Real-World Outcome Analysis of Continuously and Intermittently Treated Patients with Moderate to Severe Psoriasis after Switching to a Biologic Agent

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Abstract

Background: Clinical studies of continuous versus intermittent biologic therapy for moderate to severe psoriasis demonstrate improved efficacy with continuous treatment. Objective: To analyse Swedish real-world data of continuously and intermittently treated biologic-naïve patients after switching to a biologic agent. Methods: This is an observational study based on PsoReg, the Swedish registry for systemic psoriasis treatment. Outcome effects in biologic-naïve patients who switched to a biologic agent (n = 351) were analysed in groups of continuous, intermittent and terminated treatment. Results: Intermittently treated patients (n = 50) reported higher Psoriasis Area and Severity Index and Dermatology Life Quality Index values after switching than patients with continuous (n = 260) or terminated treatment (n = 41). Study Limitations: The reason for intermittent treatment was not recorded. The intermittently treated patients may be a heterogeneous group and a limitation is that it cannot be determined whether less than continuous use was offered to handle negative aspects. Conclusion: Patients with continuous biologic treatment tend to achieve better outcomes compared to intermittently treated patients.

Introduction

Psoriasis is a chronic inflammatory skin disease with a prevalence of about 3% [1]. Patients with mild disease are usually treated with topical treatments, while patients with moderate to severe disease require systemic treatments. Patients with moderate to severe psoriasis (defined as Psoriasis Area and Severity Index [PASI] ≥10 and Dermatology Life Quality Index [DLQI] ≥10) who do not respond to or are intolerant to conventional treatment may be prescribed biologic agents [2]. Biologic agents were introduced for psoriasis treatment in 2004 in Sweden. PsoReg, the Swedish registry for systemic psoriasis treatment [3, 4], was established in 2006 to follow up the long-term effectiveness and safety of biologic agents. The inclusion criteria for PsoReg are planned or initiated systemic psoriasis treatment. In PsoReg the clinical out-
come measure PASI as well as two outcome measures for health-related quality of life (HRQoL), DLQI and Euro-Qol-5D (EQ-5D), are registered. According to Swedish guidelines a follow-up assessment should be conducted 3–4 months after initiation with a biologic agent [2]. If PASI is improved by ≥75% the recommendation is continued treatment. The same recommendation is valid if PASI is improved by 50–75% and DLQI is ≤5 [2].

Observational studies based on national registries constitute complements to clinical trials as they represent the real patient population and enable for studying effects over a longer period of time. In a previous study based on PsoReg outcomes of biologic-naïve patients who switched to a biologic agent, data were analysed before switch and at first follow-up. Patients significantly improved in EQ-5D, DLQI and PASI, and the patients with the highest benefits were those with high scores of PASI and DLQI before treatment initiation [5].

The introduction of biologic agents in psoriasis has changed the treatment of moderate to severe psoriasis patients. Conventional systemic treatments have traditionally been given intermittently in order to cope with toxicities, while biologic treatment allow for continuous treatment [6]. Data presented in a review of continuous versus intermittent therapy for moderate to severe psoriasis support the use of continuous biologic treatment based on improved efficacy and safety [6]. However, observational studies on intermittent and continuous biologic treatment in patients with moderate to severe psoriasis are limited.

The objective of this study is to analyse Swedish real-world outcomes of continuously and intermittently treated biologic-naïve patients with moderate to severe psoriasis after switching to a biologic agent.

Data and Methods

This analysis is based on data extracted from PsoReg in August 2013. The patient group consisted of patients who were biologic-naïve and switched to a biologic agent during registration in PsoReg. The patients identified in PsoReg were matched with the Swedish pharmaceutical registry at the National Board of Health and Welfare in order to capture data on dispatched biologic and conventional agents (methotrexate) as well as pharmaceutical costs. Data from the pharmaceutical registry from January 2007 to December 2011 were employed.

The focus was on biologic treatment overall, and not with specific agents. We defined three analysis groups from the registration in PsoReg: (1) Patients with continuous treatment were prescribed biologic agents without breaks longer than 14 days before initiating a new treatment period with the same or other biologic agent (with special consideration taken to infliximab and ustekinumab, which are given with longer intervals). (2) Intermittent treatment was defined as treatment with biologic agents during periods with breaks of at least 14 days for etanercept and adalimumab, but longer according to the Summary of Product Characteristics for infliximab and ustekinumab [7]. (3) Terminated treatment was defined as patients who initiated and terminated a spell of biologic treatment without recommencing a new treatment spell within the study period.

The clinical outcome measure PASI includes the severity of the three main signs of psoriasis (redness, scaliness and thickness) weighted by the coverage of the body part affected (legs, body, arms and head). The score is on a scale of 0 to theoretically 72, with a higher score indicating higher severity [8].

DLQI is a dermatology-specific measure of patients’ HRQoL [9]. The index relates to how the skin disease has affected the patient’s life over the past 7 days. The questionnaire consists of ten questions in six dimensions: (1) symptoms and feelings, (2) daily activities, (3) leisure, (4) work and school, (5) personal relationships, and (6) treatment, where each question has four alternative answers associated with different scores. 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). The utility of 1 year of perfect health is equal to one QALY and the utility of death is equal to zero. 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 three levels of severity, which results in 243 possible health profiles [10]. These health profiles are associated with utility weights. In this analysis the population-based utility weights from the UK [11] were used.

The outcome assessments of patients treated with biologic agents were analysed before switch and at different follow-up intervals. Based on Swedish guidelines [2] recommending a follow-up assessment after initiation with biologic treatment after 3–4 months, the first follow-up interval period in this study was defined as 12–24 weeks. The next interval was defined as 24–52 weeks and the third interval as >52 weeks.

Differences in characteristics and outcome measures between groups of patients and different follow-up intervals were analysed through statistical tests. The one-way ANOVA test was used for the normally distributed variables, the Kruskal-Wallis test was used for the not normally distributed variables, and the χ² test was used for categorical variables. The Wilcoxon signed-rank test was used to determine whether there was a difference in outcomes before and after switch to a biologic agent. All statistical analyses were performed using STATA statistical software release version 13.1.

Results

At the time of the data extraction there were 4,065 patients registered in PsoReg. In total 351 biologic-naïve patients switched to a biologic agent between January 2007 and August 2013 (fig. 1) and had assessments of PASI,
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DLQI and/or EQ-5D before and after switch. Patients without follow-up after initiation (n = 57) were excluded from the analysis as well as patients who were prescribed efalizumab as their first biologic agent, since the drug was withdrawn in 2009 (n = 13). Approximately 53% of patients had etanercept prescribed as their first biologic agent, 36% adalimumab, 8% ustekinumab and 3% infliximab.

Among the patients who had assessments before and after switch to a biologic agent, 260 were identified as being continuously treated with biologic agents and 50 were identified as being treated intermittently. Forty-one patients terminated treatment with biologics without switching to another agent within the study period.

Patient characteristics for the total cohort and for the three analysis groups are presented in table 1. The mean age at switch and the distribution of sex differed with a lower mean age and a lower proportion of men in the intermittently treated group, although not statistically significant (p = 0.107 and p = 0.103, respectively). More than 75% of patients have disease onset before age 30 years, and the mean duration of disease differed significantly between patients with continuous, intermittent and terminated treatment (p = 0.024). More than 75% of patients had been prescribed one biologic agent during the study period, while almost 20% had been prescribed two different biologic agents. Only a minor part (6%) had been pre-

Table 1. Characteristics of biologic-naïve psoriasis patients who switched to a biologic agent during registration (2007–2013) in PsoReg

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Continuous</th>
<th>Intermittent</th>
<th>Terminated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>351 (100%)</td>
<td>260 (74%)</td>
<td>50 (14%)</td>
<td>41 (12%)</td>
<td></td>
</tr>
<tr>
<td>Age at switch, years (mean ± SD)</td>
<td>46.4±14.2</td>
<td>46.7±13.5</td>
<td>42.7±15.6</td>
<td>48.6±16.2</td>
<td>0.107</td>
</tr>
<tr>
<td>Men</td>
<td>221 (63%)</td>
<td>171 (66%)</td>
<td>25 (50%)</td>
<td>25 (61%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Plaque psoriasis</td>
<td>323 (92%)</td>
<td>240 (92%)</td>
<td>46 (92%)</td>
<td>37 (90%)</td>
<td>0.902</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>123 (35%)</td>
<td>93 (36%)</td>
<td>16 (32%)</td>
<td>14 (34%)</td>
<td>0.870</td>
</tr>
<tr>
<td>Disease duration, years (mean ± SD) (n = 331)</td>
<td>22±13</td>
<td>23±13</td>
<td>19±12</td>
<td>28±17</td>
<td>0.024</td>
</tr>
<tr>
<td>Number of biologic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>268 (76%)</td>
<td>219 (84%)</td>
<td>20 (40%)</td>
<td>29 (71%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64 (18%)</td>
<td>34 (13%)</td>
<td>21 (42%)</td>
<td>9 (22%)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>19 (6%)</td>
<td>7 (3%)</td>
<td>9 (18%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mean number of biologic agents</td>
<td>1.30</td>
<td>1.18</td>
<td>1.82</td>
<td>1.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>249 (72%)</td>
<td>187 (72%)</td>
<td>36 (72%)</td>
<td>26 (63%)</td>
<td>0.528</td>
</tr>
</tbody>
</table>
scribed more than two different biologic agents. Among the patients being prescribed only one biologic agent, the majority (82%) was continuously treated. Among the intermittently treated patients, 60% had been prescribed two or more different biologic agents. The mean number of different biologic agents during the study period was significantly higher for the intermittently treated patients than for the continuously treated ones or those who had terminated biologic treatment within the study period (p < 0.001). According to the PsoReg registration, the majority of patients (72%) had been treated with methotrexate during some time of the study period.

Figures 2–4 present mean values of PASI (fig. 2), DLQI (fig. 3) and EQ-5D (fig. 4) before switch and at follow-up 24–52 weeks after switch (the number of patients with assessments is largest within this interval) for patients with continuous, intermittent and terminated biologic treatment. Since the number of PASI, DLQI and EQ-5D assessments varied between patients, the values presented are based on the mean value for the patients during the follow-up interval. Online supplementary tables S1–S3 (for all online supplementary material, see www.karger.com/doi/10.1159/000371881) present results on PASI, DLQI and EQ-5D at all follow-up intervals (12–24 weeks, 24–52 weeks and >52 weeks) by analysis groups.

Before switch to a biologic agent no significant differences in PASI, DLQI or EQ-5D were identified between patients with intermittent, continuous or terminated treatment. Significant differences (p < 0.001) between before switch and 24–52 weeks after switch were found in PASI, DLQI and EQ-5D regardless of whether patients were treated continuously or intermittently. Both at 24–52 weeks and >52 weeks after switch, significant differences in PASI were found between the analysis groups, with continuously treated patients having lower values. After switch significant differences were found in DLQI, with again lower values for continuously treated patients.

**Fig. 2.** Mean PASI values before switch and 24–52 weeks after switch to biologic treatment.

**Fig. 3.** Mean DLQI values before switch and 24–52 weeks after switch to biologic treatment.

**Fig. 4.** Mean EQ-5D values before switch and 24–52 weeks after switch to biologic treatment.
At 24–52 weeks after switch, no significant differences were found in EQ-5D between the continuously and the intermittently treated patients. However, at follow-up 12–24 weeks and >52 weeks after switch, significant differences were found, with higher quality of life values for continuously treated patients (online suppl. tables S1–S3).

Table 2 presents pharmaceutical data for patients registered in PsoReg based on drug data retrieved from the pharmaceutical registry. The number of days with treatment among the intermittently treated patients is based on the total intermittent period, including breaks, and not only the actual days with treatment. Continuously treated patients had higher mean annual cost than intermittently treated patients, although this was not statistically significant (p = 0.177). The median annual cost nevertheless differed less, indicating that the distribution of costs is skewed and that some patients account for very high costs. The quartile with the highest annual costs in the continuously treated group (n = 56) differs regarding the number of different biologic agents, the number of days with treatment and the defined daily dose. Comparing the quartile with the highest annual cost with the other patients in the continuously treated group, the number of days with treatment was smaller and the defined daily dose was higher for high-cost patients. Also, approximately 40% of high-cost patients had been prescribed two or more different biologic agents compared to 20% for the other patients.

According to data from the pharmaceutical registry, approximately 30% of patients in the continuous and intermittent group (higher for patients with terminated treatment) had filled prescriptions of methotrexate together with biologics. This figure considers methotrexate that is dispatched during the actual time the patient is treated with biologic treatment compared to the much higher figure (approximately 70%) in table 1, which refers to patients who were treated with methotrexate during some period when registered in PsoReg.

| Table 2. Data on number of days, total cost (SEK), total annual cost (SEK) and defined daily dose for biologic agents according to data on dispatched pharmaceuticals from the pharmaceutical registry for patients registered in PsoReg |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| All patients | Continuous | Intermittent | Terminated |
| Number of patients | 257 | 176 | 46 | 35 |
| Number of days | 623±426 | 635±426 | 650±428b | 526±425 |
| Mean ± SD | 558 | 580 | 575 | 364 |
| Median | 294–914 | 311–954 | 347–960 | 216–813 |
| IQR | 186,915 | 208,980 | 164,925 | 131,940 |
| Total cost | 238,553±175,993 | 250,326±176,929 | 234,343±188,322 | 184,888±146,439 |
| Mean ± SD | 194,851±277,721 | 133,454±52,713 | 142,623±53,842 |
| Median | 145,033 | 135,078 | 145,373 |
| Defined daily dose | 1.29±1.68 | 1.43±1.99 | 0.95±0.38 | 1.00±0.38 |
| Mean ± SD | 1.01 | 0.95 | 1.00 |
| Median | 0.84–1.24 | 0.87–1.30 | 0.72–1.14 |
| IQR | 1.01 | 1.03 | 0.95 |

IQR = Interquartile range.

*The number of patients is fewer than in table 1 since the data extraction period in the pharmaceutical registry was shorter (until December 2007) than in PsoReg (until August 2013). Total treatment period including treatment gaps. Calculated as (total cost/number of days) × 365.

Discussion

We analysed biologic treatment of moderate to severe psoriasis in real-world practice based on PsoReg, the Swedish registry for systemic psoriasis treatment. The most common treatment pattern for biologics among patients switching from conventional to biologic treatment was...
continuous treatment (74%). The intermittently treated patients (14%) differed in some aspects. The mean number of biologic agents was greater (p < 0.001). No significant differences in PASI, DLQI and EQ-5D were identified before switch, but intermittently treated patients reported higher PASI and DLQI values after switch compared to the two other groups. Intermittently treated patients also tended to report poorer quality of life in terms of lower EQ-5D values after switch. While distributions of annual costs and days of treatment overlapped, mean and median values indicated potentially important differences.

Our observational real-world data on prescription patterns for patients initiating biologic agents during 2007–2013 in clinical practice corroborated results from clinical trials: intermittent treatment with biologics has an inferior effect compared to continuous treatment [6]. On the other hand, continuous treatment with biologics is costly [6], which is also shown in our data from the pharmaceutical registry, where continuously treated patients had a higher mean annual cost than intermittently treated patients. Nevertheless, results from other studies indicate that continuous treatment with biologics might decrease overall costs due to improved adherence, patient quality of life and patient productivity [6]. In addition, the fact that the acquisition costs of biologics will go down in Europe, based on two recent decisions of the European Medicines Agency (i.e. the acceptance of biosimilars for infliximab and the acceptance of second-generation biologics as first-line treatment for psoriasis [12, 13]) should be considered when interpreting the results.

Our inclusion criteria selected a subgroup of all patients with psoriasis on biologics. We required at least one follow-up and also a registration of outcome measures before treatment initiation with biologics. PsoReg contains another 800+ patients on biologic treatment, but those had already been prescribed biologics at the time of registration in PsoReg. This means that although we found a limited number of patients on intermittent treatment, the actual number and proportion are likely to be much larger.

**Study Limitations**

The reason for intermittent treatment was not recorded. The intermittently treated patients may be a heterogeneous group, and a limitation is that it cannot be determined whether less than continuous use was offered to handle negative aspects (e.g. side effects, poor clinical effect, comorbidities), positive aspects (e.g. ‘curative’ or seasonal variation in disease), cost containment at the hospital department level or contraindications such as pregnancy. It is also possible that intermittent treatment could be associated with difficulties in finding the appropriate treatment for the individual patient as 60% had two or more biologic agents. This may be contrasted with 84% of people with continuous treatment who remained on the first biologic agent throughout the study period.

Future research should try to address the reasons for being intermittently or continuously treated, i.e. whether there is an intention for intermittent treatment beforehand or whether intermittent treatment is decided on based on treatment outcome, as well as an analysis of the overall health care costs and indirect costs.

Further, we did not apply an experimental design with the aim of measuring treatment efficacy. Instead we had an explorative design where the analysis groups were defined by actual treatment decisions made in clinical practice. The results highlight the importance of further research not in the majority that do well on the prescribed treatment, but where changes and interruptions indicate the need for new strategies to improve treatment outcome. The results presented here would not recommend a registry-based randomized clinical trial as trends point at intermittent treatment being inferior, and it may be considered unfeasible and even unethical to conduct an experimental trial randomizing people to a treatment that is likely to reduce patient benefits. Instead, future studies should further explore the potential of using large sample and nation-wide observational data and statistical methods that correct for selection bias in the sampling for further causal inference [14, 15].

In summary, our observational data indicate that it is unlikely that intermittent treatment gives similar outcomes to continuous treatment with biologics. While intermittent treatment is associated with lower annual costs of pharmaceuticals, these cost savings were associated with lower patient benefits.

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This research was done in adherence to the Declaration of Helsinki guidelines and was approved by the Umeå Ethical Review Board, Sweden. The project was conducted with informed consent from the patients. Patients were registered after informed consent had been obtained. Both data and consent were collected electronically to assure effective logistics in this nationwide project.

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**Disclosure Statement**

None of the authors has any conflict of interest to declare.

**References**