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Drug survival of biologic therapies for the treatment of psoriasis: Results of Slovenian national registry

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ABSTRACT

The study was designed as observational retrospective analysis of the data from Slovenian Registry of patients with moderate and severe psoriasis treated with adalimumab, etanercept, infliximab or ustekinumab from 2005 to 2015. The survival rates of biologics were compared using survival analysis, and predictors of discontinuation were evaluated using a Cox regression model. All biologics have been prescribed as a first line therapy for moderate or severe psoriasis; 650 (94.9%) adalimumab, 254 (72.0%) ustekinumab, 76 (69.7%) infliximab, 68 (67.3%) etanercept. The overall biologics survival rate was 83.2% in the first line and 79.1% in the second line treatment. Drug survival for the first and second line of therapy was significantly longer for ustekinumab than for anti-TNFα agents ($p < 0.001$ and $p = 0.014$, respectively). Loss of efficacy accounted for 63% of all treatment discontinuations. Multivariate regression analysis showed that younger patients, being on etanercept, systemic conventional co-therapy, lower BSA and higher DLQI were independent predictors for treatment discontinuation. Our data showed the real-life situation in the treatment of moderate to severe psoriasis with biologics. Since longevity of drug survival is considered as a measure of treatment success, this data represents an important information when selecting a biologic treatment for individual patient.

1. Introduction

Psoriasis is a systemic chronic illness most commonly present in young adults that lasts for entire life [1]. Patients require long-lasting therapy, which may expose them to undesired side-effects [2]. The long-term effects and relative risks of these treatments are unknown and poorly studied [3]. Treatment with biologics represents an important therapeutic approach for the patients with moderate to severe psoriasis, especially those in whom systemic conventional therapy has failed [4,5].

Biologic agents completely changed the perspective of dermatology and revolutionized the treatment of patients with moderate and severe psoriasis. Clinical studies have proved short and long term efficacy of biologics in the treatment of psoriasis patients with favourable safety profile compared to conventional systemic therapies, which put patients at risk of potential toxic side effects. Biologics for psoriasis include inhibitors of tumor necrosis factor alfa (anti-TNFα) adalimumab, etanercept, infliximab, and an IL-12/IL-23 inhibitor ustekinumab [6]. In 2016 first IL-17 inhibitor secukinumab has become available for the treatment of severe psoriasis patients in Slovenia as well.

It has been shown in clinical trials as well as in real life that all biologic therapies gradually lose their effectiveness. Still there is a lack of prospective clinical trials assessing long term effectiveness of different biologics. Moreover, the long-term performance of these agents regarding efficacy and safety in “real-world” cannot be adequately assessed in clinical trials, where inclusion criteria are strict, therefore patient's population does not reflect daily clinical practice in the treatment of psoriasis patients [7]. Therefore, the real-world data represent the most reliable source of information about long term treatment outcomes with different biologics. This is recognized in increasing number of reports from different national registries where psoriasis patients treated with systemic therapies are followed. Although predominantly consistent, some of these real-world data analyses yielded some different survival rates for biologics when assessing some subpopulation cohorts (i.e. biologic-naive vs. biologic experienced patient). Drug survival represents a marker of drug effectiveness, safety, and real-world utility [8]. Patient's persistence with the therapy, as another term used to describe long term treatment success reflects effectiveness

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Table 1
Basic characteristics of patients with psoriasis at enrolment.

Characteristics	N = 1048	Adalimumab (N = 650)	Etanercept (N = 68)	Infliximab (N = 76)	Ustekinumab (N = 254)	p-value
Age [years]	50.3 ± 17.0	50.0 ± 17.0	56.4 ± 15.7	55.8 ± 17.5	47.9 ± 16-7	< **0.001**
Gender M/F[a]	628/420	404/246	40/28	41/35	143/111	0.272
Weight [kg]	83.5 ± 17.9	83.4 ± 18.1	82.2 ± 15.9	85.2 ± 15.7	83.7 ± 18.3	0.786
History of psoriasis	520 (49.6%)	320 (49.2%)	40 (58.8%)	36 (47.4%)	124 (48.8%)	0.496
Disease duration [years]	19.9 ± 14.9	19.7 ± 14.9	22.9 ± 14.2	21.0 ± 14.2	19.3 ± 15.4	0.307
PASI[a]	9.1 ± 14.4	8.3 ± 14.1	6.3 ± 9.8	7.0 ± 11.4	12.9 ± 16.5	**0.004**
BSA[a]	17.0 ± 12.8	17.3 ± 12.5	15.6 ± 10.8	18.1 ± 14.9	16.1 ± 13.8	< **0.001**
DLQI[a]	6.0 ± 8.9	5.3 ± 8.7	2.9 ± 6.8	7.8 ± 10.4	8.0 ± 9.3	**0.037**
Systemic conventional co-therapy	63 (6.0%)	37 (5.7%)	4 (5.9%)	14 (18.4%)	8 (3.1%)	< **0.001**
Methotrexate	51	30	3	14	4	
Acitretin - retinoid	3	1	1	0	1	
Cyclosporine	0	0	0	0	0	
PUVA[a]	9	6	0	0	3	

[a] M/F – male/female; PASI – Psoriasis Area Severity Index, BSA – Body Surface Area, DLQI – Dermatology Quality of Life Index, PUVA - Psoralen and Ultraviolet A (photo-chemotherapy).

and safety profile of the drugs, as well as patient's satisfaction. Large-scale cohorts are required to fully understand the factors influencing survival with these drugs [9].

The objectives of our study were to retrospectively analyse and report the long-term drug survival for adalimumab, etanercept, infliximab and ustekinumab from the National Registry of patients with moderate to severe psoriasis in Slovenia, and further identify which relevant risk factors influenced drug discontinuation. The Slovenian National Register is part of the network of European registries of patients, being treated by systemic agents (Psonet).

2. Material and methods

2.1. Study design

The study was designed as observational retrospective analysis of the data from Slovene Registry of patients with moderate and severe psoriasis treated with adalimumab, etanercept, infliximab or ustekinumab during the period 2005 to 2015. This register was designed according to the guidelines described by Burden et al 2012 [10] and holds data from patients with psoriasis being treated under real-life conditions, collected demographic data, data on drug survival, adverse events of systemic psoriasis treatments, data about conventional therapy and different measures of psoriasis severity. PASI (Psoriasis Area and Severity Index), DLQI (Dermatology Life Quality Index) and BSA (Body Surface Area) were taken at the time the patient started the biologic therapy. Institutional ethics committee confirmed the study design.

2.2. Study population

Register contains data from 1048 patients, ≥18 years of age with chronic plaque psoriasis that had been treated with at least one course of adalimumab, etanercept, infliximab or ustekinumab. Details of the treatment with biologic agents were recorded, including gaps in treatment, dates of therapy initiation and termination, and reasons for discontinuation.

2.3. Assessment of drug survival

A treatment episode was defined as a prescription of a biologic agent to a patient. Drug survival was defined as the time from initiation to discontinuation (stop/switch) of biologic therapy in individual patient. Discontinuation of therapy was defined as gap in treatment for more than 3 months, loss of patients' track, or temporary non-compliance to treatment due to clinical reasons (another or same biologic, but for other inflammatory disease treatment).

2.4. Statistical analysis

Statistical analysis of the data was performed using SPSS 21 software (IBM, New York, USA). Continuous (quantitative) variables that were normally distributed were analysed by Student's t-test and for the abnormal distribution of variables Kruskal-Wallis test was used. Pearson's chi-square test was used for the evaluation of categorical (qualitative) variables. Significant statistical difference was set at P value < 0.05.

Multivariate Cox regression with hazard ratios was used to predict the influence of variables (risk factors) on the therapy discontinuation. We also performed the Spearman's correlation coefficient to assess the correlation between the variables. Drug survival for adalimumab, etanercept, infliximab and ustekinumab was assessed by Kaplan-Meier survival curve. The log-rank test was used to compare the survival distributions of patients treated by different biologics.

3. Results

In the data analysis total of 1048 patients with moderate to severe psoriasis were included. Demographic data of patients are presented in Table 1. Patients assigned to different biologics at enrolment in the registry statistically differed in age, PASI, BSA, DLQI and systemic conventional co-therapy. At the time of biologics initiation methotrexate was used as a concomitant therapy in 51 (4.9%) of all patients, most commonly together with infliximab (18.4%) and least frequently with ustekinumab (3.1%).

1258 treatment episodes (adalimumab N = 685, etanercept N = 101, infliximab N = 109, and ustekinumab N = 353) in 1048 patients for up to 10 years were analysed. All biologics have been prescribed as a first line treatments, after failing the conventional systemic therapy for moderate or severe psoriasis. 650 (94.9%) of adalimumab prescriptions were first line prescriptions, followed by 254 (72.0%) of ustekinumab, 76 (69.7%) of infliximab and 68 (67.3%) of etanercept. Ustekinumab was most frequently prescribed biologic in the second and third line of therapy (Table 2). 10 patients were treated with secukinumab at the end of study in 2015, therefore survival curve was not calculated.

872 out of 1048 patients at the last visit were still receiving the same biologic as at the time of enrolment in the registry, they continued the treatment with the first biologic, demonstrating overall survival rate of 83.2% in the first line. 140 out of 177 patients who have been introduced to different biologic in the second line, continued to receive the same drug until the last visit (survival rate 79.1%) (Table 3).

Reasons for treatment termination or drug switch were recorded for 203 out of 210 patients and were similar across the groups (Table 4). The main reason was loss of efficacy (N = 128, 63.0%), followed by