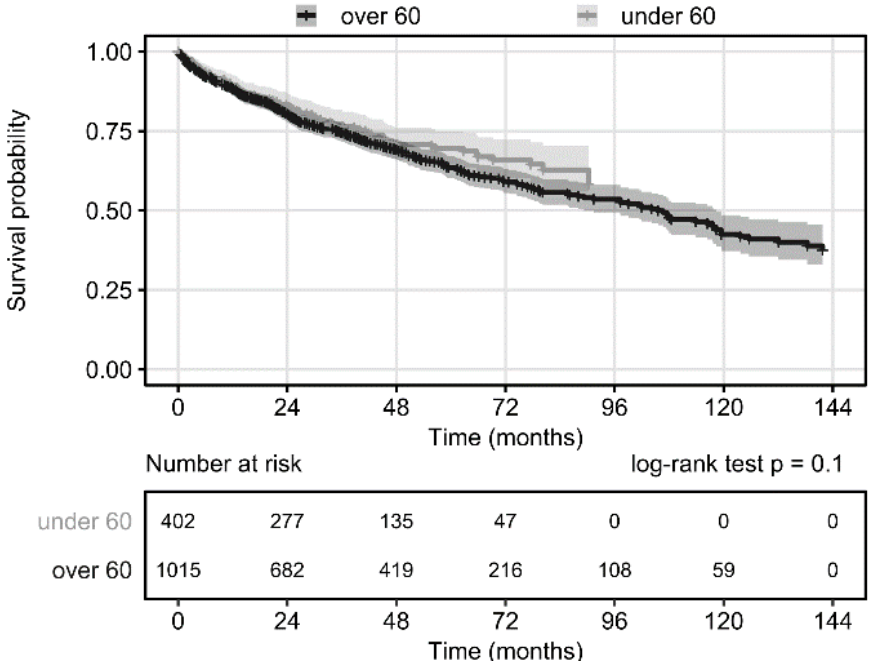

Figure 12 Overall survival of CRC patients among the UC population from the diagnosis of CRC by age. Start: CRC diagnosis date. Event: death. Censoring: end of data availability (end of 2016). Shaded areas denote 95% confidence bands.

5. DISCUSSION

The introduction of biological therapies and the favourable results of landmark studies have changed the traditional therapeutical algorithm of IBD [14, 15]. With the possibility of complete mucosal resolution, new therapeutic goals have become available: endoscopic - and mucosal healing; however, in some studies histological healing has appeared as well. Mucosal healing may be a major sign of effective therapy and a prognostic factor of long-term outcome. It is expected that the early administration of biologicals may alter the natural course of the disease; however, recently published results are conflicting [31, 32]. The widespread use of biologicals has placed a substantial financial burden on health care systems all over the world. Because of the high cost of originator anti-TNF agents, after the expiration of patents for innovator products, interest has grown in biosimilars that are cost-effective and may effectively substitute the reference product. CT-P13, the first biosimilar was approved for the same indications as its originator IFX. According to economic studies, IFX biosimilars may cost 15-75% less than originator products [58–61]. On the other hand, specific evidence confirming the effectiveness in IBD is needed, because the extrapolation of clinical data from rheumatic indications to IBD may raise concerns. Therefore, collecting and assessing post-marketing data is absolutely necessary to confirm the numerical effectiveness and explore the potential adverse events of biosimilars. Increasing data on comparable efficacy and safety profiles may further decrease the fear of using biosimilar IFX routinely [24, 27, 62, 63].

The results of our prospective, observational study from our tertiary IBD centre revealed continuous clinical response in 51-51% of CD and UC patients at week 54. Before the publication of our study, most other studies had 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. In the discussion of this study, we are going to overview newly published data as well. 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 [64], 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 [65]. The first long-term data have become available from a Korean study by *Jung et al.* [20]. Their clinical response rates proved to be high; 87.5% and 100% at week 54 in anti-TNF-naïve CD and UC patients representing a very favourable efficacy of CT-P13. However, if we consider the number of patients who completed the induction phase of the therapy as responders, the rates of responders will decrease to 21.8% of CD and 31.6% of UC. Moreover, we should be

cautious when interpreting the data; the retrospective nature of the study and the small number of patients completing week 54 provide only limited information on the long-term efficacy of CT-P13. In our study, response rates at weeks 14 and 54 proved to be relatively high. 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%) [11, 14]. However, response rates are generally better in the real life compared to clinical trials, and we should also take into consideration that 36.7% and 60% of our CD patients received concomitant corticosteroid and/or immunomodulator therapy – both may improve therapeutic outcome at least in the short term. Notably, in the PROSIT cohort, efficacy after one year was 71% in TNF-naïve patients [66]. At week 54, response rates proved to be 75.5% and 81.3% in week 14 responder CD and UC patients. According to the Hungarian multicentre study, clinical remission and response rates at week 54 varied as 48% and 65% in CD and 43% and 50% in UC [67]. In a newly published systematic review and meta-analysis where thirty-two studies were analysed, high clinical response rates were detected among CD and UC patients: at week 8-14 the rate was 0.81 for CD (95% CI, 0.72-0.87) and 0.68 for UC (95% CI, 0.63-0.72), and at week 48-63 it was 0.69 for CD (95%CI, 0.48-0.85) and 0.54 for UC (95%CI, 0.45-0.63), respectively [68].

Our study of mucosal healing adds supplementary data to this topic, since we proved in an appropriate number of UC patients that long-term MH could be reached in 62.1% of the cases. Previous studies had assessed mucosal healing only in a small number of subjects and/or as a secondary endpoint without evaluating any influencing factors [20, 69, 70]. A placebo-controlled, double-blind study with originator IFX including 728 moderate-to-severe UC patients confirmed that mucosal healing at weeks 8, 30 and 54 was significantly higher in UC patients treated with originator IFX than placebo [71]. In this study, the rate of MH with IFX was approximately 50% at week 54. Moreover, the complete MH (Mayo Endoscopic subscore 0 point) provides even better outcomes, which indicates the significance of endoscopic remission. Based on a systematic review, the pooled rate of mucosal healing in naïve UC patients at week 54 was 0.63 (95% CI, 0.50-0.73) [68].

Factors predicting poor outcome have high clinical importance. A nationwide prospective and observational Hungarian cohort study in 210 consecutively recruiting patients with CD or UC revealed that 67.2% of week 14 responder CD and 80% of week 14 responder UC patients maintained clinical response to CT-P13 at week 30 [29]. The authors demonstrated 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 of short- and medium-term clinical efficacy in UC but were associated only with short-term clinical outcomes in CD [72]. In the PROSIT Cohort, anti-TNF naïve patients and patients previously exposed to anti-TNF versus patients switched from IFX to CT-P13 and UC versus CD patients had a significantly higher hazard ratio to lose response, while significantly decreased HRs were observed in patients without steroids at the last follow-up. The HRs for serious adverse events were significantly higher in the previously exposed group versus the IFX-CT-P13 switch group and lower in males compared with females and patients without steroids at the last follow-up. In our first study, we were not able to show that any of the examined parameters could predict the outcome of CT-P13 therapy at week 54 either in CD or in UC. Faecal calprotectin concentration decreased significantly during the 54-week treatment period in UC. In the second study, we aimed to determine predictors of MH, but we did not find any associated factors, only the serum albumin levels were higher in patients with endoscopic Mayo subscores 0-1 at week 54. This finding supports the results of a previous study that found a correlation between clinical outcome and albumin levels [73]. Evidence from studies conducted with originator IFX predominantly suggest that endoscopic remission is closely correlated with faecal calprotectin [74–77]. Recent evidence draws attention to complete mucosal healing. A study from Portugal suggests that an eMayo score of 1 is significantly associated with an increased risk of relapse at 1 year [78]. In our study population, complete MH was achieved in 38% of patients; the rates of clinical remission, response and non-response were 51.7%, 36.7%, and 11.6%, respectively at one year, and this did not differ from the rate detected in the induction period.

In our first and second study, only 14.0 and 6.6% of patients have a positive history of previous anti-TNF therapy; thus, these small subgroups are not eligible for a statistical assessment, but a few other studies have proved the significance of immunogenicity. A large, nationwide Norwegian randomised, controlled trial (NOR-SWITCH) suggests that clinical response, maintenance of remission and the rate of adverse events are similar when considering CT-P13 and its originator [79]. Immunogenicity and anti-drug antibody (ADA) formation is a well-known complication of treatment with anti-TNF agents. Serum ADA positivity is associated with alterations in drug serum levels, LOR and adverse events like allergy or infusion reactions. A systematic review found the cumulative incidence of ADA to be 12.7% in any anti-TNF-treated patients and 25.3% in IFX therapy [80]. Anti-CT-P13 antibody positivity showed an increasing tendency from week 14 to week 54; however, this trend did not influence MH. In the study of *Gönczi et al.* ATI positivity rates were significantly higher in patients with previous

anti-TNF exposure, while concomitant AZA prevented ATI formation in anti-TNF-naïve patients [67].

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 [70]. 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), respectively [68].

Despite the available, highly effective, new therapeutic options postoperative relapse is still a major issue in Crohn's disease. More than 70% of patients require surgery during their lifetime [33]. Intestinal resection is often required in case of stenosis, abscess, fistulas or refractory disease. The majority of patients will experience recurrence and require further surgery within 5 years after the operation [35]. A recently published randomised study revealed that it is essential to optimise treatment according to the clinical risk of recurrence and to monitor low risk patients routinely as well for the prevention of postoperative Crohn's disease recurrence [81]. Several studies tried to identify different predictive factors for postoperative recurrence like terminal ileal location, stricturing, penetrating disease behaviour, age younger than 40 years at diagnosis, smoking, steroid use and previous use of two or more anti-TNFα agents [37–40]. Histological changes in the enteric nervous system are common in CD. In 2006, *Ferrante et al.* were the first to describe a positive association between myenteric plexitis and postoperative recurrence [42]. Since then several similar studies have been conducted to identify myenteric or submucosal plexitis as a risk factor for postoperative recurrence [43–49].

In the third study we demonstrated that in Crohn's disease 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. *Ferrante et al.* demonstrated that inflammation of the myenteric plexus was significantly associated with postoperative CD endoscopic recurrence; moreover, they found a positive correlation between the severity of the inflammatory infiltration of the plexus and the severity of endoscopic recurrence [42]. Studies have found myenteric plexitis in 42.5-88% of proximal surgical margins [42–44]. On the other hand, *Sokol et al.* demonstrated an association between

submucosal plexitis and early clinical recurrence; they found that mast cell-associated submucosal plexitis in proximal resection margins is a predictor of early postoperative clinical recurrence [45]. Further studies in association with submucosal plexitis found the following: *Bressenot et al*. revealed that submucosal plexitis of >0 eosinophils and/or > 6 lymphocytes in the proximal resection margins and early surgical revision after the first ileocecal resection are predictive of a second surgery in CD [46]; *Lemmens et al.* found that submucosal lymphocytic plexitis in the proximal surgical margin was significantly associated with a higher risk of endoscopic recurrence after ileocolonic resection [47]. All these studies found that plexitis is more frequent in the proximal resection margin, but the data on the prognostic value of histological factors in postoperative CD recurrence are conflicting. This is the reason why we used a comprehensive approach by analysing all inflammatory cell types in both submucosal and myenteric plexuses in proximal resection margins. Data of the most severely inflamed plexus were involved in the study. We could evaluate myenteric and submucosal plexitis of different severity in every sample, in accordance with the findings of *Bressenot et al.* [46], while the rate of typical CD-lesions was low (5.7%) in proximal resection margins. We found no relationship between the presence of granulomas and clinical or surgical recurrence; however, we could find granulomas only in approximately half of the samples. A few studies found a positive association between the presence of granulomas and the likelihood of recurrence or a more aggressive disease process [82–84], while other studies suggested the opposite [85, 86]. Our data of surgical recurrence are in concordance with previously published one: surgical recurrence has been reported in 11-32% of the patients in the first 5 years after the index surgery [87]. It has also been reported that the need for immunosuppressive therapy and surgical interventions was significantly higher in patients with granulomas. *Ferrante et al*. found that patients who had both neural hypertrophy in the terminal ileum and myenteric plexitis in the proximal resection margin had a tendency to develop a higher endoscopic recurrence rate compared with patients who only had myenteric plexitis [42]. Our results could not confirm that.

Studies have shown that the early administration of oral mesalazine following surgery is effective in preventing postoperative endoscopic recurrence in CD over a 2-year period [88] and it can also decrease the rate and severity of endoscopic recurrence or symptomatic relapse [89, 90]. In a prospective, open-label randomised study, azathioprine was more effective than mesalazine in preventing clinical relapse in patients with previous intestinal resections [91]. In our study we did not find any association between postoperative recurrence and preoperative or postoperative prophylactic treatment.

The fourth study was the first population-based study in Eastern Europe which simultaneously estimated prevalence and incidence rates, mortality, morbidity and the associated malignancy data based on the Hungarian NHIF database. During our study, the prevalence of UC in the Hungarian population increased from 0.24% to 0.34%. Based on previous Hungarian studies, the prevalence rate of UC was 0.01% between 1962 and 1992, 0.14% between 1991 and 2001, 0.21% between 2002 and 2006, and 0.34% between 2011 and 2013 [57, 92–94]. Based on the results of the previously mentioned Hungarian studies, the incidence rate of UC has been increasing: it was 1.4/100 000 between 1962 and 1992, 5.89/100 000 between 1997 and 2001, 11.9/100 000 between 2002 and 2006 [92–94]. The incidence of 21.7/100 000 inhabitants in 2015 found in our study is considerably higher than the one reported in 2006. The increasing incidence is in concordance with the published data from industrialised countries [95, 96]. Most studies reported the peak incidence of UC in early adulthood (in the second to fourth decade of life); however, in some studies a second modest rise in incidence in later decades of life has also been reported (between 50-70 years) [97]. In contrast, our study found two peaks in the onset of ulcerative colitis (30-39 years and over 50 years), which is similar to the findings of the IBSEN study group [98].

It is still questionable whether UC-patients are at a 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 that of the general population (overall standardised mortality ratio of 1.1 (95% CI, 0.9-1.2, p=0.42)); however, the cause-of-death distribution seemed to be different, with a higher risk of gastrointestinal diseases [99]. 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 in the Hungarian UC population were CRC, malignant neoplasm of the skin and malignant neoplasm of the prostate. These findings are in accordance with the results of a Danish population-based cohort study conducted between 1962 and 1987. They found an increased risk of colorectal cancer and among men, for melanoma, but no increased risk for other cancers could be detected [100]. In our study, 8.5% of the incident UC population was diagnosed with colorectal carcinoma between 2010 and 2016. The median age at the diagnosis of colorectal cancer was 65.8 years, which is higher than the average age previously found in Hungary, but similar to that in the general population [92]. When comparing the survival of younger and older populations, no significant difference was found

between patients diagnosed with CRC at an age below or above 60. A study from 2006 found that the incidence of CRC was 2.5%, 7.6% and 10.8% after 20, 30 and 40 years of disease duration of UC, respectively [101]. A Swedish study of colonoscopic surveillance for UC found a lower risk of CRC development, namely 2.0%, 3.0% and 9.4% at 20, 30 and 40 years. They found a threefold increased risk of CRC compared to the general population [102].

Our study has some strengths and limitations that should be mentioned. A nationwide claims and insurance database was used in the study, which is based on the sole insurance fund in Hungary with close to full population coverage. A major limitation is the retrospective nature of the study, where the primary aim of data collection was not the clinical evaluation of patients, but rather financial and reimbursement purposes. Therefore, no data were available on clinical outcomes, such as laboratory values, disease severity indices, access to healthcare or patient reported outcomes. Dosing information on all pharmaceutical products was limited. Only all-cause deaths data could be analysed, because cause of death data (cancer or disease-specific) were not available for all deaths and they were highly inconsistent even when they were available. Therefore, the cause of death was chosen not to be analysed in this study. Another major limitation of our study was the limited amount of information on the matched general population – only the date of death could be obtained in addition to the age (date of birth) and gender, which the matching was based on.

6. CONCLUSION

To the best of our knowledge, at the time of publication, our study was the first prospective study that evaluated and confirmed the long-term efficacy and safety of CT-P13 therapy in IBD. The results of randomised trials 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.

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 rates among Hungarian ulcerative colitis patients, and it also updated previously available data on 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 significantly worse survival of UC patients than that of the general population. These findings emphasize the importance of colorectal cancer surveillance programs 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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1.sz. melléklet

Társszerzői lemondó nyilatkozat

Alulírott **Kunovszki Péter** (felelős társszerző, megosztott elsőszerző) kijelentem, hogy **dr. Milassin Ágnes Eszter** (pályázó) PhD értekezésének tézispontjaiban bemutatott - közösen publikált - tudományos eredmények elérésében a pályázónak meghatározó szerepe volt, ezért ezeket a téziseket más a PhD fokozat megszerzését célzó minősítési eljárásban nem használta fel, illetve nem kívánja felhasználni.

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PLoS One. 2020 May 14;15(5):e0233238.

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Alulírott **dr. Farkas Klaudia** (felelős társszerző) kijelentem, hogy **dr. Milassin Ágnes Eszter** (pályázó) PhD értekezésének tézispontjaiban bemutatott - közösen publikált - tudományos eredmények elérésében a pályázónak meghatározó szerepe volt, ezért ezeket a téziseket más a PhD fokozat megszerzését célzó minősítési eljárásban nem használta fel, illetve nem kívánja felhasználni.

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