Dermatologic Therapy, Vol. 24, 2011, 355–363
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DERMATOLOGIC THERAPY
ISSN 1396-0296

Topical and intralesional therapies for alopecia areata

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ABSTRACT: Alopecia areata is a common form of nonscarring alopecia. It affects males and females equally and has no racial predilection. It usually affects the scalp, but any hair-bearing area can be involved. It presents as patchy hair loss, loss of hair on the entire scalp (alopecia totalis), or the whole body (alopecia universalis). The histopathology varies according to the disease stage, but usually a perifollicular lymphocytic infiltrate is seen. The course of the disease and response to treatment are unpredictable. Various therapeutic modalities are used including topical, intralesional, and systemic agents, although none are curative or preventive. This article will review the available topical and intralesional agents that are used in the treatment of alopecia areata and suggest a management approach based on the age of the patient and extent of the disease.

KEYWORDS: alopecia areata, corticosteroids, immunotherapy, intralesional, topical

Introduction

Alopecia areata (AA) is a common inflammatory nonscarring alopecia that occurs in 0.7–3.8% of patients attending dermatology clinics (1). The lifetime risk in the United States was estimated to be 1.7% (2). AA affects males and females equally (3), and more than half of the patients will present in the first two decades of life (4). AA classically presents as well-demarcated skin-colored patches of hair loss. The disease can be classified clinically based on the extent of hair loss into patchy hair loss (most common), alopecia totalis (AT), in which the entire scalp hair is lost, or alopecia universalis (AU), in which there is 100% loss of all body hair (FIG. 1). A characteristic feature of AA is exclamation mark hairs (hairs that are tapered proximally and wider distally) (3). The diagnosis is usually straightforward, and no further investigation is required. AA can be associated with nail changes, autoimmune diseases, psychiatric and ophthalmologic abnormalities (1). The most important prognostic factor is the extent of hair loss (1). Other factors associated with a poor prognosis include a long duration of hair loss, atopy, a positive family history, the presence of other autoimmune diseases, nail involvement, and young age of first onset (5).

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The histopathologic picture of AA varies according to the stage of the disease (6). In the acute stage, anagen follicles are targeted by peribulbar lymphocytic infiltrate "swarm of bees." In the subacute stage, increased percentage of catagen/telogen hairs is seen. In chronic cases, there is marked hair follicle miniaturization. The pathogenesis of AA is poorly understood. AA is likely an autoimmune inflammatory process (7,8). However, genetic and environmental factors may play a role in the development of AA (1).

Many therapeutic options are used by dermatologists, but none are curative or preventive (9). Randomized controlled trials assessing treatment modalities are few. Moreover, many reports lack an ideal objective parameter to measure treatment response. The high spontaneous remission rate in patchy AA makes it even harder to assess treatment efficacy. The severity of alopecia tool score is one of the tools suggested by leading investigators to increase the reliability, objectivity, and comparability of clinical trials (10).

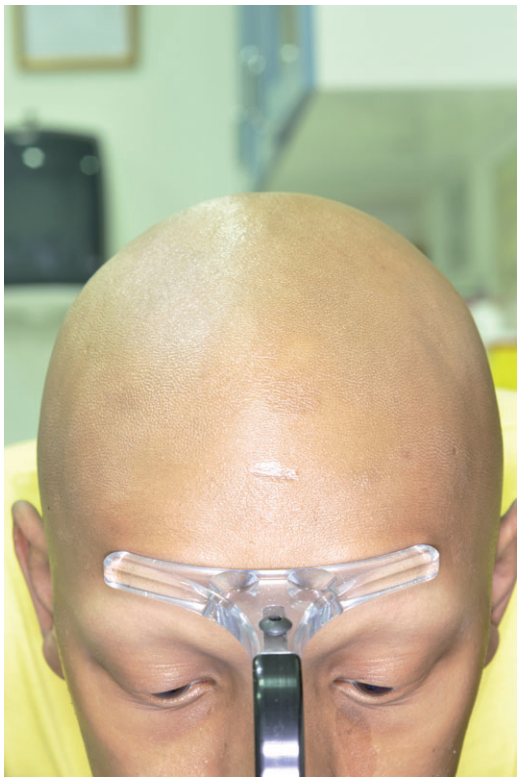

FIG. 1. Alopecia universalis with 100% loss of body hair.

Treatment

Topical corticosteroids

Midpotent and potent topical corticosteroids are widely used in the treatment of AA. The evidence for their efficacy is limited. A double-blind, half-head, placebo-controlled study compared 0.2% fluocinolone acetonide cream twice a day with base vehicle and showed unilateral regrowth in 54% in the treatment arm compared with 0% in the vehicle group (11). A multicenter prospective, randomized, controlled, investigator-blinded trial in patients with less than 26% hair loss showed a more than 75% hair regrowth rate in 61% of patients using 0.1% betamethasone valerate foam in comparison with 27% in the 0.05% betamethasone dipropionate lotion group (12). Another study on extensive AA (AT/AU) showed that eight patients (28.5%) had almost complete hair regrowth with 0.05% clobetasol ointment under occlusion (13). However, only five patients (17.8%) had long-term results. In another randomized, double-blind, placebo-controlled trial, 47% of 0.05% clobetasol propionate foam-treated patients had greater than 25% hair regrowth, and 25% of participants had hair regrowth greater than 50% (14). No significant modifications in cortisol and adrenocorticotropic hormone blood levels were observed during this trial. On the other hand, another randomized, double-blinded, placebo-controlled trial using desoximetasone cream 0.25%, the complete regrowth rates in the active and control groups were 57.6 and 39.2%, respectively. These results were not statistically significant when compared with placebo (15).

Side effects include folliculitis (more with ointment compared with foam formulations) and rarely skin atrophy and telangiectasia (9).

Intralesional corticosteroids

The use of intralesional corticosteroids (ILCs) in AA was first described in 1958 with the use of hydrocortisone (16). Despite their widespread use as first-line treatment in patchy AA, there are no randomized controlled trials on ILCs in AA (17). Hair regrowth has been reported in 71% of patients with subtotal AA treated by triamcinolone acetonide injections three times every 2 weeks, and in 7% of control subjects injected with isotonic saline (18). Porter and Burton showed that hair regrowth was possible in 64 and 97% of AA sites treated by intralesional injections of triamcinolone acetinoide and its less soluble derivative triamcinolone hexacetonide, respectively (19). An uncontrolled study of 62 patients with AA on monthly intralesional injection of triamcinolone acetonide showed complete regrowth in 40 (63%) patients at 4 months. Regrowth was likely in young adults with few lesions (less than five patches), lesions of short durations (less than 1 month), and patches less than 3 cm in diameter (20). Six of ten patients with extensive AA (>50% involvement) responded to intralesional triamcinolone acetonide in one report (21).

ILCs are injected in the deep dermal/upper subcutaneous plane using a 0.5-inch-long 30-gauge needle (FIG. 2A,B). ILCSs (0.1 mL) are injected at 0.5- to 1-cm intervals every 4–6 weeks. Various concentrations (2.5–10 mg/mL) are used, but 5 and 2.5 mg/mL are the preferred concentrations used by the author for the scalp and face, respectively. The maximum dose per session was suggested to be 20 mg of triamcinolone acetonide (22). If there is no improvement after 6 months of treatment, ILCs should be stopped. The decreased expression of thioredoxin reductase 1 in the outer root sheath may be the cause for glucocorticoid resistance in some AA patients (23).

The most common side effect is atrophy, which can be minimized by avoiding injecting too superficially, minimizing the volume and concentrations injected, and spacing the injection sites.

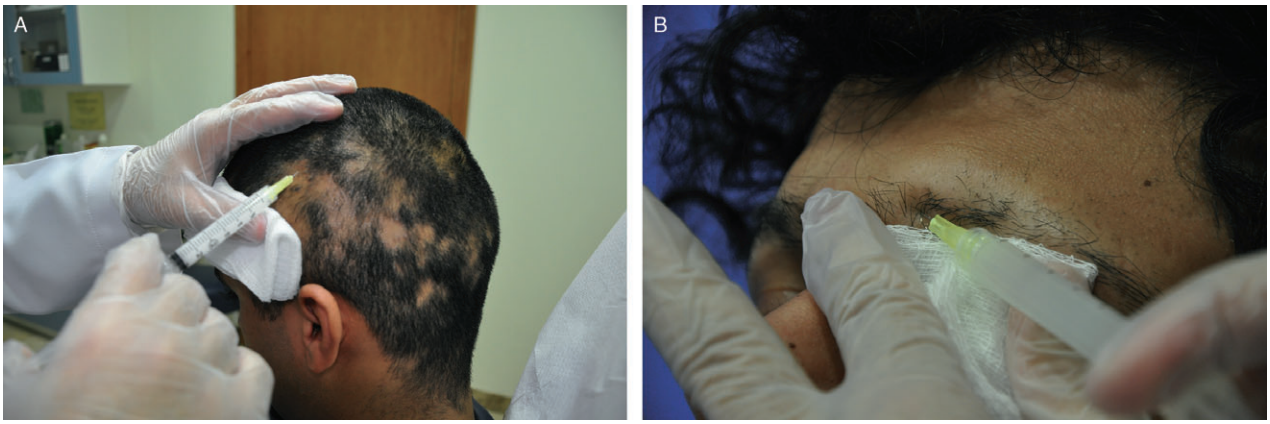

FIG. 2. Intralesional corticosteroid injection into the scalp (A) and the eyebrow (B).

Minoxidil

Minoxidil mechanism of action in promoting hair growth is not fully understood. Vasodilatation (24,25), angiogenesis (26), enhanced cell proliferation (27,28), and potassium channel opening (29,30) have all been proposed. In a double-blind, placebo-controlled trial on extensive AA, 3% minoxidil under occlusion with petrolatum resulted in hair regrowth in 63.6% compared with 35.7% in the placebo arm (31). Only 27.3% of minoxidil patients had cosmetically acceptable hair growth. A dose–response efficacy was shown in a study comparing 1 and 5% topical minoxidil in the treatment of patients with extensive AA. The response rates were 38 and 81% with 1 and 5% topical minoxidil, respectively (32,33).

Minoxidil 5% solution twice daily is used as adjuvant treatment to conventional AA therapy (mainly topical or ILCs). Contact dermatitis and hypertrichosis are the most common side effects (34,35).

Anthralin

In mice, anthralin has been shown to decrease the expression of tumor necrosis factor-alpha and tumor necrosis factor-beta in the treated area in comparison to vehicle-treated sites (36). Its mechanism of action in AA treatment is unknown. There are a few uncontrolled case series assessing anthralin efficacy in the treatment of AA. Response rates of 75% in patchy AA patients and 25% in AT patients have been reported (37). Anthralin cream 0.5–1.0% was used to treat 68 patients with severe AA. Cosmetic response was seen in 25% of the patients (38).

Anthralin 1% cream can be used as short-contact therapy. It is applied daily for 15–20 minutes initially then washed. The contact time is increased by 5 minutes weekly up to 1 hour, or until low-grade dermatitis develops. The contact time is then fixed and continued daily for at least 3 months before judging the response to treatment. The treated area should be protected from the sun. Anthralin should produce a mild irritant reaction in order to be effective (39). Side effects include severe irritation, folliculitis, regional lymphadenopathy, and staining of skin (FIG. 3), clothes, and fair hair (37,40,41).

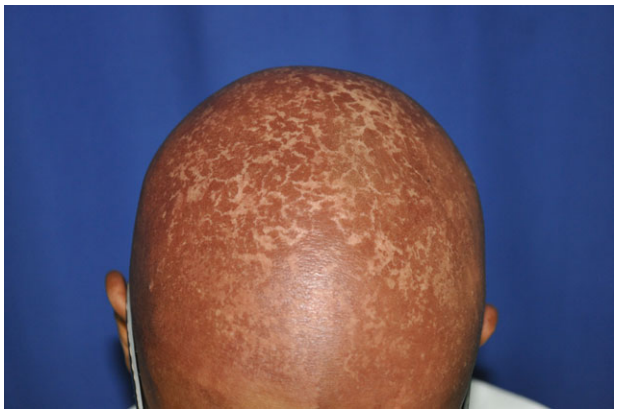

FIG. 3. Scalp hyperpigmentation secondary to anthralin 1% cream.

Topical immunotherapy

Dinitrochlorobenzene was the first topical sensitizer to be used in the treatment of extensive AA since 1976, but it has been discontinued because it has been shown to be mutagenic in the Ames test (42,43). Squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP) are the two compounds still in use today. DPCP is preferred because it is cheaper and is more stable in acetone

(44,45). The mechanism of action of topical sensitizers is poorly understood. Many theories have been suggested including antigenic competition (46), perifollicular lymphocytes apoptosis (47), changes in the peribular CD4/CD8 lymphocyte ratio (48,49), and interleukin-10 secretion after DPCP application (50).

Although no randomized controlled trials have evaluated the effectiveness of topical immunotherapy in AA, observational studies have used the half-head method to control for spontaneous regrowth of hair. A comprehensive review of published topical immunotherapy studies (SABDE = 13 trials; DPCP = 17 trials) found little difference between the two agents (51,52). The success rate of DPCP and SADBE is about 50–60% with a wide range of 9–87% (52) (FIG. 5). The largest reported series of DPCP treatment found that cosmetically acceptable regrowth was achieved in 17.4% of patients with AT/AU, 60.3% with 75–99% AA, 88.1% with 50–74% AA, and 100% with 25–49% AA. A lag of 3 months was present between initiation of therapy and development of significant hair regrowth in the first responders. Relapse after achieving significant regrowth developed in 62.6% of patients with median time to relapse being 2.5 years (53). Although contact immunotherapy has been used mainly for adults, there are reports of success in the pediatric population (54,55).

Because DPCP is very light sensitive, it should be stored in amber bottles to protect it from exposure to ultraviolet light (FIG. 4) (44). DPCP 2% is applied to a 4-cm circular area on the scalp to sensitize the patient. Two weeks later, a 0.001% DPCP solution is applied to the same half of the scalp (FIG. 6). The concentration of DPCP is increased gradually each week until a mild dermatitis reaction is obtained. The goal is to achieve a low-grade erythema and mild pruritus on the treated area for 24–36 hours after application (56).

After establishing the appropriate concentration for the patient, therapy should be continued on a weekly basis. DPCP should be left on the scalp for 48 hours and then washed off. Patients should not expose the treated area to the sun during this time. Treatment of both sides is recommended only after achieving a trichogenic response on the treated side. If there is no improvement at 6 months, DPCP

FIG. 4. Diphenylcyclopropenone is applied using a cotton swab.

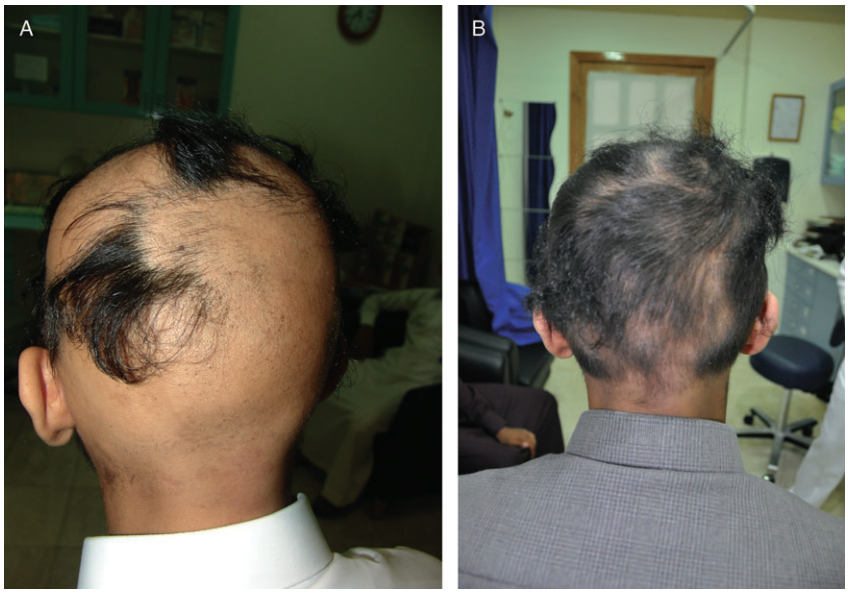

FIG. 5. Extensive alopecia areata before (A) and after (B) diphenylcyclopropenone treatment.

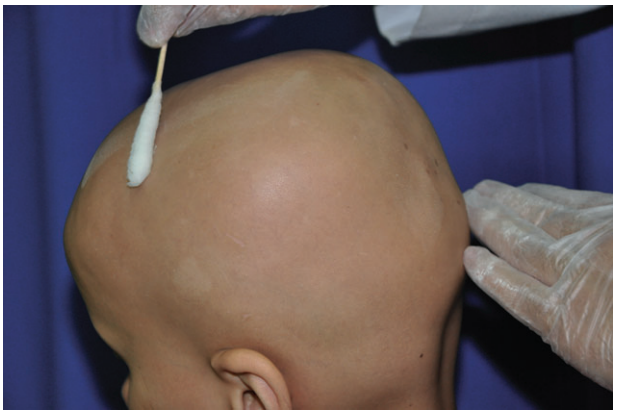

FIG. 6. One side of the scalp is painted with two diphenylcyclopropenone coatings (anteroposterior and lateral).

is less likely to be successful. If the patient does not develop an allergic reaction to 2% DPCP, SADBE can be tried (54,57).

A vesicular or bullous reaction is one of the undesired adverse effects of topical sensitizers. If this reaction develops, the patient should wash off the contact sensitizer and a topical corticosteroid should be applied to the affected area. Other adverse effects include cervical and occipital lymphadenopathy (58,59), facial and scalp edema, contact urticaria (60–62), flu-like symptoms, erythema multiforme-like reactions (58,63), and pigmentary disturbances (hyperpigmentation, hypopigmentation, dyschromia in confetti, and even vitiligo) (59,64,65).

Prostaglandin analogues

Latanoprost, a prostaglandin F2α analogue, and bimatoprost, a synthetic prostamide F2α analogue, are used in the treatment of open-angle glaucoma patients. Hypertrichosis of the eyelashes and vellus hair on the malar area is one of the reported side effects (66–69). Prostaglandin F2α and its analogues showed stimulatory effects on murine hair follicles and follicular melanocytes in both the telogen and anagen stages, and stimulated conversion from the telogen to the anagen phase (70). Bimatoprost (Lattisse, Allergan, Inc., Irvine, CA, USA) received approval from the US Food and Drug Administration for the treatment of hypotrichosis of the eyelashes. Latanoprost and bimatoprost failed to induce regrowth in a blinded randomized controlled trial on 11 patients with extensive (>50%) eyelash AA (71). Another 16-week randomized, right–left, investigator-blinded study of eight patients with severe eyebrow AA showed the same result (72). In a larger trial, 26 patients with symmetrical eyelash and eyebrow AA were treated over 4 months with topical latanoprost for one side. This trial also failed to show a difference between the treated and the untreated sides (73). On the other hand, a recent nonblinded, nonrandomized trial showed a cosmetically acceptable response in 45% of the latanoprost-treated group compared with none of the control group (74). Patients with less extensive eyelash loss caused by AA may benefit from treatment with instilled bimatoprost (75). This attractive area of AA therapy needs further evaluation with blinded prospective right–left controlled trials to confirm either of the conflicting evidence we have so far. The treatment is usually well tolerated. Side effects include transient mild eye irritation or hyperemia (75).

Phototherapy

Randomized controlled trials for phototherapy with oral or topical psoralen plus ultraviolet A light are lacking. Two large retrospective studies showed that the response rate is no better than the spontaneous remission rate (76,77). Insufficient evidence as well as the risk of cutaneous malignancies with psoralen plus ultraviolet A light make it a less favored treatment option. A few case series have shown successful results with a 308-nm excimer laser in treating patchy AA (78–82). The initial fluences were 50 mJ/cm^2 less than the minimal erythema dose. Fluences were then increased by 50 mJ/cm^2 every two sessions. Each patch was treated twice a week for a maximum of 24 sessions. Hair regrowth has been shown in 41.5% of patches (81).

Potential topical treatments

Bexarotene 1% gel treatment on half head was evaluated in a single blinded study involving 42 patients with AA. Five patients (12%) had 50% or more partial regrowth on the treated side, and six patients (14%) had a response on both sides. Seventy-three percent of the subjects had some degree of dermal irritation (83). Capsaicin ointment was comparable to clobetasol 0.05% ointment in a nonblinded study of 50 subjects with patchy AA (84). This finding should be supported with blinded randomized controlled trials with a large number of subjects.

Treatment failures

Topical tacrolimus and pimecrolimus have been tried in several case series in the treatment of AA,

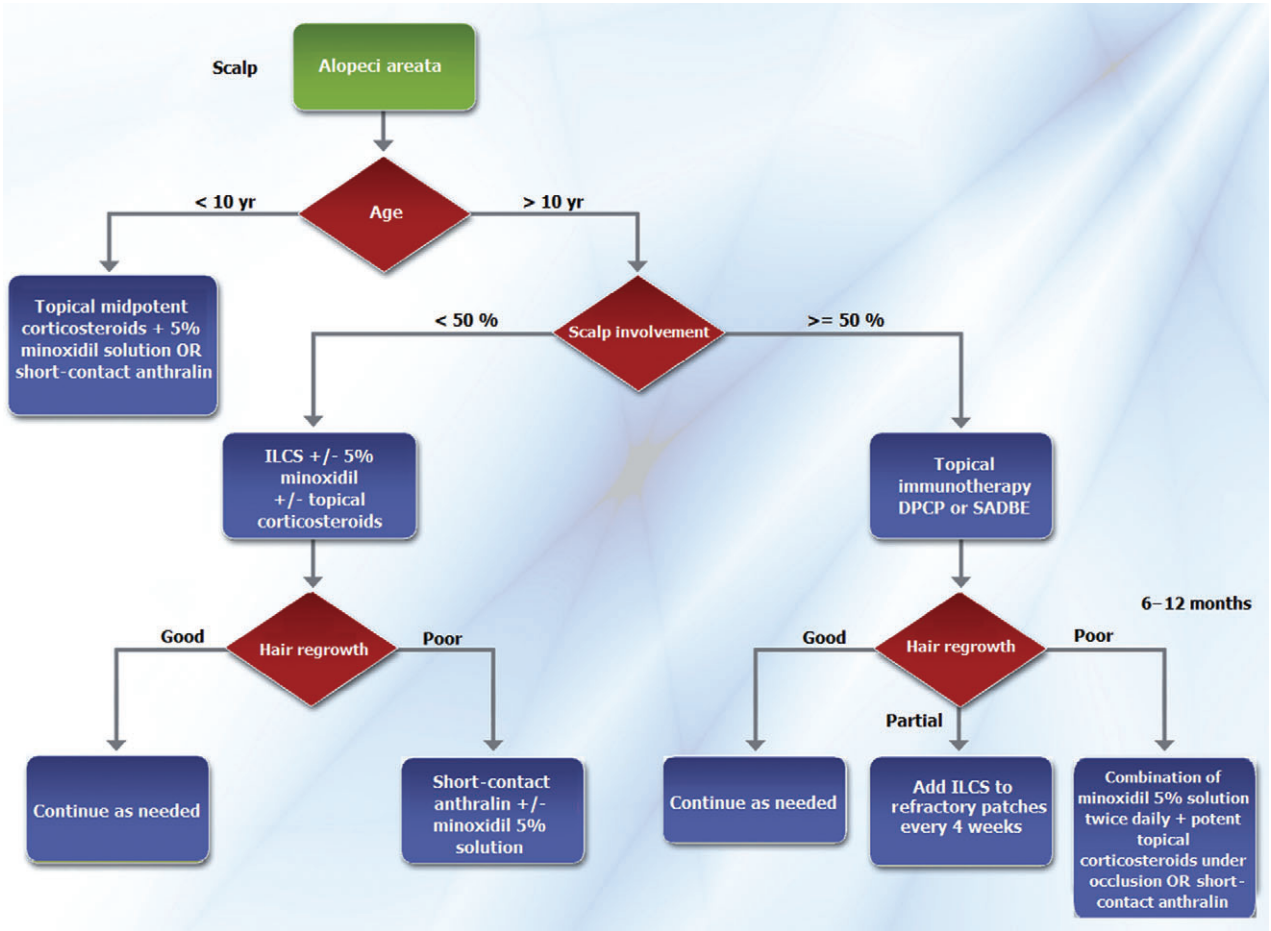

FIG. 7. Treatment algorithm for alopecia areata involving the scalp. DPCP, diphenylcyclopropenone; ILCs, intralesional corticosteroids; SADBE, squaric acid dibutylester.

but the results have not been encouraging (85–89). Imiquimod was tried on patchy and extensive AA but failed to show positive results (90,91). Photodynamic therapy was shown to be ineffective in the treatment of AA patients (92,93).

Management plan

At the patient's first visit, a careful medical history and a good physical examination should be carried out, including an examination of all hair-bearing areas and nails. Full information about his or her disease, including the relapsing nature of AA, prognosis, and risk/benefit ratio of treatment options, should be provided. No routine testing is required for AA patients. Because of the possibility of spontaneous remission in 34–50% of patients within 1 year (39), some patchy AA patients can be just followed up without active intervention. If the patient opted for active treatment, options are offered according to the patient's age and extent of the disease (FIG. 7).

For children less than 10 years of age, a combination of 5% minoxidil solution twice daily with a midpotent topical corticosteroid is the first line of therapy. If there is no response after 6 months, short-contact anthralin can be tried. For patients older than 10 years of age with less than 50% scalp involvement, intralesional injections of triamcinolone acetinoide is the author's first option for therapy. If there is no improvement after 6 months, other therapeutic options can be offered, including 5% topical minoxidil twice a day, potent topical corticosteroid under occlusion at night, and short-contact anthralin.

For those with more than 50% scalp involvement, topical immunotherapy with DPCP is the treatment of choice. For those patients who only partially respond, intralesional triamcinolone acetinoide injections are used to treat the resistant alopecic patches. DPCP may be discontinued if there is no response by 6 months of treatment. Alternative remedies include 5% minoxidil solution, topical clobetasol propionate nightly under

occlusion, or short-contact anthralin. Minoxidil 5% solution with or without intralesional injections of triamcinolone acetinoide 2.5 mg/cc (maximum, 1 cc) can be administered to AA of the eyebrows.

Dermatography or medical tattooing of the eyebrows may be suggested to AA patients with prolonged eyebrow loss. Scalp prostheses, such as wigs, hairpieces, or other scalp coverings, may be valuable options for AA patients during treatment or when treatment fails.

Conclusion

Existing therapeutic options for AA are neither curative nor preventive. Their efficacy is hard to assess because of the high rate of spontaneous remission and paucity of randomized controlled trials. Furthermore, long-term outcomes have been ignored, or not adequately followed, by most studies. Topical corticosteroids and ILCs are the first choice for localized disease, whereas contact immunotherapy is the preferred treatment method for extensive AA.

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