Dermatol Ther (Heidelb) (2022) 12:1027–1040
https://doi.org/10.1007/s13555-022-00710-4

ORIGINAL RESEARCH

Economic Burden and Healthcare Resource Use of Alopecia Areata in an Insured Population in the USA

Arash Mostaghimi · Jason Xenakis · Aster Meche · Timothy W. Smith · David Gruben · Vanja Sikirica

Received: December 14, 2021 / Accepted: March 11, 2022 / Published online: April 5, 2022

ABSTRACT

Introduction: Comparative data on the economic burden of alopecia areata relative to the general population are limited. The objective of this retrospective database analysis was to evaluate healthcare resource utilization and direct medical costs among patients with alopecia areata from the US payer perspective compared with matched controls.

Methods: Validated billing codes were used to identify patients with alopecia areata from the IQVIA PharMetrics Plus (2016–2018) who had continuous pharmacy and medical enrollment for 365 days both before (baseline period) and after (evaluation period) the index date. Demographic and clinical characteristics were characterized, and baseline comorbidities were assessed with the Quan Charlson Comorbidity Index.

Results: Using the exact matching feature from Instant Health Data, 14,340 patients with alopecia areata were matched with 42,998 control patients aged ≥ 12 years. Patients with alopecia areata had higher healthcare resource utilization and adjusted total all-cause mean medical costs versus matched controls ($8557 versus $6416; $p < 0.0001$), because of higher inpatient costs, emergency department visits, ambulatory visits, number of prescriptions and prescription costs, and other costs such as durable medical equipment and home healthcare. The number of inpatient visits did not significantly differ between the two groups. Mean ambulatory costs were $3640 for patients with alopecia areata and $2062 for controls, and mean pharmacy costs were $3287 and $1843, respectively ($p < 0.0001$ for both). Pharmacy costs related to immunologic agents represented 50.0% of the total difference in pharmacy spending between patients with alopecia areata and controls. Surgery on the integumentary system accounted for 9.5% of the total difference in ambulatory costs.

Conclusion: Alopecia areata is associated with significant incremental healthcare resource utilization and costs relative to matched controls due to increased spending in areas such as surgical procedures and psychological and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-022-00710-4.

A. Mostaghimi (✉)
Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave, Boston, MA 02115, USA
e-mail: amostaghimi@bwh.harvard.edu

J. Xenakis · A. Meche · T. W. Smith
Pfizer Inc, New York, NY, USA

D. Gruben
Pfizer Inc, Groton, CT, USA

V. Sikirica
Pfizer Inc, Collegeville, PA, USA

pharmacological interventions. Costs are primarily driven by ambulatory and pharmacy spending.

Keywords: Alopecia areata; Autoimmune; Economic burden; Healthcare costs; Healthcare resource utilization

Key Summary Points
Why carry out this study?
Comparative data on the economic burden of alopecia areata relative to the general population are limited.
The objective of this retrospective database analysis was to examine healthcare resource utilization and direct medical costs among patients with alopecia areata in the USA compared with matched controls.
What was learned from the study?
In this retrospective database analysis, 14,340 patients with alopecia areata had higher healthcare resource utilization and adjusted total all-cause mean medical costs versus matched controls, attributable to increased inpatient costs, emergency department visits, ambulatory visits, number of prescriptions, and prescription costs.
Costs are mainly driven by ambulatory and pharmacy spending, including additional surgical procedures and psychological and pharmacological interventions.
Additional research is needed to examine the impact of specific alopecia-areata-related factors on cost, including age, comorbidities, duration, and severity of alopecia areata.

INTRODUCTION

Alopecia areata (AA) is a T-cell-mediated autoimmune disease characterized by partial or complete nonscarring hair loss [1]. The cause of AA is unknown, although genetic predisposition, environmental factors, and a history of autoimmune disease may contribute to its development [2, 3]. AA has a global lifetime incidence of approximately 2% with initial onset usually before the age of 30 years [2, 4, 5]. In the USA, AA affects approximately 5.3 million people [6], with a current prevalence of approximately 0.21% [7]. AA may be limited to small areas of discrete hair loss; however, 7% of AA cases may progress in clinical severity to affect all scalp hair (alopecia totalis; AT) or all scalp, facial, and body hair (alopecia universalis; AU) [8, 9].

AA therapy has limited success, with no treatment approved by the US Food and Drug Administration to date [10]. Although off-label use has been attempted with several agents, including intralesional steroids for mild disease and topical/oral steroids for more severe disease [11], the efficacy is difficult to interpret because of varied study methods, nonhomogeneous patient populations and outcome measures, inconsistent assessment of disease severity [12], and failure to control for spontaneous regrowth [13]. As a result, a treatment pathway is not clearly defined. Treatment options include topical, locally injected, or systemic steroids; topical immunotherapy; topical minoxidil; topical irritants (e.g., anthralin); and systemic immunosuppressants (e.g., cyclosporine and methotrexate) [10, 11, 14]. Fewer therapeutic options exist for children, with topical steroids being the first-line treatment. Recent expert opinion consensus updates in AA have included the production of an international consensus statement on treatments [11] and the development of a disease severity scale for use in clinical practice [12].

Although not associated with an increase in mortality, studies have shown that AA places a substantial emotional and psychosocial burden on patients [15–17]. AA may also be associated with other systemic diseases, including other

autoimmune disorders (e.g., vitiligo, systemic lupus erythematosus, psoriasis, inflammatory bowel disease, rheumatoid arthritis), thyroid disorder, metabolic syndrome, and anemia [18, 19].

There are no published studies that quantify the healthcare resource utilization (HCRU) and medical costs among patients with AA in the USA, which include direct costs (pharmacy, medical), indirect medical costs (travel, caregivers), indirect costs (work loss, productivity loss), and intangible costs, and compare them with a matched control population.

Determining medical costs among patients with AA will help to identify the main expenditure predictors and spending patterns and inform whether current spending is effectively allocated. The objective of this study therefore was to evaluate the total direct medical cost of AA from the US third-party commercial payer perspective. The all-cause direct medical and pharmacy costs and HCRU among patients with AA were compared with matched controls.

METHODS

Data Source

This retrospective cohort study utilized US claims data extracted from PharMetrics Plus, which contains fully adjudicated health plan claims and is representative of the US commercially insured population. This dataset comprises health plan information, demographics (age, sex, region, payer type), diagnoses, and medical and pharmacy claims for over 210 million US health plan enrollees after 2006 [20]. Permission was obtained from PharMetrics Plus to access and use the data. All data were fully de-identified before study cohort selection in accordance with the Health Insurance Portability and Accountability Act of 1996 to protect patients' privacy. As a result, no institutional review board approval was required.

Patient Selection and Data Extraction

Data for the study encompassed 1 January 2016, through 31 December 2018. All members with continuous pharmacy and medical enrollment between 1 January and 31 December 2017 were included in the initial study population. A modification of the Charlson Comorbidity Index (CCI) was used to estimate comorbidity burden. The Quan Charlson's Comorbidity Index (Quan CCI) adaptation reduced the original number of diseases to 12 and changed the weighting of the score [21].

Study Cohort Selection

The study population comprised patients with AA and matched controls at least 12 years of age who were required to have continuous pharmacy and medical enrollment in the database for 365 days before the index date (baseline period) and for 365 days after the index date (evaluation period) (Fig. 1).

Criteria for cohort assignment of patients were as follows: AA cohort: one or more diagnoses of AA (ICD-10 = L63.*) [22], which included AT or AU, in any ICD-10 code position between 1 January and 31 December 2017; the first encountered AA diagnosis was assigned as the index date. Control cohort: no diagnosis of AA between 1 January and 31 December 2017; a randomly selected date was assigned to each member as the index date. Members were excluded from the control cohort if they had a diagnosis of AA (ICD-10 = L63.* or ICD-9 = 704.01) at any time before or after the index date, using all available data. Exact matching was implemented employing a 1:3 ratio of patients with AA to patients without AA matched by age, sex, geographic region, and payer. For efficiency of data management, a 25% randomly selected sample of patients without AA was employed for this analysis.

Variables/Measures

All cost and utilization measures were identified in the 365-day post-index period while variables (age, sex, region, and payer) were measured at

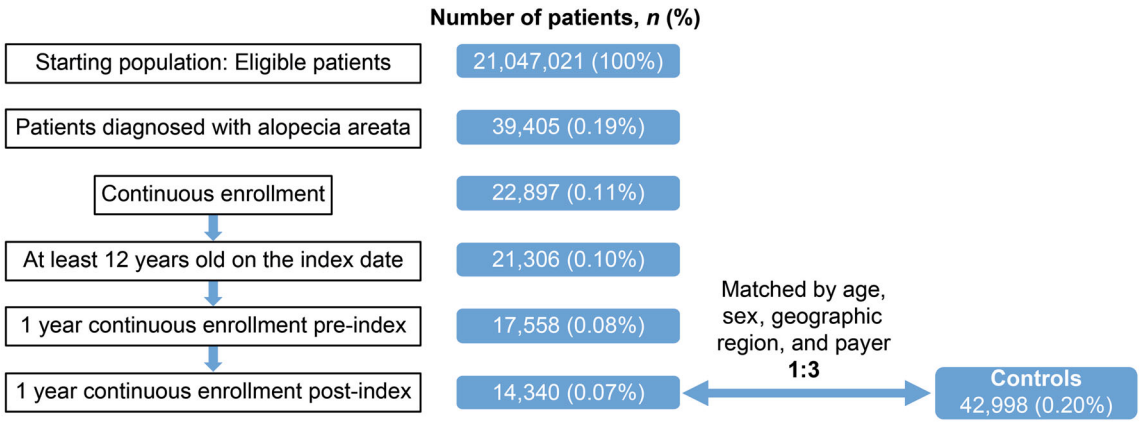

Fig. 1 Cohort selection

index, and Quan CCI was measured during the 365-day baseline period. Claims occurring on the index date were considered part of the post-index period.

Cost measures included the total allowed amount (inclusive of amount paid by the health plan and the patient). HCRU was evaluated by counting total outpatient pharmacy prescriptions filled, ambulatory visits (office and outpatient encounters), emergency department (ED) visits, and hospital inpatient admissions. Total all-cause HCRU costs were computed as the combined health plan and patient-paid amounts. In addition to total costs, costs were separated into pharmacy costs, ambulatory costs (office and outpatient, including procedures), ED costs, inpatient costs, and other costs (e.g., durable medical equipment). Costs were adjusted to 2018 US dollars using the Medical Care component of the Consumer Price Index as a basis [23].

Statistical Analysis

Demographics, clinical characteristics, comorbidities, direct medical costs, and HCRU were analyzed descriptively using the IHD platform (Boston Health Economics, Boston, MA). The mean, median, and standard deviation were reported on unadjusted observed costs. Analyses on adjusted mean costs were performed using R, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

All variables were analyzed descriptively. HCRU and cost outcomes were evaluated as incremental differences between cohorts for patients with AA and non-AA matched controls. Categorical variables were compared using the Pearson chi-squared test, and continuous variables were compared using unpaired *t*-tests. A generalized linear model (GLM) with a gamma distribution and a log-link function [24] was used to assess the incremental difference in total healthcare costs between groups. Covariates included 12-month pre-index total healthcare cost, 12-month pre-index Quan CCI comorbidity score, and 12-month pre-index presence of cardiovascular disease (CVD), autoimmune disorder, atopic disease, or anemia (Appendix 1, Supplementary Material). Missing or unavailable data were not imputed. Results were considered statistically significant for $p < 0.05$.

A sensitivity analysis was conducted that excluded patients with cancer during the 12 months pre- and post-index date. For this subgroup, the direct medical costs and HCRU for patients with AA versus non-AA matched controls were descriptively analyzed.

Table 1 Baseline patient demographics, clinical characteristics, and costs

Characteristic	AA cases (N = 14,340)	Matched controls (N = 42,998)	p value
Age on index date, median (range), years	41 (30–53)	41 (30–52)	0.99
Age group, *n* (%), years			0.99
12–17	1048 (7.3)	3141 (7.3)	
18–44	7156 (49.9)	21,459 (49.9)	
45–64	5691 (39.6)	17,067 (39.6)	
65+	445 (3.1)	1331 (3.1)	
Sex, *n* (%)			0.99
Female	9088 (63.3)	27,248 (63.3)	
Male	5252 (36.6)	15,750 (36.6)	
Region, *n* (%)			1
Midwest	3801 (26.5)	11,399 (26.5)	
Northeast	3347 (23.3)	10,036 (23.3)	
South	5428 (37.8)	16,283 (37.8)	
West	1764 (12.3)	5280 (12.2)	
Payer, *n* (%)			0.93
Commercial	14,040 (97.9)	42,120 (97.9)	
Medicaid	199 (1.3)	581 (1.3)	
Medicare	101 (0.7)	297 (0.6)	
Physician diagnosing AA, *n* (%)			
Dermatologist	7266 (50.7)	–	
Primary care	1813 (12.6)	–	
Hospitalist, internist, physician assistant	1948 (13.6)	–	
Other	3313 (23.1)	–	
Pre-Quan-CCI score			< 0.0001
Mean (SD)	0.3 (0.8)	0.2 (0.7)	
Median	0	0	
Quan CCI categories, *n* (%)			< 0.0001
0 comorbidities	11,678 (81.4)	37,327 (86.8)	
1–2 comorbidities	2315 (16.1)	5003 (11.6)	
3–4 comorbidities	247 (1.7)	470 (1.1)	
5+ comorbidities	100 (0.7)	198 (0.4)	
CVD at baseline, *n* (%)	1953 (13.6)	4497 (10.4)	< 0.0001
Autoimmune disorder at baseline, *n* (%)	836 (5.8)	1088 (2.5)	< 0.0001

Table 1 continued

Characteristic	AA cases (N = 14,340)	Matched controls (N = 42,998)	p value
Atopic disease at baseline, n (%)	3501 (24.4)	6729 (15.6)	< 0.0001
Anemia at baseline, n (%)	1096 (7.6)	1657 (3.8)	< 0.0001
Pre-index dermatologist visit, n (%)	5647 (39.3)	4089 (9.5)	< 0.0001
Pre-index count of dermatologist visits			
Mean (SD)	1.18 (2.48)	0.16 (0.80)	< 0.0001
Median	0	0	
Pre-index total cost (12 months), $			
Mean (SD)	7490 (14,617)	5008 (11,983)	< 0.0001
Median	2543	1282	

AA alopecia areata, *CVD* cardiovascular disease, *Quan CCI* Quan Charlson Comorbidity Index, *SD* standard deviation
Clinical characteristics are within 365 days pre-index

RESULTS

Patient and Clinical Characteristics

After applying inclusion and exclusion criteria, a total of 14,340 patients with AA and 42,998 control patients were identified (Table 1). The median age was 41 years, and 63.3% were female. AA was most prevalent in the 18- to 44-year-olds (49.9%). Over one-third of patients (37.8%) were from the South, while the lowest proportion of patients (12.3%) was from the West. Diagnosis of AA was most frequently made by dermatologists (53.4%), followed by primary care physicians (13.3%), hospitalists/internists/physician assistants (13.5%), and other (23.1%) (Table 1).

Comorbidities

Patients with AA had a higher comorbidity burden than controls: 18.5% and 13.1% of patients with and without AA, respectively, experienced one or more comorbidity ($p < 0.0001$; Table 1). The proportions of patients with the comorbidities of atopic disease, CVD, anemia, and autoimmune disorder were significantly higher for the patients with AA than the controls ($p < 0.0001$). Additionally, patients with AA had more dermatologist visits (39.3%) at baseline compared with controls (9.5%), and mean pre-index total costs were higher ($7490 versus $5008; $p < 0.0001$).

Healthcare Resource Utilization and Costs

Patients with AA had higher HCRU and total all-cause medical costs versus controls ($9154 versus $5787; $p < 0.0001$) as a result of higher inpatient costs, ED visits, ambulatory visits, number of prescriptions and prescription costs, and other costs (e.g., durable medical equipment, home healthcare) (Table 2). There was no significant difference in the number of inpatient visits between the two groups. In adjusted analyses, total annual mean (95% CI) costs remained higher for patients with AA [$8557 ($7679–$9535)] versus controls [$6314 ($4455–$8947)]; $p < 0.0001$ (Table 2).

Pharmacy Costs

Mean pharmacy costs were $3287 for patients with AA and $1844 for controls ($p < 0.0001$). Looking at broad drug categories, immunologic agents represented 50.0% of the total difference in pharmacy spending between patients with

Table 2 Healthcare resource utilization and costs within 365 days post-index

Variable	AA cases (*N* = 14,340)	Matched controls (*N* = 42,998)	*p* value	Difference	% of total difference
Inpatient visits, no.					
Mean (SD)	0.05 (0.28)	0.05 (0.29)	0.50		
Median (IQR)	0 (0–0)	0 (0–0)			
Costs, $	1173 (9620)	1157 (11,456)	< 0.0001	16	0.5
Emergency department visits, no.					
Mean (SD)	0.23 (0.66)	0.18 (0.73)	< 0.0001		
Median (IQR)	0 (0–0)	0 (0–0)			
Costs, $	491 (2067)	327 (1592)	< 0.0001	164	4.9
Ambulatory visits, no.					
Mean (SD)	13.7 (13.2)	7.6 (10.2)	< 0.0001		
Median (IQR)	10 (5–17)	4 (2–10)			
Costs, $	3640 (7625)	2062 (6257)	< 0.0001	1578	46.9
Other visits[a], no.					
Mean (SD)	1.02 (4.33)	0.65 (3.50)	< 0.0001		
Median (IQR)	0 (0–1)	0 (0–0)	< 0.0001		
Costs, $	561 (2960)	396 (4303)		165	4.9
Pharmacy prescriptions filled, no.					
Mean (SD)	16.9 (21.6)	14.6 (21.3)	< 0.0001		
Median (IQR)	10 (3–23)	6 (1–20)			
Costs, $	3287 (15,727)	1843 (12,306)	< 0.0001	1444	42.9
Total costs, $					
Mean (SD)	9154 (23,963)	5788 (21,511)	< 0.0001	3367	100
Median (IQR)	2986 (1266–7500)	1310 (347–4144)			
Adjusted total all-cause costs, mean, $ (95% CI)	8557 (7679–9535)	6314 (4455–8947)	< 0.0001	–	–

AA alopecia areata, *SD* standard deviation

[a]Includes durable medical equipment, home healthcare, and additional miscellaneous categories

AA and controls (Table 3). Additionally, the combined cost of topical agents and anti-infectives accounted for 24.1% (14.9% and 9.2%, respectively) of the difference in spending. Looking at more specific drug categories, immunosuppressive agents represented 43.3% of the total difference in pharmacy spending between patients with AA and controls

Table 3 Pharmacy expenditure and the proportion of patients using medication in each category: broad drug categories

	Related spending, mean, $			% of total difference	Patients using medication, *n* (%)	
	AA cases	Matched controls	Difference		AA cases	Matched controls
Total pharmacy costs	3287	1844	1443			
Immunologic agents	1253	531	722	50.0	2121 (14.8)	4426 (10.3)
Topical agents	306	91	215	14.9	9021 (62.9)	12,507 (29.1)
Anti-infectives	219	86	133	9.2	8089 (56.4)	21,083 (49.0)
Hormones/hormone modifiers	211	118	93	6.4	9565 (66.7)	17,301 (40.2)
Antineoplastics	312	226	87	6.0	626 (4.3)	1415 (3.3)
Central nervous system	164	122	42	2.9	6160 (42.9)	16,507 (38.4)
Gastrointestinal agents	82	53	29	2.0	2688 (18.7)	6688 (15.6)
Cardiovascular agents	90	69	21	1.5	3901 (27.2)	10,810 (25.1)
Respiratory agents	91	77	14	1.0	3846 (26.8)	9583 (22.3)
Psychotherapeutic agents	70	57	13	0.9	2450 (19.8)	8787 (20.4)
Other	490	416	74	5.1	–	–

AA alopecia areata
AA cases, $N = 14{,}340$; matched controls, $N = 42{,}998$

(Table S1, Supplementary Material), and within that category, tumor necrosis factor (TNF)-α inhibitors accounted for almost 50% of the difference (Table S2, Supplementary Material). The top three drug categories for spending, after immunosuppressive agents, were dermatological agents, antivirals, and immunoglobulins (Table S2, Supplementary Material). Within these four drug categories, topical corticosteroids was the subcategory most commonly used by patients with AA (40.9% versus 6.9% for controls).

Ambulatory Procedure Costs

Total ambulatory costs were $3641 for patients with AA compared with $2063 for controls (Table S3, Supplementary Material). Total ambulatory costs that could be explained by current procedural terminology (CPT) codes were $3198 and $1849, respectively. These totals include costs associated with visits, procedures, and diagnostic imaging. The number of ambulatory visits was also higher for patients with AA (13.7 ± 13.2 versus 7.6 ± 10.2 for controls; $p < 0.0001$), leading to a cost

differential of 46.9% (Table 2). This cost differential is driven by expenditures related to AA (estimated to be an average of $416 per patient; data not shown).

Analysis of the ambulatory procedures reveals that the greater spending for patients with AA is driven by surgical, radiologic, medical, and psychiatric costs (Table S3, Supplementary Material). Surgery accounted for 15% of the total difference in ambulatory costs, and this was driven by surgery on the integumentary system (9.5% of the total difference). Surgery also included injection of corticosteroids; 41.9% of patients had a procedural code indicative of injection of steroids into the scalp or other such interventions. Radiology accounted for 14.2% of the total difference in ambulatory costs, driven by diagnostic imaging (6.1% of the total difference). Medicine services and procedures accounted for 16.3% of the total difference in ambulatory costs, and the largest drivers were psychiatric services and chemotherapy administration (4.3% and 1.5% of the total difference, respectively). Hormones/hormone modifiers, antineoplastics, and psychotherapeutic agents accounted for 6.4%, 6.0%, and 0.9% of the total difference in pharmacy spending, respectively (Table 3).

Sensitivity Analysis

A sensitivity analysis that excluded patients with cancer identified the same trends of higher total costs, increased numbers of ED and ambulatory visits, and greater prescription costs and costs for other visits ($p < 0.0001$ for all; Table S4, Supplementary Material). Unlike the analysis that included patients with cancer, the costs of inpatient visits in the sensitivity analysis did not differ significantly between patients with AA and controls. Patients with AA were more likely to have higher costs than matched controls, based on odds ratio (OR) 1.33 (1.25–1.42) ($p < 0.0001$).

DISCUSSION

This retrospective healthcare claims database study is the first large analysis of HCRU and economic burden of AA in the USA. These results demonstrate that patients with AA require significantly more HCRU and incur significantly higher costs compared with non-AA controls, even though there are no therapies specifically approved for AA.

To our knowledge, this is one of limited studies to document and quantify the higher HCRU among patients with AA compared with matched controls using insurance claims. A similar recent uncontrolled analysis of the prevalence of comorbidities, treatments, and HCRU among patients with AA in the USA observed a high comorbidity burden and lack of treatment utilization, with costs incurred above AA-related expenses. The results of our study are consistent with this analysis, which utilizes claims data from a different source (IBM MarketScan Database) [25]. The total costs for AA that we report are similar to the $11,241 all-cause total costs identified by Senna et al. [25]. In both studies, nearly half of patients were diagnosed with AA by non-dermatologists. Topical corticosteroids were the most frequently prescribed medication in both studies.

The results of our study also align with studies that have evaluated the costs of other autoimmune diseases. In a retrospective claims database analysis of patients with atopic dermatitis who initiated therapy after the availability of dupilumab in March 2017, mean annualized total costs were $20,722, comprising $11,196 in medical costs, $7973 in costs for outpatient visits, and $9526 in pharmacy costs [26]. While these expenses were higher than in our study, likely driven by the cost of dupilumab, the cost drivers of outpatient visits and pharmacy spending were the same. Similarly, a systematic literature review of costs associated with psoriasis found that, compared with controls, patients with psoriasis incurred incremental annual medical costs of $2284 that included $952 in outpatient costs and $948 in pharmacy costs [27].

These increased costs can in part be attributed to a higher rate of comorbidities among patients with AA. Similar to previously published studies, patients with AA in this cohort had higher rates of autoimmune disorders and malignancy [18, 28, 29]. Senna et al. reported

that hyperlipidemia and hypertension were the most prevalent comorbid conditions among their cohort of patients with AA [25], whereas our study found atopic disease and CVD to be most prevalent. We identified an elevated risk of CVD at baseline (13.6% versus 10.4%). Correspondingly, cardiovascular agents accounted for 1.5% of the total difference in pharmacy spending, with 27.2% of patients with AA taking them compared with 25.1% of controls. Cardiovascular surgical procedures and CVD medical procedures accounted for 1.2% and 0.2% of the difference in ambulatory spending, respectively. The data in the literature are mixed on the cardiovascular associations of AA. A large retrospective study conducted in Korea that used health insurance data to match patients with AA to controls found an increased risk of acute myocardial infarction (AMI) over 12 years in patients with AA [30]. Conversely, another matched cohort study conducted in the USA found a decreased risk for stroke and a trend toward a decreased risk for AMI in patients with AA [31]. Studies have found higher levels of cardiovascular biomarkers in the serum of patients with AA compared with controls, suggesting they may be at an increased risk for CVD [32–34]. Further study is needed to evaluate the risk of CVD in patients with AA.

To date, studies in the literature examining an association between cancer risk and AA are limited and appear inconclusive [35, 36]. In our study, radiation oncology treatment and chemotherapy administration costs represented 3.3% and 1.5% of the total difference in ambulatory spending, respectively. In the sensitivity analysis that excluded patients with cancer, the significant difference in the number and cost of ambulatory visits between patients with AA and controls was still present. Additional research is needed to better understand the reasons for these visits.

Patients with AA were much more likely than controls to require ambulatory visits; however, they did not require more inpatient visits. Surgery on the integumentary system (including corticosteroid injection) accounted for 9.5% of the total difference in cost, which is consistent with known patterns of patient care. AA can lead to increased emotional and psychosocial burden for patients [15–17], and psychiatric services accounted for 4.3% of the total difference in cost.

Another key contributor to the cost differential was prescriptions, which were elevated for patients with AA across all categories of drugs. Not surprisingly, the largest difference in medication use between patients with AA and controls was topical corticosteroids (40.9% of patients with AA versus 6.9% of controls). An important driver of costs was TNF-α inhibitors, which were used by 1.2% of patients with AA compared with 0.6% of controls. While this is somewhat unexpected considering the lack of efficacy of TNF-α inhibitors for AA, more patients with AA (5.8%) had another autoimmune disease at baseline, compared with controls (2.5%), which may be contributing to the observed difference. Another possibility is that the directionality of the association is reversed, as there have been some case reports of AA occurring secondary to TNF inhibitor treatment, although the estimated prevalence of this is only 1.5–5% [37]. Further research is required to elaborate on this possible use and association.

These data must be interpreted in the context of our study design. Inherent limitations of claims data include incomplete, inaccurate/misclassified, or missing data. In this analysis, patients were only included in the claims database if they had a diagnosis code of AA (including AT or AU), which is reliant on accurate diagnosis and coding. Owing to a lack of clinical information in administrative claims, patients with a diagnosis of AA could not be stratified by severity, aside from AT and AU subtypes. This limited the ability to accurately assess disease severity and thus limited understanding of the impact of disease severity on visits and costs.

Consistent with the approach used in similar articles, we compared all insurance claims costs among patients with AA with the same costs from a matched control group. The study design and the nature of claims databases do not allow the separation of "direct" costs from treatment of AA with "adjacent" costs from comorbidities associated with AA, as a clinician may indicate and treat multiple conditions during a visit. Despite this limitation, our approach is

consistent with standard guidelines for assessing disease-associated costs [38–40] and represents best practice for complete assessment of costs associated with a disease. Given the range of entry points into the medical system (only 53.4% of patients were diagnosed by a dermatologist), a control group from a general medical population was selected. A different control group with a primary dermatologic condition may yield different results and should be explored by future research.

Additionally, baseline comorbidity may be underreported owing to limited pre-index data. However, this common limitation of claims studies should impact all patients equally. Unmeasured confounders may not be accounted for, such as the severity of disease and the presence of more than one medical condition. There is also the potential that AA was not coded for if it is not covered by the commercial US insurer as a medical disease. As these data were collected from members who were enrolled in a commercial health insurance plan, the findings may not be applicable to other populations who do not have insurance or have a different insurance provider. Finally, only 53% of patients with AA in this analysis were diagnosed by a dermatologist, which may represent under- or overreporting of the diagnosis. Additional work is required to better ascertain the long-term costs of AA, since patients may not remain with the same health plan.

CONCLUSION

AA imposes a substantial economic burden on the US managed care population, driven largely by ambulatory and pharmacy spending. Increased costs were observed across many areas of healthcare including surgical procedures and psychological and pharmacological interventions. With new drugs for AA at different stages of clinical development, cost analyses will be necessary to assess the incremental impact of these drugs on overall healthcare costs and on the health-related quality of life of patients with AA. Further research is needed to examine the impact of specific comorbidities, severity of AA, and newly diagnosed versus established AA on the cost of care.

ACKNOWLEDGEMENTS

Funding. This study was sponsored by Pfizer Inc, New York, NY, USA. Pfizer Inc. funded the Rapid Service Fee.

Medical Writing Assistance. Medical writing support was provided by Sharmy Blows, PhD, of Engage Scientific Solutions and was funded by Pfizer Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Aster Meche had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Arash Mostaghimi, Vanja Sikirica. Acquisition, analysis, or interpretation of data: Arash Mostaghimi, Vanja Sikirica. Drafting of the manuscript: Arash Mostaghimi, Vanja Sikirica. Critical revision of the manuscript for important intellectual content: All authors (Arash Mostaghimi, Jason Xenakis, Aster Meche, Timothy W. Smith, David Gruben, Vanja Sikirica). Statistical analysis: Arash Mostaghimi. Administrative, technical, or material support: Arash Mostaghimi, Vanja Sikirica. Supervision: Vanja Sikirica.

Disclosures. Arash Mostaghimi reports consulting fees from Pfizer Inc., Concert, Eli Lilly, AbbVie, hims™, and Digital Diagnostics and equity from Lucid and hims™; and he is an associate editor at *JAMA Dermatology*. Jason Xenakis, Aster Meche, and David Gruben are employees and stockholders of Pfizer Inc. Timothy W. Smith and Vanja Sikirica were employees of Pfizer Inc. at the time the study was conducted. Timothy W. Smith is currently

employed by Real world Evidence & Data Science, Novartis Pharmaceuticals Corporation as Director. Vanja Sikirica is currently employed by Moderna Therapeutics as Senior Director, Lead Epidemiologist.

Compliance with Ethics Guidelines. This retrospective cohort study utilized US claims data extracted from PharMetrics® Plus, which contains fully adjudicated health plan claims and is representative of the US commercially insured population. Permission was obtained from PharMetrics® Plus to access and use the data. All data were fully de-identified before study cohort selection in accordance with the Health Insurance Portability and Accountability Act of 1996 to protect patients' privacy. As a result, no institutional review board approval was required.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available under the data sharing agreement with Pfizer Inc on behalf of PharMetrics® Plus.

REFERENCES

1. Darwin E, Hirt PA, Fertig R, Doliner B, Delcanto G, Jimenez JJ. Alopecia areata: review of epidemiology, clinical features, pathogenesis, and new treatment options. Int J Trichology. 2018;10(2):51–60.

2. Jabbari A, Dai Z, Xing L, Cerise JE, Ramot Y, Berkun Y, et al. Reversal of alopecia areata following treatment with the JAK1/2 inhibitor baricitinib. EBioMedicine. 2015;2(4):351–5.

3. Barahmani N, Schabath MB, Duvic M. National Alopecia Areata Registry. History of atopy or autoimmunity increases risk of alopecia areata. J Am Acad Dermatol. 2009;61(4):581–91.

4. Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, et al. Alopecia areata: disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol. 2018;78(1):1–12.

5. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ III. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc. 1995;70(7):628–33.

6. Petukhova L, Cabral RM, Mackay-Wiggan J, Clynes R, Christiano AM. The genetics of alopecia areata: what's new and how will it help our patients? Dermatol Ther. 2011;24(3):326–36.

7. Benigno M, Anastassopoulos KP, Mostaghimi A, Udall M, Daniel SR, Cappelleri JC, et al. A large cross-sectional survey study of the prevalence of alopecia areata in the United States. Clin Cosmet Investig Dermatol. 2020;13:259–66.

8. Hordinsky MK. Overview of alopecia areata. J Investig Dermatol Symp Proc. 2013;16(1):S13–5.

9. MacLean KJ, Tidman MJ. Alopecia areata: more than skin deep. Practitioner. 2013;257(1764):29–32, 3.

10. Shapiro J. Current treatment of alopecia areata. J Investig Dermatol Symp Proc. 2013;16(1):S42–4.

11. Meah N, Wall D, York K, Bhoyrul B, Bokhari L, Sigall DA, et al. The Alopecia Areata Consensus of Experts (ACE) study: results of an international expert opinion on treatments for alopecia areata. J Am Acad Dermatol. 2020;83(1):123–30.

12. King BA, Mesinkovska NA, Craiglow B, Kindred C, Ko J, McMichael A, et al. Development of the alopecia areata scale for clinical use: results of an academic-industry collaborative effort. J Am Acad Dermatol. 2022;86:359–64.

13. Harries MJ, Sun J, Paus R, King LE Jr. Management of alopecia areata. BMJ. 2010;341:c3671.

14. Karimkhani C, Boyers LN, Prescott L, Welch V, Delamere FM, Nasser M, et al. Global burden of skin disease as reflected in Cochrane Database of Systematic Reviews. JAMA Dermatol. 2014;150(9):945–51.

15. Hunt N, McHale S. The psychological impact of alopecia. BMJ. 2005;331(7522):951–3.

16. Titeca G, Goudetsidis L, Francq B, Sampogna F, Gieler U, Tomas-Aragones L, et al. "The psychosocial burden of alopecia areata and androgenetica": a cross-sectional multicentre study among dermatological out-patients in 13 European countries. J Eur Acad Dermatol Venereol. 2020;34(2):406–11.

17. Okhovat JP, Marks DH, Manatis-Lornell A, Hagigeorges D, Locascio JJ, Senna MM. Association between alopecia areata, anxiety, and depression: a systematic review and meta-analysis. J Am Acad Dermatol. 2019;S0190–9622(19):30890–4.

18. Lee S, Lee H, Lee CH, Lee WS. Comorbidities in alopecia areata: a systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(2):466–77.e16.

19. Conic RZ, Miller R, Piliang M, Bergfeld W, Atanaskova MN. Comorbidities in patients with alopecia areata. J Am Acad Dermatol. 2017;76(4):755–7.

20. IQVIA. IQVIA PharMetrics Plus: Fact Sheet; 2020. https://www.iqvia.com/library/fact-sheets/iqvia-pharmetrics-plus. Accessed Jan 11, 2021.

21. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–82.

22. Lavian J, Li SJ, Lee EY, Bordone LA, Polubriaginof FCG, Christiano AM, et al. Validation of case identification for alopecia areata using International Classification of Diseases Coding. Int J Trichology. 2020;12(5):234–7.

23. The TC, Rate ERE. Principles of international finance and open economy macroeconomics. Waltham: Academic Press; 2015. p. 103–43.

24. Flórez-Tanus Á, Parra D, Zakzuk J, Caraballo L, Alvis-Guzmán N. Health care costs and resource utilization for different asthma severity stages in Colombia: a claims data analysis. World Allergy Organ J. 2018;11(1):26.

25. Senna M, Ko J, Tosti A, Edson-Heredia E, Fenske DC, Ellinwood AK, et al. Alopecia areata treatment patterns, healthcare resource utilization, and comorbidities in the US population using insurance claims. Adv Ther. 2021;38(9):4646–58.

26. Eichenfield LF, DiBonaventura M, Xenakis J, Lafeuille MH, Duh MS, Fakih I, et al. Costs and treatment patterns among patients with atopic dermatitis using advanced therapies in the United States: analysis of a retrospective claims database. Dermatol Ther (Heidelb). 2020;10(4):791–806.

27. Vanderpuye-Orgle J, Zhao Y, Lu J, Shrestha A, Sexton A, Seabury S, et al. Evaluating the economic burden of psoriasis in the United States. J Am Acad Dermatol. 2015;72(6):961–7.e5.

28. Huang KP, Mullangi S, Guo Y, Qureshi AA. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. JAMA Dermatol. 2013;149(7):789–94.

29. Lim CP, Severin RK, Petukhova L. Big data reveal insights into alopecia areata comorbidities. J Investig Dermatol Symp Proc. 2018;19(1):S57–61.

30. Shin JW, Kang T, Lee JS, Kang MJ, Huh CH, Kim MS, et al. Time-dependent risk of acute myocardial infarction in patients with alopecia areata in Korea. JAMA Dermatol. 2020;156(7):763–71.

31. Huang KP, Joyce CJ, Topaz M, Guo Y, Mostaghimi A. Cardiovascular risk in patients with alopecia areata (AA): a propensity-matched retrospective analysis. J Am Acad Dermatol. 2016;75(1):151–4.

32. El-Sayed Mahmoud Marie R, El-Sayed GAK, Attia FM, Gomaa AHA. Evaluation of serum cardiac troponin I and N-terminal pro-B-type natriuretic peptide levels in patients with alopecia areata. Clin Exp Dermatol. 2021;46(1):153–6.

33. Glickman JW, Dubin C, Renert-Yuval Y, Dahabreh D, Kimmel GW, Auyeung K, et al. Cross-sectional study of blood biomarkers of patients with moderate to severe alopecia areata reveals systemic immune and cardiovascular biomarker dysregulation. J Am Acad Dermatol. 2021;84(2):370–80.

34. Wang EH, Santos L, Li XY, Tran A, Kim SSY, Woo K, et al. Alopecia areata is associated with increased expression of heart disease biomarker cardiac troponin I. Acta Derm Venereol. 2018;98(8):776–82.

35. Lee JH, Song Y, Do Han K, Park YM, Lee JY, Park YG, et al. Cancer risk by the subtype of alopecia. Sci Rep. 2018;8(1):9748.

36. Chen CC, Chang YT, Liu HN, Chen YJ. Cancer risk in patients with alopecia areata: a nationwide

population-based matched cohort study. Cancer Med. 2018;7(5):2153–9.

37. Ribeiro LB, Rego JC, Estrada BD, Bastos PR, Pineiro Maceira JM, Sodre CT. Alopecia secondary to anti-tumor necrosis factor-alpha therapy. An Bras Dermatol. 2015;90(2):232–5.

38. Mishra OP, Delivoria-Papadopoulos M. Lipid peroxidation in developing fetal guinea pig brain during normoxia and hypoxia. Brain Res Dev Brain Res. 1989;45(1):129–35.

39. Merola JF, Herrera V, Palmer JB. Direct healthcare costs and comorbidity burden among patients with psoriatic arthritis in the USA. Clin Rheumatol. 2018;37(10):2751–61.

40. Feldman SR, Vrijens B, Gieler U, Piaserico S, Puig L, van de Kerkhof P. Treatment adherence intervention studies in dermatology and guidance on how to support adherence. Am J Clin Dermatol. 2017;18(2):253–71.