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RESEARCH ARTICLE

Real-world treatment patterns of patients with atopic dermatitis in Japan: Analysis of the JMDC Claims Database

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Abstract

Objectives: This study was conducted to assess changes in the real-world treatment of atopic dermatitis (AD) in Japan.

Methods: Patients from the JMDC Claims Database with ≥1 confirmed diagnosis of AD, an identifiable medical care start date for AD, and ≥2 AD–related treatments on separate dates between January 1, 2005, and May 31, 2019, were included; data were analyzed on a yearly basis.

Results: In total, 411,102 patients were included. The average age of patients increased from 12.0 to 18.8 years between 2005 and 2017. In any given year, the prevalence of AD was highest in patients aged <2 years and lowest in patients aged ≥50 years. Dermatology (65.1%-69.5% from 2005 to 2017) and clinics (92.3%-93.4%) were the main department and medical facility, respectively, providing daily medical care for AD. The proportion of patients who were given the thymus and activation-regulated chemokine test increased from 2008 to 2017 (0.03%-3.5%). From 2005 to 2017, the proportion of patients who received moisturizer (68.8%-79.1%), topical calcineurin inhibitors (8.2%-17.8%), very strong topical corticosteroids (26.0%-40.6%), strongest topical corticosteroids (3.5%-7.8%), cyclosporine (0.01%-0.3%), or phototherapy (0.06%-1.8%) increased, and the proportion of patients who received topical non-steroidal anti-inflammatory drugs (12.0%-3.1%) decreased. Annual costs for medication associated with AD per person/visit increased between 2005 and 2017; however, the ratio of medication to total cost did not.

Conclusions: The results of this analysis show that Japanese patients used increasingly potent treatments for AD, and overall AD-related medication costs increased between 2005 and 2017.

KEYWORDS
atopic dermatitis, database, healthcare costs, Japan, therapeutics

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disorder characterized by immune-mediated inflammation, intense itching, and eczematous lesions.[1] Treatment of patients with AD in Japan involves several strategies that depend on disease severity. For patients with any severity of disease, it is recommended that exacerbating factors, such as nonspecific irritation, allergens, sweat, and bacteria/fungi, be eliminated.[1] Patients with slight AD (defined by dryness with negligible inflammation) are recommended topical emollients, which can improve moisture content on the skin surface.[1] For patients with mild AD (mild dry skin, mild erythema, and scales) or severe AD, treatments such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs), which have comparable effectiveness,[1,2] are recommended. Drug therapy with such anti-inflammatory drugs can promptly reduce AD-related inflammation. For severe refractory cases, high-potency TCSs or TCSs with phototherapy, psychotherapy, oral cyclosporine, or systemic corticosteroids are recommended.[1] Other topical agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) have a weak anti-inflammatory effect and can cause contact dermatitis, limiting their use in treating patients with AD.[1]

The treatment landscape of AD in Japan has been changing with the availability of new treatments. Until dupilumab,[3] delgocitinib,[4] and baricitinib[5] were approved in 2018, 2020, and 2020,[6] respectively, new agents had not been introduced to the market since oral cyclosporine was approved for the treatment of AD in 2008.[6] Furthermore, newer treatments such as abrocitinib, upadacitinib, nemolizumab, tralokinumab, lebrikizumab, difamilast, and crisaborole are under development.[7-9] This suggests that patients with AD in Japan could soon have more treatment options. Hence, a comprehensive assessment of the real-world treatment patterns of AD in Japan and identification of current unmet medical needs are important. The objective of this study was to assess the changes in the therapeutic landscape of AD in Japan, using data from a large-scale claims database.

2 | METHODS

2.1 | Data source and sample

This study used a nationwide health insurance claims database provided by JMDC Inc., an epidemiologic receipt database that has accumulated inpatient, outpatient, dispensing receipts, and medical examination data from multiple health insurance associations since 2005.[10] Patients included in the current analysis had ≥1 confirmed diagnoses of AD (ICD-10, L20); an identifiable medical care start date for AD from January 1, 2005, to December 31, 2018; and received ≥2 AD-related treatments (topical emollient, TCSs, TCIs, systemic corticosteroids, cyclosporine, biologic, or phototherapy) on separate dates before May 31, 2019 (Figure 1). Data were extracted for eligible patients, including types of departments and facilities, and medical interventions such as medical management, drug, procedure, surgery, laboratory test, imaging, and cost. Data were analyzed from January 1, 2005, to December 31, 2018, on a yearly basis.

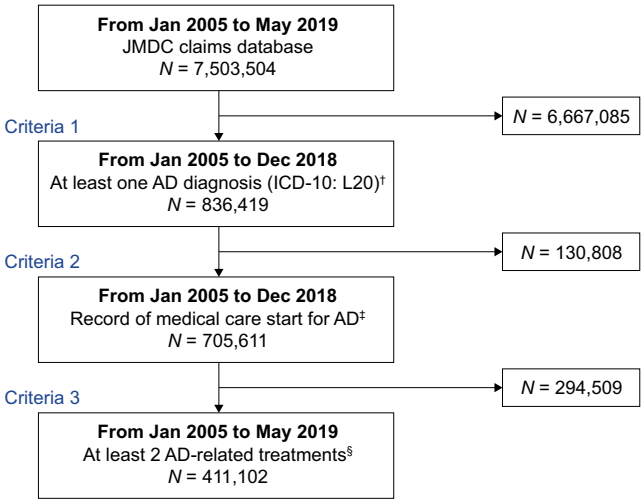

FIGURE 1 Patient selection. †At least one confirmed AD diagnosis (ICD-10, L20) from January 1, 2005, to December 31, 2018. ‡Record of medical care start for AD existed from January 1, 2005, to December 31, 2018. §At least two AD-related treatments (topical emollients, TCSs, TCIs, systemic immune suppressants, biologic, or phototherapy) on separate dates from January 1, 2005, to May 31, 2019. AD, atopic dermatitis; ICD, International Classification of Diseases; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

2.2 | Outcome measures

The prevalence of AD in patients from the JMDC Claims Database was calculated by age (<2, 2-5, 6-11, 12-17, 18-29, 30-49, and ≥50 years); if there were more than two records in the same year, the age described in the first record was used for classification. Age distribution in the total sample of insurance subscribers is shown in Table S1.

For medical examinations in which AD was recorded as the confirmed diagnosis, the type of department and facility for each patient was assessed. Departments were classified as dermatology, pediatrics, internal medicine, and other. Facilities were classified as university hospital, public hospital, other hospitals, clinic, and unknown. Patients could have visited multiple departments and facilities; therefore, multiple answers were allowed. The proportion of patients who received immunoglobulin E (IgE) and thymus and activation-regulated chemokine (TARC) tests more than once a year (from January 1 to December 31) was assessed when a confirmed AD diagnosis (ICD10, L20) was recorded. The same analysis was performed for the use of AD-related treatments, which included moisturizer, herbal medicine, antihistamine or antiallergic agent, topical NSAID, TCI, weak TCS, medium TCS, strong TCS, very strong TCS, strongest TCS, oral corticosteroid, injection corticosteroid, cyclosporine, biologic, and phototherapy.

Medical costs were calculated on a per-patient or per-visit basis for each year. Medical expenses for AD were calculated for visits/hospitalizations in patients with a confirmed AD diagnosis (ICD10, L20), and the cost of AD-related treatment was calculated except for patients/visits lacking price information for medical interventions. In addition, the proportion of the cost for AD-related treatment to the total medical cost was calculated by dividing the cost for the AD-related treatment in each year by the total medical cost for each individual patient.

2.3 | Disease severity definition

Given that the JMDC Claims Database does not contain disease severity measures, disease severity was defined based on prescribed treatment. Patients who did not receive medical treatment and those who were treated with topical moisturizers, herbal medicine, antihistamines or antiallergic agents, or topical NSAIDs were classified as severity level 1 (mildest class). Patients treated with TCIs or weak, medium, or strong TCSs (e.g., hydrocortisone acetate, alclometasone dipropionate, dexamethasone propionate) were classified as severity level 2. Patients treated with very strong or strongest TCSs (e.g., betamethasone butyrate propionate, clobetasol propionate) were classified as severity level 3. Patients treated with systemic corticosteroids, cyclosporine, biologic, or phototherapy were classified as severity level 4 (most severe class). Disease severity was redefined for each patient every year. If patients received several treatments, they were categorized in the higher disease severity level.

2.4 | Statistical analysis

Continuous variables were reported with descriptive statistics. Categorical variables were reported using frequencies and proportions. For proportions, 95% confidence intervals were calculated using the Wilson score method,[11] when appropriate. Statistical analysis was performed using SAS Release 9.4 (SAS Institute) and/or R version 3.4.0 (R Foundation for Statistical Computing). Statistical tests for between-group comparisons were not conducted.

3 | RESULTS

3.1 | Patients

Data from 7,503,504 patients were extracted from the JMDC Claims Database: 411,102 patients met all inclusion criteria (Figure 1). The interval between first and second treatments was not uniform for all patients. The interval between the first and second treatments was measured, and the percentage of patients for whom the interval was within 0.5, 1.0, and 1.5 years was 70.3%, 84.1%, and 89.7%, respectively. These data indicate that the third inclusion criterion (i.e., patients who received ≥2 AD-related treatments on separate dates before May 31, 2019) was strict for the patients who were first diagnosed in 2018. Because some eligible patients from 2018 may have been missed, the data from 2017 were used as the latest information.

The percentage of male patients ranged from 50.9% to 52.2% between 2005 and 2017 (Table 1). In each age group, the proportion of males aged 12-17, 30-49, and ≥50 years was lower than the overall data in any single year; the proportion of male patients ranged from 44.2% to 57.4% across all age groups and years (data not shown).

The mean age increased every year, from 12.0 to 18.8 years between 2005 and 2017 (Figure 2A). For example, in 2005, 36.4% of patients with AD were aged ≥12 years; however, in 2017, 52.7% of the patients were aged ≥12 years. Age was identified as a factor for the prevalence of AD; the prevalence of AD was highest in patients aged <2 years and lowest in patients aged ≥50 years (Figure 2B).

3.2 | Medical facilities and departments for AD-related medication

Dermatologists (65.1%-69.5% from 2005 to 2017) and clinics (92.3-93.4%) were consistently the main specialists and medical facilities, respectively, for the daily medical management of AD. However, the proportion of patients who visited university hospitals increased every year (Table 2). Between 2005 and 2017, 96.3% to 97.3% of patients visited only one type of medical facility within a year (Figure S1A); similarly, many patients (89.9%-92.4% in 2005-2017) visited only one type of department within a year (Figure S1B).

Among departments that examined patients with AD, pediatric departments had the highest proportion of minors (<18 years old), ranging from 88.3% to 93.3% between 2005 and 2017. Lower proportions of minors were seen in dermatology (51.5%-71.5%), internal medicine (57.2%-74.1%), and other departments (54.9%-67.5%) (Figures S2A-D). Patients aged <2 years old were less likely to be given an AD medical examination in a dermatology department (proportions ranged between 9.8% to 16.4% in 2005-2017) than in a pediatric (34.6%-39.7%), internal medicine (15.6%-24.7%), or other department (15.5%-25.5%) (Figures S2A-D).

The proportion of patients aged ≥30 years who received medical examinations at university hospitals ranged from 14.0% to 36.8% between 2005 and 2017, and the proportion of patients aged ≥50 years who received medical examinations at university hospitals ranged from 0% to 14.0% (Figure S3B). In public hospitals, patients aged ≤11 years comprised the core group of patients: 71.9% to 77.2% from 2005 to 2017 (Figure S3C); the proportion of patients aged ≤11 years was lower for clinics, university hospitals, and other hospitals (45.9%-63.6%, 42.0%-70.2%, 56.4%-64.8%, respectively; Figures S3A,B,D). Patients aged <2 years formed the largest group who visited multiple departments or multiple hospitals.

TABLE 1 Demographic characteristics by year

	Year							
	2005 *N* = 9895	2006 *N* = 14,769	2007 *N* = 18,000	2008 *N* = 23,150	2009 *N* = 30,761	2010 *N* = 47,356	2011 *N* = 64,564	2012 *N* = 84,436
Enrollment, *n* (%)								
Newly enrolled	9895	5922	5025	7359	10,506	20,616	23,059	28,939
Sex, *n* (%)								
Male	5165 (52.2)	7692 (52.1)	9352 (52.0)	12,023 (51.9)	15,848 (51.5)	24,123 (50.9)	32,951 (51.0)	43,129 (51.1)
Female	4730 (47.8)	7077 (47.9)	8648 (48.0)	11,127 (48.1)	14,913 (48.5)	23,233 (49.1)	31,613 (49.0)	41,307 (48.9)
Age, years, *n* (%)								
<2	1947 (19.7)	2805 (19.0)	3040 (16.9)	3522 (15.2)	4384 (14.3)	6921 (14.6)	9747 (15.1)	12,584 (14.9)
2-5	2618 (26.5)	3761 (25.5)	4667 (25.9)	5858 (25.3)	7131 (23.2)	10,220 (21.6)	13,541 (21.0)	17,431 (20.6)
6-11	1728 (17.5)	2725 (18.5)	3502 (19.5)	4589 (19.8)	6044 (19.7)	9055 (19.1)	12,073 (18.7)	15,451 (18.3)
12-17	921 (9.3)	1400 (9.5)	1679 (9.3)	2204 (9.5)	3098 (10.1)	4609 (9.7)	6229 (9.7)	8355 (9.9)
18-39	1342 (13.6)	2016 (13.7)	2461 (13.7)	3231 (14.0)	4474 (14.5)	7157 (15.1)	9485 (14.7)	12,018 (14.2)
39-49	1229 (12.4)	1863 (12.6)	2402 (13.3)	3317 (14.3)	4831 (15.7)	7988 (16.9)	11,409 (17.7)	15,468 (18.3)
≥50	110 (1.1)	199 (1.4)	249 (1.4)	429 (1.9)	799 (2.6)	1406 (3.0)	2080 (3.2)	3129 (3.7)

The proportion of patients in severity level 2 decreased from 2005 to 2017 (57.2%-45.3%; Table 2). The proportion of patients in severity level 4 ranged between 7.8% to 9.1% in each year from 2005 to 2017, but the proportion of patients in severity level 3 increased from 2005 to 2017 (23.5%-37.6%; Table 2). From 2005 to 2017, the percentage of male patients was comparable among severity levels 2, 3, and 4, ranging from 50.0% to 52.1%, 51.1% to 53.6%, and 51.6% to 56.5%, respectively.

From 2005 to 2017, the average number of hospital visits was highest for those classified as severity level 4, ranging from 4.1 to 5.1 between 2005 and 2017. For severity level 3, the number ranged from 3.0 to 3.4, and, for severity level 2, the number ranged from 2.8 to 3.2, suggesting that the number of hospital visits correlated with disease severity (Figures S4A-C).

3.3 | Laboratory tests

From 2005 to 2017, the proportion of patients who received IgE tests each year ranged from 8.8% to 11.4% (Figure 3A). The proportion of patients who received TARC tests has increased every year since 2008, which is when medical insurance in Japan began to pay for the tests.[12]For patients who received at least one IgE or TARC test, most patients received one test per year (Figure 3B). Between 2005 and 2017, 88.4%-92.5% of patients received one IgE test per year, and, from 2010 to 2017, 84.1%-86.2% received one TARC test per year (Figure 3A,B).

3.4 | AD-related treatments

The proportion of patients who received moisturizers to treat AD increased from 2005 (69.1%) to 2017 (79.1%; Figure 4A). The proportion of patients who received antihistamines or antiallergic agents in each year ranged from 56.8% to 61.3% between 2005 and 2017 (Figure 4A). The use of herbal medicine remained low from 2005 to 2017, ranging from 0.7% to 1.5% (Figure 4A). Medium, strong, and very strong TCSs were the major topical anti-inflammatory agents used every year (Figure 4B). From 2005 to 2017, medium TCSs were used the most often, followed by strong TCSs and very strong TCSs (Figure 4B). Although the proportions of patients who received TCI and strongest TCSs were lower, proportions steadily increased to 17.8% and 7.8% in 2017, respectively (Figure 4B). Conversely, the proportion of patients who received topical NSAIDs decreased over time to 3.1% in 2017 (Figure 4B).

For systemic treatments, oral systemic corticosteroids were the main treatment option, used by 7.3% of patients by 2017 (Figure 4C). Although the proportion of patients who received phototherapy remained low, it increased from 0.06% to 1.8% between 2005 and 2017 (Figure 4C). The proportion of patients who received cyclosporine, systemic corticosteroid injection, or biologic remained very low (<0.05%) from 2005 to 2017 (Figure 4C).

The proportion of patients who received moisturizers was similar among patients classified as severity levels 2, 3, and 4 (Figure 4D); however, the proportion of patients who received antihistamines or antiallergic agents was higher for severity level 4 than for the other two severity levels. The proportion for severity level 4 ranged from 82.2% to 89.9% between 2005 and 2017, compared with 63.8% to 70.2% for severity level 3 and 48.6% to 58.2% for severity level 2 (Figure 4E).

The top AD-related treatments for patients in the severe level 4 group were moisturizer, antihistamines or antiallergic agents, and medium to very strong TCSs (Figure 4F). The leading topical agents for patients categorized with severity level 4 were medium to strong TCSs; the proportion was 46.9% to 52.1% for medium TCS, 51.2% to 58.9% for strong TCS, and 52.0% to 59.4% for very strong TCS in 2005-2017, respectively (Figure 4F).

2013 *N* = 118,805	2014 *N* = 141,978	2015 *N* = 176,843	2016 *N* = 201,979	2017 *N* = 218,496	2018 *N* = 193,548
46,950	41,112	58,192	57,286	59,596	36,645
60,550 (51.0)	72,349 (51.0)	90,043 (50.9)	102,739 (50.9)	111,624 (51.1)	100,343 (51.8)
58,255 (49.0)	69,629 (49.0)	86,800 (49.1)	99,240 (49.1)	106,872 (48.9)	93,205 (48.2)
17,002 (14.3)	19,959 (14.1)	22,922 (13.0)	25,134 (12.4)	26,708 (12.2)	21,800 (11.3)
23,960 (20.2)	28,524 (20.1)	34,510 (19.5)	38,615 (19.1)	40,773 (18.7)	35,638 (18.4)
21,069 (17.7)	24,803 (17.5)	30,183 (17.1)	33,725 (16.7)	35,797 (16.4)	31,337 (16.2)
11,742 (9.9)	14,220 (10.0)	18,096 (10.2)	20,507 (10.2)	21,577 (9.9)	18,723 (9.7)
17,339 (14.6)	20,491 (14.4)	26,311 (14.9)	30,181 (14.9)	33,241 (15.2)	29,888 (15.4)
22,684 (19.1)	27,365 (19.3)	35,383 (20.0)	41,782 (20.7)	46,309 (21.2)	41,983 (21.7)
5009 (4.2)	6616 (4.7)	9438 (5.3)	12,035 (6.0)	14,091 (6.5)	14,179 (7.3)

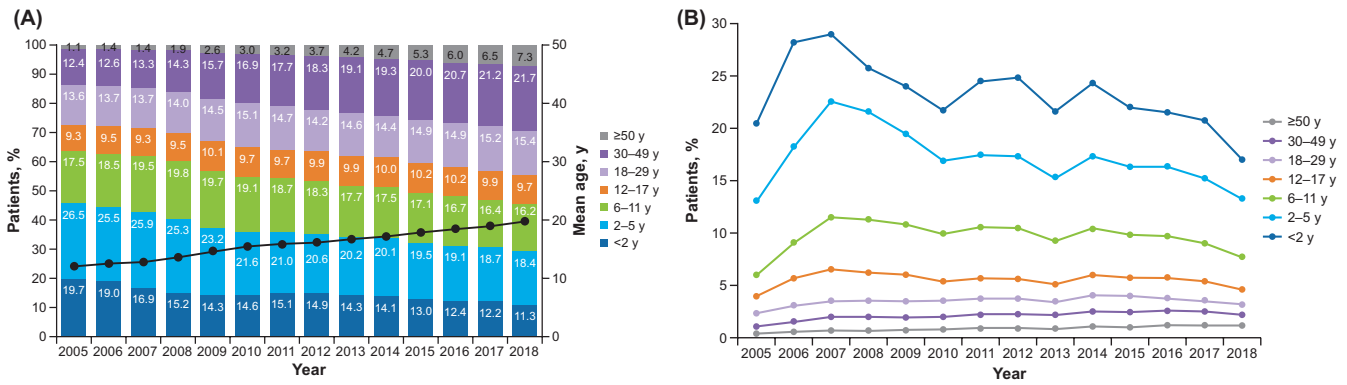

FIGURE 2 Prevalence of AD by (A) year and (B) age groups by year from 2005 to 2018. Black dots represent mean age of patients with AD for each year in A. AD, atopic dermatitis

3.5 | Medication costs

Annual costs for AD-related medication (including AD drug therapy and phototherapy) per person and per visit increased from 2005 to 2017 (Figure 5A,B). The median annual costs per person were JPY (¥) 2545.1 (interquartile range [IQR], 908.0-6798.9) in 2005 and JPY 4590.6 (1617.2-12,202.4) in 2017 (Figure 5A). The median costs per visit were JPY 1472.0 (535.6-3255.0) in 2005 and JPY 2445.0 (1011.0-4716.6) in 2017, respectively (Figure 5B). Analysis of annual costs for AD-related drug therapy without phototherapy yielded similar results, with both costs per person and per visit increasing from 2005 to 2017 (Figures S5A,B). However, the ratio of AD-related medication costs to total medical expenses did not increase over time (Figure 5C).

Annual costs for AD-related medication per person increased with disease severity from 2005 to 2017 (Figure 6A-C). For patients classified as severity level 4, the median annual costs for AD-related medication per person were JPY 8409.7 (IQR, 3403.2-19,796.0) in 2005 and JPY 11,706.0 (IQR, 4249.5-29,073.5) in 2017 (Figure 6C). Consistent with these findings, the proportion of AD-related medication costs to total medical expenses also increased with disease severity, but the median values were ≤31.7% in any single year in patients classified as severity level 4 (Figures S6A-C).

4 | DISCUSSION

Treatment of AD focuses on using emollients to rehydrate the skin and using TCSs and TCIs to attenuate inflammation.[1] The results of the current study showed that the use of emollients increased from 2005 to 2017, suggesting that healthcare providers and patients increasingly recognized the importance of skincare in the management

TABLE 2 Demographic characteristics by year for patients who answered that they visited the hospital

	Year							
	2005 N = 9895	2006 N = 14,769	2007 N = 18,000	2008 N = 23,150	2009 N = 30,761	2010 N = 47,356	2011 N = 64,564	2012 N = 84,436
Any hospital visit, *n* (%)								
Yes	9895 (100.0)	12,221 (82.7)	13,614 (75.6)	17,487 (75.5)	23,327 (75.8)	38,162 (80.6)	51,165 (79.2)	66,331 (78.6)
Department,[a] *n* (%)								
Dermatology	6544 (66.1)	7957 (65.1)	8920 (65.5)	11,786 (67.4)	15,788 (67.7)	26,269 (68.8)	34,978 (68.4)	44,753 (67.5)
Internal medicine	2243 (22.7)	2783 (22.8)	3033 (22.3)	3560 (20.4)	4682 (20.1)	7430 (19.5)	9875 (19.3)	12,936 (19.5)
Pediatrics	1354 (13.7)	1768 (14.5)	1978 (14.5)	2424 (13.9)	2902 (12.4)	4768 (12.5)	6548 (12.8)	8615 (13.0)
Other	784 (7.9)	1033 (8.5)	1096 (8.1)	1418 (8.1)	2057 (8.8)	3084 (8.1)	4278 (8.4)	5886 (8.9)
Facility,[a] *n* (%)								
Clinic	9160 (92.6)	11,282 (92.3)	12,612 (92.6)	16,329 (93.4)	21,677 (92.9)	35,629 (93.4)	47,681 (93.2)	61,610 (92.9)
University hospital	57 (0.6)	88 (0.7)	123 (0.9)	176 (1.0)	304 (1.3)	481 (1.3)	651 (1.3)	899 (1.4)
Public hospital	349 (3.5)	498 (4.1)	500 (3.7)	567 (3.2)	720 (3.1)	1052 (2.8)	1425 (2.8)	1881 (2.8)
Other hospital	671 (6.8)	798 (6.5)	835 (6.1)	977 (5.6)	1314 (5.6)	2141 (5.6)	2914 (5.7)	3959 (6.0)
Unknown	21 (0.2)	20 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	21 (0.0)
Treatment severity (disease severity), *n* (%)								
2	5657 (57.2)	6715 (55.0)	7341 (53.9)	9093 (52.0)	11,715 (50.2)	19,030 (49.9)	25,206 (49.3)	32,488 (49.0)
3	2327 (23.5)	3094 (25.3)	3544 (26.0)	5143 (29.4)	7267 (31.2)	12,221 (32.0)	16,525 (32.3)	22,008 (33.2)
4	767 (7.8)	1103 (9.0)	1217 (8.9)	1420 (8.1)	1938 (8.3)	3230 (8.5)	4482 (8.8)	5692 (8.6)

[a]Multiple answers allowed.

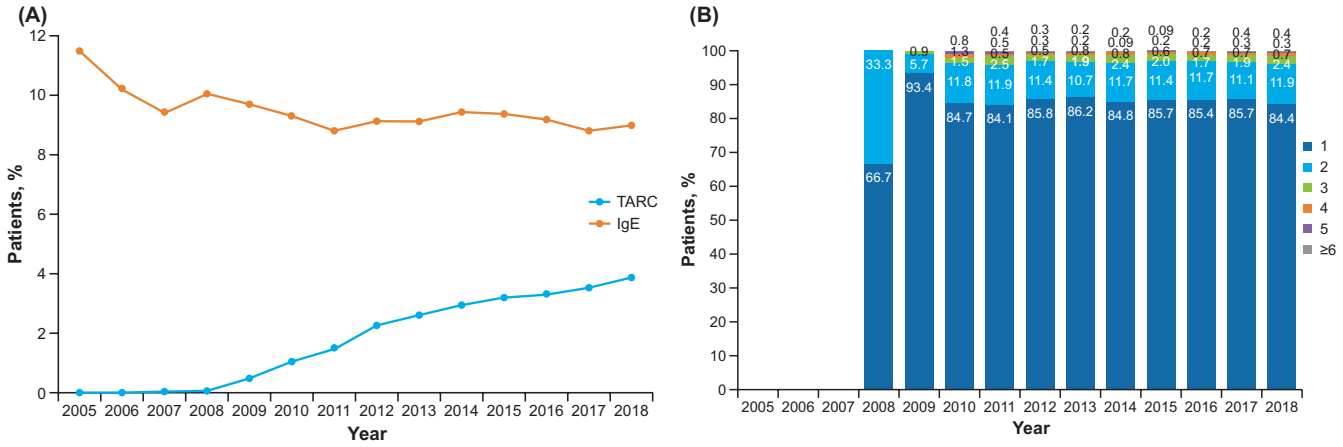

FIGURE 3 (A) Proportion of patients with AD who received laboratory tests at least once a year and (B) proportion of TARC test results received per year in patients who received TARC tests at least once a year from 2005 to 2018. AD, atopic dermatitis; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine

of AD. The results of the current study showed that medium to very strong TCSs are the main treatment for patients with AD.

Antihistamine use in patients with AD has not been fully positioned in the current guidelines in Europe[13] and the United States[14] because of the limited effectiveness of antihistamines in clinical studies. In Japan, antihistamines are positioned as an adjuvant to anti-inflammatory topical therapy.[1] The results of the current study showed that almost 60% of patients received antihistamines or antiallergic agents for the treatment of AD. In the current study, patients who received any systemic treatments at least once a year were categorized as severity level 4. Interestingly, 80% to 90% of patients received antihistamines or antiallergic agents, possibly highlighting the unmet medical need for severe itch relief.

Interestingly, the number of patients who received very strong and strongest TCSs and systemic treatment (e.g., oral corticosteroids) increased over time in the current study. This is potentially

2013 *N* = 118,805	2014 *N* = 141,978	2015 *N* = 176,843	2016 *N* = 201,979	2017 *N* = 218,496	2018 *N* = 193,548
96,142 (80.9)	112,471 (79.2)	144,991 (82.0)	169,218 (83.8)	193,675 (88.6)	193,548 (100.0)
65,394 (68.0)	76,441 (68.0)	99,445 (68.6)	117,349 (69.4)	134,675 (69.5)	134,471 (69.5)
18,204 (18.9)	21,530 (19.1)	27,286 (18.8)	30,969 (18.3)	35,061 (18.1)	35,415 (18.3)
12,007 (12.5)	14,178 (12.6)	17,600 (12.1)	20,013 (11.8)	22,885 (11.8)	23,412 (12.1)
8488 (8.8)	9948 (8.8)	12,482 (8.6)	14,488 (8.6)	16,704 (8.6)	16,831 (8.7)
89,359 (92.9)	104,271 (92.7)	134,743 (92.9)	157,363 (93.0)	179,988 (93.0)	179,719 (92.9)
1338 (1.4)	1663 (1.5)	2151 (1.5)	2556 (1.5)	3039 (1.6)	3252 (1.7)
2719 (2.8)	3424 (3.0)	4158 (2.9)	4900 (2.9)	5812 (3.0)	6200 (3.2)
5613 (5.8)	6467 (5.8)	7974 (5.5)	9133 (5.4)	10,277 (5.3)	10,279 (5.3)
19 (0.0)	25 (0.0)	21 (0.0)	17 (0.0)	14 (0.0)	7 (0)
46,718 (48.6)	53,722 (47.8)	67,733 (46.7)	77,487 (45.8)	87,735 (45.3)	85,044 (43.9)
33,004 (34.3)	39,010 (34.7)	52,146 (36.0)	62,613 (37.0)	72,817 (37.6)	74,235 (38.4)
8148 (8.5)	9978 (8.9)	13,177 (9.1)	15,216 (9.0)	17,516 (9.0)	19,237 (9.9)

a result of the emerging concept of proactive therapy, in which patients with AD are initially treated with intensive topical anti-inflammatory therapy, followed by long-term, low-dose, intermittent anti-inflammatory therapy and daily application of emollients to unaffected skin, even when AD lesions are mostly healed.[15] Importantly, the Japanese and international AD guidelines discourage the long-term use of systemic corticosteroids because of severe side effects,[16] especially in children,[17] but the results of the current study showed that oral corticosteroid use is approximately 8% in Japan. A recent analysis of a US claims database showed similar results, with 73.4% of patients who initiated treatments associated with moderate-to-severe AD beginning treatment with a systemic corticosteroid.[18] For short-term management (≤1 week) of AD, clinicians might use oral corticosteroids in patients with severe AD because of the low cost and lack of better treatment options,[16] highlighting the need for alternative treatments. New treatments such as biologics and oral Janus kinase (JAK) inhibitors might address the unmet needs observed with antihistamine use; studies have shown that treatment with JAK inhibitors,[19] such as nemolizumab[20] and dupilumab,[3] can result in early and sustained itch relief.

In the early 2000s, there was concern that TCIs could increase the risk for lymphoma and skin cancer.[21] However, the 2018 Japanese guideline for AD concluded that there was no evidence to support this claim.[22] A survey of Japanese physicians showed that 85.4% considered TCIs to be safe in terms of cancer risk.[23] This opinion may be reflected in the results of the current study, given that the proportion of patients who received TCIs increased over time. Conversely, the use of topical NSAIDs for the management of AD is not recommended in the Japanese guidelines because NSAIDs "have an extremely weak anti-inflammatory effect and are not an uncommon cause of contact dermatitis."[1] Results of the current study showed that the use of topical NSAIDs decreased over time, which was possibly related to guideline recommendations.

AD is frequently observed in clinical practice in Japan.[1] According to a survey conducted by the Japanese Ministry of Health, Labor and Welfare, the percentage of adult patients (aged ≥20 years) also increased from 55.7% in 2005[24] to 62.4% in 2017.[25] The results from the current study corroborate this point. The increasing average age of patients with AD may be a result of Japan's decreasing birth rate and aging population.[26]

Results of several studies in Japan have estimated the prevalence of AD to be higher in children than in adults.[27-29] The results of the current study showed a similar trend, but the prevalence of AD in infants and children (aged <2 years) was higher than previously reported.[27,30] The results of the current study possibly overestimate the incidence of infantile AD because some infantile eczema may have been recorded as AD in the database owing to the difficulty in distinguishing infantile eczema from AD.

According to the JMDC Claims Database, dermatologists were the main specialists, followed by internal medicine physicians, pediatric physicians, and others, who diagnosed or treated AD. Although dermatologists made the majority of diagnoses and treatment

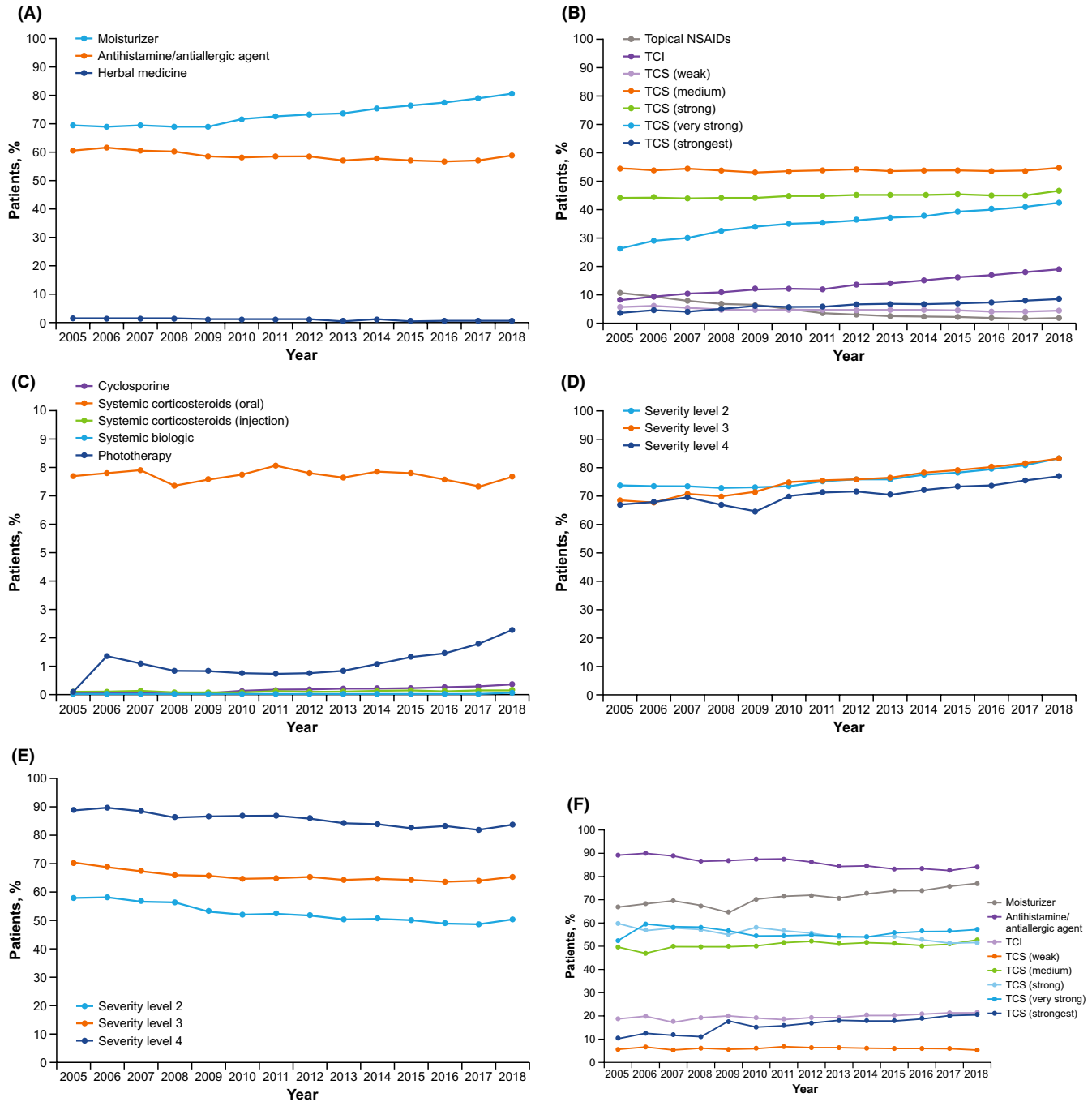

FIGURE 4 Proportion of patients with AD from 2005 to 2018 who received (A) moisturizer, antihistamines or antiallergic agents, and herbal medicine; (B) topical medications; and (C) systemic medications. Proportion of patients from 2005 to 2018 in severity levels 2, 3, and 4 who received (D) moisturizer and (E) antihistamines or antiallergic agents. (F) Proportion of patients from 2005 to 2018 classified as severity level 4 who received moisturizer, antihistamines or antiallergic agents, and systemic medications. AD, atopic dermatitis; NSAID, non-steroidal anti-inflammatory drug; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

decisions, approximately 35% were made by other healthcare providers, suggesting that such specialists may benefit from becoming familiar with AD diagnostic criteria and treatment guidelines. Clinics were the main facility that patients used for daily AD medical treatment. Although a lower proportion of patients visited university hospitals than clinics, the proportion of patients who visited a university hospital increased every year, suggesting that university hospitals may be becoming more important for the daily medical practice of AD.

Serum TARC level is one of the reliable biomarkers of disease progression,[1] and some physicians might use TARC levels to educate patients and improve treatment adherence.[12] In the current study, the proportion of patients who received the TARC test increased over the study period, which may have resulted from

implementation of medical insurance coverage of the TARC test in Japan in 2008. It is anticipated that more patients will receive TARC tests in the future.

AD-related medication cost per visit increased over time. The current study shows that the 25th percentile value was similar through the years, but the median and the 75th percentile values increased from 2005 to 2017. The results may indicate that treatments for mild AD cases are not changing but that treatments for moderate-to-severe cases are, potentially because of an increased number of prescriptions owing to healthcare providers' understanding of the importance of prescribing topical agents; more expensive drugs (e.g., TCIs) being used more frequently; and prescription of multiple drugs for individual patients. Conversely, the proportion of AD-related medication to total medical expenses was not high in patients across severity levels, even for those classified as severity level 4. The modest proportions may be due to other factors, such as AD-associated comorbidities (e.g., cardiovascular diseases[31]).

The current study had several limitations. Diagnosis codes on claims were used to identify and extract patients with AD, and they do not always represent the true presence of the diseases. However, the inclusion criteria for this study resulted in a positive predictive value in 90% of children and 82% of adults in a study conducted in the United Kingdom, suggesting the use of diagnosis codes to identify patients with AD is acceptable.[32] Non-AD patients were excluded as much as possible by combining three inclusion criteria, but additional studies are needed to evaluate whether the results of the current study reflect the Japanese real-world setting. Additionally, the JMDC Claims Database mostly includes health insurance data from employers, which misses data for patients aged ≥75 years and contains limited data for patients aged ≥60 years. Results of a previous Japanese epidemiologic study showed that the prevalence rates of AD in patients aged 50-60 years was 2.5%.[30] Hence, the presence of limited data for older populations is not expected to have a major impact on the study results. Finally, the database contained limited data on newly approved treatments. Dupilumab is the only approved biologic for the treatment of moderate-to-severe AD, and, because dupilumab was approved in 2018 in Japan,[6] prescription data were limited. Additional studies are needed.

In conclusion, from 2005 to 2017, the average age for the Japanese patient with AD; the proportion of patients using treatments that are more potent (including TCIs, very strong TCSs, and strongest TCSs); and AD-related treatment costs have all increased. Because of the limitations listed previously, additional studies are necessary to include more data on older patient populations, on patients who may have left their original payers, and on newly approved treatments for AD.

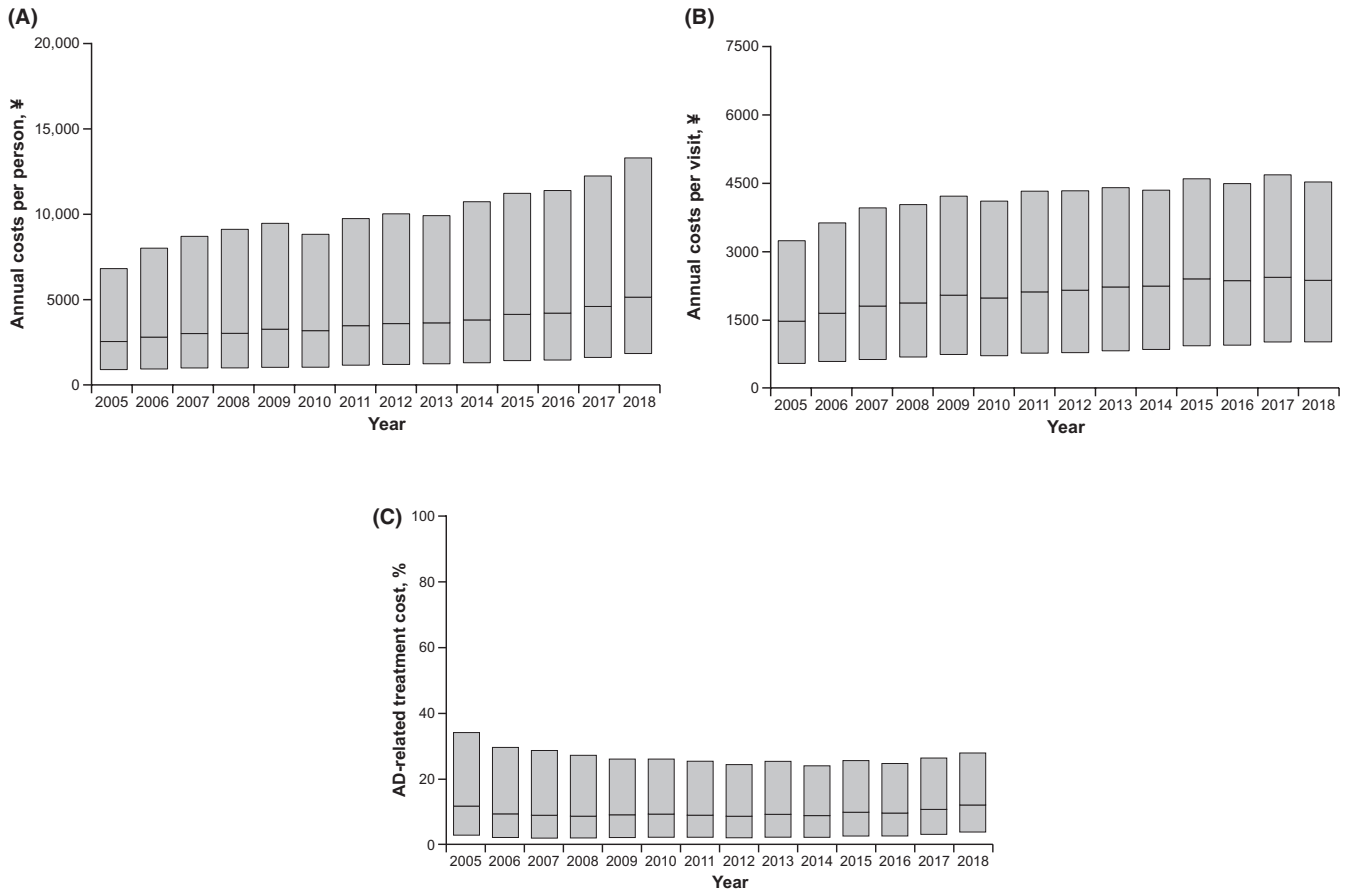

FIGURE 5 AD-related treatment costs from 2005 to 2018 (A) per person, (B) per visit, and (C) relative to total medical expenses. AD, atopic dermatitis

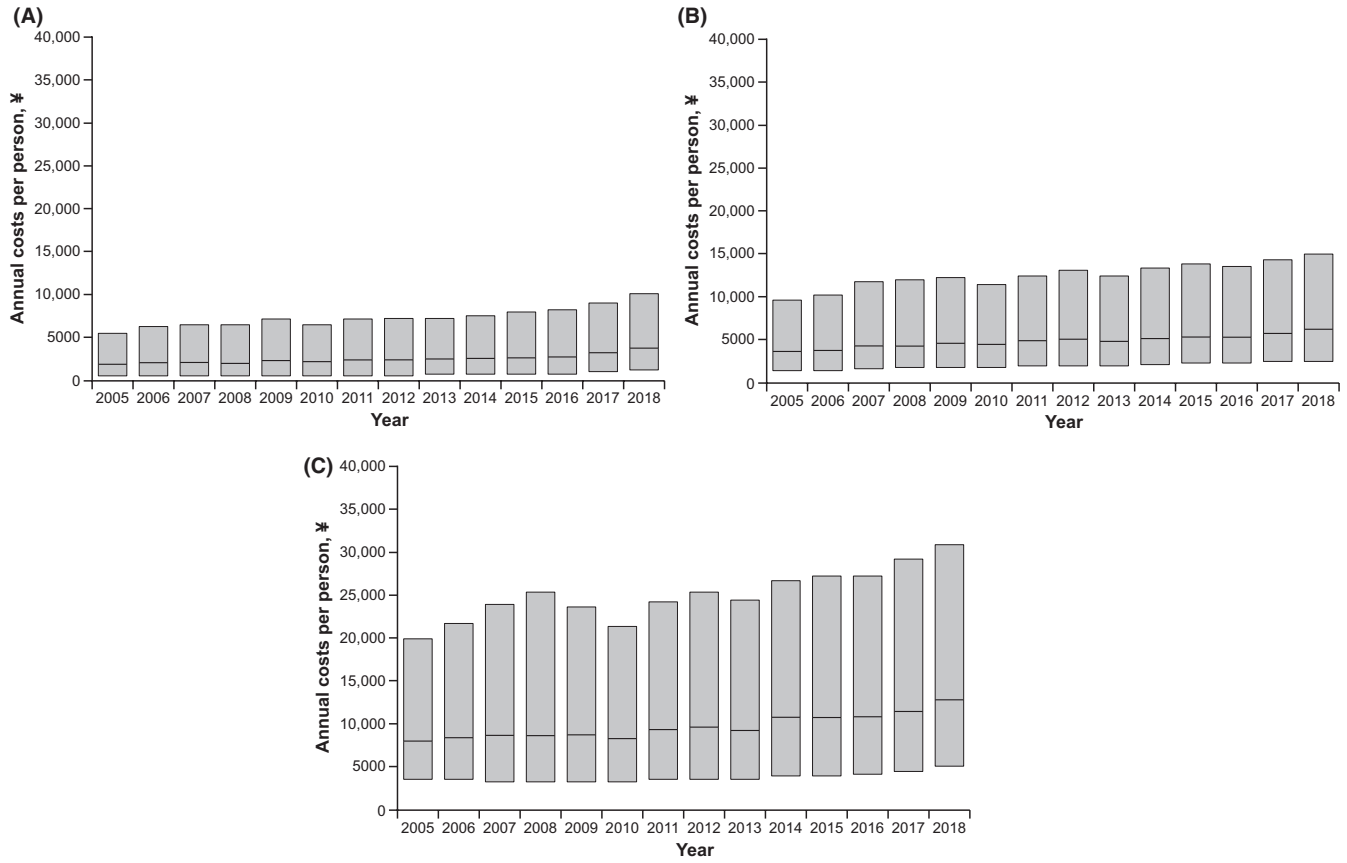

FIGURE 6 Annual AD-related medication costs per person, from 2005 to 2018, for patients classified as (A) severity level 2, (B) severity level 3, and (C) severity level 4. AD, atopic dermatitis

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DECLARATION SECTION

Approval of the research protocol: No human participant was involved in this study.

Informed Consent: N/A.

Registry and the Registration Number: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

HS reports lecture fees from Mitsubishi Tanabe, Maruho, Taiho, Kyowa Kirin, Kyorin, and Sanofi; scholarship donations from Tokiwa, Mitsubishi Tanabe, Maruho, Torii, and Eisai; and honoraria for consultancy from Pfizer, AbbVie, Sanofi, and LEO Pharma. SI reports lecture fees from Mitsubishi Tanabe, Maruho, Taiho, Kyowa Kirin, Sanofi, Janssen, AbbVie, and Daiichi Sankyo; scholarship donations from Mitsubishi Tanabe, Maruho, Torii, Eisai, and AbbVie; and honorarium for a consultancy from Pfizer, AbbVie, LEO Pharma, and Kyowa Kirin. KK is an employee of Pfizer Japan Inc. (Tokyo, Japan). TT, TH, EC-A, FM, and NY are employees of Pfizer Japan Inc. and shareholders of Pfizer Inc.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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