Epidemiological data and utilization patterns of anti-TNF alpha therapy in the Hungarian ulcerative colitis population between 2012-2016

Kunovszki P[1], Szántó KJ[2], Gimesi-Országh J[1], Takács P[1], Borsi A[3], Bálint A[2], Farkas K[2], Milassin Á[2], Lakatos PL[4,5], Szamosi T[6], Molnár T[2].

1: Janssen Pharmaceutica NV, Budapest, Hungary.

2: First Department of Medicine, University of Szeged, Szeged, Hungary.

3: Janssen-Cilag Limited, High Wycombe, UK.

4: Department of Medicine, Semmelweis University, Budapest, Hungary.

5: Division of Gastroenterology, McGill University, Montreal, Canada.

6: Department of Gastroenterology, Military Hospital-State Health Centre, Budapest, Hungary.

Abstract

Background: Anti-TNF therapy is efficacious in maintenance of remission in ulcerative colitis (UC), however, long-term data on real life use of these agents are lacking.

Methods: This observational, retrospective, epidemiological study using the National Health Insurance Fund social security database aimed to understand patient characteristics and therapeutic patterns of anti-TNF therapy. Data of adult Hungarian, UC patients treated with anti-TNF agents (IFX-infliximab, ADA-adalimumab) between 2012 and 2016 were analysed.

Results: 568 UC patients were identified. Approximately 70-80% of the patients reached maintenance therapy. A large proportion of patients stopped therapy after 10 to 12 months due to the reimbursement policy. Corticosteroid use decreased significantly after the initiation of biological therapy. The dose escalation rate was 19.8% for ADA and 10.9% for IFX, respectively, and was performed earlier along the treatment timeline for patients on ADA. In the present study, the rate of primary non-response (PNR) was 11.6% and the rate of secondary loss of response (LOR) was 36.5%.

Summary: Treatment length is in correspondence with the Hungarian reimbursement policies. The mandatory stop of treatment in the reimbursement policy is suboptimal in UC

patients requiring biological therapy. The corticosteroid sparing effect of biological therapy was demonstrated.

1. Introduction

In the past decades, the prevalence of ulcerative colitis (UC) increased worldwide [1,2]. According to the epidemiologic data from North America and Europe, more than 1.5 and 2 million people are affected by inflammatory bowel diseases (IBD; UC and Crohn's disease [CD]), respectively [3]. A review based on unselected population-based cohort studies revealed the incidence of UC ranging from 0.9-24 per 100 000 person-years and the prevalence of UC varying between 2.4-294 cases per 100 000 people in Europe [4]. A recent systematic review reported the highest prevalence of IBD in Europe and in North America [5].

IBD is a chronic, disabling gastrointestinal disorder that diminishes the quality of life of the patient and puts remarkable burden on the healthcare system. Treatment algorithms and goals have changed favourably with the appearance of biological therapy in the market. The traditional step-up algorithm was shifted to the top-down or to the accelerated step-up algorithm. Thus, early introduction of immunosuppressive and biological therapies became more frequent. Infliximab (IFX) and adalimumab (ADA) are IgG1 monoclonal antibodies against tumour necrosis factor (TNF) alpha molecules, which play a key role in the inflammatory cascade. IFX was the first biological agent, which was approved by the European Medicines Agency (EMA) to treat CD in 1999, while 7 years later it was introduced for UC as well. ADA was registered in 2007 to treat CD and it began to be used in UC 5 years later. Regarding other agents, golimumab received authorization in 2013 for the treatment of UC in Switzerland and in the USA [6].

Data are available from the Inflammatory Bowel Disease Epidemiologic Database, University of Manitoba about the prevalence of anti-TNF alpha therapy among IBD patients. According to this, the cumulative prevalence of patients with current or prior anti-TNF alpha exposure in 2014 was 20.4% for CD and 6.0% for UC. In 2014, the cumulative incidence of anti-TNF alpha exposure within 5 years from the diagnosis was 23.4% in case of patients with CD and was 7.8% amongst patients with UC [7].

A population-based cohort study from Denmark analysed data of 623 IBD patients receiving IFX therapy throughout a 15-year period. They found IFX to be introduced at a younger age than the median age in the UC population. In UC patients, the median interval from first prescription of IFX to therapy discontinuation increased significantly throughout the

observational period. Median treatment length increased from 0.34 year (between 2005 and 2009) to1.11 years (between 2010 and 2014) [8].

According to a review by Rencz et al., the estimated proportion of UC patients treated with biological therapy in Central and Eastern European countries vary between 0%-6.4% [6].

In Hungary starting from late 2012, a register of special drug reimbursement (hereinafter, Patient Registry) brings us the opportunity to monitor all administrations of biological therapies. Beside other data, this registry contains data on the dose of drug and thus it is more detailed than data from the preceding times. Therefore, this analysis focuses on the time period from 2012 September to the end of 2016 that corresponds to 4 years of data follow-up.

Since the start of the current reimbursement of IFX and ADA used for IBD treatment, there is a requirement in the reimbursement and medical protocol according to which treatment has to be stopped after one year of continuous therapy in case of remission. If a later relapse occurs, the treatment can be reinitiated based on medical need. However, in case of clinical, biochemical or endoscopic activity after the one-years therapy, the patients could be kept on the therapy based on the decision of the treating physician, in which case the treatment is continued to be reimbursed. (The conditions of reimbursement are described in Hungarian ministerial decrees, the full text of which is not available in English.)

Long-term data on the real-life use of IFX and ADA in IBD is still lacking. Our manuscript focused on filling the gaps about the treatment patterns of anti-TNF alpha therapies in Hungary. Our aim was to investigate treatment length, dose-escalation, therapeutic switch and concomitant corticosteroid use in UC patients treated with these agents in our country between 2012 and 2016.

Keywords: anti-TNF therapy, corticosteroids, loss of response, primary non response, ulcerative colitis

2. Materials and methods

2.1. Data source

This is an observational, non-interventional, retrospective, epidemiological study using the National Health Insurance Fund (Hungarian acronym: NEAK) social security database that

includes data of in- and outpatient care, prescription medicine and special drug reimbursement. Database was analysed between 2012 and 2016.

2.2. Data collection

All patients suffering from UC were captured in the database based on the ICD-10 (International Classification of Diseases) diagnosis code K51. Those patients were included in the analysis who started biological therapy after September of 2012, as financial reimbursement and adequate Patient Registry is available since then. Biological therapy could be captured based on prescription data before 2012 September and patients with any during this time period were excluded from the analysis. Therefore, these patients have a record in the Patient Registry corresponding to each of their biological therapy administrations.

The date of the UC diagnosis was defined by the first UC diagnosis code appearing in the in- and outpatient care or medication database.

The start of biological therapy was defined by the date of the first Patient Registry sheet, as the first appearance means the first received biological agent.

To define the time interval elapsed from the diagnosis to the start of biological therapy, the difference of these dates were calculated and recorded.

The active substance for all biologic therapy administrations was determined based on the procedure code (ICHI – International Classification of Health Interventions). Dispense of corticosteroids was captured using ATC codes (Anatomical Therapeutic Chemical Classification System).

The drug named Remicade (IFX; later its biosimilar also appeared under the name of Inflectra) was approved in Hungary in 2006, while Humira (ADA) was approved by the second half of 2012. Starting from late 2012, these drugs are obtainable through itemized reimbursement, where a detailed documentation is required to support the responsible use of these agents.

The biological treatments of the patients were compiled into treatment episodes. A treatment episode was defined as a series of treatments from the same substance (regardless of the number of treatments), where the time between two consecutive treatments is no longer than 180 days. Every treatment episode started with the induction period which was defined differently for ADA and IFX based on the medical and reimbursement protocols. All

treatments were called maintenance therapy after the induction period. An episode could end due to three different reasons. Firstly, when the patient received no more biological treatment in the study period. Secondly, when the patient stopped biological treatment and the treatment was restarted with the same drug after more than 180 days. Thirdly, when the patient started to use a different active substance.

The length of the treatment period was defined as the time from the starting date of the induction to the date of the last registry sheet in the current treatment episode. Due to this definition, treatment length could not be calculated for those episodes which consisted of only one treatment. Furthermore, as the effect of the treatment lasts longer than the date of the last register sheet, the treatment length was slightly underestimated.

Due to the low number of patients who received more than one episode from the treatment (defined by the above mentioned criteria), only the first treatment episode could be analysed in this study.

All treatments during maintenance therapy were categorized as dose-escalated (DE) or non-dose-escalated (non-DE) treatments. A treatment was considered DE if the dose was greater than 1.5 times the median dose of the compound across all patients. All other treatments were considered to be non-DE. The DE period incorporates the time interval of all dose-escalated treatments of a patient, while the time of dose escalation was the date of the first DE treatment.

There was a possibility for patients to change medication in case of ineffectiveness as there were two different available active substances (IFX and ADA). A patient was only considered to switch when the patient started the treatment with the other agent within less than 180 days from stopping the treatment with the previous one.

A patient was considered to have a primary non-response (PNR) if their first episode of biological treatment consisted of only an induction period. The therapeutic episode could end due to treatment stopping or switching. A patient was considered to have a secondary loss of response (LOR) if the therapy was stopped, the dose was escalated or the drug was switched after the induction period of the biological therapy but before 1 year of continuous biological therapy. To check whether the therapy was stopped or switched within 1 year from the start of therapy, the end date of the last administration of the biological agent had to be estimated. In case of ADA this was calculated by adding 30 days to the date of the last registry sheet of

ADA treatment. In case of IFX 60 days were added. In both cases the treatment stop could only be ascertained if there was an at least 180-day-long follow-up period after the last registry sheet of for the current patient with the corresponding treatment. Therefore, there were some patients in case of whom PNR or LOR status could not be determined, so these patients were censored in these analyses. It was assumed that this censoring is independent from the fact whether the patient experiences PNR or LOR or not in real life, so that the bias is negligible.

Analysis of concomitant corticosteroid use was performed on the following subgroup of patients. The first biological episode of the analysed patients had to be at least 6 months long (adequate length of biological therapy) and they had to have at least 2 years of follow-up after the initiation of biological therapy. The number of corticosteroid dispensings was counted in the 2-year-period preceding and following the start of biological therapy.

2.3. Endpoints

The primary endpoint was the length of treatment with anti-TNF alpha agents and the reducing effect of biological therapy on concomitant corticosteroid usage for these patients. Secondary endpoints were the description of dose-escalation and switching of biological therapy.

2.4. Statistical analysis

Number of patients on biological therapy was described using patient counts. Demographics data were characterized using histograms and median age.

Since all patients in the study started biological therapy, there was no censoring in the time to biologic initiation data, thus it was characterized using a histogram.

Survival analysis was performed to study length of treatment, time to dose escalation and time on escalated dose, Kaplan-Meier estimators were used to characterize the survival function.

When analysing corticosteroid use, the number of corticosteroid prescriptions was not used as continuous variable, ordinal scale was assumed instead. A nonparametric Mann-Whitney test was used to compare the corticosteroid usage before and after the start of biological therapy.

The statistical analysis was performed using R.3.5.1. software.

2.5. Ethical approval

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

3. Results

3.1. Description of the patient population

The number of patients in Hungary treated with UC increased from 21,809 to 23,280 between 2012 and 2016. In total 568 UC patients treated with anti-TNF alpha agents were identified during the study period. Out of these patients 172 (30%) started with ADA, while 396 (70%) started with IFX (Inflectra: 218 and Remicade: 178). The usual onset of anti-TNF alpha therapy was between 30 and 39 years with a median age of 39 years. Furthermore, a slight majority of males (54%) was found among the biologically treated population. Demographic data of the enrolled patients are shown in Table 1.

3.2. Length of biological therapy episodes

Looking at the first therapeutic episode of all patients, a distinct drop in therapy length between 10-12 months can be observed. This is at least partly contributable to the mandatory stop rule after one year of therapy present in the NEAK reimbursement policy. Approximately 70-80% of the patients reached maintenance therapy; half of the patients stopped anti-TNF alpha therapy after one year; there is no difference between patients treated with IFX and ADA (Figure 1). Despite the reimbursement rule that requires treating physicians to stop biological treatment after one year, roughly 45% of patients continued the initial treatment.

3.3. Corticosteroid therapy before and after anti-TNF alpha therapy

Figure 2 shows the distribution of corticosteroid prescription within 2 years before and after the start of anti-TNF alpha therapy. It was found that patients used significantly less corticosteroids after starting anti-TNF alpha therapy than before ($p<0.001$). This shows that starting anti-TNF alpha therapy reduces the need of corticosteroid usage compared to pre-biological treatment period.

3.4. Other treatment characteristics

3.4.1. Time from UC diagnosis to biologics initiation

Thirty-five% of anti-TNF alpha treated patients started their first anti-TNF alpha therapy within 3 years from diagnosis. A third of these patients began anti-TNF alpha therapy within

the first year. On the other hand, 33.3% of the patients started anti-TNF alpha therapy more than 10 years after the diagnosis of UC (Figure 3).

3.4.2. Dose escalation and medication switch

Dose escalation is a potential therapeutic event only for those patients who reach maintenance therapy in a given treatment episode. Due to the low patient numbers, dose escalation analysis could only be performed in the first treatment episode for all patients. A total of 13.6% (n=77) of the patients were DE. Higher proportion of ADA treated patients (19.8%) underwent dose escalation compared to IFX treated patients (10.9%) (Figure 4). While long term likelihood of being DE was similar in both treatment arms (about 30% after 18 months), the time passed until dose escalation differed remarkably in the two agent groups. The majority of dose escalations of ADA patients occurred within the first 2 months of the therapy. On the other hand, IFX patients were mainly escalated after 1 year (Figure 4). The median time on escalated dose was 3.3 months (95% CI: 1.9-4.8 months) with no significant difference between the arms (Figure 5).

Frequency of switch was 15.7% with 89 patients switching medications. Switching was more common for previously dose escalated patients (19.5% of them switched medications).

3.4.3. Loss of response

In total 112 patients had no observable maintenance treatment on their first biological drug due to treatment stopping, switching or insufficient follow-up. Out of these patients, treatment stop could not be ascertained for 52 patients. Therefore, 60 patients out of 516 were determined to experience PNR (11.6%).

All other patients except the aforementioned 112 were at risk for experiencing LOR (456 patients in total). Out of these patients LOR status could not be determined due to insufficient follow-up for 53 patients. Among the remaining patients 147 experienced LOR and 256 did not. Therefore, there were 147 patients out of the 403 possible patients who experienced LOR (36.5%).

4. Discussion

This is a complex population-based study from Hungary describing the utilization of anti-TNF alpha therapy including treatment length, dose escalation and switching rates based on data from the National Health Insurance Fund database. We observed that anti-TNF alpha exposure is low among the Hungarian UC population; while one third of these patients started their first course of anti-TNF alpha therapy within 3 years of diagnosis. Due to the reimbursement policy, there is a distinct drop in the therapy length around 1 year, however in approximately 50% of the patients an immediate restart of the therapy was needed. Furthermore, our results proved the corticosteroid sparing effect of anti-TNF alpha therapy in real-life settings.

According to a meta-analysis from 2017, the incidence and the prevalence rates of IBD are high in Hungary; this is consistent with our results [5]. In our cohort 568 UC patients started anti-TNF alpha therapy between late 2012 and 2016, that is only about 2.5% of the total Hungarian UC population. Although use of biologics is much more common in CD than in UC all over the world, exposure to anti-TNF alpha agents among the Hungarian UC population is lower than expected – based on the prevalence values of 6.0% in Canada and 0%-6.4% in Central and Eastern European countries found in the literature [6,7]. More patients started with IFX (70%) than with ADA (30%). The usual onset of anti-TNF alpha therapy is between 30 and 39 years with a median age of 39 years. Furthermore, a slight overrepresentation of males (54%) were found among the biologically treated population. Thirty-five% of our anti-TNF alpha treated patients started their first anti-TNF alpha therapy within 3 years from diagnosis, one third of them began it within the first year. The effect of the requirement of stopping treatment after one year can be observed from the data with 55% of patients having therapy lengths of less than a year. The remaining patients were kept on therapy for a longer period of time based on the decision of the treating physician due to the persisting clinical symptoms and/or incomplete mucosal healing. Two Hungarian prospective studies assessed the disease course and frequency of relapse of UC and CD following discontinuation of IFX therapy after 1 year in patients with remission. According to these studies anti-TNF alpha therapy was restarted at a median of 4 months after discontinuation in 35% of UC patients and it was restarted at a median of 6 months after discontinuation in 45% of CD patients [9,10]. One of the main objectives of biological therapy is to reduce the corticosteroid dependency of patients, and although steroid-sparing effects were observed in vast majority of studies, real-world data are still lacking. A retrospective analysis

demonstrated that while both azathioprine and anti-TNF alpha therapy cut back corticosteroid prescriptions, patients on anti-TNF agents were more likely to be in corticosteroid-free remission through 24 months [11]. A significant decrease of corticosteroid usage could be observed in our patients with adequately long (at least 6 months) biological therapy. Dose escalation and switching is performed for patients who cannot maintain remission or lose response to the anti-TNF alpha agent. The long term (after one year) dose escalation numbers are similar for the two drugs with a total of 30% requiring dose escalation. However, most dose escalations happen relatively soon (after 1-2 months) for patients on ADA while this happens later (after 1 year) for patients on IFX. As the number of patients on therapy after one year of treatment is much lower than in the second month, the total number of dose-escalated patients on ADA is higher (19.8%) than on IFX (10.9%). Switching therapy is less common than dose escalation, 15.7% of all patients required switching, while the frequency of switch in the dose-escalated population was 19.5%. Dose escalation rates have been reported in a wide range in the literature. In a study from the United States approximately 8% of patients on ADA were dose escalated up until 1 year of treatment [12]. Another study reported higher percentages with around 20% of biologics-naïve ADA-treated patients being dose-escalated at 1 year [13]. Even higher numbers were published from a study in England where roughly 40% of ADA-treated patients had their dose escalated within the first year of treatment [14]. Our results tend to be in the middle of this range. In case of IFX the reimbursement protocol discourages dose escalation for patients following standard treatment. However, in cases where the treatment is continued after one year more freedom is given to the treating physician based on their assessment of the medical need. Our results clearly demonstrate this behaviour with dose escalations being extremely rare in the first year but the frequency increasing to the same level that of ADA later. This could indicate that many physicians consider dose escalation of IFX to be a proper therapeutic option in patients with insufficient response. Therapeutic drug monitoring would be a great tool in the management of these complicated cases, however it is not routinely used in Hungary because of the lack of reimbursement. Individualized therapy based on bioavailability and immunogenicity in these cases would be more cost-effective than dose intensification [15]. In the present study the rate of PNR was 11.6% and the rate of LOR was 36.5%. According to the literature, for anti-TNF alpha therapy PNR rates vary between clinical trials and clinical practice from 10 to 30% and the annual risk of secondary non-response from 13% for IFX to 20.3% for ADA [16]. There is limited data about LOR in UC patients. The ACT-1 and 2 trials evaluated LOR in UC patients. Clinical non-remission was 66% at week 54 in ACT-1 and 74.4% at week 30 in

ACT-2 [17]. Among our patients PNR rates are consistent with the literature data. In case of LOR the mandatory stop rule makes a reliable estimation difficult and our results may be underestimated due to the statistical method used.

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 almost complete population coverage. All patients receiving biologics in Hungary in the given timeframe could be captured. A major limitation is the retrospective nature of the study, as the primary aim of the data collection was not the clinical evaluation of patients, but to serve financial and reimbursement purposes. No data were available on clinical outcomes, such as lab values, disease severity indices or patient reported outcomes. Dosing information on corticosteroid dispensing is limited. Due to the low number of deaths in the study population, mortality could not be analysed. Due to the high cost of biological therapy yearly limits exist on the amounts that can be reimbursed in the Hungarian system. Therefore, biologic treatment is only available for patients with the most aggressive IBD phenotype. This may cause that the clinical outcomes of Hungarian patients are worse that can be observed in other western countries. It should be noted that the amount available for reimbursement continuously increased during the years studied.

Real-life data about anti-TNF alpha usage and treatment characteristics are limited worldwide. Our analysis fills in the gaps about treatment patterns of the Hungarian IBD patients, moreover these real-life data could contribute to the alteration of reimbursement protocols not only in Hungary but also in other countries. Analysis from real-life data could serve as an example not only for gastroenterologists but also for governmental institutions and serve as a feedback for the national health care system.

5. Conclusion

In this retrospective real-world data study, the treatment patterns of 568 UC patients treated with biological agents between late 2012 and 2016 were analysed. In most cases the treatment lasted for nearly a year when the majority of the patients stopped therapy, which reflects the reimbursement and medical protocols requiring them to do so. In a large proportion of UC patients – based on the decision of the treating physician and the medical need – the treatment

was continued past this time point, which might suggest that the firm one year stop policy is not optimal for UC patients requiring biological therapy. Concomitant corticosteroid usage of the patients was also analysed. It was found that for patients with adequately long biological therapy the corticosteroid usage was significantly reduced after initiation of biological therapy. Additionally, dose escalation and switching patterns within biological therapy were also analysed as secondary endpoints.

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Conflicts of interest:

P.K., J. G-O., A.Bo., P.T.: are employees/contractors of Janssen.

P.L.L.: has been a speaker and/or advisory board member: AbbVie, Arena Pharmaceuticals, Celltrion, Falk Pharma GmbH, Ferring, Genetech, Janssen, Merck, Pharmacosmos, Pfizer, Roche, Shire and Takeda and has received unrestricted research grant: AbbVie, MSD and Pfizer.

T.Sz.: has served as advisory board member for AbbVie, EGIS, Pfizer and Takeda, received speaker's honoraria from Abbvie, Takeda and Ferring and served as part time medical advisor for Hungarian National Health Insurance Fund (OEP-NEAK).

T. M.: received speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer and Teva.

K.F.: received speaker's honoraria from AbbVie, Janssen and Ferring.

A.Bá.: received speaker's honoraria from Janssen and Ferring.

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Authors' contributions:

P.K.: Research plan, research protocol, statistical analysis plan, data analysis, methods review, publication plan, publication writing and summary, approval of final publication

K.Sz.: Research plan, research overview, methods review, critical review of results and publication, final approval of publication

J. G-O.: Research plan, research protocol, statistical analysis plan, data analysis, methods review, publication plan, publication writing and summary, approval of final publication, project coordination

P.T.: Research plan, research overview, methods review, critical review of results, manuscript review, approval of final publication

A.Bo.: Research plan, research overview, methods review, critical review of results, manuscript review, approval of final publication

A.Bá.: Research plan, research overview, methods review, approval of final publication

K.F.: Research plan, research overview, methods review, approval of final publication

Á.M.: Literature overview, research plan, medical support at all steps of research, final approval of publication

P.L.L.: Methods review, medical plan and review, manuscript review, approval of final publication

T.Sz.: Literature overview, research plan, medical support at all steps of research, final approval of publication

T.M.: Methodology review, medical plan and review, manuscript review, approval of final publication

Figure legends:

Figure 1. Kaplan-Meier estimation of the length of the first episode of biological treatments with 95% confidence interval

Start: start of biological therapy, event: end of first episode, censoring: death, end of follow-up

Figure 2. Distribution of patients based on the number of corticosteroid prescriptions dispensed within the periods 2 years prior to and after the start of biological therapy

BT – biological therapy

Figure 3. Distribution of patients based on the time elapsed between the diagnosis of UC and the start of biological therapy

y – years

Figure 4. Cumulative probability function of dose escalation by time within the first episode of biological therapy with 95% confidence interval

Start: start of maintenance therapy, event: dose-escalation, censor: end of therapy, death, end of follow-up

Figure 5. Kaplan-Meier estimation of time on escalated dose with 95% confidence interval

Start: dose escalation, event: de-escalation or end of treatment, censor: death or end of follow-up while on escalated dose

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