Management of alopecia areata

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Alopecia areata is a common condition characterised by sudden onset of patchy hair loss without signs of skin inflammation or scarring. It accounts for about 2% of new referrals for dermatology in the UK and United States and has an estimated lifetime risk of 1.7%.[1] Data from the National Health and Nutrition Examination Survey indicated a prevalence of 0.15% in the population of the United States.[w1] The extent of hair loss can vary greatly, ranging from a single coin sized patch to very extensive alopecia involving the entire scalp and the rest of the body. The condition is unpredictable; spontaneous regrowth of hair can occur at any time during its course with the possibility of subsequent relapse. Alopecia areata is particularly difficult to manage and most of the available therapeutic options are unsatisfactory. It is a psychologically distressing disease and doctors should provide patients with realistic advice about treatments and their effectiveness.

Although several medical treatments have been reported for the condition, the evidence is quite difficult to interpret because of differing study methods, non-homogeneous patient populations, variability in outcome measures, and failure to control for spontaneous regrowth. A recent Cochrane review concluded that "there is no good trial evidence that any treatment provides long-term benefit to patients with alopecia areata."[2] However, this review did not take into account studies using the "half head" treatment method, in which only half the scalp is treated until unilateral regrowth of hair is observed (fig 1). This method is regarded by hair specialists as a robust way to differentiate treatment response from spontaneous regrowth.[w2] We aimed to review evidence for the management of alopecia areata in a balanced way and discuss which treatments may help patients. We also discuss potentially interesting new treatments that require further investigation.

SUMMARY POINTS

Alopecia areata is a common cause of patchy hair loss in adults and children and can greatly affect quality of life.

Spontaneous hair regrowth occurs within a year in over half of people with patchy disease.

Objective assessment of treatment efficacy is very difficult due to the high but unpredictable rate of spontaneous remission.

First line treatments are topical immunotherapy for extensive disease and intralesional corticosteroids for localised patchy hair loss.

Half-head treatment regimens can be used to control for spontaneous hair regrowth in trials of topical treatment.

Standardised trial methods with clinically meaningful endpoints should be adopted by all future studies to help identify optimal treatments

SOURCES AND SELECTION CRITERIA

We used our knowledge of the medical literature, treatment guidelines from national organisations (including the National Alopecia Areata Foundation, United States), the Cochrane Library, and searches of PubMed (search term: alopecia areata).

Who gets alopecia areata?

Forty to fifty per cent of patients develop alopecia areata before age 21 years, while 20% develop it after the age of 40. Men and women are affected equally, and there is no well defined racial preponderance. Around 20% of patients have a positive family history for the disease.[3]

What are the characteristic clinical features?

Alopecia areata most frequently presents as a single round patch or multiple patches of hair loss that may coalesce into larger areas of alopecia (fig 2). Complete loss of terminal hairs from the entire scalp (alopecia totalis) or the scalp and body (alopecia universalis) can sometimes develop, as may a band-like pattern of hair loss at the occipital scalp margin (ophiasis). Although the scalp is the most common site, any hair bearing skin may be affected. The involved skin looks normal apart from being devoid of hair. The extent and location of alopecia can vary greatly between patients and within individuals over time. A pathognomonic sign is the "exclamation mark" hair—this term describes a broken hair that is thicker towards the distal end and thinner at the base, usually found at the edge of an active area of hair loss (fig 2). Nail changes such as pitting are seen in around 10% of patients.[3 w3]

The characteristic histological feature is a variably dense lymphocytic infiltrate around the growing hair bulb.

Box 1 | Differential diagnoses

- Tinea capitis should be suspected in any case of patchy hair loss when evidence of scalp inflammation exists, particularly in children. Fungal microscopy and culture should be performed.
- Trichotillomania is where hairs are removed by the patient. The hair loss is usually incomplete with multiple broken hairs of varying length. Younger children often grow out of this disorder but in older children and adults it may signify more marked psychological problems.
- Cicatricial (scarring) alopecias are uncommon inflammatory disorders that target and destroy the hair follicle, resulting in permanent alopecia. They are characterised clinically by loss of visible follicular ostia. Scalp biopsy is often diagnostic.[w36]

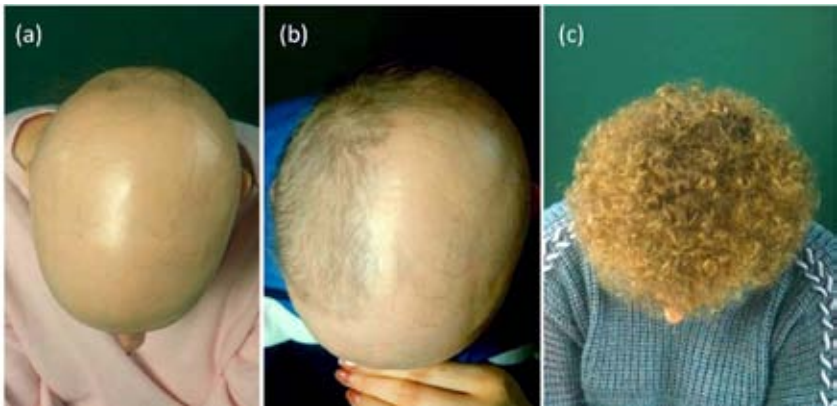

Fig 1 | Alopecia totalis treated with topical immunotherapy (2,3-diphenylcyclopropenone): (A) before treatment; (B) unilateral hair regrowth after 15 weeks of unilateral treatment; (C) complete regrowth after 42 subsequent weeks of bilateral treatment. Courtesy of R Happle, University of Marburg, Marburg, Germany

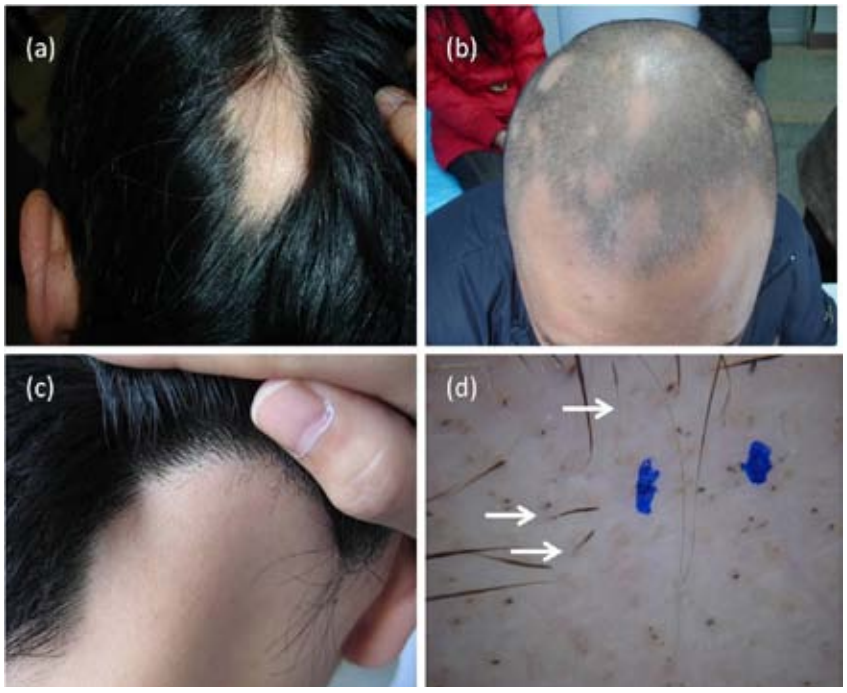

Fig 2 | Clinical presentations of alopecia areata: (A) single patch; (B) multiple patches; (c) ophiasis pattern; (d) dermatoscopy view of "exclamation mark" hairs (arrows; x30 magnification); note also monomorphic yellow dots, a common dermatoscopic feature of alopecia areata[w40]

Hairs are prematurely converted from the growth (anagen) to regression phase (catagen) with ongoing inhibition resulting in dystrophic, miniaturised hairs.[w4] Importantly, follicles are not destroyed by this inflammatory process, so hair can potentially regrow even after many years. Box 1 lists possible differential diagnoses.

What causes alopecia areata?

Alopecia areata is a T cell dependent autoimmune disease that is specific to the skin. It occurs in genetically susceptible individuals when defects occur in localised immunosuppressive mechanisms that normally "hide" defined tissue compartments from immune attack (termed "immune privilege") in the proximal anagen hair follicle. These mechanisms include reduced expression of major histocompatibility complex class I and upregulation of locally generated immunosuppressants. In mice, alopecia areata lesions can be induced by the transfer of activated T-cells but not by serum, suggesting that autoreactive T-cells rather than autoantibodies play a part in disease pathogenesis.[4] Large case reviews have shown that alopecia areata is associated with several different autoimmune conditions, particularly thyroid disease and vitiligo.[w3 w5]

How is alopecia areata diagnosed?

Alopecia areata is generally diagnosed clinically; although fungal cultures (to identify dermatophyte infections that can mimic annular lesions of alopecia areata) and scalp biopsy (to identify diagnostic histological features of alopecia areata or exclude other hair loss conditions) may help in difficult cases. A history of patchy hair loss that has regrown is highly indicative of alopecia areata. Routine screening for associated autoimmune conditions is not currently recommended by the British Association of Dermatologists.[3]

What is the natural history if untreated?

At least 50% of patients with patchy disease lasting less than a year will experience spontaneous remission, although further episodes are common.[w6] A follow-up study identified remission rates of 34-50% within a year in patients who had reached secondary care; however, sustained remission is rare in patients with extensive disease and reportedly occurs in less than 10% of cases.[3 5 6] The high, but unpredictable, rate of spontaneous remission means that it is difficult to objectively assess the efficacy of treatment.

Most patients (86-100%) will develop further episodes of alopecia areata and data from large case series suggest that around 30% of patients with patchy disease will eventually progress to complete hair loss.[5 w3] The most important prognostic factors are the extent and pattern of disease. Alopecia totalis, alopecia universalis, and ophiasis have the worst outcomes, with lower rates of spontaneous remission and poorer responses to therapy than other presentations. Onset before puberty, co-existing atopy, associated autoimmune diseases, nail dystrophy, long disease duration, and a positive family history are risk factors for more severe disease.[3]

How is alopecia areata managed?

General advice

If eyelashes are lost, glasses should be worn outdoors to protect the eyes from airborne particles. Exposed scalp skin should be protected from sun damage with a hat or sunscreen. Many patients find wigs or scalp cosmetics useful ways to cope with their hair loss, and dermatography (tattooing) of eyebrows can produce good cosmetic results. The psychological effect of alopecia areata should be explored with the patient (box 2). Sources of information and support, such as patient support groups (see Additional Resources) can be invaluable.

To treat or not to treat?

Since as many as half of patients will spontaneously regrow hair within a year,[3 6] opting not to treat is perfectly reason-

Box 2 | Psychological toll of alopecia areata

The individual level of psychosocial distress caused by alopecia areata is often underestimated. Significantly impaired quality of life (measured using dermatology life quality index[w33]) along with increased anxiety and depression scores and low self esteem are common findings in patients with the condition.[w34] Patient support networks (see www.naaf.org) and psychological therapies may help patients to develop positive coping strategies and improve quality of life.[w35] The doctor should direct the patient to such non-medical supportive services.

able for many patients. Discussion of poor prognostic factors and the relapsing nature of the condition with patients is important to help them to make up their mind.

Treatment options supported by controlled clinical trials or half-head studies

Intralesional corticosteroids and topical immunotherapy (fig 1) are the only current treatments that are generally agreed by hair experts to be effective. They are thus recommended by widely accepted guidelines as first line treatment options for alopecia areata.[3 w7 w8]

Intralesional corticosteroids

No studies of intralesional corticosteroids fulfilled the recent Cochrane review's criteria for inclusion.[2] However, practitioners have frequently observed that a tuft of terminal hairs grows at the site of corticosteroid injection and this observation has been considered a treatment response.[7 8] Prospective studies have shown that intradermal injections of corticosteroid, usually in the form of triamcinolone acetonide (5-10 mg/ml) used every two to six weeks, stimulate localised regrowth at 60-67% of injection sites.[7-9] Side effects include pain, localised atrophy, and skin depigmentation. Textbooks and national guidelines from the British Association of Dermatologists recommend this approach as first line therapy for localised patchy disease,[3 w8] although recently this treatment has also been successfully used in extensive disease (>50% scalp area) with a reported response rate of 60%.[10]

Topical immunotherapy

Contact immunotherapy, usually with 2,3-diphenylcyclopropenone (DPCP) or squaric acid dibutylester (SADBE), has been used in the treatment of extensive alopecia areata for over 30 years.[w9] The objective of treatment is to induce a low grade allergic contact dermatitis by initially sensitising the patient, and then applying very weak concentrations of the compound directly to the scalp once a week (web appendix). Although no randomised controlled trials have evaluated the effectiveness of topical immunotherapy in alopecia areata,[2] observational studies have used the half-head method to control for spontaneous regrowth of hair (fig 1).

A comprehensive review of published topical immunotherapy studies (SABDE=13 trials; DPCP=17 trials) found little difference between the two agents. A weighted analysis found that 58% patients across all the studies achieved at least 30% regrowth, although relapse rates were high and increased with longer follow-up periods.[11] The largest reported series (n=148) of DPCP treatment found cosmetically acceptable regrowth in 17% of patients with alopecia totalis or universalis, 60% of those with 75-99% hair loss, 88% with 50-74% hair loss, and 100% of patients with less than 50% hair loss.[12] DPCP has also been widely used to treat children with extensive alopecia areata, with rates of cosmetically acceptable regrowth of 27-33%.[w10 w11] Those with a long disease duration or extensive scalp involvement respond less well.[11] Interestingly, in limited disease (<40% hair loss) there was no difference in treatment response compared with placebo, reflecting the high rates of spontaneous remission in patchy disease. Thus, topical immunotherapy should be reserved for extensive disease only.[w12]

Topical corticosteroids

Topical corticosteroids are widely used, although reports of efficacy are conflicting.[2] A randomised controlled trial of 0.25% dexamethasone cream versus placebo over 12 weeks (n=70) found no statistically significant difference in regrowth between the groups.[13] A half-head comparison of 0.05% clobetasol proprionate foam versus placebo (n=34) found over 50% regrowth in seven of 34 patients in the active group compared with one of 34 with placebo, but no formal statistical analyses were performed.[14] Betamethasone valerate foam was significantly more effective at regrowing hair in patchy disease compared with betamethasone diproprionate lotion, although an effect of the vehicle (the base compound in which the active drug is mixed) could not be excluded.[15] In a small half-head study of 28 patients with alopecia totalis or universalis who used clobetasol proprionate ointment under polythene occlusion daily for six months, eight (29%) had cosmetically acceptable regrowth, although three of these subsequently relapsed and failed to respond to re-treatment. Painful folliculitis was a common side effect.[16] A double blind half-head placebo controlled study (n=13) compared 0.2% fluocinolone acetonide cream twice a day (under occlusion at night) with base vehicle and showed unilateral regrowth in 54% in the treatment arm compared with 0% in the vehicle group.[17]

Therefore, potent topical corticosteroids, as a foam formulation or non-foam product under occlusion, seem beneficial in some patients even when disease is extensive. Reassuringly, no evidence of systemic absorption was noted in adults who treated the whole scalp with super-potent steroids under occlusion for six months.[16] The efficacy of weaker preparations and the systemic effects of corticosteroids under occlusion in children have not yet been addressed.

Systemic corticosteroids

Only one study of systemic corticosteroids in alopecia areata has used a placebo controlled design.[18] A weekly single oral dose of prednisolone (200 mg) was compared with placebo in 43 patients with "extensive" disease (>40% hair loss). After three months, eight of 23 patients using prednisolone had substantial (>31%) regrowth compared with none in the placebo group ($p<0.03$; confidence intervals not supplied). However, relapse was seen in 25% of responders within three months. Uncontrolled studies of pulsed oral or intravenous corticosteroid regimens have also showed benefit. An "excellent" (>75%) regrowth response was observed in 44-66% patients after six months

of treatment with 5 mg oral dexamethasone (or betamethasone) on two consecutive days a week.[19 20] A review of all published reports of the use of high dose intravenous corticosteroids (218 patients) found that 68% achieved greater than 50% regrowth of hair in multifocal alopecia areata, 30% regrowth in ophiasis, and 23% in alopecia totalis and universalis, although as many as a third of responders relapsed within a year and the number of relapses increased with time.[21] Interestingly, topical application of 2% minoxidil after systemic corticosteroid treatment augmented or helped to maintain hair growth in patients who initially responded.[w13]

Most experts reserve systemic corticosteroids for extensive or rapidly progressive disease because of the known side effects of prolonged systemic treatment with steroids and because patients often relapse after stopping treatment.[w14]

Dithranol

The aim of treatment with topical dithranol is to induce low grade irritant scalp dermatitis (web appendix). Its therapeutic role is supported by the observation of half-head regrowth in some reports.[22 w7] An uncontrolled trial of dithranol cream (0.5-1%) applied overnight in patients with "extensive alopecia areata" (n=66) found that 25% of patients were eventually able to stop wearing their wig (mean duration of treatment 28 weeks; range 8-200 weeks).[23] One study (n=32) reported "cosmetically good results" in 75% of patients with limited disease (including ophiasis) and 25%of those with alopecia totalis after short term applications of 0.2-0.8% dithranol ointment; half-head regrowth was clearly demonstrated in these patients.[22] The combination of 5% minoxidil and 0.5% dithranol cream overnight resulted in 11% of patients with "extensive, treatment resistant" alopecia areata experiencing cosmetically acceptable regrowth after 24 weeks, which persisted in 80% of responders with continued treatment.[24] Topical dithranol is thus a potentially effective second line treatment for adults and children with persistent disease.

Minoxidil

The evidence for the effectiveness of topical minoxidil is conflicting. Some half-head studies have failed to report significant treatment effects in alopecia totalis and universalis[w15-w17] and there appears to be no additional benefit of using 5% minoxidil in conjunction with DPCP treatment.[w18] However, two small placebo controlled trials have reported benefit in patchy alopecia areata[25 26] and a small (n=32) randomised trial of topical 2% minoxidil versus vehicle after a six week course of oral corticosteroids showed that minoxidil seems to prevent relapse in patients who responded to steroids (six of seven minoxidil treated steroid responders compared with one of six vehicle treated steroid responders).[w13] Minoxidil is frequently used by experts as second line therapy or in conjunction with other treatments.[w7]

Others

A phase I/II randomised bilateral half-head comparison of topical bexarotene 1% gel (n=42) identified a 26% response rate in treated patients.[27] A randomised controlled trial of aromatherapy (n=86) in which essential oils (thyme, rosemary, lavender, cedarwood) were massaged into the scalp daily showed significant regrowth compared with the carrier oil alone (P=0.008 for "improvement" *v* "no improvement").[28] Oral inosiplex (inosine pranobex) showed significantly better hair re-growth compare with placebo in one small randomised controlled trial.[29] All these results require confirmation in larger controlled trials before they can be recommended.

Treatments in use that are not supported by randomised controlled trials

Psoralen plus ultraviolet A photochemotherapy (PUVA)

No controlled studies of PUVA therapy in alopecia areata have been reported, so the reported "complete" regrowth rate of 48-53% from various studies is difficult to interpret.[w19] Other studies have shown much lower response rates (6-13%) that are thought to be comparable with expected rates of spontaneous remission.[w20 w21] High relapse rates in responders, uncertainty about efficacy, inconvenience of multiple treatment sessions, and concerns about PUVA induced skin carcinogenesis make this a rarely used treatment in today's practice.

Systemic immunosuppressants

Oral ciclosporin, methotrexate, and sulphasalazine all show potentially encouraging results in uncontrolled studies either as monotherapy or in combination with oral corticosteroids.[w22-w25] Randomised controlled trials are needed to confirm these provisional results.

Treatments with no effect in randomised controlled trials

The biological agents alefacept,[w26] efalizumab,[w27] and etanercept[w28 w29] are not effective at promoting hair regrowth in alopecia areata. Photodynamic therapy is also ineffective.[w30] Topical prostaglandin analogues were inef-

A PATIENT'S PERSPECTIVE

For more than 20 years I have suffered from alopecia areata. Although I have great support from family and friends, my life as a bald girl and now woman has been a struggle. When I was 3 my mom found a bald spot on my head. Just as the doctor said it would, the hair grew back. When I was 7, I lost 75% of my hair when we moved from New York to Pennsylvania. Then at age 10 I lost just about all of it when we moved to Tennessee. Through the years some grew back but I always had patches until about high school age. For the past 10 years or more I have had alopecia universalis—no hair on my scalp and other body sites. I don't have eyebrows and lose my eyelashes. The hardest part is losing your eyelashes and eyebrows; something that always increases my anxiety level. Having no eyebrows and eyelashes make you look different—like an alien with no facial expression. People ask you if you have had cancer treatment. Thank god for eyebrow pencils and fake eyelashes, though they don't make being obviously different easier. I hope and pray an effective treatment for alopecia areata will be found soon.
Shannon O'Neill

TIPS FOR NON-SPECIALISTS

- A history of patchy hair loss that has regrown is highly indicative of alopecia areata
- Exclamation mark hairs are pathognonomic for alopecia areata (fig 2)—look for these at the edges of the patch
- Initial regrowth of white hairs within an area of pigmented hairs is a characteristic finding
- Always look closely for signs of inflammation (such as redness, scaling, pustules, swelling) and send samples for bacterial and fungal culture if they are present. Fungal scalp infections are common, particularly in children, and are easily treated
- Spontaneous regrowth is common but always warn your patient that the condition may relapse

QUESTIONS FOR FUTURE RESEARCH

Use the National Alopecia Areata Registry to identify genetic determinants[w37]
Explore immunopharmacological ways to re-establish immune privilege within the proximal hair follicle—a possible way of blocking immune mediated attack of the hair follicle
Use animal models (such as C3H/HeJ mouse) as a preclinical screening tool for candidate drugs[w38]
Clarify the role of natural killer cells, natural killer cell activating ligands, and cytotoxic T-cells in alopecia areata[w39]

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Alopecia areata management (www.cks.nhs.uk/alopecia_areata)
—UK National Health Service clinical knowledge summary for alopecia areata
Alopecia areata (www.niams.nih.gov/Health_Info/Alopecia_Areata)—questions and answers from the US National Institute of Arthritis and Musculoskeletal and Skin Diseases site

Information resources for patients

National Alopecia Areata Foundation (www.naaf.org
)—clinical information and links to the US National Alopecia Areata Registry
Wigs for kids (www.wigsforkids.org)
—US based charity that provides wigs for children with hair loss
British Association of Dermatologists (www.bad.org.uk)
—patient information leaflets and links to UK based patient support groups

fective in inducing eyebrow or eyelash regrowth in alopecia areata despite efficacy in healthy people.[w31 w32]

Treatment in children

Generally treatment in children is similar to that in adults,[3] although intralesional corticosteroids are usually not well tolerated and doctors are often reluctant to recommend treatments with substantial or unknown side effects for children.

Conclusion

For the entire, limited, repertoire of treatment options for alopecia areata, researchers now need to focus on long term outcomes and clinically meaningful end points (such as quality of life measures) to identify the best strategies. Recognition of outcomes from half-head trials of topical treatments, and adoption of the standardised study methodology proposed by the National Alopecia Areata Foundation in their investigational assessment guidelines, should help to improve future study design and appraisal of the literature.[30]

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