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The Alopecia Areata Consensus of Experts (ACE) Study: Results of an International Expert Opinion on Treatments for Alopecia Areata

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ABSTRACT

Background: A systematic review failed to identify any systemic therapy used in alopecia areata (AA) where use is supported by robust evidence from high quality randomized controlled trials (RCTs).

Objective: To produce an international consensus statement on the use and utility of various treatments for AA.

Methods: Fifty hair experts from 5 continents were invited to participate in a 3 round Delphi process. Agreement ≥66% was considered consensus.

Results: In the first round, consensus was achieved in 22 of 423 (5%) questions. Following a face-to-face meeting in round 3, overall, consensus was achieved for only 130 (33%) treatment specific questions. There was greater consensus for intralesional treatment of AA 19 (68%) followed by topical treatment 25 (43%). Consensus was achieved in 45 (36%) questions pertaining to systemic therapies in AA. The categories with the least consensus were phototherapy and non-prescription therapies.

Limitations: The study included a comprehensive list of systemic treatments for AA, but not all treatments used.

Conclusion: Despite divergent opinions amongst experts, consensus was achieved on a number of pertinent questions. The concluding statement also highlights areas where expert consensus is lacking and where an international patient registry could enable further research.

CAPSULE SUMMARY

1. This is the first international consensus document to comprehensively address expert assessment of treatment of AA
2. An international patient registry for AA is proposed to enable research to address areas where consensus is currently lacking, and data are limited.

INTRODUCTION

Alopecia areata (AA) is a relapsing and remitting autoimmune condition that produces variable degrees of hair loss in genetically susceptible individuals in response to as yet unknown environmental triggers. Randomized controlled trials (RCTs) of skin-directed therapies determine efficacy of individual agents but the overall utility and order of preference of use varies widely among dermatologists sub-specialized in alopecia areata (defined here as experts). A range of systemic medications are currently used to treat AA[1] however, a recent systematic review identified no systemic therapy supported by robust RCT evidence.[2] Limited evidence supports oral corticosteroids use, however there is no international consensus to guide systemic steroid therapy in AA.

Expert guidelines and consensus statements can guide appropriate therapy selection and treatment duration.[1, 3, 4] The Alopecia Areata Consensus of Experts (ACE) is an international expert consensus statement that aims to help medical practitioners select optimal AA management strategies.

This manuscript complements, but does not supersede international efforts to establish consensus on objective outcome measures and collection of meaningful data on AA.[5] Agreed outcome measures are critical enablers of RCTs evaluating existing and emerging treatments.

Patient age, disease duration and disease extent may influence treatment use in AA. For example, intralesional injections may be tolerated by adolescents and adults with limited disease extent, but poorly tolerated by children or by patients with extensive disease. In such cases, topical corticosteroids may be preferred, despite lower perceived efficacy. Systemic steroids may be considered for acute AA that has a favourable long-term prognosis but may not be favoured for chronic AA due to safety considerations associated with prolonged treatment.[3] Treatment algorithms specific to patient age and disease extent are considered in this statement.

METHODS

Expert Panel Selection

Fifty dermatologists from five continents with recognized expertise in hair and scalp disorder management were invited to participate.

Delphi survey

Questions, supported by a comprehensive literature review, were formulated to cover: epidemiology, aetiopathogenesis, diagnosis, investigation, treatment and prognosis of AA. Particular focus was placed on addressing controversial issues.

AA can undergo spontaneous remission. As the current episode duration is an important prognostic indicator, AA was categorised as acute (<12 months) or chronic (>12 months). Treatment questions were posed with respect to age-range defined subgroups (0-6 years; 7-12 years; 13-18 years and > 18 years).

The Delphi questionnaire was distributed using an online e-management survey system, Delphi Manager, maintained by the COMET (Core Outcome Measures for Effectiveness Trials) Initiative.[6]

Delphi process

The Delphi process aims to achieve convergence of opinion concerning real-world knowledge extrapolated from experts for predetermined topic areas.[7] Respondent answers are anonymised to minimise bias. A series of sequential iterations enables revision of judgement based on peer review to achieve consensus, where possible.[7-10] The Delphi technique has been validated in numerous studies to determine core outcomes [11] and define diagnostic criteria.[12, 13]

ACE involved two questionnaire rounds followed by a face-to-face meeting (Figure 1). Participants scored each question from 1-9 or “unable to score”. A score of 1 corresponded with strong disagreement and 9 indicated strong agreement.

After consideration of consensus values set by previous Delphi studies, [11, 13-15] consensus threshold for ACE was defined as ≥66% participant agreement (scores 7-9) or disagreement (scores 1-3) for each statement. Questions with scores 4-6 were determined as non-consensus. Consensus achieving questions were excluded from the next round, together with questions achieving ≤33% due to low probability of achieving consensus.

Questions with consensus values between 33% and 66% were included in the subsequent round.

Statistical analysis

R version 3.5.3 statistical software package was used for data analysis.[16]

RESULTS

Expert Panel

Of 50 invited hair experts, 41 (82%) completed round 1, 39 (78%) round 2 and 30 (60%) attended the face-to-face meeting at the 11th World Congress for Hair Research (WCHR) in Barcelona, Spain. Thirty-six (88%), routinely managed adults and children with hair loss disorders. Twenty-three (56%) work in public (academic institutions) and private practice, 13 (32%) exclusively in private, and 5 (12%) exclusively in public practice. Participants were from Europe (15; 37%); Asia (3; 7%), Australia (9; 22%) and North America (14; 34%).

Delphi rounds

Figure 2 summarizes this Delphi process. 423 questions related to treatment, prognosis and registry development. Expert consensus was achieved in 134 questions (32%), 22, 59 and 53 questions following rounds 1, 2 and 3 respectively. One round 2 question was revisited in round 3.

389 questions related specifically to treatment; topical therapy, intralesional treatment, phototherapy, non-prescription therapies, systemic therapy and timing of treatment discontinuation. Consensus was achieved in 130 (33%) treatment specific questions. The category with the greatest consensus was intralesional treatment 19 (68%) questions followed by topical treatment 25 (43%) questions.

The least consensus achieved was for phototherapy and non-prescription therapies.

1.0 Treatment Modalities

1.1 Topical Therapy

Consensus was achieved in 25 (43%) of 58 questions (Table 1) addressing; choice, duration, assessment of efficacy and site of application of topical treatment.

1.2 Intralesional Therapy

Consensus was achieved on the effectiveness of intralesional corticosteroid (ILC) in AA. Specifically, consensus was achieved in 19 (68%) of 28 questions relating to optimal dosage, administration and complications of ILC:

- A solitary patch of scalp AA is best initially treated with 2.5-5mg/ml of triamcinolone acetonide and should not be ≥10mg/ml. Caution is required near the frontal hair line due to increased risk of atrophy.
- Approximately 0.1ml of ILC should be injected 1cm apart into the dermis ± subcutis. Appropriate sites include areas of disease activity (e.g. exclamation mark hairs; positive hair pull test; black dots) or depigmented vellus hair, the entire patch and hairy scalp at the margin of an alopecic patch.
- The maximum dose of triamcinolone acetonide administered in one session to an average adult is 10-20mg.
- ILC injections are more effective than ultra/potent topical steroid, for inducing regrowth and a more durable remission.
- ILC's may be complicated by sub/dermal atrophy which is expected to resolve over 8-16 weeks or longer, but not <4 weeks.

1.3 Phototherapy

Consensus was not achieved on any of the 6 questions relating to phototherapy, including its effectiveness in AA.

1.4 Non-Prescription Therapies

Literature review identified reports of non-prescription treatment or complementary therapy use in AA. Therapies considered by the group included: aromatherapy, acupuncture, homeopathy,

ayurvedic medicine, traditional Chinese medicine, St John's wort, chiropractic, meditation, mindfulness and faecal transplantation. Consensus was not achieved on the use of any of these therapies.

1.5 Systemic Therapies

Consensus was achieved in 45 (36%) of 125 questions on the use of systemic therapies in AA. Therapies considered by the group included: systemic corticosteroids, ciclosporin, methotrexate, azathioprine. Efficacy of other second line agents (JAK inhibitors, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, IL-17A inhibitors, apremilast) were briefly explored.

Potential side-effects associated with long term use and the risk of relapse on dose reduction or treatment cessation are considerations that affect use of systemic therapies for AA.

1.51 Systemic corticosteroids

Consensus was achieved on the effectiveness of systemic corticosteroid therapy in AA. Specifically, consensus was achieved in 7 (23%) of 30 questions.

- Where appropriate, prednisolone (or prednisone) is the preferred choice of systemic corticosteroid and daily administration is optimal.
- Systemic corticosteroids are appropriate for treatment of severe AA in adolescents age 13-18 years. The initial dose of prednisolone may be 0.4-0.6mg/kg/day with gradual taper over >12 weeks to achieve durable remission.
- To achieve durable remission in adults, prednisolone may require gradual taper over >12 weeks.

1.52 Steroid Sparing therapies

Steroid-sparing agents are commonly used to mitigate the risk of side-effects associated with prolonged use of high-dose systemic corticosteroids.

Ciclosporin

Consensus was achieved in 5 (23%) of 22 questions.

- In adults with severe AA the target dose of ciclosporin should be 3-5mg/kg/day and maximum treatment duration should be 6-12 months.
- In adults with AA, ciclosporin is an effective monotherapy agent.

Methotrexate

Consensus was achieved in 5 (28%) of 18 questions. It was acknowledged that methotrexate is sometimes used as monotherapy in severe AA and agreed that:

- In adults the target dose of methotrexate should be 15-20 mg weekly.
- Methotrexate is appropriate for the treatment of severe AA in adolescents age 13-18 years.
- When methotrexate is commenced in patients <18 years with severe AA, the target dose should be 0.4 mg/kg/week.

Azathioprine

- Consensus was not achieved in any (14) questions.

Other

Consensus was achieved in 2 (25%) of 8 questions exploring the effectiveness of other steroid sparing therapies (JAK inhibitors, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, IL IL-17A inhibitors, apremilast) as monotherapy agents in adults.

- In adults with AA, JAK inhibitors are effective monotherapy agents; dapsone is not.

Efficacy in combination with systemic corticosteroids

Consensus was achieved in 16 (73%) of 22 questions:

- In adults, the following agents are effective when used in combination with systemic corticosteroids: methotrexate, ciclosporin or JAK inhibitors. Dapsone, simvastatin/ezetimibe, sulfasalazine or ustekinumab are not effective in combination with systemic steroids.
- Where appropriate, in adolescents (13-18 years), JAK inhibitors may be prescribed in combination with systemic corticosteroids. Adolescents (13-18 years), who have no history of chickenpox, should be vaccinated against varicella.
- In patients <18 years, the following agents should not, ideally be prescribed in combination with systemic corticosteroids: ciclosporin, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, IL-17A inhibitors and apremilast.

Preferred second line agent

Consensus was achieved in 1 (9%) of 11 questions

- If all treatments were equally reimbursed, JAK inhibitors would be the ideal choice of systemic therapy in adults.

1.6 First line treatment in Specific Age Groups

Table 2 summarizes consensus achieved regarding treatment of AA in specific patient age groups with respect to disease severity (SALT 0-30%, 31-50%, >50%) and chronicity (acute vs chronic). Consensus was achieved in 26 (36%) of 72 questions for treatment of acute and 15 (21%) of 72 questions for chronic AA.

1.61 Patients (>18 years) with Alopecia Areata

Acute AA

In adults the most appropriate first line treatment, when:

- SALT 0-30% is ILC.
- SALT >30% is oral or ILC, alone or combined.
- SALT >50% is topical or oral corticosteroids, alone or combined.

Chronic AA

In adults the most appropriate first line treatment, when:

- SALT 0-30% is ILC.
- SALT 31-50% is topical or ILC.
- SALT >50% is topical or oral corticosteroids.

1.62 Patients (<18 years) with Alopecia Areata

Acute AA

In children age <6 years, the most appropriate first line treatment, regardless of SALT, is topical corticosteroid. Consensus was not achieved on any use of ILC or oral corticosteroids in children <6 years with acute AA.

In children age 7-12 years, the most appropriate first line treatment, when:

- SALT 0-30% is topical corticosteroid. ILC is not advised.
- SALT 31-50% is topical corticosteroid.
- SALT >50% is topical or oral corticosteroids, alone or in combination. ILC alone is not advised.

In adolescents age 13-18 years, the most appropriate first line treatment, when:

- SALT 0-30% is topical or ILC. Combination oral and topical/ILC are not advised.
- SALT 31-50% is topical or oral corticosteroids.
- SALT >50% is topical or oral corticosteroids, alone or in combination.

Chronic AA

In children up to age 12 years, regardless of SALT, the most appropriate first line treatment is topical corticosteroid. Consensus was not achieved on the use of ILC in this cohort with chronic AA. While there was consensus on the use of oral corticosteroids in acute AA with SALT>50%, consensus was not achieved for chronic AA with SALT >50%.

In adolescents age 13-18 years, the most appropriate first line treatment, when:

- SALT 0-30% is ILC.
- SALT 31-50% is topical or oral corticosteroids.
- SALT >50% is topical or oral corticosteroids, alone or in combination.

1.7 Treatment Discontinuation

Consensus was achieved in 9 (50%) of 18 questions relating to the appropriate timing of systemic treatment discontinuation:

- Indications for discontinuation of systemic treatment (other than toxicity) include: complete response; full coverage of alopecic scalp with terminal hair; cosmetically acceptable regrowth or no response.
- Systemic treatment is best discontinued once complete regrowth has been achieved and maintained for six months or when regrowth is sufficient to be managed topically.
- If vellus regrowth fails to convert to terminal hair, systemic treatment should continue for six months, but not longer.

2.0 Prognosis

Consensus was achieved in 3 (9%) of 32 questions relating to prognostic indicators concerning impact of treatment on AA progression.

- Systemic corticosteroids reduce the risk of multifocal AA progressing to AT/AU.
- JAK inhibitors reduce the risk of multifocal AA progressing to AT/AU and of disease relapse.

3.0 Registry

Consensus was achieved in 1 (50%) of 2 questions

- Agreement on the development of an international AA registry.

DISCUSSION

ACE is the first large-scale international consensus study on expert use of treatments for AA. The lack of consensus for treatment reflects the paucity of RCT data to support choice from the available therapies. [2, 17]

Choice of therapy is clearly influenced by patient age, disease duration and disease extent. Safety concerns override treatment efficacy in children ≤6 years irrespective of disease severity. Systemic therapy may be considered as first line treatment in adolescents 13-18 years and in adults presenting with severe disease.

There was some consensus on the effectiveness of topical corticosteroids, topical calcineurin inhibitors, topical prostaglandin analogues and contact immunotherapy. Due to limited therapeutic options available to treat AA, these agents are used by hair experts to treat patients when ILC or systemic therapy are not appropriate due to patient age, disease extent or disease chronicity.

There was consensus on the effectiveness of ILC in AA, but their use in an individual is conditional on ability to tolerate multiple injections and the potential for sub/dermal atrophy. ILC were favored in adolescents and adults with limited disease, but topical or oral corticosteroids were preferred for extensive disease and topical corticosteroids were preferred in children.

There was consensus on the effectiveness of monotherapy with oral corticosteroids, ciclosporin and JAK inhibition therapy as well as combination therapy of oral corticosteroids together with ciclosporin or methotrexate when used as 'steroid sparing' agents. There was consensus on the use of systemic therapy in adults and children >13 with chronic severe AA, but not children <6 years. For children aged 7-12, there was consensus on the use of oral corticosteroids for acute, but not chronic AA. This takes into consideration the poorer prognosis of chronic AA in children 7-12 and the potential toxicity associated with the likely requirement for prolonged treatment.

Potential limitations of this study are noteworthy. The questionnaire design did not include all skin directed or systemic therapies for AA: systemic side effects were not elaborated upon, and specific

patient groups, e.g. pregnant women and breastfeeding mothers, or those with a prior history of malignancy were not explored. Though ambiguity and wording were considered at length in questionnaire design, feedback revealed a divergence of interpretation in some questions. This was addressed at the final face-to-face meeting and where appropriate, statements were clarified by the Chairperson before votes were cast. Finally, the face-to-face meeting was limited in time, and not chaired by an independent, non-voting individual, which may have introduced influencer bias.

CONCLUSION

In revealing the current diversity in expert opinion, ACE provides a framework to build consensus on treatment of AA through the identification of evidence gaps. ACE has united a global network of alopecia areata experts who recognize and support a global alopecia areata disease registry to facilitate surveillance of current and emerging treatments. ACE has also built a community of dermatologists connected with patient groups, pharmaco-economists and pharmaceutical representatives committed to improving patient outcomes and safety.

There is a call for robust research in therapeutics for AA.

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FIGURE LEGENDS

Figure 1: The Delphi process in ACE

Figure 2: Summary of results from all Delphi rounds

Table 1: Expert consensus for topical treatments in AA

Table 2: Consensus agreement for appropriate first line treatment(s) in specific patient age groups

Table 1

Topical Treatment	Consensus achieved n= (%)	Statements where consensus was achieved
Corticosteroids	15 (63%)	Topical corticosteroid can be prescribed as first line topical treatment; (alone or in combination) to treat scalp, eyebrow or beard AA. In scalp AA a potent topical corticosteroid should be applied daily for at least 6-12 weeks and at most 3-6 months. Potent topical corticosteroid should not be applied to the eyelashes. Ultra-potent (class IV) topical corticosteroid is more likely than potent (Class II and III) topical corticosteroid to induce regrowth. Topical corticosteroid should be first line treatment, irrespective of disease severity, in children up to 12 years of age. Compete regrowth, (rather than the first sign of regrowth or ≥ 50% regrowth), should be considered the clinical indication for cessation of topical corticosteroid.
Calcineurin inhibitors	4 (60%)	Topical calcineurin inhibitors can be applied to treat scalp, eyebrow or beard AA, but should not be considered first line topical treatment, alone or in combination, for beard AA.
Prostaglandin analogues	1 (25%)	Topical prostaglandin analogues (e.g. bimatoprost; latanoprost) can be prescribed as first line topical treatment; (alone or in combination) to treat eyelash AA.
Minoxidil	2 (22%)	Topical minoxidil can accelerate the linear growth rate of hair re-growing within a patch of AA. It can be prescribed in conjunction with other topical or systemic agents, but does not need to be used in all patients with AA.
Anthralin (Dithranol)	0 (0%)	No consensus was achieved.
Contact immunotherapy (Diphenylcyclopropenone, Squaric acid dibutyl ester, Dinitrochlorobenzene)	3 (33%)	Children with AU/AT/ophiasis should be offered contact immunotherapy prior to consideration of systemic therapy. Clinical indication for cessation of topical immunotherapy is complete regrowth, not first sign of regrowth.

	SALT 0-30%		SALT 31-50%		SALT >50%	
Patient Group	**Acute AA**	**Chronic AA**	**Acute AA**	**Chronic AA**	**Acute AA**	**Chronic AA**
0 - 6 years	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
7 - 12 years	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
13 - 18 years	Topical corticosteroids Intralesional corticosteroids	---------- Intralesional corticosteroids	Topical corticosteroids ---------- Oral corticosteroids	Topical corticosteroids ---------- Oral corticosteroids	Topical corticosteroids ---------- Oral corticosteroids Combination of oral and topical corticosteroids	Topical corticosteroids
Adults (>18years)	---------- Intralesional corticosteroids	---------- Intralesional corticosteroids	---------- Intralesional corticosteroids Oral corticosteroids Combination of oral and intralesional corticosteroids	Topical corticosteroids Intralesional corticosteroids	Topical corticosteroids ---------- Oral corticosteroids Combination of oral and topical corticosteroids	Topical corticosteroids ---------- Oral corticosteroids

Table 2

Figure 1

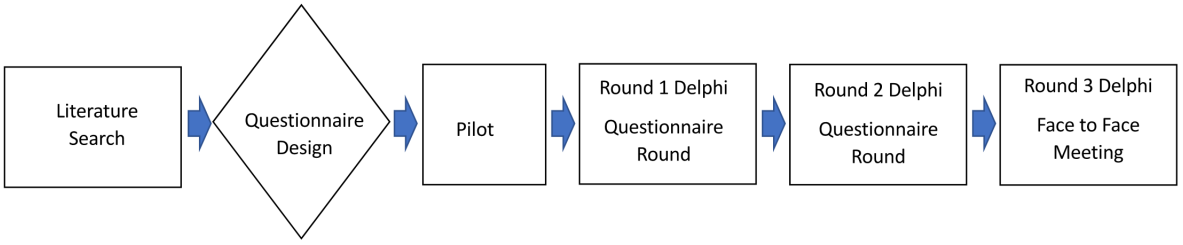
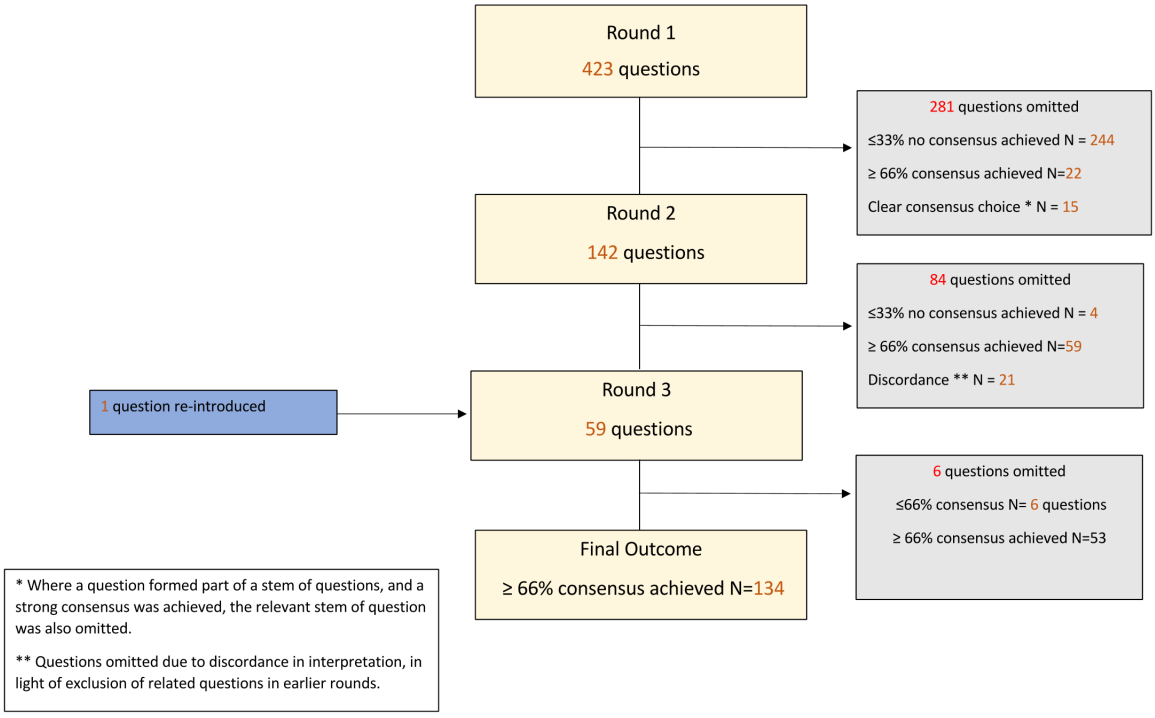


Figure 2


Round 1
423 questions
281 questions omitted
≤33% no consensus achieved N = 244
≥ 66% consensus achieved N=22
Clear consensus choice * N = 15
Round 2
142 questions
84 questions omitted
≤33% no consensus achieved N = 4
≥ 66% consensus achieved N=59
Discordance ** N = 21
1 question re-introduced
Round 3
59 questions
6 questions omitted
≤66% consensus N= 6 questions
≥ 66% consensus achieved N=53
Final Outcome
≥ 66% consensus achieved N=134
* Where a question formed part of a stem of questions, and a strong consensus was achieved, the relevant stem of question was also omitted.
** Questions omitted due to discordance in interpretation, in light of exclusion of related questions in earlier rounds.