Long-term drug survival and predictor analysis of the whole psoriatic patient population on biological therapy in Hungary

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Abstract

Persistence is an important component of therapeutic success, which depends on a variety of factors. Persistence measured under optimal conditions during clinical trials does not necessarily coincide with persistence observed in the real-world settings.

The aim of the present study was to compare persistence rate of TNF-alpha inhibitors and interleukin 12/23 inhibitor in all psoriasis patients in Hungary, as well as to analyze the predictors of persistence. Data collected from 1263 patients over a period of 46 months were subjected to a retrospective analysis. Drug survival rate has been calculated according to Kaplan-Meier analysis and Cox regression was used to study the predictors.

The overall persistence rate for the 4 biologicals exceeded 60% after 3 years. The persistence rate of ustekinumab at 3 years was 67.83%, which was superior compared to that of the TNF-alpha inhibitors, where the mean persistence rate was shown to be 50.76% ($p<0.05$). Male patients showed significantly higher persistence than females (HR = 0.76, $p<0.05$ CI: 0.63, 0.92). Age, therapy naïve status and use of concomitant MTX did not have significant effect on drug survival. Persistence rate of ustekinumab was significantly higher than that of TNF-alpha inhibitors, and among predictors, only male gender influenced persistence significantly.

Key words: biological therapy, comparison, hazard ratios, persistence, predictors, psoriasis

Introduction

Psoriasis is a common, chronic, immune-mediated skin disease. The disease and the comorbidities that frequently develop during its course not only impact the quality of life negatively, but also worsen life expectancy [1,2]. Epidemiological studies have shown that psoriasis patients have shorter life expectancy, particularly those who develop cardiovascular comorbidities [1]. Even though the disease is currently not curable, there are a number of therapeutic options which ensure a symptom-free status, although requires a long-term, often life-long treatment [3,4]. Optimal drug survival is fundamental in the management of psoriasis and comorbidities [5].

Drug survival, i.e. persistence, is a comprehensive measure of therapeutic success, which depends on a variety of factors, including efficacy, safety, tolerability and patient satisfaction [5]. Suboptimal persistence is a common and complex problem among patients with chronic diseases, including psoriasis [6, 7, 8]. Frequent switches between therapies and clinical research aiming to develop new therapeutic options to address persistence issues both confirm this [6]. An important breakthrough was the development of biological therapies, which became available for the treatment of moderate to severe psoriasis. Biological therapies that are now widely available for psoriasis patients and include the TNF-α inhibitor adalimumab, infliximab, etanercept, the IL-12/23 inhibitor ustekinumab, as well as the IL-17 inhibitor secukinumab and ixekizumab.

Drug survival rate of biologicals seems to be better compared to local and conventional systemic therapies [9]. Persistence measured under optimal (standardized) conditions in prescreened, highly motivated patient populations, using tight protocols and independent investigators during clinical trials does not necessarily coincide with the drug survival of therapies prescribed in the real-world settings [10,11]. There are studies on the short-term persistence of biological therapies used in psoriasis, however, very limited comparative evidence is available on the long-term persistence of biological therapies used in the real-world settings [12]. The objectives of this study were to analyze the characteristics of all psoriasis patients treated with any of the biological therapies currently marketed in Hungary (adalimumab, etanercept, infliximab, ustekinumab), to compare long-term drug survival of such therapies in the real-world settings, and also to assess the impact of additional factors, like patient age, gender, biological therapy naïve status or the use of methotrexate (MTX) on drug survival.

Methods

Patient enrollment

The data source for this retrospective analysis was the database of the Hungarian National Health Insurance Fund (NHIF), which ensured the comparative analysis of all relevant data collected in the real-world settings. NHIF's database covers healthcare data of the entire Hungarian population (nearly 10 million people) and allows identifying all patients in Hungary with a record of any reimbursed drug prescription and provides non-identified patient data on healthcare services and medical outcomes. Based on the available data provided by NHIF, it was possible to analyze patients' age and gender, onset of disease, the collected data of in- and outpatient care and previous therapies. As the NHIF database includes PASI and DLQI scores of psoriasis patients only since February 2012, PASI and DLQI scores were obtained from the registries of participating university centers instead of the NHIF database. In Hungary patients suffering from psoriasis are eligible for biologic treatment in case of severe disease (PASI $\geq$ 15 or BSA $\geq$ 10 or DLQI $\geq$ 10) and documented intolerance or contraindication of standard systemic treatments. Hungarian Guideline on Psoriasis Therapies is based on and synchronized with the European S3 Psoriasis Guideline in accordance with the financing protocol of the NHIF [13].

All psoriasis patients, who started at least one biological therapy in Hungary, within the 46-months study period from 1 June, 2010 to 1 April, 2014, were enrolled in this study. Data of 1574 treatment episodes of 1263 patients were analyzed (since some patients received more than one biological therapy over the study period, the number of treatment episodes exceeded the number of patients).

Treatment discontinuation was defined by the occurrence of any of the following events: termination (no more prescription) or reinduction of the biological therapy (at least 180 days pause of biological therapy until the next prescription[1]), or switching to a different biological

[1] Sensitivity analysis was carried out in order to identify the most appropriate gap length for treatment discontinuation. After a 180 day gap in the biological treatment there were only very limited number of patients who continued on the same treatment with no other biological treatment in between. These cases were considered as reinduction of biological therapy.

therapy. There were several reasons of treatment discontinuation however this kind of data were not captured in the NHIF registry. Since the authors have used the database of the NHIF no information was available on the reason of therapy discontinuation. Data were censored for patients where death of any cause occurred over the study period.

Statistical methods applied

Kaplan-Meier survival curve was used for the comparative analysis of drug survival. Cox proportional hazard model was applied to analyze the impact of patient age, gender, biological therapy naïve status and additional MTX therapy on drug survival. In order to compare patients' baseline characteristics, conservative WALD test was used. ANOVA test, i.e. two-factor variance analysis was used to compare PASI and DLQI scores of treated patients as these are continuous variables. Mean PASI and DLQI scores were calculated using data collected from 641 patients treated by the 4 university centers.

Results

Patients' baseline characteristics

Data collected from a total number of 1263 patients were analyzed. Demographic data of patients are shown in *Table 1*.

Although the vast majority of the enrolled patients, (n=972, 76.96%) received only one biological therapy over the study period, 18.69% (n=236) and 4.35% (n=55) of the patients were administered 2 and 3 or more biological therapies, respectively. Since certain patients could have received several biological therapies due to the therapeutic switches, the number of treatment episodes (1574) exceeded the total patient number. All further data will refer to treatment episodes.

Patients' characteristics were also analyzed and compared between subgroups receiving different biological therapies (*Table 2*). The most frequently administered therapies were adalimumab and ustekinumab (n=491 and n=487, respectively), followed by etanercept (n=330), and infliximab (n=266) The analysis of each therapeutic groups showed that the distribution by gender, age and additional MTX usage was comparable among the different therapeutic groups, however, the ratio of biological therapy naïve patients was significantly different between the infliximab and adalimumab groups as well as between the ustekinumab and TNF-alpha inhibitors groups ($p<0.05$). *Table 2* shows side-by-side comparison of data of various treatment groups comparing patient age, gender, additional MTX therapy, and biological therapy naïve status. Possible inhomogeneities in different treatment groups were handled by using all of these 4 grouping variables as covariates in the fitted Cox models, hence the findings on drug survival analysis were not impacted by them. The comparison of PASI ($p=0.18$) and DLQI ($p=0.50$) scores showed no significant differences among the 4 subgroups using different biological therapies.

Drug survival of biological therapies

The persistence was calculated by using the Kaplan-Meier method, and illustrated as a survival curve (*Figure 1*). The results of the database analysis showed that the drug survival rate of biological therapies in psoriasis patients is high as a whole, since the overall survival rates are 79.70%, 68.52%, and 60.75% in the first, second, and third year of therapy, respectively.

The cumulative data of the 3 TNF-alpha inhibitors showed that drug survival probability was 73.28% in the first year, which dropped to 60.22% in the second year to decrease as low as 50.76% in the third year.

Kaplan-Meier survival analysis of the individual TNF-alpha inhibitors showed that drug survival of etanercept was 71.96% in the first year, which dropped to 60.03% one year later to reach 49.49% after the third year. Drug survival of adalimumab and infliximab was 68.98% and 70.92% in the first year, which dropped to 58.13% and 49.79% one year later to reach 51.95% and 36.26% after the third year respectively. The comparison of the drug survival rates of the 3

TNF-alpha inhibitors showed that adalimumab had the highest probability of patients staying on the therapy for three consecutive years, although based on Cox model results no significant difference among the 3 therapies could be detected.

Drug survival rate of ustekinumab was 86.50% in the first year, 74.17% in the second year, and 67.83% after the third year. The comparison of drug survival rates of ustekinumab and TNF-alpha inhibitors showed that the persistence of ustekinumab was significantly higher if persistence was compared head-to-head with the TNF-alpha inhibitors ($p<0.05$), and this difference also persisted if ustekinumab was compared to the cumulative data of the 3 TNF-alpha inhibitors ($p<0.05$).

Predictors of biological survival

The Cox regression analysis of the impact of predictors such as patient age, gender, biological therapy naïve status and additional MTX use on persistence is shown in *Figure 2*. The analysis of all biological therapies together revealed that the probability of staying on the therapy was significantly higher in male patients than in female patients ($p < 0.05$, CI: 0.63, 0.92). Therapy naïve status, older age and the use of MTX all decreased the risk of dropping out of therapy, although the impact was not significant (*Figure 2*).

The analysis of the cumulative data of all TNF-alpha inhibitor therapies revealed that the impact of patient gender was significant on drug survival: the risk of discontinuing the therapy was 0.71 times lower for male patients compared with female patients. (HR=0.71, $p<0.05$, CI: 0.58, 0.87).

The analysis of the individual therapy groups revealed the following: male gender had a favorable impact on the persistence of adalimumab (HR=0.73, $p<0.05$ CI: 0.54, 0.99) and infliximab (HR=0.71, $p<0.05$, CI: 0.49, 1) but did not influence the persistence of etanercept. Patients over 40 years on etanercept showed a significantly better persistence on the drug than patients younger than 40 years of age (HR=0.57, $p<0.05$, CI: 0.4, 0.81). None of the investigated predictors had a significant impact on drug survival of ustekinumab.

Discussion

Suboptimal persistence was identified as a significant drawback in the management of psoriatic patients, which considerably hinders successful therapy, and can result in therapy discontinuation and increased treatment costs [6,7]. No conclusive findings have been reached so far regarding the long-term drug survival rates of biological therapies in psoriasis and predictors of their persistence. This study is the first long-term study performed in Hungary on the whole psoriatic patient population treated with biologicals, to analyze the drug survival of all available biological therapies and to investigate predictors of persistence in the real-life settings. A further advantage of this study is that this is the first comprehensive analysis on this topic in the literature using the database of the NHIF of a given country.

The analysis of the present study population showed that adalimumab and ustekinumab were administered to almost equal numbers of patients, while infliximab and etanercept were also used in identical proportions, although less commonly than the first two agents. Since all four biological therapies can be used under the same circumstances in Hungary, the choice of drug depended mostly on dermatologists' preferences. The comparison of the subgroups receiving different biological therapies revealed that although there were certain differences among the 4 therapy groups in terms of patients' biological therapy naïve status, ultimately this factor didn't prove to have statistically meaningful effect on drug persistence rate or on predictor analysis, since the statistical methods have addressed this issue. At the same time, no significant differences were found in terms of PASI and DLQI scores across the subgroups of patients on different biologicals.

The available literature has already shown, that biological therapies used in psoriasis have superior drug survival rates compared to the rates seen with conventional systemic therapies [9]. Nevertheless, until recently there was only a lack of data obtained on large patient population treated for long time with TNF-alpha inhibitors and IL-12/23 inhibitor in the real-life settings [11, 14]. *Table 3* summarizes all the studies published so far, where data were collected from large patient population of 2 or more centers, the follow-up period was at least one year, and the authors compared at least 3 or more biological therapies. The list includes 5 prospective registry-based studies and 3 retrospective studies [5,11,15,16,17,18,19]. *Table 3* shows, that those studies which included ustekinumab have found drug survival of ustekinumab superior to the drug survival of TNF-alpha inhibitors. The largest study was published by Menter et al. analyzing data of 4000 patients taken from the PSOLAR registry, and their results indicated that drug

survival of ustekinumab was better than that of TNF-inhibitors for both biological-naïve and biological-experienced patients with psoriasis [19]. This concurs with the results from the British register (BADBIR) of 3523 bionaïve patients, where the drug survival rate of ustekinumab has been found nearly 80% at 3 years, which is significantly higher than that seen with TNF-inhibitors [16]. Gniadecki et al. has also performed an updated study involving 1277 psoriasis patients treated with biological therapy and found that ustekinumab had the highest survival rate (81.9%) at 4 years, followed by adalimumab and infliximab. Between the TNF-inhibitors no significant differences were detected [11]. Our results are comparable to the above investigations, and showed that drug survival rates of biologic therapies were excellent compared to other therapies, even if they diminished over time: 79.70% after the first year, 68.52% after the second year and 60% after the third year. At 3 years, drug survival rates were 67.83% of ustekinumab, 51.95% of adalimumab, 49.49% of etanercept, and 36.26% of infliximab. Our findings also showed that drug survival of ustekinumab was superior to TNF-alpha inhibitors, and the significant difference persisted over the 3-year study period. Adalimumab was shown to have the highest drug survival rate of all TNF- inhibitors studied, however, no significant difference was found among these drugs over the 46 months of the study period.

In addition to the analysis of persistence rates, it is also very important to explore predictors of drug survival. No conclusive evidence has yet been provided on the predictors of biological drug survival in psoriasis. Studies done so far discussed the role of several factors such as PASI, DLQI, comorbidities, age, gender, weight, disease onset, duration of psoriasis, presence of psoriatic arthritis, concomitant MTX or biological therapy naïve status and smoking. In *Table 4* we summarized results of long-term survival analyses performed on large psoriasis patient populations, investigating predictors of biological therapies only [11,15,17,19,20]. Three studies have shown that female gender is a predictor of discontinuation of biological therapies, [11,17,19] however Menter's data are not directly comparable with the aforementioned studies since these authors analyzed biological naïve and experienced patients' predictors separately. On the other hand other predictors of discontinuation like previous treatment with biologics, smoking status, higher DLQI, strict adherence to approved dose, presence of comorbidities, were detected only in one of the aforementioned investigations [11,15,17,19,20].

In the present study factors which could be extracted from the database of the NFIH were investigated. In accordance with the aforementioned authors, we could demonstrate the positive impact of male gender on the persistence of infliximab and adalimumab, while it had no effect on the persistence of ustekinumab and etanercept. It is not yet clear how gender impacts the persistence of biological therapy in psoriasis, but remarkably, female rheumatoid arthritis patients are also more likely to discontinue therapy than males [21]. Possible hypothetical explanations could be that female patients may develop anti-drug antibodies more frequently resulting in decreased therapeutic efficacy, or alternatively, psychological factors, such as dissatisfaction with treatment, may play more important role in females, but until now comparative studies were not performed.

In our study in the etanercept group, patients over 40 years were more likely to stay on the therapy than their younger peers. To our knowledge, no other previous investigations showed similar effect of age on the persistence of biological therapies.

In our study biological naive status and the use of MTX all decreased the risk of dropping out of therapy, although the impact was not significant. Biological therapy naïve status was shown to be a positive predictor for persistence in psoriasis by Gniadecki et al., and, similarly, Lopez-Ferrer could also demonstrate reduction of adalimumab drug survival in patients with prior exposure to another TNF-alpha inhibitor. On the other hand, there are studies which, similar to the current study did not find previous biological therapy usage as a negative predictor of persistence [11,15,19,20,23]. Although concomitant MTX usage has been shown to be associated with a better persistence of biologicals in rheumatological settings, there is no conclusive evidence in psoriasis about additional MTX as a positive predictor [24,25]. In a systematic review Bezooijen et al. selected eight studies, which generally showed that combination therapy of biologicals and MTX had higher efficacy than biological monotherapy, which could also indicate a positive effect of MTX on the drug survival, however, persistence was not investigated in this study [26]. On the other hand, Menter and colleagues unexpectedly reported that patients receiving MTX were significantly more likely to discontinue biological treatment compared with those without concomitant MTX in bionaïve group, but not in biologic experienced patients [19]. Our present study did not show any significant impact of the addition of MTX to the biological therapy on drug survival rates of any of the biological drugs studied.

Based on the findings of this study drug survival rates of biologic therapies can be regarded as excellent as the vast majority of the patients (nearly 80%) received only one biological over the 3 years' study period, and the mean survival rate did not diminish below 60% even after 3 years. The IL-12/23 inhibitor ustekinumab was shown to have significantly better drug survival rate than the TNF-alpha inhibitors, and when analyzing consolidated data of all assessed biologic therapies, male patients had better persistence than female patients. One of the advantages of the present study is that it is based on real-life data from the NHIF database, which allowed to analyze the whole psoriatic patient population treated with biological therapy in Hungary over a long period of time.

Limitations of the study

This is a retrospective analysis. Since the authors have used the database of the NHIF no information is available on the reason of therapy discontinuation. It is also worthwhile mentioning that while there is a patient support program for ustekinumab with potential impact on drug survival rates, there is no information available as to the existence of similar programs for the TNF-inhibitors. An additional limitation of the study is that the NHIF database did not include the PASI and DLQI scores of patients on biological therapies, and, therefore, such data were taken from the databases of the participant university centers, and, as such, the data do not cover the full patient population.

Disclosure. The use of NHIF database is not free of charge, the costs of using the database had been provided by Janssen-Cilag Hungary Ltd..The sponsor of the study did not participate in the data collection and data analysis. *Conflict of interest:* András Borsi and Péter Takács are an employees of Janssen-Cilag Ltd. Hungary. The research leading to the study results has received funding from Janssen-Cilag Hungary Ltd., Budapest, Hungary. Éva Remenyik has been supported by Janssen-Cilag and Abbvie for scientific international conference attendance. Lajos Kemény is paid consultant for Janssen and Novartis, speaker for Janssen, Novartis, Galderma, Ewopharma. Sarolta Kárpáti is paid consultant for Janssen, Abbvie. Péter Holló has received consultant or lecture fees from Abbvie, Janssen, MSD and Pfizer. Norbert Wikonkál served as a consultant and advisory board member for companies – Pfizer, MSD, Abbvie, Janssen-Cilag, Lilly, Amgen – that work on field of biological therapies in dermatology. Rolland Gyulai have received consultancy/speaker honoraria from Abbvie, Janssen-Cilag, MSD, Novartis, Pfizer, Bristol-Myers Squibb, and Roche, and has been reimbursed for international conference

attendance by Abbvie, Janssen-Cilag, MSD, Novartis, and Pfizer. Pál Rakonczai and Tamás Balázs are employees of Healthware Consulting Ltd an independent consulting company. Healtware Consulting Ltd which received funding for contribution to the study design and data analyses. Andrea Szegedi is paid consultant for Janssen, Novartis, speaker for Janssen, Novartis, Abbvie, Ewopharma.

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Tables and figures

Table 1 Characteristics of the study population

Number of patients	**1263**
Mean age in years (SD)	**49.3 (14.3)**
Male / female (%)	**61.3 / 38.7**
Patients under 40 years / 40 years or above (%)	**29.3 / 70.7**
Biological therapy naïve / previously treated (%)	**81.3 / 18.7**
Number of patients receiving MTX in addition to the biological therapy	**97**
Mean PASI (SD)	**20.5 (6.4)**
Mean DLQI (SD)	**20.0 (5.8)**

Table 2 Baseline characteristics of patients receiving different biological therapies and pairwise comparison of the 4 groups regarding gender, age, ratio of biological naïve patients and MTX usage

Therapy	Adalimumab	Etanercept	Infliximab	Ustekinumab
Treatment episodes (1574)	491 (31.2%)	330 (21.0%)	266 (16.8%)	487 (31.0%)
Mean age (SD)	47.24 (13.77)	47.55 (15.39)	49.92 (13.63)	47.71 (13.31)
Male / Female %	59.1% / 40.9	56.4% / 43.6	64.3% / 35.7	61.4% / 38.6
Patients under 40 years / 40 years or above (%)	33.0 / 67.0	31.5 / 68.5	22.9 / 77.1	31.2 / 68.8
Biological therapy naïve / previously treated (%)	64.4 / 35.6	73.2 / 26.8	77.8 / 22.2	50.1 / 49.9
Patients receiving methotrexate in addition to the biological therapy (treatment episode)	40	16	26	32
P values of the conservative Wald tests, adjusted for the pairwise comparison of the proportion of gender				
Adalimumab	-	1	1	1
Etanercept	1	-	0.972	1
Infliximab	1	0.972	-	1
Ustekinumab	1	1	1	-
age groups				
Adalimumab	-	1	0.192	1
Etanercept	1	-	0.385	1
Infliximab	0.192	0.385	-	0.385
Ustekinumab	1	1	0.385	-
biological naïve patients				
Adalimumab	-	0.106	0.012*	0.004*
Etanercept	0.106	-	0.356	<0.001*
Infliximab	0.012*	0.356	-	<0.001*
Ustekinumab	0.004*	<0.001*	<0.001*	-
patients receiving MTX in addition to the biological therapy				
Adalimumab	-	0.85	1	1
Etanercept	0.85	-	0.6	1
Infliximab	1	0.6	-	1
Ustekinumab	1	1	1	-

Data are reported for treatment episodes

*significant differences

Table 3 Studies on long term drug survival of biological therapies in psoriasis

Study	Biologics	Patients/Treatment periods	Follow-up time (months)	Best survival	Source/ regimen
R. Gniadecki et al. (2011)	ADA, ETN, INF	747 patients/882 treatment episodes	48	INF (70%)	DERMBIO; Danish prospective registry
M. Esposito et al. (2013)	ADA, ETN, INF	650 patients	28.9 ± 15.4	ETN (72.6%)	Retrospective analysis from three Italian referral centers
van der Reek et al. (2014)	ADA, ETN, UST	249 treatment episodes	12	UST (85%)	Bio-CAPTURE Dutch prospective registry
R.B. Warren et al. (2015)	ADA, ETN, INF, UST	3523 patients	36	UST	BADBIR registry; Prospective British cohort study
R. Gniadecki et al. (2015)	ADA, ETN, INF, UST	1277 patients/1867 treatment episodes	followed for up to 10 years	UST (81.9% after 5 years)	DERMBIO Danish prospective registry
E. Vilarrasa et al. (2016)	ADA, ETN, INF, UST	427 patients/703 treatment episodes	48	UST	retrospective study, from 2 Spanish center
A. Menter et al (2016)	ADA, ETN, INF, UST	4000 patients	74	UST	PSOLAR; prospective registry from USA and European countries
L. Pogácsás et al. (2016)	ADA, ETN, INF, UST	1263 patients/1574 treatment episodes	46	UST 67.83%	retrospective study, database of NHIF, Hungary

Data of those studies are summarized, which investigated persistence of at least 3 biologicals and were collected on large psoriasis patient population of 2 or more centers and over long follow up period (least one year). IFN: infliximab, ADA: adalimumab, ETN: etanercept, UST: ustekinumab

Table 4 Studies on the predictors of biological therapies in psoriasis

Study	Biologics	Examined predictors/covariates	Significant covariates
R. Gniadecki et al. (2015)	INF, ADA, ETN, UST 1277 patients/1867 treatment episodes	age, sex, previous biologic treatment, weight, duration of psoriasis, presence of PsA, baseline PASI and DLQI, concomitant MTX, number of co-morbidities	**predictors of discontinuation:** female gender; previous biologic treatment
R.B. Warren et al. (2015)	INF, ADA, ETN, UST 3523 patients	age, sex, BMI, smoking status, presence of PsA, number of co-morbidities, disease duration, disease onset, PASI, DLQI, unstable psoriasis, concomitant MTX, concomitant cyclosporine	**predictors of discontinuation**: female gender, being current smoker, higher DLQI **predictors of drug survival**: presence of PsA
A. Menter et al. (2016)	INF, ADA, ETN, UST 4000 patients	age, gender, ethnicity, BMI, familial psoriasis history, smoking status, alcohol use status, duration of psoriasis, age at the diagnosis of psoriasis, presence of PsA, study site/geographic region, history of immunmodulator use, types of insurance, previous biologic treatment, reasons for discontinuation of prior biologics, PSA, concomitant MTX use	**predictors of discontinuation:** in bio naïve patients: concomitant MTX, female gender and geographic region (North America vs. Latin America)
E. Vilarrasa et al. (2016)	INF, ADA, ETN, UST 427 patients	sex, presence of PsA, biologic naïve status, use of combination treatment, weight, strict adherence to approved doses, PASI75 and PASI 90 response	**predictors of discontinuation** obesity, strict adherence to approved doses; **predictors of drug survival:** PASI75 and PASI90 response at week 16

A. Jacobi et al. (2016)	INF, ADA, ETN, UST, Efalizumab 125 treatment episodes	biologic naïve status, presence of PsA, and comorbidity with the presence of metabolic syndrome	**predictors of discontinuation:** comorbidities **predictors of drug survival:** presence of PsA
L. Pogácsás et al. (2016)	INF, ADA, ETN, UST 1263 patients/1574 treatment episodes	gender, age, additional MTX therapy, biologic naïve status	**predictors of discontinuation:** female gender

Data of those studies are summarized, which investigated predictors of at least 3 biologicals and were collected on large psoriasis patient population and over long follow up period (least one year).

IFN: infliximab, ADA: adalimumab, ETN: etanercept, UST: ustekinumab MTX: methotrexate

PASI: psoriasis area severity index, DLQI: Dermatology Life Quality Index

PSA: Physician's Global Assessment

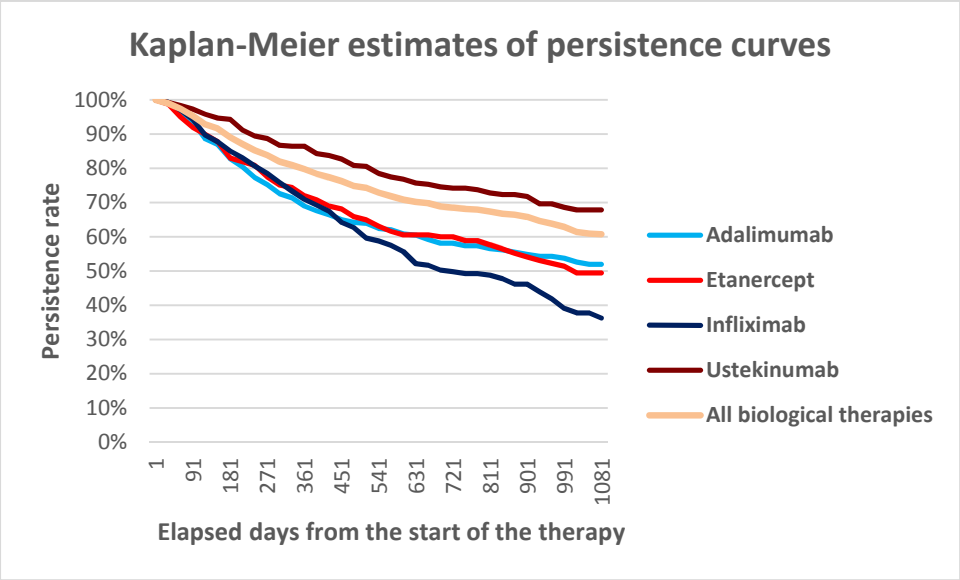

Fig. 1. Kaplan-Meier survival curve of the 4 biologicals individually and in summary (all biological therapies). Data include 1574 treatment episodes. 491 adalimumab treatment series, 330 etanercept series, 266 infliximab series, and 487 ustekinumab series.

Predictors of biological survival

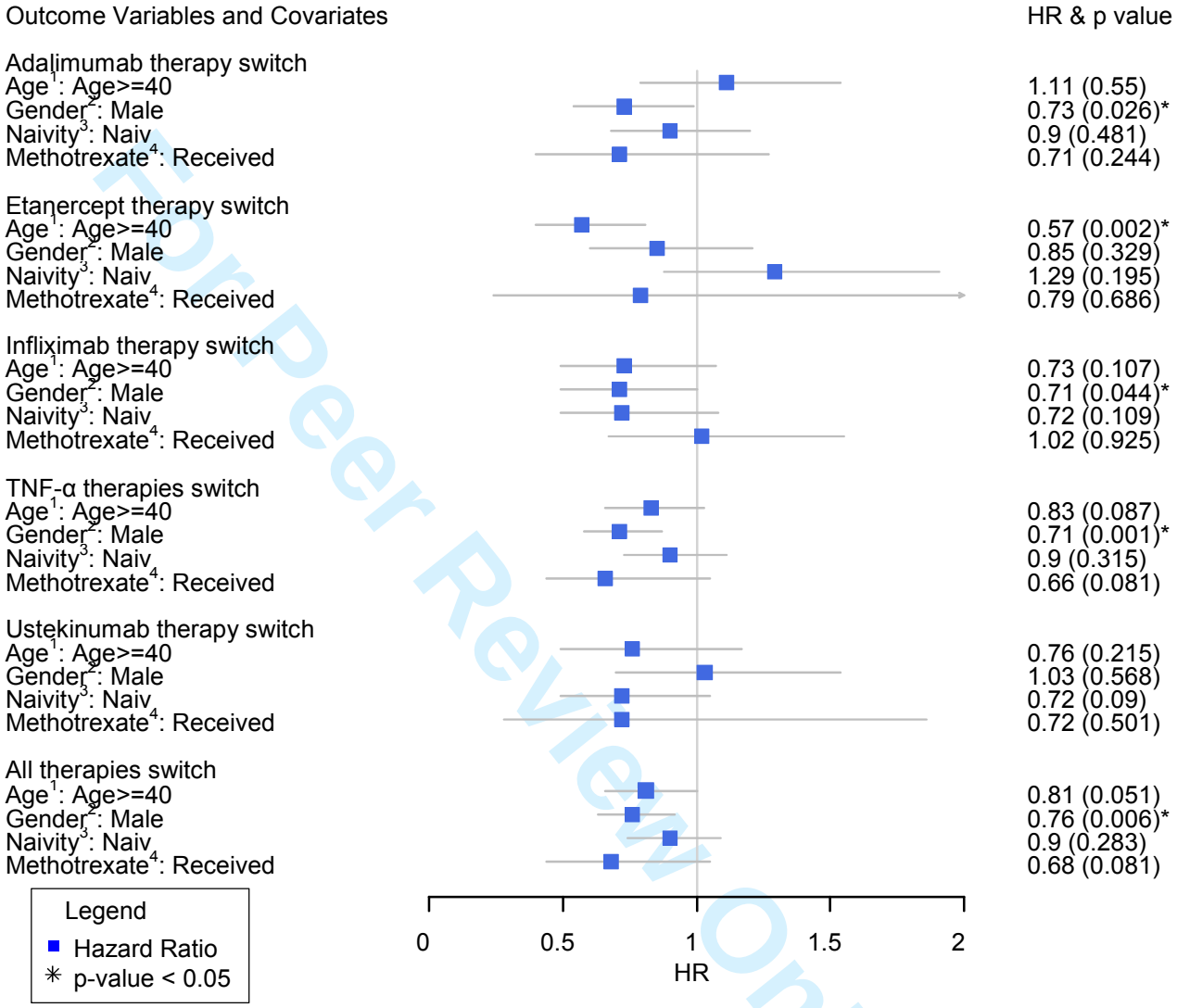

Fig. 2. Multivariate analysis of predictors on biological therapies' persistence rate (Cox proportional hazard and regression model). The figure shows the risk of drop out of therapy by predictors such as patient age, gender, biological therapy naïve status and additional MTX usage.

[1]Reference category: Age<=40

[2]Reference category: female gender

[3]Reference category: biological-experienced patients

[4]Reference category: patients who do not receive MTX

Long-term drug survival and predictor analysis of the whole psoriatic patient population on biological therapy in Hungary

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Key words: biological therapy, comparison, hazard ratios, persistence, predictors, psoriasis

Long-term drug survival and predictor analysis of the whole psoriatic patient population on biological therapy in Hungary

Abstract

Persistence is an important component of therapeutic success, which depends on a variety of factors. Persistence measured under optimal conditions during clinical trials does not necessarily coincide with persistence observed in the real-world settings.

The aim of the present study was to compare persistence rate of TNF-alpha inhibitors and interleukin 12/23 inhibitor in all psoriasis patients in Hungary, as well as to analyze the predictors of persistence. Data collected from 1263 patients over a period of 46 months were subjected to a retrospective analysis. Drug survival rate has been calculated according to Kaplan-Meier analysis and Cox regression was used to study the predictors.

The overall persistence rate for the 4 biologicals exceeded 60% after 3 years. The persistence rate of ustekinumab at 3 years was 67.83%, which was superior compared to that of the TNF-alpha inhibitors, where the mean persistence rate was shown to be 50.76% ($p<0.05$). Male patients showed significantly higher persistence than females (HR = 0.76, $p<0.05$ CI: 0.63, 0.92). Age, therapy naïve status and use of concomitant MTX did not have significant effect on drug survival. Persistence rate of ustekinumab was significantly higher than that of TNF-alpha inhibitors, and among predictors, only male gender influenced persistence significantly.

Key words: biological therapy, comparison, hazard ratios, persistence, predictors, psoriasis

Introduction

Psoriasis is a common, chronic, immune-mediated skin disease. The disease and the comorbidities that frequently develop during its course not only impact the quality of life negatively, but also worsen life expectancy [1,2]. Epidemiological studies have shown that psoriasis patients have shorter life expectancy, particularly those who develop cardiovascular comorbidities [1]. Even though the disease is currently not curable, there are a number of therapeutic options which ensure a symptom-free status, although requires a long-term, often life-long treatment [3,4]. Optimal drug survival is fundamental in the management of psoriasis and comorbidities [5].

Drug survival, i.e. persistence, is a comprehensive measure of therapeutic success, which depends on a variety of factors, including efficacy, safety, tolerability and patient satisfaction [5]. Suboptimal persistence is a common and complex problem among patients with chronic diseases, including psoriasis [6, 7, 8]. Frequent switches between therapies and clinical research aiming to develop new therapeutic options to address persistence issues both confirm this [6]. An important breakthrough was the development of biological therapies, which became available for the treatment of moderate to severe psoriasis. Biological therapies that are now widely available for psoriasis patients and include the TNF-α inhibitor adalimumab, infliximab, etanercept, the IL-12/23 inhibitor ustekinumab, as well as the IL-17 inhibitor secukinumab and ixekizumab.

Drug survival rate of biologicals seems to be better compared to local and conventional systemic therapies [9]. Persistence measured under optimal (standardized) conditions in prescreened, highly motivated patient populations, using tight protocols and independent investigators during clinical trials does not necessarily coincide with the drug survival of therapies prescribed in the real-world settings [10,11]. There are studies on the short-term persistence of biological therapies used in psoriasis, however, very limited comparative evidence is available on the long-term persistence of biological therapies used in the real-world settings [12]. The objectives of this study were to analyze the characteristics of all psoriasis patients treated with any of the biological therapies currently marketed in Hungary (adalimumab, etanercept, infliximab, ustekinumab), to compare long-term drug survival of such therapies in the real-world settings, and also to assess the impact of additional factors, like patient age, gender, biological therapy naïve status or the use of methotrexate (MTX) on drug survival.

Methods

Patient enrollment

The data source for this retrospective analysis was the database of the Hungarian National Health Insurance Fund (NHIF), which ensured the comparative analysis of all relevant data collected in the real-world settings. NHIF's database covers healthcare data of the entire Hungarian population (nearly 10 million people) and allows identifying all patients in Hungary with a record of any reimbursed drug prescription and provides non-identified patient data on healthcare services and medical outcomes. Based on the available data provided by NHIF, it was possible to analyze patients' age and gender, onset of disease, the collected data of in- and outpatient care and previous therapies. As the NHIF database includes PASI and DLQI scores of psoriasis patients only since February 2012, PASI and DLQI scores were obtained from the registries of participating university centers instead of the NHIF database. In Hungary patients suffering from psoriasis are eligible for biologic treatment in case of severe disease (PASI $\geq$ 15 or BSA $\geq$ 10 or DLQI $\geq$ 10) and documented intolerance or contraindication of standard systemic treatments. Hungarian Guideline on Psoriasis Therapies is based on and synchronized with the European S3 Psoriasis Guideline in accordance with the financing protocol of the NHIF [13].

All psoriasis patients, who started at least one biological therapy in Hungary, within the 46-months study period from 1 June, 2010 to 1 April, 2014, were enrolled in this study. Data of 1574 treatment episodes of 1263 patients were analyzed (since some patients received more than one biological therapy over the study period, the number of treatment episodes exceeded the number of patients).

Treatment discontinuation was defined by the occurrence of any of the following events: termination (no more prescription) or reinduction of the biological therapy (at least 180 days pause of biological therapy until the next prescription[1]), or switching to a different biological

[1] Sensitivity analysis was carried out in order to identify the most appropriate gap length for treatment discontinuation. After a 180 day gap in the biological treatment there were only very limited number of patients who continued on the same treatment with no other biological treatment in between. These cases were considered as reinduction of biological therapy.

therapy. There were several reasons of treatment discontinuation however this kind of data were not captured in the NHIF registry. Since the authors have used the database of the NHIF no information was available on the reason of therapy discontinuation. Data were censored for patients where death of any cause occurred over the study period.

Statistical methods applied

Kaplan-Meier survival curve was used for the comparative analysis of drug survival. Cox proportional hazard model was applied to analyze the impact of patient age, gender, biological therapy naïve status and additional MTX therapy on drug survival. In order to compare patients' baseline characteristics, conservative WALD test was used. ANOVA test, i.e. two-factor variance analysis was used to compare PASI and DLQI scores of treated patients as these are continuous variables. Mean PASI and DLQI scores were calculated using data collected from 641 patients treated by the 4 university centers.

Results

Patients' baseline characteristics

Data collected from a total number of 1263 patients were analyzed. Demographic data of patients are shown in *Table 1*.

Although the vast majority of the enrolled patients, (n=972, 76.96%) received only one biological therapy over the study period, 18.69% (n=236) and 4.35% (n=55) of the patients were administered 2 and 3 or more biological therapies, respectively. Since certain patients could have received several biological therapies due to the therapeutic switches, the number of treatment episodes (1574) exceeded the total patient number. All further data will refer to treatment episodes.

Patients' characteristics were also analyzed and compared between subgroups receiving different biological therapies (*Table 2*). The most frequently administered therapies were adalimumab and ustekinumab (n=491 and n=487, respectively), followed by etanercept (n=330), and infliximab (n=266) The analysis of each therapeutic groups showed that the distribution by gender, age and additional MTX usage was comparable among the different therapeutic groups, however, the ratio of biological therapy naïve patients was significantly different between the infliximab and adalimumab groups as well as between the ustekinumab and TNF-alpha inhibitors groups ($p<0.05$). *Table 2* shows side-by-side comparison of data of various treatment groups comparing patient age, gender, additional MTX therapy, and biological therapy naïve status. Possible inhomogeneities in different treatment groups were handled by using all of these 4 grouping variables as covariates in the fitted Cox models, hence the findings on drug survival analysis were not impacted by them. The comparison of PASI ($p=0.18$) and DLQI ($p=0.50$) scores showed no significant differences among the 4 subgroups using different biological therapies.

Drug survival of biological therapies

The persistence was calculated by using the Kaplan-Meier method, and illustrated as a survival curve (*Figure 1*). The results of the database analysis showed that the drug survival rate of biological therapies in psoriasis patients is high as a whole, since the overall survival rates are 79.70%, 68.52%, and 60.75% in the first, second, and third year of therapy, respectively.

The cumulative data of the 3 TNF-alpha inhibitors showed that drug survival probability was 73.28% in the first year, which dropped to 60.22% in the second year to decrease as low as 50.76% in the third year.

Kaplan-Meier survival analysis of the individual TNF-alpha inhibitors showed that drug survival of etanercept was 71.96% in the first year, which dropped to 60.03% one year later to reach 49.49% after the third year. Drug survival of adalimumab and infliximab was 68.98% and 70.92% in the first year, which dropped to 58.13% and 49.79% one year later to reach 51.95% and 36.26% after the third year respectively. The comparison of the drug survival rates of the 3

TNF-alpha inhibitors showed that adalimumab had the highest probability of patients staying on the therapy for three consecutive years, although based on Cox model results no significant difference among the 3 therapies could be detected.

Drug survival rate of ustekinumab was 86.50% in the first year, 74.17% in the second year, and 67.83% after the third year. The comparison of drug survival rates of ustekinumab and TNF-alpha inhibitors showed that the persistence of ustekinumab was significantly higher if persistence was compared head-to-head with the TNF-alpha inhibitors ($p<0.05$), and this difference also persisted if ustekinumab was compared to the cumulative data of the 3 TNF-alpha inhibitors ($p<0.05$).

Predictors of biological survival

The Cox regression analysis of the impact of predictors such as patient age, gender, biological therapy naïve status and additional MTX use on persistence is shown in *Figure 2*. The analysis of all biological therapies together revealed that the probability of staying on the therapy was significantly higher in male patients than in female patients ($p < 0.05$, CI: 0.63, 0.92). Therapy naïve status, older age and the use of MTX all decreased the risk of dropping out of therapy, although the impact was not significant (*Figure 2*).

The analysis of the cumulative data of all TNF-alpha inhibitor therapies revealed that the impact of patient gender was significant on drug survival: the risk of discontinuing the therapy was 0.71 times lower for male patients compared with female patients. (HR=0.71, $p<0.05$, CI: 0.58, 0.87).

The analysis of the individual therapy groups revealed the following: male gender had a favorable impact on the persistence of adalimumab (HR=0.73, $p<0.05$ CI: 0.54, 0.99) and infliximab (HR=0.71, $p<0.05$, CI: 0.49, 1) but did not influence the persistence of etanercept. Patients over 40 years on etanercept showed a significantly better persistence on the drug than patients younger than 40 years of age (HR=0.57, $p<0.05$, CI: 0.4, 0.81). None of the investigated predictors had a significant impact on drug survival of ustekinumab.

Discussion

Suboptimal persistence was identified as a significant drawback in the management of psoriatic patients, which considerably hinders successful therapy, and can result in therapy discontinuation and increased treatment costs [6,7]. No conclusive findings have been reached so far regarding the long-term drug survival rates of biological therapies in psoriasis and predictors of their persistence. This study is the first long-term study performed in Hungary on the whole psoriatic patient population treated with biologicals, to analyze the drug survival of all available biological therapies and to investigate predictors of persistence in the real-life settings. A further advantage of this study is that this is the first comprehensive analysis on this topic in the literature using the database of the NHIF of a given country.

The analysis of the present study population showed that adalimumab and ustekinumab were administered to almost equal numbers of patients, while infliximab and etanercept were also used in identical proportions, although less commonly than the first two agents. Since all four biological therapies can be used under the same circumstances in Hungary, the choice of drug depended mostly on dermatologists' preferences. The comparison of the subgroups receiving different biological therapies revealed that although there were certain differences among the 4 therapy groups in terms of patients' biological therapy naïve status, ultimately this factor didn't prove to have statistically meaningful effect on drug persistence rate or on predictor analysis, since the statistical methods have addressed this issue. At the same time, no significant differences were found in terms of PASI and DLQI scores across the subgroups of patients on different biologicals.

The available literature has already shown, that biological therapies used in psoriasis have superior drug survival rates compared to the rates seen with conventional systemic therapies [9]. Nevertheless, until recently there was only a lack of data obtained on large patient population treated for long time with TNF-alpha inhibitors and IL-12/23 inhibitor in the real-life settings [11, 14]. *Table 3* summarizes all the studies published so far, where data were collected from large patient population of 2 or more centers, the follow-up period was at least one year, and the authors compared at least 3 or more biological therapies. The list includes 5 prospective registry-based studies and 3 retrospective studies [5,11,15,16,17,18,19]. *Table 3* shows, that those studies which included ustekinumab have found drug survival of ustekinumab superior to the drug survival of TNF-alpha inhibitors. The largest study was published by Menter et al. analyzing data of 4000 patients taken from the PSOLAR registry, and their results indicated that drug

survival of ustekinumab was better than that of TNF-inhibitors for both biological-naïve and biological-experienced patients with psoriasis [19]. This concurs with the results from the British register (BADBIR) of 3523 bionaïve patients, where the drug survival rate of ustekinumab has been found nearly 80% at 3 years, which is significantly higher than that seen with TNF-inhibitors [16]. Gniadecki et al. has also performed an updated study involving 1277 psoriasis patients treated with biological therapy and found that ustekinumab had the highest survival rate (81.9%) at 4 years, followed by adalimumab and infliximab. Between the TNF-inhibitors no significant differences were detected [11]. Our results are comparable to the above investigations, and showed that drug survival rates of biologic therapies were excellent compared to other therapies, even if they diminished over time: 79.70% after the first year, 68.52% after the second year and 60% after the third year. At 3 years, drug survival rates were 67.83% of ustekinumab, 51.95% of adalimumab, 49.49% of etanercept, and 36.26% of infliximab. Our findings also showed that drug survival of ustekinumab was superior to TNF-alpha inhibitors, and the significant difference persisted over the 3-year study period. Adalimumab was shown to have the highest drug survival rate of all TNF- inhibitors studied, however, no significant difference was found among these drugs over the 46 months of the study period.

In addition to the analysis of persistence rates, it is also very important to explore predictors of drug survival. No conclusive evidence has yet been provided on the predictors of biological drug survival in psoriasis. Studies done so far discussed the role of several factors such as PASI, DLQI, comorbidities, age, gender, weight, disease onset, duration of psoriasis, presence of psoriatic arthritis, concomitant MTX or biological therapy naïve status and smoking. In *Table 4* we summarized results of long-term survival analyses performed on large psoriasis patient populations, investigating predictors of biological therapies only [11,15,17,19,20]. Three studies have shown that female gender is a predictor of discontinuation of biological therapies, [11,17,19] however Menter's data are not directly comparable with the aforementioned studies since these authors analyzed biological naïve and experienced patients' predictors separately. On the other hand other predictors of discontinuation like previous treatment with biologics, smoking status, higher DLQI, strict adherence to approved dose, presence of comorbidities, were detected only in one of the aforementioned investigations [11,15,17,19,20].

In the present study factors which could be extracted from the database of the NFIH were investigated. In accordance with the aforementioned authors, we could demonstrate the positive impact of male gender on the persistence of infliximab and adalimumab, while it had no effect on the persistence of ustekinumab and etanercept. It is not yet clear how gender impacts the persistence of biological therapy in psoriasis, but remarkably, female rheumatoid arthritis patients are also more likely to discontinue therapy than males [21]. Possible hypothetical explanations could be that female patients may develop anti-drug antibodies more frequently resulting in decreased therapeutic efficacy, or alternatively, psychological factors, such as dissatisfaction with treatment, may play more important role in females, but until now comparative studies were not performed.

In our study in the etanercept group, patients over 40 years were more likely to stay on the therapy than their younger peers. To our knowledge, no other previous investigations showed similar effect of age on the persistence of biological therapies.

In our study biological naive status and the use of MTX all decreased the risk of dropping out of therapy, although the impact was not significant. Biological therapy naïve status was shown to be a positive predictor for persistence in psoriasis by Gniadecki et al., and, similarly, Lopez-Ferrer could also demonstrate reduction of adalimumab drug survival in patients with prior exposure to another TNF-alpha inhibitor. On the other hand, there are studies which, similar to the current study did not find previous biological therapy usage as a negative predictor of persistence [11,15,19,20,23]. Although concomitant MTX usage has been shown to be associated with a better persistence of biologicals in rheumatological settings, there is no conclusive evidence in psoriasis about additional MTX as a positive predictor [24,25]. In a systematic review Bezooijen et al. selected eight studies, which generally showed that combination therapy of biologicals and MTX had higher efficacy than biological monotherapy, which could also indicate a positive effect of MTX on the drug survival, however, persistence was not investigated in this study [26]. On the other hand, Menter and colleagues unexpectedly reported that patients receiving MTX were significantly more likely to discontinue biological treatment compared with those without concomitant MTX in bionaïve group, but not in biologic experienced patients [19]. Our present study did not show any significant impact of the addition of MTX to the biological therapy on drug survival rates of any of the biological drugs studied.

Based on the findings of this study drug survival rates of biologic therapies can be regarded as excellent as the vast majority of the patients (nearly 80%) received only one biological over the 3 years' study period, and the mean survival rate did not diminish below 60% even after 3 years. The IL-12/23 inhibitor ustekinumab was shown to have significantly better drug survival rate than the TNF-alpha inhibitors, and when analyzing consolidated data of all assessed biologic therapies, male patients had better persistence than female patients. One of the advantages of the present study is that it is based on real-life data from the NHIF database, which allowed to analyze the whole psoriatic patient population treated with biological therapy in Hungary over a long period of time.

Limitations of the study

This is a retrospective analysis. Since the authors have used the database of the NHIF no information is available on the reason of therapy discontinuation. It is also worthwhile mentioning that while there is a patient support program for ustekinumab with potential impact on drug survival rates, there is no information available as to the existence of similar programs for the TNF-inhibitors. An additional limitation of the study is that the NHIF database did not include the PASI and DLQI scores of patients on biological therapies, and, therefore, such data were taken from the databases of the participant university centers, and, as such, the data do not cover the full patient population.

Disclosure. The use of NHIF database is not free of charge, the costs of using the database had been provided by Janssen-Cilag Hungary Ltd..The sponsor of the study did not participate in the data collection and data analysis. *Conflict of interest:* András Borsi and Péter Takács are an employees of Janssen-Cilag Ltd. Hungary. The research leading to the study results has received funding from Janssen-Cilag Hungary Ltd., Budapest, Hungary. Éva Remenyik has been supported by Janssen-Cilag and Abbvie for scientific international conference attendance. Lajos Kemény is paid consultant for Janssen and Novartis, speaker for Janssen, Novartis, Galderma, Ewopharma. Sarolta Kárpáti is paid consultant for Janssen, Abbvie. Péter Holló has received consultant or lecture fees from Abbvie, Janssen, MSD and Pfizer. Norbert Wikonkál served as a consultant and advisory board member for companies – Pfizer, MSD, Abbvie, Janssen-Cilag, Lilly, Amgen – that work on field of biological therapies in dermatology. Rolland Gyulai have received consultancy/speaker honoraria from Abbvie, Janssen-Cilag, MSD, Novartis, Pfizer, Bristol-Myers Squibb, and Roche, and has been reimbursed for international conference

attendance by Abbvie, Janssen-Cilag, MSD, Novartis, and Pfizer. Pál Rakonczai and Tamás Balázs are employees of Healthware Consulting Ltd an independent consulting company. Healtware Consulting Ltd which received funding for contribution to the study design and data analyses. Andrea Szegedi is paid consultant for Janssen, Novartis, speaker for Janssen, Novartis, Abbvie, Ewopharma.

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Long-term drug survival and predictor analysis of the whole psoriatic patient population on biological therapy in Hungary

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Table 1 Characteristics of the study population

Number of patients	**1263**
Mean age in years (SD)	**49.3 (14.3)**
Male / female (%)	**61.3 / 38.7**
Patients under 40 years / 40 years or above (%)	**29.3 / 70.7**
Biological therapy naïve / previously treated (%)	**81.3 / 18.7**
Number of patients receiving MTX in addition to the biological therapy	**97**
Mean PASI (SD)	**20.5 (6.4)**
Mean DLQI (SD)	**20.0 (5.8)**

Table 2 Baseline characteristics of patients receiving different biological therapies and pairwise comparison of the 4 groups regarding gender, age, ratio of biological naïve patients and MTX usage

Therapy	Adalimumab	Etanercept	Infliximab	Ustekinumab
Treatment episodes (1574)	491 (31.2%)	330 (21.0%)	266 (16.8%)	487 (31.0%)
Mean age (SD)	47.24 (13.77)	47.55 (15.39)	49.92 (13.63)	47.71 (13.31)
Male / Female %	59.1% / 40.9	56.4% / 43.6	64.3% / 35.7	61.4% / 38.6
Patients under 40 years / 40 years or above (%)	33.0 / 67.0	31.5 / 68.5	22.9 / 77.1	31.2 / 68.8
Biological therapy naïve / previously treated (%)	64.4 / 35.6	73.2 / 26.8	77.8 / 22.2	50.1 / 49.9
Patients receiving methotrexate in addition to the biological therapy (treatment episode)	40	16	26	32
P values of the conservative Wald tests, adjusted for the pairwise comparison of the proportion of gender				
Adalimumab	-	1	1	1
Etanercept	1	-	0.972	1
Infliximab	1	0.972	-	1
Ustekinumab	1	1	1	-
age groups				
Adalimumab	-	1	0.192	1
Etanercept	1	-	0.385	1
Infliximab	0.192	0.385	-	0.385
Ustekinumab	1	1	0.385	-
biological naïve patients				
Adalimumab	-	0.106	0.012*	0.004*
Etanercept	0.106	-	0.356	<0.001*
Infliximab	0.012*	0.356	-	<0.001*
Ustekinumab	0.004*	<0.001*	<0.001*	-
patients receiving MTX in addition to the biological therapy				
Adalimumab	-	0.85	1	1
Etanercept	0.85	-	0.6	1
Infliximab	1	0.6	-	1
Ustekinumab	1	1	1	-

Data are reported for treatment episodes

*significant differences

Table 3 Studies on long term drug survival of biological therapies in psoriasis

Study	Biologics	Patients/Treatment periods	Follow-up time (months)	Best survival	Source/ regimen
R. Gniadecki et al. (2011)	ADA, ETN, INF	747 patients/882 treatment episodes	48	INF (70%)	DERMBIO; Danish prospective registry
M. Esposito et al. (2013)	ADA, ETN, INF	650 patients	28.9 ± 15.4	ETN (72.6%)	Retrospective analysis from three Italian referral centers
van der Reek et al. (2014)	ADA, ETN, UST	249 treatment episodes	12	UST (85%)	Bio-CAPTURE Dutch prospective registry
R.B. Warren et al. (2015)	ADA, ETN, INF, UST	3523 patients	36	UST	BADBIR registry; Prospective British cohort study
R. Gniadecki et al. (2015)	ADA, ETN, INF, UST	1277 patients/1867 treatment episodes	followed for up to 10 years	UST (81.9% after 5 years)	DERMBIO Danish prospective registry
E. Vilarrasa et al. (2016)	ADA, ETN, INF, UST	427 patients/703 treatment episodes	48	UST	retrospective study, from 2 Spanish center
A. Menter et al (2016)	ADA, ETN, INF, UST	4000 patients	74	UST	PSOLAR; prospective registry from USA and European countries
L. Pogácsás et al. (2016)	ADA, ETN, INF, UST	1263 patients/1574 treatment episodes	46	UST 67.83%	retrospective study, database of NHIF, Hungary

Data of those studies are summarized, which investigated persistence of at least 3 biologicals and were collected on large psoriasis patient population of 2 or more centers and over long follow up period (least one year). IFN: infliximab, ADA: adalimumab, ETN: etanercept, UST: ustekinumab

Table 4 Studies on the predictors of biological therapies in psoriasis

Study	Biologics	Examined predictors/covariates	Significant covariates
R. Gniadecki et al. (2015)	INF, ADA, ETN, UST 1277 patients/1867 treatment episodes	age, sex, previous biologic treatment, weight, duration of psoriasis, presence of PsA, baseline PASI and DLQI, concomitant MTX, number of co-morbidities	**predictors of discontinuation:** female gender; previous biologic treatment
R.B. Warren et al. (2015)	INF, ADA, ETN, UST 3523 patients	age, sex, BMI, smoking status, presence of PsA, number of co-morbidities, disease duration, disease onset, PASI, DLQI, unstable psoriasis, concomitant MTX, concomitant cyclosporine	**predictors of discontinuation**: female gender, being current smoker, higher DLQI **predictors of drug survival**: presence of PsA
A. Menter et al. (2016)	INF, ADA, ETN, UST 4000 patients	age, gender, ethnicity, BMI, familial psoriasis history, smoking status, alcohol use status, duration of psoriasis, age at the diagnosis of psoriasis, presence of PsA, study site/geographic region, history of immunmodulator use, types of insurance, previous biologic treatment, reasons for discontinuation of prior biologics, PSA, concomitant MTX use	**predictors of discontinuation:** in bio naïve patients: concomitant MTX, female gender and geographic region (North America vs. Latin America)
E. Vilarrasa et al. (2016)	INF, ADA, ETN, UST 427 patients	sex, presence of PsA, biologic naïve status, use of combination treatment, weight, strict adherence to approved doses, PASI75 and PASI 90 response	**predictors of discontinuation** obesity, strict adherence to approved doses; **predictors of drug survival:** PASI75 and PASI90 response at week 16

A. Jacobi et al. (2016)	INF, ADA, ETN, UST, Efalizumab 125 treatment episodes	biologic naïve status, presence of PsA, and comorbidity with the presence of metabolic syndrome	**predictors of discontinuation:** comorbidities **predictors of drug survival:** presence of PsA
L. Pogácsás et al. (2016)	INF, ADA, ETN, UST 1263 patients/1574 treatment episodes	gender, age, additional MTX therapy, biologic naïve status	**predictors of discontinuation:** female gender

Data of those studies are summarized, which investigated predictors of at least 3 biologicals and were collected on large psoriasis patient population and over long follow up period (least one year).

IFN: infliximab, ADA: adalimumab, ETN: etanercept, UST: ustekinumab MTX: methotrexate

PASI: psoriasis area severity index, DLQI: Dermatology Life Quality Index

PSA: Physician's Global Assessment

Fig. 1. Kaplan-Meier survival curve of the 4 biologicals individually and in summary (all biological therapies). Data include 1574 treatment episodes. 491 adalimumab treatment series, 330 etanercept series, 266 infliximab series, and 487 ustekinumab series.

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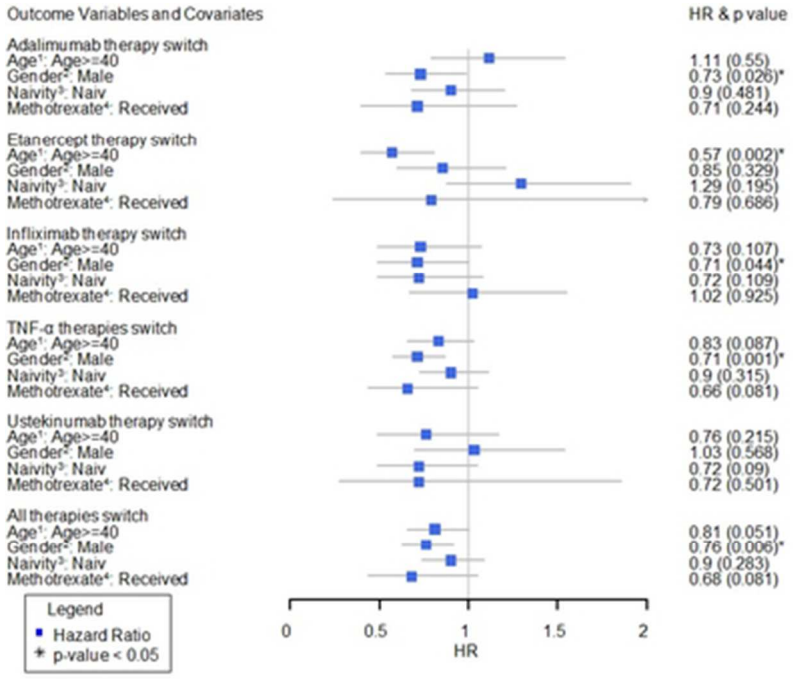

Fig. 2. Multivariate analysis of predictors on biological therapies' persistence rate (Cox proportional hazard and regression model). The figure shows the risk of drop out of therapy by predictors such as patient age, gender, biological therapy naïve status and additional MTX usage.
[1]Reference category: Age<=40
[2]Reference category: female gender
[3]Reference category: biological-experienced patients
[4]Reference category: patients who do not receive MTX

16x14mm (600 x 600 DPI)