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Alopecia Areata: Evidence-Based Treatments

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Alopecia areata is a common condition causing nonscarring hair loss. It may be patchy, involve the entire scalp (alopecia totalis) or whole body (alopecia universalis). Patients may recover spontaneously but the disorder can follow a course of recurrent relapses or result in persistent hair loss. Alopecia areata can cause great psychological distress, and the most important aspect of management is counseling the patient about the unpredictable nature and course of the condition as well as the available effective treatments, with details of their side effects. Although many treatments have been shown to stimulate hair growth in alopecia areata, there are limited data on their long-term efficacy and impact on quality of life. We review the evidence for the following commonly used treatments: corticosteroids (topical, intralesional, and systemic), topical sensitizers (diphenylcyclopropenone), psoralen and ultraviolet A phototherapy (PUVA), minoxidil and dithranol.
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Alopecia areata (AA) is a chronic inflammatory condition causing nonscarring hair loss. The lifetime risk of developing the condition has been estimated at 1.7% and it accounts for 1% to 2% of new patients seen in dermatology clinics in the United Kingdom and United States.[1] The onset may occur at any age; however, the majority (60%) commence before 20 years of age.[2] There is equal distribution of incidence across races and sexes. In recent decades, the role of genetic predilection has started to be explained. Approximately 20% of affected people have a family history of the disease, suggesting a genetic predisposition.[3] A small twin study found an inherited component in approximately 55% of those afflicted by the disease, suggesting there is also a contribution from environmental factors.[4] Associations have been reported with chromosome 21 (increased incidence in Down's syndrome), major histocompatibility complex, and cytokine and immunoglobulin genes indicating a polygenic basis. A genome-wide scan identified additional loci that also are implicated in other hair disorders and psoriasis.[5]

AA is considered a tissue-restricted autoimmune condition as the result of association with other autoimmune diseases, both within the affected person and their family. Circulating antibodies against follicular components are detected more frequently in people with AA.[6,7] A hallmark of AA is a peribulbar lymphocytic infiltrate that consists primarily of activated T-lymphocytes.[8] Experiments using human hair follicles transplanted onto immunoincompetent mice strongly implicate a T-cell–mediated pathomechanism.[9]

Affected people develop single or multifocal smooth, well-circumscribed patches with short broken hairs at the periphery (exclamation mark hairs). The pattern and severity of hair loss varies greatly. All hair-bearing skin may be involved, with approximately 10% of those with AA having nail involvement. Recovery can occur spontaneously, although hair loss can recur and progress to alopecia totalis (total loss of scalp hair) or universalis (both body and scalp hair). Diagnosis is usually made clinically, and investigations usually are unnecessary. Poor prognosis is linked to the presence of other immune diseases, family history of AA, young age at onset, nail dystrophy, extensive hair loss, and ophiasis (AA of the scalp margin).[10]

AA can cause significant psychological problems. The unpredictable nature of the condition, with apparent improvement followed by deterioration can be distressing. One of the most important aspects of management is counseling the patient and the family members of a young child about the nature and course of the condition as well as the available effective treatments with details of what they involve and their side effects.

Treatment

The hair follicle in AA is not destroyed. Therefore, there is potential for regrowth, although there is no cure and no treatment has been shown to alter the course of the disease. Many treatments can induce hair growth. However, assessing efficacy is difficult in patchy AA as a result of the frequency of spontaneous recovery. On the other hand, studies incorporating patients with severe disease are hampered by the poor response to any form of treatment in this group of patients.

There are few randomized controlled trials of treatments for AA,[11] although for common treatment modalities none have shown a significant long-term benefit compared with placebo. There are numerous reports of treatments for AA that have assessed efficacy with less-than-ideal criteria. Many of these studies and reports are of doubtful value; however, some treatments that have not been evaluated in randomized controlled trials may benefit some patients.

No Treatment

Because there is a high proportion of spontaneous recovery, with 34% to 50% recovering within 1 year,[12] not all patients require treatment.

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However, the relapsing nature of the disease needs to be discussed with patients. Patients with AA normally are highly motivated and compliant, but some patients may not want treatment or may not respond and alternatives such as wigs, should also be discussed.

Corticosteroids

Topical Corticosteroids

Potent topical steroids are widely used to treat AA, but the evidence for their efficacy is limited. A 12-week within-patient study (right vs. left side of scalp) in moderate-to-severe disease with a 0.05% clobetasol propionate foam formulation showed regrowth of at least 50% in 7 of 34 of the treated sites compared with 1 of 34 on the nontreated sites.[13] A previous study of 0.05% clobetasol propionate under occlusion in patients with alopecia universalis/totalis showed that 29% (n = 8) benefited; however 3 patients, relapsed in the 6-month follow-up, giving a 17.8% overall long-term benefit.[14] In a randomized study comparing betamethasone valerate foam to betamethasone dipropionate lotion in 61 patients with mild-to-moderate AA, the foam formulation produced significantly greater regrowth at 12 weeks.[15] However, a study by Charuwichitratana et al[16] of 0.25% desoximetasone cream in moderate alopecia failed to show significant benefit over placebo after 12 weeks of treatment.

Intralesional Corticosteroids

Intralesional corticosteroids also are used frequently in AA. Their use was first described in 1958 with the use of hydrocortisone.[17] Steroids with low solubility are preferred for their slow absorption from the injection site, promoting maximum local action with minimal systemic effect. A study of intralesional corticosteroids showed the time from injection to visible hair growth was 2-4 weeks and subsequent growth occurred at a constant linear rate. Tufts grew at 33 of 34 sites injected with triamcinolone hexacetonide and at 16 of 25 injected with triamcinolone acetonide.[18] The steroid is injected into the upper sub cutis every 4 to 6 weeks. Preparations used include triamcinolone acetonide (5-10 mg/mL) and hydrocortisone acetate (25 mg/mL). There are no randomized controlled trials on intralesional steroids. An uncontrolled study from Saudi Arabia found 63% of patients receiving monthly triamcinolone injections showed complete regrowth. The outcome was more favorable in younger adults with less than 5 patches of short duration (less than 1 month) and less than 3 cm diameter.[19] Side effects are minimal. Skin atrophy is common but resolves within a few months. The risk of prolonged atrophy can be reduced by the use of smaller quantities, limiting the number of injections per site and ensuring the injection is not too superficial. Intralesional corticosteroids are most suitable for patchy, relatively stable hair loss of limited extent. This modality is not appropriate in rapidly progressive AA or in alopecia totalis/universalis.

Systemic Corticosteroids

Systemic corticosteroids have been used in the treatment of AA since the 1950s.[20] There is little doubt that systemic steroid treatment will induce hair regrowth but, in patients with more severe forms of the disease, relapse is common when treatment is discontinued. Concerns over the side effects of long-term treatment mean that many physicians are not prepared to use systemic steroids to treat alopecia areata.[21] In an attempt to reduce systemic side effects, various high-dose pulsed therapy regimens have been tried. Regimens include prednisolone, 2 g intravenous single dose or 0.5 g daily for 5 days,[22] alternating daily dose,[21] tapering oral dose over 6 weeks,[23] intravenous methylprednisolone 250 mg twice daily for 3 days[24] and 300 mg monthly for at least 4 months.[25] Most studies have reported a good initial response to therapy, ranging from 11.4% to 47%. However, benefit is only maintained while the patient continues treatment. A randomized controlled trial showed patients receiving 200 mg prednisolone once weekly for 3 months were more likely to develop significant regrowth than were those given placebo. However, 25% relapsed within 3 months of discontinuation of treatment.[26] Two other studies found, after an initial response, that 6 months to 15 months after treatment there was no substantial benefit.[21,22] A further trial showed 2% minoxidil lotion following 6 weeks of tapering prednisolone may decrease the hair loss.[23] Pulsed corticosteroids appear to be well tolerated. However, those receiving daily or alternate day oral regimes developed the expected side effects, including: acne, obesity, mild hypertension, impaired ACTH reserve, and lenticular opacities.[21] Oral steroids appear to work well initially on recent-onset disease, but ophiasis and universalis respond poorly.[24]

Contact Immunotherapy

Contact immunotherapy is defined as the induction and periodic elicitation of an allergic contact dermatitis by topical application of a potent contact allergen. Topical sensitizers have been the mainstay of treatment in severe AA since 1976 when dinitrochlorobenzene (DNCB) was first used. As the result of concerns over the mutagenic properties of DNCB in *Salmonella enteritides* serotype typhimurium and its absorption through the skin with ultimate excretion in urine, its use has been discontinued. Squaric acid dibutylester (SADBE) has also been used because it is not mutagenic in the *Salmonella* microsome test. However, it is expensive and not as stable in acetone as diphenylcyclopropenone (DPCP). DPCP, first introduced by Happle,[27] has become the topical sensitizer of choice. It shows no mutagenic properties in the Ames test.[28] A precursor of DPCP is a potent mutagen and may be a potential contaminant in commercial samples, although Wilkerson found no detectable contaminants in their analysis of commercial DPCP. It is soluble in acetone but it is very light sensitive and must be shielded from light.

The mechanism of action of topical sensitizers is poorly understood. Skin treated with topical sensitizers shows decreases in the peribulbar CD4/CD8 lymphocyte ratio,[29] supporting a theory of immunomodulation. Theories include the contact sensitizer allowing for the recovery of the hair follicle by driving autoreactive T cells into activation-induced cell death,[30] antigenic competition,[31] and modulation of proinflammatory cytokines in the follicular milieu.[32]

Patients are first sensitized by the use of 2% DPCP in acetone applied to the scalp. One week later, if there is no evidence of severe dermatitis, treatment begins with a 0.001% solution. This is repeated weekly at increasing concentration until erythema and pruritus are observed, and then weekly treatments are continued at the concentration that induces a mild dermatitis reaction. Treatment generally has to be continued indefinitely or intermittently in responders. Most practitioners discontinue treatment after 6 months if there is no sign of hair regrowth. However, one study reported an increased response rate in patchy alopecia, but not in totalis/universalis, when treatment was continued for up to 32 months.[33] Opinions are divided over whether patients should be allowed to treat themselves. The most common side effects are occipital and cervical lymphadenopathy and eczematous eruptions, which may extend to other body sites. Other side effects include scalp edema, high fever, vitiligo,[34] contact urticaria[35] and the pigmentary disturbance "dyschromia in confetti," which is more frequent in darker skin.

Initially Happle, and colleagues[27] found 67% of treated patients had a satisfactory response to DPCP. The large study by van der Steen and colleagues[36] of 139 patients showed a response rate of 50.4%. A review of 17 reported case series concluded that 50-60% of patients achieve a worthwhile response to DPCP, but the range

was very wide (9-87%).[37] Despite good initial effects, the true long-term efficacy is difficult to assess. Gordon and colleagues followed 32 responders for an average of 30 months. Nine maintained cosmetically acceptable regrowth without further DPCP for an average of 19.8 months; a further 9 with continued treatment (mean follow-up 25.6 months). However, 9 had poor regrowth despite continued treatment, and the last 5 discontinued treatment as the result of side effects.[38] Similar regrowth and relapse rates have been found in children (32-33% improvement after 6 months).[39,40] Poor prognostic factors for response to DPCP include disease severity and duration, age of onset, family history, nail changes, and atopy.[36,38]

Photochemotherapy (PUVA)

There are many uncontrolled studies of PUVA treatment in a range of modalities (local, whole body, and oral or topical psoralen) claiming response rates of up to 60%.[41-43] However, two retrospective reviews of clinical experience suggested that the response rate is low (6.3-13.1% after at least 3 months treatment)[44] or was no better than spontaneous improvement.[45]

Minoxidil

Most clinical trials of topical minoxidil lotion have failed to show a significant treatment response.[46-48] One study of extensive AA, in which 3% minoxidil lotion was used under petrolatum occlusion, hair regrowth occurred more frequently in patients receiving active treatment than in control subjects.[49] However, the number of patients treated was small and the experience of most clinicians is that topical minoxidil is of little value in AA.

Dithranol

There have been a small number of uncontrolled case series evaluating dithranol (anthralin) in the treatment of AA.[50-52] The largest treated 68 patients with dithranol, 0.5-1.0%. Twenty-five percent responded, although only 17.6% maintained a good cosmetic response. The mean time to cosmetic response was 23 weeks.[51]

Miscellaneous

Cyclosporin appears to stimulate hair growth in some patients with AA,[53] but the results are not good enough to justify the risks.[54] Published case series have also reported responses to sulfasalazine[55,56] and methotrexate,[57] but these need to be confirmed in controlled trials. Ineffective treatments include topical tacrolimus,[58] mycophenolate mofetil,[59] and photodynamic therapy.[60,61]

Biological Drugs

Initial optimism that biological drugs would introduce a new era in the treatment of AA has so far not been realized. The anti-tumor necrosis factor drugs appear ineffective. There are case reports of worsening or onset of AA during treatment with infliximab[62-64] and a series of 17 patients showed no response to etanercept.[65] In a randomized controlled trial of 62 patients the anti-CD11a biological efalizumab also was ineffective.[66] A case report of alopecia universalis responding to alefacept needs to be confirmed in a larger study.[67]

Conclusions

Although many treatments exist for AA, none alters the natural history of the disease, and assessment of each treatment is difficult because of a lack of controlled trials and the occurrence of spontaneous remission. Most studies are short term, lasting less than 6 months, and those that last longer show poor long-term benefit from the interventions. Contact immunotherapy is the best-documented treatment for severe AA, including extensive patchy loss, alopecia totalis and universalis. However, a relatively small proportion of patients achieve good long-term cosmetic results, and contact immunotherapy is not licensed or widely available. Potent topical steroids or intralesional steroids form the mainstay of treatment for limited disease but are of little value in rapidly progressive alopecia or alopecia totalis/universalis.

The Cochrane review highlighted the paucity of good-quality controlled trials in AA and also noted the absence of patient assessments of the outcomes.[11] In most patients with extensive AA, hair loss is a lifelong affliction—in a long-term follow-up study of 191 patients seen with AA between 1983-1990, almost all those presenting with alopecia totalis/universalis still had severe disease and only about half of those presenting with patchy alopecia were disease-free.[68] Consequently, management aimed at helping patients cope with their lack of hair is probably of greater importance than medical treatment. Such measures are inherently difficult to evaluate because they depend on doctor–patient relationships that cannot be easily standardized. Nevertheless, until more effective therapies become available, clinical research in AA should perhaps place greater emphasis on the value of areas such as counselling services, prosthetic support, and self-help groups than has been the case to date.

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