The role of the biosimilar drugs and the fast-track MR in the treatment of inflammatory bowel disease

PhD thesis

dr. Iliás Ákos

Clinical Medicine Doctoral School

Semmelweis University

Supervisor: Péter László Lakatos, MD, DSc

Official reviewers: Tibor Glasz, MD, PhD
András Taller, MD, PhD

Head of the Complex Examination Committee:

Gabriella Lengyel, MD, PhD

Members of the Complex Examination Committee:

Áron Somorácz, PhD
Ákos Balázs, PhD

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Introduction

The exact etiology and pathomechanism of inflammatory bowel disease (IBD) is still unknown. The course and appearance of the disease varies greatly from patient to patient, and finding the best therapeutic options for each patient is challenging. Crohn's disease (CD) and ulcerative colitis (UC) shows an undulating course, which requires a tight doctor-patient relationship and tight monitoring of the disease progression.

In the last decades, the diagnosis of IBD and patient follow-up strategies has changed a lot. This was influenced partly by the spread of novel diagnostic methods, such as magnetic resonance enterography (MRE), capsule endoscopy, fecal calprotectin, and the spread of new guidelines and expert opinions based on large prospective studies.

Based on its several properties, abdominal MRE examination is one of the most appropriate imaging modality to examine and monitor CD patients. It is suitable for detecting transmural abnormalities, as well as for determining the extent of intestinal wall inflammation and searching for perianal abnormalities.

The introduction of biological therapy has fundamentally changed the treatment of inflammatory bowel disease and became the gold standard drugs in the treatment of severe IBD. In different countries, due to federal regulations and accessibility, the place of different biologicals in the treatment algorithm is varying.

Infliximab (IFX original brand name REMICADE), being one of the first and fundamental biological drug in IBD therapy, is a 25% murine 75% human chimeric TNFα inhibitor antibody. This design explains that anti-drug antibody formation is possible, which may have an effect on primary non-response and secondary loss of response, as well as on the development of infusion reactions. Its efficacy in UC and CD has been demonstrated in several studies.

The huge cost globally on biological treatments is a large burden on health insurers, so there has been a growing interest in developing cheaper biosimilar products after expiring patent protection of the original drug. The European Medicines Agency defines a biosimilar product as a biological medicine that is very similar to another biological agent (reference medicine) which is already on the market in the EU. The similarity to the reference product is manifested in qualitative characteristics and biological activity as well as efficacy and safety, and these properties are based on the results of large prospective studies. CT-P13 was the first biosimilar infliximab which was accepted for all indications of the original drug was used. Despite existing safety data, there was a certain resistance towards the use of biosimilars among clinicians, especially in cases when switching from the original to the biosimilar formulation, or even sequential switches had to be considered.

Objectives

Outcomes of patients with IBD switched from maintenance therapy with a biosimilar IFX to Remicade

According to the directive of the National Health Insurance Fund of Hungary (NEAK), the use of biosimilar IFX was mandatory in Hungary between May 2014 and September 2017 in anti-TNFα antibody naïve patients. In 2017, the financing of IFX tender was again put out to tender by the NEAK and was won by the original product, Remicade. As a result of this, the original product, Remicade, became the only NEAK-funded IFX biological product in Hungary from September 2017. Due to this regulation, all inflammatory bowel patients treated with the IFX biosimilar drug in Hungary had to be switched back to the original product.

The aim of the present research was to determine the short-term drug sustainability, efficacy, safety and immunogenicity profile during the reverse switch from a biosimilar IFX drug to the original in a Hungarian multicenter IBD cohort.

The effect of Fast-Track MRI on patient management and outcomes in Crohn's disease

Several studies aimed to evaluate the accuracy of MRI in assessing disease activity in CD, however data on the value of routine, rapid-access MRI in the everyday clinical practice are scarce. Objective patient evaluation and disease monitoring became standard in many IBD centers, including regular assessment of biomarkers, endoscopy and cross-sectional imaging. However, due to limited access, the routine use of 'fast-track' MRI is infrequent. Therefore, the present study aim was to evaluate the impact of fast-track MRI on treatment optimization, clinical decision-making and outcomes in a specialized Hungarian tertiary care IBD center.

Methods

Outcomes of patients with IBD switched from maintenance therapy with a biosimilar IFX to Remicade

This is a multicenter prospective observational study enrolling unselected and consecutive patients who were switched from the biosimilar IFX CT-P13 (Inflectra) to the originator Remicade during maintenance therapy. Patients received intravenous infusions of IFX (5 mg/kg or 10 mg/kg of body weight) every 8 weeks. Four referral IBD centers participated in the study: 3 university centers and 1 county hospital. Patient demographics, previous and concomitant medications were recorded; disease location and behavior in CD and disease extent in UC were assessed according to the Montreal classification. A harmonized monitoring strategy was applied in all participating centers. Biochemical activity was evaluated using serum C-reactive protein (normal cutoff 10 mg/L). Infusion-related adverse events were registered at baseline and weeks 8, 16, and 24. Serum drug trough level (TL) and anti-drug antibody (ADA) were measured at baseline and week 16. For the measurement of IFX TL and ADAs, conventional and bridging enzyme-linked immunosorbent assay methods were used. For better stratification of patients, we defined the ADA titer >200 ng/mL as “high” ADA titer. Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU (292/2014).

The effect of Fast-Track MRI on patient management and outcomes in Crohn's disease

Consecutive IBD patients who had underwent fast-track MRI between January 2014 and June 2016 in a single tertiary referral IBD center were included. Magnetic resonance imaging studies were performed to evaluate disease activity in patients with or without disease flares. All examinations were performed as 'rapid-access' procedures with a maximum waiting time of two weeks. Clinical data were collected and comprehensively reviewed. Clinical remission was defined as CDAI <150 points or no fistula drainage as assessed by the Fistula Drainage Assessment in CD. Biomarker activity was defined as CRP levels >10mg/L. Clinically active disease was defined based on the combination of the clinicians' evaluation, CDAI score and laboratory parameters. Available colonoscopy and US/CT results within three months after MRI were also collected. Magnetic resonance imaging scans were carried out by a 3.0T MR unit (Philips Achieva and Insignia) at the Magnetic Resonance Imaging Research Center of Semmelweis University, Budapest. All scans were MRE procedures. One expert radiologist with extensive knowledge in the treatment of IBD patients evaluated the MRI scans. An MRI score was not calculated. The MRI results were compared to the clinical activity scores (CDAI) and laboratory activity markers (CRP) for correlation. Clinical outcomes were collected. Changes in medical therapy,

hospitalizations and surgery requirements were also evaluated. All changes in medical therapy were registered including antibiotics, local or systemic corticosteroids, immunosuppressive agents and biologics. Escalation in medical therapy was defined as an initiation of a higher therapeutic step (immunosuppressives or biologics) or a dose intensification of current biological therapy. The study protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE TUKEB 142/2010).

Results

Outcomes of patients with IBD switched from maintenance therapy with a biosimilar IFX to Remicade

A total of 174 IBD patients (136 CD and 38 UC) were included in this cohort. Complicated disease behavior and perianal manifestation was present in 39.7% and 48.5% of CD patients. 54.1% of UC patients had extensive colitis. Concomitant steroid and immunosuppressive therapy (azathioprine) was present in 8.8% and 50.7% and 27.0% and 35.1% of CD and UC patients at baseline, respectively. Previous anti-TNF use was 19.9% and 16.2% in CD and UC patients, respectively. A total of 11% and 7.9% of CD and UC patients, respectively, have already been exposed to the originator IFX previously**.**

Median CDAI and pMayo scores were 57 (IQR, 32–112) and 1 (IQR, 0–2) at baseline (switch); 68 (IQR, 35–125.5) and 1 (IQR, 0–1) at week 16; and 60 (IQR, 31–100) and 1 (IQR, 0–2) at week 24.

Mean CDAI and pMayo scores at week - 8, baseline, week 16, and week 24 were compared, with 1-way variance analysis showing no statistically significant variance between clinical activity scores (CD: $P = 0.53$; UC: $P = 0.57$). Mean C-reactive protein levels also showed no statistically significant difference throughout the follow up-period (CD: $P = 0.23$; UC: $P = 0.53$). 90.3% of all patients who were in clinical remission at switch and baseline sustained clinical remission up to week

16 and 88.2% up to week 24 (figure 1). There was no significant difference between the proportions of patients in clinical remission at week 8

before switch, at switch and baseline, and at week 16 and 24 (CD: 82.6%, 80.6%, 77.5%, and 76.3%, respectively, P = 0.60; UC: 82.9%, 81.6%, 83.7%, 84.8%, respectively, P = 0.98). Clinical outcomes were not different in the cohort of patients with a previous exposure to the originator IFX (13.9% of all patients, n = 18; clinical remission rates at week 8 before switch, at switch and baseline, and at week 16 and 24 were 86.7%, 100%, 94.4%, and 93.3%, respectively; P = 0.46) or in patients with the biosimilar IFX as first IFX (82.4%, 78.5%, 77.0%, and 76.7%, respectively; P = 0.65).

No significant difference was observed in mean serum IFX TLs between switch and baseline and week 16 (5.33 and 4.70 mg/mL vs 5.69 and 4.94 mg/mL; P = 0.71). No significant differences were observed in ADA formation (overall ADA positivity: 16.2% vs 16.9% at baseline and week 16, P = 0.87; rates of high ADA positivity: 8.5% and 8.5%, P = 1).

Fourteen patients with TDM at baseline and week 16 of this cohort have previously been exposed to the originator IFX. By separately analyzing these patients, also no statistically significant difference was observed between baseline and week 16 TLs (6.51and 4.65 mg/mL vs 8.11 and 4.44 mg/mL, P = 0.25). ADA positivity rates were also identical at

baseline and week 16 (14.3%; n = 2 for both). The rate of concomitant azathioprine therapy remained unchanged during the follow-up period.

A total of 174 patients were evaluated for infusion related adverse events. Three infusion reactions occurred up to week 16 follow-up and altogether 4 infusion reactions up to week 24. No anaphylactic reaction was observed. All patients with infusion reaction had detectable ADAs at baseline and none of these patients have previously been exposed to the originator IFX.

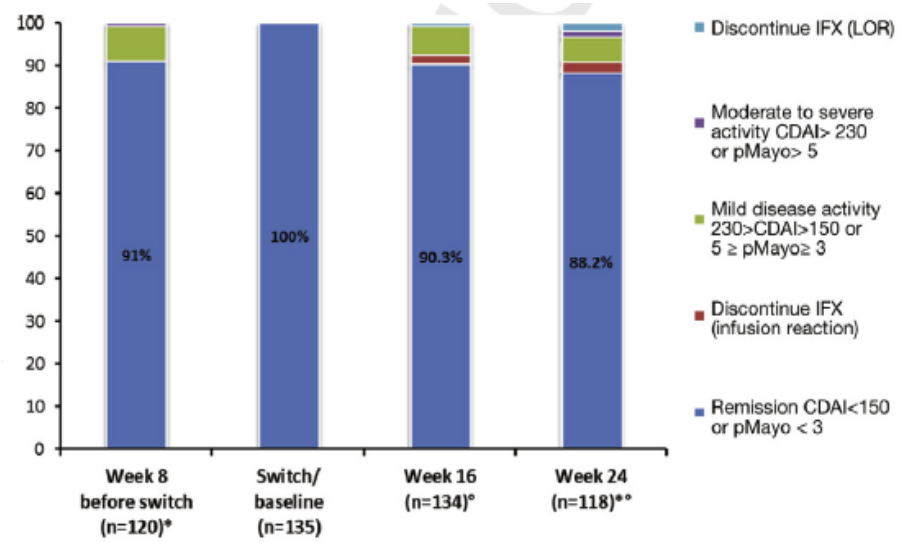

Figure 1. Clinical activity before and after reverse switch in IBD patients in remission at switch.*Week 8 data before baseline and week 24 data are only available from 3 centers. o Two patients were lost to follow-up. LOR: loss of response.

The effect of Fast-Track MRI on patient management and outcomes in Crohn's disease

A total of 90 fast-track MRIs were performed in 75 referral CD patients. Location of CD was ileo-colonic in 61%, colonic in 28%, with perianal fistulas in 56% of patients. Magnetic resonance imaging identified luminal activity, fistula, abscess and stenosis in 44.4%, 35.6%, 22.2% and 13.3% of the scans, respectively. The MRI performed on patients with clinical or biomarker activity identified intestinal as well as extraintestinal findings in a much larger proportion than in patients with clinical and biomarker remission. Fast-track MRI was followed by a change in the medical therapy (including initiation of antibiotics, corticosteroids, immunosuppressive agents and biologics) in 50.0% of all patients, with a surgery and hospitalization rates of both 21.1%.

The indication for fast-track MRI examination was active disease (clinical or biomarker activity) in 55.6% (n=50) of the patients. The MRI identified radiological activity (including mild radiological signs to severe lesions) in 94% and significant MRI activity (severe radiological lesions) in 68% (n=34) of these patients. The MRI resulted in a therapeutic strategy change in 80% of the patients with clinical or biomarker activity (94.1% vs. 50% in patients with significant/severe vs. no severe MRI radiological activity; p=0.001). The therapeutic step was accelerated (initiation of immunosuppressives or biologics) and/or

current biologic therapy was dose-optimized or switched to another biologic in a greater proportion of patients with significant MRI activity compared to patients with only a clinical/biomarker but no severe MRI activity (52.9% vs. 18.8%; p = 0.022).

Significant MRI radiological activity resulted in significantly higher surgery rates compared to patients without MRI radiological activity (50% vs. 12.5%, p = 0.013). Hospitalization rates were altogether 36%, higher in patients with severe MRI activity compared with patients without MRI activity (44.1% vs. 18.8%; p=0.057). In a sensitivity analysis, in clinically active patients with known perianal manifestation (n=34), therapeutic strategy change (92.9% vs. 50.0%, p=0.029), initiation of antibiotics (78.6% vs. 16.7%, p=0.008) and surgery (50.0% vs. 0.0%, p=0.031) rates were significantly more frequent following severe radiological findings on MRI (active fistula or abscess) compared to patients with no severe radiological activity.

Significant MRI activity was detected only in 5.0% of patients in clinical and biomarker remission, while any radiological sign of active disease was confirmed in 37.5% (n=15) of these patients (mainly discrete activity signs). Change in medical therapy was recorded in 20.0% of patients with any radiological activity on MRI, compared to 8.0% in patients with no signs of radiological disease activity (p=0.098). No surgery was required in patients with clinical and biomarker remission based on the MRI result, and only one patient

required hospitalization. Agreement between clinical activity and biomarker positivity (CRP >10mg/L) vs. significant MRI radiological activity was moderate (kappa: 0.654 and 0.59). Agreement between luminal active disease on MRI and colonoscopy was moderate (kappa: 0.652). Overall agreement between luminal active disease on MRI and other imaging methods (US or CT) assessing luminal activity was good (kappa: 0.717); however, the sample size was small.

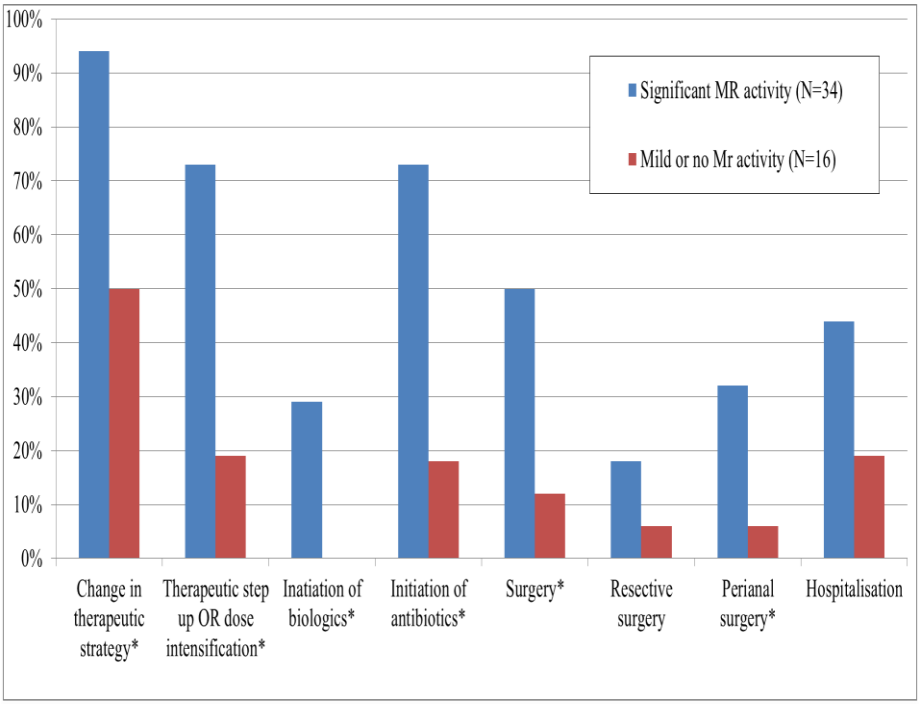

Figure 2. Change in therapeutic strategy, surgery and hospitalization rates following the MRI scans in patients with clinical or biomarker activity. * significant

Conclusions

In our multicentre prospective study to evaluate the efficacy and safety of reverse switching from the biosimilar IFX to the originator drug, we came to the following conclusions.

1, In our IBD cohort switching from the biosimilar IFX to the originator was safe.

2, During the reverse switching, the efficacy of the biological treatment was maintained.

3, No increased number of allergic reactions was observed during the reserve switching and in the follow-up period.

4, There was no change in mean serum drug levels and anti-drug antibody positivity rates during the study period .

5, Efficacy was maintained in the subgroup of patients previously exposed to the originator IFX as well, and no allergic reactions or new anti-drug antibody formation was observed after the reverse switching, suggesting that multiple switching between biosimilar and original IFX drugs is safe.

Based on our retrospective study of the role of fast-track MRI in CD patients, I make the following statements.

1, It is recommended to use fast-track MRE as a comprehensive imaging method in CD patients with complicated disease phenotype in case of clinical or biochemical activity.

2, Fast-track MRE enables more accurate, objective assessment of patients, which greatly contributes to our therapeutic decisions.

3, In CD patients without biochemical or clinical disease activity, the use of fast-track MRE for monitoring of disease activity is not recommended, because it does not provide substential new information to guide further therapeutic decisions.

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