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The treatment of alopecia areata

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ABSTRACT: This article reviews the different treatments of alopecia areata (AA). The information includes both a review of the literature as well as practical aspects regarding the use of the most commonly used therapies for AA. These modalties are summarized in a practical algorithm that can be used as a guide. For patients less than 10 years of age, the options are topical corsticosteroids, topical minoxidil, and anthralin. For adults with less than 50% scalp involvement, the first option is usually the use of intralesional corticosteroids, followed by topical corticosteroid creams, minoxidil solution, or anthralin cream. For adults with more than 50% scalp involvement, topical immunotherapy and phototherapy are added to the other options. Other modalities such as cyclosporine, tacrolimus, interferon, dapsone, and cosmetic coverups are also discussed.

KEYWORDS: alopecia areata, corticosteroids, diphencyprone, minoxidil, treatment.

Alopecia areata (AA) is a recurrent, nonscarring type of hair loss. The lifetime risk of developing AA is estimated to be 1.7% (1). Men and women are equally affected and the prevalence is the same for all ethnic groups (2,3). AA can occur at any age, from birth to later in life, but the peak incidence appears to be between 15 and 29 years of age (2,4). Although it is a medically benign condition, AA can cause great emotional distress to affected patients and their family (5).

Alopecia areata is most often asymptomatic. Occasionally patients feel mild burning or pruritus in the affected area (2,3). It can affect any hair-bearing area, but the scalp is more commonly affected (2,3). The presence of smooth, slightly erythematous (peach color) or normal-colored hairless patches is characteristic. The presence of exclamation point hairs, that is, hairs that are tapered near the proximal end can help confirm the diagnosis if present. Nonscarring loss on other hair-bearing areas favors the diagnosis. A positive pull test at the periphery of a patch usually means that the disease is active and further hair loss is expected.

The hair loss is most often localized and patchy, but different clinical patterns can be seen. Extensive forms of AA are less common. AA involving more then 40% hair loss is seen in 11% of patients (2), while alopecia totalis (AT) or alopecia universalis (AU) were reported to occur in about 7% of patients (1). The presence of nail abnormalities, atopy, onset at a young age, and severe forms of AA have all been implicated as negative prognostic factors (6–8).

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Treatment

Alopecia areata is a benign condition that tends to recur, and unfortunately, at this time there is no cure. Treatments used have varying efficacies. Assessment of the efficacy of any given treatment for AA must be considered in light of the fact that the condition is highly unpredictable in its presentation, evolution, and response to treatment. There are few data on the natural evolution of the condition.

Patchy AA involving less than 40% of the scalp is usually self-limited and regrowth can be expected within a year in the majority of patients with or without treatment (9). One study showed no benefit of treatment (minoxidil 1% and topical immunotherepy) over placebo in patients with less than 40% scalp involvement (7). The high spontaneous remission rate sometimes makes it difficult to clearly assess the true efficacy of a

given therapy. The rate of spontaneous remission in patients with extensive AA (more than 40% hair loss) appears to be less than for those with less than 40% involvement. Vestey and Savin (10) reviewed 50 patients with extensive AA. Twenty-four percent experienced spontaneous nearly complete or complete regrowth at one stage or another during the observation period of 3–3$\frac{1}{2}$ years. However, the relapse rate is reportedly high in patients with extensive forms of AA. Patients with alopecia totalis/universalis (AT/AU) usually have a poorer prognosis, especially if it is a long-standing condition (9,11).

Patients who do not respond to therapy constitute a heterogeneous population. Therapeutic failure can only be predicted in those who show scarring on a scalp biopsy (12), although even this is not always true. Knowing these facts and knowing that AA is a benign condition, some patients decide not to attempt treatment and let nature run its course. For those who do want treatment, the most commonly used agents are corticosteroid injections and topical medications, such as minoxidil solution, anthralin cream, and topical immunotherapeutic agents. Ultra-violet (UV) light therapy [UVB and psoralenplus UVA (PUVA)] can also be used. Other treatment modalities have been studied and will be discussed in this article. Treatment options should be discussed with patients and the final decision is usually a matter of personal preference.

Treatment modalities are usually first considered according to the extent of hair loss and the patient's age. The University of British Columbia and the University of San Francisco have designed a treatment protocol that can be used as a guide to choose the appropriate option (13) (Fig. 1). Each treatment modality is discussed in more detail in the following paragraphs.

Corticosteroids

Corticosteroids are most likely effective via their immunosuppressive effects.

Intralesional corticosteroids. Although they are widely used for the treatment of AA, few studies have been done evaluating the efficacy of intralesional corticosteroids. It is usually the treatment of choice in adults with localized patchy AA. In a study of 84 patients, regrowth on treated areas occurred in 92% of patients with patchy alopecia and 61% of patients with AT. Regrowth following treatment usually appeared after 4–6 weeks in responsive patients. Patients with rapidly progressive, extensive, or long-standing AA tend to respond poorly (14). Another study showed regrowth in the majority of patients (480 patients) treated with intralesional steroids, except for patients with AU, who did not respond (15). The hair growth may persist for 6–9 months even after a single injection (15,16). Charuwichitratana

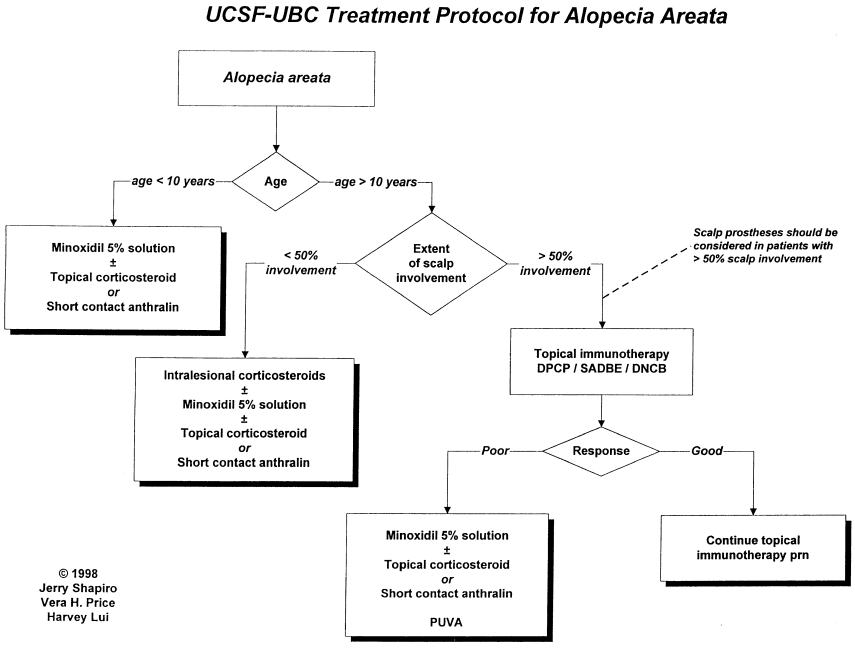

Fig. 1. UCSF-UBC treatment protocol for alopecia areata. (Courtesy of Jerry Shapiro, Vera H. Price, Harvey Lui.)

reported that 13 patients out of 19 showed complete regrowth after one to three monthly injections (97). The extent and duration of the alopecia is not specified. More recently, Wiseman et al. reported that the use of intralesional corticosteroids to residual patches slower to respond to dipencyprone therapy increased the likelihood to achieve clinically significant regrowth, independent of baseline extent of alopecia areata (96). Unfortunately these studies were not controlled and, again, because of the high unpredictability of AA, it is difficult to assess the true efficacy of this treatment.

Injections are intradermal with a 3 cc syringe and a 30-gauge needle (Fig. 2). Triamcinolone acetonide is most commonly used. Concentrations vary from 2.5 to 10 mg/cc. Less than 0.1 cc is injected per site and injections are spread out to cover the affected areas for a maximum volume of 2–3 cc (11). The lower concentration (2.5 mg/cc) is used on the face and higher concentrations (5–10 mg/cc) are used on the scalp. Some authors use 10 mg/cc regardless of the area, but use only very small amounts for each injection (Price VH, unpublished data).

Side effects associated with intralesional theraphy include pain (most commonly) during injection (more than 90% of patients) and minimal transient atrophy (10% of patients) (15). Rarely the atrophy will be severe and permanent (17). Allowing 4–6 weeks between injections and avoiding reinjecting the area of depression is usually associated with resolution of the atrophy (11).

Topical steroids. Few studies have been performed to assess the efficacy of topical steroids in the treatment of AA, and their usefulness is still being debated. In a study using fluocinolone acetonide cream 0.2% twice a day, 61% of patients showed a satisfactory to excellent response. This initial response was sustained in 71% of patients. Children less than 10 years of age having AA of less than 1-year's duration responded better (18). The dropout rate (40%) in this study was very high. A significant number of the dropouts may have been non responders, which limits the significance of the data. More recently, a randomized, double-blind placebo-controlled study using topical desoximetasone (Topicort) cream twice a day for 12 weeks was published. The rate of complete hair growth was not statistically significant compared to placebo (97). According to their experience, some authors feel that topical corticosteroids are not very effective when used alone (11,98). Betamethesone dipropionate cream 0.05% showed similar efficacy (17).

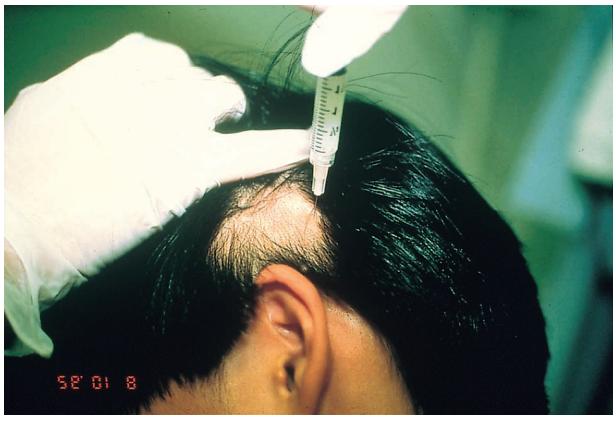

Fig. 2. Intralesional corticosteroid injection with a 30-gauge needle into a patch of alopecia areata.

High-potency topical corticosteroids should be used continuously for at least 3 months before regrowth can be expected and maintenance therapy is often necessary. We do not feel that monotherapy with topical corticosteroids has been of great benefit in our patients.

Local folliculitis is a common side effect of topical corticosteroid therapy and it usually appears after a few weeks of treatment. Telangiectases and local atrophy can also occur. Systemic side effects have not been reported if drug usage is monitored (17,18).

Systemic steroids. The use of systemic steroids for the treatment of AA is still controversial. Some authors believe systemic steroids halt the progression of active AA (19–21), but others disagree (22–26). The rate of regrowth varies greatly (27–89%) and is difficult to compare because different dose regimens are used in different studies. The initial regrowth with prednisone may be promising, but the dose usually needs to be increased to maintain hair growth. The relapse rate may be high after therapy is discontinued (26). A dose of 1 cc of minoxidil 2% solution applied twice a day following a 6-week course of tapered prednisone proved to be somewhat beneficial in one study, but the relapse rate was still at least 50% at 4 months in the treated group (27).

There is no formal concensus regarding the dosing regimen of systemic corticosteroids. Short courses of prednisone are usually preferred. For adults weighing more than 60 kg, the following dosage regimen has been suggested for prednisone (11): 40 mg for 3 days, 35 mg for 3 days,

30 mg for 3 days, 25 mg for 3 days, 20 mg for 3 days, 15 mg for 3 days, 10 mg for 3 days, 5 mg for 3 days, and then discontinuing the drug.

Side effects from systemic therapy are common and include diabetes, weight gain, hypertension, psychological changes, osteoporosis, suppression of the adrenocorticotropic axes, striae, acne, hypertrichosis and purpura (23,25,26). We personally only rarely use oral prednisone and we have never used intravenous steroids for the treatment of AA.

Minoxidil

Minoxidil is a piperidinopyrimidine derivative that was originally used orally as an antihypertensive drug. Because hypertrichosis was one of its side effects, a topical solution was formulated and studied for the treatment of hair loss. Its exact mechanism is unknown, however, minoxidil was not found to have any hormonal or immunosuppressant effects (13,28). Minoxidil most likely has a direct mitogenic effect on epidermal cells and prolongs the survival time of keratinocytes (29,30). More recently it has been suggested that its mechanism of action could be related to opposition to intracellular calcium entry. Intracellular calcium entry normally enhances epidermal growth factors (EGFs), which inhibit hair growth. One of minoxidil's degradation products, minoxidil sulfate, is a potassium channel agonist and enhances potassium ion permeability, thus opposing the entry of calcium into cells (31,32). Although minoxidil can promote local vasodilation, this mechanism is unlikely to play a major role in hair growth (33,34).

The efficacy of minoxidil is debated. It is mostly used in AA patients with extensive disease (40–99% hair loss), and the response rate in that group ranges from 8 to 45% (35,36). Topical minoxidil is usually of no benefit in patients with AT/AU. Some authors feel that topical minoxidil is ineffective in the treatment of AA. However in many of these negative studies, AT and AU comprised a large portion of the patient population, thus making it difficult to prove efficacy. On the other hand, topical minoxidil solution has been found to be effective in patchy AA.

A 5% minoxidil solution appears to be most effective (35). No more than 25 drops are applied twice a day regardless of the extent of the affected area. Initial regrowth can be seen within 12 weeks, but continued application is needed to achieve cosmetically acceptable regrowth (11,17,35,36). Topical minoxidil is usually well tolerated. Common side effects include hypertrichosis (~5%) and irritation (~7%).

Anthralin

Anthralin has been used successfully in the treatment of psoriasis for many years. Since psoriasis is also considered an autoimmune condition, it was hypothesized that anthralin could be effective in the treatment of AA. The mechanism of action of anthralin is unknown. It most likely creates inflammation by generating free radicals, which have antiproliferative and immunosuppressive actions (17,37).

The efficacy of anthralin was assessed in three uncontrolled studies. One study showed no benefit in using this agent (38). The other two studies showed a response rate of 20 to 75% for patchy alopecia (37,39) and a 25% response rate for AT (37). The mean time to response was 11 weeks and the mean time to cosmetic response was 23 weeks (17). Cosmetically acceptable regrowth was maintained during therapy in 71% of the responders (17). There was no correlation with duration of the current episode and response to treatment (39).

Both short contact and overnight treatments have been used. Anthralin concentrations vary from 0.1 to 3.0%. Lower concentrations (0.1–0.4%) are used for overnight treatments and higher concentrations (1–3%) are used for short contact treatments.

Most patients using anthralin experience an irritant contact dermatitis. Other side effects include pruritus, erythema, scaling, folliculitis, local pyoderma, and regional lymphadenopathy. Withholding of treatment for a few days allows side effects to resolve. Treatment can then be reinstituted, but the medication should be left on for shorter periods of time. Staining of clothes and skin can also be a problem (17,40).

Topical immunotherapy

Topical immunotherapy consists of the induction and periodic elicitation of an allergic contact dermatitis by topical application of potent contact allergens. Two agents are commonly used in the treatment of AA: diphencyprone (DPCP) and squaric acid dibutylester (SADBE). Dinitrochlorobenzene (DNCB) has been shown to be a potential carcinogen and has therefore been used less in most centers (41).

Neither DPCP nor SADBE is US Food and Drug Administration (FDA) approved since no rigorous

toxicologic and pharmacologic studies have been done on these chemicals (17). Furthermore, their production is not regulated. Contrary to DNCB, DPCP and SADBE have not been found mutagenic in the Ames assay. Despite these unknowns, topical immunotherapy with DPCP and SADBE has been used since 1983 without any major adverse reactions and with good patient satisfaction.

No contaminants have been found in SADBE (42). Acetone solutions and alcohol solutions of SADBE are equally stable over 2 months under storage conditions (42). In contrast to SADBE some sources of DPCP have been shown to contain mutagenic contaminants (α-dibromodibenzylketone) (43). DPCP is unstable to light and heat, and therefore should be kept in amber bottles and refrigerated at 4 °C (www.fda.gov/cder/pharmcomp/meeting/dpcp.ppt).

The exact mechanism of action of topical immunotherapy is unknown. One theory is antigenic competition. According to this theory, the introduction of a second antigen brings a new infiltrate containing suppressor T cells and suppressor macrophages which modifies the preexisting infiltrate and allows regrowth (44).

Both SADBE and DPCP appear to be equally effective. Cosmetically acceptable regrowth in patients with severe AA (more than 40% involvement) ranged from 22 to 68% (7,8,17,45–64). Most studies have a success rate of 30 to 50%. The relapse rate once treatment is stopped remains high in long-term follow-ups (11–45% at 6–16 months) (7,48,54,58,60) (Fig. 3). Wiseman et al. recently published their experience with the use of diphencyprone. They reported an overall response rate of 80% at 2.5 years. An interval of 3 months is necessary before regrowth can be seen and 12 months is usually necessary to achieve cosmetic regrowth. Their analysis suggests that a significant number of non responders at 6 months will respond if therapy is continued for up to 2 years. All cases of limited AA (25–50%) experienced complete regrowth while patients with alopecia totalis/universalis had a 17% response rate. Relapse rate was 62% at 3 years and was not associated with the initial extent of the alopecia or the use of maintenance therapy. Adverse prognosis factors included early age at onset, extensive alopecia, high concentration of DPCP necessary to induce a contact dermatitis and finally longer interval before initiation of regrowth (97).

Response to treatment may be influenced by significant adverse prognostic factors such as the type of AA before treatment (AT/AU), duration of the outbreak, and presence of nail changes. Sex does not appear to influence the response to treatment (61). In one study, the presence of atopy was found to be an adverse prognostic factor (50).

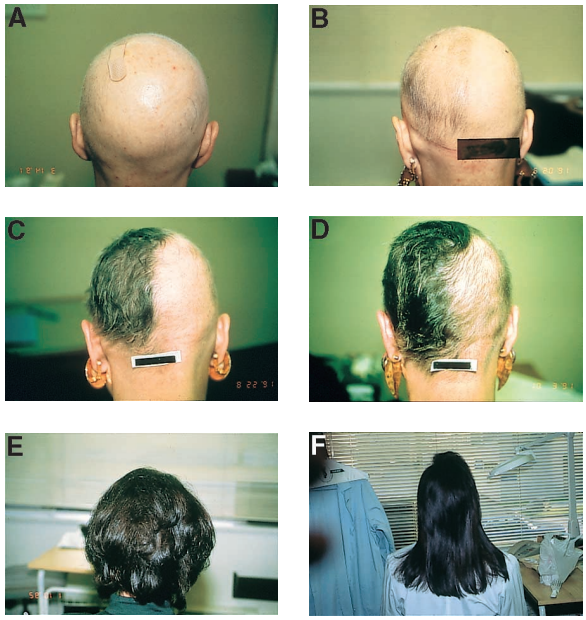

Fig. 3. A 40-year-old patient with a 18-year history of alopecia subuniversalis (A) baseline; (B) 12 weeks after unilateral application of DPCP; (C) 24 weeks after unilateral application of DPCP; (D) 30 weeks of DPCP application on the left side and 6 weeks on the right side; (E) 1 year of treatment; (F) 5 years of treatment intermittently.

We believe the treatment should be applied by a physician or nurse whenever possible, and not by the patient at home. Acetone-based solutions are preferred because they evaporate quickly, which allows the patient to put on a hat or a wig immediately after treatment and minimizes the risk of allergic contact dermitits to other body parts. Treatment is done once a week. The patient is first sensitized directly on the scalp with a 2% concentration on a small area (2 cm). The following week the lowest concentration (0.0001%) is applied. The concentration is slowly increased every week as needed until a mild, tolerable allergic contact dermatitis is elicited. Severe contact dermatitis should be avoided. Patients should cover their scalp with a hat or a wig for 48 hours because light, including indoor light, degrades the chemical. The solution must stay on the scalp for 48 hours so patients are advised not to wash their scalp for that period. Half the head is treated first. The other half is used as a control (Figs. 7 and 8).

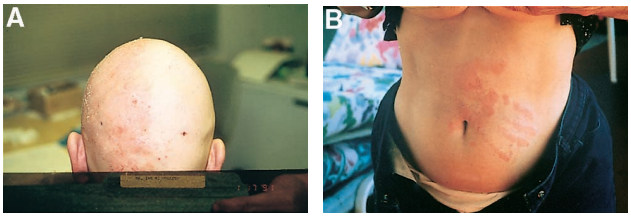

Fig. 4. Eczema as a side effect of DPCP. (A) Marked eczema unilaterally. (B) Allergic contact dermatitis on an area remote to the scalp.

Once there is regrowth on the treated half, the treatment can be applied to the whole scalp. If regrowth occurs on both sides when only half is treated, a spontaneous remission is likely, although one cannot exclude that it could be from the treatment. Initial regrowth should not be expected before 12 weeks. Once cosmetically acceptable regrowth is achieved, the treatment can be tapered off gradually. Most patients need a maintenance treatment to avoid relapse.

Topical immunotherapy has been used for almost 20 years and no serious long-time side effects have been reported. The most common side effect is a mild allergic contact dermatitis (Fig. 4). Other side effects include vesicules (45%), hyperpigmentation (0.75–12%), autoeczematization (10%), hypopigmentation (2%), and cervical lymph node (2%) (65,96) (Fig. 5). Cervical lymphadenopathy is seldom a problem and appears to be reversible. In one study, vitiligo developed on the site of application in 6.7%–7.5% of patients (65). The majority of patients had no history of vitiligo. Transient leukoderma on distant, untreated areas has also been reported (66). Dyschromia in confetti, that is, hyper- and hypopigmentation occurred in 1.6% of 243 patients treated (67) (Fig. 6). Uncommon side effects include erythema multiforme-like eruptions (68) and urticaria (69,70).

Because topical immunotherapy is not yet approved for the treatment of AA, it is best to provide the treatment with ethics review board approval and to have the patient sign an informed consent.

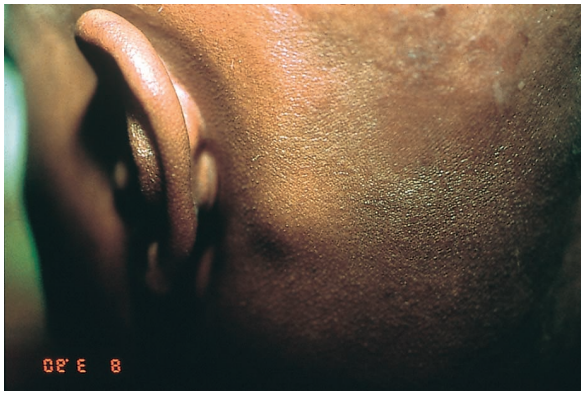

Fig. 5. Cervical lymphadenopathy.

PUVA

PUVA is a combination of psoralen and UVA light. It has been used successfully in many dermatologic conditions, some of which are thought to be autoimmune diseases. In general, PUVA has been shown to have immunosuppressive activity within the skin. PUVA can decrease the number of T cells, mostly $CD3^+$, $CD4^+$ and $CD8^+$ cells. It also decreases the number of interleukin (IL)-2 receptors. Although it does not decrease the number of Langerhans cells, PUVA decreases the expression of immunohistochemical markers and thus may decrease antigen presentation.

Many studies have been done using PUVA for the treatment of AA. The initial response rate ranges from 20 to 73%, but the relapse rate is high (50–88%). Most patients relapse within only a few months (mean 4–8 months) after treatment is stopped. The age of onset, long duration of disease, and AT or AU are adverse prognostic factors (17,71–74). Most patients need maintenance treatments (Fig. 9). Both systemic and topical PUVA therapies have been used, according to the extent of the condition. The number of treatments required varies, but 20–40 treatments are usually sufficient in most cases to achieve good to excellent regrowth (72,73).

Taylor and Hawk (74) published their 10-years' experience with PUVA. Their initial response rate (more than 90% regrowth) was comparable to other studies and was 43.8% for partial AA and

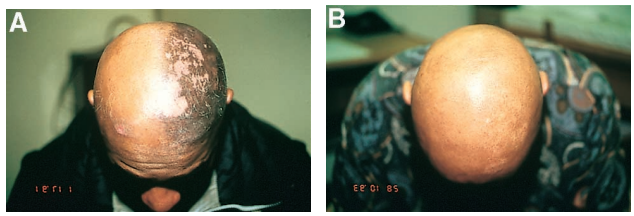

Fig. 6. (A) Dychromia in confetti in a patient showing marked hypo- and hyperpigmentation. (B) One year later showing marked resolution of the pigmentary alteration.

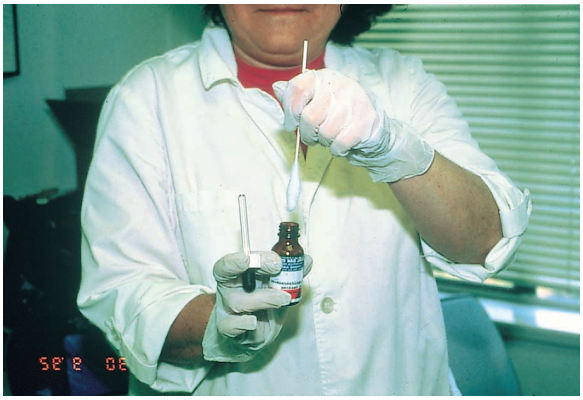

Fig. 7. DPCP is stored in amber bottles. Health care professional must wear gloves when applying the immunogen. An applicator is immersed into the solution.

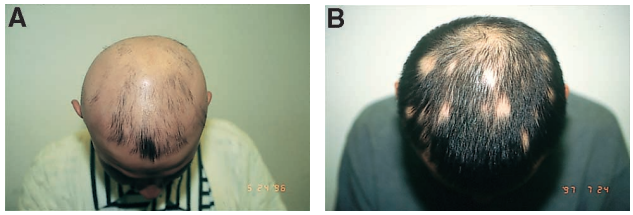

Fig. 9. (A) Alopecia areata affecting 95% of the scalp before PUVA therapy. (B) After 14 months of PUVA treatment, showing marked regrowth with some refractory patches.

50% for AT and AU. However, after they excluded patients with only vellus hair regrowth and those who relapsed within 4 months, they found the success rate to be at best 6.3% for partial AA and 12.5% for AT and AU. They concluded that PUVA is generally not effective for long-term treatment of AA (74).

Side effects of PUVA include burning and potentially an increased risk of skin cancer (including both melanoma and nonmelanoma skin cancer), which is of concern because most patients need long-term, maintenance treatments.

OTHER TREATMENTS

Cyclosporine

Cyclosporine (CsA) has been used both topically and systemically for the treatment of AA. Topical cyclosporine has shown limited efficacy. In two studies using 5% and 10% solutions twice a day for a minimum of 4 months (up to 12 months),

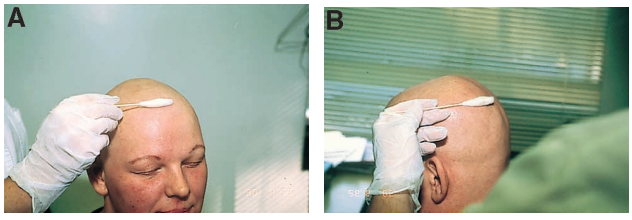

Fig. 8. DPCP is applied to the scalp with a cotton applicator. (A,B) Initial unilateral application. Once unilateral regrowth is established the contralateral side is treated.

the majority of patients (18 of 24) showed no regrowth. Only three patients showed terminal hair growth and three showed vellus hair growth with the 10% solution (75,76). Both studies showed no systemic absorption of CsA and routine blood examination showed only a transient increase of hepatic enzymes in one patient (75,76). Oral cyclosporine was effective in the DEBR model for AA. All rats had a full pelage after 5 weeks of treatment with 10 mg/kg/day, 5 days/week for 7 weeks (77). Systemic cyclosporine has also been shown to be effective in humans using doses of 6 mg/kg/day for 3 months. Six patients experienced some hair regrowth, which was cosmetically acceptable in three patients. Unfortunately they all relapsed within 3 months after cyclosporine was discontinued (78). A second study used oral cyclosporine 5 mg/kg/day in combination to oral prednisone 5 mg/day for 6 months. Two of eight patients experienced cosmetically acceptable regrowth. Unfortunately they both relapsed after discontinuation of therapy. Three patients had to drop out because of side effects (generalized edema, hypertension, abnormal liver function tests, abnormal lipid levels, and hypertrichosis) (79). There is no evidence that cyclosporine can prevent hair loss during an active episode of AA since there are reports of patients on cyclosporine for unrelated conditions who developed AA while being treated (80–83). Although systemic cyclosporine appears to be effective in AA, the high recurrence rate after discontinuation and the side effect profile make cyclosporine a mediocre agent for the treatment of AA.

The mechanism of action of cyclosporine is unclear. It could be effective because of its immunosuppressive activity (78), but cyclosporine can also cause hypertrichosis in patients treated for conditions unrelated to hair loss. The mechanism by which cyclosporine stimulates hypertichosis is still unknown.

Tacrolimus

Two studies with the Dundee experimental bald rat model have shown regrowth at the site of application of topical tacrolimus (98,99). Oral tacrolimus was ineffective. One case report showed no benefit in the use of topical tarolimus for AA (84).

Interferon

A study on 11 patients with AA ranging from patchy to AU showed no benefit from using intralesional interferon (IFN)-2 (1.5 million IU, three times a week for 3 weeks) (85).

Dapsone

Dapsone 50 mg twice a day was used in a 6-month double-blind placebo-controlled study. The high incidence of side effects such as malaise forced 54% of patients (7 of 13) to withdraw from the treatment group. Three patients out of six who remained in the study experienced generalized growth of terminal hair. In the placebo group, 4 of 13 patients experienced only sparse patchy regrowth of vellus hair. Although dapsone showed some efficacy, the authors concluded that the high incidence of side effects rendered it unacceptable (86). Another study reported a success rate comparable to the occurrence of spontaneous regrowth reported in the literature (87). A third study concluded that dapsone was not effective in the treatment of AA (88). Further studies are needed to confirm its efficacy. Cimetidine may help decrease the incidence of side effects (86).

Other treatments

Many other treatment modalities have been used for the treatment of AA, including nitrogen mustard (89), massage and relaxation (90), isoprinosine (91), acupuncture (92), and aromatherapy (93,94) to name a few. The efficacies of most of these treatments need to be confirmed.

Alternatives

Unfortunately, cosmetically acceptable regrowth is not always achieved following treatment and patients may look for alternatives to camouflage their alopecia. Cosmeticians can sometime assist patients with practical tips in applying makeup to simulate eyebrows and eyelashes. Dermatography (tattooing) can also be used to simulate eyebrows. One study with a 4-year follow-up showed that 77% (30 of 39) of patients had excellent cosmetic results and 8% (3 of 39) had good results with this cosmetic approach. Two to three dermatography sessions of 1 hour are usually required for each patient. No side effects were reported (95). Hairpieces are another very useful alternative for patients with extensive disease and allow them to carry on a normal social life. Patients should be assisted in finding a hairpiece that provides a natural look.

Last but not least, it is important that physicians address the psychologic aspects of the condition. Support groups are available in many cities (National Alopecia Areata Foundation, 710 C St. Suite 11, San Rafael, CA 94901, www.alopeciaareata.com).

Conclusion

The most commonly used therapies are corticosteroid injections, cortcosteroid creams, minoxidil, anthralin, topical immunotherapy, and phototherapy. The decision to choose one agent over the others depends on the age of the patient (as children do not always tolerate side effects), the extent of the condition (localized versus extensive), and the patient's personal preference.

The treatment protocol (Fig. 1) summarizes the most commonly used modalities in a practical algorithm. Again, this protocol is not restrictive and should only be used as a guide. For patients less than 10 years of age, the options are corticosteroid creams, minoxidil, and anthralin. For adults with less than 50% scalp involvement, the first option is usually intralesional corticosteroid, followed by corticosteroid cream, minoxidil solution, and anthralin cream. For adults with more than 50% scalp involvement, topical immunotherapy and phototherapy are added as options.

There is ongoing research on all fields of AA and new treatments are being developed. Hopefully we will eventually find a cure for AA.

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