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ORIGINAL ARTICLE

Real world evidence: patients with alopecia areata in Italy

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ABSTRACT

BACKGROUND: This real-world analysis aimed at characterizing patients hospitalized for alopecia areata (AA) in Italy, focusing on comorbidities, treatment patterns and the economic burden for disease management.

METHODS: Administrative databases of healthcare entities covering 8.9 million residents were retrospectively browsed to include patients of all ages with hospitalization discharge diagnosis for AA from 2010 to 2020. The population was characterized during the year before the first AA-related hospitalization (index-date) and followed-up for all the available successive period. AA drug prescriptions and treatment discontinuation were analyzed during follow-up. Healthcare costs were also examined.

RESULTS: Among 252 patients with AA (mean age 32.1 years, 40.9% males), the most common comorbidities were thyroid disease (22.2%) and hypertension (21.8%), consistent with literature; only 44.4% (112/252) received therapy for AA, more frequently with prednisone, triamcinolone and clobetasol. Treatment discontinuation (no prescriptions during the last trimester) was observed in 86% and 88% of patients, respectively at 12 and 24-month after therapy initiation. Overall healthcare costs were 1715€ per patient (rising to 2143€ in the presence of comorbidities), mostly driven by hospitalization and drugs expenses.

CONCLUSIONS: This first real-world description of hospitalized AA patients in Italy confirmed the youth and female predominance of this population, in line with international data. The large use of corticosteroids over other systemic therapies followed the Italian guidelines, but the high discontinuation rates suggest an unmet need for further treatment options. Lastly, the analysis of healthcare expenses indicated that hospitalizations and drugs were the most impactive cost items.

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KEY WORDS: Comorbidity; Adrenal cortex hormones; Costs and cost analysis.

Alopecia areata (AA) is an autoimmune condition that targets hair follicles, leading to hair loss, ranging from a few round hairless patches to complete loss in all hair-bearing body areas.[1] The evolution of AA is highly variable, ranging from mild cases with spontaneous remission to severe chronic forms, often refractory to therapy.[2, 3]

Recently, the Global Burden of Disease Study 2019 estimated the annual percentage changes (EAPCs) to assess the trends over time in the number of AA patients worldwide.[4] The incidence of AA increased by 49.14% from 2009 to 2019, with no substantial differences between sexes. The overall prevalence of AA has been estimated to be in the range of 0.1-0.58% in population-based studies from various geographic areas,[5-10] but it rises up to 1.7-2.1% in subjects experiencing an episode of AA during their lifetime.[1, 11] To date, there are no specific estimations on the prevalence and incidence of AA in Italy. The only epidemiological data on AA at national level are available from patients' associations[12] or periodical surveys from the National Association of Alopecia Areata (ANAA).[13]

Similar to other skin diseases such as atopic dermatitis or psoriasis, AA can result in a markedly decreased health-related quality of life (HRQoL)[14] and elevated rates of concomitant medical or psychological conditions (*e.g.* depression and anxiety), with the related social effects in terms of work productivity loss.[15, 16] There was no therapy authorized by the European Medicines Agency before the approval of baricitinib, a Janus kinase (JAK)1/JAK2 in 2022. Traditional treatments include topical, intralesional, and systemic glucocorticoids, conventional immunosuppressants, and contact immunotherapy.[3]

Recent data on the economic burden related to AA patients, in both adults and adolescents, highlighted elevated healthcare resource utilization and costs, mostly due to surgical procedures, psychological interventions and drug expenses, although often managed in the ambulatory setting.[17, 18]

Due to the limited data available on AA patients in Italy, the present real-world analysis was undertaken to characterize a sample population of hospitalized AA patients in Italy in terms of comorbidity profile, treatment patterns and the economic burden associated with their management, focusing on healthcare costs sustained by the Italian National Health Service (NHS).

Materials and methods

Data source

A retrospective analysis was carried out based on secondary data from administrative databases of a pool of Italian entities (Local Health Units, LHUs) covering 8.9 million health-assisted individuals with data available from January 2009 to December 2021.

The analysis was conducted using the following databases: 1) demographic database, which includes patients' demographic data, namely sex, age and date of death; 2) pharmaceutical database, which reports data on medicinal products reimbursed by the Italian NHS, such as the Anatomical Therapeutic Chemical (ATC) code, number of packages, number of units per package, unit cost per package, and prescription date; 3) hospitalization database, which collects all hospitalization data, such as discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge (provided by the NHS); 4) outpatient specialist service database, which supplies all information about visits and diagnostic tests (date and type of prescription, description activity and laboratory test or specialist visit charge); and 5) payment exemption database, for information of exemption codes by which patients are discharged from paying services/treatments in case of specific disease diagnoses.

An anonymous univocal numeric code was assigned to each participant to ensure privacy, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). This patient code permitted the electronic linkage between the various databases. All the results coming out from the analyses were produced as aggregated summaries and were never attributable to a single institution, department, doctor, individual, or individual prescriber behavior.

The analysis was conducted in accordance with the principles of the Helsinki declaration and approved by the local Ethics Committees of the Healthcare Departments involved.

Identification of the study population

Inclusion and exclusion criteria

Between January 2010 and December 2020 (inclusion period), children, adolescents, and adults with AA were identified with at least one hospitalization discharge diagnosis (either primary or secondary) of AA (ICD-9-CM: 704.01). Among the patients meeting the above inclusion criteria, the index-date was considered as that of the first hospitalization for AA. The characterization period was defined by the time of data availability of at least 12 months before the index-date and the follow-up was determined from all the data available in the period after the index-date (at least 12 months). Patients with no continuous data during the study period or with less than one year of available data before and after the index-date were excluded. The flow chart is reported in Figure 1.

Demographic and clinical characteristics

For the whole sample population included in the study, the following patient data were collected: age at index-date, age groups (<18 years, 18-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, ≥65 years), and sex (expressed as the percentage of male patients). The overall patients' clinical status was explored through the Charlson Comorbidity Index (CCI), a scoring system that sums the weight of 19 concomitant diseases and provides numeric clusters of comorbid conditions: CCI score 0 indicates no comorbidities, 1-2 mild level, 3-4 moderate level and ≥5 severe level of comorbidities.[19] As previously reported for retrospective observational analyses, summary comorbid-

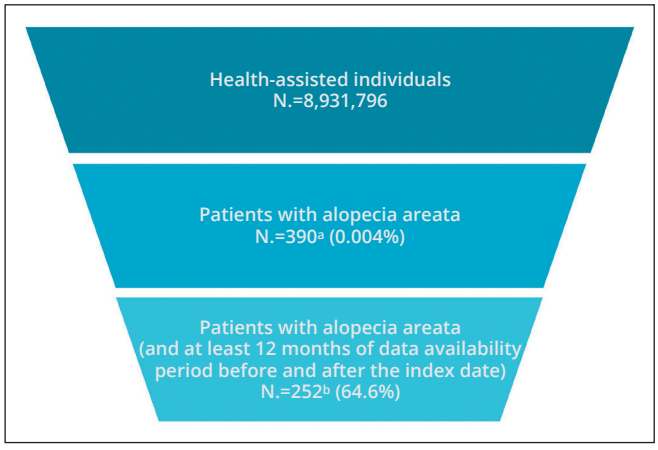

Figure 1.—Flow chart for the identification of the study population.
[a]The percentage of patients with AA was calculated on the total number of Italian health-assisted residents covered by the participating healthcare entities (390 out of 8931,796); [b]the percentage of hospitalized AA patients was calculated on the total number of patients with AA (252 out of 390).
AA: alopecia areata.

ity measures, such as the CCI used here, can provide a clearer clinical framing and mortality risk within patients' groups who share the same diagnosis, delineating the main differences on co-existing diseases, not directly related to the diagnosis itself.[20-22]

During the period preceding inclusion (namely the time of the first hospitalization for AA), patients were also investigated for diseases that are commonly associated with AA (*i.e.* some autoimmune and inflammatory disorders) by searching data to the hospitalizations, drug treatments, and concomitant conditions,[3] namely: 1) the 10 most frequent hospitalizations (excluded index-date), grouped by Major Diagnostic Categories (MDC); 2) the 10 most frequent drugs, grouped by ATC Classification System, at the second level; and 3) the comorbidities that occurred during all the available periods (the ICD-9-CM codes, ATC codes and exemption codes for each of comorbidity are detailed in Supplementary Digital Material 1: Supplementary Table I).

Treatment patterns

Analysis of AA treatments

The following therapies/procedures were evaluated in the sample population of hospitalized AA patients, during all the available period before and after the index-date: 1) systemic immunosuppressive agents, including methotrexate, ciclosporin, sulfasalazine, azathioprine; 2) topical prostaglandin analogues, including latanoprost, bimatoprost; 3) topical minoxidil; 4) potent topical corticosteroids, including desoximethasone, clobetasol, betamethasone; 5) systemic glucocorticoids, (among the prescriptions, only the orally administered formulation of prednisone was found); 6) JAK inhibitors, including tofacitinib, and ruxolitinib; 7) intralesional corticosteroids, including triamcinolone; and 8) photochemotherapy consisting of psoralen plus ultraviolet A (PUVA) photochemotherapy. The list of ATC codes for drugs and procedure code for PUVA are provided in Supplementary Digital Material 2, Supplementary Table II.

Treatment discontinuation

Treatment discontinuation was defined as the absence of prescriptions for AA treatment during the last quarter of the 1st year and the last quarter of the 2nd year of follow-up. The number and percentage of patients who discontinued treatment for AA at 12 months and at 24 months after therapy initiation were estimated.

Analysis of healthcare costs for the Italian NHS

During the follow-up period, healthcare average direct total costs subsidized by the Italian NHS for each surviving patient were assessed in terms of the number of drug treatments administered, hospital admissions (ordinary and day hospital) and outpatient specialist services (specialist visits, laboratory tests, diagnostic procedures). Deaths and outlier values (those 3X standard deviation over the mean value) were excluded from the analysis.[23]

Statistical analysis

A descriptive statistical analysis of observed data was performed including continuous variables, presented as the mean±standard deviation (SD), and categorical variables, presented as frequencies and percentages.

According to "Opinion 05/2014 on Anonymization Techniques" drafted by the "European Commission Article 29 Working Party," analyses involving fewer than 3 patients were not disclosed as potentially traceable to single individuals. Therefore, the results referring to ≤ 3 patients were presented as NR (not reported). All analyses were performed using STATA SE, version 17.0 (StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics of the study population

The baseline demographic and clinical features of the overall population of hospitalized AA patients are detailed

TABLE I.—*Demographic and baseline clinical characteristics of hospitalized AA patients. Continuous variables are presented as the mean±SD, while categorical variables are presented as numbers and percentages.*

	Overall hospitalized AA patients (N.=252)
Male gender	103 (40.9%)
Age at index-date, years	32.1±18.4
Age groups	
<18 years	66 (26.2%)
18-24 years	30 (11.9%)
25-34 years	45 (17.9%)
35-44 years	37 (14.7%)
45-54 years	43 (17.1%)
55-64 years	24 (9.5%)
≥65 years	7 (2.8%)
Charlson comorbidity index (CCI)	0.6±1.1
CCI = 0	146 (57.9%)
CCI=1	78 (31.0%)
CCI≥2	28 (11.1%)
Follow-up, years	4.7±2.3

AA: alopecia areata; CCI: Charlson Comorbidity Index; SD: standard deviation.

TABLE II.—*Concomitant diseases in hospitalized AA patients. Data are presented as numbers and percentages.*

Comorbidity profile, N. (%)	Overall hospitalized AA patients (N.=252)
Thyroid disease	56 (22.2%)
Hypertension	55 (21.8%)
Mental health problems	40 (15.9%)
Hyperlipidemia	38 (15.1%)
Diabetes mellitus	22 (8.7%)
Psoriasis	15 (6.0%)
Atopic dermatitis	4 (1.6%)
Atopy	14 (5.6%)
Celiac disease	4 (1.6%)
Gastroesophageal reflux disease	4 (1.6%)
Systemic lupus erythematosus	-
Rheumatoid arthritis	NR
Vitiligo	NR
Myasthenia gravis	NR
Ulcerative colitis	NR
Autoimmune hemolytic anemia	NR

AA: alopecia areata; NR: not reported for data privacy (in line with "Opinion 05/2014 on Anonymization Techniques" drafted by the "European Commission Article 29 Working Party," results from subgroups less than 3 patients were not disclosed as potentially reconductable to single individuals).

in Table I. Among the sample population of 252 hospitalized AA patients, including children, adolescents and adults, the mean age at index-date was 32.1 years, and 40.9% were males. The general clinical status of the AA patients, evaluated through the CCI during the characterization period, indicated a mild comorbidity profile (CCI: 0.6±1.1).

Then, the complications commonly associated with AA[3] were investigated by collecting data on concomitant diseases, drug cotreatments, and causes of hospital admission. As shown in Table II, in the included population of hospitalized AA patients, 22.2% had thyroid disease, 21.8% had hypertension, 15.9% had mental health problems, 15.1% had hyperlipidemia, and 6.0% had psoriasis. The 10 most common causes of hospitalizations and the 10 most frequently administered cotreatments during all the available period and during the 1-year period before and after the index-date are listed in Supplementary Digital Material 3, Supplementary Table III, Supplementary Table IV, respectively. Concerning the causes of hospitalizations, divided by MDC, in most (23.8%) of the cases, admissions were related to skin, subcutaneous tissue and breast diseases, distantly followed by complications of the endocrine, nutritional and metabolic system which accounted for 4% of hospitalizations. Regarding cotreatments, it was observed that 68.7% of patients had a prescription for antibacterial agents, 37.7% for systemic corticosteroids, and 29.0% for drugs for obstructive airway diseases.

Treatment patterns

Among the 252 patients included in the study, only 112 (44.4%) received at least one treatment for AA (herein referred as treated hospitalized AA patients), while 140 (55.6%) remained untreated during the whole period of data availability before and after the index-date. Table III details the pattern of treatment regimens captured in overall and treated hospitalized AA patients throughout all the available period, revealing that prednisone, triamcinolone and clobetasol were the most commonly prescribed medi-

TABLE III.—*Pattern of treatment regimens during all the available period before and after inclusion in overall and treated hospitalized AA patients. Data are presented as numbers and percentages.*

Treatments for AA, N (%)	Overall hospitalized AA patients (N.=252)	Treated hospitalized AA patients (N.=112)
Prednisone	72 (28.6%)	72 (64.3%)
Clobetasol	38 (15.1%)	38 (33.9%)
Triamcinolone	37 (14.7%)	37 (33.0%)
Bimatoprost	5 (2.0%)	5 (4.5%)
Methotrexate	4 (1.6%)	4 (3.6%)
Azathioprine	4 (1.6%)	4 (3.6%)
Ciclosporin	NR	NR
Sulfasalazine	NR	NR
Latanoprost	NR	NR
Desoximetasone	NR	NR
Betamethasone	NR	NR
PUVA	NR	NR

AA: alopecia areata; NR: not reported for data privacy (in line with "Opinion 05/2014 on Anonymization Techniques" drafted by the "European Commission Article 29 Working Party," results from subgroups less than 3 patients were not disclosed as potentially reconductable to single individuals).
PUVA: psoralen plus ultraviolet A photochemotherapy.

cations. Focusing on steroid-based therapies among the 112 treated patients, 30% received prednisone alone, 15% received triamcinolone alone, 11% received clobetasol alone, and 8% received clobetasol followed by prednisone (data not shown).

Moreover, treatment discontinuation, defined as the absence of prescriptions during the last trimester, was observed in 86% and 88% of AA hospitalized patients at the first and second year of follow-up, respectively. The number and percentage of patients who discontinued treatment after 12 months and at 24 months were 96 (86%) and 99 (88%) respectively.

Healthcare cost analysis for the Italian NHS

Figure 2A reports the average costs per patient, censored for deaths and outliers, evaluated during the first year of follow-up in overall hospitalized AA patients (N.=246) and those with at least one comorbidity (N.=129). In the total sample population, the average total direct cost per patient was 1715€. Hospitalization was the most impactive item, accounting for 76% of the total expenses, followed by drugs (16%) and specialist services (8%). In patients with at least one comorbidity, the total mean healthcare cost was 2143€, and once again, the hospitalization expenses were the main cost drivers (67%), followed by drugs (23%) and specialist services (9%).

Figure 2B focuses on the healthcare costs in patients without treatment discontinuation. The average total cost per patient was 2057€ and 1405€ respectively during the first year and the second year after the start of therapy for AA. During the first year from the AA treatment initiation, hospitalizations accounted for 55% of total expenditures, drugs accounted for 31% and specialist services accounted for 14%. During the second year after AA treatment initiation, hospitalization expenses were 40% of the total, drugs 49% and specialist services 11%.

Discussion

This real-world analysis provided the first description of a sample of hospitalized AA patients retrieving data from

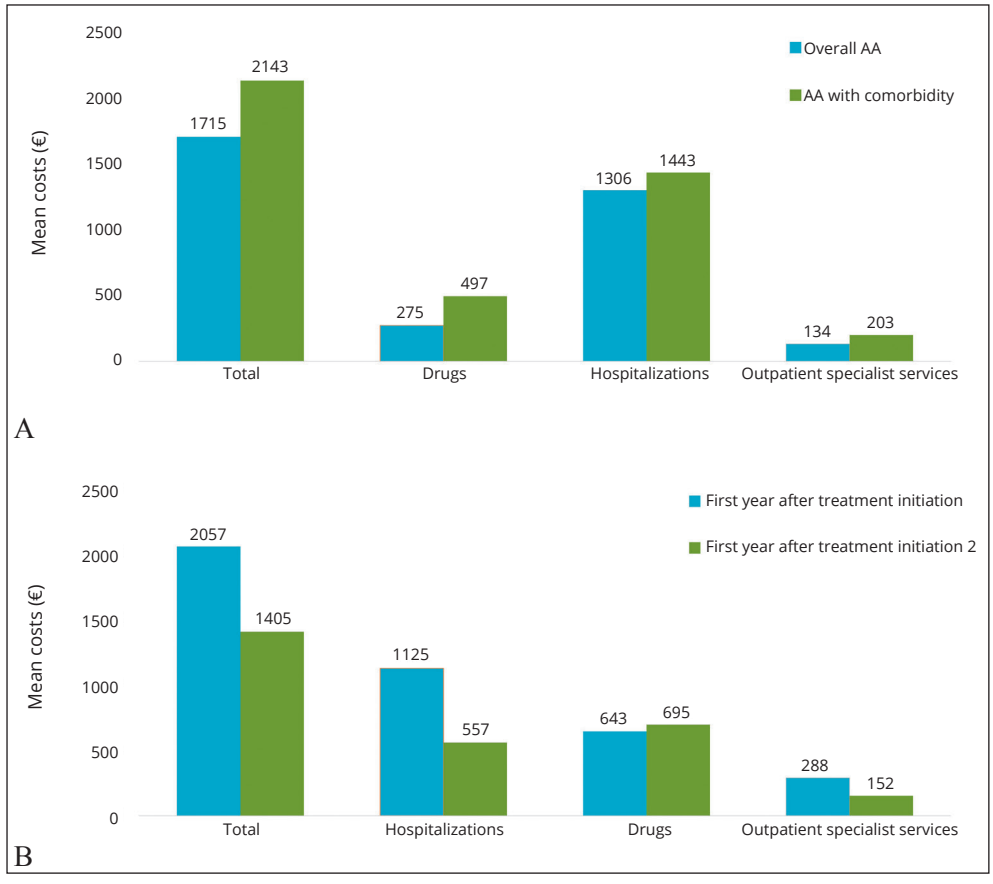

Figure 2.—A) Average cost per patient (total and divided into cost items) during the first year of follow-up in overall hospitalized AA patients (deaths and outliers excluded, N.=246), and those with at least one comorbidity (deaths and outliers excluded, N=129); B) healthcare costs in treated hospitalized AA patients without treatment discontinuation during the first (deaths and outliers excluded, N.=15) and second (deaths and outliers excluded, N.=12) year after AA treatment initiation.

the administrative databases of a pool of Italian healthcare entities corresponding to approximately 15% of the Italian population.

Our 252 hospitalized AA patients were characterized by young age, with a slight female predominance. In general, the characteristics of our study population mirrored those of previous reports. A systematic review by Villasante Fricke confirmed the youth of AA patients, with an average onset age ranging between 25.2 and 36.3 years.[24] The review also emphasized the inconsistency of literature data on gender-related susceptibility to AA: in line with our findings, ten hospital-based studies showed that AA occurred from 1.2-times to 2.6-times more frequently in women compared to men. Besides, other authors have not reported significant differences in the incidence of AA between males and females, and some other found a male predominance, more evident at younger age. In particular, in these studies male children were 1.4-time more frequently affected by AA, and with a worse clinical presentation in the majority of the studies.[24]

The review by Villasante Fricke also focused on the related psychiatric and medical comorbidities, reporting an enhanced risk for depression and anxiety, atopy, thyroid disease, and other autoimmune conditions (*i.e.* psoriasis and psoriatic arthritis) associated with AA.[24] The pattern of the most common comorbidities in our sample population highlighted that thyroid disease, hypertension, and psychological distress were the most represented coexisting diseases, and subsequently, the related treatments were also more commonly found among the prescribed comedications (in addition to those for AA treatment). The proportion of comorbidities in our sample was partially consistent with existing evidence from international studies.[25] An observational analysis performed in the US showed that 25% of AA patients suffered from mental health problems, 24% from hyperlipidemia, 15% from thyroid disease, and 11% from diabetes mellitus.[26] However, the reasons for these discrepancies among currently available literature might lie in the different study designs, the sample population enrolled, and the many influential components potentially involved in a multifactorial disease such as AA.[27] In this analysis, AA patients showed a mild comorbidity profile as documented by the low CCI of 0.6, confirming that although AA can have a detrimental effect on patients' quality of life, it is not a life-threatening condition.[28]

Concerning therapeutic interventions, 56% of patients did not receive any treatment for AA. On the other hand, prednisone, triamcinolone and clobetasol were the most frequent prescribed drugs among the AA patients who received at least one treatment during the whole study period, consistent with the Italian guidelines for AA treatment.[3] In our sample, a notable number of patients discontinued treatment, specifically 86% after one year and 88% after two years from starting therapy. Even though data on the rates of discontinuation of therapies for AA are limited, these elevated numbers observed in our study population might have several underlying reasons. On one hand, the changing clinical course of the disease characterized by periods of remission followed by relapse might partly explain the intermittent use of AA treatments. On the other hand, a tendency towards discontinuation can also be due to the limited efficacy of some of the available treatment options, manifestation of toxicity, adverse effects (*i.e.* immunosuppressive agents, systemic corticosteroids) and also an attitude to refuse more stressful procedures like intralesional injections, especially from younger patients and children.[3]

To date, this is the first real word study in Italy to analyze the economic burden of AA management on NHS expenditures, with a total annual healthcare cost of 1715€ per patient in the overall sample. Of note, in patients who remained on treatment, there was a reduction of costs for hospitalization at the second year of follow-up, while increased drug expenses were observed. This finding can be interpreted in light of the growing availability of effective therapies that might have led to a better control of disease worsening over time, ultimately leading to reduced requirements for hospital admissions. In the sample population analyzed here, the healthcare expenses were mainly driven by hospitalizations, and this is only partially consistent with other international reports, indicating that the most impactful areas in AA management are surgical procedures on the integumentary system, psychological interventions and drugs.[17, 18] However, this discrepancy might be due to the selection of patients which was solely based on the specific ICD-9-CM 704.01 code that identifies hospitalization discharge diagnosis (either primary or secondary) for AA.

Strengths and limitations of the study

One of the key points of the present analysis lies in the utilization of administrative databases with their great advantages to address clinical or health services questions over other research approaches which include small sample sizes (*i.e.* single-center studies), with poor generalizability. Moreover, our findings provide novel insights in the current Italian landscape, characterized by the lack of real-life descriptions of hospitalized AA patients. The present analysis paves the way to further investigations

on this important health issue. However, there are also some limitations: firstly, the retrospective observational nature and the extraction of data from administrative databases could lack some information. For instance, given that the pharmaceutical databases collect information primarily gathered for reimbursement purposes, drug treatments were extrapolated from medical prescriptions and dispensing information; this means that all private medication consumption not covered by the NHS (*i.e.*, out-of-pocket drugs and galenic preparations, which embrace a large market share in this setting) were untraceable. Perhaps further studies on private medication consumption could provide additional information on the burden of AA management. Secondly, hospital discharge AA diagnosis was used to select patients, so the cases managed in the ambulatory outpatient setting or those without a hospital admission for AA during the study period were missed. Finally, the reasons behind treatment discontinuation cannot be extrapolated from the dataset.

Conclusions

To the best of our knowledge, this analysis is the first description in a real-life clinical setting in Italy on the therapeutic patterns of patients previously hospitalized for AA and the related economic burden on the NHS. In line with international data, we found that this is a strikingly young population and women seem to be slightly more represented. The type and frequency of comorbidities was aligned with existing literature, corroborating the significant burden of AA and the associated conditions. Moreover, such an elevated rate of concomitant conditions and related comedications other than those indicated for AA itself seems to suggest that this disease implies a complex and multidisciplinary approach in an effort to provide proper care in terms of medical therapy, quality of life and psychological support.

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Conflicts of interest

Valentina Perrone, Melania Dovizio, Melania Leogrande and Luca Degli Esposti have no conflicts of interest to disclose regarding this work. Silvia Sabatino and Arianna Avitabile are employees of Eli Lilly Italy S.p.a., Italy.

Authors' contributions

Valentina Perrone: conceptualization, supervision, original draft preparation, reviewing; Melania Dovizio: original draft preparation, and editing; Melania Leogrande: data analysis, methodology; Silvia Sabatino and Arianna Avitabile: conceptualization, methodology; Luca Degli Esposti, conceptualization, methodology, supervision. All authors read and approved the final version of the manuscript.

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Supplementary data

For supplementary materials, please see the HTML version of this article at www.minervamedica.it