J Res Development 6(2), 2021, 53-61
An Open Access Journal
ISSN: 2311-3278

Journal of
Research and Development

Research Article | Homepage: www.arabianjbmr.com | AGJ

CONSENSUS ON THE TREATMENT OF ALOPECIA AREATA: MAYO HOSPITAL PAKISTAN

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ABSTRACT

Alopecia areata is a common autoimmune disease that encountered world-wide. Many modalities have been used but no one was universally effective. Zinc sulphate has been used in the treatment of many skin diseases. Zinc supplement is popular trace element gave for hair loss. To estimate the efficacy of oral zinc sulfate in patients of patchy alopecia areata presenting in a tertiary care hospital. Randomized controlled trail study design was employed. Study was conducted at Dermatology Department Unit-II, Mayo Hospital, Lahore. Total 60 clinically diagnosed cases of patchy alopecia areata of scalp as non scarring alopecia for less than one year duration were included in the study. Patients were divided into two groups A & B by draw box methods, 30 patients in each group. In group A, oral zinc was given in the form of zinc sulfate capsules in a dose of 5 mg/kg/day in a single or two divided doses according to weight of the patient. In group B, patients received placebo in the form of brown sugar capsules once a day. Patients were followed on monthly basis till recovery or maximum upto four months. The response was assessed according to SALT score (annexure 1).10,11 Photographs were taken on each visit. All the above information was collected through a predesigned proforma. The data was entered and analyzed by using SPSS version 12.0. Mean of patients in Group-A and in Group-B was 33.23±7.03 and 33.00±7.55 years. In Group-A mean Salt score before and after treatment was 7.53±4.79 and 3.26±4.32. While in Group-B mean Salt score before and after treatment was 6.05±4.34 and 5.46±4.98. Improvement was defined as 50% or more reduction in SALT score. As per this criteria in Group-A there were 20(66.7%) patients who had improvement while in Group-B only 2(6.7%) patients had improvement. According to p-value improvement was significantly associated with treatment groups. i.e. (p-value=0.000) Improvement rate of Group-A was high as compared to that of Group-B. Among male and female patients significant improvement was seen in Group-A patients. Based on these results it can be said that oral Zinc therapy had a positive and significant role in treating patients with patchy alopecia areata. In terms of SALT scoring system improvement (>50% reduction in SALT score.) was seen in 66.7% patients who were treated with oral zinc.

ARTICLE INFO

Keywords:
Zinc, Patchy alopecia areata, SALT scoring system, Improvement

Article History:
Received: 10 May 2021
Accepted: 26 Sep 2021
Available Online: 05 Dec 2021

1. INTRODUCTION

Alopecia areata is an autoimmune disorder of hair characterized by rapid and complete or partial loss of hair inone or more, round or oval, nonscarring patches that can affect any hairbearing area.[1]In 10% cases of alopecia areatapitting and sandpaper changes are seen in the nails.[2, 3] At any given time 0.2% of the world population sufferfrom alopecia areata with an estimated lifetime risk of 1.7%.[2]Usual age of onset for alopecia areata is less than 25 years with an equal incidence in males and females.[4] Various genetic and environmental factors are suggested in etiology of alopecia areata.[1] About 20% have family history.[5] Association with other autoimmune disorders such as Hashimoto's thyroiditis, pernicious anaemia, diabetes, rheumatoid arthritis, vitiligo and myasthenia gravis suggest its autoimmune basis.[1, 6] Data shows that 34-50% of patients will recover within one year, 14-25% may progress to alopecia totalis or universalis from which recovery is less than 10 %.[7] Many treatment modalities have been used for its treatment including topical and systemic corticosteroids, minoxidil, phototherapy, dithranol, contact immunotherapy and others.[1]Oral zinc is used in various dermatological disorders such as cutaneous leishmaniasis, recalcitrant viralwarts, recurrent aphthous stomatitis, Bechet's disease, rosacea and perifolliculitis abscedens et suffodiens.[8]

2. REVIEW OF LITERATURE

2.1 Historical aspects

The first clinical description of alopecia areata is attributed to Celsus (14 to 37 B.C.), and the designation alopecia areata is by Sauvages. Hebra demonstrated the incorrectness of the hypothesis of fungal etiology as proposed by Willan and Gruby (1843). Later, Von Baresprung proposed the neurotrophic theory, and Jacquet elaborated the dystrophic theory, considering

the disease to be caused by infectious focuses, particularly dental, a hypothesis today that has been totally discarded. Nowadays, alopecia areata is interpreted as an autoimmune disease with a genetic substrate.[11, 12]

2.2 Dynamic of hair loss

Hair follicle growth occurs in cycles. Each cycle consists of a long growing phase (anagen), a short transitional phase (catagen) and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle beginning the cycle again. There are considerable variations in the length of the three phases, with the duration of the anagen determining the type of hair produced, particularly its length. Normally about 100 strands of hair reach the end of their resting phase each day and fallout.[13] Hair loss in non scarring alopecias, including alopecia areata essentially represents a disorder of hair follicle cycling [14]. It is believed that in AA, an as yet unidentified trigger stimulates an autoimmune lymphocytic attack on the hair bulb. This inflammation is specific for anagen hairs and causes anagen arrest. A disruption of the growing phase, that is anagen arrest, causes abnormal loss of anagen hairs (anagen effluvium), clinically recognized as dystrophic anagen hair with tapered proximal ends and lack of root sheaths. A related but distinct entity observed very frequently in women is 'telogen effluvium'. This is an umbrella term inclusive of conditions wherein the affected hairs undergo an abrupt conversion from anagen to telogen (anagen release), clinically seen as localized shedding of hair in the telogen and morphologically identified as hair with a depigmented bulb [15].

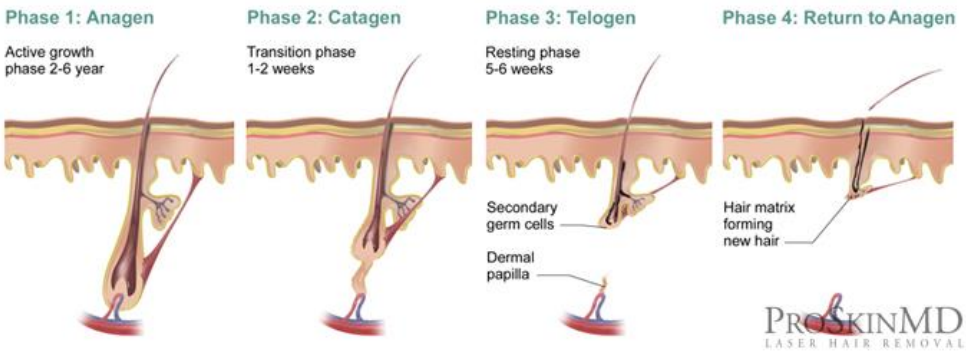

Figure 1
Phases of hair growth

2.3 Epidemiology & demography

AA is a relatively frequent disease with a prevalence of 0.1%-0.2% worldwide[16, 17]. Among different races and ethnic groups, the prevalence can range, from 0.9% to 6.9% [18]. Notably, individuals with Down's syndrome seem to have a slightly higher incidence [19]. In the United States, one study reported that about 14.5 million patients suffer from AA, constituting about 2% of the national population [18], while another study suggested that only about 5.3 million in the U.S. are clinically affected [20]. Overall, AA seems to account for about 0.7%-3% of all patients in the United States [21], and about 2% in the United Kingdom [19]. The likelihood of diagnosis of AA during one's lifetime is thought to be around 1.7%, regardless of demographical location, affecting both genders and all age groups [16, 22]. Although both men and women are affected, men seem to be more frequently associated with [18]the more severe cases of alopecia than women [18]. The onset of AA is more likely early in life For example, various studies have reported that the peak incidence of AA occurs prior to 20years of age, with about 60% of cases experiencing their first manifestation of hair loss during their late childhood/early adulthood [18, 19]. Others studies report that only 44% of patients manifest disease onset before their 20s, but still agree that less than half of AApatients are diagnosed after age 40 [16]. In fact, study of a cohort of Asian AA patients reported that 85.5% of the AA patients had their first episode of AA before the age of 40 years [21].

2.4 Pathophysiology

The exact pathophysiology of alopecia areata remains unknown. The most widely accepted hypothesis is that alopecia areata is a T-cell–mediated autoimmune condition that is most likely to occur in genetically predisposed individuals.[25]

2.5 Autoimmunity

Much evidence supports the hypothesis that alopecia areata is an autoimmune condition. The process appears to be T-cell mediated, but antibodies directed to hair follicle structures also have been found with increased frequency in alopecia are at a patients compared with control subjects. Using immune fluorescence, antibodies to anagen-phase hair follicles were found in as many as 90% of patients with alopecia areata compared with less than 37% of control subjects. Studies in humans also reinforce the hypothesis of autoimmunity. Studies have shown that hair re-grows when affected scalp is transplanted onto SCID (severe combined immunodeficiency) mice that are devoid of immune cells. Autologous T lymphocytes isolated from an affected scalp were cultured with hair follicle homogenates and autologous antigen-presenting cells. Following initial re-growth, injection of the T lymphocytes into the grafts resulted in loss of re-grown hairs. Injections of autologous T lymphocytes that were not cultured with follicle homogenates did not trigger hair loss. [26]

A similar experiment on nude (congenitally athymic) mice failed to trigger hair loss in re-grown patches of alopecia areata after serum from affected patients was injected intravenously into the mice. However, the same study showed that mice injected

with alopecia areata serum showed an increased deposition of immunoglobulin and complement in hair follicles of both grafted and non-grafted skin compared with mice injected with control serum, which showed no deposition. In addition, research has shown that alopecia areata can be induced using transfer of grafts from alopecia areata–affected mice onto normal mice. Transfer of grafts from normal mice to alopecia areata–affected mice similarly resulted in hair loss in the grafts. [26]

2.5.1 Genetics

Many factors favor a genetic predisposition for alopecia areata. The frequency of positive family history for alopecia areata in affected patients has been estimated to be 10-20% compared with 1.7% in control subjects[27]. Another gene of interest is the interleukin 1 receptor antagonist gene, which may correlate with disease severity. Finally, the high association of Down syndrome with alopecia areata suggests involvement of a gene located on chromosome 21. In summary, genetic factors likely play an important role in determining susceptibility and disease severity. Alopecia areata is likely to be the result of polygenic defects rather than a single gene defect. The role of environmental factors in initiating or triggering the condition is yet to be determined. [28]

2.5.2 Innervation and vasculature

Another area of interest concerns the modification of perifollicular nerves. The fact that patients with alopecia areata occasionally report itching or pain on affected areas raises the possibility of alterations in the peripheral nervous system. Circulating levels of the neuropeptide calcitonin gene-related peptide (CGRP) were decreased in 3 patients with alopecia areata compared with control subjects. CGRP has multiple effects on the immune system, including chemotaxis and inhibition of Langerhans cell antigen presentation and inhibition of mitogen-stimulated T-lymphocyte proliferation. [29] CGRP also increases vasodilatation and endothelial proliferation. Similar findings were reported in another study, in which decreased cutaneous levels of substance P and of CGRP but not of vasoactive intestinal polypeptide were found in scalp biopsy specimens. The study also noted a lower basal blood flow and greater vasodilatation following intradermal CGRP injection in patients with alopecia areata compared with control subjects. More studies are needed to shed light on the significance of these findings. [29]

2.6 Environmental input

The onset and progression of AA probably requires input from multiple factors including; genetics[31], stress [32], hormones [33], diet [34], infectious agents [35], vaccinations [36], and several other possible inputs. Potentially, these factors may increase or reduce susceptibility to AA onset, influence the disease pattern, severity, duration, and response to treatment, by modifying the physical and biochemical status of the immune system and/or hair follicles [37]. Different factors may be prevalent for different individuals with AA. The potential impact of genetics on AA is described elsewhere in this issue and will not be considered here; it suffices to say that specific genes are likely to play very important roles in AA [31]. However, the influence may vary from person to person. For some, genetics may play the dominant role with little environmental input. For others, environmental influence may be more dominant while genetics makes a relatively minor contribution. Thus, when dermatologists and scientists argue in support of “stress” being a trigger versus “infectious agents” versus “genetic susceptibility,” each of these factors may be important for different subsets of patients. Many hypotheses have been raised as to what may trigger and modulate AA but the specific environmental risk factors and their relative contributions are still largely to be determined.[38]

2.7 Stress

Differential expression of several stress related genes was identified in the brains of the AA-affected mice. In the skin of AA mice and human patients, there is increased expression of local HPA hormone receptors such as corticotrophin-releasing hormone receptor 2 (CRH-R2) at both mRNA and protein levels [44, 45]. CRH-R2 is a major receptor in dermal compartments and its aberrant expression could contribute to the local HPA axis and response to inflammation [44, 46]. Estrogen receptor 1 (esr1)expression was also elevated in AA-affected mouse hair follicles and esr1 is known to regulate the HPA response to stress [44]. This suggests that the observed changes to the local skin HPA and the aberrant central HPA activity are a consequence of the immune system activity in AA and may be expressed as an inability to cope with stress. The evidence that stress can modulate AA is less clear, but the functional data thus far suggests it is possible. CRH can induce mast cell differentiation from hair follicle mesenchyme [47] and the above suggests CRH/receptor activity is high in AA skin. Differences in neuropeptide substance P expression occur with AA development [48, 49].

2.8 Diet

There is argument as to the true significance, if any, of dietary iron intake in hair loss and AA [53]. However, some dermatologists evaluate iron deficiency as an aid to diagnosis and iron supplements are sometimes used as a adjunctive treatment for women with hair loss [51].In mice, it was found that dietary soy oil increases resistance to the development of AA [31]. A high soy oil content diet was given to mice grafted with AA skin and re-growth of hair on the skin graft was observed while comparative controls on a normal diet developed AA. The antioxidant enzyme enhancement and estrogen receptor binding properties of soy derivatives might block the onset of AA in mice [31, 54].

2.9 Classic forms

2.9.1 Alopecia totalis

There is total loss of terminal hair of the scalpwithout affecting other body hair, there can also beungual involvement.

2.9.2 Alopecia universalis

There is total loss of body hair, involving thescalp, eyelashes, eyebrows, beard and mustache,armpits and genital areas. In general, it occurs in association with a variety of ungual lesions. Besides these forms that are considered classic,there are atypical presentations of alopecia areata:[60]

2.10 Atypical Forms

2.10.1 Sisaifo type alopecia areata (inverse ophiasis)

In this form, the hair loss involves the entirescalp except for the lower margins, along the line oftemporo-occipital implantation. It is the inverse clinical image of the ophiasis form.

2.10.2 Reticular alopecia areata

In this form, multiple alopecic plaques occur separated by narrow bands of preserved hair, conferring areticulated aspect to the picture.

2.10.3 Diffuse alopecia areata

In this form, the hair loss is acute and widespread. It can be the initial form, mainly among children and adolescents, or can develop from plaqueforms. Most of these cases develop into the more serious alopecia totalis or universalis forms. It is the mostdifficult form to diagnose, demanding a differentialdiagnosis with acute telogen deffluvium, androgenetic alopecia and also alopecia syphilitica. Thus necessitating complementary exams in general and evenhistopathological exam by biopsy.[31, 60]

3. DIFFERENTIAL DIAGNOSIS

Though alopecia areata is a form of non scarring alopecia, it is sometimes confused with different varieties of scarring alopecia as well. This is also because many alopecia types are biphasic in their natural history. The first step, therefore is to distinguish between scarring and non scarring alopecias. Scarring alopecias have loss of follicular ostia, or atrophy. Clinical inflammation is frequently, but not always, present. Histologic inflammation may be present. Ultimately, histologic confirmation is the best method to confirm the presence of a fibrosing/ scarring process with loss of hair follicles. A few entities in scarring alopecias are Lichen planopilaris, Central centrifugal cicatricial alopecia, Pseudopelade, Discoid lupus and Traction alopecia. The main confounders in diagnosis are the other varieties of non scarring alopecias.[67] They are:

- Trichotillomania
- This condition probably causes most confusion and it is possible that it coexists with alopecia areata in some cases. The incomplete nature of the hair loss in trichotillomania and the fact that the broken hairs are firmly anchored in the scalp (i.e. they remain in the growing phase, anagen, unlike exclamation mark hairs) are distinguishing features.
- Tinea capitis
- The scalp is inflamed in tinea capitis and there is often scaling but the signs may be subtle.
- Early scarring alopecia.
- Telogen effluvium.
- Anagen effluvium (drug-induced) may mimic diffuse alopecia areata.
- Systemic lupus erythematosus.
- Secondary syphilis.
- Loose anagen hair syndrome
- This is a disorder of abnormal anagen hair anchorage. It is commonly found in children and has an autosomal dominant inheritance [69].
- ADTA
- Acute diffuse and total alopecia (ADTA) is a new subtype of alopecia areata with favorable prognosis. ADTA has been reported to have a short clinical course ranging from acute hair loss to total baldness, followed by rapid recovery, sometimes even without treatment [70].
- SISAPHO
- This is an unusual form of Alopecia, in which a band-like pattern is found on the frontal hairline. This can be clinically confused with frontal fibrosing alopecia. The opposite of ophiasis type, where hairs are lost centrally and spared at the margins of the scalp, is called sisiapho. It may mimic androgenetic alopecia [71].

Raunatha et al. in their case report have demonstrated infantile scurvy also, as a cause of diffuse non scarring alopecia of the scalp [72].

3.1 HISTOPATHOLOGY

The histology findings in AA vary with the duration of disease. It is ideal to perform two 4 mm punch biopsies including subcutaneous fat. One specimen should be processed with vertical sectioning and the other with horizontal sectioning. If only a single specimen is planned, horizontal sections will give a better representation of the histopathology. A horizontally-sectioned scalp biopsy is helpful in confirming the diagnosis of AA but also provides information about possible regrowth. [77] However, Chaitra *et al*. reported that vertical ections are adequate to ascertain the diagnosis. [78] The best place to take a biopsy is at the advancing border of hair loss. This helps to view the hair follicles at different levels in dermis to quantify the hair follicle density, follicle diameter, and to assess the proportion of hair follicles in various stages. A mean count of less than one follicle/mm ^{2} usually indicates less chances of regrowth. [77] In acute cases, peribulbar and intrabulbar lymphocytic inflammatory infiltrate around anagen follicles, resembling 'swarm of bees,' is characteristic. The lymphocytes are mainly around the hair matrix and dermal papilla and spare the bulge area, causing follicular edema, cellular necrosis, microvesiculation, and pigment incontinence. A dense lymphocytic inflammation can cause weakening of the hair shaft resulting in a trichorrhexis nodosa-like fracture, leading to the exclamation mark hairs. [79] In subacute lesions, high proportion of catagen/telogen hair follicles are seen. In chronic cases, follicular miniaturization with variable inflammatory infiltrate are seen in papillary dermis. The terminal to vellus

hair ratio is decreased to 1:1 in contrast to 7:1 in normal population. Androgenetic alopecia also shows follicular miniaturization, but more number of telogen hairs with decreased anagen to telogen ratio may be a clue towards AA[77].

4. TREATMENT

Treatment is not mandatory because the condition is benign, and spontaneous remissions and recurrences are common. Treatments used are believed to stimulate hair growth, but no evidence indicates they can influence the ultimate natural course of alopecia areata. Treatment modalities usually are considered first according to the extent of hair loss and the patient's age. Assessment of the efficacy of a treatment must be considered with care because the condition is highly unpredictable in presentation, evolution, and response to treatment. Little data exist regarding the natural evolution of the condition. For example, in patients with less than 40% scalp involvement, a study showed no benefit with treatment (minoxidil 1% and topical immunotherapy) over placebo.[80] The high spontaneous remission rate makes clearly assessing the true efficacy of a therapy difficult unless appropriate controls with placebo treatment are studied. For patients with extensive alopecia areata (>40% hair loss), little data exist on the natural evolution. The rate of spontaneous remission appears to be less than in patients with less than 40% involvement. Vestey and Savin[81] reviewed 50 patients with extensive alopecia areata. Of the 50 patients, 24% experienced spontaneous complete or nearly complete regrowth at some stage during the observation period of 3-3.5 years. The relapse rate is high in patients with severe forms of alopecia areata. Patients with alopecia totalis or alopecia universalis usually have a poorer prognosis, and treatment failure is seen in most patients with any therapy. Because alopecia areata is believed to be an autoimmune condition, different immunomodulators have been used to treat this condition. Additional treatment options for alopecia areata include minoxidil and other treatment modalities.[81]

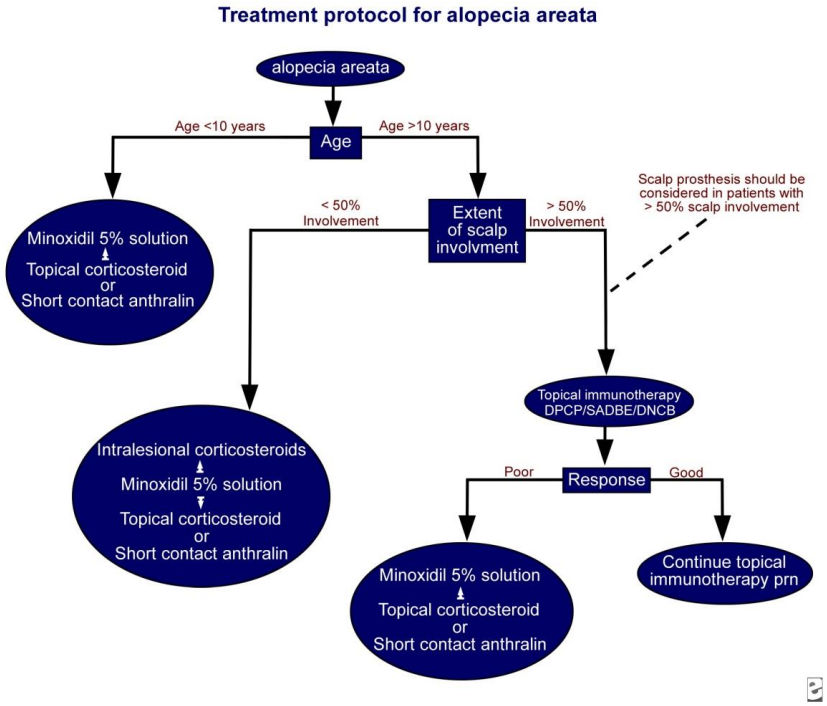

Figure 2
Algorithm for management of Alopecia areata in different age groups.[82]

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