Inadequate response and treatment patterns in adults diagnosed with atopic dermatitis and treated with topical therapy

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ABSTRACT

Background: Treatment for atopic dermatitis (AD) is complex, particularly in patients with inadequate response to topical therapies. Currently, there is little clinical guidance for the treatment of these patients.

Methods: A real-world retrospective study utilizing electronic medical records (EMR) and administrative claims data selected patients with AD between January 01 2016 and June 30 2018. Patients had a written prescription for a topical therapy (first observed script = index date) and no prior systemic treatment. Disease severity at index, follow-up treatment response and prescriptions patterns were assessed. A subset of patients linked to claims was evaluated for treatment patterns.

Results: We identified 137,214 adult topical-treated AD patients with no prior systemic therapy. Among the 16,035 patients with available Physician Global Assessment (PGA) at index, 8169 (50.9%) had the moderate-to-severe disease. Among these patients, 60% had an inadequate response to topical therapy. Of 4475 patients linked to claims, 13.0% had claims for systemic therapy during follow-up, most initiated systemic steroids (95.2%), and oral immunosuppressants and biologics were initiated in 3.3% and 3.8%, respectively.

Conclusion: In this real-world study, inadequate response to topical therapy among moderate-to-severe AD patients was high and initiation of systemic treatment was low which suggests a need for additional AD-indicated systemic treatment options in this patient population.

Background

Atopic dermatitis (AD), a chronic, relapsing, pruritic, inflammatory skin disease, affects roughly 7.3% of adults in the United States (1). Treatment of AD is complex, particularly in patients who do not respond to topical anti-inflammatory treatment.

Currently, there are no standard clinical guidelines for the management of patients with AD who are inadequately controlled with topical treatments and need systemic therapy. In response to this gap, Lynde and colleagues (2) developed clinical criteria for selecting adult candidates for systemic treatment of AD. The authors recommended that patients with moderate-to-severe AD initiate therapy with topical therapy. If after 1–2 months of topical therapy with a moderate- or potent/super-potent steroid and/or calcineurin inhibitor a patient has an inadequate response or a relapse/flare of symptoms within 1 week of topical therapy discontinuation, phototherapy, systemic or biologic therapy should be initiated if the following criteria are met: 1) Pruritus numerical rating scale (NRS) ≥ 4; 2) Body surface area (BSA) ≥ 10%; 3) Physician global assessment (PGA) score ≥ 3; 4) Dermatology Life Quality Index (DLQI) score ≥ 10. The inadequate response was defined as the absence of meaningful improvement, as judged by the clinician and patient, or as a relapse or flare of symptoms within one week of topical treatment discontinuation.

The primary aim of this study was to identify inadequate responders to topical treatment in adults with moderate-to-severe AD and assess their prescription patterns using electronic medical records (EMR). We also attempted to use the criteria proposed by Lynde and colleagues (2), to identify patients who were candidates for systemic therapy. Finally, linked insurance claims data were used to assess treatment patterns among topical-treated patients with AD.

Methods

Data were derived from Modernizing Medicine’s Electronic Medical Assistant (EMATM) specialty-specific EMR database for dermatology and the IQVIA PharMetrics Plus database. EMA encompasses over 42 million unique patients with at least 1 visit across all U.S. geographic regions and contains structured, real-world data from over 9000 dermatology providers. PharMetrics Plus contains adjudicated medical and pharmacy claims for more than 150 million health plan members across the United States from 2006 onwards and is representative of the U.S. commercially insured population. All patient-level data were de-identified by Modernizing Medicine Data Services, Inc. (MMDS) and IQVIA in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data from EMA were used to identify patients with AD, establish baseline...
disease severity and treatment response, and assess prescribing patterns. PharMetrics Plus data were used to conduct claims data analysis on treatment patterns in adult patients with AD treated with topical therapy.

Adult (≥18 years) patients with at least one record of a clinical diagnosis for AD (ICD-10-CM codes L20.0, L20.8, L20.89, L20.9) were identified in EMA between January 1 2016 and June 30 2018. Patients with a record of a written prescription for topical therapy, including TCS, TCI, or topical PDE4 inhibitor, and no prior systemic therapy (not including phototherapy) were included, and the index date was defined as the date of the first observed topical therapy prescription. To assess treatment response to topical treatment, patients were followed for 2 months per criteria suggested by Lynde and colleagues (2). For prescribed treatment patterns assessment, patients were followed through the end of available follow-up in EMA.

For the claims analysis, the de-identified data from EMA were linked to PharMetrics Plus using a deterministic matching algorithm. This type of algorithm used actual patient information, rather than the statistical probability to ensure continuity of patient records across datasets. The index date in PharMetrics Plus was defined within 45 days of the EMA index date to account for date shifting (±15 days) that was applied to the data sources separately for patient privacy measures, and to include an additional 15-day grace period between written and dispensed prescriptions. Patients in the linked cohort were required to have at least 6 months of continuous health plan enrollment with medical and pharmacy benefits after the index date in PharMetrics Plus.

Descriptions of the ICD-10-CM codes used to identify AD are provided in Supplemental Table 1. Medications included in the study are reported in Supplemental Table 2.

**Baseline AD severity, treatment response and prescription patterns**

The Physician Global Assessment (PGA) from EMA was used to determine the index severity of AD and the follow-up response to topical treatment. Index and follow-up BSA and the Pruritus NRS were also assessed. The PGA is a physician-reported measure assessing overall disease severity at a given point in time on a five-point scale ranging from 0 to 4, 0–1 indicating clear/almost clear, 2 indicating mild, 3 indicating moderate and 4 indicating severe AD (3). BSA is a measure of the percent of body surface area that is involved with AD which does not incorporate disease severity. The Pruritus NRS is a patient-reported measure of itch intensity on a scale of 0 (no itch) to 10 (worst imaginable itch) over a period of time (4).

Baseline severity was defined as the last observed PGA result prior to or on the index date. Per the criteria proposed by Lynde and colleagues (2), treatment response was assessed in patients with moderate-to-severe AD (PGA score ≥3) at baseline who had a follow-up PGA score within 2-months after the index date. Inadequate response to treatment was defined as less than a 2-point decrease in the follow-up PGA score from baseline. In patients identified as inadequate responders, we applied modified Lynde criteria to identify patients considered good candidates for initiation of systemic therapy. The modified algorithm did not include the DLQI criteria since it was not available in EMA.

Prescribed and office-administered AD medications observed in EMA after the index date are reported overall and by treatment response.

**Treatment patterns: PharMetrics plus linked cohort**

Treatment patterns observed during the 6 months after the treatment index date are reported in a subset of patients who were linked to PharMetrics Plus and had at least one pharmacy claim for a topical therapy (TCS, TCI, or topical PDE4 inhibitor) within 45 days of the EMA index date. The date of the topical therapy claim closest to the index date was defined as the treatment index date. Results include the type of therapy at index, number of unique topical therapy drugs received during the 6 months after the treatment index date, and within-class and between-class cycling. Within-class cycling was defined as moving between different drugs in the same drug class (e.g. betamethasone to clobetasol) and between-class cycling was defined as moving from one drug class to another (e.g. topical corticosteroid to TCI). Among patients who received systemic therapy during the 6 months after the index date, the topical treatment patterns observed prior to initiating systemic therapy, the time to initiation of systemic therapy, first-class of systemic therapy received, and all systemic therapies received during the 6 months following the index date are reported.

**Statistical analysis**

Mean, standard deviation (SD), and median are reported as measures of central tendency and variance for continuous variables. Frequency and percentages are reported for categorical variables. Student’s t and Chi-Square tests were used to compare continuous and categorical variables, respectively, between patients with clear-to-mild vs. moderate and clear-to-mild vs. severe disease. Standardized mean differences were also used to compare the characteristics of the linked and unlinked samples. No post-hoc adjustments were used for multiple comparisons. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

**Results**

**Patient cohort from EMA**

**Baseline characteristics**

Overall, 137,214 adult topical-treated AD patients with no prior systemic therapy were identified in the de-identified data from EMA™ (Figure 1). Table 1 describes the demographic and clinical characteristics of the EMA patient cohort, as well as therapies prescribed on and after the index date. The mean (standard deviation: SD) age was 48.1 (19.1) years and 63.5% of the sample was female. Patients were primarily from the South (40.0%) and West (23.3%) regions of the US. The most common comorbid conditions were allergic contact dermatitis (61.5%), pruritus (29.1%), and asthma (24.7%). A baseline PGA score was available for 16,035 (11.7%) patients. Of these, half had moderate (41.3%) or severe (9.6%) disease. The most common lesion locations were arms (28.3%), trunk (23.6%), and legs (21.3%).

Topical corticosteroids were the most commonly prescribed index therapy (94.0%), while 8.1% and 4.1% of patients had prescriptions written for TCI and topical PDE4 inhibitors, respectively. By the end of available follow-up (mean: 253 days; SD:
298 days), 7.3% of patients had prescriptions for systemic therapy, with systemic steroids (5.4%) and biologics (2.3%) being the most prescribed.

Several differences were observed between patients with the clear-to-mild disease compared to patients with moderate and severe disease (Table 1). On average, patients with moderate and severe disease were younger than patients with the clear-to-mild disease (mean [SD]: 45 (10.9), 42.9 (18.7), and 48.1 (19.2), respectively; \( p < .0001 \) for both). At index, orders for TCI and topical PDE4 inhibitors were more common in patients with severe disease compared to those with clear-to-mild disease (14.8% and 11.2% vs. 9.5% and 4.8%, respectively; \( p < .0001 \)). After the index, orders for systemic therapy were more common in patients with moderate (8.4%) and severe disease (24.4%) than in patients with the clear-to-mild disease (4.2%; \( p < .0001 \) for both).

**Treatment response**
Among the 8169 patients with moderate-to-severe AD at baseline, 1764 (21.6%) patients had a follow-up PGA measure within 2-months after initiation of topical therapy (mean (SD): 31.2
Table 1. Demographics, clinical characteristics, and treatments prescribed in adults with AD identified in EMATM, overall and stratified by baseline disease severity.

| Age on index date (years) | | | | | p-value (clear-mild vs. moderate) | p-value (clear-mild vs. severe) |
|---------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Patient cohort from EMA | Patient with baseline PGA = 0.1-2 | Patient with baseline PGA = 3 | Patient with baseline PGA = 4 | | | |
| N = 137,214 | (clear-mild) | (moderate) | (severe) | N = 7866 | N = 6630 | N = 1539 |
| Mean | 48.1 | 48.1 | 45.0 | 42.9 | <.0001 (–109) | <.0001 (–221) |
| SD | 19.1 | 19.2 | 19.0 | 18.7 | | |
| Gender (n, %) | | | | | | |
| Female | 50,137 (36.5%) | 2859 (36.3%) | 2504 (37.8%) | 658 (42.8%) | | |
| Male | 37,178 (27.1%) | 2060 (26.9%) | 1839 (27.2%) | 485 (31.6%) | | |
| Race (n, %) | | | | | | |
| White | 66,510 (48.5%) | 3903 (49.6%) | 2908 (43.9%) | 518 (33.7%) | <.0001 (.122) | <.0001 (.341) |
| African American | 10,577 (7.7%) | 600 (7.6%) | 568 (8.6%) | 186 (12.1%) | | |
| Asian | 5298 (3.9%) | 287 (3.6%) | 363 (5.5%) | 94 (6.1%) | | |
| Other | 6477 (4.7%) | 357 (4.5%) | 315 (4.8%) | 74 (4.8%) | | |
| Unknown | 48,352 (35.2%) | 2719 (34.6%) | 2476 (37.3%) | 667 (43.3%) | | |
| Geographic region (n, %) | | | | | | |
| Northeast | 52,210 (38.1%) | 2920 (37.1%) | 2513 (37.9%) | 587 (38.1%) | | |
| Midwest | 26,171 (19.0%) | 1442 (18.5%) | 1291 (18.9%) | 371 (24.6%) | | |
| South | 54,857 (40.0%) | 3162 (40.4%) | 2679 (40.4%) | 607 (39.4%) | | |
| West | 31,915 (23.3%) | 1790 (22.8%) | 1562 (23.6%) | 343 (22.3%) | | |
| Unknown | 1360 (1.0%) | 71 (0.9%) | 26 (0.4%) | 10 (0.6%) | | |
| Index year (n, %) | | | | | | |
| 2016 | 55,573 (40.5%) | 2982 (37.9%) | 2421 (36.5%) | 500 (32.5%) | .2234 (.028) | <.0001 (.126) |
| 2017 | 52,210 (38.1%) | 2920 (37.1%) | 2513 (37.9%) | 587 (38.1%) | | |
| 2018 | 29,431 (21.4%) | 1964 (25.0%) | 1695 (25.6%) | 452 (29.4%) | | |
| Baseline PGA score – atopic dermatitis (n, %) | | | | | | |
| 0 – clear | 16,035 (11.7%) | 7866 (100.0%) | 6630 (100.0%) | 1539 (100.0%) | | |
| 1 – almost clear | 590 (4.3%) | 587 (7.5%) | 587 (7.5%) | 587 (7.5%) | | |
| 2 – mild | 6224 (43.8%) | 6224 (79.1%) | 6224 (79.1%) | 6224 (79.1%) | | |
| 3 – moderate | 6630 (41.3%) | 6630 (100.0%) | 6630 (100.0%) | 6630 (100.0%) | | |
| 4 – severe | 1539 (9.6%) | 1539 (100.0%) | 1539 (100.0%) | 1539 (100.0%) | | |
| Baseline body surface area (BSA) categorical (n, %) | | | | | | |
| BSA < 10% | 6575 (4.8%) | 1901 (24.2%) | 2290 (34.5%) | 793 (51.5%) | <.0001 (.229) | <.0001 (.588) |
| 10% ≤ BSA < 15% | 2896 (40.0%) | 1302 (68.5%) | 939 (41.0%) | 93 (11.7%) | <.0001 (.575) | <.0001 (.1421) |
| BSA ≥ 15% | 1150 (17.5%) | 304 (16.0%) | 421 (18.4%) | 65 (8.2%) | .0415 (.064) | <.0001 (.241) |
| BSA > 50% | 2529 (38.5%) | 295 (15.5%) | 930 (40.6%) | 635 (80.1%) | <.0001 (.582) | <.0001 (.1694) |
| Baseline itch score categorical (n, %) | | | | | | |
| NRS < 4 | 1088 (8.9%) | 467 (5.9%) | 395 (6.0%) | 118 (7.7%) | .9579 (.000) | .0102 (.069) |
| NRS ≥ 4 | 512 (47.1%) | 322 (69.0%) | 130 (32.9%) | 15 (12.7%) | <.0001 (.773) | <.0001 (.1395) |
| Most common body locations (n, %) | | | | | | |
| Leg | 29,178 (21.3%) | 1811 (23.0%) | 2037 (30.7%) | 586 (38.1%) | <.0001 (.174) | <.0001 (.331) |
| Arm | 38,886 (28.3%) | 2555 (32.5%) | 2704 (40.8%) | 777 (50.5%) | <.0001 (.173) | <.0001 (.372) |
| Trunk | 32,421 (23.6%) | 1940 (24.7%) | 2321 (35.0%) | 825 (53.6%) | <.0001 (.228) | <.0001 (.621) |
| Hand | 14,117 (10.3%) | 850 (10.8%) | 1084 (16.3%) | 269 (17.5%) | <.0001 (.162) | <.0001 (.192) |
| Face | 16,703 (12.2%) | 1226 (15.6%) | 1081 (16.3%) | 391 (25.4%) | .2387 (.020) | <.0001 (.245) |
| Neck | 9900 (7.2%) | 680 (8.6%) | 716 (10.8%) | 244 (15.9%) | <.0001 (.073) | <.0001 (.221) |
| Common comorbid conditions* (n, %) | | | | | | |
| Allergic contact dermatitis | 84,422 (61.5%) | 4512 (57.4%) | 4325 (65.2%) | 1194 (77.6%) | <.0001 (.162) | <.0001 (.442) |
| Allergic rhinitis | 22,915 (16.7%) | 1361 (17.3%) | 1206 (18.2%) | 359 (23.3%) | .1631 (.023) | <.0001 (.150) |
| Anxiety | 17,385 (12.7%) | 956 (12.2%) | 832 (12.5%) | 228 (14.8%) | .4707 (.012) | .0040 (.078) |
| Asthma | 33,903 (24.7%) | 1912 (24.3%) | 1777 (26.8%) | 580 (37.0%) | .0006 (.057) | <.0001 (.292) |
| Depression | 24,701 (18.0%) | 1240 (15.8%) | 1054 (15.9%) | 257 (16.7%) | .0826 (.004) | .3591 (.025) |

*Body location = leg, thigh.
*Body location = arm, shoulder, upper arm.
*Body location = hand, finger, fingernail, nail.
Patients with pruritus NRS score within 2 months after topical therapy initiation
Criteria #2: Among those with available NRS score, patients with NRS $\geq 4$
Patients with a BSA score within 2 months after topical treatment initiation
Criteria #3: Among those with available BSA, patients with BSA $\geq 10$
Patients with NRS and BSA scores within 2 months after topical therapy initiation
Criteria #4: Patients with PGA score $\geq 3$ within 2 months after topical therapy initiation

Lynde (8) criteria:
- Inadequate responders with follow-up NRS $\geq 4$ and BSA $\geq 10$ (denominator: $n = 86$)
- Inadequate responders with follow-up NRS $\geq 4$ and PGA score $\geq 3$ (denominator: $n = 327$)

Inadequate responders with follow-up PGA scores is shown in Supplemental Table 3. Among the
patients who met all Lynde [8] criteria that were available in the data.

Treatment patterns observed in claims data
Most patients (92.2%) were being treated with only topical corticosteroids at index. During the
6-month follow-up, 87.0% of patients continued treatment solely with topical therapies; within-
and between-class cycling was observed in 31.5% and 7.9% of these patients, respectively. Claims for systemic therapy during follow-up were observed in 580 (13.0%) patients, with a
median of 3.6 months from the index topical treatment to the start of systemic therapy. Prior to initiating systemic therapy, 31.0% and 8.8% of patients cycled within- and between-topical
therapy drug classes, respectively. Most patients with systemic therapy used systemic steroids (95.2%); oral immunosuppressants and biologics were used in 3.3% and 3.6% of systemic
therapy users, respectively (Table 3).

Differences in treatment patterns were observed by disease severity. A lower proportion of patients with severe disease had only topical corticosteroids at index compared to a patient with clear-to-mild disease (77.8% vs. 90.8%; $p = .018$) and a higher proportion was treated with only topical immunosuppressants (13.9% vs. 5.2%; $p = .044$). Among patients who remained on topical only treatment, a higher proportion of patients with severe compared to clear-to-mild disease cycled within (46.7%
vs. 26.9%; $p = .026$) and between (33.3% vs. 7.1%; $p < .0001$) topical therapy drug classes. Only 16.7% of patients with severe disease and 10.6% of patients with moderate disease received systemic therapy within 6-months after the index date (Table 3).

Discussion
In this real-world study of adults with moderate-to-severe atopic dermatitis who inadequately responded to topical therapy, about 28% of topical users might be ready for systemic therapy and about 71% of these patients had a prescription for systemic therapy. About 60% had an inadequate response and 25% of these patients had a prescription for a systemic treatment any time during the follow-up consistent with a previous report (5) defining inadequately controlled AD as currently flaring, deteriorating or changeable AD based on physician assessment, or physician dissatisfaction with control; a definition that while not validated and based on clinical measures provided very similar results to the current study.

The Lynde criteria were developed to help guide treatment decisions in adults with AD, and not all clinical measures included in the criteria were available in the EMR data limiting
| Therapy at index\textsuperscript{a} | Patients with AD diagnosis and topical therapy \(N = 4475\) | Patients with baseline PGA \(= 0,1,2\) (clear-mild) \(N = 251\) | Patients with baseline PGA \(= 3\) (moderate) \(N = 216\) | Patients with baseline PGA \(= 4\) (severe) \(N = 36\) | \(p\)-value (clear-mild vs. moderate) | \(p\)-value (clear-mild vs. severe) |
|----------------------------------|------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Topical corticosteroids monotherapy | 4,127 (92.2%) | 228 (90.8%) | 195 (90.3%) | 28 (77.8%) | .8367 | .0182 |
| Topical calcineurin inhibitors monotherapy | 185 (4.1%) | 13 (5.2%) | 8 (3.7%) | 5 (13.9%) | .4430 | .0438 |
| Topical PDE4 inhibitors monotherapy | 48 (1.1%) | 7 (2.8%) | 7 (3.2%) | 5 (13.9%) | .0898 | .0898 |
| Topical therapy combination therapy | 115 (2.6%) | 7 (2.8%) | 7 (3.2%) | 5 (13.9%) | .0898 | .0898 |
| Patients who remain on topical therapy only during the 6-month follow-up \((n, \%)\) | 3,895 (87.0%) | 212 (84.5%) | 193 (89.4%) | 30 (83.3%) | .1205 | .8617 |
| Total number of unique topical drugs (by generic name) | Mean | 1.5 | 1.4 | 1.6 | 2.1 | .0129 | <.0001 |
| | SD | 0.7 | 0.7 | 0.8 | 1.1 | .1104 | .0438 |
| | Median | 1.0 | 1.0 | 1.0 | 2.0 | .0001 | <.0001 |
| Patients who cycle within same topical drug class \((n, \%)\) | 1,227 (31.5%) | 57 (26.9%) | 69 (35.8%) | 14 (46.7%) | .0543 | .0259 |
| Total number of switches between same drug class | Mean | 1.2 | 1.2 | 1.3 | 1.5 | .3700 | .0971 |
| | SD | 0.5 | 0.5 | 0.6 | 0.8 | .0001 | <.0001 |
| | Median | 1.0 | 1.0 | 1.0 | 1.0 | <.0001 | <.0001 |
| Patients who cycle between different topical drug classes \((n, \%)\) | 307 (7.9%) | 15 (7.1%) | 21 (10.9%) | 10 (33.3%) | .1789 | <.0001 |
| Total number of switches between different drug classes | Mean | 1.4 | 1.4 | 1.6 | 1.8 | .4466 | .1350 |
| | SD | 0.7 | 0.7 | 0.8 | 0.8 | .0001 | <.0001 |
| | Median | 1.0 | 1.0 | 1.0 | 2.0 | .0001 | <.0001 |
| Patients who receive systemic therapy during the 6-month follow-up \((n, \%)\) | 580 (13.0%) | 39 (15.5%) | 23 (10.6%) | 6 (16.7%) | .1205 | .8617 |
| Total number of unique topical drugs (by generic name) received prior to initiating systemic therapy | Mean | 1.5 | 1.2 | 1.5 | 2.2 | .0314 | <.0001 |
| | SD | 0.7 | 0.4 | 0.8 | 1.2 | .1892 | <.0001 |
| | Median | 1.0 | 1.0 | 1.0 | 2.0 | .0001 | <.0001 |
| Patients who cycle within same topical drug class prior to initiating systemic therapy \((n, \%)\) | 180 (31.0%) | 6 (26.1%) | 6 (26.1%) | 10 (33.3%) | .1016 | .0124 |
| Total number of switches between same drug class | Mean | 1.2 | 1.0 | 1.2 | 1.7 | .4468 | .2856 |
| | SD | 0.5 | 0.0 | 0.4 | 1.2 | .0001 | <.0001 |
| | Median | 1.0 | 1.0 | 1.0 | 1.0 | .0001 | <.0001 |
| Patients who cycle between different topical drug classes prior to initiating systemic therapy \((n, \%)\) | 51 (8.8%) | 5 (5.4%) | 5 (2.2%) | 10 (33.3%) | .0383 | .0049 |
| Total number of switches between different drug classes | Mean | 1.5 | 2.0 | 1.0 | 1.0 | .0041 | <.0001 |
| | SD | 0.8 | 0.0 | 0.0 | 0.0 | .6625 | .6625 |
| | Median | 1.0 | 2.0 | 1.0 | 1.0 | .6642 | .6642 |
| Months to systemic therapy | Mean | 3.6 | 4.0 | 3.0 | 4.2 | .0041 | <.0001 |
| | SD | 1.4 | 1.4 | 1.0 | 1.7 | .0002 | <.0001 |
| | Median | 3.6 | 4.0 | 3.0 | 4.9 | .0114 | <.0001 |
| First systemic therapy received during 6-month post-index period \((n, \%)\)\textsuperscript{b} | | | | | | |
| | Systemic steroid | 551 (94.8%) | 39 (100.0%) | 23 (100.0%) | 5 (51.4%) | <.0001 | <.0001 |
| | Oral immunosuppressant | 14 (2.4%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .0099 | .0099 |
| | Injectable immunosuppressant | 7 (1.2%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .0099 | .0099 |
| | Biologic | 16 (2.8%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .0002 | .0002 |
| All systemic therapies received during 6-month post-index period \((n, \%)\)\textsuperscript{b} | | | | | | |
| | Systemic steroid | 553 (95.2%) | 39 (100.0%) | 23 (100.0%) | 5 (51.4%) | <.0001 | <.0001 |
| | Oral immunosuppressant | 19 (3.3%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .1892 | .0099 |
| | Injectable immunosuppressant | 5 (0.9%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .0002 | <.0001 |
| | Biologic | 21 (3.6%) | 5 (12.8%) | 5 (21.7%) | 5 (51.4%) | .1892 | .0099 |

\textsuperscript{a}Drug therapy observed in claims data within 45 d of index date.

\textsuperscript{b}Denominator is patients who received systemic therapy.
In the linked claims data, systemic therapy was observed in 13.0% of AD patients within 6 months of topical treatment initiation, which aligns with a study from Germany which reported that over 10% of adults diagnosed with AD were treated with systemic steroids (7). This observed proportion of patients with filled prescriptions of systemic therapy is higher than the proportion of patients with written prescriptions observed in EMA. This discrepancy appears to be driven by claims for systemic steroids, which have a broad indication and are possibly being used to treat other comorbid conditions.

The use of systemic therapy in patients with moderate-to-severe AD was low, with only 11% of moderate and 17% of severe patients having systemic treatment. This potential under-treatment of adult AD patients was not surprising given the current treatment landscape and complexity of disease management. There are few systemic therapies indicated for AD. Until recently, systemic treatment of moderate-to-severe AD relied primarily on systemic corticosteroids and systemic immunosuppressants, many of which have been used off-label. While these drugs are efficacious, they are associated with significant adverse events (8). Oral corticosteroids are effective as a short-term therapy, however, long-term use is not recommended due to side effects, including diabetes, hypertension, gastric ulcer, osteoporosis, glaucoma, and Cushing syndrome. Cyclosporine is used for short-term treatment of moderate-to-severe AD that is inadequately controlled with topical therapy; side effects include nephrotoxicity, hypertension, tremors, headaches, nausea and diarrhea. Methotrexate and mycophenolate mofetil, which are also used off-label, also have significant side effects (8). Dupilumab is effective with few adverse events compared to other systemic therapies (9).

While reasons for inadequate response to therapy are not captured in the current study, it is important to understand what is driving inadequate response to therapy. While lack of treatment options may be one driver, another important factor may be treatment adherence. As with many chronic diseases, poor adherence to therapy plays a significant role in the lack of treatment success (10). In patients with AD, adherence to topical therapies tends to be greatest at the start of treatment and decreases with extended duration (10), which could be an indication of treatment fatigue or medication access issues (e.g. medication costs or formulary access). Poor medication adherence may result from complex treatment regimens for AD (11). For example, some regimens may include up to three emollient therapies and two topical corticosteroids specific to different body locations. Furthermore, patients may have safety concerns associated with specific therapies. For example, steroid phobia (patient and caregiver negative feelings and beliefs regarding topical corticosteroids), has been correlated with poor adherence to treatment. One study reported a prevalence of steroid phobia ranging from 21% to 83.7% (12). Additional real-world studies assessing reasons for inadequate treatment response are warranted.

The findings from this study highlight the need for new systemic therapies in treating moderate-to-severe AD patients. Inadequate response to topical therapy was fairly common, while the use of systemic therapies was low. Given the paucity of real-world studies measuring treatment response due to the lack of available clinical data and the rapidly evolving treatment landscape for AD, future studies developing a claims-based algorithm for assessing disease severity and treatment response are warranted.

**Limitations**

This study has several limitations. First, the data used in this study were not collected for research purposes and only a small proportion of patients had the necessary severity measures available to assess treatment response and apply the Lynde (2) criteria to determine readiness for systemic therapy. These gaps in data may limit the generalizability to the entire adult AD population, particularly if patients with the available data have the more active or severe diseases than patients with no measures available. The sample size was further reduced when requiring multiple measures of disease activity to assess readiness for systemic therapy. Furthermore, although the PGA is considered the gold-standard clinical assessment tool (13) health care providers do not always interpret PGA severities the same way and are not trained in its use. A systematic review of Investigator Global Assessment (IGA; also known as PGA in clinical practice) in AD trials revealed that although global assessment measures are frequently used in clinical trials to measure treatment response, there is a lack of standardization and implementation across studies (13).

Finally, to minimize the risk of re-identification of patients with the linkage between EMR and claims data, dates in each database were independently randomly shifted by ± 15 days, which added a level of uncertainty around dates of disease assessments, therapies ordered in EMA and treatments received by patients by PharMetrics Plus.

**Acknowledgments**

The authors would like to thank Wei-Ti Huang and Yiyun Lin from IQVIA for their programming and statistical expertise.

**Disclosure statement**

At the time of this study, NB, WM, and OG were full-time employees and stockholders of Eli Lilly and Co. MG, XW and RW are employed full time by IQVIA, Inc., which received funding from Eli Lilly and Co. to carry out this study.

**Funding**

This work was supported by Eli Lilly and Company.

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