„Prevalence and treatment strategy of inflammatory bowel disease based on a nationwide study and the potential complications of the therapies.”

Doctoral thesis

Dr. Zsuzsanna Kürti

Semmelweis University
Clinical Medicine PhD School

Tutor: Dr. Péter László Lakatos, DSc

Reviewers: Dr. Viktória Venglovecz, med. habil.
Dr. Attila Zaránd, PhD

Exam board: Prof. Dr. András Kiss, DSc
Dr. Krisztina Hagymási PhD
Dr. Patrícia Sarlós, PhD

Budapest
2018

Introduction

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC) are multifactorial chronic inflammatory disorders of the gastrointestinal tract involving genetic predispositions, environmental factors, intestinal microbial flora and the immune system. During the course of the disease, complications evolve in a significant proportion of patients, affecting the patient's quality of life. Besides the basic sciences, the **clinical and epidemiological studies** can provide significant knowledge on the etiology and disease course of IBD. Up to now, several epidemiological studies aimed to better define the burden of IBD, especially from the developed countries. A number of them established markedly increased IBD incidence over the past decades, and it seems to become a global disease in the 21st century. Traditionally, IBD was regarded as a disease of the westernised nations, the highest prevalence values were reported from North-America, Western-Europe and Australia (~0.3%). However, newer epidemiological studies suggest increasing incidence in the newly industrialised countries of Eastern-Europe, South-America and Asia, where IBD was uncommon previously.

In Hungary, the most extensive epidemiological studies were published from the population-based Veszprem Province database enrolling all IBD patients diagnosed in Veszprem province from 1977 (the data collection is prospective from 1985). In the study by Lakatos et al., rapidly increasing incidence of IBD was established between 1977 and 2001, and the incidence rates in 2006 were relatively high (29.9 per 100000 persons), similar to those reported from the high-incidence areas in Western European countries. The estimated prevalence were 211.1 cases per 100000 persons for UC, 115.3 cases per 100000 persons for CD, and 11.8 cases per 100000 persons in IBD-unclassified (IBD-U) in 2006. Nevertheless, no nationwide data on the current epidemiology and therapeutic strategy of IBD were reported from Hungary so far.

To our present knowledge, IBD is an incurable disease, but a significant change was observable in the patient management and **therapeutic strategy** in the last decades. Till the 1960s the therapeutic strategy based on supportive therapies and surgical procedures providing symptomatic remission. In contrast, the current therapeutic goals comprise not only symptomatic control but also long-term clinical, biochemical and endoscopic remission, prevention of surgery or hospitalization, and ultimately aim at changing the natural history by preventing disease progression. Similarly, the therapeutic armamentarium have also been improved during the last decades: first the steroids and aminosalicylates, later the

immunosuppressives and biological therapies have been introduced to the management of IBD. Nowadays, early introduction of aggressive therapies (including immunomodulators and/or biological therapies) have become common and novel therapies are on the horizon.
In paralell to these developments, the frequency of **hospitalization** and **surgery** has been decreased significantly in the 1990s and the early 2000s. However, less data are available from the recent years, when the early agressive therapy and tight disease control has become widespread.

Patients with IBD should not be routinely considered to be immunocompromised, but IBD patients treated with steroid, immunomodulator or biological therapy are at risk of opportunistic infections. Therefore, screening for risk of opportunistic infections and documentation of vaccination history should be completed, preferably at the diagnosis of IBD and before the beginning of biological therapy. **Mycobacterium tuberculosis (TB)** is one of the most important opportunistic infections in anti-TNF treated IBD patients, namely that tumor necrosis factor-alfa (TNF-α) is the key cytokine involved in host defense against TB playing a major role in the formation and durability of the granulomas that prevent the dissemination of TB bacilli. Anti-TNF treatment impairs the structural integrity of granulomas which control the TB bacilli, and leads to the dissemination of the TB bacilli and TB reactivation. Thus, screening for latent tuberculosis is mandatory prior to initiation of anti- TNF therapy. Nevertheless, there is no gold standard screening process of latent TB infection. Conflictive data are available on the accuracy of the **Tuberculin Skin Test (TST)** and the **Interferon Gamma Release Assay test (IGRA).** Both tests have been shown to be influenced by immunosuppression and TST by Baccilus Calmette Guerin (BCG) vaccination, too. IGRA is characterized by lower interobserver variability and is not influenced by nontuberculous Mycobacteria, but indeterminate results are common, especially in immuncompromised patients. All in all, the diagnosis of latent TB remains problematic, particularly in patients treated with immunosuppressive therapy and in countries with a high proportion of BCG vaccination.

Another important issue for gastroenterologists is the **Clostridium difficile infection (CDI)**, that is one of the most important healthcare associated infection. The incidence of CDI increased dramatically in the 21st century and its rising severity is well represented by more frequent transfer to the intensive care unit, colectomy and infection associated mortality. It results in remarkable healthcare system costs and eventually leads to an important healthcare and economic burden. However, most of the data on the incidence, possible risk factors,

treatment strategy and outcome of CDI infections were reported from North America and only limited retrospective data are available from Eastern Europe.

Aim

In the first part of our studies, our aim was to estimate the nationwide age and gender specific prevalence of IBD in Hungary and in the different regions of the country, based on the administrative database of the National Health Insurance Fund (traditional abbreviation: OEP). Additionally, our secondary aim was to investigate the treatment strategy in different age groups both in CD and UC.

In the second study of the administrative database, we aimed to estimate the early treatment strategy and outcomes in newly diagnosed patients with Crohn's disease (CD) between 2004-2008 and 2009-2015 in the whole IBD population in Hungary. Since the prescription regulations changed significantly at the end of 2008 with easier access to biologicals, it has been aimed to evaluate the therapeutic strategy, surgical outcomes and hospitalization rates before and after the change of prescription-regulations.

There are few data available on simultaneous evaluation of TST and IGRA in BCG vaccinated immunosuppressed IBD patients. Therefore, in the third study, our aim was to define the accuracy of the TST test compared to the IGRA test in a BCG vaccinated referral IBD cohort treated with immunosuppressives at around initiation of the biological therapy.

Finally, we aimed to analyze prospectively the incidence, possible risk factors, treatment strategy and outcome of Clostridium difficile infections in hospitalized patients treated at an academic center of internal medicine, since there are only limited retrospective data are available from Eastern Europe.

Main objectives of the thesis:

5. To estimate the nationwide age and gender specific prevalence and therapeutic strategy of IBD in Hungary between 2011 and 2013 based on the administrative database of the National Health Insurance Fund.

6. To estimate the early treatment strategy and outcomes in newly diagnosed patients with Crohn's disease between 2004-2008 and 2009-2015 in the whole IBD population in Hungary based on the administrative database of the National Health Insurance Fund

7. To define accuracy, predictors and agreement of TST and IGRA in a BCG-vaccinated immunosuppressed referral IBD cohort.

8. To analyze incidence, outcomes and possible risk factors of Clostridium difficile infection in hospitalized patients at 1st Department of Medicine, Semmelweis University, Budapest, Hungary.

Methods

1. Nationwide prevalence and drug treatment practices of inflammatory bowel diseases in Hungary: A population-based study based on the National Health Insurance Fund database

IBD Patients were identified through International Classification of Diseases (ICD-10) codes in the health administrative database of the National Health Insurance Fund (OEP), which is the only state-owned health care purchaser in Hungary. It provides universal health insurance for most residents (roughly 96% of the population), including free-of-charge coverage for general practitioner, specialists' care and in-hospital services. It is mandatory to report all in- and outpatient events including patients' demographic data, diagnosis, drug prescription, any interventions and hospitalization data to the OEP. Patients were identified by using ICD-10 codes for IBD in the OEP inpatient, non-primary outpatient and drug prescription databases. Besides demographic data (age, gender), postal code, in- and outpatient visits and drug prescription data were collected. Data on the background population were obtained from the Hungarian Central Statistical Office (KSH). Population of Hungary was stable between 2011 and 2013.

We used different diagnosis definitions to calculate the nationwide IBD prevalence. In the primary analysis we identified patients with at least yearly one IBD-related code in the in- or outpatient databases (ICD10 K50, K51) between 01.01.2011 and 31.12.2013. Thereafter, in

the sensitivity analysis we used multiple different diagnostic criteria (e.g. need for more IBD-related visits and drug prescription) to identify IBD patients. Additionally, we added patients with more than 10 IBD-related drug dispensing events even if there was no out- or inpatient visit recorded during the observational follow-up period.

Data regarding medical treatment including the current use of aminosalicylates, corticosteroids, immunosuppressives (IS) and biologic agents were also retrieved from the OEP-database. The frequency of combination therapy (steroid+IS, biological agent+IS, steroid+biological agent+IS) was also calculated.

2. Therapeutic preferences and outcomes in newly diagnosed patients with Crohn's diseases in the biological era in Hungary. A nationwide study based on the National Health Insurance Fund database

We used the administrative database of the National Health Insurance Fund (OEP). Patients were identified through previously reported algorithms using the ICD-10 codes for Crohn's disease (K50..) in the out- and inpatient (medical, surgical) non-primary care records and drug prescription databases between 1st of January 2004 and 1st of January 2015.[**Hiba! A könyvjelző nem létezik.**] Hospitalizations, surgical episodes and drug prescriptions were identified through the database of the OEP, which contains data on in- and outpatient stays, outpatient procedures and filled drug prescriptions. Any event with a CD-related ICD-10 code was regarded as related.

New patients with Crohn's disease was defined as no CD-related outpatient visits and/or IBD-related drug prescriptions in the last 3 years before the start of the observational period and at least 2 CD-related outpatient visits and/or IBD-related drug prescription during the observational period. Patients with less than 3 years follow up were excluded from the study. Patients were stratified according to the year of diagnosis and the maximum treatment step during the first 3 years after diagnosis.

We determined time to prescription of different drug classes, (5-ASA, steroid, IS and biologicals) and stratified patient groups according to the maximal therapeutic step (1. group – maximum therapeutic step: 5-ASA therapy (oral and/or topical 5-ASA treatment), 2. group – maximum therapeutic step: steroid therapy (systemic or topical steroids), 3. group – maximum therapeutic step: IS therapy (azathioprine, 6-mercaptopurine, cyclosporine or methotrexate), 4. group – maximum biological therapy (infliximab or adalimumab)). Finally, we calculated hospitalization and surgery rates according to the maximal treatment step and the diagnostic period (diagnosis in 2004-2008 vs. 2009-2015).

SPSS® 20 (SPSS Inc., Chicago, IL) was used for statistical analysis. Khi-square test and Fischer-exact tests were used to compare categorical variables. Kaplan-Meier analysis and Cox-Mantel LogRank test was used for time dependent change of the categorical variables.

3. Tuberculin skin test and Quantiferon in BCG vaccinated patients with moderate- to-severe inflammatory bowel disease

One hundred and sixty-six consecutive patients with moderate-to-severe IBD were enrolled in the study between 1st September, 2013 and 31st September, 2014 in three referral centers from Hungary, First Department of Medicine, Semmelweis University, Budapest, Department of Medicine, Csolnoky F. Province Hospital, Veszprem, and First Department of Medicine, University of Szeged. Both in- and outpatient records were collected and comprehensively reviewed.

Data of 122 CD and 44 UC patients were analyzed (male/female: 86/80, median age at diagnosis: 24.0; IQR: 18-30.2 years, median disease duration: 7.0; IQR: 4-13 years). All patients were treated with immunosuppressive agents (azathioprine or steroids) at the time of the study, and all of them were at around the initiation of anti-TNF therapy. Patients' demographic data are presented in Table I. At testing, 49.2% of CD patients received steroids, 71.3% AZA and 59% anti-TNF therapy. These rates in UC were 68.2% for steroids, 38.6% for AZA and 59.1% for biological therapy.

BCG vaccination is mandatory in Hungary at first life week than in 6 and 14 year olds, therefore the Hungarian IBD patients are vaccinated against TB infection.

Diagnosis of IBD was based on the Lennard-Jones Criteria. The disease phenotype (age at onset, duration, location, and behavior) was determined according to the Montreal Classification. Medical records, including data regarding the presence of major extraintestinal manifestations, previous frequency of flare-ups (frequent flare-up: >1 clinical relapse/year), previous surgical procedures (resections and/or perianal procedures), the presence of familial IBD, smoking habits and perianal involvement were determined by a thorough review of the patients' medical charts, which had been collected in a uniform format. Previous and concomitant medical therapy (steroid and/or immunosuppressive, or biological therapy) was registered.

Patients' medical history was screened for predefined TB risk factors including active malignant diseases, active hematological or oncological diseases, severe disease phenotype, need for immunosuppressive therapy, number of immunosuppressive therapy, contact person

in daily life of patient, workplace risk for infection, travel to high risk countries, previous TB infection and positive chest x-ray.

Blood samples for IGRA test were collected during routine laboratory testing on the same day when TST was performed. A whole-blood IFN-γ release assay (QuantiFERON TB-Gold in Tube, Cellestis, Carnegie, Australia) based on specific peptides ESAT-6, CFP-10, and TB7.7, was performed and evaluated according to the manufacturer's recommendations.

Standard TST was performed, which consists of an intradermal injection of tuberculin RT23 purified protein derivative (PPD) in 0.1 ml solution for injection into the inner surface of the forearm. A positive Mantoux reaction was defined with a predefined cut-off rate as a skin induration diameter ≥5mm after 48 and 72 hours from skin test. However, this standard cut-off rate refers only to non-BCG-vaccinated and non-immuncompromised patients, therefore we tested alternative cut-off values (see also statistical methods).

SPSS® 20 (SPSS Inc., Chicago, IL) was used for statistical analysis. D-test and ANOVA-Scheffe test were used to compare continuous variables, Khi^2, Fischer-exact tests were used to compare categorical variables. Categorical variables if appropriate were further tested in a multivariate analysis by using logistic regression analysis. Variables with a p of <0.1 were included in the multivariate testing. ROC curve analysis was used to define the best cut off value for TST positivity to identify IGRA positivity. Kappa values were calculated for the different cut-off values. A p-value of <0.05 was considered significant.

4. The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe

All patients admitted to the 1st Department of Medicine, Semmelweis University, Budapest, Hungary between 1 January 2010 and 1 May 2013 prospectively evaluated. Our institution is an academic center with a secondary referral center including all specialities of internal medicine and oncology and provides primary internal medical care for a region of about 225 000 inhabitants with a secondary referral area of 750 000 to 1 500 000 inhabitants for specialized care.

CDI was defined as an acute diarrheal disease (more than three liquid stools per day) with a positive cytotoxin stool assay or a positive cytotoxin stool assay associated with the diagnosis of pseudomembranous colitis by imaging or endoscopic methods, surgery, or autopsy. Repeated exotoxin positivity in 3 months were defined as recurrence. Community acquired CDI defined as symptoms developed before hospital admission or less than 48 hours after. In our department we apply standardized medical protocols and surveillance guidelines

for HAI including CDI, and thus evaluation of symptomatic patients and treatment strategy is harmonized.

For defining the possible risk factors a 1:3 matching was used. Data of inpatients matched for age, gender, inpatient care period and unit were compared to the CDI population. Inpatient records were collected and comprehensively reviewed, including inpatient ward, co-morbidities (according to Charlson Comorbitiy Index and age-adjusted Charlson Comorbidity Index), medication use (including previous or current antibiotic treatment, proton pump inhibitors and any medication for the treatment of co-morbidities and the current CDI episode), laboratory parameters (white blood cell count (WBC), creatinine, C- reactive protein (CRP), serum albumin level).

Three different outcomes were uses, such as recovered, recurrence after healing (within 12 weeks), and death. Recurrence was defined as a clinical relapse including symptoms and positive stool test within 12 weeks from the discharge.

Our studies comply with the principles of the Declaration of Helsinki. The study protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE ETT TUKEB 52/2014; SE ETT TUKEB 34821- 4/2013/EKU és ETT 431/2013 és SE ETT TUKEB 56/2013).

Results

1. Nationwide prevalence and drug treatment practices of inflammatory bowel diseases in Hungary: A population-based study based on the National Health Insurance Fund database

Nationwide IBD Prevalence according to the different case definitions

A total of 55 039 IBD patients with any IBD were identified equaling a prevalence rate of 0.55% (95% CI, 0.54–0.56). In total 19 911 CD patients (44.3% males, prevalence: 0.20% (95% CI, 0.19–0.20)), and 33 760 UC patients (44.7% males, prevalence: 0.34% (95% CI, 0.33–0.34)) had at least yearly one IBD-related health care visit reported. In total, there were slightly more females (30475, 55.4%) compared to males (24 564 44.6%).

Thereafter we determined the IBD prevalence by using different case definitions. If we identified IBD patient by at least yearly two IBD-related visits as case definition, the IBD-

prevalence decreased from 0.55% to 0.37% (37695 IBD patients), with 15165 CD (prevalence 0.155% (95% CI, 0.15-0.16)) and 22539 UC patients (prevalence 0.23% (95% CI, 0.225-0.23)).

Actively treated disease was defined as two or more IBD-related visits, plus at least yearly one dispensed prescription of IBD-related drugs in 2011-2013. Using this definition the prevalence rates were 0.13% for CD (13073 CD patients (95% CI, 0.13-0.14)), and 0.195% for UC (19244 UC patients (95% CI, 0.19-0.20)).

IBD prevalence according to the geographic regions

We determined the prevalence also in different Hungarian regions using the original IBD ascertainment definition. The highest prevalence was found in Western Hungary (prevalence: 0.77% for IBD, 0.49% for UC and 0.26% for CD), and in the South-West region (prevalence: 0.63 % for IBD, 0.35% for UC and 0.27% for CD). Interestingly, the prevalence in the region including the Veszprem province was somewhat lower, rates were similar to those published previously. The lowest prevalence was found in the East and North regions, which are the lesser developed parts of Hungary.

IBD prevalence according to age-groups and gender

We analyzed the prevalence according to the different age groups by using a more stringent IBD case ascertainment criteria of two or more IBD-related in- or outpatient visits. In CD, the prevalence was significantly the highest in the 30-39 year-old age group, while in UC an equally high prevalence was found in the 30-39 and 50-59 year-old age group. Distribution of prevalence by age was similar both in men and women. Of note, the majority of the patients had at least one drug dispensing event with an IBD-related code, thus the majority of the patients were actively treated.

Nationwide treatment patterns according to age-groups

Medical therapy was evaluated according to the different age-groups (0-19y, 20-59y, >60y). The overall exposure to 5-ASAs was 66% (0-19y), 73% (20-59y) and 72% (>60y) in UC, while was it similarly high, 68%, 71% and 69% in CD. Approximately one-third of the patients received steroid both in CD and UC. In addition, use of biological therapy was slightly more frequent in CD patients compared to UC (15%/4% (0-19y), 9%/3% (20-59y) and 2%/1% (>60y) in CD/UC). The highest exposure of IS and biological therapy was found in pediatric CD patients (IS: 44% (0-19y) vs. 33% (20-59y) vs. 14% (>60y), biological therapy: 15% vs. 9% vs. 2%). Similarly, the use of combination therapy

(biological+IS+/steroid) was more frequent in CD compared to UC and highest rates were found in pediatric patients (in CD 24% (0-19y), 10% (20-59y) and 1,3% (>60y) while in UC: 6% (0-19y), 4% (20-59y) and 0,6% (>60y)).

2. Therapeutic preferences and outcomes in newly diagnosed patients with Crohn's diseases in the biological era in Hungary. A nationwide study based on the National Health Insurance Fund database

Patient characteristics

A total of 6173 (male/female: 46.12%/53.87%) newly diagnosed CD patients with physician-diagnosed Crohn's disease were found between 2004 and 2015. 4458 and 1715 newly diagnosed CD patients with an available 3-year follow up period were identified between 01.01.2004 and 31.21.2008 and between 01.01.2009 and 01.01.2015. Distribution of age at diagnosis was similar in the two diagnostic eras, the most prevalent age group at the diagnosis of Crohn's disease was the 20-29 years old group in both gender and in both diagnostic eras.

Therapeutic strategy

Drug exposures were calculated in a time dependent analysis. The cumulative probability of 5-ASA, steroid, IS and biological therapy were 95.7%, 74.8%, 37.1% and 4% after 12 months and 97.7%, 81.3%, 49.4% and 9.9% after 3 years from diagnosis.

The use of 5-ASA was 93%/90.8% after 3 months and 97.9%/97.1% after 3 years from the diagnosis in the whole patient groups diagnosed before and after 2009, and it did not differ according to the different maximal treatment steps. Use of 5-ASA was similar in the two diagnostic eras in each patient group.

Cumulative steroid exposure was also comparable in both groups (64.4%/66% after 3 months, 72.6%/74.2% after 12 months, 79.8%/79.9% after 3 years in patients diagnosed before and after 2009). Probability of early steroid exposure was different according to the maximum treatment step but not according to the year of diagnosis: it was 48.9%/53.5% after the first 3 months from diagnosis in patients with steroids as maximum treatment step (pLogRank=0.09), 74%/74.8% in patients with IS as maximum treatment step (pLogRank=0.95) and 81.2%/78.7% in patients with biological therapy as maximum step (pLogRank=0.31), in patients diagnosed before and after 2009.

Exposure to immunosuppressive therapy was frequent in both diagnostic eras, with higher probability (pLogRank<0.001 for the max. IS group and p=0.007 for the max. biological group) and earlier initiation in the second period. Probability of immunosuppressive therapy was 17.5% vs. 22.9% at 3 months, 29.3% vs. 35.4% at one year and 39.9% vs. 45.2% at 3 years in 2004-2008 vs. 2009-2015 in patients with IS as maximum treatment step. Exposure of IS was higher in patients needing anti-TNF therapy: 31.5% vs. 40.3% at 3 months, 66.7% vs. 73.1% at one year and 86.7% vs. 91.8% at 3 years in 2004-2008 vs. 2009-2015.

The probability of biological therapy was significantly higher in patients diagnosed between 2009 and 2015 (pLogRank<0.001). It was 1% vs. 1.2% after 3 months, 2.9% vs. 6.4% after 1 year and 8.4% vs. 13.7% after 3 years in 2004-2008 vs. 2009-2015.

Hospitalizations and surgery rates according to the maximal treatment steps in the biological era

Probability of hospitalizations in the first 3-years after the diagnosis was significantly lower in patients diagnosed in 2009-2015 than in patients diagnosed in 2004-2008 (total probability: 55.7% vs. 47.4% in patients diagnosed in 2004-2008 vs. in 2009-2015, pLogRank<0.001 for the total cohort). When we analysed the hospitalization rates according to the maximal treatment steps, the difference was significant in the steroid and IS group (total probabilities: 5-ASA group: 32.6% vs. 26.7% pLogRank=0.16, Steroid group: 44.2% vs. 36.8% pLogRank=0.007, IS group: 64.6% vs. 56.1% pLogRank<0.001, Biological group: 73% vs. 66.7% pLogRank=0.10).

In contrast, surgery rates were altogether low and not significantly different in the two periods, but they were associated with the maximum therapeutic step. A proportion of patients underwent surgery at around the time of diagnosis (within 3 months from diagnosis) in both diagnostic eras, regardless of the maximum treatment step (9.1%/8.6% in the total cohort in 2004-2008/2009-2015). Thereafter the probability of surgery remained unchanged in patients with 5-ASA and steroid only, while it increased continuously in the IS and biological group (at 1 year: overall: 12% vs. 11.9%, biological therapy: 20.9% vs. 19.6%, IS: 17.4% vs. 17.3%, steroid 5.8% vs. 6%, 5-ASA 8.9% vs. 9.1%, at 3 years: overall: 16.0% vs. 15.3% (pLogRank=0.672), biological therapy: 26,7% vs. 27.2% (pLogRank=0.993), IS: 24.1% vs. 22.2% (pLogRank=0.565), steroid 8.1% vs. 7.9% (pLogRank=0.896), 5-ASA 10% vs. 11% (pLogRank=0.816) in patients diagnosed in 2004-2008 vs. 2009-2015).

3. Tuberculin skin test and Quantiferon in BCG vaccinated patients with moderate-to-severe inflammatory bowel disease

Prevalence of TST and IGRA positivity and outcome of latent TB screening

TST positivity rates were 23.6%, 21.2%, 14.5% and 13.9% with cut-off values of 5, 10, 15 and 20mm. Table II. The IGRA positivity rate was 8.4% with indeterminate result in 0.6%. Chest X-ray was suggestive in only 2 patients. None of our patients had epidemiological risk factors for TB. Of note 1 patient had developed active TB with a negative pretreatment TST and IGRA result after induction anti-TNF therapy.

Predictors of TST and IGRA positivity and agreement between TST and IGRA

A TST of 14-17mm was identified as best cut-off value to identify IGRA positivity in the ROC analysis (AUC: 0.76, $p=0.03$). The correlation between TST and IGRA was significant, with moderate-to-good kappa values if TST positivity cut-off was ≥15mm (kappa: 0.39-0.41, $p<0.001$). (Figure 1, Figure 2)

There was no association between the type and number of immunomodulators (steroid, immunosuppressives, anti-TNF or combination) used or any disease phenotype characteristics and the TST or IGRA positivity. Similarly, there was no significant difference in TST or IGRA positivity between anti-TNF treated and anti-TNF naïve patients (data not shown). Additionally, we did not found any association between IBD activity (with Harvey-Bradshaw Index) and TST or IGRA positivity.

Importantly, smoking was identified as a risk factor for TST but not IGRA positivity in the full cohort (OR: 2.70, 3.14, 5.02 and 4.62, $p<0.007$, for $TST_{cut\text{-}off}$ 5, 10, 15 and 20mm) and in CD (OR: 4.07, 4.84, 9.92 and 9.05, $p<0.001$, for $TST_{cut\text{-}off}$ 5, 10, 15 and 20mm).

4. The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe

Incidence of Clostridium difficile infection

During the follow-up period, a total of 11751 inpatients were admitted in our clinic, including all cause of hospital admission. Six hundred and one stool sample were tested for CDI in the Microbiology Department of Semmelweis University, including 168 positive and 433 negative result and including recidive cases. Testing density was 5.11/10000 patient-days. A total of 247 inpatients had a confirmed diagnosis of CDI based on the clinical symptoms, laboratory results and cytotoxin stool testing and/or stool culture. Data of 732 patients

matched for age, gender, inpatient care period and unit were compared to the CDI population. Patient data were collected from the hospital electronic database.

The crude incidence of CDI infection was 21.0 per 1000 all-cause hospital admissions (2.1% of all-cause hospitalizations). 4.45% of total inpatient days were related to CDI (4326/96284 days, equaling 25.6 cases per 10 000 patient-days) during the observed period. The majority of the patients were 60 years or older (<40 year-olds: 4.7%, 40-60 year-olds: 11.9%, >60 year-olds: 83.4%). Community acquired infection rate was 45.3%. Symptoms were detected at hospitalization in 82 patients (33.2%) and within 3 days from admission in further 30 patients (12.1%). Mean time to presence of CDI symptoms was 2.75 days (SD: 5.3) from hospital admission.

The incidence of severe CDI was 12.6% (2.63/1000 of all cause hospitalizations). In severe CDI patients were older (severe: 84.2% vs all: 69.6% of patients were >65 years, $p<0.001$) and duration of hospitalization was longer (18.4 (SD 11.7) vs 17.3 (SD 10.3) inpatient days, $p<0.001$).

The incidence of CDI was different according to the unit type, with highest incidence rates in hematology, gastroenterology and nephrology units (32.9, 25 and 24.6/1000 admissions) and lowest rates in 1.4% (33/2312) in endocrinology and general internal medicine (14.2 and 16.9/1000 admissions) units. Incidence did not differ between genders.

Risk factors for CDI

Risk factors for CDI included previous "risk" antibiotic therapy (clindamycin, penicillins, third generation cephalosporins and fluoroquinolones, $p<0.001$), use of proton pump inhibitors (OR: 2.08, $p<0.001$), previous hospitalization within 12 months (OR: 3.16, $p<0.001$), previous CDI (OR: 15.3, $p<0.001$). The presence of diabetes mellitus was associated with a decreased risk for CDI (OR: 0.48, $p<0.001$).

Treatment strategy

Treatment of primary infection was started with metronidazole in 70.8% of the patients (28.4% i.v. and 42.4% oral), vancomycin alone in 7.7% or combination therapy in 21.5%. Change in the antibiotic treatment was required in 11.9%. The mean length of antibiotic treatment was 12.1 days. The initial treatment of severe CDI included combination therapy in 31.6%, metronidazole in 60.5% or vancomycin alone.) in 7.9% of the cases. Change in the antibiotic therapy was required in 15.8% of the patients. The length of the treatment was 13.6 days (SD: 5.9 days), and 12.6 days (SD: 7.1 days) in severe cases.

Treatment strategy was different in community vs. hospital-acquired cases with a tendency towards higher metronidazole (p=0.07) and lower vancomycin (p=0.004) and/or combination therapy (p=0.04) rates in the community acquired cases. A similar proportion of the patients required a change of the first therapy.

Treatment of recurrent cases was significantly different from primary infections (86.7% vancomycin based including 53.3% combination vancomycin-metronidazolevs. 29.2% vancomycin-based therapy in primary CDI , p<0.001). Length of treatment recurrent infections was 16.6 days, longer compared to the primary cases (p=0.03 vs. primary CDI).

Clinical and laboratory parameters and outcomes of CDI

Serum creatinine level, white blood count (WBC) and C-reactive protein (CRP) were higher while serum albumin level was lower in patients with CDI compared to controls. Charlson Comorbity Index and age-adjusted Charlson Comorbidity Index were also significantly higher in CDI cases compared to controls (5.6, SD: 3.1 and 6.8, SD: 2.7 vs. 4.8, SD: 3.0 and 5.9, SD: 2.7, p<0.001).

Duration of hospital stay was longer (17.6 (SD: 10.8) vs. 12.4 (SD: 7.7) days (p<0.01)) in patients with CDI infection compared to the controls. Length of hospitalization was not different between age-groups (data not shown). 8.1% of the patients required ICU therapy during the CDI infection.

The 30-day mortality rate was 21.9% in CDI patients (54/247 cases), equaling 6.3% of all-inpatient deaths (37/555). In addition, mortality rates were different according to age with highest mortality in the eldest patients (21.7% in >60 year-olds, 16.7% in 40-60 year-olds and 0% in younger patients, p=0.053).

Recurrence of CDI infection was 11.3% (n=26) 12 weeks after discharge. The outcome of recurrent cases was not significantly different from that of the primary infection. The rate of severe CDI was 5.9% and 30-day mortality was 23.8%.

Conclusion

Hereby I summarize the main conclusions of the studies presented in my thesis:

1. **Nationwide prevalence and drug treatment practices of inflammatory bowel diseases in Hungary: A population-based study based on the National Health Insurance Fund database**

1) Our results confirm that Hungary belongs to the group of moderate-high IBD prevalence countries. We found a high IBD prevalence, equaling 0.55% for IBD, 0.20% for CD and 0.34% for UC. The prevalence was lower (0.31% for IBD, 0.13% for CD and 0.18% for UC) if only actively treated IBD patients were considered.
2) The distribution of age-groups were similar to that reported in previous studies: in CD the peak of the age-adjusted prevalence was observed in the 30–39 year olds without a second peak in later years, while in UC the initial peak was followed by a plateauing and then possibly a second peak in later years.
3) The use of 5-ASA in UC was relatively low (66%/73%/72%). whereas comparable high 5-ASA exposure rates were found in CD (68%/71%/69%).
4) Current medical strategy was significantly different according to the age-groups. The younger age-group was treated with more aggressive therapeutic strategy, including more frequent use of IS and anti-TNFs.

2. Therapeutic preferences and outcomes in newly diagnosed patients with Crohn's diseases in the biological era in Hungary. A nationwide study based on the National Health Insurance Fund database

5) After the change of prescription-regulations in 2009, significant changes were observable in the therapeutic strategy of Crohn's disease: an accelerated treatment strategy was used with the earlier and more frequent use of IS and biologicals.
6) Hospitalization decreased after 2009, while surgery remained low but constant during the observation period.
7) The frequency of the early (within 3 years) surgical procedures were low in the whole cohort.
8) The association between maximal treatment step and hospitalization and surgery rates suggests that maximal treatment steps can be regarded as proxy severity markers in patients with IBD when analysing administrative health databases.

3. Tuberculin skin test and Quantiferon in BCG vaccinated patients with moderate-to-severe inflammatory bowel disease

5) The accuracy of both TST and IGRA was comparable to identify the risk patients for latent TB. The IGRA positivity rate was 8.4% with indeterminate result in 0.6%, in line with the previous results from low TB incidence countries

6) Agreement between the TST and IGRA was moderate using a >15mm cut-off value in TST. This suggests that latent TB may be tested with TST in BCG-vaccinated immunosuppressed patients with >15mm cut-off value.
7) TST and IGRA tests are partly complimentary methods if TST positivity measured with >15mm cut-off to identify patients at risk for latent TB and the accuracy is acceptable also in BCG-vaccinated, immunosuppressed IBD patients.
8) TST positivity is affected by smoking thus IGRA is the preferred method in smokers.

4. The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe

5) The incidence rate of CDI was 21/1000 all cause hospital admission and it was responsible for 4.5% of inpatients stays between 1st of January, 2010 and 1st of May, 2013 at the First Department of Medicine, Semmelweis University, Budapest, Hungary.
6) The majority of the patients were 60 years or older (83.4%). The 30-day mortality rate was 21.9% in CDI patients (54/247 cases), equaling 6.3% of all-inpatient deaths.
7) Recurrence of CDI infection was 11.3% (n=26) 12 weeks after discharge. The outcome of recurrent cases was not significantly different from that of the primary infection.
8) Risk factors for CDI included previous "risk" antibiotic therapy (clindamycin, penicillins, third generation cephalosporins and fluoroquinolones, $p<0.001$), use of proton pump inhibitors (OR: 2.08, $p<0.001$), previous hospitalization within 12 months (OR: 3.16, $p<0.001$), previous CDI (OR: 15.3, $p<0.001$).

List of own publications

Publications on that my thesis based

1. Kurti Z, Vegh Z, Golovics PA, Fadgyas-Freyler P, Gecse KB, Gonczi L, Gimesi-Orszagh J, Lovasz BD, Lakatos PL. Nationwide prevalence and drug treatment practices of inflammatory bowel diseases in Hungary: A population-based study based on the National Health Insurance Fund database. Dig Liver Dis. 2016 Nov;48(11):1302-1307.
2. Kurti Z, Ilias A, Gonczi L, Vegh Z, Fadgyas-Freyler P, Korponay G, Golovics PA, Lovasz BD, Lakatos PL. Therapeutic preferences and outcomes in newly diagnosed patients with Crohn's diseases in the biological era in Hungary: a nationwide study based on the National Health Insurance Fund database. BMC Gastroenterol. 2018 Jan 30;18(1):23.
3. Kurti Z, Lovasz BD, Gecse KB, Balint A, Farkas K, Morocza-Szabo A, Gyurcsanyi A, Kristof K, Vegh Z, Gonczi L, Kiss LS, Golovics PA, Lakatos L, Molnar T, Lakatos PL. Tuberculin Skin Test and Quantiferon in BCG Vaccinated, Immunosuppressed Patients with Moderate-to-Severe Inflammatory Bowel Disease. J Gastrointestin Liver Dis. 2015 Dec;24(4):467-72.
4. Kurti Z, Lovasz BD, Mandel MD, Csima Z, Golovics PA, Csako BD, Mohas A, Gönczi L, Gecse KB, Kiss LS, Szathmari M, Lakatos PL. Burden of Clostridium difficile infection between 2010 and 2013: Trends and outcomes from an academic center in Eastern Europe. World J Gastroenterol. 2015 Jun 7;21(21):6728-35.

Other publications

1. Kurti Z, Gonczi L, Lakatos PL. Progress with infliximab biosimilars for inflammatory bowel disease. Expert Opin Biol Ther. 2018 Jun;18(6):633-640.
2. Gonczi L, Kurti Z, Golovics PA, Lovasz BD, Menyhart O, Seres A, Sumegi LD, Gal A, Ilias A, Janos P, Gecse KB, Bessisow T, Afif W, Bitton A, Vegh Z, Lakatos PL. Quality of care indicators in inflammatory bowel disease in a tertiary referral center with open access and objective assessment policies. Dig Liver Dis. 2018 Jan;50(1):37-41.
3. Gonczi L, Gecse KB, Vegh Z, Kurti Z, Rutka M, Farkas K, Golovics PA, Lovasz BD, Banai J, Bene L, Gasztonyi B, Kristof T, Lakatos L, Miheller P, Nagy F, Palatka K, Papp M, Patai A, Salamon A, Szamosi T, Szepes Z, Toth GT, Vincze A, Szalay B, Molnar T, Lakatos PL. Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort. Inflamm Bowel Dis. 2017 Nov;23(11):1908-1915.

4. Farkas K, Rutka M, Ferenci T, Nagy F, Bálint A, Bor R, Milassin Á, Fábián A, Szántó K, Végh Z, Kürti Z, Lakatos PL, Szepes Z, Molnár T. Infliximab biosimilar CT-P13 therapy is effective and safe in maintaining remission in Crohn's disease and ulcerative colitis - experiences from a single center. Expert Opin Biol Ther. 2017 Nov;17(11):1325-1332.
5. Gonczi L, Kurti Z, Rutka M, Vegh Z, Farkas K, Lovasz BD, Golovics PA, Gecse KB, Szalay B, Molnar T, Lakatos PL. Drug persistence and need for dose intensification to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases. BMC Gastroenterol. 2017 Aug 8;17(1):97.
6. Jo I, Szalay B, Végh Z, Kürti Z, Olajos F, Vásárhelyi B.High titers of anti-infliximab antibody do not interfere with Abbott immunoassays. Clin Chem Lab Med. 2017 Oct 26;55(12):e276-e278.
7. Bálint A, Rutka M, Végh Z, Kürti Z, Gecse KB, Banai J, Bene L, Gasztonyi B, Kristóf T, Lakatos L, Miheller P, Palatka K, Patai Á, Salamon Á, Szamosi T, Szepes Z, Tóth GT, Vincze Á, Bor R, Milassin Á, Fábián A, Nagy F, Kolar M, Bortlik M, Duricova D, Hruba V, Lukas M, Mitrova K, Malickova K, Lukas M, Lakatos PL, Molnár T, Farkas K. Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in inflammatory bowel diseases: results from Central European nationwide cohort. Expert Opin Drug Saf. 2017 Aug;16(8):885-890.
8. Vegh Z, Kurti Z, Golovics PA, Lakatos PL. Can we Predict Disease Course with Clinical Factors? Curr Drug Targets. 2018;19(7):791-797.
9. Vegh Z, Kurti Z, Lakatos PL. Real-Life Efficacy, Immunogenicity and Safety of Biosimilar Infliximab. Dig Dis. 2017;35(1-2):101-106.
10. Vegh Z, Kurti Z, Lakatos PL. Epidemiology of inflammatory bowel diseases from west to east. J Dig Dis. 2017 Feb;18(2):92-98.
11. Gönczi L, Kürti Z, Golovics P, Végh Z, Lovász B, Dorkó A, Seres A, Sümegi L, Menyhárt O, Kiss L, Papp J, Gecse K, Lakatos PL. [Indications, diagnoses and quality markers in upper and lower endoscopies in 2010 and 2011 at the 1st Department of Medicine, Semmelweis University, Budapest]. Orv Hetil. 2016 Dec;157(52):2074-2081.
12. Gonczi L, Vegh Z, Golovics PA, Rutka M, Gecse KB, Bor R, Farkas K, Szamosi T, Bene L, Gasztonyi B, Kristóf T, Lakatos L, Miheller P, Palatka K, Papp M, Patai Á, Salamon Á, Tóth GT, Vincze Á, Biro E, Lovasz BD, Kurti Z, Szepes Z, Molnár T, Lakatos PL. Prediction of Short- and Medium-term Efficacy of Biosimilar Infliximab Therapy. Do Trough Levels and Antidrug Antibody Levels or Clinical And Biochemical Markers Play the More Important Role? J Crohns Colitis. 2017 Jun 1;11(6):697-705.
13. Kurti Z, Vegh Z, Golovics PA, Lakatos PL. 'Treat to Target' - Lessons Learnt. Dig Dis. 2016;34(1- 2):147-52.
14. Vegh Z, Kurti Z, Lakatos PL. Adenomatous polyps in ulcerative colitis and colonic Crohn's disease: less frequent, but does this change surveillance strategy? Endoscopy. 2016 Mar;48(3):210-2.
15. Vegh Z, Kurti Z, Gonczi L, Golovics PA, Lovasz BD, Szita I, Balogh M, Pandur T, Vavricka SR, Rogler G, Lakatos L, Lakatos PL. Association of extraintestinal manifestations and anaemia with disease outcomes in patients with inflammatory bowel disease. Scand J Gastroenterol. 2016 Jul;51(7):848-54.

16. Golovics PA, Lakatos L, Mandel MD, Lovasz BD, Vegh Z, Kurti Z, Szita I, Kiss LS, Balogh M, Pandur T, Lakatos PL. Does Hospitalization Predict the Disease Course in Ulcerative Colitis? Prevalence and Predictors of Hospitalization and Re-Hospitalization in Ulcerative Colitis in a Population-based Inception Cohort (2000-2012). J Gastrointestin Liver Dis. 2015 Sep;24(3):287-92.
17. Golovics PA, Lakatos L, Mandel MD, Lovasz BD, Vegh Z, Kurti Z, Szita I, Kiss LS, Pandur T, Lakatos PL. Prevalence and predictors of hospitalization in Crohn's disease in a prospective population-based inception cohort from 2000-2012. World J Gastroenterol. 2015 Jun 21;21(23):7272-80.
18. Kiss M, Deshpande RR, Nemeskéri Á, Nguyen TT, Kürti Z, Kovács S, Pápai Z, Németh K, Szuák A, Dudás I, Kóbori L.Optimal line of hepatotomy for left lateral living donor liver transplantation according to the anatomical variations of left hepatic duct system. Pediatr Transplant. 2015 Aug;19(5):510-6.
19. Vegh Z, Golovics PA, Lovasz BD, Kurti Z, Gecse KB, Szita I, Balogh M, Pandur T, Lakatos L, Lakatos PL. Low incidence of venous thromboembolism in inflammatory bowel diseases: prevalence and predictors from a population-based inception cohort. Scand J Gastroenterol. 2015 Mar;50(3):306-11.
20. Mandel MD, Balint A, Golovics PA, Vegh Z, Mohas A, Szilagyi B, Szabo A, Kurti Z, Kiss LS, Lovasz BD, Gecse KB, Farkas K, Molnar T, Lakatos PL. Decreasing trends in hospitalizations during anti-TNF therapy are associated with time to anti-TNF therapy: Results from two referral centres.Dig Liver Dis. 2014 Nov;46(11):985-90.
21. Mandel MD, Bálint A, Lovász BD, Gulácsi L, Strbák B, Golovics PA, Farkas K, Kürti Z, Szilágyi BK, Mohás A, Molnár T, Lakatos PL. Work disability and productivity loss in patients with inflammatory bowel diseases in Hungary in the era of biologics. Eur J Health Econ. 2014 May;15 Suppl 1:S121-8.