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Research Article

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Past, Present and Future Treatment of Alopecia Areata

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Abstract

Alopecia Areata (AA) is a complex autoimmune condition causing hair loss. In this article, we review the range of published conventional and unconventional treatments. While we explored the effectiveness of commonly used treatments such as topical and intralesional corticosteroids, we have focused on more advanced treatment methods such as the use of phototherapy and biological therapy. Furthermore, we explored published work for the role of unconventional treatments such as garlic, herbal lotions, essential oils and onion juice on AA. While various treatment options exist for AA, their effectiveness and long-term benefits require further research. Biological therapies, particularly JAK inhibitors, offer the most promising possibilities for well-tolerated and effective treatment. More studies are needed to optimize treatment strategies and personalize care based on individual needs and disease severity. Sources were gathered from the Cochrane database and PubMed using the following keywords: alopecia, alopecia areata, hair loss, treatments, systematic reviews and clinical trials.

Keywords: Alopecia Areata, JAK Inhibitors, Intralesional Corticosteroids, Biological Therapy

Introduction

Alopecia areata (AA) is a relatively common auto-immune conditions causing hair loss in children and adults. In this literature review, we will present the range of unconventional and conventional treatments for the management of AA published and compare their effectiveness along with their associated risks.

Unconventional Treatments of AA

Essential oils

Different essential oils derived from plants, wood, and resins, had been used in the treatment of alopecia areata.

A randomised, double blind, placebo-control trial by Hay et al, showed that daily application of Cedar wood, Lavender, Thyme, and rosemary oil significantly reduced areas of hair loss at 3- and 7-months assessment (p=0.008) [1].

Another randomised, double blind, placebo-control trial done by Ozmen et al. showed improvement in hair growth in patients' group from control group (p=0.001), clinical assessment (0.007) and the extent of the affected area (p=0.007) These results achieved after twelve weeks of topical application of Rosemary, thyme, lavender, evening primrose oil and cedrus in a carrier oil [2].

Both above studies, only used essential oils used without conventional treatment.

Garlic

Garlic is very popular agent in dermatology, and it's known for its antioxidant properties.

Garlic *(Allium sativum*) constituents are enzymes (for example, alliinase), sulphur-containing compounds such as alliin, and compounds produced enzymatically from alliin (for example, allicin) [3,4].

Other constituents like arginine, oligosaccharides, flavonoids, and selenium are available in garlic [3,4].

The mechanism of how garlic induce hair growth is not clear but thought to be attributed to the antibacterial and sterilizing properties of Allicin, cause of vasodilation and induction of the immune response [5].

A double-blind study by Hajheydari used a combination of Garlic gel with betamethasone which showed a significant good and moderate response to treatment with garlic and steroid (P=0.001) and concluded that the use of garlic is an effective adjunct to other treatment like Dexamethasone to achieve good response [5].

Another therapeutic trial done in Iraq by Maluki tested the use of garlic extract for two months and proved that garlic is effective in the treatment of alopecia areata [6].

Preparations: The Garlic preparations that is used in dermatology are divided into four main preparations which include raw garlic juice (RGJ) heated garlic juice (HGJ), dehydrated garlic powder (DGP) and aged garlic extract (AGE) in addition that some advice the use of a garlic clove cut in half and rub them against the lesion [7].

Onion Juice

The onion has similar effect of garlic, but the mechanism of action is still controversial, with some consider it as anti-inflammatory and the others think it's the opposite and induce local dermatitis.

A single-blind: Placebo controlled trial done by Al-Sharqie showed statistical significance and clinical improvement with hair growth (P=0.0001), the clinical response was over three phases: week2, 4, and 6 with the peak in week 4, this study also showed that this treatment is more effective in male (93.7%) compared to females (71.4%), mild erythema was reported during this treatments as a side effect of the treatment [8].

Primula Obconica

Both leaves and flowers of Primula Obconica had been used to induce hair growth after sensitisation of the affected area [9]. A single case series study of five patient is all what we must support the use of this plant in Alopecia Areata which gives a week evidence to support its use in clinical practice. In this study they applied the plant twice a week and showed the growth of hair happened after one month and more evident growth after two months.

Herbal Lotion

Two herbal extracts used in as an alternative therapy for AA: salvia miltiorrhiza radix (SMR) A study found that when SMR removed from a specific herbal lotion, the effectivement of hair growth reduced by 10% [10].

Urginea maritima (white squill) it's a traditional medicine used in Iran for Alopecia Areata. A randomised double-blind trial (n=42) over 12 weeks compared topical Clobetasone 0.05% lotion and 2% White squill, After 3 months moderated regrowth of terminal hair (defined as 50%) were observed in 45% in the 2% white squill and 55% with 0.05% Clobetasone [11].

However, there were no statistically significant differences in mean hair growth rates between the two groups, suggesting that both treatments may facilitate hair regrowth.

Conventional Treatments

Topical Steroids

The effectiveness of potent topical steroids, such as 0.25% desoximetasone cream and 0.05% clobetasol propionate foam, for treating alopecia areata lacks substantial evidence. In a randomized controlled trial with 70 patients having patchy alopecia areata, the application of 0.25% desoximetasone cream showed a higher number of patients experiencing slight improvement compared to a placebo. However, this result didn't achieve statistical significance (level of evidence 2+) [13].

Another trial involving 34 patients with moderate to severe alopecia areata used 0.05% clobetasol propionate foam [14]. Participants were randomly assigned to apply clobetasol to one side of the scalp and a placebo to the other side. After 12 weeks, more individuals treated with clobetasol experienced at least 50% hair regrowth compared to the placebo group (7 out of 34 vs. 1 out of 34).

Additionally, using 0.05% clobetasol propionate ointment under an occlusive dressing for six out of seven nights over six months showed potential for long-term hair regrowth in patients with AT/AU experiencing hair loss for about 7 years. Among 28 patients in this study, 18% saw hair regrowth. Notably, initial treatment was applied to only one side of the scalp, and regrowth didn't occur on the untreated side [14]. However, it's crucial to note that using potent topical steroids like clobetasol propionate can lead to folliculitis, a common side effect associated with this type of treatment.

Intralesional Corticosteroids

Intralesional corticosteroids (ILCs) have shown effectiveness (level of evidence 3) in stimulating hair regrowth at the injection site for certain patients with alopecia areata [15]. Studies reported that triamcinolone hexacetonide and triamcinolone acetonide injections stimulated hair tufts in alopecia areata patients, lasting approximately nine months. In another study, monthly injections of triamcinolone acetonide resulted in 62% of patients achieving full regrowth, especially in those with fewer and smaller patches. For patchy hair loss, particularly in cosmetically sensitive areas like eyebrows, ILCs are suitable. Hydrocortisone acetate (25 mg/mL) and triamcinolone acetonide (5-10 mg/mL) are commonly used. The corticosteroid is injected just below the skin's surface in the upper subcutaneous layer.

In managing adult patients with less than 50% scalp involvement, intralesional corticosteroids (ILCs), especially triamcinolone acetonide, are the preferred first-line therapy. Concentrations typically range from 2.5 to 10 mg/mL for different areas, with the recommended scalp concentration being 5 mg/Ml [16].

Triamcinolone acetonide is administered intradermally using a 0.5-inch long, 30-gauge needle, with multiple 0.1-mL injections spaced at 1-cm intervals. Saline is preferred over Xylocaine as a diluent to reduce discomfort.

Treatment sessions are repeated every four to six weeks, with initial regrowth observed within four to eight weeks. If no improvement occurs after six months, discontinuation of ILC therapy is recommended. However, ILCs are typically avoided for children under 10 due to localized pain at the injection site.

In some cases of alopecia areata, resistance to glucocorticoids may occur due to reduced expression of thioredoxin reductase 1 in the outer root sheath. Optionally, topical anesthetics can be used before the procedure to minimize injection pain, particularly for eyebrow treatments. Additionally, needleless devices like Dermajet™ can be utilized if sterilized between patients [17].

Contact Immunotherapy

The contact immunotherapy protocol involving DPCP, as described by Happle et al., follows a systematic approach to stimulate hair regrowth by modulating the immune response [18]:

- Sensitization: Initially, a 2% DPCP solution is applied to a small scalp area to prime the immune response.
- Progressive Application: Two weeks later, weak DPCP solutions (starting at 0.001%) are applied weekly to the scalp.
- Concentration Increment: DPCP concentration is increased gradually until a mild dermatitis reaction occurs, indicating an active immune response.
- Unilateral Treatment: Some opt for treating only one side initially to distinguish treatment response from spontaneous recovery.
- Bilateral Treatment: Both sides are treated once hair regrowth is confirmed, though this might not be necessary in severe, long-standing cases.
- Self-Treatment: There's debate about patients administering the treatment themselves, based on comfort and required supervision.

This gradual approach allows monitoring and risk minimization. Treatment frequency is often reduced after achieving maximum response, and discontinuation is considered upon full regrowth.

Studies suggest a varied response rate (9-87%), with 50-60% achieving worthwhile response [19]. Extensive hair loss and certain factors (nail changes, early onset, positive family history) may impact response likelihood. Treatment discontinuation typically follows six months of no response.

A Canadian case series indicated clinically significant regrowth in 30% after 6 months, rising to 78% after 32 months, supporting prolonged treatment [20]. However, patients with AT/AU showed less favourable responses (17%), unaffected by treatment duration beyond 9 month.

Minoxidil

Minoxidil Comparison (5% vs. 1%) in Alopecia Areata: A study comparing 5% and 1% minoxidil in extensive alopecia areata showed more frequent hair regrowth in individuals using 5% minoxidil. However, achieving cosmetically significant results was rare. Topical minoxidil was found ineffective for cases of alopecia totalis/alopecia universalis (AT/AU) [21].

Dithranol (Anthralin) and Irritants in Alopecia Areata Treatment: Case report series on dithranol and other irritants for alopecia areata treatment lack control groups, making it difficult to accurately evaluate response rates. Evidence indicates only a small number of patients achieve cosmetically significant results. In one study, 18% of patients with extensive alopecia areata experienced cosmetically meaningful hair regrowth. Application of dithranol at a high enough concentration and frequency to induce an irritant reaction is deemed necessary for effectiveness [22].

The findings suggest that while 5% minoxidil showed more hair regrowth compared to 1% minoxidil in alopecia areata, achieving cosmetically significant results was limited. Similarly, treatments involving dithranol and irritants exhibited modest success rates, emphasizing the need for careful application at suitable concentrations to yield noticeable hair regrowth [23].

Prostaglandin analogues

The relationship between prostaglandin F2a analogues (like latanoprost and bimatoprost) used in treating open-angle glaucoma and eyelash alopecia has been explored. Some studies have reported eyelash hypertrichosis as a side effect of these medications [24].

In a study involving 40 alopecia universalis (AU) patients, topical latanoprost treatment for 2 years resulted in complete or moderate regrowth of eyelashes for 45% of the patients, while no regrowth was observed in a nonrandomized control group. However, conflicting results were found in a 16-week controlled study with 11 patients having eyelash alopecia, where neither latanoprost nor bimatoprost showed a significant response. Similarly, in another 16-week controlled study involving 26 patients using latanoprost, only one patient showed partial regrowth [25]. The conflicting outcomes from these studies highlight the need for more extensive and prolonged randomized controlled trials (RCTs) to better understand and reconcile these differing findings.

Dithranol

Studies have reported varying degrees of hair regrowth with dithranol (anthralin), but these trials used low concentrations (ranging from 0.1% to 1.25%) and inconsistent measurements of AA severity [26]. Considering patients who haven't responded to potent topical or intralesional steroids, treatment trials extending up to 12 months with dithranol at higher concentrations might be a viable option, irrespective of the severity of AA. However, there's a need for randomized trials utilizing less staining formulations of dithranol to further assess its efficacy in treating AA.

Narrowband ultraviolet B Phototherapy

While narrowband ultraviolet B (NB UVB) phototherapy is a widely used treatment for various dermatological conditions, its efficacy for AA treatment lacks substantial evidence in the literature.

A retrospective review was conducted on 25 AA patients treated with NB UVB, some of whom also received intramuscular triamcinolone acetonide injections monthly if there were no contraindications [27]. Among the patients, 32% received monthly intramuscular corticosteroid injections. Of the patients with extensive patchy hair loss, 22.2% achieved an excellent response, while 20% of those with complete scalp hair loss had an excellent

response. Notably, 4 out of 6 patients who achieved an excellent response also received monthly intramuscular corticosteroid injections. A statistically significant difference was observed in patients who achieved an excellent response when comparing those receiving systemic corticosteroid injections alongside NB UVB versus patients receiving only NB UVB. The study concluded that NB UVB alone showed a limited effectiveness, with only 20% demonstrating excellent treatment responses, particularly in severe AA cases, most of whom also received systemic corticosteroids.

Pulsed Methylprednisolone Therapy

The use of pulse methylprednisolone for severe alopecia areata (AA) has shown effectiveness, but prolonged therapy is limited due to potential side effects. However, the effectiveness of a single intravenous pulse of methylprednisolone hasn't been assessed in patients experiencing ongoing hair loss for less than 12 months [28]. In a study, a single series of intravenous pulse methylprednisolone was found to be well tolerated and effective in patients with rapidly progressing extensive multifocal alopecia areata. However, this treatment did not exhibit the same effectiveness in patients with ophiasic and universalis types of AA.

Biological Therapies

Genomic studies have unravelled the genetic underpinnings of AA and their similarities to other autoimmune disease such as Type 1 diabetes mellitus and rheumatoid arthritis, paving the way for the use of biologic therapies such as JAK inhibitors (baricitinib, ritlectinib, deuruxolitinib, brepocitinib) in the treatment for AA [29]. Other biologics such as dupilumab, secukinumab, and aldesleukin have been considered for the treatment of AA.

The JAK-STAT signalling pathway is an intracellular cascade that is used by cytokines and growth factors to transmit signals between cells playing a key role in inflammatory processes. It's inhibition has been hypothesized to obstruct these inflammatory processes and hence lead to immunomodulatory functions. A meta-analysis by Phan and Sebaratnam on JAK inhibitors use on AA concluded that there is statistically significant improvement across 30 studies and 289 cases, with oral route being more superior than topical. [30] A more recent systemic review of 12 randomized-controlled trials showing induction of significant hair regrowth with limited adverse effects [31].

Baricitinib, a selective reversible inhibitor of JAK1 and JAK2 has recently been granted FDA approval for the management of severe AA; the oral dose being 2mg once daily increased to 4mg once daily if tolerated. A phase 3 randomized double blinded trial showed significantly improved hair regrowth based on the Severity of Alopecia Tool (SALT) in over 30% of cases [32]. Ritlecitinib, a JAK3 inhibitor and Beprocitinib, a TYK2/JAK1 inhibitor have also been assessed in a phase 2 trial showing a dose-dependent impact on hair regrowth in AA [33]. Tofacitinib, a selective JAK1/3 inhibitor, has also been reviewed in a meta-analysis of 14 studies including 275 patients showing good hair regrowth in 54% of participants [34].

The biggest challenge in the management of AA is the high risk of recurrence, averaging at 2-3 months post-cessation of treatment. [30] One suggestion is the use of JAK inhibitors could be used as maintenance once hair regrowth has occurred, with an eventual tapering down regime to reduce the risk of relapses [29]. Another barrier for the use of JAK inhibitors remains the high cost of the treatments [35].

Dupilumab is an anti-IL and anti-IL13 monoclonal antibody that targets the Th2 signalling pathway has also been implicated in the management of AA. A randomized-placebo controlled trial by Guttman-Yassky et al. reviewed weekly subcutaneous dupilumab (300mg) on 40 patients with AA showing moderate hair regrowth, with better results for patients with a higher baseline serum IgE [36]. Disappointingly, the systematic review by Gupta et al. suggested limited efficacy for dupolimuab and aldeslukin in the management of AA [31]. Secukinumab, an anti-IL17A monoclonal antibody has also been shown to have low to no impact on AA according to a pilot study [37].

Conclusion

Various approaches have been hypothesized for the treatment of alopecia areata with widely variable outcomes. In this review, unconventional and conventional treatments were listed along with their risks. It is however imperative that further research is needed to better understand the long-term benefits of all the outlined treatments. There is growing hope in the role of biologics as well-tolerated and advanced treatment modality for auto-immune conditions such as AA.

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