An In-Depth Analysis of the Skin Condition of Alopecia Areata

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DOI: 10.47750/pnr.2023.14.03.228

Abstract

Alopecia areata is a chronic, immune disorder which targets hair follicle epithelium and characterised by hair loss as localised patches. It is a disease that is associated with other auto-immune diseases. This review aims to describe etiopathogenesis, differential diagnosis and treatment of Alopecia. The basic aetiology of Alopecia is the interaction between Human Leukocyte Antigen – DR isotype (HLA-DR) and Human Leukocyte Antigen – DQ isotype (HLA-DQ) on T cells and autoimmunity. The available treatments are limited. The treatments approved by the Food and Drug Administration (FDA) include corticosteroids and anti-inflammatory agents. There is a strong need for developing new pharmacological treatments for alopecia and selected treatments like Janus kinases (JAK) inhibitors therapy is changing the way to treat Alopecia areata.

Keywords: Alopecia areata, autoimmune disease, hair, Janus kinase inhibitors.

INTRODUCTION

Alopecia is the loss of hair from the body or scalp [1]. There are many forms of alopecia depending upon the pattern, cause etc [2]. One of the forms is alopecia areata (AA) [3]. It is a common non-scarring alopecia which occurs in a form of patchy and diffused pattern [4]. It is characterised by severe hair loss from some areas of body and scalp [5]. This is initiated with a single patch and followed by development of multiple patches which enlarge in a centrifugal way [6]. Other major forms of alopecia include alopecia totalis which is a state where entire scalp is affected and alopecia universalis is a state in which entire epidermis is affected (Table 1) [7-9].

Table 1: Classification of alopecia [10]

Based on extent
Patchy alopecia
Alopecia totalis
Alopecia universalis
Based on pattern
Reticular
Ophiasis
Sisaipho
New variants
Acute
Diffuse
Unusual patterns
Perinevoid alopecia
Linear

It accounts for 2-3 % of new dermatological cases in US and USA and 0.7 % in India [11, 12]. Both males and females are equally affected [13, 14]. This disease occurs in all group of people irrespective of age, sexes, etc [15]. It has been reported 0.1- 0.2 % with a lifetime risk of 1.7 % population are being affected [16]. Highest prevalence was seen in 30–59-year-old patients [17].

The pathology of AA had been investigated for years and strongest is linked with autoimmune disorder [18]. It results from the disturbances in hair follicle immune privilege [19]. The occurrence of AA in persons related with auto immune disorders like

diabetes mellitus, thyroiditis was been reported [20]. In the recent studies mood prevalence, despair and nervousness disorders in patient with AA are observed [21]. Gene polymorphisms related to immune system, proteins and antioxidant enzymes increase the susceptibility in this case [22].

Adipose tissue is gaining popularity as a non-inert tissue and can produce and secrete proteins, adipokines with regulating properties of metabolism. It plays an important role in the pathogenesis of autoimmune diseases that are associated with the alopecia areata [23, 24]. Melanocyte derived autoantigen is the target of immune response in alopecia areata [25]. Adipokines were also reported in the pathogenesis of alopecia areata and adiponectin is considered as a biomarker for the severity of the disease [24, 26]. Corona virus disease 2019 (COVID-19) is also indicated to be a risk factor for this disease [27].

The therapy for AA starts with a review on medication, supplements used and medical conditions [28]. There are several treatment options like glucocorticoids, steroids, immunomodulators etc. for the management of AA [29]. The present article's aim is to systematically review the history of AA, treatment modalities and future availability of new dosage forms [30].

Dynamics of hair fall

The growth of hair follicles occurs in three stages: long growing phase (anagen), traditional phase (catagen) and resting phase (telogen) [31, 32]. In general hair falls out at the end of resting phase and new hair starts growing in the follicle and the cycle repeats [33]. In AA an unidentified trigger stimulates the lymphatic attack on the hair bulb at a specific phase i.e., growing phase, interruption of the growing phase causes loss of hair and recognised as a dystrophic anagen hair [7, 34-36].

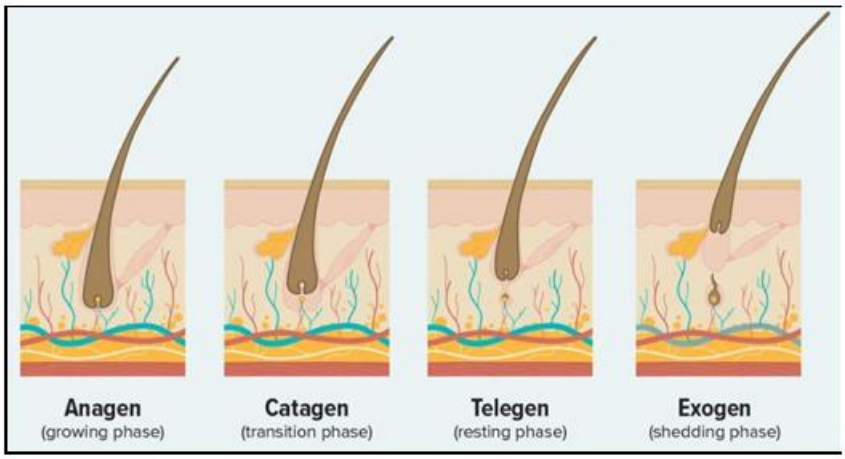

Fig. 1: Phases of hair growing

Etiopathogenesis

Immune privilege (IP) protects organs from potential harm of immune recognition by creating an anergic state that could sometimes tolerate a foreign graft within the tissue [34, 37]. The well-known IP sites are central nervous system, testes, placenta and eyes [38]. Hair follicles are also thought to immune privileged sites exactly the bulge throughout the hair cycle and the bulb in the anagen phase [39, 40]. Many studies have succeeded in providing proof of the different aspects of immune privilege breakdown in AA [18, 34, 41]. The main two main theories of privilege collapse are the stressed hair follicle theory and the immune system dysregulation hypothesis [18, 42]. Other factors that are involved in the pathogenesis are IL-15, T helper-17, mast cells, plasmacytoid dendritic cells, vitamin D receptors and the neuroendocrine immune system [43]. The actual presence of lymphocytes, dendritic cells and NK cells in the peribulbar area of the anagen hair follicle is a solid proof of immune privilege collapse in AA [7, 18, 44]. This IP collapse can be explained by two theories explaining the initial events in local defects in hair follicles and dysregulated immune system [7, 18, 45].

The pathology of AA was experienced over the years and resulted in varied aetiologies [46]. The genetic study found that about 8.4 % patients because of hereditary [47]. The existence of peritubular lymphocytes around the tuber of anagen region is the major cause for AA [48]. Patients with AA had human leukocyte antigen HLA-A1, HLA-B62, HLA-DQ1 and HLADQ3 and HLA class two molecules have three subclasses i.e., DR, DQ, DP which are found on the specific immune cells [49, 50]. The interactivity among HLA-DR and HLA-DQ plays a role on T cells in AA and autoimmunity [51, 52]. Other proposed causation of AA is stress, hypothyroidism and diabetes [16, 53, 54].

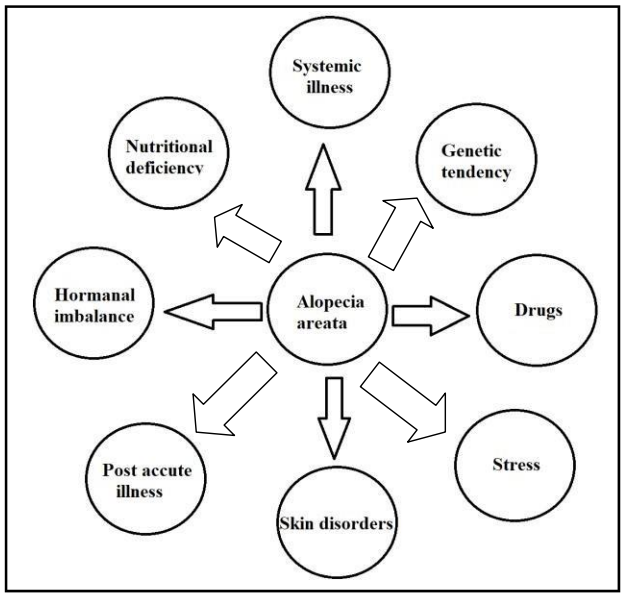

Fig. 2: Multiple factorial pathology of alopecia [55]

Clinical Features

The clinical examination should be focused on age, duration, assessment of skin health, progression of disease, relations record of AA and history of other auto immune diseases [7, 46]. General investigation like total hemogram, serum calcium, serum protein test and specific tests like skin biopsy and autoimmune panel in some selected cases should be tested [56]. AA is linked with fall of hair in a localised area in the shape of patch or solitary or numerous. Scalp is the major region caused by AA (90 %) [44, 57]. Other body parts such as eyelashes, eyebrows may be affected [6, 58]. The affected areas of skin seem to be no grossly and with signs of scaling and follicular abnormalities [59]. The regrowth hair lacks pigment which result in blonde or white hair [60].

Quantitating Hair Loss

Quantitative tests are conducted at the lesion and which determines the aetiology of AA [61].

Pull test: This test evaluates disperse scalp hair loss. Traction of hair is exerted from the three different areas of scalp. The count of the extracted hair is identified and examined under the microscopy. Normally, the count of hair less than 3 should come out for each pull, if it is > 10 hairs for each pull then test is positive for AA [62].

Pluck test: Individual hair is plucked by the roots and tested under microscopy to decide the augmentation stage and is employed to identify the imperfection of telogen, anagen [63]. Telogen hair appears as bulb with non- sheaths at their line. Anagen hair have sheath around their roots [5].

Daily hair count: by counting the number of hairs lost per day. Hair is gathered for 14 days and strands are recorded. If count > 100/ day, it results in abnormality [64, 65].

Trichoscopy: It is non-invasive method. This test is done by the employ of had held dermoscopy. In alopecia, trichoscopy shows yellow dots and black dots [66, 67]. Yellow dots are referred as hyperkeratotic plugs and black dots are referred as destroyed hair in hair follicle opening [68].

Gauging severity of disease

Researchers had developed a clinical scale to access the severity [69]:

Mild: Patches less than three and diameter <3 cm, limited to eyebrows and lashes [70].

Moderate: patches more than 3 with diameter >3 cm, without universalis [71].

Severe: Alopecia totalis or alopecia universalis. Salt score is the sum of % of hair loss in vertex, left, posterior of scalp surface area [72].

TREATMENT

Curing of AA is the challenge task because of the number of risk factor been concerned in the pathology management [73]. There are several treatments options which are not approved by the U. S food and drug administration and recommend to the patients [74]. Treatment of AA depends up on age, sex, disease extent, other medication and other history of auto- immune diseases [20]. The curing of AA includes topical, or intralesional corticosteroids, topical minoxidil, immunosuppressive agents, etc [75].

Glucocorticoids

These are first choice of drug to treat AA. Glucocorticoids have been employed to cure overarching anti- inflammatory effect. Oral corticoids in children do not any good result, but the use of high dose systemic corticoids showed good results [76].

Intralesional corticosteroids

These are first drug choice when AA involving less than fifty percent of the scalp [77]. Triamcinolone acetonide concentration of 10 mg/ml is administrated using gauge needle in multiple 0.1 ml injections. Initial results are seen in 1-2 months and continued treatment for 4-6 weeks respectively. This drug is preferred treatment for eyebrows AA in USA for affected adults [78].

Topical corticosteroids

Some of the topical dosage forms include fluocinolone acetonide cream, fluocinolone scalp gel, clobetasol propionate ointment. Topical corticosteroids have been reported for varying results in efficacy. These are first line drug preferred in children because of painless application and wide safety margin [79].

Systemic corticosteroids

Blood corticosteroids are not the first line treatment drug because of extensive side effects. The daily dose 30- 150 mg/ day is essential for the regeneration of hair in AA, period of the dosage ranges from 1-6 months. In certain cases, these drugs are preferred for cure with short course only. The studies with methyl prednisone 250 mg twice daily for three days showed good results. Contraindication and side effects should be discussed and monitored with patients for this therapy [80].

Minoxidil

It is an originally marketed as a anti -hypertensive agent. During clinical trials male patients with AA have experienced regrowth of hair during the treatment course. This led to reproduce drug for the topical administration. This drug stimulates the proliferation phase at the base of the follicle. Patients with AA, AU, AT showed good result to minoxidil. The oral administration of minoxidil produces various side effects like tachycardia, swelling, etc. Topical application minimises the side-effects. Minoxidil 5% lotion and anthralin combination therapy reported good results and the employ of 2% or 5% topical minoxidil gel when fine vellus or in determine hair growth showed good result [81].

Topical immunomodulators

Topical immunomodulators like phenyl-cyclopropenone (DPCP), squaric acid dibutyl ester accepted for the cure of AA. The contact sensitizers act by immunomodulating the skin at several points. Dinitrochlorobenzene (DNCB) was the first contact sensitizer used for AA Inosiplex is the new immunomodulating agent used for cure of AA. DPCP alone was equally effective as DPCP and anthralin combination n a clinical study [82].

Cyclosporin A

It is an immune-suppressant drug used for the cure of AA, AU, AT. These agents block the transcription of cytokines gene in T- cells. They act directly on hair follicles which promote transition from telogen phase to anagen phase. Combination of cyclosporin A and glucocorticoids show enhanced responses. The side effects produced by cyclosporin A include cancer and hyperglycaemia as result it is not referred drug for treating AA [83, 84].

Pharmacological therapies for AA under development

There are many therapies for the cure of AA, AU, AT which act in a range of stages of progress. Future treatment of AA includes JAK inhibitors, androgen receptors antagonists, vitamin D analogues, parathyroid hormone analogues, neurotropic activator [84].

Janus kinase (JAK) inhibitors

These have been originally developed as an immune-suppressant therapy for rheumatoid arthritis. JAK is an intracellular enzyme: JAK1, JAK2, JAK3 and tyrosine kinase 2[85]. The JAK pathway is activated when the extra cellular cytokines bind to the cell surface cytokine receptors. These pathways are implicated in pathogenesis of AA. Inhibition of JAK enzyme has been employed to treat various immune –mediated diseases [86]. The unpleasant causes are associated with high dose of JAK inhibitors, common adverse effects are nasopharyngitis, non- melanoma skin cancer, pulmonary embolism, head ache, weight gain, fatigue, etc.

Oral Tofacitinib

Open label studies showed that tofacitinib is effective in a proportion of adults. Study describes a case sequence of ninety patients, most of patients had AU, AT [87]. The dosage of 5-10 mg twice daily was administered by increasing 5mg per month up to 25 mg was reached. The results showed that 20 % of patients achieved response greater than 90% change, result suggest that tofacitinib as an effective treatment for AA [88]. Topical tofacitinib has been used for children aged 4-16 years and patients had complete hair regrowth with tofacitinib 2

% [87].

Drug delivery in AA

As the AA is a skin disease most of the formulations are topical formulations. The topical route of drug delivery is fundamental route to treat dermatological ailments [89]. Systemic application of drugs in the treatment of AA is often associated with the toxicology [90]. Corticosteroids, minoxidil etc come in topical formulations such as solutions, sprays and creams. Few oral formulations are also available for the treatment of AA. Tofacitinib for example is available in oral

formulations [91].

Skin is an effective barrier which possesses proper barrier properties the external agents. Thus, chemical, physical, and mechanical methods can be used in order to optimize skin penetration of the drug. Drug delivery assisted by lasers and the use of microneedles have been reported in some scientific articles recently as alternative or complementary options in alopecia treatments [92].

Laser-assisted drug delivery increases the distribution and penetration of topically applied drugs leading to enhanced bioavailability. The therapeutic application of laser-assisted drug delivery in clinical practice in cases alopecia areata enhances topical agent efficacy, potentially reducing the agent concentration and tie for the topical treatment [93].

The conventional topical dosage forms available in the market have shortcomings in the management of alopecia areata. Nanoparticulate-based delivery are thought to enhance the permeability properties of the drug [94]. The nanoparticles can be targeted to the hair follicles where they can stay for longer durations releasing the entrapped drug. This novel approach has the potential to revolutionize the drug delivery in case of AA given that the drugs are efficacious [89].

CONCLUSION

AA has an impact on appearance of the afflicted individual. Moreover, uniformly treatment is unknown. Corticosteroids, anti-inflammatory drugs that showed promising result in executive of AA over the years. Other medications have been used are minoxidil, DPCP, anthralin. There are large numbers of compounds in a variety of stages of growth. JAK family of enzymes are the incremental advances in treatment of AA. These agents are FDA approved and marketed for inflammatory arthritis and are under investigation for skin diseases like dermatitis and psoriasis. Clinical trials of JAK inhibitors, tofacitinib have commenced and optimal dose, requirement for loading doses and optimal targets with in the JAK family are to be studied further. In subsequently few years the information will be accessible along with other ideal treatments.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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