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ORIGINAL ARTICLE

Economic Factors as Major Determinants of Ustekinumab Drug Survival of Patients with Chronic Plaque Psoriasis in Korea

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Background: Drug survival, defined as the time until discontinuation, is a parameter reflecting real-world therapeutic effectiveness. Few studies have examined the influence of economic factors on the drug survival of biologic agents for psoriasis, particularly in Asian countries. **Objective:** To determine the drug survival for ustekinumab in real-life settings and investigate the factors affecting drug survival for psoriasis patients in Korea. **Methods:** We evaluated 98 psoriasis patients who were treated with ustekinumab at a single center. We analyzed the efficacy and drug survival of ustekinumab. Cox proportional hazard analysis and competing risk regression analysis were performed to reveal the factors affecting the drug survival of ustekinumab. **Results:** The overall mean drug survival was 1,596 days (95% confidence interval [CI], 904～2,288). Among the 39 cessations of ustekinumab treatment, 9 (23.1%) patients discontinued treatment after experiencing satisfactory results. Multivariate Cox proportional hazard analysis revealed that paying on patients' own expense was the major predictor for the discontinuation of ustekinumab (hazard ratio [HR], 9.696; 95% CI, 4.088～22.998). Competing risk regression analysis modeling of discontinuation because of factors other than satisfaction of an event also revealed that ustekinumab treatment at the patient's expense (HR, 4.138; 95% CI, 1.684～10.168) was a predictor of discontinuation rather than satisfaction. **Conclusion:** The results of our study revealed that the cost of biologics treatment affects the drug survival of ustekinumab and suggested that economic factors affect the drug survival of ustekinumab treatment in Korea. **(Ann Dermatol 30(6) 668～675, 2018)**

-Keywords-
Costs and cost analysis, Drug survival, Economic factors, Psoriasis, Ustekinumab

INTRODUCTION

Psoriasis is a chronic and relapsing inflammatory skin disorder. Because the skin lesions of psoriasis can be a psychological burden to patients, effective treatment is very important. Physicians and patients choose their treatment modalities based on the severity and activity of psoriasis as well as patient's characteristics such as comorbidity or responses to past treatments[1]. Among the wide range of treatment modalities, newly introduced biological agents that disrupt the action of cytokines related to the pathogenesis of psoriasis have advantages over conventional systemic treatment modalities: they maintain their therapeutic effects during long-term continuous treatment and have no cumulative toxicities[2,3].

Numerous studies have evaluated the effectiveness of biological agents in the treatment of psoriasis. However, the

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results of randomized clinical trials have not provided sufficient information on the long-term therapeutic effects and the results may be biased when only eligible patients are included[4]. Drug survival of biological agents is a newly introduced method to evaluate the long-term effectiveness[5]. Drug survival is defined as the time period between the initiation and cessation of a certain drug and is a comprehensive measure reflecting the therapeutic effect as well as other factors such as adverse effects, compliance, and preferences of physicians and patients[3-7]. Thus, analysis of drug survival can overcome the limitations of the results of clinical studies[5]. In addition, studies of drug survival can identify predictors of the survival of a specific drug[7-9]. Previous studies revealed that efficacy loss, gender, and previous exposure to biologic agents are associated with the discontinuation of biological agents for psoriasis[7-9].

In this study, we evaluated the drug survival of ustekinumab for the treatment of psoriasis in South Korea. Moreover, we analyzed the predictors of drug survival of ustekinumab.

MATERIALS AND METHODS

Patients and data acquisition

This was a retrospective analysis of 98 psoriasis patients treated with ustekinumab in a psoriasis clinic in a tertiary referral hospital. To investigate factors affecting the drug survival of ustekinumab, we analyzed ustekinumab treatment of the enrolled patients. The enrolled subjects were real-world psoriasis patients who received ustekinumab for psoriasis between November 2011 and April 2016. This study was approved by the institutional review board of our hospital (IRB no. B-1603-338-102).

We collected demographic data, comorbid disease, previous therapies for psoriasis, and baseline psoriasis characteristics of patients. The data concerning the treatment of ustekinumab such as Psoriasis Area and Severity Index (PASI) scores at baseline and at each follow-up visit, adverse events during treatment, and reasons for discontinuation of ustekinumab treatment were also acquired. The reasons for discontinuation were classified as sufficient improvement, adverse events, treatment failure, patient' request, and lost to follow-up.

To investigate the influence of economic factors on the drug survival of biological agents for psoriasis, we collected data for the method of payment for ustekinumab treatment. In South Korea, the National Health Insurance only pays for ustekinumab treatment when the severity of psoriasis is moderate to severe and previous treatments with conventional systemic agents or phototherapy failed to achieve sufficient efficacy. However, psoriasis patients who do not meet these requirements can be treated with ustekinumab at their own expense if desired.

Ustekinumab treatment and analysis of drug survival

For all enrolled patients, the treatment regimen was as follows: ustekinumab was administered subcutaneously at a dose of 45 mg at weeks 0 and 4 and every 12 weeks thereafter. To assess the severity and response to ustekinumab treatment, we collected the PASI score at baseline and at each follow-up visit and calculated the PASI75 and PASI90 (reduction in PASI score by 75% and 90%, respectively) at 16 weeks and 28 weeks of ustekinumab treatment.

Drug survival was calculated based on the duration of ustekinumab treatment between the date of initiation and date of discontinuation. The date of discontinuation was defined as the date on which the treatment modality was changed to other modalities or the presumed visit date of the first missed ustekinumab injection (date of discontinuation is the date at 4 weeks after the last injection day if the patient was treated with ustekinumab once or date of discontinuation is the date of 12 weeks after last injection if the patient was treated with ustekinumab at least twice). We defined the discontinuation of ustekinumab as changes to the psoriasis treatment modality from ustekinumab to other treatment modalities or interrupted ustekinumab treatment for more than the presumed visit date of the first missed ustekinumab injection.

Statistical analysis

Overall drug survival was calculated with the reasons for discontinuation by Kaplan-Meier analysis. Cumulative 1-year, 2-year, and 3-year drug retention rates were calculated based on life tables. We also performed univariate Cox proportional hazard analysis to identify covariates affecting the drug survival of ustekinumab treatment. Covariates related to demographics, comorbid disease, previous therapies for psoriasis, characteristics of baseline psoriasis, and responses to ustekinumab treatment were analyzed to identify predictors of drug survival. To reveal the predictive factors for discontinuation of ustekinumab treatment, multivariate Cox proportional hazard analysis was also performed incorporating the covariates which were statistically significant in univariate Cox proportional hazard analysis.

We categorized the reasons for ustekinumab discontinuation as reaching sufficient improvement, adverse events, treatment failure, patient's request, and lost to follow-up. However, patients who discontinued their treatment after reaching sufficient improvement were satisfied with the re-

sult of treatment, and discontinuation after satisfactory improvement should differ from discontinuation because of other reasons. To identify the predictive factors associated with discontinuation of ustekinumab treatment for reasons other than satisfaction, we performed competing risk regression analysis. Thus, we categorized the reasons for discontinuation because of adverse events, treatment failure, patient's request, and lost to follow-up as discontinuation as reasons other than satisfaction. Next, we performed competing risk regression analysis modeling the discontinuation for reasons other than satisfaction of an event of interest in the presence of a competing event of discontinuation after satisfactory improvement. In addition, multivariate competing risk regression analysis was performed incorporating the covariates which were statistically significant in competing risk regression analysis to reveal predictive factors for discontinuation of ustekinumab treatment for reasons other than satisfaction.

The results are expressed as the mean±standard deviation and a *p*-value of <0.05 was considered statistically significant. Data were analyzed using R software (R Foundation, Vienna, Austria) and IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patient characteristics

Between November 2011 and April 2016, 98 psoriasis patients were treated with ustekinumab for psoriasis and enrolled in this study. A total of 98 ustekinumab treatment courses were analyzed (Table 1). Among the 98 enrolled patients, the course of ustekinumab treatment was covered by insurance in 63 (64.3%) patients, while 35 (35.7%) patients were treated at their own expense. The mean age of enrolled patients was 43.6±13.8 years and mean disease duration was 218.9±143.2 months. Female patients accounted for 32 (32.7%) of enrolled patients and the mean body mass index of all patients was 24.2±3.5 kg/m^2. Comorbidity with at least one or more diseases was found in 56 (57.1%) of enrolled patients. Among the enrolled patients, 90 (91.8%) underwent phototherapy for psoriasis treatment and 76 (77.6%) were administered oral treatment such as cyclosporine, methotrexate, and acitretin. Among the enrolled patients, 20 (20.4%) were previously administered biological agents for psoriasis treatment: 19 were administered etanercept and one patient was administered adalimumab.

Overall drug survival rate for ustekinumab treatment and factors affecting drug survival

Thirty-nine patients discontinued ustekinumab during the study period. The overall mean drug survival for ustekinumab treatment was 1,596 days (95% confidence interval [CI], 904~2,288) (Table 2). The overall drug retention rates in the first, second, and third years were 69.1%, 46.4%, and 37.3%, respectively. A total of 38.5% of patients discontinued ustekinumab treatment because they were lost to follow-up, 35.9% by the patients' request, 23.1% after reaching sufficient improvement, and 2.6% because of the development of adverse events.

The results of univariate Cox proportional hazard analysis

Table 1. Baseline demographics and characteristics of patients (n=98)

Characteristics	Value
Age when starting the ustekinumab (yr)	43.6±13.8
Gender	
Male	66 (67.3)
Female	32 (32.7)
Body mass index (kg/m^2)*	24.2±3.5
Comorbidities	
Heart diseases and stroke	9 (9.2)
Diabetes	5 (5.1)
Hyperlipidemia	24 (24.5)
Hypertension	14 (14.3)
Chronic hepatopathy	14 (14.3)
Latent tuberculosis	32 (32.7)
Renal insufficiency	1 (1.0)
Duration of psoriasis (mo)†	218.9±143.2
Previous therapy	
Topical agents	98 (100.0)
Phototherapy	90 (91.8)
Oral agents	76 (77.6)
Cyclosporine A	55 (56.1)
Methotrexate	38 (38.8)
Acitretin	22 (22.4)
Biologic agents	20 (20.4)
Baseline PASI when starting ustekinumab treatment‡	16.1±7.3
PASI75 at 16 weeks§	12 (15.6)
PASI90 at 16 weeks§	3 (3.9)
PASI75 at 28 weeks‖	67 (88.2)
PASI90 at 28 weeks‖	27 (35.5)
Way of paying for ustekinumab treatment	
Treatment covered by national insurance	63 (64.3)
Paying on their own expense	35 (35.7)

Values are presented as mean±standard deviation or number (%). PASI: Psoriasis Area and Severity Index. *Fifteen patients with unknown weight or height were omitted from the calculation. †Two patients with duration not known were omitted from the calculation. ‡Ten patients with baseline PASI not known were omitted from the calculation. §Twenty-one patients with unknown baseline PASI or PASI at 16 weeks were omitted from the calculation. ‖Twenty-two patients with unknown baseline PASI or PASI at 28 weeks were omitted from the calculation.

Table 2. Drug survival for ustekinumab treatment (n=98) and the reasons for discontinuation of ustekinumab treatment (n=39)

Characteristics	Value
Overall median drug survival (d)	1,596 (904~2,288)
Overall drug retention rate	
1-year survival	70 (71.4)
2-year survival	50 (51.0)
3-year survival	29 (29.6)
Reason for ustekinumab discontinuation	
After reaching sufficient improvement	9 (23.1)
Adverse events	1 (2.6)
Treatment failure	0 (0.0)
Loss to follow-up	15 (38.5)
Patients' request	14 (35.9)

Values are presented as mean survival (95% confidence interval) or number (%).

are presented in Table 3. The results showed that high baseline PASI score at the initiation of ustekinumab treatment (hazard ratio [HR], 0.940; 95% CI, 0.886~0.996), previous experience of phototherapy (HR, 0.312; 95% CI, 0.137~0.712), and oral agents (HR, 0.513; 95% CI, 0.265~0.993) were predictors of drug survival, whereas ustekinumab treatment at the patient's expense (HR, 6.901; 95% CI, 3.355~14.198) was a predictor of discontinuation (Fig. 1). In addition, multivariate Cox proportional hazard analysis adjusted for previous phototherapy and oral agents, baseline PASI score at the initiation of ustekinumab treatment, and method of paying for biologics treatment revealed that only ustekinumab treatment at the patient's own expense was a predictor of discontinuation (HR, 9.696; 95% CI, 4.088~22.998) (Table 4).

Table 3. Univariate Cox proportional hazard analysis for ustekinumab treatment (n=98)

Characteristics	Hazard ratio	95% confidence interval	*p*-value
Age when starting the ustekinumab	0.981	0.958~1.004	0.105
Gender			
Female			
Male	0.941	0.486~1.822	0.858
Body mass index*	0.980	0.889~1.081	0.688
Comorbidities	0.966	0.732~1.275	0.807
Heart diseases and stroke	1.303	0.460~3.692	0.618
Diabetes	0.502	0.069~3.663	0.497
Hyperlipidemia	1.224	0.594~2.523	0.584
Hypertension	0.953	0.372~2.442	0.920
Chronic hepatopathy	0.572	0.202~1.617	0.292
Latent tuberculosis	1.019	0.512~2.031	0.957
Renal insufficiency	NA	NA	NA
Previous therapy			
Topical agents	NA	NA	NA
Phototherapy	0.312	0.137~0.712	0.006
Oral agents	0.513	0.265~0.993	0.048
Cyclosporine	0.890	0.470~1.686	0.722
Methotrexate	0.611	0.309~1.207	0.156
Acitretin	0.943	0.433~2.056	0.883
Biologic agents	0.949	0.434~2.075	0.895
Baseline PASI when starting ustekinumab treatment†	0.940	0.886~0.996	0.036
PASI75 at 16 weeks‡	2.323	0.844~6.394	0.103
PASI90 at 16 weeks‡	4.292	0.961~19.181	0.056
PASI75 at 28 weeks§	0.949	0.281~3.202	0.932
PASI90 at 28 weeks§	1.445	0.623~3.347	0.391
Way of paying for ustekinumab treatment			
Treatment covered by insurance			
Paying on their own expense	6.901	3.355~14.198	<0.001
Adverse events	1.772	0.424~7.407	0.433

PASI: Psoriasis Area and Severity Index, NA: not applicable. *Fifteen patients with unknown weight or height were omitted from the calculation. †Ten patients with unknown baseline PASI were omitted from the calculation. ‡Twenty-one patients with unknown baseline PASI or PASI at 16 weeks were omitted from the calculation. §Twenty-two patients with unknown baseline PASI or PASI at 28 weeks were omitted from the calculation.

Competing risk regression analysis and factors affecting discontinuation of ustekinumab for reasons other than satisfaction

Considering that discontinuation after reaching sufficient improvement differs from discontinuation for other reasons, we performed further analysis using a competing risk regression model to reveal the factors affecting ustekinumab discontinuation for reasons other than satisfaction. We categorized reasons of discontinuation because of adverse events, treatment failure, patient's request, and lost to follow-up as discontinuation for reasons other than satisfaction. Next, we performed competing risk regression analysis modeling the discontinuation for reasons other than satisfaction of an event of interest, in the presence of a competing event of discontinuation after satisfactory improvement. We found that ustekinumab treatment at the patient's expense (HR, 4.668; 95% CI, 2.159～10.090) and PASI90 at 16 weeks (HR, 4.774; 95% CI, 1.735～13.134) were predictors of discontinuation for reasons other than satisfaction (Table 5). In addition, multivariate competing risk regression analysis adjusted for PASI90 at 16 weeks and the method of paying for biologics treatment revealed that ustekinumab treatment at the patient's expense (HR, 4.138; 95% CI, 1.684～10.168) was a predictor of discontinuation for reasons other than satisfaction (Table 6).

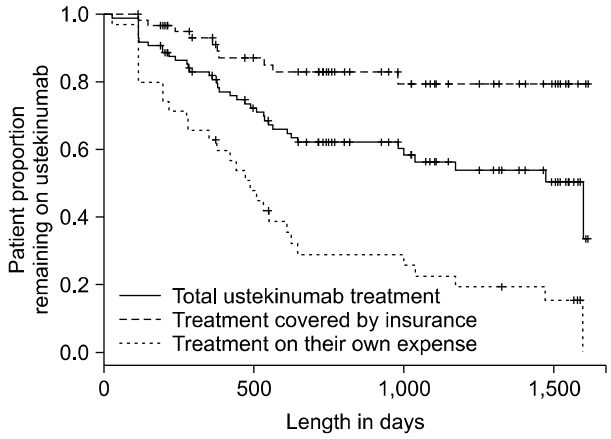

Fig. 1. Overall ustekinumab drug survival and comparison of drug survival between treatment covered by insurance and treatment paid at their own expense. Log-rank test revealed significant differences in drug survival between ustekinumab treatment covered by insurance and on their own expenses ($p<0.001$).

DISCUSSION

Studies on the pathogenesis of psoriasis have enabled the development of biological agents for treating psoriasis. A biological agent inhibits the action of specific molecules that play a role in the pathogenesis of psoriasis[10]. Randomized clinical trials and open label extension studies have shown that the newly introduced biological agents have sustained efficacies and good safety profiles for long-term continuous use[8,11-13]. However, there are significant gaps between the real-life experience and results of randomized clinical trials or open label extension studies[5,8,14]. To overcome these gaps, drug survival, a new measure of effectiveness, was introduced. By analyzing the duration of treatment with a certain drug, drug survival can reveal overall effectiveness including drug efficacy, adverse events, and patient satisfaction[4-6,11,14,15]. This study was a single center, retrospective drug survival analysis of ustekinumab treatment for psoriasis to determine the factors affecting drug survival in Korea. Korea has specialized national insurance coverage standards for the use of biologic agents for plaque psoriasis. Only a small number of moderate to severe psoriasis patients can be reimbursed the cost for biologic agents. Regulation of the use of biologic agents in each country typically affects the prescription pattern of biologic agents of a certain country, as biologic agents are costly worldwide. In this study, we found that the method of paying for treatment with biologics determined the drug survival of ustekinumab treatment: ustekinumab treatment at the patient's expense was

Table 4. Multivariate Cox proportional hazard analysis for ustekinumab treatment (n=98)

Characteristics	Hazard ratio	95% confidence interval	*p*-value
Previous therapy			
Phototherapy	0.955	0.322～2.829	0.934
Oral agents	1.856	0.791～4.354	0.155
Baseline PASI when starting ustekinumab treatment*	0.987	0.934～1.042	0.630
Way of paying for ustekinumab treatment			
Treatment covered by insurance			
Paying on their own expense	9.696	4.088～22.998	<0.001

PASI: Psoriasis Area and Severity Index. *Ten patients with unknown baseline PASI were omitted from the calculation.

Table 5. Univariate competing risk regression analysis for ustekinumab treatment (n=98)

Characteristics	Hazard ratio	95% confidence interval	*p*-value
Age when starting the ustekinumab	0.986	0.961~1.012	0.280
Gender			
Female			
Male	1.239	0.577~2.661	0.580
Body mass index*	0.998	0.897~1.111	0.970
Comorbidities	1.030	0.792~1.340	0.820
Heart diseases and stroke	1.108	0.361~3.399	0.860
Diabetes	0.681	0.087~5.329	0.710
Hyperlipidemia	1.200	0.542~2.657	0.650
Hypertension	0.930	0.324~2.666	0.890
Chronic hepatopathy	0.818	0.288~2.325	0.710
Latent tuberculosis	1.328	0.637~2.769	0.450
Renal insufficiency	NA	NA	NA
Previous therapy			
Topical agents	NA	NA	NA
Phototherapy	0.575	0.213~1.551	0.270
Oral agents	0.548	0.273~1.100	0.091
Cyclosporine	0.894	0.439~1.823	0.760
Methotrexate	0.734	0.345~1.562	0.420
Acitretin	1.443	0.623~3.343	0.390
Biologic agents	0.879	0.349~2.213	0.780
Baseline PASI when starting ustekinumab treatment†	0.980	0.916~1.048	0.550
PASI75 at 16 weeks‡	1.226	0.370~4.065	0.740
PASI90 at 16 weeks‡	4.774	1.735~13.134	0.003
PASI75 at 28 weeks§	1.159	0.274~4.909	0.840
PASI90 at 28 weeks§	1.065	0.399~2.844	0.900
Way of paying for ustekinumab treatment			
Treatment covered by insurance			
Paying on their own expense	4.668	2.159~10.090	<0.001
Adverse events	2.374	0.480~11.737	0.290

PASI: Psoriasis Area and Severity Index, NA: not applicable. *Fifteen patients with unknown weight or height were omitted from the calculation. †Ten patients with unknown baseline PASI were omitted from the calculation. ‡Twenty-one patients with unknown baseline PASI or PASI at 16 weeks were omitted from the calculation. §Twenty-two patients with unknown baseline PASI or PASI at 28 weeks were omitted from the calculation.

Table 6. Multivariate competing risk regression analysis for ustekinumab treatment (n=98)

Characteristics	Hazard ratio	95% confidence interval	*p*-value
PASI90 at 16 weeks*	1.874	0.632~5.552	0.260
Way of paying for ustekinumab treatment			
Treatment covered by insurance			
Paying on their own expense	4.138	1.684~10.168	0.002

PASI: Psoriasis Area and Severity Index. *Twenty-one patients with unknown baseline PASI or PASI at 16 weeks were omitted from the calculation.

found to be the main predictor of discontinuation of ustekinumab treatment.

In this study, 39 patients discontinued ustekinumab during the 5-year study period. The overall median drug survival assessed by Kaplan-Meier survival analysis was 1,596 days (95% CI, 904~2,288). In addition, the analysis also revealed that the overall retention rates of the first, second, and third years were 69.1%, 46.4%, and 37.3%, respectively. Compared to the results of studies in other countries, the overall drug retention rates of our study were low[15-17]. Studies in Germany and the United Kingdom reported that the retention rates of ustekinumab in first, second, and

third years were 90%, 83%, and 83% in Germany and 89%, 82%, and 75% in the United Kingdom, respectively[16,17]. The major difference in Korea affecting the retention rate was the insurance coverage rate for the use of biologic agents in the treatment of psoriasis. In addition, previous studies reported that the occurrence of adverse events, lack of efficacy, and lost to follow-up were reasons for discontinuation of ustekinumab treatment[14,17,18]. In this study, experiencing sufficient improvement accounted for 23% (9 patients) of the total cessation of ustekinumab treatment, which differed from the findings of previous studies[14,17,18]. Based on the results, we revealed that the relatively short duration of ustekinumab treatment and discontinuation of ustekinumab treatment even after experiencing a sufficient improvement were characteristic of the ustekinumab treatment pattern in South Korea.

To identify the factors affecting drug survival of ustekinumab treatment, we performed further analysis using Cox proportional hazard analysis and competing risk regression analysis. The results of univariate Cox proportional hazard analysis revealed that the baseline PASI score at the initiation of ustekinumab treatment, previous experience of phototherapy and oral agents, and the method of paying for biologics treatment affect drug survival of the first ustekinumab treatment. Moreover, multivariate Cox proportional hazard analysis revealed that only treatment at the patient's own expense was a predictor for discontinuation of ustekinumab. Considering that the cost for ustekinumab treatment is high in South Korea if the treatment is not covered by insurance, economic factors affect the drug survival of ustekinumab. Previous studies reported that female sex, presence of comorbidity, and biologic naivety affected the drug survival of ustekinumab[5,16,18]; however, such factors were not found to affect the drug survival of ustekinumab in this study.

Patients discontinue or change their treatment modalities for psoriasis for various reasons. Among the reasons for the discontinuation of ustekinumab, patients who reached sufficient improvement (n=9) were satisfied with the result of ustekinumab treatment and were analyzed separately from the discontinuation because of other reasons (n=30). Thus, we performed further analysis using competing risk regression analysis to identify factors associated with the drug survival of ustekinumab for reasons other than satisfaction and found that ustekinumab treatment at the patient's own expense and PASI90 at 16 weeks affected discontinuation. Multivariate competing risk regression analysis showed that only the ustekinumab treatment at the patient's expense affected discontinuation of ustekinumab for reasons other than satisfaction. The results of competing risk regression analysis were consistent with those of Cox proportional hazard analysis and suggested that socioeconomic factors play an important role in the treatment of ustekinumab for psoriasis.

In conclusion, we found that economic factors influence the drug survival of ustekinumab treatment in South Korea. The duration of ustekinumab treatment was relatively shorter and enrolled patients discontinued their treatment after experiencing sufficient improvement. Moreover, biologics treatment at the patient's own expense was a predictor of discontinuation of ustekinumab. Unlike conventional treatment modalities for psoriasis, newly introduced biologic agents can be used continuously, and previous studies reported that long-term continuous treatment is the most effective option for ustekinumab treatment[2,13]. However, the economic burden of long-term continuous treatment can result in discontinuation of biologic agents[19]. The expansion of insurance coverage for ustekinumab reduces the economic burden of psoriasis patients and enables long-term effective treatment for psoriasis.

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CONFLICTS OF INTEREST

Dr. Youn has served as an advisor, received speaker honoraria and participated in clinical trials for AbbVie, CKD-pharma, Elli-Lilly, Janssen, and Novartis. He participated in a clinical trial for Kyowa-Kirin. He also served as an advisor for Cellgene.

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