Original Article

Alopecia areata; combination therapy with minoxidil (2%) solution and isotretinoin (0.05%) gel

Ijaz Ahmed*, Zarnaz Wahid, Sarwat Nasreen***

* Department of Dermatology, Ziauddin Medical University, Karachi.
** Department of Dermatology, Dow Medical College and Civil Hospital, Karachi.

Abstract

Background Alopecia areata is a common cause of nonscarring hair loss. The cause is unknown but it is associated with an alteration in the immunological system. Treatment for alopecia areata includes topical corticosteroids, dithranol, tretinoin, minoxidil, systemic cortisone, PUVA therapy, irritants and immunosuppressive drugs.

Objective Our objective was to assess the efficacy of combination of topical 2% minoxidil lotion and isotretinoin (0.05%) gel in the treatment of alopecia areata.

Patients and methods From 1st October 2003 till 30th September 2004, over a period of 1 year, clinically diagnosed, fresh cases of alopecia areata, fulfilling the inclusion criteria were enrolled. All the patients were advised to apply minoxidil (2%) solution in the daytime and isotretinoin (0.05%) gel in the night to avoid photosensitivity. The daily treatment was advised for a period of four months and thereafter every alternate day for another two months as a maintenance therapy. Clinical assessment was carried out by patient's self-assessment, investigator assessment and clinical evaluation on follow up visits.

Results The total number of patients studied was 54 comprising 31 males (57.4%) and 23 females (42.6%), male to female ratio being 1.3. Twenty-nine patients (53.7%) had three lesions, 18 (33.3%) had two lesions and seven (13%) only one lesion. Complete restoration of hair follicles was noted in 45 (83.3%, $p<0.001$) by the end of therapy. All the patients with single patch responded (100%), while 15 patients (83.3%) with 2 lesions recovered completely. Twenty-three patients (79.3%) with 3 lesions had a complete restoration of hair follicles.

Conclusion The combination therapy of minoxidil (2%) solution and isotretinoin (0.05%) gel for alopecia areata is cost effective, stimulating hair regrowth within a shorter interval and is well-tolerated.

Key words
Alopecia areata, minoxidil, isotretinoin, hair follicles.

Introduction

Alopecia areata is a common disease that causes loss of hair on the scalp and elsewhere. Alopecia areata may cause patchy hair loss over vast portions of the scalp; however, any hair-bearing area on the body may be affected. Most often, it affects scalp (66.8-95%) followed by beard (28%), eyebrows (3.8%) and extremities (1.3%).

Address for correspondence
Dr. Ijaz Ahmed,
H. No. 36/2, Khayaban e Shujaat D-H-A,
Phase 5, Karachi.
Ph # 021 2528910, 021 2541152

Alopecia areata occurs at all ages but children are the most commonly affected with equal frequency in both sexes.[1] Although medically benign, the disease can cause tremendous emotional and psychosocial stress in affected patients and their families.[2-4] It is estimated that over two million people have the disease.[5,6]

Prevalence in the general population is 0.1-0.2%. The lifetime risk of developing the disease is estimated to be 1.7%. It is reported in 0.7-3% of all patients seen by dermatologists.[7]

The cause is unknown but it is associated with an alteration in the immunological system, as immunomodulators e.g. sulfasalazine[8] have been proved to be effective in the management of alopecia areata. The most widely accepted hypothesis is that alopecia areata is a T cell-mediated autoimmune condition that is most likely to occur in genetically predisposed individuals.[9] The role of environmental factors in initiating or triggering the condition is yet to be determined. Little data exists regarding the natural evolution of the condition. Assessment of the efficacy of a treatment must be considered with care, since the condition is highly unpredictable in presentation, evolution, and response to treatment. The high spontaneous remission rate makes it difficult to assess clearly the true efficacy of a therapy. Treatment must be continued for a minimum of 3 months before regrowth can be expected, and maintenance therapy is often necessary. Treatments for alopecia areata can be divided into two groups based on the area of involvement i.e. therapies for less then 50% hair loss include topical corticosteroids,[10] dithranol, tretinoin and minoxidil, while therapy for patients with more then 50% hair loss comprises systemic cortisone, PUVA therapy, irritants and immunosuppressive drugs.[11] A role of topical nitrogen mustard has recently been indicated as well.[12]

The current study was carried out to see the combined effect of isotretinoin (0.05%) gel and minoxidil (2%) solution in the treatment of alopecia areata.

Patients and methods

The study was carried out in the outpatient department of dermatology "Ziauddin Medical University (KDLB campus)", Karachi, from 1st October 2003 till 30th September 2004, over a period of 1 year. A clinical diagnosis of alopecia areata was made and freshly registered cases, fulfilling the inclusion criteria were studied. Patients belonging to both sexes, aged 11-20 years and having the disease localized to scalp were enrolled. Patients with more than three patches of alopecia were ruled out. Patients with patches of more then 2 inches diameter were also excluded. Patients with oophiasis, personal or family history of atopy were not included, while patients with a family history of an autoimmune disease or any other systemic disease were ruled out, as well. All patients did not receive any sort of therapy over the past 2 months. After a detailed history, a clinical examination comprising general, systemic and dermatological, was carried out and all the findings were recorded on a preformed pro forma. In addition to the routine investigations, any relevant investigations when required were carried out as well e.g.

scraping for fungus, skin biopsy and histopathology.

All the patients were advised to apply minoxidil (2%) solution in the daytime and isotretinoin (0.05%) gel in the night-time to avoid photosensitivity. The daily treatment was advised for a period of initial four months and thereafter every alternate day for another two months as a maintenance therapy. All the patients were followed up fortnightly to look for regrowth of hair follicles as well as any side effects. Clinical assessment was carried out by patient's self-assessment, investigator assessment and clinical evaluation on follow up visits. After the completion of therapy, patients were followed up for another 3 months.

Results

The total number of patients studied, was 54 including 31 males (57.3%) and 23 females (42.7%), male to female ratio being 1.3. Minimum age of presentation was 11 years and maximum 20, mean age being 14.3 years. Twenty-nine patients (53.7%) suffered from three lesions, 18 (33.3%) had two lesions and 7 (13%) with one lesion.

In the study, noticeable regrowth on treated areas was present in 39 (72.2%) of these patients within 4-6 weeks of therapy while complete restoration of hair follicles was the feature in 45 (83.4%, $p<0.001$) by the end of therapy. All the patients with single patch responded (100%), while 15 patients (83.3%) with 2 lesions recovered completely. Twenty-three patients (79.3%) with 3 lesions had a complete restoration of hair even 3 months after completion of the therapy. Thereafter, they were lost to follow up. During this study the only significant side effect noted was slight irritation with mild erythema and burning seen in 5 patients only. However, the complaints were temporary. Two patients complained of slight headache off and on, which settled as the therapy progressed.

Discussion

Alopecia areata is a common disease that causes loss of hair on scalp and elsewhere.[9] It belongs to a group of organ specific autoimmune diseases sharing a common hereditary susceptibility, the presence of organ specific antibodies in the serum and an altered T cell response.[13,14]

The high spontaneous remission rate makes it difficult to assess clearly the true efficacy of a therapy. The current study is based on Lewenberg's formula, named after Dr Adam Topical tretinoin appears to increase the beneficial effects of minoxidil due to its increased absorption through alteration of the stratum corneum barrier. Minoxidil mostly effects vertex but the combination of tretinoin and minoxidil results in hair growth in all regions of the scalp.[15] Moreover, it stops excessive hair loss as well as thickens and improves existing hair. At any age, this formula is claimed to grow or improve hair dramatically in 90% of the treated patients.

Minoxidil is a direct acting peripheral arterial dilator that reduces blood pressure by decreasing peripheral vascular resistance. Minoxidil topical solutions stimulate hair growth in individuals with androgenetic alopecia and in females with diffuse hair loss or thinning in the frontoparietal areas. Minoxidil is thought to have a direct effect

on hair follicles to sustain the anagen phase of the hair cycle. It has also been shown to have a vasodilatory effect on the scalp.[16-19] Topical minoxidil acts as a temporary measure in alopecia areata, bridging the gap until hair starts growing again on its own.[20]

Retinoids are normally used in the treatment of acne vulgaris and have more recently been used in the treatment of alopecia areata stimulating hair growth by an unknown mechanism. However, evidence suggests that retinoids decrease cohesiveness of follicular epithelial cells, acting on the skin as a mild chemical peel. A more impressive result is observed when tretinoin is combined with minoxidil.[21-24] Tretinoin has been shown to promote and regulate cell proliferation and differentiation in the epithelium and may promote vascular proliferation.[25-29]

In the current study, 54 patients were put on a combined regimen of minoxidil 2% solution in the morning and isotretinoin (0.05%) gel at night for four months and thereafter the same treatment was given for another two months every alternate day. Minoxidil was advised to be applied in the morning and isotretinoin in the night-time, because it increases skin sensitivity to sunlight.

The patients were followed up fortnightly. Noticeable regrowth on treated areas was present in 39 (72.2%) of these patients within 4-6 weeks of therapy. Complete restoration of hair follicles featured in 45 patients (83.3%, $p<0.001$) by the end of therapy. Nine patients (16.7%) showed no response. On further follow up, regrowth persisted even 3 months after completion of the therapy in all the responders. The response was good in all those patients having a single patch i.e. 13% while patients with two patches; formed 27.8% and 42.6% responders had 3 lesions.

Despite the fact that the medicaments seem to have an unknown mode of action, response was good in combination therapy. Minoxidil lotion as a monotherapy has to be used for at least 4 months before significant regrowth of hair follicles is achieved. Thus, the cost of treatment becomes considerably high. Not all patients respond to minoxidil, approximately 20-50% quote acceptable improvement. Thus, the combined therapy is effective and economical. The hair regrowth starts earlier than the minoxidil monotherapy, which may require four months for an initial response. Studies have shown that retinoids alone can result in moderate to good hair growth, but the time interval required is long. Therefore, it can be observed from the above study that the effect of tretinoin on hair growth is enhanced when used in combination with topical minoxidil. Bazzano *et al.*[23] reported a success rate of 66% in his study on a similar combination regimen. Bazzano *et al.*[23] using tretinoin as a monotherapy further reported the regrowth of hair follicles in 58% of his patients with alopecia areata. Therefore, the results of our study correlate well with the literature.

Side effects of isotretinoin include blistering, altered pigmentation and increased sensitivity to light. Minoxidil is usually well tolerated. Adverse effects include distant hypertrichosis and irritation. As far as the tolerability of the therapy is concerned, the only significant side effect

noted was slight irritation with mild erythema and burning seen in five patients. However, complains were temporary. Two patients complained of slight headache off and on, which settled as the therapy progressed. Thus, the therapy was tolerated well. Moreover, all the patients were advised to apply the isotretinoin gel at nighttime to avoid photosensitivity. This further helped to minimize the side effects.

Conclusion

The combination therapy of minoxidil (2%) solution and isotretinoin (0.05%) gel for alopecia areata is cost effective, stimulating hair regrowth within a shorter interval and is well tolerated. However, the synergistic effect of isotretinoin in combination with topical minoxidil should also be further investigated for the disease with poor prognosis e.g. alopecia totalis, alopecia universals, etc.

References

1. Hoffman R. Alopecia areata in children. *J Pak Assoc Dermatol* 1999; **9**: 33.
2. Carolyn Thiedke C. Alopecia in women. *Am Fam Physician* 2003; **67**: 1007-14, 1017-8.
3. Tosti A, Gentilomi G, Venturoli S *et al*. No correlation between cytomegalovirus and alopecia areata. *J Invest Dermatol* 1996; **107**: 443.
4. Mitchell AJ, Krull EA. Alopecia areata: pathogenesis and treatment. *J Am Acad Dermatol* 1984; **11**:763-75.
5. Coskey RJ, Drake LA, Hordinsky MK *et al.* ML. Guidelines of care for alopecia areata. *J Am Acad Dermatol* 1992; **26**: 247-50.
6. Gollnick H, Orfanos CE. Alopecia areata: pathogenesis and clinical picture. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases.* New York: Springer-Verlag; 1990. p. 529-69.
7. Madani S, Shapiro J. Alopecia areata update. *J Am Acad Dermatol* 2000; **42**: 549-66.
8. Ellis CN, Brown MF, Voorhees JJ. Sulfasalazine for alopecia areata. *J Am Acad Dermatol* 2002; **46**: 541-4.
9. Ihm CW, Hong SS, Mun JH, Kim HU. Histopathological pictures of the initial changes of the hair bulbs in alopecia areata. *Am J Dermatopathol* 2004; **26**: 249-53.
10. Tosti A, Piraccini BM, Pazzaglia M, Vincenzi C. Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. *J Am Acad Dermatol* 2003; **49**: 96-8.
11. Shapiro J. Alopecia areata: update on therapy. *Dermatol Clin* 1993; **11**:35-46.
12. Bernardo O, Tang L, Lui H, Shapiro J. Topical nitrogen mustard in the treatment of alopecia areata: a bilateral comparison study. *J Am Acad Dermatol* 2003; **49**: 291-4.
13. Whiting DA. Histopathologic features of alopecia areata: a new look. *Arch Dermatol* 2003; **139**: 1555-9.
14. Gu SQ, Ros M, Thyresson N *et al.* Spontaneous cell mediated cytotoxicity in patients with alopecia areata. *Acta Venereol Dermatol* 1982; **61**: 434-9.
15. Shapiro J, Price VH. Hair regrowth. Therapeutic agents. *Dermatol Clin* 1998; **16**: 341-56.
16. Linas SL, Nies AS. Minoxidil. *Ann Intern Med* 1991; **94**: 61-74.
17. Weiss VC, West DO Fu TS *et al.* Alopecia areata treated with topical minoxidil. *Arch Dermatol* 1984; **120**: 457-66.
18. Price VH. Topical minoxidil in the management of alopecia areata, long-term efficacy. *J Am Acad Dermatol* 1987; **16**: 737-47.
19. Feidler Wiess VC, Buys CM. Response to minoxidil in severe alopecia areata correlates with T lymphocyte stimulation. *Arch Dermatol* 1987; **123**: 1491-7.
20. Fiedler VC. Alopecia areata: a review of therapy, efficacy, safety, and mechanism. *Arch Dermatol* 1992; **128**: 1519-29.
21. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, *et al.* Guidelines of care for androgenetic alopecia. American

Academy of Dermatology. *J Am Acad Dermatol* 1996; **35**: 465-9.
22. Sommer M, Wilson C. Therapeutic approaches to the management of common baldness. *Int J Clin Pract* 1999; **53**: 381-5.
23. Bazzano GS, Terezakis N, Galen W. Topical tretinoin for hair growth promotion. *J Am Acad Dermatol* 1986; **15**: 880-3, 890-3.
24. Freyschmidt PP, Hoffmann R, Levine E *et al.* Current and potential agents for the treatment of alopecia areata. *Curr Pharm Dis* 2001; **7**: 213-30.
25. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; **61**: 53-69.
26. Madani S, Shapiro J. Alopecia areata update. *J Am Acad Dermatol* 2000; **42**: 549-66; quiz 567-70.
27. MacDonald N. Alopecia areata: identification and current treatment approaches. *Dermatol Nurs* 1999; **11**: 356-9.
28. Hoffmann R, Happle R. Alopecia areata. Part 2: Therapy. *Hautarzt* 1999; **50**: 310-5.
29. Fiedler VC, Alaiti S: Treatment of alopecia areata. *Dermatol Clin* 1996; **14**: 733-7.