Association Between Short-Term PASI90 Achievement and Drug Survival of Biologics in Patients with Psoriasis

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Background: With accumulating evidence that achieving a 90% improvement in the Psoriasis Area and Severity Index score (PASI90) has better correlation with improved health-related quality of life as compared to PASI75 achievement, there has been demand for establishing new treatment goals for psoriasis.

Objective: We investigated whether the short-term PASI90 achievement would predict longer drug survival as compared to PASI75 achievement.

Methods: This single-center retrospective cohort study reviewed 180 treatment series in 128 patients with plaque psoriasis, who were treated with tumor necrosis factor-alpha inhibitors (n=12), ustekinumab (n=88), secukinumab (n=23), guselkumab (n=45), and ixekizumab (n=12). The first effectiveness assessment, usually performed within 12 to 20 weeks, was considered a short-term treatment response to biologics.

Results: After adjustment for covariates, time-dependent Cox proportional hazards regression analysis showed that moderate responders (short-term achievement of ≥PASI75 but <PASI90) were more likely to discontinue therapy than the excellent responders (short-term achievement of PASI90; adjusted hazard ratio, 3.159; 95% confidence interval, 1.180~8.457; p=0.0220).

Conclusion: The short-term PASI90 achievement is a better predictor of longer drug survival as compared to PASI75 achievement.

Keywords: Biological products, Prognostic factor, Psoriasis, Survival analysis, Treatment outcome

INTRODUCTION

Biologics have revolutionized the treatment of psoriasis with their high levels of efficacy, safety, and convenience¹. Achieving a 75% improvement in the Psoriasis Area and Severity Index score (PASI75) from the baseline was initially considered the optimal treatment goal for psoriasis. However, with the recent developments in biologics, PASI90 or even PASI100 has been considered the treatment goal². In addition, a recent review article revealed that PASI90 provides better discriminatory value as compared to PASI75, based on its better association with achieving a Dermatologic Life Quality Index (DLQI) score of 0~1. This score indicates that the disease has no effect on the patient’s health-related quality of life (HRQoL)²⁻⁴.

Drug survival is defined as the duration of time patients remain on a certain drug⁵. Since the patient population in the real world is different from that in clinical trials, and factors such as long-term safety, administration interval, and patient or doctor preferences are as important as the effectiveness of drug, the concept of drug survival has become important⁵⁻⁷. Although the results vary between studies, factors such as female sex and previous exposure to biologics were associated with shorter drug survival in psoriasis⁸⁻¹².

In Korea, PASI is evaluated regularly in patients with psoriasis undergoing treatment with biologics and receiving insurance benefits. The first PASI assessment is performed...
within 12 to 20 weeks after the first administration, based on the reimbursement plans. We investigated whether short-term PASI90 achievement, PASI90 achievement at the first PASI assessment, would predict drug persistence better as compared to PASI75 achievement in patients with psoriasis.

MATERIALS AND METHODS

Data source
This single-center retrospective cohort study reviewed the electronic medical records of patients with psoriasis who underwent treatment with biologics at SMG-SNU Boramae Medical Center, an academic hospital in Korea from January 2010 to February 2021. These biologics included tumor necrosis factor-alpha (TNF-α) inhibitors (adalimumab, etanercept, and infliximab), ustekinumab, guselkumab, secukinumab, and ixekizumab. This study was approved by the Institutional Review Board (IRB) of SMG-SNU Boramae Medical Center (IRB no. 30-2021-3).

Study population and data acquisition
All patients were diagnosed with plaque psoriasis by experienced dermatologists and were included in this study only if they received more than one dose of biologics. We extracted the following data from the patients’ medical records: age at the start of biologic therapy; sex; height; weight; body mass index; comorbid disease (psoriatic arthritis, diabetes mellitus, hypertension, dyslipidemia, hepatic disease, and renal disease); biologics used; number of previously used biologics; documented PASI scores; and reasons for discontinuation of biologics (lack of effectiveness, economic reasons, adverse events, or others).

Regular PASI assessment for reimbursement is mandatory to maintain health insurance coverage for biologics, except for patients undergoing treatment at their own expense. In Korea, patients with PASI score >10, who fulfill specific requirements such as treatment failure after more than 3 months of phototherapy and conventional systemic agents (cyclosporine and methotrexate), respectively, are eligible to receive reimbursement for biologics. The effectiveness of biologics must be regularly evaluated in them. The first effectiveness assessment is usually performed within 12 to 20 weeks, which is when the efficacy of the biologics nearly reaches a peak according to clinical trials. The first assessment schedules for different biologics are as follows: after 12 weeks of use for etanercept, secukinumab, ixekizumab, and guselkumab; after 14 weeks of use for infliximab; and after 16 weeks of use for adalimumab and ustekinumab. For instance, patients on secukinumab are evaluated between 12 weeks (after the 7th dose) and 16 weeks (before the 8th dose) after the initiation of secukinumab. Considering that biologics are usually used over a long period, the first effectiveness assessment was considered a short-term treatment response to biologics. The follow-up assessment is performed every 6 months for all biologics. Achieving PASI75 at every assessment is necessary; if not, the physician should change the biologics or return to conventional treatments. All patients receive biologics at an approved dose in Korea. Dose escalation due to inadequate response is only possible if the treatment is at the patient’s own expense, which was not the case in this study.

Drug survival
Drug survival was defined as the duration of time for which a patient remained on a biologic until an event had occurred, and an event was defined as the discontinuation of the drug. If a patient was lost to follow-up or had a shorter follow-up period than the study period, the patient was censored. In case the biologic treatment was interrupted for ≥3 months (≥6 months in case of ustekinumab), each treatment course was counted separately.

Statistical analysis
Data are expressed as means±standard deviations (SD) for continuous variables and frequencies with percentages for categorical variables. A preliminary Shapiro-Wilk test was first conducted to test the normality of the continuous variables, followed by either one-way analysis of variance or Kruskal-Wallis test, as appropriate, to evaluate the differences in the distribution. For categorical variables, the chi-square test or Fisher’s exact test was used. Kaplan-Meier plots were constructed to depict descriptive unadjusted survival curves and then compared using the log-rank test. Predictors influencing biologic drug survival were analyzed using time-dependent Cox proportional hazards regression analysis for patients who received multiple treatment series. Univariable analysis was conducted with p-value set at <0.05. Extracted covariates and frequently reported predictors (sex and biologic naivety) were then incorporated into the multivariable Cox regression analysis. The following covariates were considered: age at start of the biologic treatment (years); sex (male or female); weight (kg); body mass index (kg/m²); presence of psoriatic arthritis;
number of comorbidities, except for psoriatic arthritis (0 or ≥1); number of previously used biologics (0, 1, or ≥2); biologics used (TNF-α inhibitors, ustekinumab, guselkumab, secukinumab, or ixekizumab); biologics use covered by insurance or not; mean baseline PASI score; and short-term treatment response to biologics (non-responders, moderate responders, or excellent responders). Non-responders were those who failed to achieve PASI75 in the first effectiveness assessment, while excellent responders were those who achieved ≥PASI90; the rest were classified as moderate responders.

All statistical tests were two-sided, with p-values <0.05 considered statistically significant. Data collection and statistical analyses were performed using IBM SPSS 27.0 (IBM Corp., Armonk, NY, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics
The patient characteristics recorded at the initiation of each treatment series are shown in Table 1. We identified 128 patients with psoriasis who received biologics. Of the total 180 treatment series, TNF-α inhibitors were administered in 12, ustekinumab in 88, secukinumab in 23, guselkumab in 45, and ixekizumab in 12. Overall, the treatment series comprised 130 (72.2%) male with a mean±SD age of 44.1±14.2 years. Age, sex, body mass index, and comorbidities were comparable across all biologics. Notable differences among biologic cohorts were noted in the mean baseline PASI scores, treatment duration, presence of psoriatic arthritis, and the number of previous biological treatments. Patients treated with TNF-α inhibitors and ixekizumab had a relatively higher baseline PASI score as compared to those treated with other treatment series. Many patients with psoriatic arthritis were treated with secukinumab. The majority of patients who received ustekinumab were biologic-naïve, while majority of those treated with ixekizumab were biologic-experienced.

Table 1. Patient characteristics at the initiation of each treatment series

| Characteristic                        | TNF-α inhibitors | Ustekinumab | Secukinumab | Guselkumab | Ixekizumab | Overall   | p-value |
|---------------------------------------|------------------|-------------|-------------|------------|------------|-----------|---------|
| Male, n (%)                           | 8 (66.7)         | 59 (67.0)   | 18 (78.3)   | 38 (84.4)  | 7 (58.3)   | 130 (72.2)| 0.181†  |
| Mean age (SD), yr                     | 49.3 (13.6)      | 43.6 (13.9) | 42.7 (15.0) | 44.0 (14.9)| 45.3 (13.4)| 44.1 (14.2)| 0.742‡  |
| Mean body mass index (SD), kg/m²      | 24.5 (3.7)       | 24.9 (3.7)  | 27.0 (4.6)  | 25.4 (3.6) | 27.5 (5.1) | 25.5 (4.0) | 0.133‡  |
| Mean baseline PASI (SD)               | 18.5 (11.5)      | 12.1 (6.5)  | 12.2 (6.8)  | 11.6 (3.7) | 17.4 (6.7) | 12.2 (6.6) | 0.021§  |
| Median treatment duration (IQR), wk   | 23.5 (12.0~04.0) | 87.4 (40.3~189.0) | 40.0 (17.0~84.9) | 60.0 (28.6~78.1) | 35.0 (16.0~64.0) | 62.9 (28.3~122.3) | <0.001§  |
| PsA, n (%)                            | 0 (0)            | 2 (2.3)     | 6 (26.1)    | 0 (0)      | 1 (8.3)    | 9 (5.0)   | 0.001†  |
| Comorbidities, excluding PsA, n (%)   |                  |             |             |            |            |          | 0.605†  |
| 0                                     | 5 (41.7)         | 52 (59.1)   | 10 (43.5)   | 29 (64.4)  | 8 (66.7)   | 104 (57.8)|        |
| 1                                     | 3 (25.0)         | 22 (25.0)   | 8 (34.8)    | 11 (24.4)  | 2 (16.7)   | 46 (25.6)|        |
| ≥2                                    | 4 (33.3)         | 14 (15.9)   | 5 (21.7)    | 5 (11.1)   | 2 (16.7)   | 30 (16.7)|        |
| Previous biological treatments, n (%)|                  |             |             |            |            |          | <0.001† |
| 0                                     | 5 (41.7)         | 82 (93.2)   | 16 (69.6)   | 28 (62.2)  | 3 (25.0)   | 134 (74.4)|        |
| 1                                     | 4 (33.3)         | 4 (4.5)     | 6 (26.1)    | 16 (35.6)  | 4 (33.3)   | 34 (18.9)|        |
| ≥2                                    | 3 (25.0)         | 2 (2.3)     | 1 (4.3)     | 1 (2.2)    | 5 (41.7)   | 12 (6.7)|        |

IQR: interquartile range, PASI: psoriasis area and severity index, PsA: psoriatic arthritis, SD: standard deviation, TNF-α: tumor necrosis factor-alpha. *Included diabetes mellitus, hypertension, dyslipidemia, hepatic disease, and renal disease. †Chi-square test. ‡One-way analysis of variance. §Kruskal-Wallis test. ¶Fisher’s exact test.
as compared to moderate responders (≥PASI75 but <PASI90) in all treatment series (p=0.003) and in biologic-naïve patients (p=0.008). This tendency was also noted in biologic-experienced patients, but the difference was not significant (p=0.177). Non-responders (<PASI75) had the lowest drug survival, because the failure to achieve PASI75 required the doctors to change the biologics or return to conventional treatments under the reimbursement plans in Korea.
Table 2 presents the results from the univariable and multivariable time-dependent Cox regression analyses examining the predictors of drug discontinuation. The univariable model showed that the following were predictors of drug discontinuation: old age (crude hazard ratio [HR], 1.029; 95% confidence interval [CI], 1.007~1.050; p=0.0083), use of TNF-α inhibitors as compared to ustekinumab (HR, 3.476; 95% CI, 1.520~7.947; p=0.0032), having comorbidities other than psoriatic arthritis (HR, 1.864; 95% CI, 1.094~3.176; p=0.0220), biologics use not covered by insurance (HR, 2.228; 95% CI, 1.034~4.798; p=0.0407), and worse short-term treatment response (HR, 12.299; 95% CI, 4.597~32.907; p<0.0001 for non-responders and HR, 2.946; 95% CI, 1.361~6.376; 95% CI, 0.579~1.677; p=0.9352).

| Variable                        | Univariable analysis     |          |          | Multivariable analysis    |          |
|---------------------------------|--------------------------|----------|----------|--------------------------|----------|
|                                 | HR (95% CI)              | p-value  | HR (95% CI) | p-value                  |          |
| Age                             | 1.029 (1.007~1.050)      | 0.0083   | 1.012 (0.986~1.040) | 0.3650                  |          |
| Sex                             |                          |          |          |                          |          |
| Female                          | 1 (reference)            |          | 1 (reference)        | 0.8941                  |          |
| Male                            | 0.978 (0.570~1.677)      | 0.9352   | 1.045 (0.543~2.013) | 0.8142                  |          |
| Weight                          | 1.001 (0.982~1.021)      | 0.8888   |          | -                        |          |
| Body mass index                 | 0.992 (0.903~1.089)      | 0.8142   |          | -                        |          |
| Comorbid PsA                    |                          |          |          |                          |          |
| Psoriasis alone                 | 1 (reference)            |          | 1 (reference)        | 0.7795                  |          |
| Comorbid PsA                    | 0.843 (0.255~2.789)      | 0.220    |          | -                        |          |
| Comorbidities excluding PsA*    |                          |          |          |                          |          |
| No comorbidity                  | 1.864 (1.094~3.176)      | 0.0022   | 1.603 (0.852~3.015)  | 0.1434                  |          |
| ≥1 comorbidities               |                          |          |          |                          |          |
| Number of previous biologics    |                          |          |          |                          |          |
| 0 (biologic-naïve)              | 1.334 (0.724~2.460)      | 0.3558   | 1.168 (0.557~2.448)  | 0.6815                  |          |
| 1                               | 1.758 (0.593~5.210)      | 0.3084   | 1.236 (0.311~4.906)  | 0.7632                  |          |
| ≥2                              |                          |          |          |                          |          |
| Biologics                       |                          |          |          |                          |          |
| Ustekinumab                     | 1 (reference)            |          | 1 (reference)        | 0.6959                  |          |
| TNF-α inhibitors                | 3.476 (1.520~7.947)      | 0.0032   | 2.271 (0.738~6.987)  | 0.1524                  |          |
| Secukinumab                     | 0.636 (0.220~1.836)      | 0.4024   | 1.373 (0.508~3.707)  | 0.5322                  |          |
| Guselkumab                      | 0.583 (0.257~1.323)      | 0.1967   | 0.835 (0.348~2.004)  | 0.6872                  |          |
| Ixekizumab                      | 0.6334 (0.105~3.816)     | 0.6183   | 0.598 (0.045~7.899)  | 0.6959                  |          |
| Biologics use covered by insurance |                          |          |          |                          |          |
| Yes                             | 1 (reference)            |          | 1 (reference)        | 0.6074                  |          |
| No                              | 2.228 (1.034~4.798)      | 0.0407   | 1.263 (0.518~3.080)  | 0.6074                  |          |
| Baseline PASI                   | 0.984 (0.958~1.011)      | 0.2391   |          | -                        |          |
| Short-term treatment response   |                          |          |          |                          |          |
| Excellent responders            | 2.946 (1.361~6.376)      | 0.0061   | 3.159 (1.180~8.457)  | 0.0220                  |          |
| Non-responders                  | 12.299 (4.597~32.907)    | <0.0001  | 10.659 (3.247~34.996) | 0.0001                  |          |

CI: confidence interval, HR: hazard ratio, PASI: Psoriasis Area and Severity Index, PsA: psoriatic arthritis, TNF-α: tumor necrosis factor-alpha. *Included diabetes mellitus, hypertension, dyslipidemia, hepatic disease, and renal disease.
S Choi, et al

**Table 3. Reasons for discontinuation of biologics (n=63)**

| Characteristic                              | Lack of effectiveness (n=43) | Economic reasons (n=13) | Adverse events (n=5) | Others (n=2) |
|---------------------------------------------|------------------------------|-------------------------|---------------------|--------------|
| **Biologics**                               |                              |                         |                     |              |
| TNF-α inhibitors (n=10)                    | 9 (90.0)                     | 1 (10.0)                | 0                   | 0            |
| Ustekinumab (n=42)                         | 26 (61.9)                    | 12 (28.6)               | 2 (4.8)             | 2 (4.8)      |
| Secukinumab (n=4)                          | 2 (50.0)                     | 0                       | 2 (50.0)            | 0            |
| Guselkumab (n=6)                           | 6 (100)                      | 0                       | 0                   | 0            |
| Ixekizumab (n=1)                           | 0                            | 0                       | 1 (100)             | 0            |
| **Biologic naivety**                       |                              |                         |                     |              |
| Naive (n=46)                               | 29 (63.0)                    | 12 (26.1)               | 3 (6.5)             | 2 (4.3)      |
| Experienced (n=17)                         | 14 (82.4)                    | 1 (5.9)                 | 2 (11.8)            | 0            |
| **Short-term treatment response**          |                              |                         |                     |              |
| Excellent responders (n=9)                 | 1 (11.1)                     | 4 (44.4)                | 2 (22.2)            | 2 (22.2)     |
| Moderate responders (n=38)                 | 29 (76.3)                    | 7 (18.4)                | 2 (5.3)             | 0            |
| Non-responders (n=16)                      | 13 (81.3)                    | 2 (12.5)                | 1 (6.3)             | 0            |

Values are presented as number (%). TNF-α: tumor necrosis factor-alpha.

**DISCUSSION**

Our study revealed that short-term PASI90 achievement was significantly associated with drug persistence as compared to PASI75 achievement after adjustment for covariates, indicating that PASI90 can be a predictor of longer drug survival of biologics. Frequently reported predictors of drug survival, such as sex and biologic naivety, did not show significant associations with drug survival in our study.

There is accumulating evidence showing that PASI90 achievement has a better correlation with HRQoL improvement and DLQI score of 0~1, indicating that the disease has no effect on the patient’s HRQoL. This explains our findings that short-term PASI90 achievement would lead to drug persistence. The 2011 European consensus on treatment goals for psoriasis defined treatment success as achieving ≥PASI75...
or achieving ≥PASI50 and DLQI score ≤5. However, it is now known that PASI90 provides better discriminatory value for better HRQoL as compared to PASI75, and the advancement of biologics has made it possible to achieve PASI90 at a high rate. Therefore, there is a demand for establishing new treatment goals for psoriasis, and even considering skin clearance as a treatment goal. Keeping pace with this change, the recent European guideline on the systemic treatment of psoriasis clarified that the aim should be for higher treatment goals such as PASI90 or PASI100.

In addition to the PASI90 and HRQoL association, the behavioral factors of patients and doctors may have contributed to our findings. First, patients may not have been satisfied with a moderate response (PASI75). Okubo et al. found a misalignment of approximately 70% in the treatment goal between patients and doctors. Patients were likely to set higher goals than the doctors and expect complete clearance. Furthermore, a study conducted in UK revealed that discordance between the patient and doctor in measuring the psoriasis severity was quite common. This discordance is known to be associated with patient dissatisfaction, lower compliance, and worse disease outcomes, which can influence the drug survival. Besides, with the development of biologics and the high rates of PASI90 achievement, even doctors may not be satisfied with only a moderate response. However, they are likely to aim for excellent responses, which is reflected in the demand for establishing new treatment goals for psoriasis.

Although the predictors of drug survival of biologics in psoriasis patients varies among different studies, a recent meta-analysis demonstrated that female sex and obesity were predictors of drug discontinuation, and some observational studies revealed that biologic naïveté was a predictor of drug persistence. However, we did not find any significant association after adjusting for short-term treatment response. Although short-term treatment response might be a missing covariate in the previous studies, race difference could partly explain the difference in the results based on a study conducted in Japan, which also found that sex and biologic naïveté were not associated with drug survival of biologics.

In the analysis of the reasons for drug discontinuation, the main reason was the lack of effectiveness, as expected. Notably, economic reasons were the second most common cause for discontinuation, especially in biologic-naïve patients receiving ustekinumab. Majority of them were not eligible for reimbursement (less severity of disease) and were treated at their own expense. These patients may have higher expectations of effectiveness as compared to those receiving insurance benefits, which would have resulted in dissatisfaction with the treatment results in the former.

Our study was limited by its retrospective design, because not all covariates were recorded precisely or there could have been some missing and unmeasured confounding factors. Second, because dose escalation is almost impossible in Korea due to insurance issues, it could influence drug survival. Last, there were not many cases treated with TNF-α inhibitors as compared to previous studies on drug survival.

In conclusion, we demonstrated that short-term PASI90 achievement is a better predictor of drug persistence as compared to PASI75 achievement. Practical treatment goals for psoriasis, such as PASI90 or absolute PASI cut-offs, need to be discussed further to keep up with the developments brought about by biologics.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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