ORIGINAL RESEARCH

Apremilast Prolongs the Time to First Biologic Therapy in Japanese Patients with Psoriasis

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ABSTRACT

Introduction: Biologic agents are used in patients with severe psoriasis who have not adequately responded to existing conventional systemic therapies. However, only a limited number of medical institutions in Japan are approved to use them, and their relatively high cost represents a substantial burden to patients. Apremilast is an oral phosphodiesterase-4 inhibitor approved in Japan for the treatment of psoriasis vulgaris in adult patients with an inadequate response to topical therapies and psoriatic arthritis in adult patients with active disease. To date, a large-scale real-world study of treatment patterns and costs associated with apremilast in Japan has not been conducted. The objective of this study was to assess whether apremilast can prolong time to first biologic therapy use and decrease total medical cost.

Methods: Using the Medical Data Vision hospital-based claims database, 506 psoriasis patients were propensity score matched and analyzed (apremilast: $n = 253$; non-apremilast: $n = 253$).

Results: The incidence rate of first biologic therapy use per 1000 patient-years was significantly lower in the apremilast group than in the non-apremilast group (30.3 vs. 107.6; $P < 0.001$), and the total medical costs per month were significantly lower in the apremilast group than in the non-apremilast group (76,594 yen/month vs. 102,411 yen/month, $P < 0.001$). In a sensitivity analysis of a propensity-score-matched subset of eligible patients prescribed biologics during the follow-up period (apremilast: $n = 14$; non-apremilast: $n = 14$), the incidence of first biologic therapy use was 2,797.6 per 1000 patient-years (95% CI: 1,656.9, 4,723.6) in the non-apremilast group and 856.1 per 1000 patient-years (95% CI: 507.0, 1,445.5) in the apremilast group.

Conclusion: These results suggest that apremilast prolongs the time to first biologic therapy use in patients with psoriasis, thereby reducing the total medical cost and decreasing the economic burden on patients.

Keywords: Apremilast; Biologic therapy; Japan medical cost; Psoriasis

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Key Summary Points

Why carry out this study?

Biologic agents for the treatment of psoriasis may be associated with high clinical and economic burden among some patients who do not respond to topical therapies.

This study aimed to assess whether oral apremilast, approved for the treatment of psoriasis in Japan, could prolong the time to biologic use and reduce treatment costs.

What was learned from the study?

Patients treated with apremilast had a lower incidence of biologic use and longer time to biologic use compared with non-apremilast users.

Treatment with apremilast may ultimately reduce the clinical and cost burden on patients with psoriasis, demonstrating an unmet need for additional non-biologic therapies in this patient population.

INTRODUCTION

Treatments for psoriasis include topical agents, oral systemic agents, phototherapy, and biologic therapies. Treatment usually begins with topical corticosteroids or vitamin D3; if topical therapy is ineffective, phototherapy with ultraviolet A or B and systemic therapy with cyclosporine or oral etretinate (a vitamin A analog) are used. The Japanese guidance for the use of biologics for psoriasis specifies that biologics should be used in severe cases in which the patient does not sufficiently respond to existing systemic therapies [1].

Although biologics are highly efficacious, their use is currently limited to institutions approved by the Japanese Dermatological Association [1], where essential examinations and care for serious adverse reactions are available. This ensures that other hospital departments are qualified to treat adverse events associated with the use of biologics, should it be needed. Such institutions are generally limited to cities and are rare in remote towns. Dermatology clinics are also approved to use biologics, in close cooperation with these approved hospitals; however, the total number of such clinics is still limited. This limited access sometimes causes inconvenience for patients who want biologic therapy, especially those who live in small towns. In addition, biologic therapy imposes some inconveniences on patients, such as injection [2] or relatively high drug costs [3]. Therefore, safe and effective systemic therapeutic modalities that are widely available in Japan are needed for patients before they escalate to biologic therapy.

Apremilast is an oral phosphodiesterase-4 inhibitor approved in 2016 in Japan for the treatment of patients with psoriasis vulgaris and psoriatic arthritis who have an inadequate response to topical therapies. Apremilast inhibits phosphodiesterase 4 and increases intracellular cyclic adenosine monophosphate, a mediator of inflammation inhibition, thereby exerting its therapeutic effects. In ESTEEM 1 [4] and ESTEEM 2 [5], which were global phase 3 studies of apremilast in psoriasis that focused on patients with moderate to severe psoriasis who were candidates for phototherapy or systemic therapy, the $\geq 75\%$ improvement from baseline in the Psoriasis Area and Severity Index (PASI-75) response rate was significantly higher for the apremilast group compared with the placebo group, and favorable tolerability was reported, with mostly mild or moderate adverse events. In addition, in the phase 2b FREEDOM study [6] of Japanese patients with moderate to severe psoriasis vulgaris, the PASI-75 response rate was also significantly higher compared with the placebo group, and apremilast showed acceptable safety and tolerability. However, real-world data of Japanese patients treated with apremilast are limited. Some single institutions in Japan have reported real-world data studies of apremilast [7–10], but no large-scale studies have been reported. The primary objective of the present study, which used a nationwide

database, was to calculate the time from the beginning of treatment to first biologic use in patients with psoriasis. Among patients who had an inadequate response to topical therapies, we analyzed the difference between two groups, namely those treated with apremilast and those not treated with apremilast. In addition, we evaluated the total medical costs for these treatment groups after they had initiated their first topical therapy, including treatment, testing, and hospitalization costs.

METHODS

Study Database

This retrospective cohort study analyzed healthcare claims from the Medical Data Vision database called EBM Provider. No institutional or ethics review was required because this analysis did not involve the collection, use, or transmittal of individually identifiable data.

EBM Provider is based on Diagnosis Procedure Combination (DPC) data and receipt data. Permission for secondary use of the data was obtained from DPC-utilizing hospitals. All data were anonymized to protect patients' personal information. DPC is a medical reimbursement system in Japan in which detailed data on, e.g., medical treatment, department, and procedures, are collected according to diagnosis. Data related to healthcare resource utilization (HCRU) outside of the individual medical institution are not captured, and the ability to track individual patients across participating hospitals is lacking. EBM Provider covers about 33 million patients at 419 institutions, which represents about 24% of DPC-utilizing hospitals in Japan [11]. Data from other dermatology clinics or non-DPC-utilizing hospitals were not captured.

Study Period and Inclusion/Exclusion Criteria

The study period was from January 2015 to June 2019 (the latest date of available data when the analysis was performed). In the analyses of time to first biologic therapy use and medical costs, the earliest date of a psoriasis medication prescription that fell after a diagnosis code for psoriasis vulgaris (International Classification of Diseases, Tenth Edition, code L40.0 or L40.9) or psoriatic arthritis (International Classification of Diseases, Tenth Edition, code L40.5) was set as the index date. The period from the index date to the last day of the month, corresponding to the last day that information was recorded in EBM Provider, was set as the follow-up period (Fig. 1). In the analyses of time to first biologic therapy use, only biologics indicated for psoriasis vulgaris or psoriatic arthritis in Japan were included (i.e., adalimumab, infliximab, secukinumab, ixekizumab, ustekinumab, brodalumab, and guselkumab). Patients with psoriasis who started treatment with a topical therapy only and received systemic treatment after topical therapy were included if they met the following inclusion criteria: (1) had two or more diagnosis codes for psoriasis vulgaris or psoriatic arthritis; (2) had been prescribed a therapeutic drug for psoriasis after diagnosis codes for psoriasis vulgaris or psoriatic arthritis; (3) had been prescribed a topical skin preparation for psoriasis at the index date; (4) had been prescribed an oral (apremilast, etretinate, epinastine, olopatadine, oral corticosteroids, cyclosporine, or methotrexate) or biologic therapy for psoriasis after the index date; (5) had not been prescribed a therapeutic drug for psoriasis at the baseline period (180 days before the index date); and (6) were ≥ 18 years of age at the index date (Figs. 1, 2).

Patients were excluded from the analysis if they: (1) had any diagnosis codes for psoriasis other than psoriasis vulgaris or psoriatic arthritis; (2) did not have a 180-day baseline period; (3) had a follow-up period of < 1 month; or (4) were prescribed oral or biologic therapy for psoriasis at the index date (Figs. 1, 2).

Cohort Definition

Patients who met the eligibility criteria and were prescribed apremilast during the follow-up period were defined as the apremilast group, and those who were not prescribed apremilast
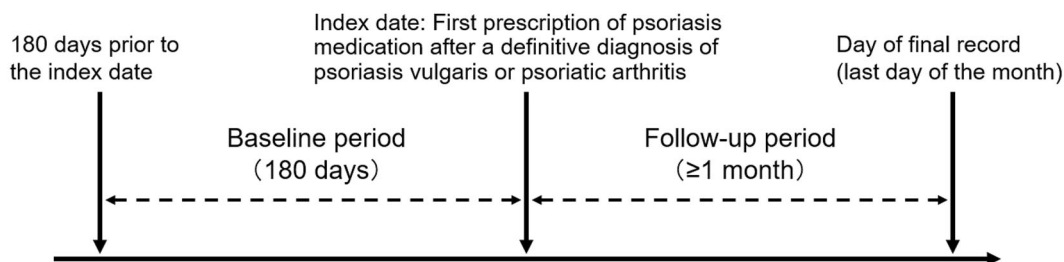
Fig. 1 Definition of the index date, baseline period, and follow-up period

during the follow-up period were defined as the non-apremilast group.

Statistical Analysis

To improve comparability, 1:1 propensity score matching using the nearest-neighbor method was used to compare cohorts and reduce the risk of confounding. A logistic regression analysis was conducted, adjusting for age at the index date, sex, disease type (psoriasis vulgaris/psoriatic arthritis), presence or absence of comorbidities (obesity, diabetes mellitus, hypertension, dyslipidemia), frequency of hospitalization during the baseline period, cumulative days of hospitalization during the baseline period, cumulative number of outpatient visits during the baseline period, duration of follow-up, starting dose of topical corticosteroids, mean dose of topical corticosteroids until oral or biologic agents were prescribed, starting dose of topical nonsteroidal agents, and mean dose of topical nonsteroidal agents until oral or biologic agents were prescribed. The patient demographics for the apremilast and non-apremilast groups were compared for the pre-matching and post-matching groups, and a balance check was performed using the standardized mean difference (SMD).

For the analysis of time to first biologic therapy use, the incidence per 1000 person-years of the first introduction of a biologic during the follow-up period after the index date and its 95% confidence interval (CI) were calculated. The chi-square test was used to compare the percentage of biologic therapy use between treatment groups. Kaplan–Meier estimates of the cumulative incidence of the first use of a biologic during the follow-up period were calculated, and the times to the 25th percentile, 50th percentile, and 75th percentile of the cumulative incidence were calculated. A log-rank test was used for between-group comparisons.

To determine monthly HCRU, the following formula was used:

$$HCRU = \frac{HCRU \text{ during follow-up period (yen)}}{Follow\text{-up period (number of months)}}$$

In addition, the monthly cost after the index date was calculated for each patient, and a figure showing the time course of the mean cost per month by group plotted against the number of months from the index date on the horizontal axis was generated.

For continuous data, the mean, standard deviation, minimum, median, and maximum values for the number of eligible patients were reported. For categorical data, the number of applicable subjects and its proportion of the total were reported.

All analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). A sensitivity analysis using an inverse probability of treatment weighting (IPTW) method was also performed for a subset of eligible patients from both treatment groups who were prescribed biologics during the follow-up period (see Supplemental Methods).
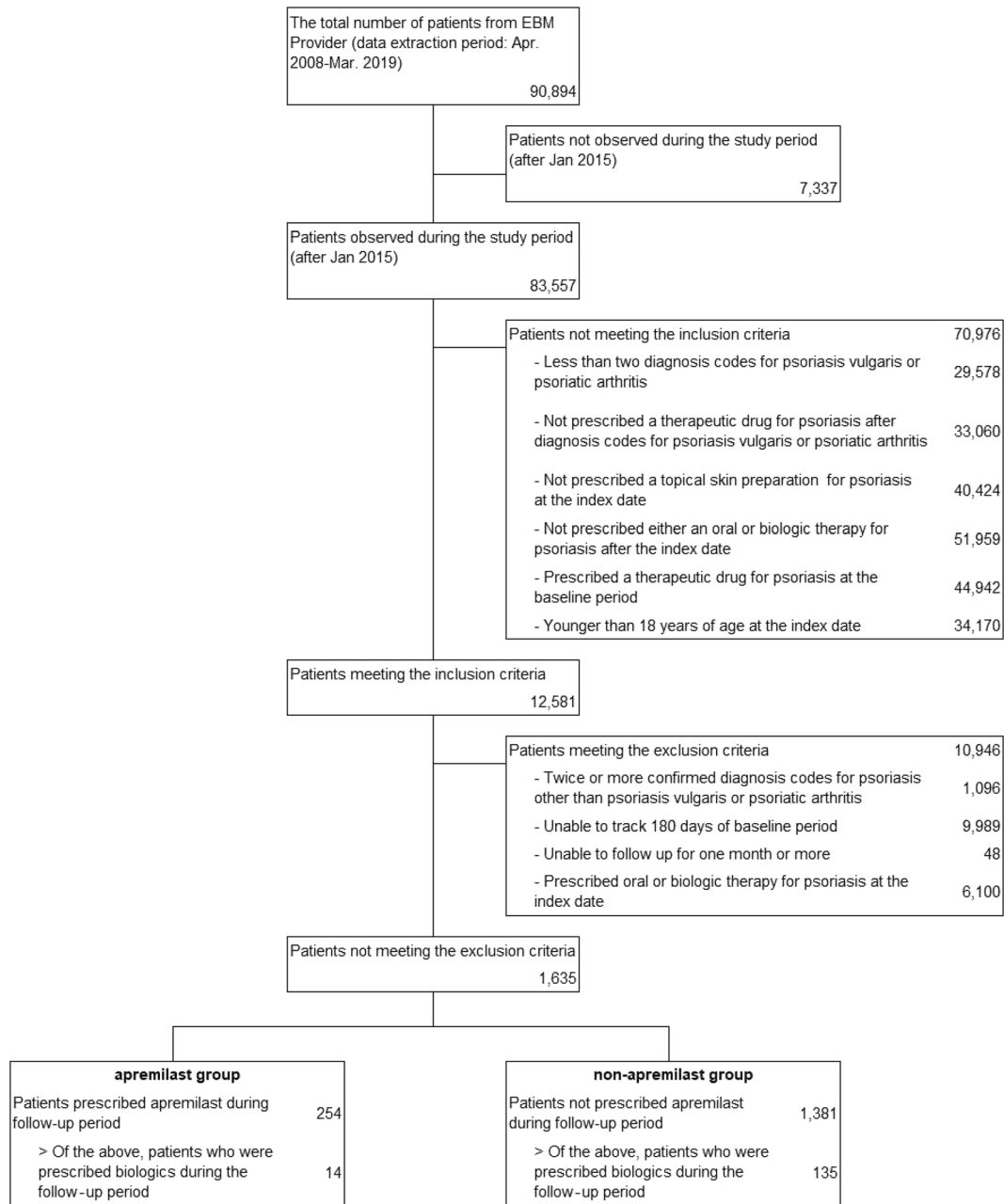
Fig. 2 Patient attrition

RESULTS

Study Population

A total of 83,557 patients had a diagnosis of psoriasis during the study period, and 1635 patients (apremilast: $n = 254$; non-apremilast:

$n = 1381$) met the eligibility criteria during the study period (Fig. 2).

Patient Characteristics

The number of patients in each group after propensity score matching and the patient

Table 1 Patient characteristics after propensity score matching

| | After propensity score matching | | | |
	Apremilast group $n = 253$	Non-apremilast group $n = 253$	Total $n = 506$	SMD[a]
Age, mean (SD), years, mean (SD)	63.1 (16.0)	62.1 (14.6)	62.6 (15.3)	
Age category, n (%)				
< 50	53 (20.9)	55 (21.7)	108 (21.3)	
50–59	40 (15.8)	46 (18.2)	86 (17.0)	
60–69	55 (21.7)	68 (26.9)	123 (24.3)	
≥ 70	105 (41.5)	84 (33.2)	189 (37.4)	
Male, n (%)	154 (60.9)	154 (60.9)	308 (60.9)	0.00
Disease type, n (%)				
Psoriasis vulgaris only	240 (94.9)	242 (95.7)	482 (95.3)	0.04
Comorbid psoriasis vulgaris and psoriatic arthritis	9 (3.6)	6 (2.4)	15 (3.0)	− 0.07
Psoriatic arthritis only[b]	4 (1.6)	5 (2.0)	9 (1.8)	0.03
Diagnosis, n (%)				
Obesity	3 (1.2)	1 (0.4)	4 (0.8)	− 0.09
Diabetes	50 (19.8)	37 (14.6)	87 (17.2)	− 0.12
Hypertension	53 (20.9)	30 (11.9)	83 (16.4)	− 0.20
Dyslipidemia	48 (19.0)	39 (15.4)	87 (17.2)	− 0.09
Treatment information during the baseline period, mean (SD)				
Hospitalization frequency	0.12 (0.40)	0.07 (0.29)	0.09 (0.35)	0.10
Length of hospital stay, days	0.9 (4.2)	0.7 (4.4)	0.8 (4.3)	0.03
Number of patients visits	3.4 (6.0)	2.8 (5.8)	3.1 (5.9)	0.07
Direct medical cost, yen	182,435 (742,129)	132,292 (362,603)	157,363 (584,014)	0.06
Length of follow-up period, months	20.8 (12.5)	20.9 (14.1)	20.8 (13.3)	0.00
Period until oral drug or biologic for psoriasis is prescribed, days	289.7 (309.9)	199.7 (240.3)	249.2 (284.0)	0.29
Use of psoriasis drug during the follow-up period				
Use of steroidal topical agent, n (%)	249 (98.4)	249 (98.4)	498 (98.4)	0.00
Use of non-steroidal topical agent, n (%)	244 (96.4)	213 (84.2)	457 (90.3)	− 0.33
Initial dose of steroidal topical agent, mean (SD), g[c]	61.2 (51.6)	61.4 (51.3)	61.3 (51.4)	0.00

Table 1 continued

	After propensity score matching			
	Apremilast group $n = 253$	Non-apremilast group $n = 253$	Total $n = 506$	SMD[a]
Maximum dose of steroidal topical agent, mean (SD), g[c]	142.2 (125.3)	106.8 (98.2)	124.5 (113.8)	0.30
Average dose of steroidal topical agent, mean (SD), g[c]	2.61 (3.28)	2.15 (3.22)	2.38 (3.25)	0.09
Class of steroidal topical agent, initial dose[c], n (%)				
Strongest	45 (17.8)	39 (15.4)	84 (16.6)	
Very strong	193 (76.3)	178 (70.4)	371 (73.3)	
Strong	6 (2.4)	24 (9.5)	30 (5.9)	
Medium	5 (2.0)	8 (3.2)	13 (2.6)	
Weak	0 (0.0)	0 (0.0)	0 (0.0)	
Missing	4 (1.6)	4 (1.6)	8 (1.6)	
Class of steroidal topical agent, strongest class[c], n (%)				
Strongest	105 (41.5)	83 (32.8)	188 (37.2)	
Very strong	141 (55.7)	145 (57.3)	286 (56.5)	
Strong	1 (0.4)	20 (7.9)	21 (4.2)	
Medium	2 (0.8)	1 (0.4)	3 (0.6)	
Weak	0 (0.0)	0 (0.0)	0 (0.0)	
Missing	4 (1.6)	4 (1.6)	8 (1.6)	
Class of steroidal topical agent, most frequently used class[c], n (%)				
Strongest	34 (13.4)	30 (11.9)	64 (12.6)	
Very strong	197 (77.9)	175 (69.2)	372 (73.5)	
Strong	9 (3.6)	25 (9.9)	34 (6.7)	
Medium	5 (2.0)	6 (2.4)	11 (2.2)	
Weak	0 (0.0)	0 (0.0)	0 (0.0)	
Missing	8 (3.2)		25 (4.9)	
Initial dose of non-steroidal topical agent, mean (SD), g	55.7 (44.8)	50.5 (44.3)	53.1 (44.6)	0.12
Maximum dose of non-steroidal topical agent, mean (SD), g	109.1 (90.2)	85.3 (93.3)	97.2 (92.5)	0.24
Average dose of non-steroidal topical agent, mean (SD), g	1.96 (2.53)	1.68 (2.76)	1.82 (2.65)	0.11

Table 1 continued

	After propensity score matching			
	Apremilast group $n = 253$	Non-apremilast group $n = 253$	Total $n = 506$	SMD[a]
Total prescription of topical agent, mean (SD), g	1318.1 (1780.7)	720.6 (1069.8)	1019.3 (1497.6)	0.42
Prescription of topical agent per day, mean (SD), g	2.30 (2.64)	1.49 (1.98)	1.90 (2.36)	0.36
Use of oral etretinate, n (%)	35 (13.8)	34 (13.4)	69 (13.6)	− 0.01
Use of oral cyclosporine, n (%)	8 (3.2)	17 (6.7)	25 (4.9)	0.18
Use of biologic, n (%)	13 (5.1)	40 (15.8)	53 (10.5)	0.40

SD standard deviation; *SMD* standardized mean difference

[a]Non-apremilast group as reference

[b]Patients who had a code for psoriatic arthritis only were considered to also have psoriasis vulgaris if they had prescription records for topical therapies at the index date

[c]Aggregated period for initial dose, maximum dose, class at the start of use, and the strongest class: follow-up period; aggregated period for average dose and the most frequently used class: until oral drugs or biologics for psoriasis were presented during the follow-up period

demographics are shown in Table 1. The post-matching population consisted of 253 patients per group with a mean age of approximately 63 years, of whom approximately 60% were men. Approximately 95% of the patients had psoriasis vulgaris only, 2% had psoriatic arthritis only, and the remaining 3% had comorbid psoriasis vulgaris and psoriatic arthritis.

Although the mean follow-up period was approximately 21 months (630 days) in both treatment groups, the mean time to first oral or biologic therapy use was 199.7 days in the non-apremilast group and 289.7 days in the apremilast group. During the follow-up period, no significant difference was observed in the mean dose of topical corticosteroids until oral or biologic therapies were prescribed between the two treatment groups; however, there was a tendency toward higher use of topical steroids in the apremilast group. No difference was noted in the presence or absence of an etretinate prescription during the follow-up period between the two treatment groups (SMD = − 0.01), but the number of cyclosporines and biologics prescribed was higher in the non-apremilast group

(SMD = 0.18 for cyclosporines and 0.40 for biologics) (Table 1).

SMDs of items not included as covariates in the logistic regression analysis for calculating the propensity score (i.e., duration from the start of follow-up to the prescription of oral or biologic therapies for psoriasis, total amount of topical skin preparation prescribed during the follow-up period, amount of topical skin preparation prescribed per day, and presence or absence of a biologic prescription) were relatively large. The values of other parameters generally fell within or close to the range of −0.1 to 0.1, showing no significant difference between the treatment groups (Fig. 3). The patient characteristics before propensity score matching are shown in Supplemental Table S1.

Time to First Biologic Therapy Use

The incidence rate of first biologic therapy use during the follow-up period was 30.3 per 1000 person-years (95% CI: 17.6, 52.2) in the apremilast group and 107.6 per 1000 person-years (95% CI: 78.9, 146.7) in the non-apremilast-group (Table 2).
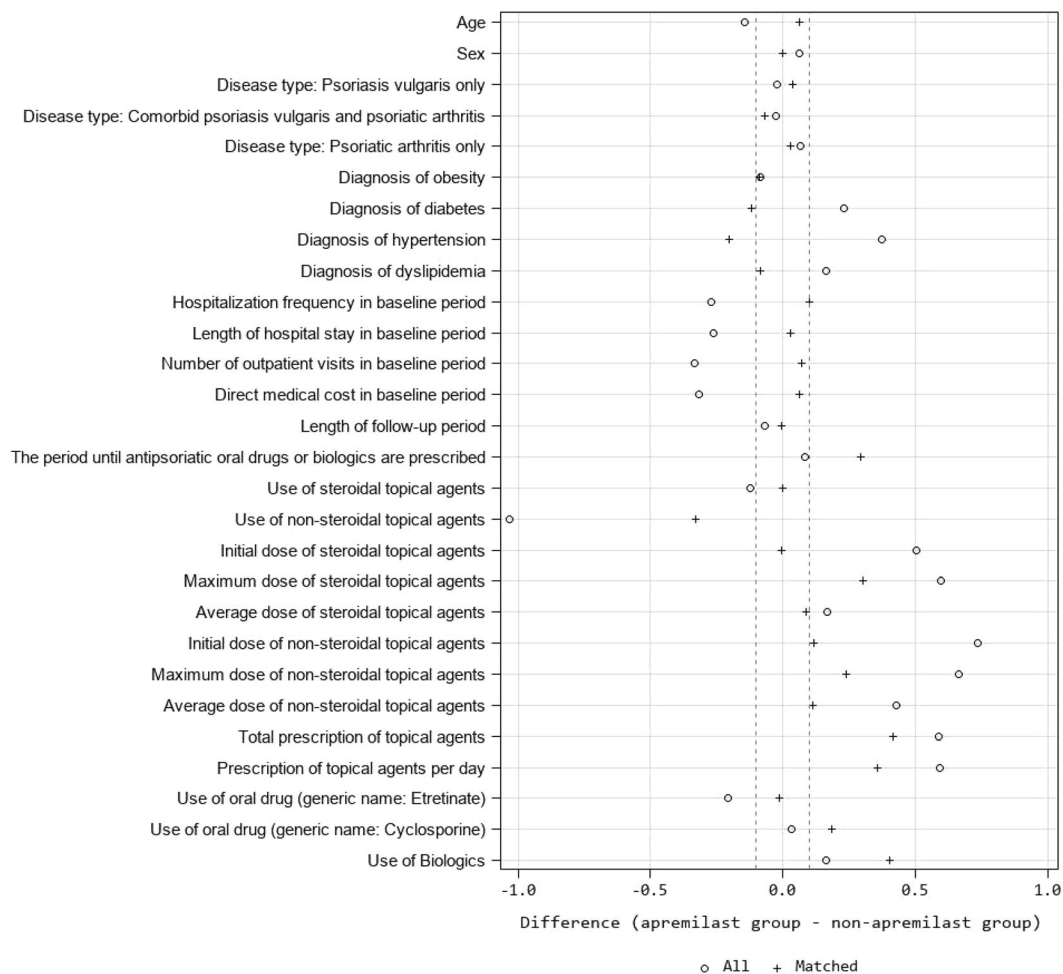
Fig. 3 Standardized mean differences plot

Table 2 Incidence of biologic therapy

	n	Biologic therapy incidence rate (per 1000 person-years)				
		Biologic therapy	Person-years	Incidence rate	95% CI[a]	P value[b]
Apremilast group	253	13	429.2	30.3	17.6, 52.2	
Non-apremilast group	253	40	371.7	107.6	78.9, 146.7	< 0.001

CI confidence interval
[a]95% CI was calculated using the Poisson distribution
[b]Chi-square test

The cumulative incidence of first biologic therapy use during the follow-up period was estimated using the Kaplan–Meier method and was significantly lower in the apremilast group (P < 0.001) (Fig. 4).

HCRU

The results for each HCRU endpoint are shown in Table 3. The frequency of outpatient visits per month was significantly higher in the
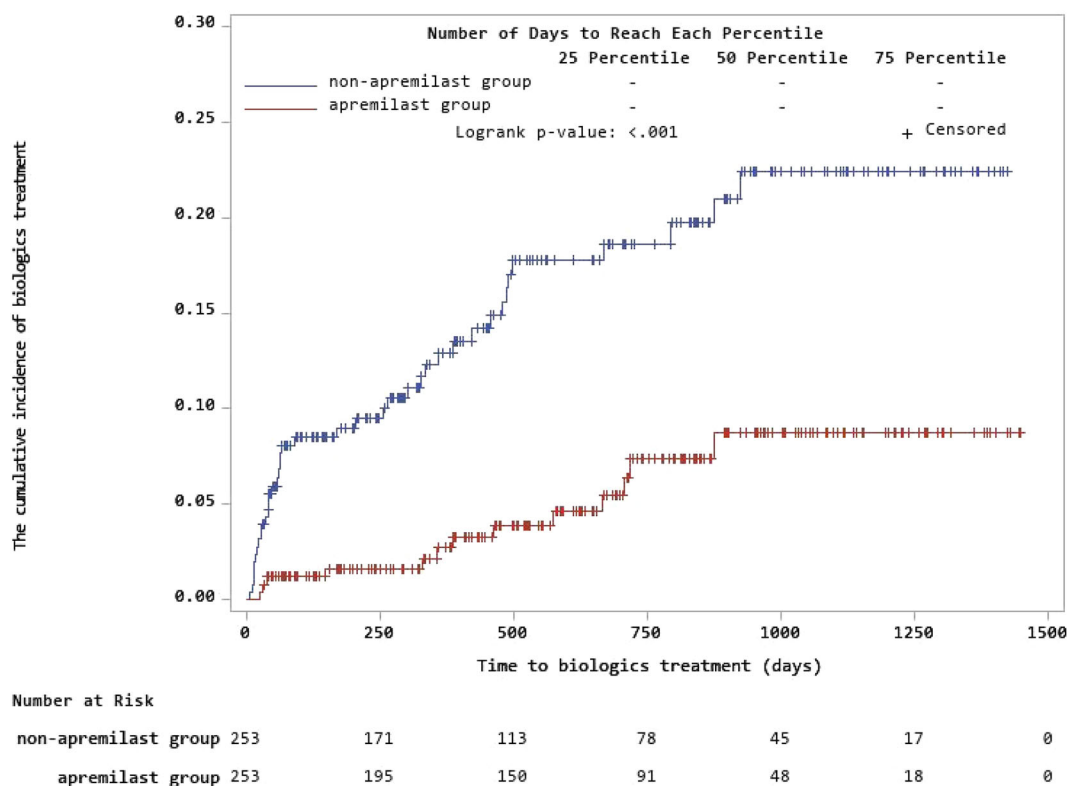
Fig. 4 Cumulative incidence of biologic therapy

apremilast group compared with the non-apremilast group (1.54 vs. 1.17; $P < 0.001$). The apremilast group also had significantly greater per-month costs for topical agents (8,830 yen vs. 4,910 yen; $P < 0.001$), phototherapy (761 yen vs. 215 yen; $P < 0.001$), and oral therapies other than methotrexate (19,285 yen vs. 1,458 yen; $P < 0.001$) than the non-apremilast group. On the other hand, the apremilast group had a significantly lower cost per month for biologics (4,887 yen vs. 26,481 yen; $P < 0.001$) or methotrexate (42 yen vs. 77 yen; $P = 0.044$) than the non-apremilast group and also had a significantly lower total medical cost per month than the non-apremilast group (mean [median, minimum–maximum], respectively: 76,594 yen [52,444 yen, 4,467–1,234,008 yen] in the apremilast group vs. 102,411 yen [26,849 yen, 1,455–2,484,115 yen] in the non-apremilast group; $P < 0.001$).

The results for the monthly changes in each HCRU cost item after the index date are presented as supplemental data (Fig. S1A–K). The apremilast group had higher mean topical skin agent, phototherapy, and oral therapy (other than methotrexate) costs for psoriasis throughout the follow-up period, although it could not be inferred from the database whether these therapies had been used before, after, or concomitantly with apremilast. On the other hand, the non-apremilast group had higher mean methotrexate and biologic costs for psoriasis in the latter half of the follow-up period. Although the total medical costs did not differ between treatment groups immediately after the start of follow-up, they tended to increase in the non-apremilast group over time as the cost of biologic therapies increased.

Sensitivity Analysis

Of the eligible patients, 149 (apremilast: $n = 14$; non-apremilast: $n = 135$) were prescribed biologics during the follow-up period. When the

Table 3 Healthcare resource utilization

	Apremilast group, mean (SD) $n = 253$	Non-apremilast group, mean (SD) $n = 253$	Absolute difference	P value[a]
Number of outpatient visits/month	1.54 (1.05)	1.17 (1.06)	0.36	< 0.001
Direct medical cost				
Cost of psoriasis drugs/ treatment procedure				
Topical agents, yen/month	8830 (9259)	4910 (6335)	3920	< 0.001
Phototherapy, yen/month	761 (1924)	215 (1077)	546	< 0.001
Oral drugs (except methotrexate), yen/month	19,285 (17,391)	1458 (3993)	17,827	< 0.001
Methotrexate, yen/month	42 (411)	77 (507)	− 34	0.044
Biologic agents, yen/month	4887 (26,013)	26,481 (74,478)	− 21,594	< 0.001
Other drugs for psoriasis, yen/month	2 (9)	20 (205)	− 19	0.138
Cost of other drugs, yen/month	16,035 (82,181)	20,104 (57,021)	− 4070	0.378
Cost of other treatment procedure, yen/month	3648 (22,619)	8842 (72,078)	− 5195	0.624
Cost of tests, yen/month	4425 (5254)	7201 (17,990)	− 2776	0.162
Basic cost of hospitalization, yen/month	8924 (24,893)	19,845 (78,327)	− 10,921	0.471
Total cost, yen/month	76,594 (107,738)	102,411 (214,261)	− 25,817	< 0.001

SD standard deviation

[a]Wilcoxon rank-sum test

incidence rate of first biologic therapy use was calculated for 14 patients in each treatment group matched by propensity score, the incidence was 856.1 per 1000 patient-years (95% CI: 507.0, 1,445.5) in the apremilast group and 2,797.6 per 1000 patient-years (95% CI: 1,656.9, 4,723.6) in the non-apremilast group (Supplemental Table S2). In addition, the cumulative incidence of first biologic therapy use estimated using the Kaplan–Meier method was significantly lower in the apremilast group ($P < 0.001$) (Supplemental Fig. S2). Thus, the incidence rate was lower in the apremilast group than in the non-apremilast group, comparable to the results

for the entire population of eligible patients (Table 2).

The results of sensitivity analysis using the IPTW method are reported as supplemental data (Table S3, S4, Fig. S3). As seen in the main analysis, a decrease in the incidence rate of first biologic therapy use, a prolongation of the time to first biologic therapy use, and a reduction in medical costs were confirmed for apremilast.

DISCUSSION

This study showed a significantly lower incidence rate of first biologic therapy use in psoriasis patients taking apremilast vs. comparable

psoriasis patients not taking apremilast using a Japanese claims database. To our knowledge, this is the first large-scale, nationwide, real-world data study to look at apremilast treatment patterns and costs in Japan.

Biologics for psoriasis are highly efficacious; however, several biologic-associated burdens are suggested by the literature and clinical practice. For example, in a discrete choice experiment study conducted by Tada et al. in Japanese patients with psoriasis to investigate preferences for biologics that differ in administration frequency, price, efficacy, and safety, it was reported that patients preferred treatments with a lower injection frequency and a lower cost burden [12]. In addition, biologics can only be used at a limited number of medical institutions, which may entail transferring patients to approved hospitals for treatment. Thus, apremilast may have the potential to reduce the treatment burden associated with biologics by decreasing the use of or prolonging the time to first biologic therapy use. The favorable safety profile, oral mode of administration (injection is used for many biologics), and lower cost of apremilast may also contribute to patient treatment choice. Finally, differences in treatment choices and time to initiation of biologic therapy may be influenced by the patient's therapeutic goals, disease severity, quality-of-life impacts, and success with previous treatments.

Although apremilast may decrease the burden of biologic therapy, the apremilast group had a higher number of outpatient visits per month than the non-apremilast group (1.54 vs 1.17, $P < 0.001$; Table 3). Although the number of outpatient visits was calculated during whole follow-up periods after the index date (including visits before apremilast or biologic prescription), high frequencies of outpatient visits may be a burden of apremilast treatment. On the other hand, in Japan, prescription amounts for new medications are limited by regulation to 2 weeks at a time until 1 year after their launch, which could have resulted in high frequencies of outpatient visits for some of the apremilast-treated patients in this study.

When this research was conducted, the latest date of available data was June 2019; the duration of the research period after the launch of apremilast was at most about 2 years (from March 2017 to June 2019). The results might have been different if the duration of the research period was longer. In the analysis of the monthly change in each HCRU cost item after the index date, the monthly cost of biologic therapies tended to increase greatly in the latter half of the follow-up period in the non-apremilast group, but was lower and relatively stable in the apremilast group throughout the entire follow-up period (Supplemental Fig. S1E). Therefore, this analysis using data from until about 2 years after apremilast launch may underestimate the costs of biologics; a greater reduction in medical costs for apremilast could potentially be observed if a longer analysis was performed. Among eligible patients, the incidence of biologic prescriptions and the time to first biologic therapy use were also analyzed for patients who were prescribed biologics during the follow-up period, but the CIs were wide and the point estimates unstable due to the small sample size. These points should be re-evaluated when more data are accumulated in the future.

Regarding the burden of medical costs, our study showed that the mean total medical cost per month after the start of treatment for psoriasis was significantly lower in patients taking apremilast than in those not taking apremilast. This finding is consistent with three US studies that used real-world data to compare healthcare costs for patients initiating treatment with apremilast or biologics [13–15]. On the other hand, it should be noted that the costs in this study were calculated during whole follow-up periods after the index date; the costs included those before the initiation of apremilast. Although the costs for the period after apremilast initiation could not be analyzed due to the limitations of the study design, this should be further investigated by selecting appropriate comparison groups in future studies.

Prescription costs can be a barrier to biologic use, and the treatment cost of biologic therapies in Japan has been reported to be about 1.2 million yen to 4.4 million yen per year [16]. A study by Sruamsiri et al. [17] compared medical expenses for 12 months before and after the start of biologics using Japanese claims data,

and reported that the start of biologics increased medical expenses by about 1.9 million yen per patient for the first year after biologic initiation, of which about 1.8 million yen was accounted for by outpatient expenses. In the current study, the cost item with the largest between-group difference was the average cost of biologic agents (the absolute difference between the apremilast and non-apremilast groups was 21,594 yen), and the major contributor to the high average total medical cost in the non-apremilast group was the high prices of biologics.

On the other hand, in our study, the average cost per month of topical agents, phototherapy, and oral drugs except for methotrexate (apremilast may have been a major contributor to this cost) was significantly higher in the apremilast group (Table 3). Due to the limitations of the study design, the cost includes the whole follow-up period (i.e., before, during, and after the apremilast prescription). In terms of topical agents, the use of apremilast in combination with topical therapy was effective in patients who were dissatisfied with stable maintenance topical therapy [18]. In addition, the effectiveness of the combination of apremilast and narrowband ultraviolet B has been reported in patients with moderate to severe psoriasis [19]. In accordance with the literature, the results of this study raise the possibility that apremilast may be preferentially used with topical therapy or phototherapy in clinical settings. A future real-world data study designed to evaluate the use of monotherapy and combination therapy with apremilast is needed.

Study Limitations

This study has several limitations.

First, the study used claims data from the EBM Provider database. Information on treatment selection is not included in the EBM Provider database. Therefore, it is unclear as to why patients were or were not initiated on apremilast. In addition, results from this study show that apremilast may reduce the treatment burden associated with biologics, and data on drug efficacy are not included in the EBM Provider database, so efficacy could not be compared with the apremilast-naive group. Similarly, further research is needed to evaluate the impact of other available oral therapies on the treatment burden associated with biologics. In addition, because information on the severity of psoriasis could not be obtained, and matching the two groups in terms of refractory patients with topical therapy was not possible, the possibility that time to first biologic therapy use was prolonged because more patients had less severe psoriasis in the apremilast group cannot be excluded. However, since similar results were obtained when the analysis was performed only in patients who were prescribed biologics during the follow-up period (Supplemental Fig. S2), the prolongation of time to biologic use in the apremilast group was unlikely to be caused only by a difference in the proportion of refractory patients with topical therapy or by differences in severity between treatment groups. Lastly, it is also possible that, because biologics can only be administered at a limited number of medical institutions in Japan, patients may have visited these DPC-utilizing hospitals for the sake of starting biologics.

The second point is attributed to the study design. In this study, the apremilast group and the non-apremilast group were matched using propensity scores. Because the number of patients in the non-apremilast group was larger, and > 80% of the eligible patients were excluded after matching, the matched non-apremilast group may not represent the entire non-apremilast cohort. Regarding this point, similar results were obtained in the main analysis when sensitivity analyses were performed by the IPTW method. Therefore, it is likely that the results of this study are relatively robust. The reason that the incidence of biologic prescriptions in the non-apremilast group was lower when the IPTW method was used than when the matching method was used may be that the IPTW method estimates the average treatment effect in the entire psoriasis patient population and thus includes patients with relatively mild psoriasis who were not eligible for treatment with apremilast or biologics. Apremilast was launched in Japan in March 2017, but the study period started in 2015; thus, some patients in

the non-apremilast group were followed in 2015 and 2016. Therefore, the treatment patterns in 2015–2016 may be different from those after March 2017, possibly affecting the results. In this regard, the number of biologics used to treat psoriasis has been increasing since the 2010s, and the rate of biologic use has also tended to increase each year. The incidence rate of first biologic therapy use and the time to first biologic therapy use in the non-apremilast group, who were followed relatively early, may have been underestimated. Thus, the results of this study may be conservative.

CONCLUSION

In conclusion, this study found that patients treated with apremilast had a lower incidence of biologic use compared with non-apremilast users, suggesting that treatment with apremilast may ultimately reduce the clinical and cost burden on patients with psoriasis. Time to first biologic therapy use was also longer among patients treated with apremilast. Because biologic therapy is associated with various treatment burdens, reducing or delaying the need to use biologic therapy may be a benefit of apremilast to patients and society. Since this study was conducted using data obtained within a short period after the launch of apremilast in Japan, it is desirable to conduct further research when more data are accumulated.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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