Alopecia Areata in Latin America: Where are We and Where are We Going?

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ABSTRACT

Alopecia areata (AA) represents an underrecognized burden in Latin America (LA), severely impacting quality of life (QoL). This impact is exacerbated by limited access to specialized dermatologic care and therapies for AA within and among nations. Many of the unmet needs for AA globally also exist in LA. The region has geographic, ethnic, cultural, and economic conditions. With new AA medicines targeting immunologic pathways on the horizon, LA must prepare regarding regulatory issues, reimbursement, awareness, and education to give adequate and timely treatment for patients with AA. To address these issues, the Americas Health Foundation convened a panel of six dermatologists from Argentina, Brazil, Colombia, and Mexico who are experts in AA and its comorbidities for a 3-day virtual meeting to discuss AA diagnosis and treatment in LA and create a manuscript offering recommendations to

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address discussed barriers. This publication examines unmet AA needs in LA, treatment, and innovative therapies and recommends improving AA care. Access constraints to conventional and novel medicines hinder appropriate treatments for patients. Therapy initiation delays can affect QoL, mental health, and disease progression. People with AA face stigmas, discrimination, and misconceptions owing to a lack of disease awareness. With promising new treatments for AA on the horizon, all stakeholders must coordinate efforts to enhance LA's AA management landscape and improve patient outcomes.

Keywords: Alopecia areata; AA treatment; Dermatologic care in LA; Latin America; Targeted therapy in AA

Key Summary Points

AA represents an underrecognized burden in Latin America and severely impacts quality of life

Research on AA in Latin America is lacking

A panel of Latin American AA professionals assembled to compile this paper outlining the challenges to AA diagnosis and treatment, as well as advice for overcoming those barriers

Delays in access to diagnosis and treatment harm patients' quality of life, mental health, and increase disease development

Promising new targeted therapies for AA are available, and all stakeholders must work together to enhance access and availability of prompt diagnosis and treatment

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INTRODUCTION

Alopecia areata (AA) is an immune-mediated disease that occurs in genetically predisposed individuals. The immune system attacks the hair follicle (HF), resulting in variable degrees of hair loss [1–4]. It affects individuals of all ages, sexes, and ethnicities and is characterized by non-scarring alopecic areas that affect small areas or the entire scalp, hairy areas of the body, and nails [5]. Psychoneuroendocrine pathways and environmental variables like viral infections, psychosocial stress, socioeconomic deprivation, and urban life can also contribute to disease development [6].

In line with global trends, AA is not a common disease in Latin America (LA); yet it represents an often underrecognized burden with a high impact on the quality of life (QoL) of affected patients. LA is a remarkably diverse region with varying access to specialized dermatologic care and treatments for AA between and within nations. Many of the unmet needs for AA globally also exist in LA. However, the region has additional unmet needs specific to its unique geographic, ethnic, cultural, and economic circumstances. With promising new AA therapies on the horizon targeting the disease's immunologic pathways, LA must prepare regarding regulatory issues, reimbursement, awareness, and education to provide adequate and timely treatment for patients with AA. Thus, this manuscript aims to assess the unmet needs of AA in LA, the existing state of treatment in the region, the landscape of novel therapies, and to make recommendations for the region to improve access to AA management.

MATERIALS AND METHODS

Americas Health Foundation (AHF) assembled a panel of six expert dermatologists on AA from Argentina, Brazil, Colombia, and Mexico. On 6–8 April 2022, they had a 3-day virtual meeting to develop recommendations for overcoming the obstacles to AA diagnosis and treatment in

LA. AHF used PubMed, MEDLINE, and EMBASE to identify the experts. Augmenting this search, AHF contacted thought leaders from LA's medical community to confirm that the list accurately represented the needs. All the experts who attended the meeting are named authors of this manuscript.

AHF developed specific questions to address barriers limiting access to AA diagnosis and treatment in LA and assigned one to each panel member. A written response to each question was drafted by individual panel members on the basis of the literature review and personal expertise. The entire panel reviewed and edited each narrative during the 3-day conference through numerous rounds of discussion until a total agreement was reached. An AHF staff member moderated the discussion. When the panel disagreed, additional discussions were held until everyone agreed on the paper's content. The recommendations developed were based on the evidence gathered, expert opinion, and personal experience and were approved by the entire panel. After the conference, the final manuscript was distributed by email to the panel for review and approval. The authors retain control over the paper's content. All images were shared with the informed consent of the patients. This article is based on previously conducted studies and the panel's personal experience and does not contain any new studies with human participants or animals performed by any of the authors.

Box 1. Search Strategy

AHF searched alopecia areata on PubMed, MEDLINE, and EMBASE. "Treatment," "diagnosis," "quality of life," "patient journey" in combination with "Latin America," and "alopecia areata" were searched with dates ranging from 01/01/2016 until 04/10/2021. The articles identified were in English, Portuguese, and Spanish. Literature and research from LA were prioritized.

RESULTS

Epidemiology

Epidemiologic data on AA, necessary to further understand disease behavior and course, are scarce and often conflicting globally. This issue is more prominent in LA, where the available data stem from very few studies [7–12]. AA prevalence is estimated at 0.2–3.8% in Mexico [10]. In Peru, AA prevalence ranges from 0.1–0.2%, accounting for 0.7–3.5% of all dermatology consults in Lima, and 2% of all new cases in dermatology clinics [12]. In Colombia, a prevalence of 0.05% was found in 2018, with a higher proportion in women [13]. Of note, the number of new cases increased during 2017–2019 but declined from 2020 to 2021, likely owing to fewer consults during the COVID-19 pandemic.

In a survey conducted by the Brazilian Society of Dermatology, AA accounted for 1.2% of all dermatologic consultations [8]. In comparison, in a major referral center in Brazil, it accounted for 16.2% of pediatric consultations and 29.4% of first-time visits [8, 10]. This contrast indirectly highlights gaps in knowledge of AA management at the primary care level, as many patients are referred for care at specialized centers.

The estimated global incidence of AA varies between 0.57% and 3.8%, with a lifetime risk of 2.8% [14–16]. In the United Kingdom, the average prevalence is 0.58% in adults and higher in the Asian population compared with the white population [17]. In the USA, the cumulative lifetime incidence is 2%, with 0.1–0.2% prevalence in the general population [15, 18]. The First National Health and Nutrition Examination Survey, conducted from 1971 to 1974, identified AA prevalence in the USA as 1–2 in 1000 people [18]. This study remains relevant because it is the largest, and more recent studies corroborate its results [19]. Two recent studies in Greece and Japan estimated the prevalence of AA at 1.27% and 2.45%, respectively. Cumulative AA incidence has been found to increase almost linearly with age [14, 20, 21].

In the USA, the prevalence of severe and very severe forms of AA, such as alopecia totalis (AT), alopecia ophiasis (AO), and alopecia universalis (AU) is low: 0.08%, 0.02%, and 0.03%, respectively. Some studies have found a higher prevalence of AA in Black populations than in white or Asian, both in general and severe subtypes [22, 23]. This finding may be relevant in LA owing to the substantial Black ancestry of the region's population. However, US population-based studies that included Hispanic/Latino populations found no differences in odds ratio compared with white populations.

Burden of Disease and Comorbidities

Despite its autoimmune component and substantial impact on QoL, payers, physicians, and the general population sometimes consider AA a cosmetic concern [24]. AA is associated with a negative impact on QoL, affecting patients personally, socially, financially, and physically. Over time, cumulative disability may perpetuate poor self-esteem, social disconnection, negative coping strategies, and failure to achieve full-life potential [24]. The uncertainty, social stigma, and misconceptions surrounding AA also contribute to the burden of the disease. A Brazilian study evaluated QoL in patients with AA using the Short-Form Health Survey and found an impact on psychological, emotional, and social aspects [25]. A Colombian multicentric survey used the validated Skindex-29 evaluated QoL and included 11 patients with AA. The presence of any dermatological lesion led to some degree of alteration in QoL and high emotional impact was reported.[26].

In addition, AA is associated with various comorbidities. Among these are psychiatric conditions found in 65–74% of people with AA, the most common being depression (38%) and generalized anxiety disorder (39–62%), approximately eightfold higher than in the general population [14]. A Mexican study found QoL disturbance in 77.6% of adults, 65.9% had signs of depression or anxiety, and 12.8% were at risk of death by suicide. A total of 76.7% of children had QoL disturbance, and 6.3% showed signs of depression [27, 28]. A Chilean study found the following comorbidities in patients with AA: depression (15%), allergic rhinitis (11%), anxiety (6.5%), hypothyroidism (3.9%), and vitiligo (2.6%) [7].

Box 2. Comorbidities Associated with AA		
Allergic rhinitis	Celiac disease	Systemic lupus erythematosus
Anxiety	Depression	Systemic sclerosis
Asthma	Pernicious anemia	Thyroid disease
Atopic dermatitis	Rheumatoid arthritis	Type 1 diabetes mellitus
		Ulcerative colitis

Pathophysiology

AA results from complex interactions of genetic factors, immune system dysregulation, neuroendocrine pathways, and environmental factors.

Genetic Factors

Susceptibility to AA is related to multiple genes involved in immune response, including *CTLA4*, *IL2RA*, *IL2*, *IL21*, *NOTCH4*, *MICA*, *EOS*, *HLA*, *IKZF4*, *IL17A/IL17RA*, *peroxiredoxin 5*, *syntaxin 17*, *HLA*, and *ULBP* [4, 29, 30]. *ULBP* gene mutations are strongly associated with AA but no other autoimmune diseases; this gene encodes the activating ligands of the receptor associated with NKG2D [27, 29–32]. Specific human leukocyte antigen (HLA) alleles such as DQB1*03 and DRB1*1104 are susceptibility markers for AA development [29]. HLA-DR11 and HLA-DQ7 alleles are associated with AU or AT [33].

Loss of Immune Privilege and Autoimmunity

The HF is a site of immune privilege (IP), a state of tolerance to antigen introduction. Loss of IP in anagen is a critical step in the immunopathology of AA. IP is characterized by reduced expression of major histocompatibility complex (MHC) class I /II and β2-microglobulin; increased production of immunosuppressive molecules such as transforming growth factor-beta 2 (TGF-β2), migration inhibition factor, insulin-like growth factor 1, α-melanocyte-stimulating hormone (MSH), indoleamine 2, 3-dioxygenase and cortisol, impaired antigen-presenting cells, and an extracellular matrix barrier that prevents the entry of CD8+ lymphocytes and natural killer (NK) cells [1, 4, 29, 34]. The cause of IP loss is unknown; however, it is believed to be secondary to skin microtrauma, infectious or emotional stress, bacterial superantigens, mast cell degranulation, or increased perifollicular secretion of interferon gamma (IFN-γ) [4].

Autoimmunity associated with AA is due to the ectopic expression of MHC I molecules in the bulge during anagen, leading to the autoantigen recognition by CD8+ T cells and subsequent naive T-cell activation and differentiation into Th1, Th2, Th17, or T$_{Reg}$ cells [4, 30, 34, 35]. Although a specific autoantigen in AA has not been identified, melanocyte-derived proteins have been proposed. Peptides derived from Gp100, and the melanoma antigen recognized by T lymphocytes stand out.

In acute phases, there is a predominantly peribulbar and a lesser intrafollicular inflammatory infiltrate in anagen HFs, composed of CD8+ (20–40%), CD4+ (60–80%) T lymphocytes, and NK cells, which impact matrix cell proliferation, causing the loss of IP and accumulation of autoreactive T cells that induce telogen prematurely [1, 4, 29, 32, 34]. Further, increased ectopic expression of MHC I and II lead to increased IFN-γ, perpetuating autoreactivity [30]. The inflammatory infiltrate decreases in chronic phases, and there is a miniaturization of the HF [4, 30]. Inflammatory infiltrate generally spares the HF stem cell reservoir, so alopecia is usually reversible [36].

AA onset is associated with the increased secretion of IFN induced by CD8+ NKG2D+ T cells (necessary and sufficient for disease development) that generate the loss of IP in the HF [4, 37, 38]. The activation of Th1 cells and secreted cytokines cause positive feedback that perpetuates the Th1 response and activates tumor necrosis factor (TNF) and IL-1α, and IL-1β that inhibit HF proliferation [30, 34]. Additionally, the loss of IP causes follicular epithelial cells to produce IL-15, which leads to positive and persistent feedback on the cytotoxic activity of NK cells and CD8+ T lymphocytes that produce IFN-γ [4, 29, 39] IL-15 activates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway [4, 29, 34, 39].

There is a positive correlation between IL-17 serum levels and the severity and duration of hair loss in AA [34]. Likewise, although some studies show an increase in Th2 cells that produce several interleukins, the role of humoral immunity has not been studied in AA [30, 34, 38]. What is clear is that there is dysregulation in the Th1, Th2, and Th17 pathways. The presence of proinflammatory serum markers such as IL-2 or TNF in patients with AA suggests that the disease is a systemic disorder not limited to HF [30, 34, 38].

Neuroendocrine Pathways

Approximately 23% of patients with AA have experienced an emotional event or crisis before disease onset [1, 32]. Neuropeptides produced by cutaneous nerves, such as substance P (SP), the peptide related to the calcitonin gene (PRCG), and the vasoactive intestinal peptide (VIP) modulate skin inflammation. Substance P mediated stress-induced hair growth inhibition in mice. PRCG induces mastocyte degranulation and liberation of TNF-α and IL-10, which may decrease antigenic presentation by inhibiting CD86 expression on Langerhans cells (LC) [40]. Additionally, expression of VIP receptors 1 and 2 is downregulated in the bulbs of patients with AA compared with controls. Still, their ligands are typical in nerve fibers, suggesting altered signaling mediated by VIP

receptors [29, 37]. Of note, patients with AA have higher corticotropin-releasing hormone and α-MSH levels in the epidermis, HF, and sebaceous glands, indicating local hormonal–neurogenic system activated by higher cortisol levels after stressful events [30].

Environmental Factors

Several lifestyle and environmental factors are associated with a higher risk of AA. Autoimmune diseases, vaccines, and viral infections (SARS-COV-2, Epstein Barr virus, Hepatitis B and C viruses) have been identified as AA triggers in genetically predisposed individuals [41]. Additionally, smoking, alcohol consumption, sleep disturbances, obesity, and medications, including some biologics, immune checkpoint inhibitor anti-PDL1, anticonvulsants, and abacavir, among others, have also been associated with triggering AA [1].

Diagnosis

AA diagnosis is primarily based on clinical history and physical examination [35]. The most common AA presentation consists of one or several auto-resolutive alopecic areas with normal or slightly erythematous skin, follicular openings, and without scarring [29]. However, multiple coalescent areas are present in some cases and may progress to diffuse scalp or body involvement. The scalp is involved in almost all AA cases, most commonly affecting the occipital area [42]. Clinical forms of AA are described in Box 3. Nail involvement can occur in 10.5–38% of cases, with a spectrum of findings from subtle nail plate pitting to total nail dystrophy [43–45]. These findings are more frequently associated with severe AA and are a poor prognostic factor (see images 1, 2, and 3). Dermoscopy may provide a valuable tool to rule out differential diagnosis and a minority of patients may benefit from a histopathological analysis [29, 35, 46]. An important differential diagnosis in LA is syphilis and traction alopecia because of their high prevalence [47, 48]. See Table 1.

Table 1 Dermoscopy and histopathologic findings and differential diagnosis of AA

	Characteristics
Dermoscopy	Peladic or exclamation mark hairs
	Broken hairs
	Vellus
	Yellow points (empty follicles)
	Black points or cadaveric hairs (a follicle opening with oxidated lipids mimicking hair keratin)
	Coudability hairs (long bent peladic hair)
	Irregular constrictions of Pohl–Pinkus (pseudomonilethrix)
	White or dystrophic hair shafts (regrowth areas)
	Circular (pigtail) hairs (found in active lesions)
Histopathology	Biopsy samples: should be taken from the margin of a patch; two samples for horizontal and vertical sections can maximize accuracy
	Findings:
	Peribulbar infiltrate of lymphocytes and Langerhans cells (in active lesions)
	Eosinophils, plasma cells, and mast cells
	HF destruction, trichomalacia, chronic infiltrate of histiocytes and giant cells (predictors of poor prognosis)
	*The horizontal section can examine additional indicators:
	Decreased anagen-to-telogen ratio
	Decreased terminal-to-vellus hair ratio (1:1 instead of 7:1)
	Decreased follicular count (seen in the subacute or chronic phases)

Table 1 continued

	Characteristics
Differential diagnosis	Telogen effluvium
	Traction alopecia
	Trichotillomania
	Syphilis
	Temporal alopecia triangularis
	Frontal fibrosing alopecia
	Pseudopelade of Brocq
	Lichen plano pilaris

AA severity is defined by clinical involvement and impact on QoL. Although several clinical evaluation tools exist, the Severity Alopecia Tool (SALT), a scale used to quantify AA severity based on the percentage of affected scalp, is the most frequently employed in clinical trials [49]. SALT calculates severity by dividing the scalp into four sections (back 24%, top 40%, both sides 18% each). A SALT score of $\geq 50\%$ indicates severe AA [49, 50]. The AA investigator global assessment (AA-IGA) can provide clinically relevant evaluations of severity and treatment response. This score also defines severe AA as a percentage of hair loss $\geq 50\%$ and considers eyebrows, eyelashes, and nails [8, 51].

Although these scales are quick and easy-to-use instruments, in this panel's experience, AA severity is not routinely assessed by most dermatologists in clinical practice in LA. Nevertheless, their application allows an objective assessment of AA progression, determining the necessity for systemic treatment and evaluating clinical response. No published consensus exists on the optimal strategy for assessing AA's QoL and psychosocial effects. Currently, no QoL assessment tools tailored to AA and validated for LA languages are currently available. Nonetheless, in this panel's experience, the

Dermatology Life Quality Index (DLQI) is the most used in LA.

The Brazilian AA consensus proposes evaluating severity with the following scale: mild AA: 20% or less scalp hair loss; moderate AA 21–49% scalp hair loss; and severe AA 50–100% scalp hair loss [52]. A mild or moderate severity rating increases to the next level if any of the following are present: negative impact on psychosocial functioning, noticeable involvement of eyebrows or eyelashes, inadequate response after 6 months of treatment, diffuse (multifocal) positive hair pull test consistent with rapidly progressive AA [52]. Implementing this severity scale could provide substantial benefits for treatment decisions and disease monitoring.

Box 3. Clinical forms of AA [53]

Patch AA: circumscribed, single, or multiple round areas of alopecia

Total AA: alopecia affecting the entire scalp

Universal AA: alopecia affecting the entire body

Ophiasis AA: alopecia in the lateral and occipital regions of the scalp

Inverted ophiasis AA (sisaipho): alopecia in the frontal–parietal area, sparing the lateral and occipital regions

Diffuse AA: overall decrease in density, without patches

AA incognita: diffuse total hair loss with positive pull test, yellow dots, short, miniaturized regrowing hairs, but without nail involvement

Diffuse acute and total alopecia of the female scalp (DATAFS): progressive and rapid hair loss, usually progressing to total AA within 3 months

Reticular AA: active, stable, and resolving patches present at the same moment

Marie Antoinette syndrome (also called canities subita): acute episode of diffuse alopecia with very sudden "overnight" greying with preferential loss of pigmented hair

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Prognosis and Course

The disease course of AA is unpredictable. Patients with AA maintain the possibility for hair regrowth for many years and possibly for life. However, if left untreated, AA may reduce the number and reserve of HF, rendering the condition irreversible. Approximately 5% of AA cases will develop into AT or AU [6]. The belief that these individuals will lose the ability to regrow hair likely stems from the ineffectiveness of conventional treatments [29]. Negative predictors for hair restoration are outlined in Box 4 [14, 35].

Box 4. Negative Predictors for Hair Restoration

Concomitant nail lesions	Hair loss beginning before puberty
Comorbidities of other autoimmune diseases	Lesions lasting longer than 1 year
Down syndrome	Ophiasis pattern
Familial history	

Local LA data on prognosis and disease progression are sparse. However, global data indicates that 34–80% of individuals recover spontaneously 1 year following disease onset; 15–25% of this population loses all head and/or body hair, and $\leq$ 10% of this group will recover [31]. In AT and AU, satisfactory regrowth is $\leq$ 10% [31]. Notably, these articles predate the use of biologics and JAK inhibitors in AA treatment. This panel's experience is consistent with global data in that severe forms of AA have a poor response to conventional treatments.

AA Treatment

Despite great improvements in understanding pathophysiology and therapy targets for AA, no treatments have been licensed by regulatory agencies in LA, and few elsewhere. Since reviews have failed to identify a therapy supported by robust evidence, treatments are based on expert opinion or consensus [2]. This might soon change, given several ongoing clinical trials evaluating different therapies, including biologics and small molecules [52, 54–57].

AA treatment is based on disease severity and extension, patient age, comorbidities, and patient expectations, among other variables. Some patients will have spontaneous hair regrowth without treatment. An international AA treatment consensus reported 68% agreement on intralesional corticoids, 43% for topical treatments (topical corticoids 63%, calcineurin inhibitors 60%, contact immunotherapy 33%), and 36% for systemic therapies [2]. However, more evaluation of the efficacy of these treatments is required to foster evidence-based treatment decisions. These decisions, including when to scale therapy up or down, should be based on disease severity and control and monitored throughout the disease course.

Explaining the nature and progression, the treatment's efficacy, and side effects, and establishing reasonable treatment expectations with patients, is an often overlooked but crucial part of management. Moreover, it is critical to clarify that, to date, no treatment has altered the long-term disease course. Consequently, the need for maintenance treatment remains to be determined. AA treatments, mechanisms of action, and their availability and accessibility in LA can be found in Table 2.

New Treatment Advances

New targeted therapies are expected to provide more effective and safer options than conventional treatment, especially for severe to very severe AA.

The JAK-STAT pathway in AA involves JAK1, JAK2, JAK3, and TYK2. After JAK phosphorylation, the STATs are translocated to the nucleus, where they bind DNA and trigger targeted gene transcription. This pathway is essential for maintaining innate and adaptive immunity. In AA, it has been determined that it functions as a

Table 2 Current treatments used for AA in LA

Type of treatment	Active component	Response rate or effectivity	Used for AA Severity	Adverse effects	Availability	Accessible through public healthcare
Topical therapy	Clobetasol	Foam 0.05%: 25% had 50% response. Cream under occlusion: 28.5% had at least a 50% response. Cream 0.05%: 85% of children has at least a 50% response	Monotherapy in mild cases or in combination with systemic therapy in moderate–severe cases	Folliculitis, local skin atrophy, striae, acneiform rash, telangiectasias, dyschromia, adrenal suppression	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✔ MEX ✔
	Minoxidil	60% response with minoxidil 5% [58]	As adjuvant therapy	Hypertrichosis, local irritation [55]	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✔ COL ✔ MEX ✘
Topical immunotherapy	Diphencyprone	30–48% [8] global 28.3–87.9% AT and AU 72.2% for chronic extensive AA [59]	Moderate–severe	Hyperpigmentation, hypopigmentation, folliculitis lymph node enlargement, severe dermatitis, blisters, and flu-like symptoms	ARG ✔ BRA ✔ COL ✔ MEX ✘	ARG ✘ BRA ✘ COL ✘ MEX ✘

Table 2 continued

Type of treatment	Active component	Response rate or effectivity	Used for AA Severity	Adverse effects	Availability	Accessible through public healthcare
Phototherapy	NB-UVB	52.9% response week 12 (23 sessions) [60]	Mild–moderate	Pain, erythema, edema, blisters	ARG ✔* BRA ✔* COL ✔* MEX ✔*	ARG ✘ BRA ✔ COL ✔ MEX ✔
	Excimer laser/light treatment	Satisfactory regrowth in 50.2% patients [61]			ARG ✔* BRA ✔* COL ✔* MEX ✔*	ARG ✔* BRA ✘ COL ✔* MEX ✘
Intralesional corticosteroids	Triamcinolone	60–75%	Mild–moderate	Pain, hemorrhage at puncture sites, headache, reversible local cutaneous atrophy, dyschromia, systemic absorption	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✔ MEX ✘
Systemic corticosteroids	Prednisone	> 75% of regrowth with pulse therapy in 43% of total and 51% of children	Moderate–severe	Adrenal suppression, weight gain, Cushing's syndrome, hypertension, osteoporosis, diabetes, immunosuppression, cataracts, acne	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✔ COL ✔ MEX ✔
	Dexamethasone	51.8% achieved SALT50 after 9 months of oral mini pulse (< 5 mg/d, 2 days/week) [62]			ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✔ COL ✔ MEX ✔

Table 2 continued

Type of treatment	Active component	Response rate or effectivity	Used for AA Severity	Adverse effects	Availability	Accessible through public healthcare
Conventional systemic immunomodulators	Methotrexate	Regrowth of > 50% in 63.2% of patients [63]	Moderate–severe	Hematologic toxicity, teratogenicity, immunosuppression, hepatotoxicity, interstitial pneumonitis	ARG ✓ BRA ✓ COL ✓ MEX ✓	ARG ✗ BRA ✗ COL ✓ MEX ✓
	Cyclosporine	< 6 months: 74% (53–88%); ≥ 6 months: 73% (47–89%); Recurrence after monotherapy: 55% (6–96%); CsA $^+$ systemic corticosteroids: 28% (6–72%) [64]		Nephrotoxicity, immunosuppression, and arterial hypertension	ARG ✓ BRA ✓ COL ✓ MEX ✓	ARG ✗ BRA ✗ COL ✓ MEX ✓
	Azathioprine	Regrowth of 52.3% after 6 months of treatment [65]		Gastrointestinal symptoms, elevated liver enzymes, pancreatitis, hematologic toxicity	ARG ✓ BRA ✓ COL ✓ MEX ✓	ARG ✗ BRA ✗ COL ✓ MEX ✓

Table 2 continued

Type of treatment	Active component	Used for AA Severity	Response rate or effectivity	Adverse effects	Availability	Accessible through public healthcare
JAK inhibitors	Ruxolitinib	Moderate–severe	6 months: 95% had > 50% regrowth 12 weeks: 75% had > 50% regrowth	Mild infections, mainly of the upper respiratory tract, dyslipidemia, leukopenia, increased liver enzymes, headache, gastrointestinal complaints, fatigue, acne, weight gain, thrombosis, acne, nausea, increase in serum creatin phosphokinase, herpes zoster**	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✘ MEX ✔
	Tofacitinib [66]		Oral 10 mg/day: Reduction in SALT 70% (50–90%) Topical twice/day: Partial regrowth in 30% of patients		ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✘ MEX ✘
	Ritlecitinib [54]		50% achieve SALT 30 score and 25% SALT 90 score after 24 months		ARG ✘ BRA ✘ COL ✘ MEX ✘	ARG ✘ BRA ✘ COL ✘ MEX ✘
	Baricitinib [57]		Oral 2 mg/day: 33.3% Oral 4 mg/day: 54.4% Severity of alopecia score: < 20% at 36 weeks		ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✘ MEX ✘

Table 2 continued

Type of treatment	Active component	Response rate or effectivity	Used for AA Severity	Adverse effects	Availability	Accessible through public healthcare
Biologics	Dupilumab [67]	32.5% of patients achieved SALT 30 22.5% achieved SALT 50 15% achieved SALT 75 After 48 weeks of treatment	Moderate–severe	Conjunctivitis (in patients with atopic dermatitis) Injection-site reactions, headache, fatigue. Some reports of new onset or recurrent cases of AA after initiation for other indications [55]	ARG ✔ BRA ✔ COL ✔ MEX ✔	ARG ✘ BRA ✘ COL ✘ MEX ✘
	Abatacept	3–50% hair regrowth		Infections, headache, upper respiratory tract infection, nasopharyngitis, and nausea		

Checkmark ✔ = yes, ✘ = no

*Limited availability (only in major cities and select centers)

downstream effector of the IFN-γ and IFN-γc cytokine receptors, yet other mechanisms may also be involved. Therefore, JAK-STAT inhibition disrupts the positive feedback loop between the follicular cell and cytotoxic CD8$^+$ NKG2D$^+$ T cells. Animal studies have shown that the inhibition of the JAK-STAT pathway promotes hair growth by stimulating HF stem cells and an anti-quiescence signal during telogen, hence expediting reentry into anagen. JAK inhibitors also prevent the development of inflammatory Th17 cells and Th1 and Th2 differentiation [29].

TEC family (tyrosine kinase expressed in hepatocellular carcinoma) members ITK, RLK, and TEC have been identified as key components of T-cell-receptor signaling. TEC kinases contribute to T-cell-receptor-driven actin reorganization and cell polarization, which are required for productive T-cell activation. They are important mediators of pathways that control the differentiation of CD4$^+$ T-helper cells [69, 70]. Additionally, TEC is expressed in mast cells and regulates their activation [71].

Tofacitinib citrate was the first JAK inhibitor successfully used to treat AA [72–74]. Since then, other specific JAK inhibitors have been developed for AA treatment, including oral baricitinib (JAK1-2), oral ritlecitinib (JAK3/TEC), oral and topical ruxolitinib (JAK1-2), CTP-543 (JAK1-2), and oral brepocitinib (TYK2/JAK1), all of which have shown promising results [73, 75]. Other drugs being evaluated for AA are dupilumab (Anti-IL-4Rα, targeting IL4 and 13), abatacept (CTLA-4), and aprelimast [55, 56].

Access to AA Treatment in LA

Access to dermatologists is limited in LA and often entails lengthy waits. Specialists are mostly concentrated in major metropolitan regions. This impacts timely and accurate diagnosis and treatment initiation. In resource-limited settings such as LA, access to dermatologic treatment depends on medication cost, physician knowledge, cultural and socioeconomic variables, and disease awareness [76]. While most AA treatments are available throughout the region, even some conventional treatments

like systemic corticosteroids are not accessible through public healthcare. So even when the drug is available, there is a lack of approvals and consequent coverage/reimbursement in many LA countries because most AA treatments are used "off label." To access basic treatment, patients often must incur out-of-pocket expenses, an option that is not feasible for all. Because of this, patients in LA often do not have adequate responses to AA therapy because they have not had access to appropriate treatment. Sometimes, this leads to irreversible HF damage and cumulative effects on QoL.

As mentioned previously, only a small proportion of patients may develop severe to very severe AA, necessitating expensive systemic treatment [6]. However, delivering targeted treatment to the appropriate patients, particularly those with severe or refractive disease, must be a priority since it can result in significant benefits for the patient, society, and healthcare systems [77, 78]. This benefit is currently not possible in most LA countries because treatments for moderate to severe AA, such as JAK inhibitors, topical immunotherapy, and biologics, are not routinely reimbursed by public healthcare systems. Patients must either incur substantial out-of-pocket expenses or seek access through legislative intervention. For mild AA cases, topical and intralesional corticosteroids provide an adequate response. However, currently accessible therapies for moderate to severe AA, mainly systemic corticosteroids and conventional immunomodulators, do not offer a safe and efficacious long-term therapy alternative. Consequently, access to novel treatment options is required.

CONCLUSION

There are unmet needs in LA's AA management continuum, including a lack of local data to understand the epidemiology, burden, and disease behavior. While AA has a low prevalence, it poses a substantial burden on QoL and can be financially straining for patients with the disease. In LA, access barriers to conventional and novel treatments hinder patients' ability to receive opportune and appropriate treatment.
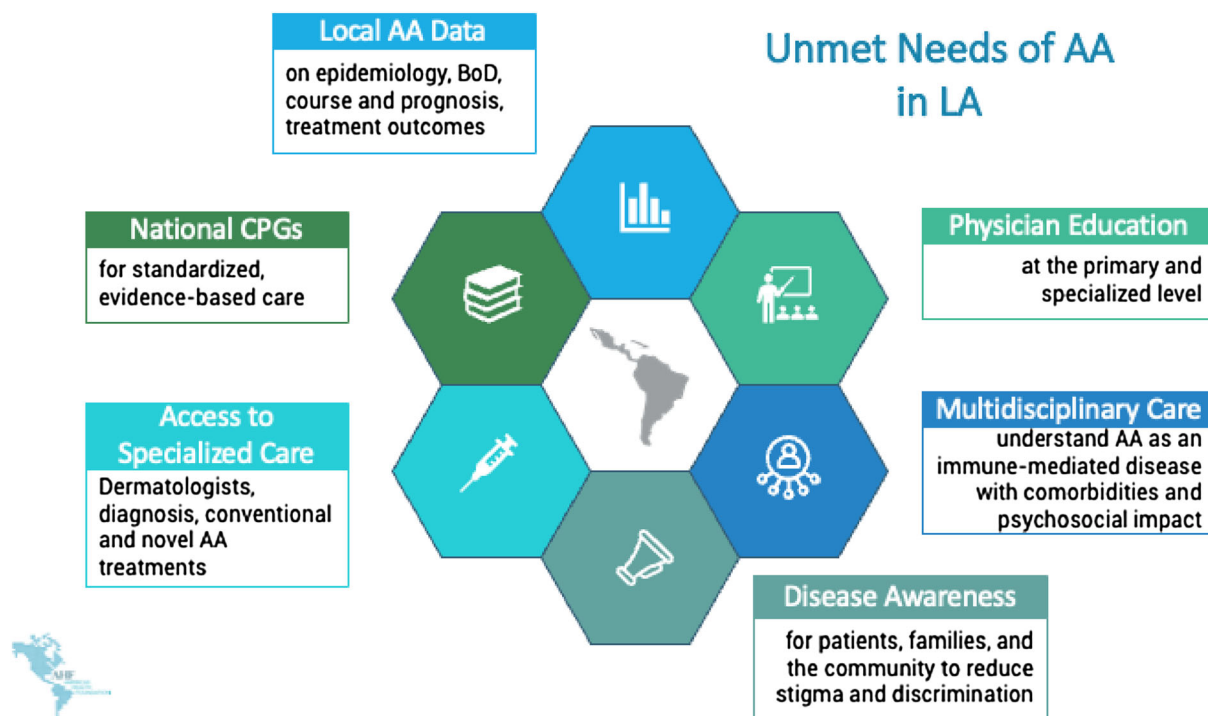
Fig. 1 Unmet needs of people with alopecia areata in Latin America

These delays in treatment initiation can lead to sustained impacts on patients' QoL, mental health, and potentially irreversible disease progression. A lack of disease awareness among the general population has resulted in stigmas, discrimination, and misconceptions surrounding patients with AA.

On the other hand, inadequate education on the correct AA treatment and diagnosis at the primary care level and even among specialists further contributes to suboptimal care. This insufficient knowledge may be in part due to the infrequent use of clinimetric scales in clinical practice to assess disease severity and QoL impact, as well as the lack of clinical practice guidelines for AA in most LA countries, resulting in unstandardized diagnostic criteria, workups, control evaluations, and treatment decisions. Additionally, AA must be recognized by both payers and healthcare providers as an autoimmune disease that is not limited to hair loss and requires specialized multidisciplinary care led by a dermatologist focused on disease and comorbidity control and psychosocial

support. The unmet needs of AA in LA are summarized in Fig. 1.

With promising new treatment options for AA on the horizon, now is the time to act and improve the AA landscape in LA. To overcome the barriers that AA presents in the region and improve patient outcomes, concerted efforts are necessary by all stakeholders. With this in mind, the authors propose the following recommendations:

Recommendations

1. **Generate local data** on AA epidemiology; burden of disease; genetic, demographic, and environmental factors; disease course and prognosis; treatment outcomes; pharmacoeconomic analyses (**Academia, medical societies, government**).
2. **Develop national clinical practice guidelines for AA** tailored to each country's unique context to promote standardized, evidence-based decisions that incorporate all relevant stakeholder perspectives, including medical societies, patient

advocacy groups, government institutions, and payers. If this is not possible in the short to medium term, each country's leading medical societies should reach a consensus on which guidelines physicians should adopt (**Medical societies, academy, ministries of health**).

3. **Increase access to AA treatment**, both conventional and novel, in both public and private healthcare systems by:

    a. **Governments, medical societies, and patient organizations:** breach inequity gaps in access to specialized care by developing and strengthening collaborative networks within and among LA countries.

    b. **Regulatory agencies:** improve local approval times for treatments once they are approved by international agencies such as the Food and Drug Administration or European Medicines Agency.

    c. **The pharmaceutical industry**: seek regulatory approval for AA treatments, even in "small" markets in benefit of the patient.

    d. **Government and payers**: ensure widespread coverage and reimbursement of basic and advanced AA treatments and explore the potential cost–benefit of providing targeted therapy to patients with moderate–severe AA.

4. **Increase physician education about** AA:

    a. **Primary care level**: basic diagnosis and treatment, appropriate referral situations.

    b. **Dermatologist:** pathophysiology, triggers, comorbidities, signs of activity, prognosis factors, and novel treatments, including biologics, JAK inhibitors, and other small molecules.

    c. **Other specialists:** because AA is often associated with comorbidities, specialists such as endocrinologists, psychologists and psychiatrists, infectious disease specialists, rheumatologists, pediatricians, and internal medicine physicians should be aware of the disease. (**Medical societies, healthcare institutions, medical community**)

5. **Ensure comprehensive care** with a multidisciplinary approach for AA management, including psychosocial support, individualized strategies for comorbidity management, and using clinimetric scales for disease severity and QoL evaluation for all AA patients at diagnosis and continuously throughout the disease course. (**Dermatologists or treating physician**)

6. **Physicians must provide patients and their families with education** on the unpredictable course of AA, its relationship with psychosocial factors, effectiveness, and adverse effects of treatments, and establish reasonable outcome expectations. Creating dedicated AA patient organizations or support groups could improve the emotional burden of the disease [77, 78]. (**Dermatologists**)

7. **Create public awareness campaigns about AA** for the public to dispel misconceptions, stigmas, and discrimination surrounding the disease and educate policymakers on the importance of timely and adequate treatment. (**Medical societies, industry, governments, PO**)

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Compliance with Ethics Guidelines. All images were shared with the informed consent of the patients. This article is based on previously conducted studies and the panel's personal experience and does not contain any new studies with human participants or animals performed by any of the authors.

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