ORIGINAL ARTICLE

Alopecia areata totalis and universalis: a multicenter review of 132 patients in Spain

S. Vañó-Galván,[1,*] P. Fernández-Crehuet,[2] R. Grimalt,[3] M.J. Garcia-Hernandez,[4] R. Rodrigues-Barata,[5] S. Arias-Santiago,[6] A. Molina-Ruiz,[7] E. Garcia-Lora,[8] J. Dominguez-Cruz,[9] A. Brugues,[10] J. Ferrando,[10] C. Serrano-Falcón,[11] S. Serrano,[12] J. Paoli,[13] F. Camacho[4]

[1]Dermatology Service, Trichology Unit, Ramon y Cajal Hospital, IRYCIS, University of Alcala, Madrid, Spain
[2]Dermatology Service, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica (IMIBIC), Córdoba, Spain
[3]Universitat Internacional de Catalunya, Barcelona, Spain
[4]Virgen Macarena, Sevilla, Spain
[5]Grupo Pedro Jaén, Madrid, Spain
[6]Unidad de Gestión Clínica de Dermatología Médico-Quirúrgica y Venereología, Hospital Universitario Virgen de las Nieves, Granada, Spain
[7]Fundación Jiménez-Diaz, Madrid, Spain
[8]Dermatology Department, Hospital Virgen de las Nieves-Granada, Madrid, Spain
[9]Virgen del Roc!ıo, Sevilla, Spain
[10]Clinic-Barcelona, Barcelona, Spain
[11]Dermatology Service, Hospital de Guadix de Granada, Granada, Spain
[12]Dermatology Department, Universidad de Granada, Granada, Spain
[13]Department of Dermatology and Venereology, Sahlgrenska University Hospital, Institute of Clinical Sciences at the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
*Correspondence: S. Vañó-Galván. E-mail: drsergiovano@gmail.com

Abstract

Background Alopecia areata totalis (AAT) and universalis (AAU) pose a therapeutic challenge.

Objective To describe the clinical and epidemiological features, therapeutic response and prognostic factors in a large series of patients diagnosed with AAT and AAU.

Methods This retrospective multicenter study included patients diagnosed with AAT/AAU with a minimum follow-up of 12 months. Response was assessed based on the regrowth of scalp hair.

Results In all, 132 patients (92 women and 40 men) – 80 (61%) diagnosed with AAU and 52 (39%) diagnosed with AAT – were included. The median time between the presentation of alopecia areata (AA) and the development of extensive AA was 1 year and it was less than 4 years in 121 patients (91%). There was an initial response to treatment in 64% of patients, although only 14% presented a persistent response. Adverse side effects from the medications used were detected in 33% of patients. The prognostic factors associated with poor response were the presence of AAU and a positive family history of AA.

Conclusions Treatment of AAT and AAU is challenging. Although an initial regrowth may be achieved, the duration of response is usually short. There were no significant differences on the effectiveness or duration of response between the various systemic therapies.

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Conflicts of interest

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Background

Alopecia areata (AA) is a common non-scarring type of alopecia with an autoimmune etiopathogenesis.[1–5] There is generally no sex predilection.[4] It tends to affect children and young adults more frequently but can present at any age.[6,7] The scalp is the most commonly affected area but any hair-bearing area can be involved. There are no available treatment options that are curative or preventive.[1] Approximately 5% of cases will progress to alopecia areata totalis (AAT) or alopecia areata universalis (AAU).[3] These are the subtypes of AA with the worst prognosis.[3,8,9] They pose a therapeutic challenge[4] and may have a devastating impact on quality of life.[10] In the cases of hair regrowth, relapse is the rule,[11] although a minority of patients may achieve a long-term response.

Several studies[9,12–14] have been published describing the characteristics and prognostic factors of patients with AA, although the majority of them include mainly patients with multifocal AA and few patients with AAT or AAU. The objective of our study was to describe the clinical and epidemiological features, therapeutic response and prognostic factors in a large series of patients diagnosed with AAT and AAU.

Methods

This multicenter study was performed in 10 Spanish centres. A retrospective observational and analytic review was designed including patients given the diagnosis of AAT and AAU from 2000 to 2014. A minimum of 12 months of follow-up was established as an inclusion criterion.

Epidemiological (gender, age, age of onset of AA, comorbidities and family history), clinical (subtype of AA at presentation, currently subtype of AA, time since presentation until extensive AA and nail involvement), diagnostic (laboratory evaluation including immunological and thyroid evaluations) and therapeutic variables (therapies given, response to therapy, time until response, regrowth duration, side effects and time of follow-up after treatment) were recorded. The serologic screening of syphilis was not routinely performed in all cases. Therapies were selected based on the clinical experience of each dermatologist. Therapeutic response was assessed as no response (no regrowth), partial response (regrowth of <75% of the scalp hair) and complete response (regrowth of 75% or more of the scalp hair). Persistent response was defined as the maintenance of >75% of regrowth after 6 months of the withdrawal of therapy. For statistical purposes, patients without any hair regrowth during the follow-up were defined as cases with a "poor prognosis".

To identify the best combination of independent factors associated with poor therapeutic response of extensive AA, multivariate (i.e., logistic regression) analysis was performed. Independent factors were expressed as: odds ratio (OR); 95% confidence interval (CI); *P* value. $P < .05$ was considered statistically significant.

Results

The study included 132 patients (92 women and 40 men). Among them, 80 (61%) were diagnosed with AAU and 52 (39%) were diagnosed with AAT. The median age at which extensive AA debuted was 26 years (range 1–72 years), with two peaks of frequency at 7 years (extensive AA with infant onset) and 33 years (extensive AA with adult onset). The median time between the presentation of AA and the development of extensive AA was 1 year (range 0–32 years) and it was less than 4 years in 121 patients (91%). The patients were followed for a mean time of 6.47 years (range: 1.5–26). A family history of AA was present in 16 patients (12%). Previous or concomitant autoimmune disease was detected in 31 patients (23%), with thyroid disease being the most prevalent (26 patients, 20%), followed by vitiligo (4 patients, 3%) and diabetes mellitus type I (3 patients, 2%). Other comorbidities were as follows: atopic dermatitis in 27 patients (20%), dyslipidemia in 12 patients (9%), high blood pressure in 7 patients (5%), psoriasis in 4 patients (3%) and previous cancer in 2 patients (breast cancer and ovarian cancer).

The most frequent initial clinical form of AA was multifocal AA (five or more patches) in 64 patients (48%), followed by AA with less than five patches in 43 patients (32%), diffuse AA in 17 patients (13%), ophiasis in five patients (4%) and beard AA in three patients (2%). Clinically, nail involvement was observed in 27 patients (20%). The most frequent affectation was trachyonichia (16 patients, 12%), followed by pitting (6 patients, 5%). The epidemiological, clinical, diagnostic and evolutive features of patients with extensive AA are shown in Table 1.

Regarding therapy, globally 30 of 132 patients (23%) showed no response to any therapy ("poor prognosis" patients), 72 patients (54%) had a partial response and 30 patients (23%) had a complete response. The initial percentage of response after a single treatment was 64% (22% with complete response and 42% with partial response). The mean time until response was 3.8 months (range 1–6) and the mean duration of response was 4.8 months (range 0–36). Adverse side effects from the medication used were detected in 44 patients (33%). Two patients (1.5%) suffered serious adverse effects (anaphylaxis with diphencyprone and bone marrow suppression with azathioprine). The data regarding the systemic therapies used, therapeutic response and adverse effects are shown in Table 2. Spontaneous regrowth during follow-up was observed in seven patients (5%). It developed in few months and was persistent after 12 months in five of seven patients. The median time of follow-up of these patients after spontaneous regrowth was 14 months. A total of 19 patients (14% of the total and 18% of the initial responders to therapy) had a persistent regrowth without systemic therapy (Fig. 1), with a median time of follow-up of 6 months (range 3–30). Of the 132 patients, 19 (14%) responded to a specific

Table 1 Epidemiological, clinical, diagnostic and evolutive features of patients with extensive alopecia areata (AA)

Variable*	Infancy onset (*n* = 45)		Adult onset (*n* = 87)		Total (*n* = 132)
	AAU (*n* = 27)	AAT (*n* = 18)	AAU (*n* = 53)	AAT (*n* = 34)	
Gender (female/male)	16/11	12/6	41/12	23/11	92/40
Most frequent initial clinical form	Multifocal AA	Multifocal AA	Multifocal AA	Patch AA (<5)	Multifocal AA
Median age of onset of extensive AA	7.5 years	11.5 years	35 years	35 years	26 years
Median age of first manifestation of AA	7.0 years	7.5 years	34 years	32 years	23 years
Family history of AA	3 (11%)	1 (5%)	7 (13%)	5 (15%)	16 (12%)
Patients with poor response (absence of regrowth with any treatment)	8 (30%)	2 (11%)	16 (30%)	4 (12%)	30 (23%)
Patients with partial response (regrowth <75%)	19 (70%)	14 (78%)	21 (40%)	18 (53%)	72 (54%)
Patients with complete response (regrowth >75%)	0	2 (11%)	16 (30%)	12 (35%)	30 (23%)
Patients with response maintained in the present without treatment	0	2 (11%)	9 (17%)	8 (24%)	19 (14%) [14% of the total and 18% of the initial responders to therapy)
Patients with spontaneous regrowth in any moment	0	1 (5%): complete regrowth	3 (6%): 1 complete and 2 partial regrowth	3 (9%): 2 complete and 1 partial regrowth	7 (5%)

Characteristics of patients with onset of AA in childhood (<18 years) vs. adulthood (18 or more years) and those with alopecia areata universalis (AAU) vs. alopecia areata totalis (AAT).

*There were no statistically significant differences between subgroups.

ANA, antinuclear antibodies; AA, alopecia areata; AAU, alopecia areata universalis; AAT, alopecia areata totalis.

treatment in a second attempt time after they did not respond to the same therapy before.

In multivariate analysis, a trend towards significance was observed for AAU [Odds Ratio: 4.77 (CI 95: 0.6–31.0); $P = 0.068$] and a family history of AA [Odds Ratio: 3.73 (CI 95: 0.7–42.8); $P = 0.089$] as prognostic factors associated with poor prognosis. Neither the nail involvement nor the time of evolution of extensive AA correlated with poor prognosis.

Discussion

Alopecia areata totalis and AAU may affect men and women of any age and can start with any form of AA. The decision to treat or not to treat AAT or AAU is sometimes arduous, and should be discussed with the patient, taking into account the expected duration of the therapy, the risk of adverse effects and the rate and duration of the response. This study reports a large series of patients with AAT and AAU, describing specific data of important value to the clinician when informing patients and discussing treatment options.

The most frequent initial presentation of AA in the patients was multifocal AA. Interestingly, the median time between the onset of AA and the development of AAT or AAU was 1 year and more than 90% of patients developed AAT or AAU 4 years after the onset of AA. Therefore, patients with long-standing patchy AA are at a low risk of developing AAT or AAU. A positive family history of AA is not infrequent in patients with extensive AA. Between 4% and 28% of patients who have AA will have at least one other affected family member,[3] which is in concordance with the rate of family history of the patients in our study (12%). Regarding comorbidities, approximately 16% of patients with any form of AA are associated with a coexistent autoimmune condition,[4,16] which is slightly inferior to the 23% observed in our study. Specifically, thyroid disease is present in 8–28% of AA patients[4] (20% in our study). In concordance with our series, several studies[17] have demonstrated a high rate of thyroid disease in patients with AA (Table 3). Therefore, we recommend including thyroid evaluation in the work-up of patients with extensive AA. Regarding atopic dermatitis, we found a similar incidence to that of the general population, (20%), whereas other studies found a higher incidence (more than 40%).[8] Clinically, extensive AA usually progresses from a pre-existing multifocal AA. However, some patients with other forms of AA may develop AAT or AAU, such as beard AA.

Treatment of extensive AA is usually disappointing. No therapy has been shown to alter the course of the disease or to have a significant long-term benefit compared to placebo according to evidence-based assessment.[2,4,18] Therefore, the objective of the treatment of extensive AA should be to achieve regrowth with systemic therapy and try to maintain regrowth with a more conservative management (topical or intralesional steroids). So, although not curative, therapy might help patients to obtain hair regrowth and even to achieve a persistent regrowth.

Table 2 Systemic therapies used, therapeutic response (total: sum of partial and complete, partial: regrowth <75% of hair of the scalp, complete: regrowth >75% of hair of the scalp), mean time until response, mean duration of response, patients with persistent response (>3 months after withdrawal of therapy) and adverse effects

Treatment and number of patients*	Dosage of therapies	Total therapeutic response (partial + complete)	Mean time until response (months)	Mean duration of response (months)	Persistent response	Adverse effects	Type of adverse effects
Systemic Corticosteroids (n = 80)	— Continuous: prednisone 0.5–1 mg/kg/day or deflazacort 0.75–1.25 mg/kg/day — Pulses: dexamethasone 0.1 mg/kg/day 2 consecutive days each week	Total: 67 (51%) Partial: 40 (30%) Complete: 27 (21%)	1.7	3.2	9 (11%)	33 (25%)	— Weight gain (20%) — Striae (5%) — Cushing (4%)
IMMUNOTHERAPY (n = 36)	Diphencyprone in a concentration between 0.01 and 0.5%	Total: 16 (44%) Partial: 13 (36%) Complete: 3 (8%)	3.9	5.1	4 (11%)	18 (50%)	— Local intense reaction (41%), lymphadenopathies (17%) — 1 case of anaphylaxis
Phototherapy (n = 16)	PUVA therapy: three sessions each week	Total: 5 (31%) PARTIAL: 2 (12%) Complete: 3 (19%)	6.0	4.2	2 (12%)	2 (12%)	— Burn (12%)
Azathioprine (n = 14)	100–150 mg daily, adjusted by TPMT (thiopurine methylstransferase)	Total: 4 (29%) Partial: 1 (7%) Complete: 3 (21%)	3.5	7.2	1 (12%)	5 (35%)	— Diarrhoea (21%) — 1 case of pancreatitis — 1 case of bone marrow suppression
Methotrexate (n = 10)	15–25 mg weekly	Total: 5 (50%) Partial: 5 (50%) Complete: 0	3.0	6.3	1 (10%)	1 (10%)	— Increase in liver enzymes (10%)
Cyclosporine (n = 8)	150–300 mg daily	Total: 4 (50%) Partial: 2 (25%) Complete: 2 (25%)	2.7	3.3	1 (12%)	3 (37%)	— High blood pressure (25%) — Tremble (25%)
Zinc (n = 6)	Zinc aspartate 50–100 mg/day	Total: 2 (33%) Partial: 2 (100%) Complete: 0	9.1	2.1	0	0	
Combination of corticosteroid and methotrexate (n = 5)	Prednisone 0.5–1 mg/kg/day + methotrexate 15–20 mg weekly	Total: 4 (80%) Partial: 1 (20%) Complete: 3 (60%)	1.7	6.8	1 (20%)	2 (40%)	— Increase in liver enzymes (20%) — Weight gain (20%)
Total (n = 190)		Total: 123 (64%) Partial: 81 (42%) Complete: 42 (22%)	3.8 months	4.8 months	19 (10%)	64 (33%)	

*There were only considered patients treated with a systemic therapy in monotherapy (except for the group of corticosteroids and methotrexate).

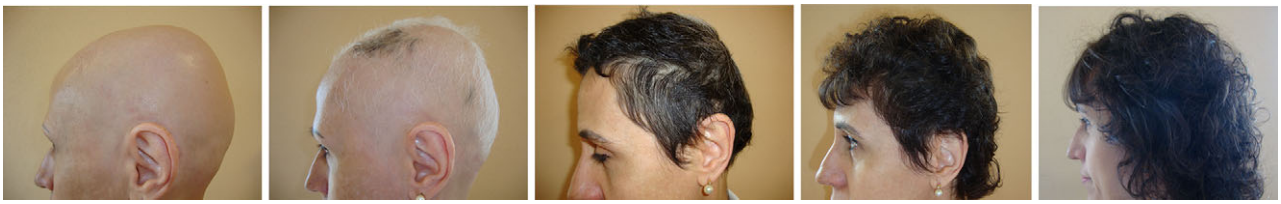

Figure 1 Alopecia areata universalis. Treatment with oral azathioprine 150 mg/day in a 48-year-old woman diagnosed with alopecia areata universalis: (a) Initial image, (b) 4 months of therapy: initial regrowth of white hair, (c) 8 months of therapy: regrowth of black hair, (d) 12 months of therapy: complete regrowth and (e) Image 18 months after the withdrawal of the drug (3 years after beginning the therapy): persistent regrowth without relapse.

Table 3 Published large series of alopecia areata totalis and universalis

	This study	Cho et el, 2012[50]	El-Zawahry, 2010[28]	Goh *et al.*, 2006[15]	Tosti *et al.*, 2006[9]	Seyrafi et al, 2005[17]	García-Hernández *et al.* 1999[7]
Number of patients with AAU/AAT	132	287	66	207	38	69	33
Males/females (%)	70/30	53/47	NS	NS	NS	46/54	60/50
AAU/AAT (%)	61/39	52/48	51/49	NS	NS	17/83	55/45
Early onset (<13 years)/Late onset (>13 years) (%)	29/71	39/61	NS	NS	NS	NS	47/53
Family history of AA (%)	12.1%	6.6%	NS	34.7%	NS	24.4%	22.8%
Nail involvement (%)	20%	7.3%	NS	NS	NS	NS	29.4%
Autoimmune comorbidities (%)	23.5%	38.4%	NS	NS	NS	NS	12.9%
Thyroid disease (%)	19.7%	3.1%	NS	25.1%	0%	8.9%	7.1%
Atopic dermatitis (%)	20.4%	7.2%	NS	49.2%	5.2%	NS	22.5%
Prognostic factors associated with poor prognosis	AAU, family history of AA	AAU, family history of AA	Baseline extent of AA	NS	NS	NS	Age of onset, nail changes

AA, alopecia areata; AAU, alopecia areata universalis; AAT, alopecia areata totalis; NS, not specified.

Nevertheless, adverse effects occur, so a positive benefit/risk ratio should always be present in the treatment of extensive AA. Although an acceptable rate of initial regrowth (64% in our study) may be obtained in AAU or AAT, the described percentage of full recovery is low (14% of persistent regrowth in our study), which is in concordance with previously published data.[3] Although local immunotherapy is considered the treatment of choice in patients with extensive AA,[2,19,20] in our experience it is not a well-tolerated therapy in some patients and our rate of response was inferior to the rates published in literature.[2] Therefore, although an interesting therapeutic option, immunotherapy is not always our treatment of choice. In our experience, oral mini-pulses with dexamethasone (0.1 mg/kg/day 2 days each week maintained at least 4 months) are an effective and well-tolerated therapy very useful for patients with extensive AA. The initial rate of response in our study with systemic therapies (30–80%, Table 2) is in concordance with the published data.[2,11–14,19–47]

Interestingly, 5% of our patients presented spontaneous regrowth. Some of them had not responded to previous systemic therapies and presented the spontaneous regrowth months or years after discontinuing the treatment, which suggests that response may be mainly influenced by the activity of AA in a specific moment. The rate of regrowth of AAU/AAT was markedly inferior to the published rate of limited patchy AA (80% within 1 year).[48]

Globally, several epidemiologic studies have identified prognostic factors associated with poor regrowth in AA patients, such as extensive hair loss,[9,49] long duration of hair loss,[13] nail involvement,[14] a history of atopy, other autoimmune diseases[14] and young age of first onset.[3] Goh et al[15] found that thyroid disease was statistically associated to severe forms of AA (AAT or AAU). In our study, only the clinical form of AAU and a positive family history of AA were associated with poor response in patients with extensive AA, although statistical significance was not achieved in the multivariate analysis. In concordance with our results, Cho et al[50] also found that the clinical form of AAU and the presence of family history of AA were associated with worse outcome (the latter only in patients with early-onset AAU). Acikgoz et al[13] described that disease duration (more than 4 years) was an important prognostic factor of poor therapeutic response to oral cyclosporine. Interestingly, the duration of extensive AA was not associated with

poor response in our study. In our experience, therapeutic response depends more on the activity of the disease in a specific moment rather than the global duration of AA. In fact, some patients of our study did not respond to a specific therapy used in the first months of evolution, and later a response was achieved with the same therapy when a second attempt was performed.

Our study presents some limitations. Firstly, it has a retrospective design. Secondly, the potential bias in the assessment of the effectiveness of the used therapies (some of the patients were treated concomitantly with oral and topical therapies). Nevertheless, the objective of the study was not to evaluate the effectiveness of different therapies for AAT and AAU, but to describe the clinical and epidemiological features, therapeutic response and prognostic factors in a large series of patients diagnosed with extensive AA.

In conclusion, extensive AA may affect men and women of any age, with two peaks of incidence at infancy and early adulthood. Treatment is challenging and should be discussed with the patient. Although the initial percentage of regrowth is acceptable (64%), the duration of response is usually short and the rate of permanent regrowth is low (14%). The prognostic factors for poor response were the presence of AAU and a positive family history of AA.

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