Alopecia areata: Updates
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ABSTRACT
Alopecia areata (AA) is a chronic, relapsing immune-mediated inflammatory disorder affecting hair follicles with genetic predisposition and an environmental trigger that causes hair loss. The severity of the disorder ranges from small patches of alopecia on any hair-bearing area to the complete loss of scalp, eyebrow, eyelash, and body hair. AA commonly manifests as sudden loss of hair in well demarcated, localized round or oval area with exclamation point hairs at the periphery of the lesion. It is believed that in AA, an as yet unidentified trigger stimulates an autoimmune lymphocytic attack, which target the bulb of anagen hairs that leads to abnormal hair loss. Many therapeutic modalities have been used to treat alopecia areata, with variable efficacy and safety profiles. The treatment plan is designed according to the patient’s age and extent of disease. This review precisely outlines the etiologic and pathogenic mechanisms, clinical features, diagnosis and management of alopecia areata.

KEY WORDS: Alopecia areata, etiology, pathogenesis, management.

INTRODUCTION
Alopecia areata (AA) is a relatively common dermatosis of autoimmune pathogenesis, characterized by non scarring hair loss in an unpredictable course. It affects males and females equally, most commonly of young age and has a serious impact on social life and self-esteem.

ETIOPATHOGENESIS
It has now been widely postulated that AA is an organ-specific autoimmune disease with genetic predisposition and an environmental trigger.

Role of genetics in alopecia areata
About 20% of people with alopecia areata have a family history of the disease indicating a genetic predisposition. Familial cases of alopecia areata are often characterized by a poorer prognosis, more rapid progression, more frequent relapses, and greater resistance to therapy. Associations have been reported with a variety of genes, including major histocompatibility complex (MHC) and cytokine genes, suggesting that the genetic predisposition is multifactorial in nature. A genome-wide association study confirmed the link with the MHC genes and also identified associations with other genes involved in regulating immune and inflammatory responses, and with some genes expressed in the hair follicle. AA has been shown to be associated with the inheritance of human leukocyte antigen (HLA) class II alleles. HLA-DQ3 appears to be the general susceptibility allele for AA. Patients with long-standing AT/AU have significant associations with HLA antigens DR4, DR11, and DQ7. Intervals on human chromosomes 6, 10, 16, and 18 were identified as potential AA susceptibility loci.

Petukhova et al. undertook a genome-wide as-
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Association study (GWAS) in a sample of 1,054 cases and 3,278 controls and identified 139 single nucleotide polymorphisms that are significantly associated with AA (P<5×10^{-7}). The investigators show an association with genomic regions containing several genes controlling the activation and proliferation of regulatory T cells (Treg cells), cytotoxic T lymphocyte-associated antigen 4 (CTLA4), interleukin (IL)-2/IL-21, IL-2 receptor A (IL-2RA; CD25) and Eos (also known as Ikaros family zinc finger 4; IKZF4), as well as the human leukocyte antigen (HLA) region. A region of strong association resides within the ULBP (cytomegalovirus UL16-binding protein) gene cluster on chromosome 6q25.1, encoding activating ligands of the natural killer cell receptor NK-G2D that have not previously been implicated in an autoimmune disease.8

Autoimmune activity in alopecia areata

It has been proposed that the hair follicle is an immunologically ‘privileged tissue’. This relative immune privilege is established mainly by suppression of the surface molecules required for presenting autoantigens to CD8+ T lymphocytes (MHC class I molecules) and by the generation of an overall immunoinhibitory local signaling milieu.9 This down-regulation of MHC class I molecules, however, entails the risk that the hair follicle may be attacked by natural killer (NK) cells, since NK cells are primed to recognize and eliminate MHC class I–negative cells.10 Healthy hair follicles appear to down-regulate the expression of ligands that stimulate the activation of NK-cell receptors (NKG2D)11 and secrete molecules that inhibit NK-cell and T-cell functions, such as transforming growth factors β1 and β2, α melanocyte–stimulating hormone, and macrophage migration inhibitory factor.12

Failure of such immune privilege plays a key role in the pathogenesis of alopecia areata.13 In AA, the patient’s immune system attacks its own hair follicles and suppresses or disrupts hair growth or formation.14 The lesion occurs as a result of local T-cell mediated cytotoxic inflammatory response including CD4+ T-lymphocytes and CD8+ T-lymphocytes. CD8+ T cells appear to be the first lymphocytes to enter the proximal follicular epithelium.15

Role of infections in alopecia areata

There is a possibility of infection to be a cause of AA either directly or as a consequence of a remote focus of infection.16 Skinner et al found cytomegalovirus viral particles within the AA patches of scalp.17 While, Rodriguez and Devic, in there study concerning the Epstein Barr Virus as a possible trigger factor for AA.18 IN 2010 Tuzun et al, suggested that Helicobacter pylori infections play a role in the pathogenesis of AA and its eradication can improve the disease.19 Tooth extraction in patients with AA can improve the hair growth indicating that, the remote focus of dental infection can be one of causative factors of AA.20

Role of emotional stress

Alopecia areata is considered to be an example of a psychosomatic disorder, leading to dramatic and devastating emotions which can negatively impact patient self-esteem, body image, and self-confidence.21

Role of neurological factors

Substance P (SP) acts as an immunomodulatory neuropeptide in AA and plays a critical role in the cutaneous neuroimmune network, together
with influencing immune cell functions through the neurokinin-1 receptor (NK-1R) which is expressed on CD8 lymphocytes and macrophages accumulating around affected hair follicles. Moreover, calcitonin gene related peptide (CGRP), which is released by cutaneous nerve ending, inhibits both mitogen-stimulated T lymphocytes proliferation and langerhans cell antigen presentation. It also blocks the action of some inflammatory mediators as well as increases vasodilatation and endothelial proliferation. It has been reported that, patients with AA have low serum level of CGRP.

Dynamics of hair follicle growth

Hair follicle growth occurs in cycles. Each cycle consists of a long phase of rapid growth, pigmentation, and hair-shaft production (anagen), a short transitional apoptosis-driven phase of organ involution (catagen), and a short period of relative quiescence phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts the cycle again. This regenerative cycle is made possible by an abundance of keratinocyte and melanocyte stem cells located for the most part in the so-called bulge area. There are considerable variations in the length of the three phases, normally about 100 hairs reach the end of their resting phase each day and fallout.

Hair follicle growth cycling modulation in alopecia areata

In AA, a significant disruption of the hair growth cycle clearly occurs and here are several possible presentations of AA. First, the anagen phase of a hair follicle can become inflammed and maintained in a dystrophic anagen state. When there is a greater intensity of inflammation, the hair follicles may be forced into a telogen phase. Finally, when AA is chronic, the hair follicles tend to persist in a prolonged telogen phase without an apparent attempt to return to an anagen growth phase.

Clinical features

Alopecia areata manifests as a sudden loss of hair in localized areas. The lesion is usually a round or oval patch of alopecia and may be solitary (alopecia areata monolocularis) or numerous (alopecia areata multilocularis). The patch of alopecia usually has a distinct border where normal hair demarcates the periphery of the lesion. The affected skin appears normal with no grossly evident epidermal alterations such as scaling or follicular abnormalities. In all forms “exclamation point hairs” are found, “hairs appear clinically as broken short hairs that taper proximally”. Alopecia areata can be classified into: patchy AA; which is round or oval patches of hair loss (the commonest), reticulor AA; which is a net-like pattern of patchy hair loss that exhibits hair loss in one site and spontaneous hair regrowth in another area of a bald lesion, ophiasis; which is band-like hair loss along the margin of the scalp. Upon regrowth, hair often initially lack pigment resulting in blonde or white hair. The scalp is the most common site affected by AA (90%). Scalp and body hair such as eyebrows, eyelashes, beard, underarm hair, and pubic hair may be affected (alopecia totalis), as well as, the entire body (alopecia universalis).

Unusual clinical presentations of AA

1. “Sudden graying,” a variant in which pigmented hair follicles are attacked, with the result that preexisting gray hairs are demasked.
2. 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.36

3. 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.37

Nail changes
It can be seen in a portion of patients (10-66%) of AA. Small shallow pits (30%) up to trachyonychia (sandpaper nails; 10%) are typical, rarely other changes. A red-spotted lunula and periungual erythema have been postulated as a sign of acute nail involvement,38 Beau’s lines, koilonychia, onychomadesis, onychorrhexis and punctuate or transverse leukonychia have also been reported.35

Association with AA39,40
Thyroid disease - 85%
Diabetes mellitus - 11.1%
Inflammatory bowel disease - 6.3%
Systemic lupus erythematosus - 10%
Rheumatoid arthritis - 3.9%
Psoriasis and psoriatic arthritis - 2.0%
Other comorbid conditions found included the following:
Atopy (allergic rhinitis, asthma, and/or eczema) -9-26%
Contact dermatitis and other eczema - 35.9%
Mental health problems (depression or anxiety) - 17-22%
Hyperlipidemia - 24.5%
Hypertension - 21.9%

SCORING OF ALOPECIA AERATA
Alopecia areata severity assessment score
1. Mild: Three or less patches of alopecia with a widest diameter of less than 3 cm or disease limited to eyelashes and eyebrows.
2. Moderate: Existence of more than three patches of alopecia or a patch greater than 3 cm at the widest diameter without alopecia totalis or universalis.
3. Severe: Alopecia totalis or alopecia universalis.
4. Ophiasis is the most severe form.41

Severity of Alopecia Tool score” (SALT score).
The National Alopecia Areata Foundation working committee has devised “Severity of Alopecia Tool score” (SALT score). Scalp is divided into 4 areas namely, Vertex - 40% (0.4) of scalp surface area; right profile of scalp - 18% (0.18) of scalp surface area; left profile of scalp -18% (0.18) of scalp surface area; Posterior aspect of scalp - 24% (0.24) of scalp surface area. Percentage of hair loss in any of these areas is percentage hair loss multiplied by percent surface area of the scalp in that area. SALT score is the sum of percentage of hair loss in all above mentioned areas.42

Hair growth index
It is a scoring system for regrowth in alopecia areata that included not only percentage of scalp hair regrowth but also the type of hairs regrowing in the areas of hair loss. This method included an assessment of non terminal hair growth. The percentage of scalp covered by vellus, indeterminate

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or terminal hair was multiplied by a weighting
factor of 1 for vellus, 2 for indeterminate, and 3
for terminal. The sum of these products (0-300)
was the hair growth index score and could be
compared at each visit.43

Diagnosis of AA
Diagnosis of AA usually can be made on clinical
grounds. A scalp biopsy seldom is needed, but it
can be helpful when the clinical diagnosis is less
certain.

Differential diagnosis of AA
Trichotillomania
This condition probably causes most confusion.
The incomplete nature of the hair loss in trichotil-
omania and the fact that the broken hairs at vari-
ous lengths are firmly anchored in the scalp (i.e.
they remain in the growing phase, anagen, unlike
exclamation mark hairs), no scaling or erythema
and negative pull test are distinguishing.44

Tinea capitis
The diagnosis is suggested by local erythema,
scaling, and crusting on the scalp.

Anagen effluvium (drug-induced) may mimic
diffuse alopecia areata

Telogen effluvium
Early scarring alopecia45
Secondary syphilis
Loose anagen hair syndrome
This is a disorder of abnormal anagen hair anchor-
age. It is commonly found in children and has an
autosomal dominant inheritance.46

Investigations
Hair pull test conducted at the periphery of the le-
sion may be correlated with disease activity tech-
nique is to gently tug at a handful of hair along
the edge of an alopecic patch with less strength
than would be required to pull out healthy hair. In
healthy hair, no hair should fall out or ripped hair
would be distributed evenly across the tugged por-
tion of the scalp. In cases of AA, hair will tend to
pull out more easily along the edge of the patch.47

Trichoscopy is a non-invasive method for visual-
alization of hair and scalp. In trichoscopy show
regularly distributed “yellow dots” (hyperkerata-
totic plugs), microexclamation mark hairs, and
“black dots” (destroyed hairs in the hair follicle
opening.47

Scalp biopsy This test is done when alopecia is
present, but the diagnosis is unsure. Hair samples
are taken from areas of inflammation, usually
around the border of the bald patch.35 The most
characteristic feature is a peribulbar lymphocytic
infiltrate around terminal follicles in active alo-
pecia areata (“swarm of bees”) versus alopecia in
the chronic phase where the hairs are miniaturized
and the infiltrate is less obvious.30

Management of Alopecia Areata
Management of patients with alopecia areata is a
challenging task as a number of risk factors have-
been implicated in its etiology.47

FIRST-LINE THERAPIES
Based upon the relative safety and the availabil-
ity, intralesional or topical corticosteroids are the
initial treatment for most patients with patchy alo-
ppecia areata. Topical immunotherapy can be used
for patients with extensive disease (greater than
50 percent scalp hair loss) as first-line treatment.48

Intralesional corticosteroids
The affected area may be pretreated with a topical
anesthetic cream (eg, EMLA cream). The cream
is applied generously, and is placed under occlusion 1.5 to 2 hours before treatment. The cream is removed immediately before injection. Triamcinolone 2.5 to 5.0 mg/ml is injected into the upper subcutis on the face for eyebrow or beard involvement; concentrations of 5 to 10 mg/ml for the scalp. 10 - 20 mg is injected per session and is administered using a 0.5-inch long 30-gauge needle in multiple 0.1 mL injections approximately 1 cm apart. New growth is usually visible within four weeks. The treatment may be repeated as necessary every 4 to 6 weeks, and is stopped once regrowth is complete. If there is no response after six months, treatment should be discontinued and alternative treatments may be attempted[^49] Side effects of intradermal injection of corticosteroids are minimal but it may include pain during injection, bleeding and local reversible skin atrophy.[^13]

**Potent topical corticosteroids**

Potent topical corticosteroids such as betamethasone dipropionate 0.05 percent (cream, lotion, ointment) are frequently used to treat alopecia areata for children and adults who cannot tolerate intrallesional injections. It is applied to affected areas and 1 cm beyond twice daily. The side effects of long-term use of highly potent topical steroids include telangiectasia, hypopigmentation, skin atrophy, folliculitis, local skin infections and adrenal suppression.[^50]

**Topical immunotherapy**

Topical immunotherapy relies on inciting an allergic contact dermatitis (ACD) by applying potent contact allergens to the affected skin. It is probably the most effective treatment for patients with extensive or recurrent scalp involvement.[^51] They include diphenylcyclopropenone, squaric acid dibutylester (SADBE), and dinitrochlorobenzene. Dinitrochlorobenzene is no longer used because it was shown to be mutagenic in the Ames test.[^52] Initially the patient is sensitized using a 2% solution of diphenylcyclopropenone applied to a 4 × 4 cm area of the scalp. After two weeks, 0.001% diphenylcyclopropenone solution is applied. The concentration is increased gradually every week until mild dermatitis is observed. The solution should be on the scalp for 48 hours. The scalp should be protected from the sun during this time.[^53] The resultant mild inflammatory reaction is associated with hair regrowth. The reason for this response remains unknown, but an immunomodulatory effect on the inflammatory infiltrate surrounding affected hair follicles is thought to play a role. Theories for the mechanism of action have focused on the inhibition of the pathologic immune response via antigenic competition,[^54] the induction of lymphocyte apoptosis,[^55] or an effect on the type or function of lymphocytes in the inflammatory infiltrate.[^56]

Adverse effects of topical immunotherapy include pruritus, mild erythema, scaling, and postauricular lymphadenopathy. Other side effects include scalp edema, high fever, vitiligo, contact urticaria and the pigmentary disturbance “dyschromia in confetti,” which is more frequent in darker skin.[^49]

**SECOND-LINE THERAPIES**

Second-line options for the treatment of alopecia areata may be used alone or in combination with first line interventions. Compared with intrallesional corticosteroids and topical immunotherapy, minoxidil and anthralin appear to be less efficacious. PUVA is considered a second-line therapy due to the potential for long term adverse effects.
Anthralin

Anthralin exerts its effect through its irritant contact properties. It also acts through its immunosuppressive and anti-inflammatory properties via the generation of free radicals. Patients are instructed to apply 0.5-1% anthralin cream to bare areas for 20-30 min daily over 2 weeks, gradually increasing daily exposure until low-grade erythema and pruritus develops which when once achieved is continued for 3 to 6 months. It is believed to be a suitable agent for children under 10 years of age. Adverse effects include scaling, staining of treated skin and fabrics, folliculitis, and regional lymphadenopacy.

Minoxidil

Minoxidil is effective in the treatment of AA in patients with extensive disease with response rates varying from 8-45%. But it is of little benefit in patients with alopecia totalis or alopecia universalis. It stimulates follicular DNA synthesis, increases proliferation of anagen-phase hair bulbs, prolongation of survival time of keratinocytes, impeding intracellular calcium entry that inhibits hair growth and regulates hair physiology independently of blood flow influences promoting hair growth. It also increases the duration of anagen and enlarges miniaturized follicles irrespective to the underlying cause of hair loss. Five percent minoxidil solution is applied twice daily. Initial regrowth of hair can be seen within 12 weeks, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil can be combined with topical corticosteroid or anthralin. The combination provides a synergistic effect and improves efficacy. The adverse effects of topical minoxidil include contact dermatitis and facial hypertrichosis.

Phototherapeutic treatment

Photochemotherapy is a treatment option for alopecia areata. Psoralen plus UVA therapy (PUVA) can be administered with the psoralen delivered topically as a gel or paint, or orally. The mechanism of action Photochemotherapy (PUVA) is believed to be a photo-immunologic action. It may affect T cell function and antigen presentation and possibly inhibit local immunologic attack against the hair follicle by depleting langerhans cells. Long-term treatment with PUVA has been associated with an increased risk for cutaneous malignancy. Furthermore, side effects included slight erythema and painful burning in patients who did not protect their scalp from sunlight after PUVA exposure.

THIRD-LINE THERAPIES

Systemic corticosteroids

The suggested dosages of prednisolone are 1mg/kg/day for adults and 0.1-1 mg/kg/day for children. The dosages necessary to maintain hair regrowth in AA are between 30 and 150 mg daily. Treatment course can range from 1 to 6 months, but prolonged courses should be avoided secondary to the numerous side effects of these drugs especially when children are treated. The use of systemic corticosteroids is limited by their side effects (hyperglycemia, weight gain, hypertension, adrenal suppression, dysmenorrhea, immunosuppression, and acneiform eruption) and the high relapse rate (14%-100%).

Pulse corticosteroid therapy

It was tested as an alternative to the prolonged oral corticosteroids to avoid steroid side effects. Friedli et al. have also reported successful therapy with pulsed methylprednisolone (250 mg IV...
twice daily for 3 consecutive days) in rapidly progressing extensive multifocal AA. In a study conducted by Pasricha et al betamethasone oral mini-pulse therapy is a convenient and fairly effective treatment modality for extensive alopecia areata.68

**Sulfasalazine**

Sulfasalazine is believed to be a good alternative treatment for alopecia areata because of its good efficacy, good adverse event profile and steroid sparing nature. The drug has immunosuppressive and immunomodulatory actions that include suppression of T cell proliferation and reducing the synthesis of cytokines, including interleukin (IL) 6, 1, and 12, tumor necrosis factor alpha, and antibody production similar to cyclosporine, sulfasalazine has been shown to inhibit the release of interleukin 2.69 Rashidi and Mahd reported in their study a good response occurred in 10 of the 39 patients (25.6%), a moderate response in 12 (30.7%), and a poor or no response in 17 patients (43.5%).70 Side effects of sulfasalazine may include gastrointestinal distress, headache, fever, rash, and less frequently hematologic disorders and hepatotoxicity. Starting therapy with a low dose may decrease gastrointestinal symptoms. Patients can be treated with 0.5 g twice daily for one month, followed by 1 g twice daily for one month and 1.5 g twice daily for at least three months. Complete blood cell counts and liver function tests should be closely monitored during the first three months of therapy, and every three to six months thereafter.71 It was also noted that sustainability of hair growth achieved by sulfasalazine was dose-dependent, meaning that a maintenance dose is necessary to preserve the regrown hair and that further reduction or interruption of treatment leads to relapse of hair loss.72

**Cyclosporine A**

Cyclosporine A is a common antimetabolite drug used in post-transplantation patients which exerts its effect via inhibition of T-cell activation. A common cutaneous side effect is hypertrichosis, which occurs in approximately 80% of patients, possibly as a result of prolongation of the anagen phase of the hair cycle. It also decreases the perifollicular lymphocytic infiltrates, particularly the mean number of helper T cells.73 The success rate with oral cyclosporine is 25%-76.6%.74 A recent study showed that a good response to oral cyclosporine can be predicted if the serum level of IL 18 is elevated and the level of soluble IL 2 receptor is low.75 The use of oral cyclosporine in patients with alopecia areata is not generally favored due to its adverse event profile (nephrotoxicity, immune suppression, and hypertension) and a high relapse rate (up to 100%).76 Also, alopecia areata incidence has been reported in several organ transplant patients receiving cyclosporine.77

**Methotrexate**

Methotrexate is an antimetabolite and antifolate drug. It acts by stopping the metabolism of folic acid, specifically by competitive inhibition of dihydrofolate reductase, an enzyme that participates in the tetrahydrofolate synthesis. There are reports of treating severe AA with methotrexate alone or in combination with oral pulse prednisolone, resulting in complete hair regrowth in approximately half of these patients in both cases. Lasting improvement required maintenance treatment.78,79

**Azathioprine**

Azathioprine interferes with the synthesis of pu-
rines, required for the synthesis of DNA. It is a prodrug metabolized to 6-mercaptopurine and to 6-thioinosinic acid, which are active metabolites and affect T and B cells. A recent study in a small cohort with moderate-to-severe AA treated with oral azathioprine, presented hair regrowth in a statistically significant rate after a 6-month period. Long-term efficacy and safety of this treatment through controlled studies on larger number of patients should be investigated since azathioprine is a low-cost and well-tolerated drug.

Biological therapy
These medications synthesized from recombinant proteins reduce the pathogenic T cells, inhibit T-cell activation and inhibit inflammatory cytokines, suggesting a potential role in the treatment of AA. Biologic agents acting on TNFα have been considered as possible treatments for AA. However, scientists found that, no hair regrowth occurred after treatment of AA with etanercept. In addition, infliximab did not prevent AA development in a patient with no previous history of this disease. Authors reported worsening of AA in a patient receiving infliximab. There is a case report of AU, occurring 4 months after adalimumab usage. The authors couldn’t attribute its occurrence to this agent or psychological stress of the patient or both together.

OTHER THERAPIES
Topical calcineurin inhibitors
1. Tacrolimus is a macrolide immunosuppressive agent that inhibits calcineurin and thus reduces IL-2 production by T cells. It is used as a topical preparation in the treatment of severe atopic dermatitis and vitiligo. Despite initial encouraging results of topical tacrolimus in experimental bald animal models, no hair regrowth was achieved in AA patients. Treatment failure with topical tacrolimus 0.1% may be caused by insufficient depth of penetration of the ointment for mulation and less than optimal patient selection. Higher concentrations of tacrolimus ointment and large scale randomized controlled trials are needed.

2. Pimecrolimus is an ascomycin macrolactam product that exhibits both anti-inflammatory and immunomodulatory qualities. It prevents calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells, which inhibits synthesis of Th1 and Th2 cytokines from T lymphocytes. Although during recent years the experimental use of pimecrolimus in AA in mice and rat models has given promising results, this has not been confirmed in clinical trials in human AA.

Prostaglandin and prostamide analogues
Latanoprost 0.005% ophthalmic solution is used for controlling the progression of glaucoma or ocular hypertension by reducing intraocular pressure. Bimatoprost 0.03% solution is also used for glaucoma treatment and has recently been approved by the US FDA for hypotrichosis of the eye lashes. Both prostaglandin and prostamide analogues have been shown to interact with prostanoid receptors in the hair follicle resulting in induction of telogen follicles into the anagen phase. They have also been shown to prolong the anagen phase of eyelashes. Knowledge of this effect led to clinical studies of the efficacy of these drugs for alopecia areata involving the eyelashes and eyebrows. However, most of the effects regard healthy eyelashes; results in the treatment AA are controversial.
Photodynamic therapy
It involves the administration of photosensitizer followed by its activation with light to generate a therapeutic effect. 5-Aminolaevulinic acid (ALA) is a photosensitizer precursor that is transformed by cells into protoporphyrin IX (PpIX), which can in turn be activated by red light to generate reactive oxygen species that interact with cellular functions. No side effects were reported apart from erythema, pigmentation and a mild to moderate burning sensation during light exposure.86

Infrared Irradiation
Super Lizer™ is a linear polarized infrared light instrument, which has been used with success in the treatment of arthralgias and neuralgias. A study in a group of 15 subjects with patchy AA irradiated intermittently for an interval of 3 min once every week or every 2 weeks demonstrated significant hair growth in half of them after a few months87 The mechanism of action of infrared irradiation is still unknown. It has been proposed that infrared irradiation may stimulate regrowth in hair bulbs directly, or promote regrowth indirectly via increased blood flow. Yamazaki et al. suggested that it could be a useful apparatus for the treatment of mild forms of AA87 The procedure is noninvasive and has no serious adverse effects apart from a local irritation and a sense of burning.

Fractional photothermolysis laser
A case report of a 35 year-old male patient who had AA for 2 years and who was nonresponsive to treatment with minoxidil, topical corticosteroids, and ILCSs had complete regrowth after multiple sessions with fractional Er: Glass laser.88 Hair growth was noted as early as 1 month, and complete re-growth was achieved at 6 months. No hair loss was reported in the 6-month follow-up period. No side effects were reported. The mechanism of action is thought to involve the induction of T-cell apoptosis and direct enhancement of hair growth.88 This report sheds some light on, and stimulates the research of the role of this fairly new technology in AA treatment.

Excimer laser
The 308-nm excimer laser is a system that offers high doses of long-wave monochromatic ultraviolet B (UVB) radiation.89 As AA is believed to be a T-cell autoimmune disorder, the mechanism of action of the 308-nm excimer laser in inducing hair regrowth is thought to be through the induction of T-cell apoptosis.90 Laser therapy was administered twice a week for a maximum of 24 sessions. Apart from erythema at the treated sites, there were no significant adverse effects. Relapses of alopecia areata were observed in two patients with patchy alopecia areata of the scalp who had shown complete regrowth earlier. Also, the use of excimer laser in children with alopecia areata has been reported to have a good success rate.91

Topical bexarotene
The mechanism of action is thought to be through immunomodulation and induction of T-cell apoptosis. The associated tretinoin-induced dermatitis might contribute to regrowth in alopecia areata. The efficacy of bexarotene needs to be confirmed in large randomized, placebo-controlled trials.92

Capsaicin
The idea of using capsaicin in AA emerged from the theory of nervous system and neuropeptide role in the development of the disease. Capsa-
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icin can release substance P (SP) and calcitonin gene-related peptide (CGRP), and after repeated application, it depletes neurons of SP. (93). Topical capsaicin may be able to stimulate vellus hair growth in alopecia areata through effects on the perifollicular neuroimmunological system. (94) However, an ability of the drug to induce cosmetically significant hair growth has not been demonstrated.

**Botulinum toxin**

Evidence for involvement of neuropeptides in the pathogenesis of alopecia areata and a case report in which alopecia areata associated with neuralgiform head pain improved after botulinum toxin A injection suggested that botulinum toxin might be useful for alopecia areata (95). Since spontaneous resolution of patchy alopecia areata is common, hair regrowth may not have been related to the treatment. Further studies are necessary to determine whether botulinum toxin may be effective for some patients with alopecia areata.

**Mesotherapy**

Mesotherapy employs multiple injections of pharmaceutical and homeopathic medications, plant extracts, vitamins, and other ingredients into the target tissue. In treatment of alopecia, mesotherapy can be of help by causing hair regrowth by delivering medications into the middle layer under the skin. Olsen (96) concluded from their study that minoxidil injected by mesotherapy is more effective than that of topical application in treatment of female pattern hair loss.

**FUTURE DIRECTIONS**

**Vitamin D**

Vitamin D (1, 25-dihydroxycholecalciferol) is a steroid hormone that is synthesized in epidermal keratinocytes under influence of UV-B lights or acquired in the diet and dietary supplements (95). It has a multitude of biologic effects interacting with the innate and adaptive immune system, mainly leading to its downregulation. It regulates the differentiation of B cells, T cells, dendritic cells, and the expression of Toll-like receptors. (97). Vitamin D also has an effective role in the proliferation and differentiation of keratinocytes. (98) The maintenance of hair follicle is dependent on the integrity of the dermis, epidermis, and the normal hair cycle. (99)

In late anagen and catagen there is increase in vitamin D receptors (VDRs), which is associated with decreased proliferation and increased differentiation of keratinocytes. These changes are thought to promote progression of hair cycle. (100) It was showed that the lack of VDR affects the hair follicle growth. (101)

**Immunomodulators from parasites**

The incidence of allergic and autoimmune diseases is increasing in developed countries compared to developing ones where there is a higher rate of nematode parasitic infections. Human infection results in decreased production of the cytokine IFN-$$\gamma$$, but increased production of the cytokines IL-4 and IL-10 and the antibody type IgG4, a type 2 T-helper (TH2) cell response. This shift may change the susceptibility to TH1-associated immune responses such as cell-mediated autoimmune diseases. The production of harmless nematode antigen that is able to elicit such a response may have some value in treating autoimmune diseases, including AA. (102)

**Ustekinumab**

Ustekinumab is a fully human monoclonal antibody to the shared p40 subunit of IL-12 and IL-23.
IL-12 is the key effector cytokine in commitment to aTH1 response. IL-23 is a newly discovered cytokine that is thought to play an important role in linking the innate and adaptive arms of the immune response. Ustekinumab was proven to be efficacious in plaque psoriasis, and studies are ongoing to assess the long-term efficacy and safety. Ustekinumab may be tried on AA patients in the future.103

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