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Costs and Treatment Patterns Among Patients with Atopic Dermatitis Using Advanced Therapies in the United States: Analysis of a Retrospective Claims Database

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ABSTRACT

Introduction: For many, atopic dermatitis (AD) is not adequately controlled with topical regimens. This analysis examined treatment using advanced therapies and associated costs.

Methods: The IQVIA Health Plan Claims data set was analyzed. Patients aged ≥ 12 years with AD who newly initiated advanced therapy after the availability of dupilumab (March 28, 2017) and had ≥ 6 months continuous enrollment

before and after their first advanced therapy claim (index date) were included. Advanced therapies included dupilumab, systemic corticosteroids (SCSs), systemic immunosuppressants (SISs), and phototherapy. A multivariate regression model was used to predict annualized follow-up healthcare costs.

Results: In total, 1980 patients were included (61.1% female; mean age, 41.2 years [SD, 17.4]; 11.3% < 18 years). Pre-index date, 65.2% of patients used topical corticosteroids (TCSs; 40.7% and 32.1% used medium and high potency, respectively). The most common advanced therapy was SCSs ($N = 1453$ [73.4%]; 69.2% prednisone) followed by dupilumab ($N = 265$ [13.4%]), SISs ($N = 99$ [5.0%]; 47.5% methotrexate), and phototherapy ($N = 163$ [8.2%]). Of patients treated with dupilumab, SISs, and phototherapy, 17.4%, 26.3%, and 14.1%, respectively, were prescribed SCSs post-index date. Overall, 62.6% of patients initiating SCSs, 49.1% initiating dupilumab, 64.6% initiating SISs, and 36.2% initiating phototherapy were prescribed TCSs post-index date. Mean annualized total costs (SD) post-index date were \$20,722 (\$47,014): \$11,196 (\$41,549) in medical costs (\$7973 [\$35,133] in outpatient visit costs) and \$9526 (\$21,612) in pharmacy costs. Mean annualized total cost (SD) varied significantly ($P < 0.05$) by index treatment: dupilumab, \$36,505 (\$14,028); SCSs, \$17,924 (\$49,019); SISs, \$24,762 (\$47,583); phototherapy, and \$17,549 (\$57,238).

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Conclusions: Switching to combination therapy with SCSs and TCSs was common within 6 months of initiating advanced therapy in patients with AD. Patients also incurred significant pharmacy and outpatient costs. These results highlight the difficulty of managing AD with these existing treatment options.

Keywords: Atopic dermatitis; Corticosteroids; Costs; Dupilumab; Immunosuppressants; Phototherapy

Key Summary Points

Why carry out this study?

Many patients with atopic dermatitis cannot manage their disease with topical treatments, requiring advanced therapy.

This analysis examined advanced therapy (systemic corticosteroids, systemic immunosuppressants, phototherapy, and dupilumab) use between March 28, 2017, and July 31, 2018, and associated costs in patients with atopic dermatitis aged ≥ 12 years using the IQVIA Health Plan Claims data set.

What was learned from the study?

Patients initiating an advanced treatment often switch to or add on another advanced treatment and often use topical treatments concomitantly.

Adherence rates to advanced treatments are not optimal.

The patterns of use of advanced therapies represent a significant burden to the healthcare system, with costs representing approximately \$20,000 per patient per year.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin and eczematous lesions [1]. The disease is relatively common, affecting approximately 20% of children and 10% of adults in the USA [2, 3]. AD is associated with several comorbidities, such as anxiety and depression, and it has a profound impact on patients' health-related quality of life [4, 5].

Many of those with AD can achieve adequate disease control with some combination of nonpharmacologic topical interventions (e.g., emollients) and/or prescription topical therapies such as corticosteroids, calcineurin inhibitors, and phosphodiesterase 4 inhibitors [6, 7]. For patients whose AD cannot be controlled with these therapies, treatment intensification with phototherapy or systemic immunosuppressants (SISs) can be considered (subsequently referred to as "advanced therapies") [8]. SISs, which include methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil, are recommended as potential treatment options even though they are not approved by the US Food and Drug Administration (FDA) for AD and have long-term toxicity issues [8]. Dupilumab, an interleukin (IL)-4 receptor antagonist that blocks IL-4 and IL-13, is a subcutaneously administered biologic therapy that represents another advanced therapy option for patients with moderate-to-severe AD after its recent approval by the US FDA in 2017 [9, 10].

As the management of AD has evolved since the introduction of dupilumab, the primary goal of this study was to evaluate the current real-world treatment patterns for patients with moderate-to-severe AD, including the distribution of advanced treatments used, adherence to and persistence with those treatments, and the frequency of combination therapy in a cohort of US commercially insured patients with AD. Recent studies showed that annual costs for patients with AD in commercial health plans who were treated with either phototherapy or systemic treatments (i.e., patients with "more severe AD") were approximately \$15,000 [11, 12]. However, these studies were conducted

using data periods prior to the availability of dupilumab. The current study will be used to provide updated information on the cost burden of AD and provide current cost figures after the introduction of dupilumab, including stratification by the specific advanced treatment(s) used. Collectively, these data will provide a current view on the management and costs associated with moderate-to-severe AD.

METHODS

Data Source

A retrospective cohort study was conducted using the IQVIA Health Plan Claims (formerly PharMetrics Plus) database. The IQVIA Health Plan Claims database is the largest non-payer owned integrated claims database of commercial insurers and consists of fully adjudicated medical (inpatient and outpatient diagnoses and procedures) and pharmacy (retail and mail-order prescriptions) claims for more than 105 million patients across the USA. It is generally representative of the commercially insured US population with respect to age and sex. Data are deidentified and compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was an analysis of secondary data and was exempt from institutional review board approval.

Sample

Patients with AD (*ICD-9/ICD-10-CM: 691.8/L20.x*) who newly initiated a treatment associated with moderate-to-severe AD between March 28, 2017 (the date of approval of dupilumab), and July 31, 2018, were included. This period was selected to reflect the current treatment options because the introduction of dupilumab might have significantly changed the treatment paradigm and costs for patients with moderate-to-severe AD. Given the lack of clinical data in claims databases, the treatments received were used as a surrogate for disease severity, as done in prior research [11, 12]. The first claim for a moderate-to-severe AD

treatment (i.e., one of the following advanced therapies: phototherapy, dupilumab, systemic corticosteroid [SCS], or SIS [methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil]) was considered the index date. A post-index date follow-up period of at least 6 months was used to assess the research questions (i.e., the 6 months after initiation of an advanced therapy). The specific inclusion criteria were as follows: (1) at least two AD diagnoses at any time during data availability (January 1, 2013–July 31, 2018), including one during the 6-month pre-index date baseline period (i.e., the 6 months before initiation of an advanced therapy); (2) at least 6 months of continuous eligibility before and after the index date; (3) at least 12 years of age on the index date; and (4) at least two claims for any treatment associated with moderate-to-severe AD on March 28, 2017, or later, with no claim for those specific agents in the baseline period. There were no exclusion criteria beyond not meeting these inclusion criteria.

Measures

Treatment Cohort

Patients were categorized into a treatment cohort based on the advanced treatment used on the index date: dupilumab, SCS, SIS, or phototherapy.

Demographics and Health History

Demographic information regarding the patients' age, sex, region, payer type, and insurance type on the index date was collected and reported. Comorbidities were evaluated during the 6-month baseline period and presented using the Quan-Charlson comorbidity index (Quan-CCI; score of 1-year mortality prediction; 0–24 scale with higher score indicating higher mortality) [13, 14].

Treatment Patterns

Persistence to the index treatment was calculated based on the time spent on therapy without a gap of > 60 days (such a gap was used to define a discontinuation). Adherence was calculated using a proportion of days covered

(PDC) method [15, 16]. To identify the use of combination therapy, all AD-related treatments (both topical and systemic) were reported before and after the index treatment.

Healthcare Resource Utilization and Costs

Costs associated with outpatient visits, inpatient visits, emergency room visits, and other medical visits (including durable medical equipment use, dental care, and vision care) were recorded and annualized to represent all-cause medical costs. Similarly, drug costs were reported and annualized as part of the all-cause pharmacy costs. Annualized costs were obtained by calculating monthly costs and then multiplying them by 12. Total costs represent the sum of these costs.

Statistical Analyses

Descriptive analyses (frequencies and percentages for categorical variables; means, standard deviations [SD], and medians for continuous variables) were reported for demographics, health history, and treatment pattern analyses. Statistical differences (P values) in baseline characteristics and adherence measures across treatment cohorts were calculated using analysis of variance models [17] for continuous variables and chi-square tests [18] or Fisher exact tests [19] (if an expected count was less than 5) for categorical variables. Patient persistence with the index treatment was described using Kaplan-Meier rates and compared using log-rank tests [20]. A multivariable linear regression model [21] based on the index treatment cohort and baseline variables was also used to predict annualized total follow-up health care costs. Cost outcomes were compared using adjusted mean cost differences and 95% CIs estimated with gamma regression models, and P values were reported. All analyses were conducted using SAS Enterprise Guide, version 7.15.

RESULTS

Sample Characteristics

A total of 1980 patients were newly initiated a treatment associated with moderate-to-severe AD (Fig. 1). The mean age (SD) of this sample was 41.2 years (17.4; 88.7% were aged ≥ 18 years), 61.1% were female, and patients were disproportionately located in the South (42.5%) versus the West (12.2%) of the US. The distribution of patients in the index treatment cohorts was as follows: 73.4% were in the SCS cohort (69.2% of whom initiated prednisone), 13.4% were in the dupilumab cohort, 8.2% were in the phototherapy cohort, and 5.0% were in the SIS cohort (47.5% and 30.3% of whom initiated methotrexate and cyclosporine, respectively).

A few significant demographic differences were observed across treatment cohorts (Tables 1 and 2). Those initiating dupilumab were the least likely to be aged < 18 years (2.3%) and the most likely to have a preferred provider organization (PPO) insurance type (89.8%) relative to other cohorts (both $P < 0.05$). Patients initiating phototherapy were least likely to be in the South (16.0%) and most

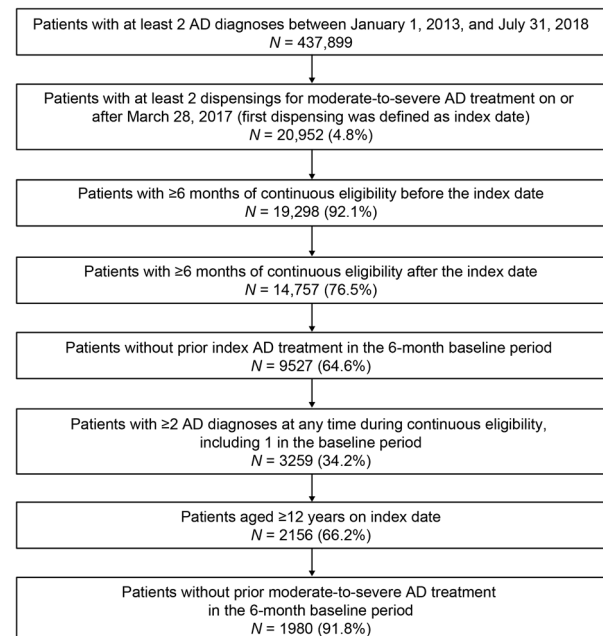


Fig. 1 Sample selection. AD atopic dermatitis

Table 1 Demographic characteristics of the sample by treatment cohort

| | Total patients (<i>N</i> = 1980) | Treatment cohorts | | | <i>P</i> value | |
|---|--------------------------------------|--------------------------------|------------------------|----------------------|--------------------|----------------------|
| | | Dupilumab (<i>N</i> = 265) | SCS (<i>N</i> = 1453) | SIS (<i>N</i> = 99) | | PT (<i>N</i> = 163) |
| Demographics | | | | | | |
| Age on index date, mean ± SD [median], years | 41.2 ± 17.4 [43.0] | 39.8 ± 14.9 [40.0] | 41.1 ± 17.3 [43.0] | 44.9 ± 18.7 [50.0] | 42.4 ± 20.2 [43.0] | 0.068 |
| Age categories on index date, <i>n</i> (%) | | | | | | |
| 12–17 years | 223 (11.3) | 6 (2.3) | 179 (12.3) | 14 (14.1) | 24 (14.7) | < 0.001 |
| ≥ 18 years | 1757 (88.7) | 259 (97.7) | 1274 (87.7) | 85 (85.9) | 139 (85.3) | < 0.001 |
| Female, <i>n</i> (%) | 1209 (61.1) | 136 (51.3) | 911 (62.7) | 62 (62.6) | 100 (61.3) | 0.006 |
| Region of the US, <i>n</i> (%) | | | | | | |
| South | 842 (42.5) | 116 (43.8) | 668 (46.0) | 32 (32.3) | 26 (16.0) | < 0.001 |
| Northeast | 465 (23.5) | 64 (24.2) | 334 (23.0) | 34 (34.3) | 33 (20.2) | 0.052 |
| Midwest | 431 (21.8) | 63 (23.8) | 291 (20.0) | 12 (12.1) | 65 (39.9) | < 0.001 |
| West | 242 (12.2) | 22 (8.3) | 160 (11.0) | 21 (21.2) | 39 (23.9) | < 0.001 |
| Payer type, <i>n</i> (%) ^a | | | | | | |
| Commercial | 1155 (58.3) | 152 (57.4) | 847 (58.3) | 61 (61.6) | 95 (58.3) | 0.909 |
| Self-insured | 777 (39.2) | 111 (41.9) | 586 (40.3) | 37 (37.4) | 43 (26.4) | 0.005 |
| Medicaid | 23 (1.2) | 1 (0.4) | 14 (1.0) | 0 (0.0) | 8 (4.9) | 0.001 |
| Medicare | 20 (1.0) | 0 (0.0) | 3 (0.2) | 1 (1.0) | 16 (9.8) | < 0.001 |
| Unknown | 5 (0.3) | 1 (0.4) | 3 (0.2) | 0 (0.0) | 1 (0.6) | 0.474 |
| Insurance type, <i>n</i> (%) ^a | | | | | | |
| PPO | 1667 (84.2) | 238 (89.8) | 1243 (85.5) | 82 (82.8) | 104 (63.8) | < 0.001 |
| HMO | 203 (10.3) | 18 (6.8) | 135 (9.3) | 10 (10.1) | 40 (24.5) | < 0.001 |
| POS | 84 (4.2) | 7 (2.6) | 56 (3.9) | 6 (6.1) | 15 (9.2) | 0.009 |

Table 1 continued

| | Total patients (<i>N</i> = 1980) | Treatment cohorts | | | <i>P</i> value | |
|---|--------------------------------------|--------------------------------|------------------------|----------------------|----------------|----------------------|
| | | Dupilumab (<i>N</i> = 265) | SCS (<i>N</i> = 1453) | SIS (<i>N</i> = 99) | | PT (<i>N</i> = 163) |
| Indemnity/traditional | 21 (1.1) | 1 (0.4) | 16 (1.1) | 1 (1.0) | 3 (1.8) | 0.470 |
| CDHC | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0.132 |
| HSA | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |
| Unknown | 4 (0.2) | 1 (0.4) | 3 (0.2) | 0 (0.0) | 0 (0.0) | 0.710 |
| Year of index date, <i>n</i> (%) | | | | | | |
| 2017 | 1978 (99.9) | 265 (100.0) | 1453 (100.0) | 99 (100.0) | 161 (98.8) | 0.009 |
| 2018 | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.2) | 0.009 |
| Site of care | | | | | | |
| ≥ 1 dermatologist visit, ^b <i>n</i> (%) | 1239 (62.6) | 208 (78.5) | 811 (55.8) | 79 (79.8) | 141 (86.5) | < 0.001 |
| ≥ 1 mental health professional visit, ^b <i>n</i> (%) | 150 (7.6) | 24 (9.1) | 114 (7.8) | 6 (6.1) | 6 (3.7) | 0.184 |
| Prescribing provider specialty, ^c <i>n</i> (%) | | | | | | |
| Primary care specialist | 619 (31.3) | 33 (12.5) | 561 (38.6) | 12 (12.1) | 13 (8.0) | < 0.001 |
| Dermatology specialist | 512 (25.9) | 105 (39.6) | 231 (15.9) | 45 (45.5) | 131 (80.4) | < 0.001 |
| Allergy specialist | 164 (8.3) | 29 (10.9) | 127 (8.7) | 7 (7.1) | 1 (0.6) | 0.001 |
| Hospital physician | 106 (5.4) | 11 (4.2) | 86 (5.9) | 5 (5.1) | 4 (2.5) | 0.222 |
| Pediatrician | 61 (3.1) | 3 (1.1) | 58 (4.0) | 0 (0.0) | 0 (0.0) | < 0.001 |
| Other | 293 (14.8) | 43 (16.2) | 227 (15.6) | 19 (19.2) | 4 (2.5) | < 0.001 |
| Unknown | 225 (11.4) | 41 (15.5) | 163 (11.2) | 11 (11.1) | 10 (6.1) | 0.031 |

Table 1 continued

| | Treatment cohorts | | P value |
|--|------------------------------|------------------------|---------|
| | Total patients (N = 1980) | Dupilumab (N = 265) | |

| | | | | | | |
|---|--------------------|--------------------|--------------------|--------------------|--------------------|-------|
| Quan-Charlson comorbidity index, ^d mean ± SD [median] | 0.30 ± 0.71 [0.00] | 0.25 ± 0.62 [0.00] | 0.31 ± 0.74 [0.00] | 0.18 ± 0.44 [0.00] | 0.31 ± 0.76 [0.00] | 0.231 |
|---|--------------------|--------------------|--------------------|--------------------|--------------------|-------|

AD atopic dermatitis, CDHC consumer-directed health care, HMO health maintenance organization, HSA health savings account, SCS systemic corticosteroid, POS point of service, PPO preferred provider organization, PT phototherapy, SIS systemic immunosuppressant.

Index date is the date at which the advanced therapy (i.e., dupilumab, SCS, SIS, or PT) was initiated. P values were tested for statistical differences in each of the baseline characteristics across the different treatment cohorts and were estimated using Fisher exact tests for categorical variables with expected cell counts < 5, chi-square tests for categorical variables with expected cell counts ≥ 5, and analysis of variance models for continuous variables.

^a Evaluated on the index date.

^b Evaluated in the baseline period, including the index date.

^c Prescribing provider specialty was based on the (1) prescribing specialty of the index AD pharmacy claim, (2) prescribing specialty of the index non-AD pharmacy claim, or (3) rendering or billing specialty (service provider to the patient) of medical claim nearest on the index date or nearest to the index date during the baseline period. Primary care specialists include general practitioners, nurse practitioners, internists, and physician assistants.

^d Evaluated in the baseline period, excluding the index date

Table 2 Treatment history by treatment cohort

| | Total patients (<i>N</i> = 1980) | Treatment cohorts | | | | <i>P</i> value |
|---|--------------------------------------|--------------------------------|---------------------------|-------------------------|-------------------------|----------------|
| | | Dupilumab (<i>N</i> = 265) | SCS (<i>N</i> = 1453) | SIS (<i>N</i> = 99) | PT (<i>N</i> = 163) | |
| Treatments initiated on the index date, <i>n</i> (%) | | | | | | |
| SCS (total) | 1453 (73.4) | 0 (0.0) | 1453 (100.0) | 0 (0.0) | 0 (0.0) | – |
| Prednisone | 1006 (50.8) | 0 (0.0) | 1006 (69.2) | 0 (0.0) | 0 (0.0) | – |
| Methylprednisolone | 387 (19.5) | 0 (0.0) | 387 (26.6) | 0 (0.0) | 0 (0.0) | – |
| Dexamethasone | 30 (1.5) | 0 (0.0) | 30 (2.1) | 0 (0.0) | 0 (0.0) | – |
| Prednisolone | 16 (0.8) | 0 (0.0) | 16 (1.1) | 0 (0.0) | 0 (0.0) | – |
| Other | 14 (0.7) | 0 (0.0) | 14 (1.0) | 0 (0.0) | 0 (0.0) | – |
| SIS (total) | 99 (5.0) | 0 (0.0) | 0 (0.0) | 99 (100.0) | 0 (0.0) | – |
| Methotrexate | 47 (2.4) | 0 (0.0) | 0 (0.0) | 47 (47.5) | 0 (0.0) | – |
| Cyclosporine | 30 (1.5) | 0 (0.0) | 0 (0.0) | 30 (30.3) | 0 (0.0) | – |
| Mycophenolate mofetil | 16 (0.8) | 0 (0.0) | 0 (0.0) | 16 (16.2) | 0 (0.0) | – |
| Azathioprine | 6 (0.3) | 0 (0.0) | 0 (0.0) | 6 (6.1) | 0 (0.0) | – |
| Dupilumab | 265 (13.4) | 265 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |
| Phototherapy | 163 (8.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 163 (100.0) | – |
| Treatments used in the 6 months before the index date, <i>n</i> (%) | | | | | | |
| TCS | 1290 (65.2) | 186 (70.2) | 962 (66.2) | 69 (69.7) | 73 (44.8) | < 0.001 |
| Low potency | 243 (12.3) | 33 (12.5) | 180 (12.4) | 11 (11.1) | 19 (11.7) | 0.976 |
| Medium potency | 806 (40.7) | 127 (47.9) | 584 (40.2) | 43 (43.4) | 52 (31.9) | 0.010 |
| High potency | 635 (32.1) | 105 (39.6) | 448 (30.8) | 41 (41.4) | 41 (25.2) | 0.001 |
| Unknown potency | 24 (1.2) | 5 (1.9) | 15 (1.0) | 1 (1.0) | 3 (1.8) | 0.437 |
| Tacrolimus ointment | 112 (5.7) | 32 (12.1) | 62 (4.3) | 7 (7.1) | 11 (6.7) | < 0.001 |
| Pimecrolimus cream | 79 (4.0) | 17 (6.4) | 54 (3.7) | 3 (3.0) | 5 (3.1) | 0.215 |
| Crisaborole ointment | 62 (3.1) | 21 (7.9) | 35 (2.4) | 5 (5.1) | 1 (0.6) | < 0.001 |

PT phototherapy, *SCS* systemic corticosteroid, *SIS* systemic immunosuppressant, *TCS* topical corticosteroid.

Index date is the date at which the advanced therapy (i.e., dupilumab, SCS, SIS, or PT) was initiated. *P* values tested for statistical differences in each of the treatment history variable across the different treatment cohorts and were estimated using Fisher's exact tests for categorical variables with expected cell counts < 5 and chi-square tests for categorical variables with expected cell counts ≥ 5

likely to be in the Midwest (39.9%), in the West (23.9%), on Medicare (9.8%), or have a health maintenance organization insurance type (24.5%) relative to other subgroups (all *P* < 0.05). Compared with the SCS and phototherapy cohorts, the dupilumab and SIS

cohorts were more likely to have used topical corticosteroids (TCSs; particularly high-potency TCSs, 39.6% and 41.4%, respectively), tacrolimus (12.1% and 7.1%), and crisaborole (7.9% and 5.1%) prior to their current therapy (all $P < 0.05$; Table 2).

Treatment Patterns

It was not uncommon for patients to use a subsequent advanced treatment after the index date (either in combination with their index treatment or as a switch from their index treatment). Forty-four (44.4%) and 54 (20.4%) patients in the SIS and dupilumab cohorts used an additional treatment, respectively, with SCSs ($n = 23$, 52.3% and $n = 46$, 85.2%, respectively) being the most frequent (Table 3). A total of 220 (15.1%) and 29 (17.8%) patients in the SCS and phototherapy cohorts used an additional advanced treatment after the index date, respectively. For the SCS cohort, this was most frequently dupilumab ($n = 114$; 51.8% of those who used an additional treatment); for the phototherapy cohort, this was most frequently SCSs ($n = 21$; 72.4%).

Significant differences in persistence with oral or injectable index treatment associated with moderate-to-severe AD were observed among treatments at 3, 6, 9, and 12 months ($P < 0.05$; Fig. 2). By 6 months, 21.9% of patients initiating dupilumab, 63.6% initiating SISs, and 97.7% initiating SCSs discontinued therapy, defined by a gap in treatment > 60 days. By 12 months, these figures were 25.0%, 72.2%, and 98.4% (Fig. 2). The median time to discontinuation was 12 days for SCSs and 124 days for SISs. Adherence to the index treatment during the first 6 months, based on mean PDC values, was 0.81, 0.58, and 0.13 for dupilumab, SISs, and SCSs, respectively (Fig. 3a). Hence, 68.7%, 32.3%, and 1.1% of patients treated with dupilumab, SISs, and SCSs, respectively, were classified as “adherent” based on the standard of $PDC \geq 0.80$ (Fig. 3b). Significant differences ($P < 0.05$) were observed among index treatments for the proportion of patients considered adherent and the mean PDC at 6 months.

Healthcare Costs

Mean per-patient annualized all-cause health-care costs were \$20,722 (SD, \$47,014; median, \$7470) across all patients with moderate-to-severe AD during the follow-up period. These costs were relatively evenly split between medical costs (\$11,196) and pharmacy costs (\$9526). However, there was significant ($P < 0.05$ for all-cause medical costs and all-cause pharmacy costs) variability in cost depending on the treatment cohort (Fig. 4), with total costs ranging from \$36,505 for the dupilumab cohort to \$17,549 for the phototherapy cohort. Total mean annualized costs for the dupilumab cohort were primarily a function of pharmacy costs (\$32,885); medical costs for this cohort (\$3620) were notably lower than those of other cohorts ($P < 0.05$), which varied between \$12,066 and \$14,944.

Additional post hoc analyses were undertaken to predict follow-up costs (Fig. 5). The strongest predictors of higher annualized follow-up costs were treatment cohort (dupilumab, specifically, contributed to an increase of \$19,435; $P < 0.05$), baseline Quan-CCI scores (\$15,495 for each increase of 1 point in the score; $P < 0.05$), and baseline all-cause total costs (\$653 for each increase of \$1000 in baseline costs; $P < 0.05$). Conversely, the strongest predictors of lower annualized follow-up costs were the presence of an atopic march condition (allergic rhinitis, asthma, food allergies) ($-\$8457$; $P < 0.05$) and the number of inpatient visits per year during baseline ($-\$13,723$; $P < 0.05$).

DISCUSSION

The aim of this study was to provide a more current assessment of the treatment patterns and costs associated with managing moderate-to-severe AD in the United States. SCSs were the most common advanced treatment initiated (prednisone, specifically) followed by dupilumab, phototherapy, and SISs (methotrexate and cyclosporine, specifically), although many of these patients concomitantly used topical therapies. Treatment selection may be partially a

Table 3 Treatments used in the follow-up period by treatment cohort

| Treatment patterns | Treatment cohort | | | |
|--|--------------------------------|---------------------------|-------------------------|-------------------------|
| | Dupilumab (<i>N</i> = 265) | SCS (<i>N</i> = 1453) | SIS (<i>N</i> = 99) | PT (<i>N</i> = 163) |
| Next treatment received during the follow-up period, <i>n</i> (%)^a | 54 (20.4) | 220 (15.1) | 44 (44.4) | 29 (17.8) |
| Dupilumab | – | 114 (7.8) | 18 (18.2) | 4 (2.5) |
| Systemic corticosteroids (total) | 46 (17.4) | – | 23 (23.2) | 21 (12.9) |
| Prednisone | 27 (10.2) | – | 20 (20.2) | 16 (9.8) |
| Methylprednisolone | 15 (5.7) | – | 2 (2.0) | 4 (2.5) |
| Dexamethasone | 2 (0.8) | – | 1 (1.0) | 0 (0.0) |
| Prednisolone | 0 (0.0) | – | 0 (0.0) | 1 (0.6) |
| Cyclosporine | 4 (1.5) | 14 (1.0) | – | 1 (0.6) |
| Mycophenolate mofetil | 1 (0.4) | 9 (0.6) | – | 0 (0.0) |
| Azathioprine | 2 (0.8) | 6 (0.4) | – | 0 (0.0) |
| Methotrexate | 0 (0.0) | 48 (3.3) | – | 3 (1.8) |
| Phototherapy | 1 (0.4) | 29 (2.0) | 3 (3.0) | – |
| All treatments during follow-up <i>n</i> (%)^b | | | | |
| Treatments for moderate-to-severe AD | | | | |
| Dupilumab | 265 (100.0) | 124 (8.5) | 21 (21.2) | 5 (3.1) |
| Systemic corticosteroids | 46 (17.4) | 1453 (100.0) | 26 (26.3) | 23 (14.1) |
| Prednisone | 33 (12.5) | 1227 (84.4) | 23 (23.2) | 21 (12.9) |
| Methylprednisolone | 16 (6.0) | 602 (41.4) | 2 (2.0) | 4 (2.5) |
| Dexamethasone | 2 (0.8) | 69 (4.7) | 1 (1.0) | 0 (0.0) |
| Prednisolone | 0 (0.0) | 25 (1.7) | 0 (0.0) | 1 (0.6) |
| Other | 2 (0.8) | 25 (1.7) | 0 (0.0) | 0 (0.0) |
| Cyclosporine | 4 (1.5) | 18 (1.2) | 30 (30.3) | 2 (1.2) |
| Mycophenolate mofetil | 2 (0.8) | 10 (0.7) | 19 (19.2) | 0 (0.0) |
| Azathioprine | 2 (0.8) | 9 (0.6) | 6 (6.1) | 0 (0.0) |
| Methotrexate | 0 (0.0) | 50 (3.4) | 48 (48.5) | 5 (3.1) |
| Phototherapy | 1 (0.4) | 31 (2.1) | 3 (3.0) | 163 (100.0) |
| Topical treatments | | | | |
| TCS | 130 (49.1) | 910 (62.6) | 64 (64.6) | 59 (36.2) |
| Low potency | 26 (9.8) | 206 (14.2) | 10 (10.1) | 12 (7.4) |
| Medium potency | 79 (29.8) | 588 (40.5) | 41 (41.4) | 40 (24.5) |

Table 3 continued

| Treatment patterns | Treatment cohort | | | |
|----------------------|------------------------|-------------------|-----------------|-----------------|
| | Dupilumab (N = 265) | SCS (N = 1453) | SIS (N = 99) | PT (N = 163) |
| High potency | 60 (22.6) | 499 (34.3) | 41 (41.4) | 32 (19.6) |
| Unknown potency | 2 (0.8) | 27 (1.9) | 0 (0.0) | 2 (1.2) |
| Tacrolimus ointment | 30 (11.3) | 87 (6.0) | 17 (17.2) | 10 (6.1) |
| Crisaborole ointment | 19 (7.2) | 66 (4.5) | 8 (8.1) | 5 (3.1) |
| Pimecrolimus cream | 13 (4.9) | 60 (4.1) | 5 (5.1) | 5 (3.1) |

AD atopic dermatitis; PT phototherapy; SCS systemic corticosteroid; SIS systemic immunosuppressant; TCS topical corticosteroid

^a “Next treatment received” is the subsequent advanced therapy after the original therapy was initiated.

^b “All treatments during the follow-up” refers to all subsequent therapies, regardless of the order and whether they were advanced

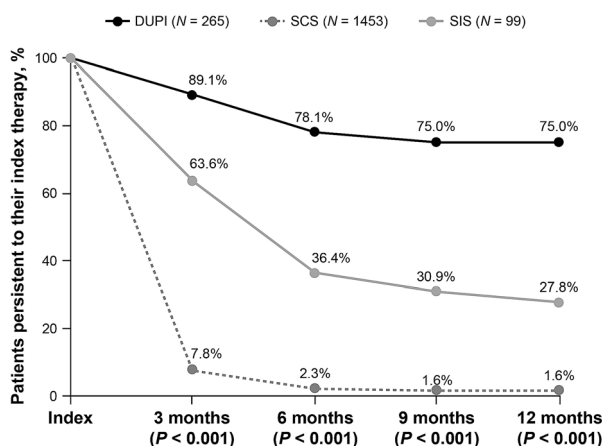


Fig. 2 Kaplan-Meier rates of persistence by treatment cohort. *DUPI* dupilumab; *SCS* systemic corticosteroid; *SIS* systemic immunosuppressant. Persistence was defined as the absence of a 60-day treatment gap. Phototherapy was excluded from this analysis because it is neither an oral nor an injectable treatment

function of access. For example, dupilumab was not indicated for adolescents during the current study period, which would likely explain the notably lower use among those aged < 18 years [9]. Phototherapy requires access to healthcare professionals with specific medical equipment,

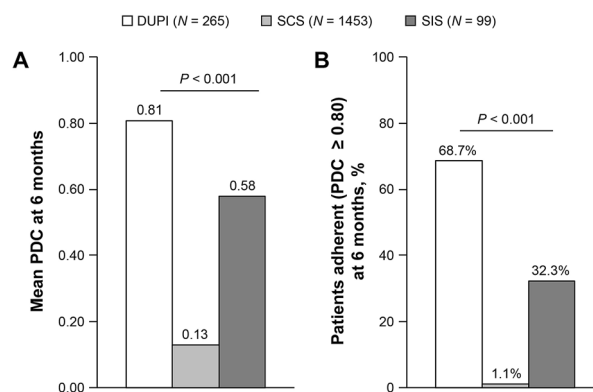


Fig. 3 Adherence to index treatment for moderate-to-severe AD during the first 6 months of follow-up: **a** based on mean PDC, **b** based on percentage of patients with PDC ≥ 0.80. AD atopic dermatitis, *DUPI* dupilumab, *SCS* systemic corticosteroid, *PDC* proportion of days covered, *SIS* systemic immunosuppressant. *P* values tested for statistical differences using chi-square tests for proportion of patients with PDC ≥ 0.80 and analysis of variance models for mean PDC. Phototherapy was excluded from this analysis because it is neither an oral nor an injectable treatment

which may be more difficult in certain areas of the country. In general, the distribution of advanced treatments is difficult to put into

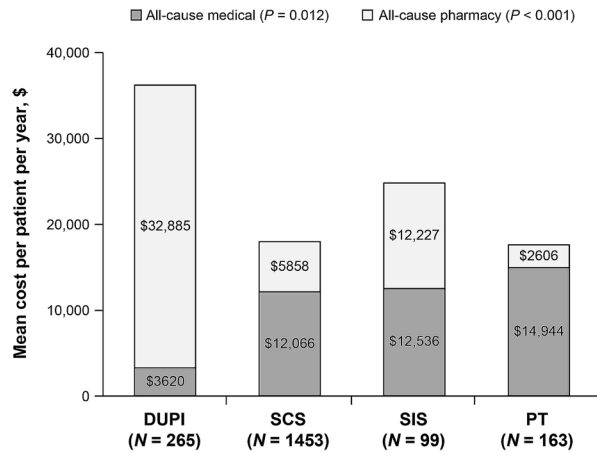


Fig. 4 Mean annualized all-cause health care costs by treatment cohort for patients initiating treatment for moderate-to-severe AD. *DUPI* dupilumab; *SCS* systemic corticosteroid; *SIS* systemic immunosuppressants; *PT* phototherapy. *P* values tested for statistical differences in costs across the different treatment cohorts and were estimated using analysis of variance models

context because the current study is, to our knowledge, the first to examine treatment patterns after the approval of dupilumab.

However, most patients were treated with SCSs, despite American Academy of Dermatology (AAD) guideline recommendations to avoid them as a treatment option because of their unfavorable benefit-risk profile in AD [8]. The use of SCSs in the treatment of patients with AD could be related to SCSs's rapid clearing of AD [22]. The quick adoption of dupilumab, as it was the second most prescribed advanced treatment so soon after its approval, potentially illustrates the historical difficulty in treating these patients with the predupilumab armamentarium.

The switching and persistence data also indicate the challenges in treating patients who have moderate-to-severe AD. Approximately 20–45% of patients who newly initiated dupilumab or SISs used an additional advanced treatment after the index date, with SCSs being the most common option. Persistence rates were highest for dupilumab, although 22% of patients still discontinued treatment within 6 months. Understanding the reasons for discontinuation (e.g., safety events, loss of response) was beyond the scope of the study

and the abilities of a commercial insurance data set; however, patients in the SISs treatment cohort were more likely to discontinue within 6 months. In part, this may be due to AAD guideline recommendations to discontinue systemic immunosuppressant treatment (e.g., cyclosporine, azathioprine) after skin clearance is achieved to avoid long-term treatment risks [8]. The low persistence rates of SCSs suggest mostly short-term use of these treatments, indicative of concerns regarding toxicity associated with long-term use and consistent with AAD guidelines [8]. However, there was a small proportion of patients that remained on SCS treatment without any substantial gap, potentially exposing them to adverse events resulting from long-term use [8].

Findings were similar for adherence. Adherence rates were highest for the dupilumab cohort (however, only 68.7% of patients were classified as adherent, defined as PDC \geq 0.8 during 6 months of follow-up) with notably lower adherence for SISs (only 32.3% of patients were classified as adherent). This could have been related to the long-term toxic effects of SIS use and the reticence of patients to take them as frequently as prescribed. Unsurprisingly, given the short-term use of SCSs, adherence rates were incredibly low. Taken together, these results suggest that adherence may be an issue with patients who have AD who are using advanced therapies.

The current study also provided an update with respect to the costs of AD since the introduction of dupilumab. Substantial costs, estimated to be $>$ \$20,000 per patient with AD per year in our analysis, suggest that costs have increased since the publication of results of prior studies [11, 12]. However, to our knowledge, this is the first time that costs have been compared as a function of the index treatment. Patients in the dupilumab cohort had the highest total costs, but this was disproportionately because of pharmacy costs; medical costs were notably lower than for other treatment cohorts, although they only partially offset the high pharmacy costs. No traditional clinical efficacy measures were available in the data set, but it is possible that dupilumab's clinical efficacy reduced medical costs (e.g.,

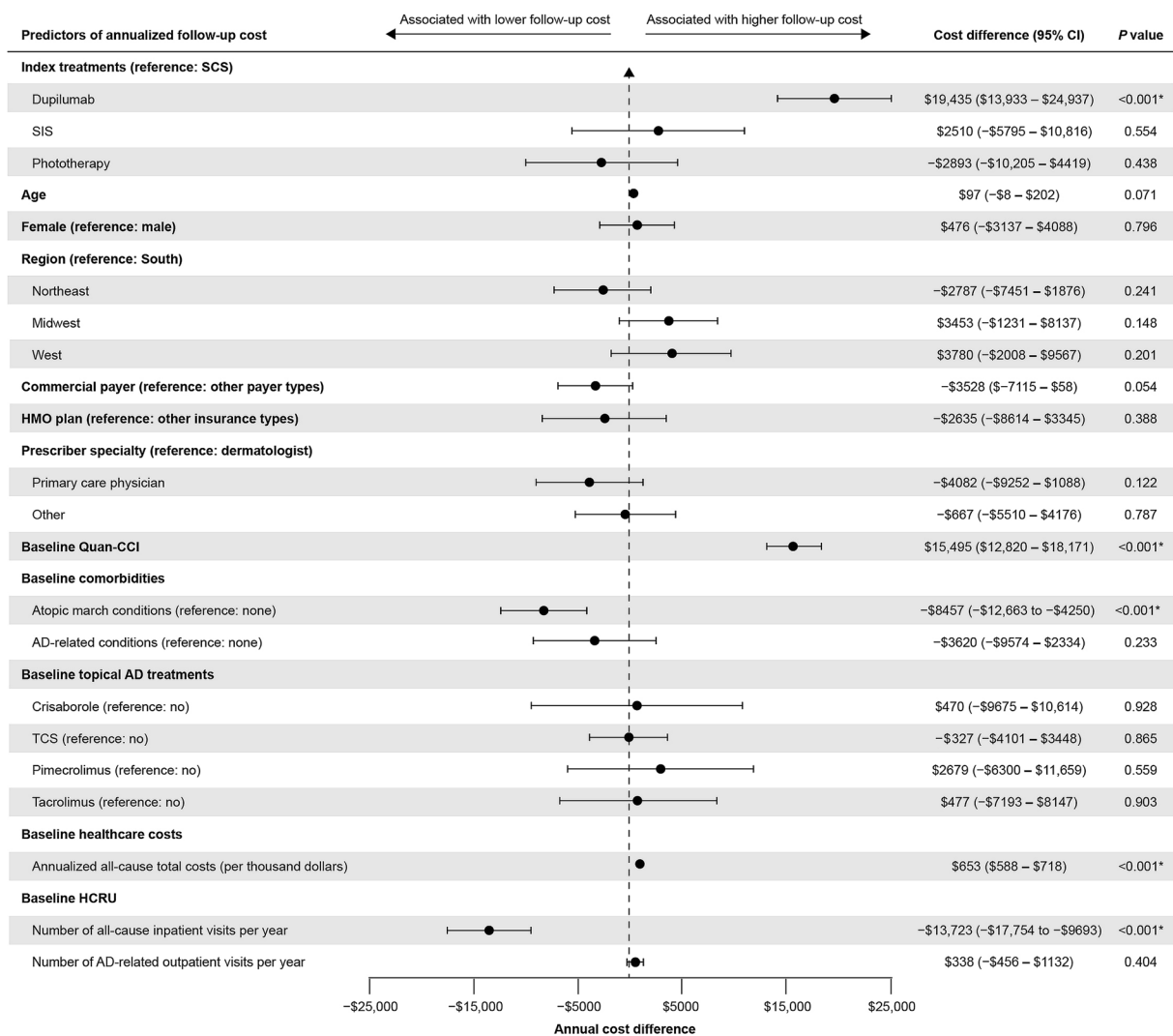


Fig. 5 Predictors of annualized all-cause health care costs in the follow-up period. *AD* atopic dermatitis; *HCRU* healthcare resource utilization; *HMO* health maintenance

organization; *SCS* systemic corticosteroid; *SIS* systemic immunosuppressants; *Quan-CCI* Quan-Charlson Comorbidity Index; *TCS* topical corticosteroid. **P* < 0.05

hospitalizations, outpatient visits) more than other treatments did, although total costs remained higher for dupilumab than for other treatment cohorts. Published results of meta-analyses have suggested greater clinical efficacy of dupilumab compared with cyclosporine, which may have translated to lower real-world medical costs [23]. More research is necessary to understand and compare real-world effectiveness among treatment options.

Limitations

This study has several limitations. Classification of moderate-to-severe AD was based entirely on the class of medication or treatment used because of the lack of disease severity data available, such as the Eczema Area and Severity Index or percentage of body surface area affected. This could have resulted in the inclusion of patients with mild disease who had a flare treated with SCSs or in the exclusion of patients with severe disease who, for whatever reason,

had not yet progressed to an advanced therapy regimen per the treating clinician's discretion. Similarly, caution should be exercised when examining differences across treatment cohorts because there might have been unobserved selection bias that would not have been possible to control (e.g., patients with dupilumab as their index treatment may have had more severe disease than patients with phototherapy as their index treatment). The healthcare costs available from the IQVIA Health Plan Claims database were limited to those for outpatient visits, inpatient visits, emergency room visits, and other medical visits and did not include indirect costs. Furthermore, the current study was designed to examine overall costs over time, with the analysis stratified according to the different treatment cohorts; it was not designed to compare directly between treatment cohorts. Future studies should aim to examine these direct comparisons and include indirect healthcare costs. The current study focused on a postdupilumab period to determine current treatment patterns. However, the period immediately after the approval of dupilumab may not be fully representative of the current postdupilumab environment because it is possible that some patients may not have had access to dupilumab immediately when it became available.

CONCLUSIONS

The results of the current study highlight some of the challenges of treating patients with moderate-to-severe AD. Patients initiating an advanced treatment often switched to or added-on an advanced treatment after the index date. Topical therapies are also routinely used concomitantly with these advanced treatments. Almost two-thirds of patients who initiated SISs and a quarter of those who initiated dupilumab discontinued within 6 months. Even for those who remained, adherence rates are not optimal. These patients with AD also represent a significant burden to the healthcare system, with costs representing approximately \$20,000 per patient per year. Additional treatment options could

help improve disease management and reduce costs for these patients.

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Compliance with Ethics Guidelines. Data are identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was an analysis of secondary data and was exempt from institutional review board approval.

Data Availability. The datasets generated during and/or analyzed during the current

study are not publicly available due to a data use agreement between IQVIA and the authors but are available from IQVIA on reasonable request.

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