Alopecia areata: medical treatments

Zonunsanga

Department of Skin and VD, RNT Medical college, Udaipur, Rajasthan-313001, India.

Corresponding author: Dr. Zonunsanga, E-mail: jrkos04@gmail.com

ABSTRACT

Alopecia areata (AA) is a non-scarring, autoimmune, inflammatory, relapsing hair loss affecting the scalp and/or body. In acute-phase AA, CD4+ and CD8+ T cells infiltrated in the juxta-follicular area. In chronic-phase AACD8+ T cells dominated the infiltrate around hair bulbs which contributes to the prolonged state of hair loss. Treatments include mainly corticosteroids, topical irritants, minoxidil, cytotoxic drugs and biologicals. This review highlights mainly the pathomechanism and pathology, classifications and associated diseases with regard to their importance for current and future treatment.

Key words: Alopecia areata; Pelade; Area Celsi; NKG2D-activating ligands

INTRODUCTION

Alopecia areata (AA) is a non-scarring, autoimmune, inflammatory, relapsing hair loss affecting the scalp and/or body. It is also known as Pelade or Area Celsi. It is commonly manifests as a sudden loss of hair in localized areas [1-3].

PATHOMECHANISM

In acute-phase AA, CD4+ and CD8+ T cells infiltrated in the juxta-follicular area. In chronic-phase AACD8+ T cells dominated the infiltrate around hair bulbs which contributes to the prolonged state of hair loss. It is postulated that the characteristic T cell “swarm of bees” infiltrate seen in alopecia areata is the result of T cells attracted to the hair follicle by NKG2D-activating ligands [1-5,7-9,11-14,19,20].

Alopecia areata may be associated with HLA-DQ3, DQ7, DR4 and DR11, Thyroid dysfunctions, Psychological problems, Atopy, Pernicious anemia, infections, including H. pylori, Vitamin D deficiency, autoimmune polyglandular syndrome type 1 (APS1), Immune thrombocytopenia and alopecia areata. Coexistence of psoriasis and alopecia areata with trachyonychia in Turner Syndrome has also been reported. Interferon alpha-2b and ribavirin therapy, possibly due to the collapse of hair follicle immune privilege [1-5,7-9,11-14,15,17,19,20].

HISTOLOGY

The early stage of AA is characterized by the presence of CD+ and CD+ T lymphocytic infiltration in the peribulbar region. The late stage is characterized by numerous miniaturized hair follicles [1-3].

CLASSIFICATIONS

Based on sites and extend of AA:
1. Diffuse Alopecia areata: When hair lost more diffusely over the whole scalp.
2. Alopecia areata multilocularis: shows multiple areas of hair loss.
3. Alopecia monolocularis: when hair loss is only in one spot which may be in anywhere of the scalp of the head.
4. Alopecia areata barbae: when the disease is only limited only in the beard.
5. Alopecia areata totalis: When patient loss all his hair.
6. Alopecia areata universalis: When hair is lost from all the body including the public hair.
Based on pattern of AA:
1. Restricted to scalp - Patchy, Ophiasis, Sisapho, Reticulate, Diffuse, Subtotal and Alopecia totalis
2. Generalized
3. Alopecia universalis

Based on Ikeda’s type:
1. Atopic type
2. Autoimmune type
3. Prehypertensive type
4. Common type

The poor prognostic indicators include early age of onset, extensive (>50%) scalp involvements, loss of eyebrows and eyelashes, Alopecia totalis, Alopecia universalis, recurrent episode, Patterns: ophiasis, sisaphio, reticular, Nail changes: pits, onychodystrophy, onycholysis, anonychia. Associated systemic disorder: Atopy, hypertension, connective tissue disorders, associated genetic disorder: Down syndrome, Patchy regrowth of terminal hairs within the patch, Family history of AA and MIF-173*C gene are also associated with poor prognosis [1-3].

TREATMENTS

Topical treatments

(A). Corticosteroids
This can be given by either intralesional injections or topical application.

Intralesional steroids - Triamcinolone acetonide is used most commonly with the concentrations vary from 2.5-10 mg/mL, the lowest concentration being used on the face. A concentration of 5 mg/mL is usually sufficient on the scalp. Less than 0.1 mL is injected per site, with approximately 1 cm between injection sites, administered every 4-6 weeks. The adverse effects mostly seen are pain during injection and minimal transient atrophy [1-3,6,8].

Topical steroids

It is useful in children who cannot tolerate injections. The adverse effects commonly seen include local folliculitis (most common), telangiectasia and local atrophy [1-3,6,8].

B. Topical immunotherapy
It is based on the principle of induction and periodic elicitation of an allergic contact dermatitis by topical application of potent contact allergens. Regarding the mechanism of action, antigenic competition has been hypothesized. The introduction of a second antigen can initiate a new infiltrate containing T-suppressor cells and suppressor macrophages that may modify the pre-existing infiltrate and allow regrowth [1-3].

The commonly used agents squaric acid dibutylester (SADBE), diphenycprone (DPCP) and Dinitrochlorobenzene (DNCB). Both SADBE and DPCP appear to be equally effective. Acetone-based solutions usually are preferred because they evaporate quickly; allow patients to wear a hat or wig immediately after treatment. Quick drying also decreases the chances of dissemination to other body parts by contact. Treatment is provided weekly. The patient first is sensitized directly on the scalp with a 2% concentration on a small area (2 cm). The following week, a low concentration (0.0001%) is applied. The concentration is increased slowly every week as needed until a mild tolerable allergic contact dermatitis is elicited (Many concentrations are available that achieve this goal). Treating only half of the head allows the physician to use the untreated half as a control. Once regrowth occurs on the treated half, treatment can be applied to the entire scalp. If regrowth initially occurs on both sides, spontaneous remission is likely, although treatment cannot be excluded as the cause. Initial regrowth may be seen at 12-24 weeks. Once cosmetically acceptable regrowth is achieved, the treatment can be tapered gradually. Maintenance treatment is needed as almost all patients relapse if the treatment is discontinued [1-3].

Precaution

1. Avoid severe contact dermatitis.
2. Patients are advised to avoid light exposure on the scalp for 48 hours because light degrades the chemical.
3. Patients also are advised not to wash the scalp for 48 hours.

The adverse effects include mild contact dermatitis (redness, scaling, itching) which is desirable, cervical lymphadenopathy, Urticaria and pigment changes. Vitiligo developed on the application site. Transient leukoderma on a distant untreated area has been reported. Hyperpigmentation, Confetti-type dyschromia (ie, hyperpigmentation, hypopigmentation) has been described as an adverse effect of DPCP Erythema multiforme–like eruptions [1-3].
**C. Anthralin**
The concentrations varied from 0.2-1%. The exact mechanism is unknown. Most likely, it creates inflammation by generating free radicals, which have antiproliferative and immunosuppressive actions. Irritant contact dermatitis, pruritus, erythema, scaling, folliculitis, local pyoderma and regional lymphadenopathy are the main adverse effects [1-3].

**D. Minoxidil**
Minoxidil appears to be effective in the treatment of alopecia areata. Response rates in that group vary from 8-45%. Little benefit in patients with alopecia totalis or alopecia universalis. Maximum of 25 drops are applied twice per day, usually 1ml per site. Initial regrowth of hair can be seen within 12 weeks. Continued application is needed to achieve cosmetically acceptable regrowth.

The Hair-growth-stimulating effect of minoxidil is stimulation of PGE2 synthesis by activating prostaglandin-H synthase (PGHS)-1. Normally, Calcium influx normally enhances epidermal growth factors to inhibit hair growth. Minoxidil is converted to minoxidil sulfate, which is a potassium channel agonist and enhances potassium ion permeability, thus opposing the entry of calcium into cells. It also seems to have direct mitogenic effect on epidermal cells and also prolongs the survival time of keratinocytes [1-3].

It is usually is well tolerated. Some adverse effects include distant hypertrichosis (5%) and irritation (7%) [1-3].

**E. Topical garlic**
Although it may not be effective as monotherapy, one study which analyzed the effect of a combination of topical garlic gel and betamethasone valerate ointment in alopecia areata in a double-blind study found the combination useful in majority of the patients with a statistically significant difference between the treatment and control groups [1-3].

**F. Topical retinoids:**
Among topical retinoids, tretinoin and bexarotene have been used. Irritation of the skin is a very common side effect. The efficacy is doubtful [1-3].

**G. Prostaglandin analogs:**
Agents usually used are Latanoprost and Bimatoprost. Prostaglandin receptor (EP)3 and EP4 mRNA are expressed in the dermal papilla cells and the outer-root-sheath cells located in the hair bulb region. In the telogen phase, the signals for both EP3 and EP4 mRNA disappear. Re expression of EP3 and EP4 mRNA and induction of cyclooxygenase (COX)-2 mRNA leads to development and regrowth of the hair follicles. Changes in hair appearance is seen with regard to increased in number, length, thickness, curvature and pigmentation [1-3,5,9,10].

**H. New immunomodulatory therapies**
The aims of this therapy include a fall in the number of pathogenic T-cells, slowing down T-cell activation, Change a type 1 cytokine response to a type 2 response and to impede activities of inflammatory cytokines [17,18].

1. **Tacrolimus**
The mechanism includes inhibiting calcineurin, thereby inhibiting both T-lymphocytes signal transduction and IL-2 Transcription, preventing cytokines (such as TNF-alpha and IFN-gamma) from activating the T-cells. Topical application of tacrolimus induces anagen during the telogen phase and stimulates hair growth [4,17,18].

2. **Pimecrolimus**
It is derived from Ascomycin. This agent is highly skin specific anti-inflammatory agent. Pimecrolimus gets lodged into macrophilin-12 and holds back Calcineurin. This, in turn, hinders the synthesis of the inflammatory cytokines IL-2 and IFN-gamma. Hence, neither the mast cells nor the T-cells are activated. It fails to target the T-cells involved in alopecia areata owing to its thick, greasy quality, the cream fails to penetrate deeper into the inner layers of skin [17,18].

3. **Topical cyclosporine**
This drug acts by inhibiting Calcineurin, which in turn slows down IL-2 production and limits CD4 lymphocyte cell activity. It poorly penetrates the skin. To overcome this hurdle, a heptamer of arginine-conjugated formulation of CsA (joined with a pH-sensitive linker) with an enhanced power to penetrate the skin has been developed of late. This hyperactive form of Cyclosporine penetrates full skin thickness (even subcutaneous fat).

**SYSTEMIC TREATMENTS**

**A. Psoralen plus UV-A**
Both systemic and topical PUVA therapies have been used. The number of treatments required for
regrowth varies between 20-40 treatments in most cases with the initial response rate varies from 20-73%. The relapse rate is high, around 50-88% which is usually seen within a few months mean 4-8 months after treatment is stopped. The adverse effects include burning sensation and increased risk of skin cancer [7,11,13].

**B. Prednisone**

Systemic steroids seems to be effective via their immunosuppressive effects. With this therapy, the rate of regrowth varies greatly (27-89%). Although the initial regrowth appears promising, the prednisone dose necessary to maintain cosmetic growth usually must be high enough that adverse effects are inevitable. The adverse effects include diabetes, weight gain, hypertension, psychological changes, osteoporosis, suppression of the adrenocorticotropic axes, striae, acne, hypertrichosis and purpura [1-3,6,8].

**C. Cyclosporine**

Cosmetically acceptable regrowth is seen with doses of 3-6 mg/kg/day in most of the studies. Unfortunately, relapse is also seen within 3 months of discontinuation of cyclosporine. There is no evidence which indicate that CsA can prevent hair loss during an active episode [1-3].

**E. Interferon**

This agent is used intralesionally with a dose interferon alfa-2 (1.5 million IU, 3 times per wk for 3 wk). Few studies had been conducted with unsatisfactory results [1-3].

**F. Dapsone**

Dapsone is usually used at a dose of 50 mg twice per day or 100 mg OD. Although dapsone showed some efficacy in few studies, the high incidence of adverse effects rendered it unacceptable [1-3].

**G. Methotrexate**

Alopecia areata responded well to methotrexate, with or without systemic corticosteroids. Regrowth greater than 50% was observed in more than 60% of patients in some studies with the therapeutic dose ranges from 10-25 mg/week. Relapse rate is around 30%. One should not forget that this agent can also cause both anagen and telogen effluvium [1-3,8].

**H. Sulfasalazine:**

It is administered orally, usually as enteric coated tablets to minimize the gastrointestinal side effects. It is started at a lower dose, usually in the range of 500 mg twice daily and then the dose is gradually increased to 1 g three times a day. Sulfasalazine helps in alopecia areata because it causes inhibitions of T cell proliferation, Natural killer cell activity, antibody production, secretion of interleukin (IL)-2, IL-1, TNF- and IFN-gamma and even IL-6. The adverse effects include gastrointestinal distress, liver toxicity and haematological side effects [1-3,12].

**I. Azathioprine:**

It has immunosuppressive effect on circulating lymphocytes as well as Langerhan cells. It is usually used with a dose of 50 mg BD/100 mg per day [1-3,14].

**J. Oral zinc sulphate**

Serum zinc levels have been found to be lower in patients with alopecia areata than in control population [15,16].

**K. Antimalarials**

The agents used for this are Plaquenil and Hydroxychloroquine. Anti-inflammatory action is because of their T cell suppression [1-3].

**L. Other treatment modalities**

These include nitrogen mustard, massage and relaxation, isoprinosine and aromatherapy.

**NEW DRUGS**

**A. FDA-approved JAK inhibitors**

They are used as 0.5% cream for topical application.

1. **Ruxolitinib**

   It blocks the NKGD-activating ligand and NKG2D receptor interaction, halst activated T cells and modifies of the inflammatory cytokine network [1-3,20].

2. **Tofacitinib**

   It inhibits the Janus kinase 3 (JAK-3) enzyme located along the IL-15 signaling pathway. Regrowth of hair can be seen within 12 weeks. The drug’s effect is long-lasting, as the new hair persisted for several months after stopping treatment in Mouse model [1-3,20].
B. Biologicals

The efficacy of all biologicals for treatment of alopecia is, so far, unsatisfactory in most of the studies. The mechanism of action of these biological agents includes four basic strategies: Reduction of pathogenic T cells, Inhibition of cell activation, Immune deviation and Blocking the activity of inflammatory cytokines [17,18].

CURRENT BIOLOGIC AGENTS IN USE

1. Etanercept

It is a human fusion protein that inhibits the inflammatory cytokine TNF- a [17,18].

2. Infliximab

It is a chimerical (mouse/human)antibody protein which inhibits the inflammatory cytokine TNF- alpha [17,18].

3. Efalizumab

This is a humanized monoclonal antibody that has several effects with potential therapeutic benefit in alopecia areata. It binds CD11a, a component of LFA-1 that binds to ICAM-1 on APCs and thus it interrupts the co-stimulatory signals. It also blocks T cell adhesion to endothelial cells and T cell migration (trafficking) into inflamed tissues [17,18].

4. Alefacept

It is a fusion protein that induces apoptosis in T cells expressing high levels of CD2. It also blocks the LFA-3/CD2 interaction necessary for the activation and proliferation of T-cells by binding to CD2 on T-cells [17,18].

New biologicals

(b) Abatacept

This agent is a CTLA4Ig is a fusion protein that blocks CD80/86 (B7)co-stimulation binding with CD2 and is being suggested as a potential treatment for alopecia areata. [17,18].

(c) Anakinra

This is an interleukin-1 (IL-1)receptor antagonist. The usual dosage is 100 mg s.c OD. Dose reduction to 100 mg s.c. every other day should be considered in patients with severe renal impairment [17,18].

(d) Rituximab, a chimeric monoclonal antibody against the protein CD20

(e) adalimumab

(f) Fontolizumab (anti-IFNgamma)

Future possible treatments

1. Interleukin injections or the administration of their cDNA sequences. This can inhibit the entry of inflammatory cells into the skin and hair follicles.

2. Blocking of the production or increasing the tolerance of lymphocyte clones reactive for hair follicle antigen epitope.

3. Blocking the antigen presentation and costimulation by antigen presenting.

4. Prevention of migration of inflammatory cells from activation sites to the follicle and skin, even after activation of the lymphocytes. The targets include CD44v10 and other activated cell surface markers. These treatment modes may be used as a cure as well as a preventive measure in the case of individuals predisposed to alopecia areata.

5. The effect of PTHrP is to stimulate and accelerate the hair cycle. So, PTHagonists would be expected to promote hair growth.

6. Dealing with the disease (after the hair follicle inflammation has already set in) by inhibiting or modulating the expression of the targeted antigens in the anagen phase hair follicles, masking the expression of these threatened antigens, modification of the harmful antigen expression, caused by inflammation and prevention of expressions of MHC antigens in the hair follicles.

7. Blocking the NKG2D-activating ligand and NKG2D receptor interaction.

8. To target the mechanism by which the inflammatory cells adversely affect hair follicle growth. This includes Fas-Fas ligand interaction, prevention of granzyme and perforin action, oxygen radical neutralization and alteration of the cytokine receptor and cytokine environment [1-3,19,20].

As far as the author’s experience, conventional therapy like intralesional steroid injection is more effective than newer treatment like targeted phototherapy. The results of unpublished data of efficacy of excimer light therapy is not satisfactory. Immunosuppressant like Methotrexate is effective for extensive cases, but side effects should always be considered. Biologicals like Tacrolimus is not satisfactory.

© Our Dermatol Online 1.2015
REFERENCES