Management of hair loss diseases

Manabu Ohyama*

Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

KEYWORDS
Alopecia areata
Androgenetic alopecia
Bulge stem cells
Scarring alopecia
Telogen effluvium
Transverse section
Trichoscopy

ABSTRACT
The treatment of hair loss diseases is sometimes difficult because of insufficient efficacy and limited options. However, recent advances in understanding of the pathophysiology and development of new remedies have improved the treatment of refractory hair loss conditions. In this article, an update on the management of hair loss diseases is provided, especially focusing on recently reported therapeutic approaches for alopecia areata (AA). An accurate diagnosis is indispensable to optimize treatment. Dry dermoscopy represents new diagnostic techniques, which could enable the differentiation of barely indistinguishable alopecias, e.g. AA and trichotillomania. An organized scalp biopsy adopting both vertical and transverse sectioning approaches also provides a deep insight into the pathophysiology of ongoing alopecias. Among various treatments for AA, intraregional corticosteroid and contact immunotherapy have been recognized as first-line therapies. However, some AA cases are refractory to both treatments. Recent studies have demonstrated the efficacy of pulse corticosteroid therapy or the combination of oral psoralen ultraviolet A therapy and systemic corticosteroids for severe AA. Previous clinical observations have suggested the potential role of antihistamines as supportive medications for AA. Experimental evaluation using AA model mice further supports their effectiveness in AA treatment. Finasteride opens up new possibilities for the treatment of androgenetic alopecia. For androgenetic alopecia patients refractory to finasteride, the combination of finasteride with topical minoxidil or the administration of dutasteride, another 5 alpha-reductase inhibitor, may provide better outcomes. Scarring alopecia is the most difficult form of hair loss disorder to treat. The bulge stem cell area is destroyed by unnecessary immune reactions with resultant permanent loss of hair follicle structures in scarring alopecia. Currently, treatment options for this hair loss disorder are extremely limited. The development of effective therapies for this form of intractable alopecia represents an important issue to be resolved.

Copyright © 2010, Taiwanese Dermatological Association.
Published by Elsevier Taiwan LLC. All rights reserved.

Introduction
Hair loss diseases, represented by alopecia areata (AA) or androgenetic alopecia (AGA), are relatively common dermatological problems encountered in daily practice. Although effective therapies are readily available for some types of alopecia, treatment options for certain subsets are extremely limited with unfavorable outcomes. Accordingly, attempts have been made to develop or improve therapeutic approaches for intractable alopecia. In this review, recent advances in the management of hair loss diseases, including new techniques that enable proper diagnosis, novel therapeutic approaches and future perspectives are summarized. Particular emphasis is placed on the treatments for severe AA. Although remarkable progress has been made in the molecular biological understanding of genetic hair loss or anomalies, these conditions are not discussed in this article because they are rare.

*Corresponding author. Department of Dermatology, Keio University School of Medicine, 35 Shinanomachi Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: manabuohy@z8.keio.jp
Advances in diagnostic procedures

A correct diagnosis is indispensable to select and perform optimal treatment for hair loss diseases. Hair loss conditions with distinct clinical manifestations, such as typical AA and AGA, can be easily diagnosed based on the pattern of hair loss or the shape of fallen out hair shafts. However, some hair loss conditions are not diagnosable just by routine clinical evaluations.

Dermoscopy is a useful device, especially for the evaluation of pigmentary lesions, including melanoma. The use of videodermoscopy or dry dermoscopy (dermoscopy without an immersion gel) enhances the diagnostic capacity in some hair loss conditions. Inui et al reported that yellow dots and short vellus hairs are the most sensitive markers of AA, while hair diameter diversity is an essential feature of AGA. Scalp dermoscopy also provides a powerful tool to differentiate clinically resembling hair loss conditions. Trichotillomania in which habitual or unconscious hair pulling causes mostly discrete alopecic patches, sometimes presents with an AA-like appearance (Figure 1A). Such lesions can be easily distinguished from AA by dermoscopy. Characteristic dermoscopic findings of trichotillomania are black dots and broken hairs without tapering hairs or small vellus hairs (Figure 1B). Dermoscopy is useful for the diagnosis of hair loss conditions as well as the evaluation of disease activity. For example, the presence of such findings as tapering hairs and short vellus hairs is correlated with AA disease activity. Collectively, the use of dermoscopy for the diagnosis of hair loss disorders is highly recommended.

Scalp biopsy may not be included in “routine” diagnostic procedures for hair loss conditions. However, histopathological investigation of alopecic lesions is sometimes necessary to make a final diagnosis (e.g. scarring alopecia) or better understand the pathophysiology of the ongoing disease. It has been reported that transverse sections of punch scalp biopsy specimens enable quantitative morphometric analysis of hair follicles. Factors that are indispensable for pathological interpretation of hair loss conditions, including total hair follicle number, the telogen/anagen ratio, and the ratio between terminal and vellus hairs, cannot be determined by conventional vertical sections (Figure 2). In addition, by slicing a sample into 3–4 disks (so that each disk contains infundibulum, isthmus, suprabulbar and bulbar regions) and embedding the same side down into the same cassette, several levels of hair follicles can be investigated on a single slide (Figure 2). Ideally, transverse sections should be prepared from both affected and unaffected sites for comparison. Although transverse scalp sections exceed conventional vertical sections in many aspects, some key pathological information is barely detectable by the transverse sectioning approach. For example, changes in the dermo-epidermal junction (interface change) cannot be appropriately assessed by the transverse approach. Thus both transverse and vertical sections are valuable in the diagnosis of hair loss disorders. In our hair disease clinic, a standard histopathological investigation includes two 4mm punch biopsy samples obtained from affected lesions (one for transverse sections and another for vertical sections and the lupus band test) and one sample taken from the nonaffected area (Figure 2). Analogous organized scalp biopsy techniques should significantly improve the quality of dermatopathological interpretation of hair loss diseases.

Treatment of AA

AA is a common hair loss problem encountered by dermatologists and various therapies have been attempted to treat this condition. However, few therapies have been...

Figure 1  Usefulness of trichoscopy (dry dermoscopy) in the diagnosis of hair loss disease. (A) Some cases of trichotillomania are barely distinguishable from alopecia areata in clinical appearance. (B) Diagnosis of trichotillomania is made by characteristic trichoscopic findings: black dots and broken hairs (arrowheads) without tapering hairs or small vellus hairs.
Management of hair loss diseases

evaluated in randomized controlled trials. Accordingly, evidenced-based therapeutic approaches are extremely limited.\(^1\)\(^4\),\(^1\)\(^5\) Although the evidence is not yet conclusive, intralesional corticosteroid injection and contact immunotherapy are considered effective therapies for AA\(^1\)\(^4\),\(^1\)\(^5\) and are listed in major guidelines, including those of the National Alopecia Areata Foundation in the USA (http://www.naaf.org/site/PageServer). Although both therapies are satisfactorily effective in many AA cases, cases with rapidly progressive AA or persisting AA totalis/universalis are frequently refractory to those treatments.

Recently, Nakajima et al\(^1\)\(^6\) reported that pulse corticosteroid therapy is effective for recent-onset, severe cases of AA (duration of AA \(\leq 6\) months from the onset of active hair loss). In their study, 59.4% of the recent-onset group responded well (>75% regrowth of alopecia lesions). Notably, 88.0% of recent-onset AA patients with less severe disease \(\leq 50\%\) hair loss) and 21.4% of recent-onset cases with 100% hair loss showed a favorable response. No serious side effects were observed. However, only 15.8% of patients with >6 months duration satisfactorily responded. Pathologically, perifollicular inflammation is apparent only in the acute phase of AA. In the chronic phase of AA, telogen hair follicles surrounded by moderate to little cell infiltration are predominantly observed.\(^1\)\(^,\)\(^9\) The difference in response against glucocorticoid pulse therapy between recent-onset and longstanding AA cases could be explained by a direct suppressive effect of corticosteroids against active inflammation in acute severe AA cases. Systemic corticosteroid therapy for AA is controversial. However, considering that the total dose of corticosteroids is smaller in pulse therapy than that in conventional systemic oral administration in the long term, pulse therapy may be beneficial for recent-onset rapidly progressing AA cases.\(^1\)\(^6\)

Ito et al\(^1\)\(^7\) reported another potential therapy for intractable AA. In their study, alopecia totalis and universalis patients received combination therapy with oral psoralen plus ultraviolet A (starting from half of the minimal phototoxic dose of 20 mg methoxsalen/day, 5 days per week) and oral prednisolone (20 mg/day for 4 weeks and then decreased to 5 mg/week). All of the six alopecia totalis patients and one of the three alopecia universalis patients demonstrated remarkable hair regrowth 3 months after the combination therapy was initiated. The treatment was well-tolerated and no severe side effects were noted. In the responders, the number of perifollicular infiltrating lymphocytes was decreased with an increase in the percentage of CD4\(^+\)CD25\(^+\)FOX3\(^+\) regulatory T cells, suggesting that the effect of the combination therapy could be explained by an immunomodulatory effect.\(^1\)\(^7\) Despite its efficacy, the treatment mostly requires hospitalization to avoid ophthalmologic complications.\(^1\)\(^7\)

We adopted the principle of their combination therapy and modified the protocol, so that the treatment could be performed for outpatients. We replaced oral psoralen plus ultraviolet A with the psoralen plus ultraviolet A-turban method, which has been previously reported as an efficient therapy for AA,\(^1\)\(^8\) and combined it with oral administration of prednisolone. Satisfactory hair regrowth was often achieved in persisting alopecia totalis and universalis cases (Figure 3). Low-dose systemic corticosteroids (about 5 mg/day) are mostly required to maintain an effect. A double-blind clinical study has not been conducted for this therapy. In addition, the number of accumulated cases is still not large enough to give statistical significance. Therefore, a definitive conclusion

Figure 2 An organized scalp biopsy procedure enables more detailed and quantitative histological examination (HE) of hair loss conditions. Transverse sections can sample all hair follicles, and thus allow quantitative analysis (e.g. total hair follicle numbers, anagen/telogen ratio), while vertical sections are best at detecting the change in interface area. Comparison between affected and nonaffected lesions enables more precise histopathological interpretation. Ideally, two samples from affected lesions (one for transverse sections and another for vertical sections and direct immunofluorescent [DIF] study) and one sample from a nonaffected lesion need to be obtained.
cannot be made. However, based on our experience in the hair disease clinic, the combination therapy should be attempted when a long-lasting severe AA patient desires a treatment that has certain efficacy.

Tosti et al\textsuperscript{19} reported an approach that can be easily introduced into office dermatology. In their study, alopecia totalis/universalis patients were treated with clobetasol propionate 0.05\% ointment under occlusion. Eight of the 28 severe alopecia patients responded with regrowth of terminal hairs. Despite the finding that three of the eight responders had a relapse, the finding that hair regrowth was exclusively observed on the treated half of the scalp indicated the efficacy of the remedy.\textsuperscript{19} In our clinic, we have combined intrale-sional corticosteroid injection and clobetasol ointment occlusive dressing therapy and have experienced a favorable response in some severe AA cases (Figure 4).

Recently, the potential role of antihistamines in AA treatment has been reported.\textsuperscript{20–22} The incidence of AA is higher in individuals with an atopic background.\textsuperscript{23} An increase in infiltrating eosinophils and mast cells has been also described in AA lesions.\textsuperscript{24,25} These observations suggest that antihistamines could be useful as medications for AA. Inui et al\textsuperscript{22} have reported that addition of oral fexofenadine hydrochloride to contact immunotherapy improves the outcome of the treatment.\textsuperscript{22} In an experimental evaluation of the efficacy of ebastine for AA, C3H/HeJ AA active disease model mice\textsuperscript{26} were orally administered either ebastine or vehicle.\textsuperscript{23} Interestingly, hair regrowth was observed only in ebastine-treated mice (Figure 5\textsuperscript{23}). Although the exact mechanism and efficacy of antihistamines in AA treatment are yet to be elucidated, these findings are supportive for antihista-mines being considered as supportive medications, at least for AA patients with an atopic background.\textsuperscript{23}

Some cases of severely affected, rapidly progressing AA spontaneously recover without intensive therapy.\textsuperscript{27} This subset of AA, named as “acute diffuse and total alopecia of the female scalp” (ADTAFS), is mostly observed in young female patients.\textsuperscript{27,28} The condition is characterized clinically by rapid hair loss progressing to total baldness with subsequent rapid recovery, and pathologically by perifollicular eosinophilic cell infiltrate.\textsuperscript{27} The prognosis of ADTAFS patients is mostly favorable.\textsuperscript{28} A similar regression has also
Management of hair loss diseases

been found in senile male cases. Thus the condition may not be restricted to females. These observations reinforce that an aggressive treatment is not always necessary for severe AA cases. Patients with ADTAFS are often barely distinguishable just based on clinical presentations. However, careful course observation, instead of immediate introduction of aggressive therapy, is recommended once ADTAFS is considered as a differential diagnosis.

Treatment of AGA

It has been widely accepted that topical minoxidil and oral finasteride provide effective remedies for AGA. However, oral finasteride administration does not always yield a satisfactory outcome in AGA cases. Because pharmacological effects of minoxidil and finasteride on AGA are distinct, a possible strategy to enhance the efficacy of AGA treatment is to combine both therapeutic approaches. Indeed, favorable responses of such combination therapy have already been reported. Another promising remedy for AGA is oral administration of dutasteride. Dutasteride is a dual blocker of 5 alpha-reductase type 1 and 2. Although not definitive, a previous clinical trial has suggested an advantage of dutasteride compared with finasteride. Further accumulation of cases is necessary to draw a definitive conclusion; however, dutasteride may be a future alternative for AGA cases refractory to oral finasteride therapy.

Laboratory tests for telogen effluvium

It has been widely accepted that laboratory tests for thyroid disease or collagen diseases should be considered for patients with telogen effluvium. It is controversial whether iron or zinc deficiency can increase the incidence of telogen effluvium. We have experienced several chronic telogen effluvium cases with low serum levels of iron or zinc. Supplementation of these elements terminated hair loss in those cases, suggesting that low iron or zinc levels could have been responsible for hair loss in those individuals. Iron and zinc levels cannot be routinely measured in telogen effluvium cases, but may deserve consideration, especially in those prone to lose iron or zinc, including hypermenorrhea, myoma or inflammatory bowel disease patients.

Understanding scarring alopecia

Recent advances in hair follicle stem cell biology have enabled a better understanding of the pathogenesis of scarring alopecia. Hair follicles are self-renewing tissues and the presence of tissue specific stem cells has been speculated. Using a label-retaining cell technique to detect slow-cycling stem cells in vivo, hair follicle stem cells were detected in the bulge region of hair follicles. The bulge region is a contiguous portion of the outer root sheath, which provides the insertion point of the arrector pili muscle. One of the most distinctive histopathological features of scarring alopecia, including cutaneous lupus erythematosus and lichen planopilaris (Figure 6A), is cell infiltration involving the bulge region of the hair follicle (Figure 6B). This characteristic inflammatory change is considered to impair hair follicle stem cells with a resultant permanent hair loss (Figure 6C). Thus it is critically important to diagnose scarring alopecia as soon as possible and initiate anti-inflammatory therapy, such as local corticosteroid injection, before the stem cells are irreversibly damaged. Biopsy is particularly important in scarring alopecia to confirm the diagnosis and to detect latent ongoing inflammation in clinically uninvolved regions.

Treatment options for scarring alopecia are extremely limited. However, it should be noted that, in addition to medications, surgical procedures such as hair transplantation and excision can provide satisfactory results in stable primary lymphocytic and secondary (post burn or traumatic) scarring alopecia. Recent studies have suggested the down-regulation of some bulge markers or that PPAR-gamma plays a role in the pathogenesis of scarring alopecia. Modulation of those targets, e.g. administration of a peroxisome proliferator-activated receptor gamma agonist, presents a possible strategy to control this intractable form of alopecia.

Conclusion and future directions

As described above, remarkable advances have been made in the understanding of the pathophysiology of hair loss
disorders. Effective treatments for previously uncontrollable forms of alopecia (finasteride for AGA is the best example) have become available. However, remedies for various forms of refractory alopecia still need to be developed. The recent progress in regenerative medicine and pharmacology is promising for future treatment. Bioengineering of hair follicles combined with hair transplantation could enable the treatment of stable but broad scarring alopecia. Likewise, immune modulation by biologics or small molecules may provide efficient treatment for severe AA.

Acknowledgments

I would like to thank Dr Wei-Ming Wang (Department of Dermatology, Tri-Service General Hospital, National Defense Medical Center) and all the board members of the Taiwanese Dermatological Association for their encouragement and support.

References


