The Alopecia Areata Consensus of Experts (ACE) study: Results of an international expert opinion on treatments for alopecia areata

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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.

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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 of 66% or greater was considered consensus.

Results: In the first round, consensus was achieved in 22 of 423 (5%) questions. After 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 nonprescription therapies.

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

Conclusion: Despite divergent opinions among 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. (J Am Acad Dermatol 2020;83:123-30.)

CAPSULE SUMMARY

- Robust treatment efficacy data for AA is limited.
- This is the first international consensus document to comprehensively address expert assessment of treatment of alopecia areata.
- An international patient registry for alopecia areata is proposed to enable research to address areas where consensus is currently lacking and data are limited.

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 who subspecialize in AA (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 corticosteroid 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 article complements, but does not supersede, international efforts to establish consensus on objective outcome measures and the collection of meaningful data on AA.[5] Agreed outcome measures are critical enablers of RCTs that evaluate 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 favorable long-term prognosis but may not be favored 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 5 continents with recognized expertise in hair and scalp disorder management were invited to participate.

Abbreviations used:

AA: alopecia areata
ACE: Alopecia Areata Consensus of Experts
IL: interleukin
ILC: intralesional corticosteroids
JAK: Janus kinase
RCT: randomized controlled trial
SALT: Severity of Alopecia Tool Score

Delphi survey

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

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

The Delphi questionnaire was distributed using an online e-management survey system, Delphi Manager, maintained by the 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 anonymized to minimize bias. A series of sequential iterations enables revision of judgment 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 2 questionnaire rounds followed by a face-to-face meeting (Fig 1). Participants scored each question from 1 to 9 or as *unable to score*. A score of 1 corresponded to strong disagreement, and 9 indicated strong agreement.

After consideration of consensus values set by previous Delphi studies,[11,13-15] the consensus threshold for ACE was defined as 66% or greater participant agreement (scores of 7-9) or disagreement (scores of 1-3) for each statement. Questions with scores of 4 to 6 were determined to indicate nonconsensus. Consensus-achieving questions were excluded from the next round, together with questions achieving 33% or less because of 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 was used for data analysis.[16]

RESULTS

Expert panel

Of 50 invited hair experts, 41 (82%) completed round 1, 39 (78%) completed round 2, and 30 (60%) attended the face-to-face meeting at the 11th World Congress for Hair Research in Barcelona, Spain. Thirty-six (88%) routinely treated adults and children with hair loss disorders. Twenty-three (56%) work in public (academic institutions) and private practice, 13 (32%) exclusively in private practice, 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

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

Overall, 389 questions related specifically to treatment, including topical therapy, intralesional treatment, phototherapy, nonprescription 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 nonprescription therapies.

Treatment modalities

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

Intralesional therapy. Consensus was achieved on the effectiveness of intralesional corticosteroids (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 to 5 mg/mL of triamcinolone acetonide and should not be 10 mg/mL or greater. Caution is required near the frontal hair line because of increased risk of atrophy.
- Approximately 0.1 mL of ILC should be injected 1 cm apart into the dermis and/or subcutis. Appropriate sites include areas of disease activity (eg, exclamation mark hairs, positive hair pull

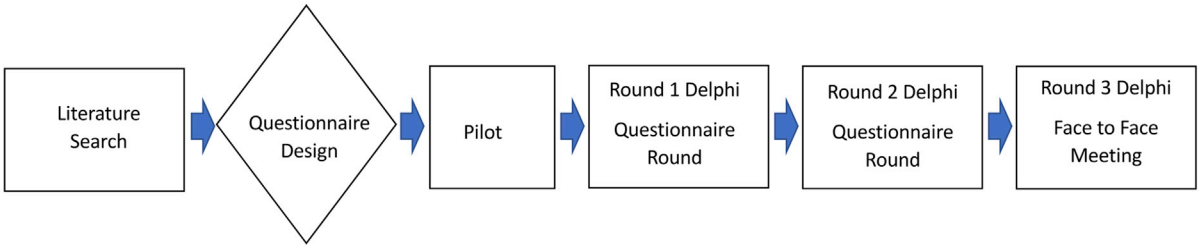

Fig 1. The Delphi process in the Alopecia Areata Consensus of Experts.

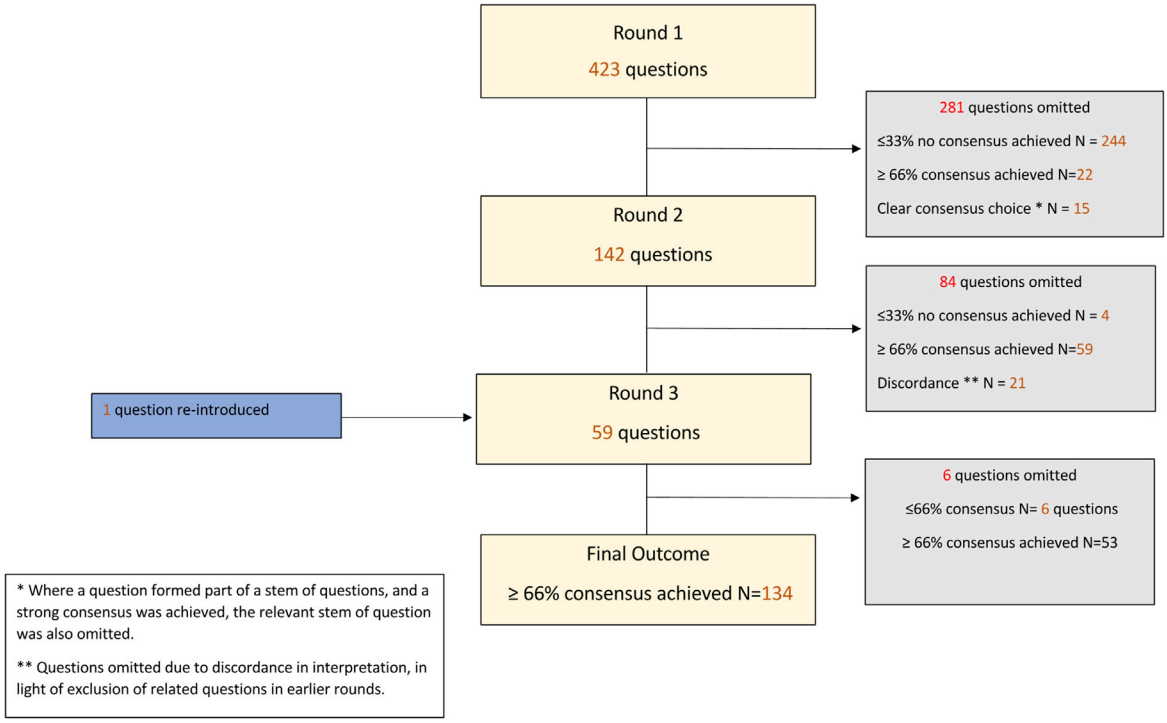

Fig 2. Summary of results from all Delphi rounds.

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 1 session to an average adult is 10 to 20 mg.
- ILC injections are more effective than ultrapotent/potent topical steroids for inducing regrowth and a more durable remission.
- ILCs may be complicated by subdermal/dermal atrophy, which is expected to resolve over 8 to 16 weeks or longer, but not less than 4 weeks.

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

Nonprescription therapies. Literature review identified reports of nonprescription 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 fecal transplantation. Consensus was not achieved on the use of any of these therapies.

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, cyclosporin, methotrexate, and azathioprine. The efficacies of other second-line agents (Janus kinase [JAK] inhibitors, mycophenolate mofetil, dapsone, simvastatin/ezetimibe, sulfasalazine, ustekinumab, interleukin [IL] 17A inhibitors, and apremilast) were briefly explored. Potential adverse effects associated with long-term use and the risk of relapse on dose reduction or treatment cessation are considerations that affect the use of systemic therapies for AA.

Table I. Expert consensus for topical treatments in alopecia areata

Topical treatment	Consensus achieved, n (%)	Statements where consensus was achieved
Corticosteroids	15 (63)	Topical corticosteroids 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 to 12 weeks and, at most, 3 to 6 months. Potent topical corticosteroids should not be applied to the eyelashes. Ultrapotent (class IV) topical corticosteroids are more likely than potent (class II and III) topical corticosteroids to induce regrowth. Topical corticosteroids should be first-line treatment, irrespective of disease severity, in children up to 12 years of age. Complete regrowth (rather than the first sign of regrowth or 50% or greater regrowth) should be considered the clinical indication for cessation of topical corticosteroids.
Calcineurin inhibitors	4 (60)	Topical calcineurin inhibitors can be applied to treat scalp, eyebrow, or beard AA but should not be considered the first-line topical treatment, alone or in combination, for beard AA.
Prostaglandin analogues	1 (25)	Topical prostaglandin analogues (eg, bimatoprost or 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 regrowing within a patch of AA. It can be prescribed in conjunction with other topical or systemic agents, but it does not need to be used for all patients with AA.
Anthralin (dithranol)	0 (0)	No consensus was achieved.
Contact immunotherapy (diphenylcyclopropenone, squaric acid dibutyl ester, dinitrochlorobenzene)	3 (33)	Children with alopecia universalis/alopecia totalis/ophiasis should be offered contact immunotherapy before systemic therapy is considered. The clinical indication for cessation of topical immunotherapy is complete regrowth, not first sign of regrowth.

AA, Alopecia areata.

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 aged 13 to 18 years. The initial dose of prednisolone may be 0.4 to 0.6 mg/kg/day with gradual taper over more than 12 weeks to achieve durable remission.
- To achieve durable remission in adults, prednisolone may require gradual taper over more than 12 weeks.

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

- **Cyclosporine:** Consensus was achieved in 5 (23%) of 22 questions.
  - In adults with severe AA, the target dose of cyclosporine should be 3 to 5 mg/kg/day, and the maximum treatment duration should be 6 to 12 months.
  - In adults with AA, cyclosporine 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 the following points were agreed upon:
  - In adults, the target dose of methotrexate should be 15 to 20 mg weekly.
  - Methotrexate is appropriate for the treatment of severe AA in adolescents aged 13 to 18 years.
  - When methotrexate is commenced in patients younger than 18 years with severe AA, the target dose should be 0.4 mg/kg/week.
- **Azathioprine**
  - Consensus was not achieved in any (n = 14) questions.

Table II. Consensus agreement for appropriate first-line treatment(s) in specific patient age groups

Patient group	SALT 0% to 30%		SALT 31% to 50%		SALT >50%	
	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	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
	Intralesional corticosteroids		Oral corticosteroids	Oral corticosteroids	Oral corticosteroids	
					Combination of oral and topical corticosteroids	
Adults (>18 years)	Intralesional corticosteroids	Intralesional corticosteroids	Intralesional corticosteroids	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids
			Oral corticosteroids	Intralesional corticosteroids	Oral corticosteroids	Oral corticosteroids
			Combination of oral and intralesional corticosteroids		Combination of oral and topical corticosteroids	

AA, Alopecia areata; *SALT,* Severity of Alopecia Tool Score.

- **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-17A inhibitors, and 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, cyclosporine, or JAK inhibitors. Dapsone, simvastatin/ezetimibe, sulfasalazine, or ustekinumab are not effective in combination with systemic steroids.
- Where appropriate, in adolescents (13-18 years old), JAK inhibitors may be prescribed in combination with systemic corticosteroids. Adolescents (13-18 years old) who have no history of chickenpox should be vaccinated against varicella.
- In patients younger than 18 years, ideally, the following agents should not be prescribed in combination with systemic corticosteroids: cyclosporine, 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.

First-line treatment in specific age groups. Table II summarizes consensus achieved regarding treatment of AA in specific patient age groups with respect to disease severity (Severity of Alopecia Score [SALT] of 0% to 30%, 31% to 50%, or >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.

Patients (>18 years) with alopecia areata.

- **Acute AA:** In adults, the most appropriate first-line treatment, when
  - SALT is 0% to 30%, is ILC.
  - SALT is 31 to 50%, is oral corticosteroids or ILC, alone or combined.
  - SALT is greater than 50%, is topical or oral corticosteroids, alone or combined.

- **Chronic AA:** In adults, the most appropriate first-line treatment, when
  - SALT is 0% to 30%, is ILC.
  - SALT is 31% to 50%, is topical or ILC.
  - SALT is greater than 50%, is topical or oral corticosteroids.

Patients (<18 years) with AA.

- **Acute AA:** In children younger than 6 years, the most appropriate first-line treatment, regardless of SALT, is topical corticosteroids. Consensus was not achieved on any use of ILC or oral corticosteroids in children younger than 6 years with acute AA.

  In children aged 7 to 12 years, the most appropriate first-line treatment, when
  - SALT is 0% to 30%, is topical corticosteroids. ILC is not advised.
  - SALT is 31% to 50%, is topical corticosteroids.
  - SALT is greater than 50%, is topical or oral corticosteroids, alone or in combination. ILC alone is not advised.

  In adolescents aged 13 to 18 years, the most appropriate first-line treatment, when
  - SALT is 0% to 30%, is topical or ILC. Combination oral and topical corticosteroids/ILC are not advised.
  - SALT is 31% to 50%, is topical or oral corticosteroids.
  - SALT is greater than 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 corticosteroids. Consensus was not achieved on the use of ILC in this cohort with chronic AA. Although there was consensus on the use of oral corticosteroids in acute AA with SALT of greater than 50%, consensus was not achieved for chronic AA with SALT of greater than 50%.

  In adolescents age 13 to 18 years, the most appropriate first-line treatment, when
  - SALT is 0% to 30%, is ILC.
  - SALT is 31% to 50%, is topical or oral corticosteroids.
  - SALT is greater than 50% is topical or oral corticosteroids, alone or in combination.

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

- Indications for the 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 6 months or when regrowth is sufficient to be managed topically.
- If vellus regrowth fails to convert to terminal hair, systemic treatment should continue for 6 months, but not longer.

Prognosis

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

- Systemic corticosteroids reduce the risk of multifocal AA progressing to alopecia totalis/alopecia universalis.
- JAK inhibitors reduce the risk of multifocal AA progressing to alopecia totalis/alopecia universalis and of disease relapse.

Registry

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

- There was 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 choices from among 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 and younger, irrespective of disease severity. Systemic therapy may be considered as first-line treatment in adolescents aged 13 to 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. Because of 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 because of 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 the ability to tolerate multiple injections and the

potential for subdermal/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, cyclosporine, and JAK inhibition therapy as well as combination therapy of oral corticosteroids together with cyclosporine or methotrexate when used as steroid-sparing agents. There was consensus on the use of systemic therapy in adults and children older than 13 years with chronic severe AA, but not in children younger than 6 years. For children aged 7 to 12 years, 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 aged 7 to 12 years 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 adverse effects were not elaborated upon, and specific patient groups, such as pregnant women, breastfeeding mothers, or those with a prior history of malignancy, were not explored. Although ambiguity and wording were considered at length in questionnaire design, feedback showed a divergence of the interpretation of 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 was not chaired by an independent, nonvoting 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 AA experts who recognize and support a global AA disease registry to facilitate surveillance of current and emerging treatments. ACE has also built a community of dermatologists connected with patient groups, pharmacoeconomists, 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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