Prediction of disease outcomes in inflammatory bowel disease patients treated with anti-TNF agents using therapeutic drug monitoring, and the evaluation of quality of care in inflammatory bowel diseases

PhD thesis

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Introduction

Inflammatory bowel diseases (IBD) – Crohn's disease (CD) and ulcerative colitis (UC) – are chronic, progressive, disabling conditions affecting mainly young adults and having substantial impact on social functioning and quality of life. Anti-tumor necrosis factor (anti-TNF) therapies are new and effective drugs in IBD, achieving clinical remission and mucosal healing, reducing the need for surgery and hospitalizations. However, approximately 10-30% of the patients do not respond to the initial treatment and app. one third of the patients lose response to anti-TNF therapy over time ('loss of response'; LOR). There are several possible causes for LOR to anti-TNF therapy, although one of the most common is decreased drug levels due to the development of anti-drug antibodies (ADA). ADAs can neutralize the anti-TNF drug connecting to the Fab segment of the protein or bind only the anti-TNF molecule leading to increased clearance. After the introduction of anti-TNF therapies it also became possible to measure drug levels and ADAs, most commonly by ELISA methods. Therapeutic drug monitoring (TDM), measuring drug trough levels (TL) and ADA levels may aid the therapeutic decision in patients who lose response to anti-TNF therapy. Several studies have indicated a correlation between clinical efficacy and serum drug levels, and an inverse correlation with the presence of ADAs in infliximab therapy. Although correlation between adalimumab drug concentrations and clinical outcome was also reported in several studies,

fewer data are available on the relevance of TDM assessment during adalimumab therapy, whether TLs and ADA levels are strongly associated with disease outcome remains questionable.

The efficacy of anti-TNF therapy in CD has been reported to be associated with several clinical factors, such as shorter disease duration, isolated colonic disease location, absence of previous surgery, young age, non-smoking status, or high C-reactive protein (CRP) level at treatment initiation. Until now, few data are available on the predictive potential of TL and ADA status measured early (during induction therapy) in IBD patients treated with infliximab. There are also virtually no data regarding the predictive potential of clinical and biochemical markers and TDM results in patients treated with the biosimilar infliximab CT-P13.

The introduction of biological drugs has revolutionized the management of IBD, however, the increasing financial burden of biologicals on the health care system is alarming. The impending or past patent expiry and high costs of certain biologics have initiated the development of ‘biosimilar’ drugs in IBD. Biosimilars are considered to be equivalent to the reference medicinal product in terms of pharmacokinetic properties, clinical effectiveness and safety. CT-P13 infliximab was the first biosimilar to be approved by the regulatory authorities EMA in September, 2013. If the biosimilar product is demonstrated to be highly similar to the reference drug after comparative analyses in one of the licensed indications, it will be granted approval for all the approved indications of the reference product. This is known as ‘indication extrapolation’. The extrapolation of the use of biosimilar

infliximab in IBD was based on the results from 2 randomized controlled trials conducted in ankylosing spondylitis and rheumatoid arthritis. As a result, there is a lack of clinical trial data about the efficacy, safety and immunogenicity of the biosimilar infliximab in IBD, which despite stringent approval processes by the regulatory authorities, led to the fact that acceptance of biosimilars among physicians encountered some resistance.

The management of IBD has become increasingly complex in recent years. Patient management including diagnostic tools, medical and surgical therapy, monitoring and follow-up strategy has changed significantly with the advent of biological therapies. We moved away from symptomatic improvement towards targeting more objective parameters/treatment goals including clinical, biochemical remission and endoscopic healing, leading ultimately to less complications and improved quality of life. To achieve this, we need multidisciplinary approach and optimized patient stratification, reassessment of monitoring and follow-up strategies and re-thinking of care pathways. However, there is considerable variation in the process of care for patients with IBD which may be associated with poor outcomes. As a result of the apparent differences in practice, a major interest was sparked in devising a standard set of measures to assess quality and provide a means to quantify quality of care (QoC). This occurred by developing quality indicators (QIs). Recently, multiple QI sets have been published by expert panels relating to three components: structure, process and outcome parameters of care. Complex evaluation of QoC provided by IBD centers based on

the above measures are however still scarce. We believe that continuous tracking and formal evaluation of QIs in IBD centers is important, improving healthcare delivery and efficiency in IBD clinics/centers and ultimately may lead to improved patient outcomes.

Objectives

1. *Prediction of short- and medium-term efficacy of biosimilar infliximab therapy – drug trough levels and anti-drug antibody levels, clinical and biochemical markers*

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

2. *Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort*

Our aim was to evaluate the medium- and long-term efficacy, safety, and immunogenicity of biosimilar IFX CT-P13 (Inflectra) in a Hungarian

consecutive, nationwide cohort of patients with IBD treated up to 54 weeks.

3. *Drug persistence and need for dose intensification to adalimumab therapy; the role of therapeutic drug monitoring and other predictive factors*

The aim of the present study was to evaluate the frequency and predictive factors of loss of response and dose intensification in adalimumab therapy and the role of TDM to predict LOR in a cross-sectional study.

4. *Quality of care indicators in inflammatory bowel disease in a tertiary referral IBD*

The aim of our present study was to evaluate structural, access/process components and outcome quality indicators based on the QI sets developed and published in literature to assess QoC in our tertiary referral IBD center.

Methods

1. *Prediction of short- and medium-term efficacy of biosimilar infliximab therapy – drug trough levels and anti-drug antibody levels, clinical and biochemical markers*

The inclusion period of this prospective, nationwide, multicentre, observational study were between 2014 and 2016. Unselected, consecutive IBD patients starting on biosimilar infliximab CT-P13 were enrolled. Patients received intravenous infusions of the biosimilar IFX CT-P13 at a dose of 5 mg/kg of body weight at weeks 0, 2, and 6, and then every 8 weeks. No patient received originator infliximab during the 12 months preceding the initiation of biosimilar infliximab therapy. Clinical (Crohn's Disease Activity Index [CDAI] in CD and partial Mayo Score [pMayo] in UC) and biochemical activity (including total blood count [TBC], serum C-reactive protein [CRP, normal cutoff: 5 mg/l], and albumin) were evaluated at baseline and at Weeks 14, 30, and 54. In CD, clinical remission was defined as a CDAI < 150 points or no fistula drainage. In UC, clinical remission was defined as a pMayo of less than three points and clinical response was defined as a decrease in the pMayo score with more than 3 points. Biosimilar infliximab TLs and ADA levels were measured using the conventional and bridging enzyme-linked immunosorbent assay [ELISA], [LISA TRACKER, Theradiag, France] at baseline, at Weeks 14, 30, and 54. Statistical analysis was performed

using SPSS software v. 20.0. Ethical approval was acquired from the National Ethical Committee (929772-2/2014/EKU [292/2014]).

2. *Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort*

The present study is a further analysis of the previously mentioned cohort. Patient demographics, previous, and concomitant medications were collected, and biochemical and clinical assessment was performed at start and every 3 months thereafter. Primary endpoints were clinical response and remission at Weeks 14. 30. and 54. Secondary endpoints were biomarker remission, immunogenicity and safety profile evaluation.

3. *Drug persistence and need for dose intensification to adalimumab therapy; the role of therapeutic drug monitoring and other predictive factors*

Patients were enrolled in this cohort between 2014 November and 2016 June from two referral IBD centres in Hungary. Demographic data, previous and current therapy, laboratory data and clinical activity at the time of TDM were recorded. Adalimumab was administered at an induction dose of 160/80 mg and then at standard doses of 40 mg every other week. Dose intensification was defined as administration of 40 mg

every week. Patients were evaluated either at the time of suspected LOR (based on clinical evaluation) or during regular follow-up visits with TDM measurement using a conventional and bridging ELISA assay. LOR was defined as discontinuation of adalimumab therapy. Our primary analysis aimed to evaluate the frequency of LOR and dose intensification in adalimumab treated patients, while secondary aims were to identify predictive factors for LOR. Statistical analysis was performed using SPSS software v. 20.0. Ethical approval was acquired from the National Ethical Committee (929772-2/2014/EKU [292/2014]).

4. *Quality of care indicators in inflammatory bowel disease in a tertiary referral IBD*

Our study was conducted at an academic tertiary referral IBD center of the Gastroenterology Unit at the 1st Department of Internal Medicine, Semmelweis University. In the first phase of the study, structural components (hospital characteristics and infrastructure, personnel and referral professionals, equipment, patient registers) of our IBD center were assessed. This was followed by the evaluation of process/access indicators in patient management (including monitoring disease activity, measures to prevent disease complications and drug adverse events, access to diagnostic tools and procedures). We present selected access and outcome QI measures, such as hospitalization rates and surgery requirements, documented relapses in disease activity. In the second phase we evaluated access, monitoring and outcome parameters in a set

of consecutive IBD patients who presented as out- or in-patients at our IBD center up until 2016. Data regarding frequency of disease flares, access to IBD specialists and imaging procedures, hospitalization and surgery rates were collected between the period of 2014 and 2016. Medical records of patients were collected and comprehensively analyzed. Statistical analysis was performed using the SPSS software v.20.0.

Results

1. *Prediction of short- and medium-term efficacy of biosimilar infliximab therapy – drug trough levels and anti-drug antibody levels, clinical and biochemical markers*

A total of 291 consecutive IBD patients─184 patients with CD and 107 patients with UC─were enrolled in the study. TLs measured at Week 2 in UC were predictive for both clinical response and remission at Weeks 14 and 30 (clinical response at Week 14: area under the curve [AUC] = 0.81, $p < 0.001$, cut-off: 11.5 μg/ml, clinical remission at Week 14: AUC = 0.79, $p < 0.001$, cut-off: 15.3 μg/ml; clinical response at Week 30: AUC = 0.79, $p = 0.002$, cut-off: 11.5 μg/ml, clinical remission at Week 30: AUC = 0.74, $p = 0.006$, cut-off: 14.5 μg/ml). Trough levels measured at Week 2 in CD were associated both with clinical response and remission

at Week 14 (clinical response at Week 14: AUC=0.72, p=0.05, cut-off: 16.9 μg/ml; clinical remission at Week 14: AUC=0.72, p=0.005, cut-off: 20.4 μg/ml).

Previous anti-TNF exposure was inversely associated with clinical remission at Week 2 (p= 0.03), and at Week 6 (p= 0.013) in UC. Previous anti-TNF exposure was associated with ADA development at Weeks 0, 2, and 6 ($p < 0.001$, $p < 0.001$, and $p = 0.012$) in UC. In CD patients, previous anti-TNF exposure was inversely associated with clinical response and remission at Week 14 (p= 0.002 and p= 0.002), clinical response and remission at Week 30 (p= 0.008 and p = 0.03), and at Week 54 ($p< 0.001$ and p= 0.004). Previous anti-TNF exposure was associated with ADA development at Weeks 0 and 2 ($p< 0.001$ for both).

In CD patients, normal CRP level at Week 14 was associated with clinical response and remission at Week 14 ($p < 0.001$ and $p < 0.001$) and at Week 30 ($p < 0.001$ and $p = 0.005$) but not with clinical response and remission at Week 54 ($p = 0.10$ and $p = 0.114$).

2. *Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort*

A total of 353 consecutive IBD (209 CD and 144 UC) patients were included. In CD, 49%, 53%, 48% and 86%, 81% and 65% of the patients reached clinical remission and response by weeks 14, 30, and 54, respectively. Clinical response rates were significantly different at weeks 14, 30, and 54 ($p<0.01$, p= 0.005, and $p< 0.001$, respectively), whereas clinical remission rates were significantly different at weeks 14 and 54

(p= 0.04 and p= 0.02, respectively) between anti–TNF-naive and anti–TNF-exposed patients with CD. In patients with UC, clinical remission and response rates were 56%, 41%, and 43% and 74%, 66%, and 50% of the patients by weeks 14, 30, and 54, respectively. Clinical response rates were significantly different at week 30 (p=0.01), whereas clinical remission rates were significantly different at weeks 14 and 30 (p= 0.02 and p=0.04) between anti–TNF naive and previously anti–TNF-exposed patients with UC, respectively.

Cumulative ADA positivity rates were 9.8% (26/266), 18.6% (58/312), 24.1% (70/290), and 33.8% (71/210) at weeks 0, 14, 30, and 54, respectively, in all patients with IBD. In CD, a significant difference was found in ADA positivity rates between anti–TNF-naive and previously anti–TNF exposed patients at baseline (p=0.001), weeks 14 (p<0.001), 30 (p= 0.03), and 54 (p= 0.03). Concomitant azathioprine (AZA) prevented ADA formation at weeks 14 (6.5% versus 21.2%, p=0.01), 30 (12.7% versus 29.2%, p= 0.02), and 54 (15% versus 45.2%, p=0.004) in anti–TNF-naive but not in previously exposed patients with CD.

At week 54, the cumulative rate of adverse events was 24%. Infusion reactions occurred in 31 (8.8%) patients.

3. *Drug persistence and need for dose intensification to adalimumab therapy; the role of therapeutic drug monitoring and other predictive factors*

112 IBD patients were enrolled. Frequency of ADA positivity was 20.5% (23/112). Cumulative ADA positivity was 12.1% and low TL rate was 17.8% after 1 year, and 17.3% and 29.5%, respectively after 2 years of adalimumab therapy in Kaplan-Meier analysis. The probability of dose intensification and LOR was 19.7% and 17.5% in the first year and 30% and 18.8% in the second year of adalimumab therapy.

Rate of low TL in patients with high ADA was 85.7%, while it was 28.6% in patients with low ADA and 27.5% in ADA negative patients ($p = 0.006$). ADA positivity was significantly associated with LOR ($p = 0.007$). There was a significant association between LOR and female gender (86.2% vs. 44.6%, $p < 0.001$, OR: 7.8 CI 95%: 2.5–24.3) both in CD and UC. Gender ($p < 0.001$, OR: 9.1, 95% CI: 2.7–30.5) and ADA positivity ($p= 0.007$, OR: 4.7, 95% CI: 1.5–14.3) remained independent predictors of LOR in a multivariate analysis.

4. *Quality of care indicators in inflammatory bowel disease in a tertiary referral IBD*

248 CD patients and 125 UC patients were included in the total analysis to evaluate quality of patient evaluation, and monitoring, while data regarding frequency of disease flares, access to IBD specialist physician

and imaging procedures, hospitalization and surgery rates were collected in a population of 163 CD and 95 UC patients. The structural and process indicators of our center meet the requirements and recommendations of international guidelines. Patient management was coupled with fast-track access and objective evaluation of our IBD patients presenting with a flare, in line with the open clinic policy applied by the center. All patients of our IBD center underwent at least one full colonoscopy at or around the time of diagnosis/referral. Ileocolonoscopy and gastroscopy was performed in 81.8% and 45.5% of CD patients. CT/MRI was performed in 66.1/49.6% of CD patients while a pelvic MRI in 83.1% of patients with a perianal disease. Patients presenting with a flare had an outpatient consultation with a specialist at the IBD clinic (not emergency room) a median of 1 day after request with same day laboratory and same day abdominal US, CT scan and surgical consult if necessary. The median waiting time for non-emergency endoscopy, CT or MRI was16, 14 and 22 days. Overall hospitalization rates were 17.3/3.2% of all CD/UC patients in 2014–2016. 20.1% of CD patients required any surgery and 1.4% of UC patients underwent colectomy.

Conclusions

Prediction of short- and medium-term efficacy of biosimilar infliximab therapy – drug trough levels and anti-drug antibody levels, clinical and biochemical markers

1. Trough levels measured at week 2 in UC were predictive for both clinical response and remission at treatment Weeks 14 and 30.

2. Trough levels measured at week 2 in CD were associated both with clinical response and remission at week 14.

3. Normalisation of CRP level at week 14 (<10mg/l) was associated with clinical response and remission at week 14 and at week 30.

4. Previous anti-TNF exposure was inversely associated with clinical response and remission at weeks 14, 30 and 54 in CD patients, while in UC patients previous anti-TNF exposure was inversely associated with clinical remission at weeks 2 and 6. Other clinical factors were not associated with clinical response or remission at weeks 14, 30, and 54.

Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort

5. The clinical response and remission rates evaluated at treatment weeks 14, 30 and 54 of the biosimilar IFX were comparable with those of the originator compound reported in previous studies.

6. The cumulative rate of adverse events observed in patients treated with CT-P13 were in line with those of the originator compound reported in previous studies.

7. Based on TDM measurements, the pharmacokinetic and immunogenic properties of biosimilar infliximab CT-P13 are comparable with the originator compound.

8. Previous anti-TNF exposure influenced clinical efficacy, the rate of infusion rections and TL and ADA status.

Drug persistence and need for dose intensification to adalimumab therapy; the role of therapeutic drug monitoring and other predictive factors

9. The probability of dose intensification and LOR was 19.7% and 17.5% in the first year of therapy in adalimumab treated patients.

10. The frequency of ADA positivity is high in adalimumab treated patients and high ADA titers correlate with sub-therapeutic drug levels.

11. ADA positivity, dose intensification and female gender were identified as predictors of loss of response

Quality of care indicators in inflammatory bowel disease in a tertiary referral IBD

12. The structural and process quality indicators of our formal IBD center at Semmelweis University meet the requirements and recommendations of international guidelines.

13. Patient management processes include an open clinic concept, objective disease evaluation and monitoring strategies, and fast-track access to specialist consultation, endoscopy and imaging.

14. Continuous tracking and formal evaluation of quality of care is important, which improves healthcare delivery and efficiency of IBD clinics/centers worldwide.

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