Dermatologic Therapy, Vol. 24, 2011, 311–319
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DERMATOLOGIC THERAPY
ISSN 1396-0296

Investigative guidelines for alopecia areata

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ABSTRACT: The reported efficacy of various treatments for alopecia is difficult to compare based on a general lack of consideration in case reports/series and clinical trials of the spontaneous regrowth or baseline prognostic factors seen in alopecia areata and a general lack of quantification of hair growth. This report will give both the investigator and clinician guidelines for clinical trial design that will take into account variables known to effect efficacy results such as baseline severity, pattern, and duration of hair loss, age of the subject, and concomitant conditions that may impact on potential regrowth. Reliable methods of assessment of efficacy and response criteria that will enable direct comparison of results between agents will also be discussed.

KEYWORDS: alopecia, alopecia areata, investigative guidelines

Introduction

Alopecia areata is an enigmatic disease. Recent genetic detective work has suggested its relationship to other autoimmune diseases including type I diabetes, and rheumatoid arthritis (1), disorders that unlike alopecia areata, have constant phenotypic expression. Alopecia areata is unique in that its clinical manifestations (hair loss, nail effects) are neither constant nor cyclic nor expressed in all relevant cells at any one time but rather are expressed sporadically. The first presentation of hair loss may begin at any age, can involve scalp and/or body hair, and can be either discrete patches or widespread rapid total hair loss. Regrowth may occur spontaneously months to years after onset of the hair loss or the hair loss may persist indefinitely despite therapeutic interventions. Onset in infancy/early childhood, the presence of atopy and the total loss of scalp hair appear to be factors that independently encourage persistence of hair loss and/or recurrent episodes of hair loss.

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To date, there is no FDA-approved treatment for alopecia areata and evidence-based efficacy data are largely lacking, much of this related to the many variables noted above that are impossible to control for in alopecia areata. The literature on therapy of alopecia areata primarily consists of small uncontrolled studies whose results cannot be directly compared because either the endpoints are poorly defined or nonquantitative or the site and severity of hair loss at baseline is not taken into account. This paper reviews the methodology necessary to not only conduct standardized placebo-controlled clinical trials but to enable determination of comparative efficacy of various therapeutic agents in alopecia areata tested under different study protocols and/or at different sites. Recommendations for study design take into account the various types and amount of hair loss, the potential for spontaneous regrowth, and the known negative prognostic factors in alopecia areata.

Study design

Up until recently, reports of efficacy of treatment in alopecia areata have been largely from uncontrolled, small cohort, case report series. The

half-head study design introduced the controlled clinical trial to the assessment of efficacy of treatments for alopecia areata. More recently, placebo-controlled, parallel group studies have been successfully conducted in alopecia areata.

Half-head studies

In these studies, a topical medication is applied to the alopecic areas on one half of the scalp and the areas of alopecia on the other side of the scalp are left untreated as the control. The reliability of this design depends on the amount of hair loss being similar on the treated and untreated sides of the scalp and is best when there is extensive versus minor hair loss on both sides of the scalp. The efficacy of the study drug is assumed when terminal hair growth occurs only on the treated side and spontaneous regrowth is generally assumed when hair growth occurs on both treated and untreated sides (FIG. 1). This method has been proven particularly useful in determining the efficacy of topical steroids or topical sensitizers, the latter when applied by the study investigator. For example, Happle et al. and Wiseman et al. used this method to determine the efficacy of topical diphencyprone (DPCP) in alopecia areata (2, 3). If terminal hair growth was shown to occur only, or to a greater extent, on the side of the topical DPCP application, the response was considered specific to the drug and the treatment was then extended to both sides of the scalp to assess overall efficacy of the treatment. The University of British Columbia group also utilized the half-head study design to prove the ineffectiveness of topical nitrogen mustard in alopecia areata: only 1/6 showed a unilateral response to therapy in a 16-week study (4). Using the half-head study model, Kaplan and Olsen proved that topical 5-fluorouracil is ineffective in alopecia areata (5).

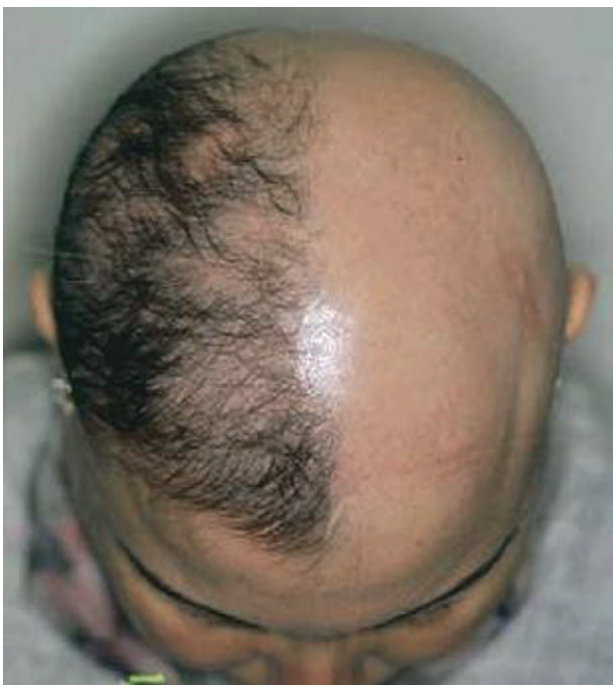

FIG. 1. Patient treated on half head only with topical clobetasol ointment with occlusion (reprinted with permission).

The main thrust for doing such half-head studies has been the ease of using the patient as his/her own control. While this may be a reasonable approach for topical sensitizers, which are applied by the investigator and which have only a local effect, there are problems with using this method with a preparation that the patient must apply or topical medications that could have an effect beyond the area of drug application. A response seen bilaterally when the patient is instructed to only apply the medication to one side of the scalp could be secondary to either spontaneous regrowth, inadvertent or purposeful application on both sides of the scalp by the patient, or a systemic effect of the topical medication. Surprisingly, the half-head studies of topical clobetasol under occlusion in patients with alopecia totalis or universalis in which one could envision a systemic effect of the corticosteroid occurring, showed hair growth on both sides only in 1/28 patients (6). However, Talpur and Duvic felt that the responses seen on the untreated side of the scalp in a study in which patients self-applied topical bexarotene, could possibly be secondary to either systemic absorption or diffusion of the study drug (7).

To use the half-head study design for clinical trials of alopecia areata, it is best to have the investigator apply the study drug and to attribute efficacy to the hair growth promoter only in those patients in which hair growth is limited to the treated side.

Double-blind, placebo-controlled parallel group studies

This type of study can be used to assess the efficacy of topical, intralesional or systemic agents in alopecia areata. In this study design, patients are matched for as many variables as seem relevant (see discussion below) and are randomized to receive active drug or placebo. Active and placebo agents, applied topically or injected intralesionally, are to be used on all alopecic areas rather than just those on one side of the scalp. This study design

requires many more patients than the half-head study design but it removes any potential for misapplication of study drug by patients and allows the investigator to be blinded as to treatment when making an assessment. It also is the only type of placebo-controlled study that can reliably be performed with a systemic agent or with any externally directed agent that may have a systemic effect.

Active-control parallel group studies

In the future, performing active-control studies may become important in alopecia areata, particularly if a single gold standard treatment is identified and has predictable results. At this point in time, the benchmark treatment is likely systemic corticosteroids but there is not general acceptance of this as first line therapy in alopecia areata. However, even if one does carry out an active-control study, a third placebo arm is recommended due to the potential for spontaneous remission in alopecia areata. In two placebo-controlled clinical trials of alopecia areata, the percentage of spontaneous regrowth at 3 months varied depending on baseline hair growth and the definition of regrowth utilized in the analysis: in patients with ≥50% hair loss at baseline, 8% (2/25) on placebo had at least 25% regrowth (8) and in patients who did not have any minimal criteria for baseline hair loss severity, 28.5% (4/14) on placebo had 50–99% regrowth (9).

Cross-over studies

A study design that has patients randomized to either placebo or active drug and then, after a set period of time, crossed over to the alternate treatment, has certain positive attributes. This type of study allows the patient assigned to placebo initially to act as his/her own control in the placebo period and then insures that all patients receive active drug, an important point for patient retention in a clinical trial. The value to the patients assigned initially to active drug is less clear since if they are having a positive response to study drug, they will have an effective treatment discontinued before full efficacy is achieved and likely resumption of further hair loss. And for the investigator, there are two potential problems to patients beginning with active drug before crossing over to placebo: it will be impossible to ferret out spontaneous hair growth versus drug induced hair growth during the active treatment phase and the active agent will most assuredly have an effect on the results in the placebo phase following it.

However, a placebo-crossover phase added on to a parallel treatment design would preserve the placebo comparative phase upfront, insure all patients of getting active drug and insure an extended treatment period for those patients initially randomized to the active treatment group. However, the only part of such a study that is controlled is while some patients remain on placebo and given the increasing potential for spontaneous regrowth over time, the time on placebo should be as long as necessary to fully assess the potential regrowth of the study drug.

Duration of study

This is an important aspect of study design. Clearly, intralesional and systemic steroids are able to initiate hair growth more rapidly (1–2 months) than topical corticosteroids (3–4 months) (Olsen, personal communication; (10)). Ultraviolet light has been reported to take an average of 3 months for a response (11) and psoralen plus UVA (PUVA) an average of 30 sessions before vellus hair appears, 50–80 sessions before full regrowth (12). Topical sensitizers generally take 3 months to show initial hair growth but 12–24 months for the maximum response (3). The study duration for any particular clinical trial should take into account the time for initiation of hair growth with that particular agent and whether the objective of the study includes determining whether full regrowth can be achieved. For example, in the topical 5-fluorouracil trial conducted at Duke University, the purpose of the study was primarily to determine any potential efficacy and hence patients were considered nonresponders and dropped from the study if no regrowth was seen by 3 months (5).

Statistical analysis

For analysis of efficacy, the intention-to-treat population, defined as all randomized patients, should be utilized.

Subject selection

Age

There is no age within the adult age range (≥18 years old) that one would need to be particularly concerned about a differential effect on hair regrowth. However, those adults whose hair loss first began when they were less than 5 years of age clearly may have a different response to therapy

than those with a first episode of hair loss as an adult. This is also true for children whose first episode of hair loss occurred in infancy versus later in childhood or adolescence. In addition, particular attention should be paid to subjects with persistent alopecia totalis/universalis since infancy as there is a potential for confusion with other inherited hair loss disorders with alopecia areata. Two particular disorders, atrichia with papular lesions and vitamin D resistant rickets, have scalp hair at birth that is shed over the first 2–3 years of life, and with persistent total scalp alopecia thereafter (14). A scalp biopsy would differentiate these conditions from alopecia areata.

Duration of current episode of hair loss

This is defined as from the time when hair growth was last normal (excluding, if present, the hair loss from the underlying conditions of male and female pattern alopecia) to the present time. The following subgroups of hair loss duration are important to consider in study design:

1. <3 months
2. 3–12 months
3. 12–24 months
4. >2–5 years
5. >5 years

The duration of hair loss is primarily regarded as a marker of the potential for spontaneous regrowth, which is greatest during the first 2 years after hair loss begins and much less likely after 5 years of continued hair loss in a given area, particularly for those with alopecia totalis or universalis. However, duration of hair loss may also be linked to activity of disease.

Activity of hair loss

Little is said of this factor in any clinical trial discussion but it has important ramifications for the initial response to therapy. Patients who are in a very active phase of loss at the beginning of a clinical trial most assuredly will have further hair loss before any regrowth can be stimulated by any agent: this is because hairs have already moved out of anagen but have not yet been shed. If patients in an active shedding phase are included in a clinical trial, the subsequent immediate hair loss could be misinterpreted as the therapy being ineffective. Active loss is easily discernable clinically by a hair pull at the periphery of any loss and throughout the scalp: if active, the hairs will readily come out on gentle traction. In addition, active loss, and corroboration of alopecia areata, can be obtained by looking for exclamation point hairs: the presence of a few exclamation point hairs only confirms the presence of alopecia areata but the presence of many is suggestive of a very active phase of loss. Finally, a biopsy of the scalp may be discriminatory of the active phase versus quiescent, persistent phase of hair loss with the lymphocytic "swarm of bees" around the follicular bulb more common with active loss: how presence or absence of the latter effects response to therapy has not been determined.

Pattern of hair loss

There are certain patterns of hair loss in alopecia areata that have a poor prognosis. Alopecia totalis (AT: 100% terminal hair loss on the scalp) and alopecia universalis (AU: 100% terminal hair loss on the scalp and body) are clearly less treatment responsive than patchy alopecia areata. An ophiasis pattern of hair loss (hair loss around the periphery of the scalp, largely sparing the central scalp) is also much more treatment resistant. Any trial including these patterns of hair loss should have stratification by pattern and the expectation that the response to treatment in these clinical subtypes will be much less than in patchy alopecia areata.

Amount of hair loss

Many of the studies in the literature have included both patients with limited (<25%) and extensive (>50%) hair loss, most without stratification by amount of hair loss at baseline when reporting results. Since the likelihood of spontaneous regrowth is inversely proportional to the amount of loss and since the methods to track efficacy are different when the hair loss is minimal versus extensive, the amount of hair loss is an appropriate variable to use to stratify the patient population in clinical studies. The data on response to treatment correlated with amount of hair loss at baseline should be part of the results section of any clinical trial of alopecia areata.

Presence of body hair loss and/or nail involvement

These should be noted as potentially their presence could imply a more generalized immune response and affect the response to treatment of scalp hair loss.

Concomitant conditions

Although there is an increased frequency of other autoimmune disorders in patients with alopecia

areata compared to the general population, most patients are free of other such conditions. However, occasionally patients may have multiple autoimmune conditions and these patients may respond very differently to treatment for their hair loss than those who have alopecia areata alone. Patients with atopy (atopic dermatitis, allergic rhinitis, hay fever) may also have a less vigorous response to treatment than those without a history of atopy.

Although family history of alopecia areata may be a negative prognostic factor, the difficulty in corroborating the history makes it difficult to use as a point of stratification of treatment groups in a clinical trial.

Efficacy assessment

Endpoints

Quantitative assessment of regrowth. The quantitative measures used to report regrowth prior to 1990 were fairly crude or nonexistent. Patients' response to therapy were reported in qualitative terms such as "patchy" or "diffuse" (15), "some response", "good response or good growth" (16), "significant regrowth" (17) or "full regrowth," "almost full regrowth" and "improvement" (11), often without attention to the amount of hair loss at baseline. Vellus as well as terminal hair was often recorded in responders (16). One parameter used to commonly assess efficacy has been "cosmetically acceptable hair growth" (17–19). "Cosmetically acceptable" has been defined as "amount of terminal hair growth sufficient to cover the scalp and conceal areas of residual loss" (19) or "patient no longer needing a wig or cap to conceal hair loss" (18,20). Most reports of "cosmetically acceptable" regrowth did not take into account the location and/or amount of the hair loss at baseline, important variables effecting results. Hair loss on the top of the scalp is much less likely to end up as cosmetically acceptable compared to hair loss on the sides and back of the scalp unless the regrowth is nearly complete. The use or nonuse of a hairpiece by the patient adds another subjective aspect to the response.

Both Fiedler-Weiss and Price independently in 1987 quantified the amount of hair loss at baseline, Fiedler-Weiss dividing hair loss into 0–24%, 25–74%, and 75–100% subgroups and Price dividing the baseline hair loss into 25–50%, 51–75%, 76–99%, and 100% hair loss (18,19). Gupta et al. also added a scoring system for hair loss at baseline and at follow-up (0 = no loss, 1 = almost totally free of hair loss, 2 = mild, 3 = mild to moderate, 4 = moderate, 5 = moderate to severe, and 6 = severe hair loss, further defined as AU, AT, or >5 patches each >4 cm in diameter) and then attached a quantitative measure to the term "cosmetically acceptable" regrowth (terminal hair regrowth on more than 90% of the scalp) (21). Although this latter group's system allowed for examination of the difference in response in those with varying degrees of hair loss at baseline, the scoring system was still very subjective in nature, making comparison of results obtained by different investigators/sites difficult.

In 1992, Olsen et al. reported on the use of a quantitative assessment measure of hair loss in a prospective clinical trial to determine the potential synergistic effect of topical minoxidil with oral steroids in the treatment of alopecia areata (10). Olsen and her colleagues stratified the patient population into the subcategories of baseline hair loss, i.e., 0–24%, 25–49%, 50–74%, 75–99%, and 100%. In determining regrowth, the % of scalp hair loss was determined and the % change in hair loss from baseline determined at each follow-up visit. This was then similarly put into categories of regrowth, i.e., <25%, 25–49%, 50–74%, 75–99%, and 100% for reporting purposes. Only terminal loss was used to assess hair loss or regrowth. This method determined the absolute quantitative change in hair growth during the treatment course but also allowed for determination of the response relative to the amount of hair loss at baseline.

At the World Congress of Dermatology in 1997, Olsen presented the utility of the use of this quantitative assessment method in the clinic as well as in clinical trials (22). Using photographs to corroborate the hair loss in patients with alopecia areata seen at Duke University over the past 10 years, she confirmed for the first time the efficacy of topical steroids in 99 patients with extensive (defined as ≥50% scalp hair loss) alopecia areata: 41% had at least 50% regrowth including 15% with 76–99% regrowth, and 18% with 100% regrowth.

In 1999, a group of physicians with expertise in hair disorders, acting on behalf of the National Alopecia Areata Foundation (NAAF), published the first of two papers creating standardized investigative guidelines for alopecia areata (23). This paper confirmed the need to perform a quantitative assessment of amount of scalp hair loss at each visit when determining efficacy of a given agent in alopecia areata. A visual aid (FIG. 2) showing the division of the scalp hair into four quadrants, back, top of scalp, and both sides, with each of the four quadrants given an accurate determination of the % of

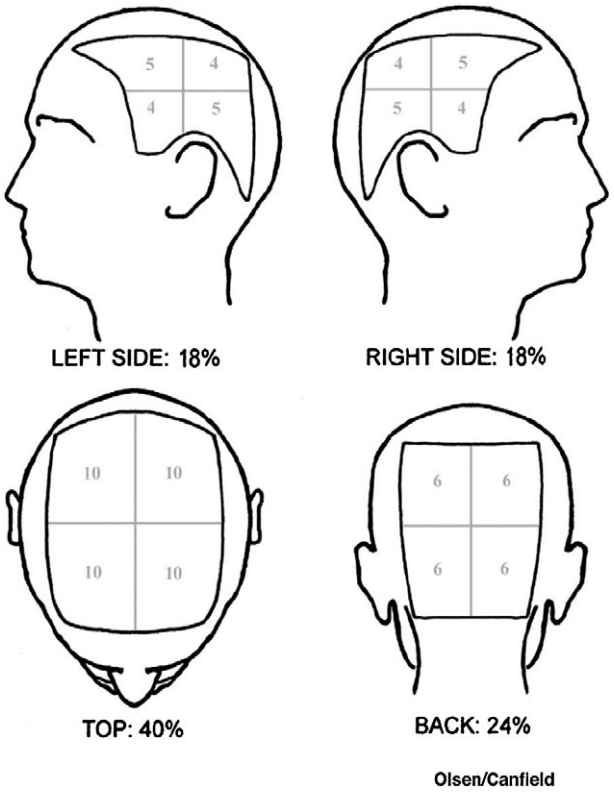

FIG. 2. Olsen/Canfield tool for determination of % scalp hair loss. Percentages represent scalp surface area (reprinted with permission).

scalp surface area covered, was provided by Olsen and Canfield. This aid facilitated a more accurate determination of hair loss and uniformity between investigators' assessments. The subcategories of % scalp hair loss were given an official shorthand designation to facilitate communication among centers, mirroring the Olsen method of 1992.

S_0 = no hair loss
$S_1 \leq$ 25% hair loss
S_2 = 25–49% hair loss
S_3 = 50–74% hair loss
S_4 = 75–99% hair loss
a = 75–95%
b = 96–99%
S_5 = 100% hair loss

Body hair was rated for the first time as none, some, or 100% (B_0, B_1, and B_2, respectively) and nail involvement as none or some (N_0 and N_1) with a subcategory of N_1 for 20 nail dystrophy (N_{1a}). In this way, the complete picture of a patient's alopecia areata at baseline could be described and classified (Example, $S_{4a}B_1N_0$ for a patient with 80% scalp hair loss, eyelash loss but no other body hair loss and no nail involvement). The publication also gave a listing of potential information to gather in the planned NAAF alopecia areata database, i.e., demographic information, details of the history of alopecia areata, family history of alopecia areata, and medical history of the patient and family.

In Part II, of the investigative guidelines, the SALT score was introduced (24). This formalized a mathematical approach to the determination of hair loss and hair regrowth. Briefly, the % of scalp hair loss in each of the sides, back and top of the scalp were determined independently, each was multiplied by the % scalp covered in that area of the scalp and the products of each section summed for a final total % hair loss, designated as the Severity Alopecia Tool or SALT score (FIG. 3a,b). This computation would be repeated at each visit during a study and the change from baseline SALT score would be the % regrowth. For example, if a patient had 60% scalp loss at baseline and 35% scalp hair loss at follow-up by SALT score determination, this is then a 42% change (regrowth) from baseline or an absolute 25% regrowth. The SALT score was used for the first time in a commercially sponsored clinical trial of alopecia areata in 2003–2005 (8).

Hair growth index. Bernardo et al. developed a scoring system for regrowth in alopecia areata that included not only % of scalp hair regrowth but also the type of hairs regrowing in the areas of hair loss (8). Unlike other methods of assessing results, this method included an assessment of nonterminal hair growth. The percentage of scalp covered by vellus, indeterminate or terminal hair was multiplied by a weighting factor of 1 for vellus, 2 for indeterminate, and 3 for terminal. The sum of these products (0–300) was the Hair Growth Index score and could be compared at each visit. Although this scoring system was used in this publication in a half-head study, it could be extended to use in a parallel group treatment study. The primary utility of the Hair Growth Index would seem to be in the determination of whether a new agent induces any particular type of hair growth rather than in the determination of overall efficacy.

Response criteria

What is considered a significant response may vary by type of alopecia areata, amount of hair loss, and duration of hair loss and whether the purpose of the study is to show any efficacy of a new agent before moving forward with further trials. Olsen et al. in the active control study of systemic steroids with or without topical minoxidil defined an objective response as at least 25% terminal regrowth compared to baseline (10). However, in her study,

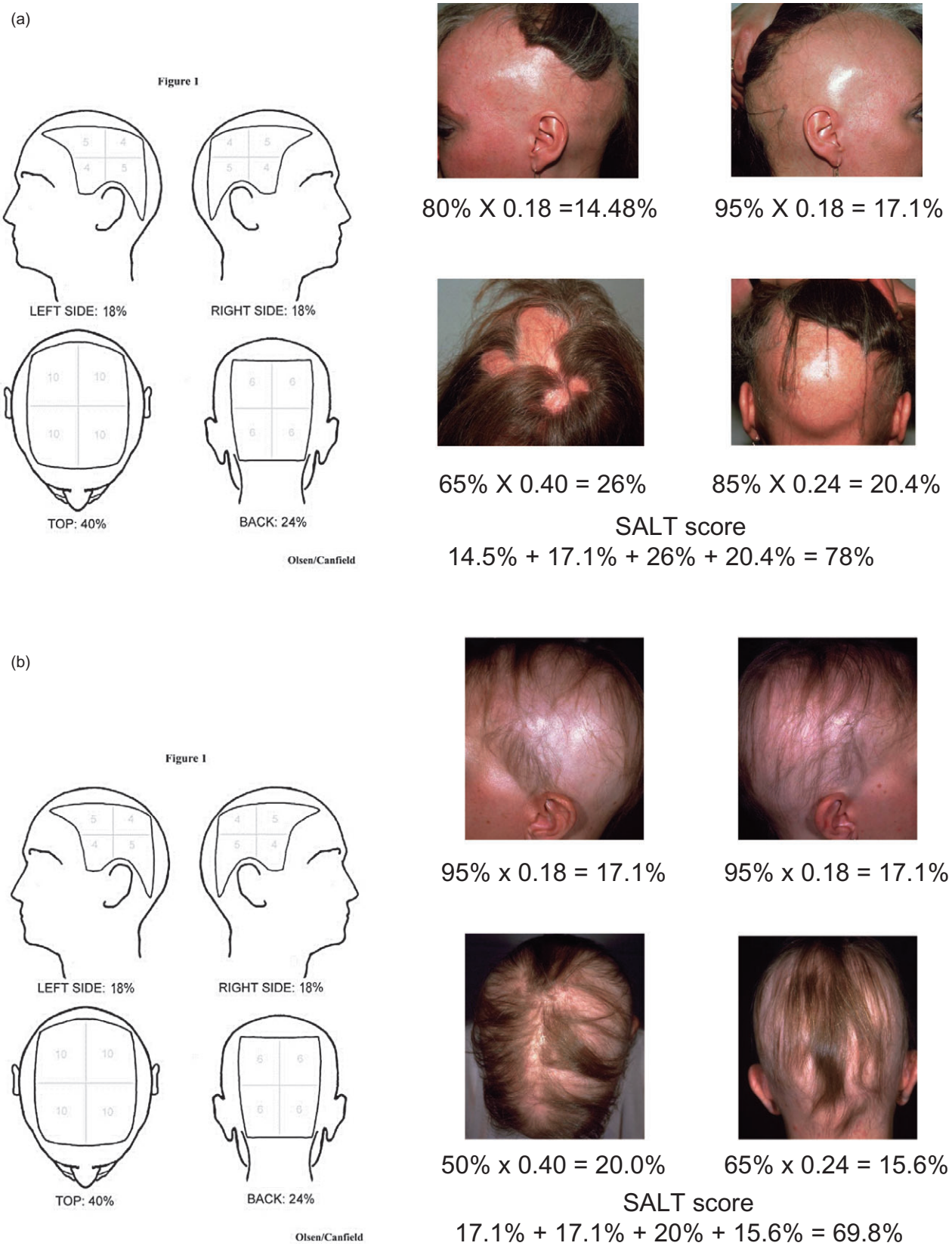

FIG. 3. (a, b) Determination of SALT score in two patients with extensive scalp hair loss. For determination of efficacy, the SALT score would be determined at baseline (BL) and each follow-up (F/U) visit and the percentage change from baseline determined by the following: $\frac{\text{SALT BL} - \text{SALT F/U}}{\text{SALT BL}} \times 100\% = \%$ **change from baseline.**

of topical steroids alone, she focused on responses of ≥50% terminal hair regrowth in those with >50% loss at baseline (22). Wiseman et al., in their study of patients who had topical DPCP applied by the investigator, defined significant regrowth as ≥75% of the scalp covered by terminal hair (3). Delemere et al. in conducting an evidence-based review of therapeutic options in alopecia areata defined clinically significant hair growth as >50% regrowth of the affected area (13). Talpur and Duvic used terminology more common with cancer studies in their study of topical bexarotene, i.e., a Physician Global Assessment of ≥50% improvement was defined as a partial response and 100% clearing defined as a complete response (7).

As with psoriasis, an arbitrary % improvement can be established as a benchmark for alopecia areata. The NAAF subgroup on investigative guidelines has suggested that this could be expressed by a subscript number attached to the SALT (example $SALT_{50}$, $SALT_{75}$). This would be useful for comparing results in various clinical trials, i.e., how many patients were able to achieve a $SALT_{50}$. However, going forward, it must be made very clear that the subscript of 50 or 75 refers to a % change in hair loss from baseline and not to an absolute change in % hair loss from baseline.

Photographs

Standardized global photographs of the four views of the scalp (top, both sides, and back) are strongly encouraged to both help to corroborate the SALT score determination at the bedside as well as to track specific areas of hair loss. The photographs can be further utilized to do a global panel review at the end of the study in which blinded experts rate the hair growth response. Taking time to comb the hair for the photographs is very important so that the location and relative size of the areas of hair loss can be tracked at subsequent visits and also to enable direct comparison of the sequential photographs of the hair loss during global panel review

Biopsy

A biopsy is not generally needed for the diagnosis of alopecia areata except in cases of diffuse alopecia. However, the presence of active alopecia areata with a peribulbar lymphocytic infiltrate around terminal follicles versus alopecia in the chronic phase where the hairs are miniaturized and the infiltrate is less obvious (25) may impact on study results. In general, accounting for the duration of current episode of hair loss likely covers for this difference in histology. Clinical trials have not routinely included biopsies but they may offer additional insight into variation of response, particularly if biologic markers of disease activity are established.

Patient assessment

Several possible methods exist for capturing patient assessment of response.

a. Descriptive Assessment. Fiedler-Weiss had patients use the same definition of "cosmetically acceptable hair growth" as the investigator in rating efficacy of topical minoxidil, i.e., no longer needing cap or wig to conceal hair loss (18). Patients in the study by Wiseman et al. were also asked to determine "cosmetically acceptable regrowth" but the definition was left open ended (3).
b. SALT Score. Patients can also be asked to use the SALT score to determine their amount of hair loss during a clinical trial but this method requires standardized photographs from the current visit be either printed out or displayed electronically for patients. This method is unlikely to be particularly useful if photographs are unable to capture the full extent of the hair loss. Before using this technique in an actual clinical trial, patients should be given adequate instruction and experience with this tool.
c. Visual analog scale (VAS). A VAS is quantifiable and easy for the patient to understand and use. In the efalizumab trial using a 100 mm VAS, patients were more likely to rate the hair loss in the placebo group as negative than investigators but both were in general accord with the results (8).
d. Quality of life (QoL) questionnaire. A standardized QoL questionnaire specifically for alopecia areata does not exist. However, validated QoL questionnaires for skin disorders are available and selected relevant questions could be utilized from them. For example, the first 17 questions of the Dermatology Quality of Life Scales was utilized in the efalizumab study (8). An alopecia areata-specific QoL questionnaire is a goal for Phase II–III clinical trials.

Conclusions

After decades of case-control series assessing the efficacy of agents used to treat alopecia areata, we are now poised to conduct controlled clinical trials of new agents. Given the recent leaps in under-

standing of the etiological factor in alopecia areata gained from the NAAF national patient registry and the subsequent genetic work done by Dr Christiano and colleagues, there is now the hope of identifying new effective treatments for alopecia areata. We also now have standardized methods to readily assess the efficacy of these agents on the pathway toward the first FDA approval of a medication for this condition.

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