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**Sustained PASI, DLQI and EQ-5D response of biological treatment in psoriasis:
10 years of real-world data in the Swedish National Psoriasis Register**

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Running title: Sustained PASI, DLQI and EQ-5D of biological treatment in psoriasis

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Conflict of interest: M Schmitt-Egenolf is responsible for dermatology and K Steen Carlsson is appointed health economic expert in the project management for the national guidelines for psoriasis at the Swedish Board of Health and Welfare. F Hjalte has no conflict of interest to declare.

Bulleterd statements:**What's already known about this topic?**

Biological treatment shows a good efficacy in clinical trials and a satisfactory effectiveness in observational studies. Most analyses have focused on short term outcomes of single biological agents and less is known about long-term outcomes in the broader patient group where personalized treatment may induce switching between biological agents.

What does this study add?

10 years of individual-level real-world data was used to analyse the long-term effectiveness of switching to biological treatment for people with moderate to severe psoriasis. Outcomes measured by PASI and by health-related quality of life instruments DLQI and EQ-5D show disease improvement at 3-5 months after switch to biological treatment. The effect of biological treatment is stable thereafter under the entire observed timespan.

Ethics: This research was done in adherence to the Declaration of Helsinki guidelines and was approved by the Umeå Ethical Review Board, Sweden. Patients were registered after informed consent was obtained. Both data and consent were collected electronically, to assure an effective logistic in this nationwide project.

Summary (Abstract): word count: 218 (max 250)

Background: Few studies have analysed the long-term effects of biological treatment in psoriasis. PsoReg, the Swedish national register for systemic psoriasis treatment, started in 2006 and includes now ten years of real-world data on effectiveness of biological treatment.

Objective: To analyse long-term real-world outcome data on biological-naïve patients with moderate to severe psoriasis after switching to biological treatment.

Methods: Observational study including biological-naïve patients with at least one registration of outcome before switching to biological treatment while included in PsoReg and at least one follow-up visit. PASI, DLQI and EQ-5D values were analysed at 3-5 months, 6-11 months, and at least once 1 year and above, up to 9 years after switch to biological treatment.

Results: 583 patients fulfilled the inclusion criteria. Of these, 399/395/373 patients had observed outcome data beyond one year on PASI/DLQI/EQ-5D, respectively, and 164/168/152 were observed in at least three time periods after switch. Significant ($p < 0.01$) improvement in PASI, DLQI and EQ-5D was observed 3-5 months after switch and sustained under the whole observation period. Mean PASI/DLQI/EQ-5D changed from 13.5 (SD 9.1)/9.0 (SD 8.1)/0.737 (SD 0.222), respectively, before switch, to 4.0 (SD 3.5)/3.7 (SD 4.7)/0.792 (SD 0.208), respectively, 1-5 years after switch.

Conclusion: Biological treatment, as used in clinical practice, show a stable long term effectiveness in all measured dimensions: PASI, DLQI and EQ-5D.

Introduction

Psoriasis is a chronic inflammatory skin disease with a prevalence of about 3 percent^{1,2}. Patients with mild disease are usually treated with topical treatments, while patients with moderate to severe disease require systemic treatments. Methotrexate is the most common form of systemic treatment, and since 2004 biological agents have been available for psoriasis treatment in Sweden.

Observational studies based on national registers constitute necessary complements to clinical trials as they represent the actual patient population in real-life and enable for studying effects over a longer period. There exist several psoriasis registers from which real world data on effectiveness of biological treatment has been reported, e.g. the British Association of Dermatologists Biologic Interventions Register (BADBIR), the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE), and the Psoriasis Longitudinal Assessment and Registry (PSOLAR)³⁻⁷. PsoReg, the Swedish national register for systemic psoriasis treatment^{8,9} was established in 2006 to follow-up the long term effectiveness and safety of biological agents. The inclusion criteria for PsoReg are patients using, or about to start using systemic psoriasis treatment. PsoReg registers the clinical outcome measure Psoriasis Area and Severity Index (PASI), and two patient-reported outcome measures for Health-Related Quality of Life (HRQoL), i.e. Dermatology Life Quality Index (DLQI) and EuroQol-5D (EQ-5D) at visits reflecting clinical practice intervals for this patient group.

In a previous study based on data from PsoReg, outcomes of biological-naïve patients who switched to biological treatment were analysed before switch and at first follow-up, where one third of the patients had follow-up assessment less than 2 months after switch, one third at between 2 and 3 months and one third at more than 3 months after switch¹⁰. Patients significantly improved in both PASI and in the patient reported quality of life measures. Since most patients were observed relatively shortly after switch, outcomes may have been underestimated if the full treatment effect had not yet been achieved. On the other hand, recent research suggests that drug antibodies may reduce the sustained clinical effectiveness of biological treatment¹¹⁻¹³ and the response among some patients might then be reduced over time. In that case, outcomes in the previous study may have overestimated the long-term effectiveness.

The objective of this study was to analyse the long-term development of the PASI alongside dermatology-specific and generic HRQoL indices in patients with moderate to severe psoriasis who switched to biological treatment. The study takes a patient perspective, thus focusing on what happens in clinical practice at assessments taking place during different follow-up time intervals.

Materials and Methods

This analysis is based on 10 years of real-world data extracted from PsoReg in May 2016. The focus was on consequences of switch to biological treatment overall, and not with the effect of specific agents. The patient group consisted of patients who were biological-naïve with one assessment of outcomes before starting biological treatment (baseline) and at least one registration of outcomes after switch. To reflect real-world practice and long-term effects of biological treatment, patients could switch between different biological agents and were not constrained to be on biological treatment during the whole study period. The study design implied that patients could have their initial switch to

biological treatment at any point from 2007 to April 2015 and still have at least one year of follow-up after switch. Patients who were prescribed efalizumab as their first biological agent were excluded from the analysis since the drug was withdrawn in 2009.

The clinical outcome measure PASI includes the severity of the three main signs of psoriasis (the average redness, thickness, and scaliness of the lesions) weighted by the coverage of the body part affected (head, trunk, arms and legs). The score is on a scale of 0 to theoretically 72, where a higher score indicates higher severity¹⁴.

DLQI is a dermatology-specific measure of patients' HRQoL¹⁵. The index relates to how the skin disease has affected the life of the patient over the past 7 days. The questionnaire consists of 10 questions in 6 dimensions: 1) Symptoms and feelings, 2) Daily activities, 3) Leisure, 4) Work and school, 5) Personal relationships, and 6) Treatment, where each question has 4 alternative answers: "not at all", "a little", "a lot" and "very much", with scores of 0, 1, 2 and 3, respectively. The overall summary score aggregates the score of each item, ranging from 0 (best health state) to 30 (worst health state).

The EQ-5D is a generic HRQoL measure, which is often used to estimate Quality Adjusted Life Years, QALYs. QALYs have previously been used in dermatological studies and have shown good validity in psoriasis patients¹⁶⁻¹⁸. QALYs are calculated by weighting the time period in which a patient is in a certain health state, with the HRQoL weight associated with that state. The EQ-5D questionnaire includes five dimensions, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and, in EQ-5D-3L, each dimension has three levels of severity: (1) no problems (2) some or moderate problems (3) extreme problems, which results in 243 possible health profiles¹⁹. These health profiles are associated with utility weights. In this analysis the population-based utility weights from the UK²⁰ were used. The utility value generally is between 0 and 1, where 1 being equal to 'perfect health' and 0 equal to 'death'. However, the value can be a negative number since one can think of health states being worse than death²⁰. PsoReg does not contain HRQoL data measured by EQ VAS.

The outcome assessments of the patients treated with biological treatment were analysed before switch and at three pre-specified follow-up intervals after switch to biological treatment: 3-5 months, 6-11 months, and at least one observation in the time interval 1 year and above (hereafter defined as 1+ year). The choice of initial follow-period (3-5 months) was based on Swedish guidelines²¹ recommending a follow-up assessment after initiation with biological treatment after 3-4 months. For patients with more than one assessment within an observation interval, the mean of these assessments was used in the analysis.

The main analysis of the long-term development of clinical and HRQoL outcomes used two subsamples of patients. The first subsample included patients who had at least four assessments, i.e. before switch, 3-5 months after, 6-11 months after, and at least once 1+ year after switch. The interval 1+ year was furthermore divided into 1-5 years and 6-9 years.

The second subsample included patients who had two assessments, i.e. before switch and at least one assessment 1+ year after switch. Thus, the first subsample of patients is included in the second subsample, but relaxed the criteria of having at least 4 assessments. The presentation of results after switch for the second subsample were divided into 2-year intervals after switch; 1-2 years, 3-4 years, 5-6 years, and 7-9 years, with pairwise comparison to the baseline assessment.

We conducted two sensitivity analyses to explore the robustness of results on group mean outcomes. The first sensitivity analysis excluded patients who had discontinued their biological treatment at some point during study period. The second sensitivity analysis investigated the exclusion of patients with other forms of skin-psoriasis than plaque psoriasis, e.g. pustular psoriasis.

Descriptive statistics of patient cohort characteristics before and at least one year after switch were obtained for comparison to other studies.

The Wilcoxon signed rank test was used to determine whether there was a difference in outcomes before and after switch to biological treatment. All statistical analyses were performed using STATA statistical software release version 14.1.

Results

At the time of the data extraction there were 5,435 patients registered in PsoReg. In total 700 biological-naïve patients switched to biological treatment between January 2007 and May 2016. Patients without follow-up after initiation of biological treatment ($n=104$) were excluded from the analysis as well as patients who were prescribed efalizumab as their first biological agent since the drug was withdrawn in 2009 ($n=13$). (Fig.1)

Figure 1. Study population

Table 1 Characteristics of biological naïve psoriasis patients who have switched to biological treatment during registration (2007-2016) in PsoReg

	All patients (n=583)	Subsample 1: Patients with 4 assessments; before switch & 3-5 months, 6-11 months and 1-9 years after switch			Subsample 2: Patients with 2 assessments; before & 1-9 years after switch		
		PASI (n=164)	DLQI (n=168)	EQ-5D (n=152)	PASI (n=399)	DLQI (n=395)	EQ-5D (n=373)
Mean age at switch ± SD, years	47.0±14.1	46.8±15.1	47.2±15.0	47.4±14.8	45.9±13.9	45.8±14.1	45.6±14.1
Men, n (%)	372(64)	110 (67)	115 (68)	104 (68)	247(62)	247(63)	232 (62)
Plaque Psoriasis, n (%)	521 (90)	158 (96)	161 (96)	145 (95)	368 (92)	364 (92)	343 (92)
Psoriatic arthritis, n (%)	183 (31)	60 (37)	59 (35)	53 (35)	127 (32)	125 (32)	115 (31)
Number of biological agents, n (%)							
- 1	441 (76)	99 (60)	103 (61)	93 (61)	268 (67)	267 (68)	251 (67)
- 2	107 (18)	44 (27)	45 (27)	41 (27)	96 (24)	94 (24)	91 (24)
- >2	35 (6)	21 (13)	20 (12)	18 (11)	35 (9)	34 (8)	31 (8)
Mean number of years since switch ± SD	2.6±2.1	3.8±1.8	3.9±1.8	4.0±1.8	3.4±1.9	3.5±1.9	3.5±1.9

In total, 583 patients fulfilled basic inclusion criteria. Patient characteristics for the whole study population as well as for the two subsamples are presented in Table 1. In the two subsamples, between 47 and 49 percent of the patients had etanercept prescribed as their first biological agent while 39-43 percent had adalimumab, 8-9 percent had ustekinumab, and 2-3 percent had infliximab. Most patients in subsamples 1 and 2 had been prescribed one biological agent during the study period, while approximately 25 percent had been prescribed two and around 10 percent had been prescribed more than two different biological agents during the study period. Before switch to a biological treatment, between 76 and 80 percent of the patients had a PASI and/or DLQI ≥ 10 , and between 25 and 31 percent had both PASI and DLQI ≥ 10 . Plaque psoriasis was the most common diagnosis and was registered for 92-96 percent of patients in the two subsamples while few had other forms of skin-psoriasis.

PASI was assessed within all three follow-up intervals (3-5 months, 6-11 months after and at least once 1+ year after switch) in 164 people (first subsample). Patient HRQoL was assessed for; DLQI n=168 and EQ-5D n=152. Figure 2 illustrates the outcome values, presented as median and the interquartile range, in PASI, DLQI and EQ-5D before switch and at the respective follow-up intervals. Median and mean values and the mean change in outcomes since baseline are presented in Table 2.

Table 2 Median and mean values in PASI, DLQI and EQ-5D of patients with four assessments; before switch and at follow-up 3-5 months after switch, 6-11 months after switch, 1-5 years after switch, and 6-9 years after switch to biological treatment

	Median	p-value	Mean± SD	Change (mean±SD)
PASI (n=164)				
Before switch	11.6		13.5±9.1	
3-5 months after switch	3.0	<0.001	4.5±4.3	9.0±8.8
6-11 months after switch	2.6	<0.001	4.1±5.0	9.4±8.1
1-5 years after switch	3.1	<0.001	4.0±3.5	9.5±8.4
6-9 years after switch ¹	2.0	<0.001	5.4±7.6	9.7±8.4
DLQI (n=168)				
Before switch	7.0		9.0±8.1	
3-5 months after switch	1.3	<0.001	3.6±5.2	5.4±7.9
6-11 months after switch	1.4	<0.001	3.6±5.3	5.4±8.2
1-5 years after switch	2.0	<0.001	3.7±4.7	5.3±7.9
6-9 years after switch ²	1.0	0.003	2.9±4.0	4.9±8.2
EQ-5D (n=152)				
Before switch	0.725		0.737±0.222	
3-5 months after switch	0.800	<0.001	0.817 ±0.193	0.080±0.222
6-11 months after switch	0.854	<0.001	0.822±0.209	0.085±0.221
1-5 years after switch	0.826	0.003	0.792±0.208	0.054±0.233
6-9 years after switch ³	0.805	0.871	0.754±0.299	0.034±0.296

Note: Number of patients with 6-9 years follow-up is ¹ n=24, ² n=25 and ³ n=24. Pairwise statistical testing conducted for each follow-up time against before switch with appropriate sample.

Significant change ($p<0.01$) was found in all outcome variables (PASI, DLQI and EQ-5D) at each assessment compared to baseline. Significant differences were also found in PASI (n=24) and DLQI (n=25) for the sub-group of patients with at least one assessment 6-9 years after baseline. We also noted a higher mean level of PASI before-switch in the latter group compared to patients with maximum 5 years follow-up (n=140) (mean (SD)15.2 (8.3) vs 13.2 (9.2)). As shown in Figure 2, the change in PASI, DLQI and EQ-5D is observed already at 3-5 months after switch to a biological treatment, thereafter the effect appears to stabilize.

Figure 2. Outcome values (median of means and IQR) in PASI, DLQI and EQ-5D before switch and at follow-up of patients with four assessments (sub-sample 1); 3-5 months after switch, 6-11 months after switch, 1-5 years after switch (PASI n=164, DLQI n=168, EQ-5D n=152) and 6-9 years after switch (PASI and EQ-5D n=24, DLQI n=25) to biological treatment.

Figure 3a-c. Box plots of outcomes of patients with two assessments (sub-sample 2). Before, 1-2 years after, 3-4 years after, 5-6 years after and 7-9 years after switch to biological treatment. **a)** PASI, **b)** DLQI and **c)** EQ-5D

Figure 3 a-c present clinical and HRQoL outcomes for nearly 400 patients who had assessments before switch and at least once 1+ year after switch to a biological treatment but where we relaxed the requirement of observations at 4 assessments. Results show a similar pattern with sustained long-term outcomes as in the more restricted first subsample. Pairwise comparisons to baseline showed sustained improved outcome ($p < 0.01$), except for EQ-5D at 5-6 years and 7-9 years.

The results from the sensitivity analyses excluding patients with a registered termination of biological treatment during study period (between 12 and 15 percent of patients depending on analysis) or excluding patients with other forms of skin-psoriasis than plaque psoriasis (between 4 and 8 percent of patients depending on analysis) demonstrated a similar pattern of results.

Outcomes for patients not included in the two main subsamples, i.e. patients with follow-up after 3 months but not beyond one year, showed the same tendency of improvements already at 3-5 months as in the main analyses for the subsamples (Data in supplementary material).

Discussion

We analysed long-term effects of biological treatment in moderate to severe psoriasis based on 10 years of real-world data from PsoReg, the national Swedish register for systemic psoriasis treatment. Significant differences between before and after switch to biological treatment were found for all outcome variables (PASI, DLQI and EQ-5D) at 3-5 months after switch, and the changes were sustained over the entire observed timespan. This pattern was stable across sub-groups where frequency of measurement varied and when excluding patients who had discontinued biological treatment or restricting the sample to only plaque psoriasis.

The strength of this study is that the analysed effects of initiating biological treatment on clinical and HRQoL outcomes are based on real-world data as opposed to efficacy analysed in randomised clinical trials with selected study populations in an experimental setting. Further, the study analysed the long-term effects of biological treatment overall which has not been subject for extensive previous research. Our results confirm the trend indicated in the previous PsoReg study where the mean follow-up was 112 days (SD=136) between switch and assessment, with about one third of patients having no more than two months of follow-up¹⁰. The results indicate that complete treatment result was not yet achieved due to too short follow-up time in this previous study.

Previous studies on long-term effect of biological treatment in psoriasis have predominantly been extensions of clinical trials²²⁻²⁶ focusing on single agents. Also, earlier real-world studies on long-term effects of biological treatment²⁷⁻³⁰ and previous register based studies³⁻⁷ focused on single agents. In contrast, the motivation of the present study was to adopt a patient perspective focusing on outcomes for patients rather than on specific agents; allowing patients to switch between treatments which results in a less selected patient group. We found only one small longitudinal, retrospective study (n=54) from Australia which also studied outcomes of biological treatment broadly³¹. Chaptini et al. investigated patients with biological treatment for at least two years up to 6.5 years and found that PASI and DLQI decreased rapidly over the first 12 months and then remained low or even declined further. The same tendency of sustained effects was observed in our study. However, Chaptini et al.³¹ reported a baseline mean PASI-score above 25 and mean DLQI above 20, indicating that their patient group was worse off compared to the average level in our PsoReg sample.

Another observation in our study is that patients with the longest follow-up (6-9 years), and therefore switched when biological treatment in psoriasis was new, had the highest PASI: PASI mean (SD) 15.2 (8.3), followed by the intermediate group (1-5 years follow up) 13.2 (9.2) and finally the < 12-month follow-up group 10.5 (7.4). This pattern is in line with the general observation that new treatments are first provided to patients with the greatest severity and then the patient population is gradually extended to broader patient groups.

None of the studies in our review captured EQ-5D. This study adds long-term data on EQ-5D for patients with moderate to severe psoriasis in addition to long-term data on PASI and DLQI. Most long-term studies are using only PASI as outcome measures even though some studies also include DLQI. The stable EQ-5D values presented here are in level with previously reported EQ-5D values from a Swedish population based study³² covering people in ages corresponding to the mean age of our PsoReg sample. Significant differences in EQ-5D before and after switch were found for all cohorts except for the cohort in the longest time interval from initiation (6-9 years) which is probably explained

by the small sample size (n=24). EQ-5D results are useful measures in economic evaluations of biological agents in psoriasis as EQ-5D has showed a good validity in psoriasis patients¹⁶⁻¹⁸. Correlation between EQ-5D and the other measures have not been investigated in the current study but elsewhere^{33,34}.

Limitations of the study include two sorts of selection bias: i) although PsoReg to date registers more than 5500 patients with moderate to severe psoriasis in Sweden, recruitment has been gradual (between 2007 and 2015) with increasing numbers of patients switching to biological treatment; and ii) the study inclusion criteria required multiple registrations which by design limit the coverage of patients who see their doctor less frequently for instance because of favourable outcomes or because of barriers to care including access. Both types of selection bias issues are inherent in real-world register data where diffusion of new treatments is gradual, registration non-mandatory, and follow-up time not limited by a study protocol. The magnitude of these potential bias is by definition intangible but the low number of patients with the longest follow-up (6-9 years) is a result of clinical practice where few patients were prescribed biological treatment during upstart phase subject to restrictions and cautiousness.

Our analysis was limited to switch from a conventional systemic treatment to biological treatment and switches between different types of biological treatment were not investigated per se. However, data from clinical trials³⁵ and an earlier observational study based on data from PsoReg, indicate that patients with continuous biological treatment tend to achieve better outcomes compared to intermittently treated patients³⁶. Thus, our analysis includes also those patients that for one or the other reason needed to switch or terminate biological treatment which might influence the observed treatment effect in this study. Further research is needed about the real world treatment patterns and switches in clinical practice as the effect of one drug may decrease over time and switches between agents may be needed to sustain good treatment outcomes³⁷.

This careful analysis of 10 years of PsoReg data shows that the scarcity of outcome measures provided by visits at the health-care provider over time limits the potential power of real-world data. In the future, the potential offered by e-health solutions opens for giving patients the opportunity to continuously register their outcomes independently to complement data input and grasp the full potential of a register.

In conclusion, our results suggest that the clinical and HRQoL effectiveness of biological treatment as used in clinical practice is sustained over time. The results from this study may support clinicians in initiating and continuing biological treatment for patients with disappointing outcomes under conventional treatment.

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Supplementary material

Table S1 PASI, DLQI and EQ-5D at three measurements for patients with only short-term follow-up (<1 year) after switch to biological treatment

	Before switch		3-5 months		6-11 months	
	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)
PASI	9.0	10.5 (7.4)	2.4	3.8 (3.9)	2.3	3.2 (3.3)
<i>n</i>	175		103		82	
DLQI	9.0	10.4 (8.0)	2.0	4.2 (6.1)	1.0	3.0 (4.4)
<i>n</i>	186		104		82	
EQ-5D	0.725	0.697 (0.235)	0.798	0.775 (0.249)	0.848	0.815 (0.211)
<i>n</i>	191		100		77	

Note: Differences before and after in all outcomes were significant at $p < 0.001$.