

STUDY OF THERAPEUTIC COMPARISON OF TACROLIMUS 0.1% AND MINOXIDIL 2% IN ALOPECIA AREATA

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Abstract

Introduction: Alopecia areata is a unique, idiopathic disease in which there is patchy hair loss. The variable and uncertain natural history of alopecia areata is accounting for the multiplicity of uncritical claims for a large variety of therapeutic procedures.

Aim: to find the therapeutic comparison between tacrolimus 0.1% ointment and minoxidil 2% solution.

Material and Methods: Patients attending skin out patient department in Navodaya medical college hospital and research centre, Raichur were screened and the consenting consecutive cases of Alopecia Areata (AA) from December 2010 to November 2011 were chosen for study. There were 75 patients in the study. It is a randomized, single blind, intention to treat study. The eligible patients for the study were randomly allocated into two groups-Group A and Group B (38 in Group A and 37 in Group B). Patients in Group A were treated with 2% Minoxidil solution to be applied twice daily over the alopecia patch, where as Patients in Group B were treated with Tacrolimus 0.1% ointment applied twice daily. Patients were followed up at 2, 4, 6, 8, 10 and 12 weeks. Alopecia Grading Score (AGS) was calculated at baseline and 12 weeks. Regrowth Score (RGS) was calculated at 12 weeks.

Results: Total 69 patients completed the study (35 in Group A and 34 in Group B). In our study $RGS \geq 3$ was observed in 65.71% of patients treated with Minoxidil 2% solution and 44.12% of patients treated with Tacrolimus 0.1% ointment.

Conclusion: In our study Minoxidil 2% solution had better stimulatory effect on hair growth compared to Tacrolimus 0.1% ointment in the treatment of mild to moderate patchy alopecia areata. The combination treatment may yield a better clinical response than either of the agents used singly.

Key words: alopecia areata; minoxidil; tacrolimus

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Introduction

Alopecia Areata is one of the most emotionally devastating, dermatological condition.

Alopecia areata is a unique, idiopathic disease in which there is a patchy hair loss that is usually confined on the scalp but may occur on beard region, moustache, eyelashes, eyebrows, axilla, genitalia & general body surface. Alopecia totalis is a condition if all the hair on the scalp is lost and Alopecia universalis is a condition if in addition to scalp, there is complete loss of body hair [1].

It occurs equally in both males and females and onset can be at any age, but most often in children and young adults [2].

The etiology of alopecia areata is not known with certainty. Factors implicated are-autoimmune theory, genetic factors, atopic state, infectious agents and emotional stress.

Alopecia areata progresses as a wave of follicles enter telogen phase prematurely. It is characterized by non-scarring round and/or oval patches of hair loss. The diagnostic hallmark of alopecia areata is an exclamation mark hair at the active hair margin. The lesions are largely asymptomatic, which may manifest either as alopecia areata classic, reticulate alopecia areata, alopecia totalis/universalis, or ophiasis and ophiasis inversa [3]. Associated clinical changes include nail involvement, cataract, vitiligo etc.

Diagnosis is based mainly on the clinical presentation and is corroborated by histology [4].

The variable and uncertain natural history of alopecia areata is accounting for the multiplicity of uncritical claims for a large variety of therapeutic procedures.

Different treatment aspects have been tried in treating alopecia areata [5]. They include,

1. Corticosteroids-topical, intra-lesional and oral.
2. Contact immunotherapy using DNCB (dinitrochlorobenzene), SABDE (squaric acid dibutylester) and diphenceprone.
3. Irritants like Phenol, Salicylic acid, Sulphur, Liquid nitrogen, Anthralin and Croton oil.
4. PUVA (Psoralen with Ultraviolet A) therapy.
5. Minoxidil- topical
6. Tacrolimus- topical

In the present study, a therapeutic comparison between topical tacrolimus 0.1% ointment and minoxidil 2% solution in the treatment of alopecia areata is undertaken.

Minoxidil:

Minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) was initially developed as a drug for antihypertensive therapy. Although minoxidil has been used as a hair regrowing agent for more than 20 years, its mode of action is not fully understood. Minoxidil does not appear to have either a hormonal or an immunosuppressant effect. Minoxidil most likely has a direct mitogenic effect on epidermal cells, both in vitro and in vivo. Anagen-phase hair bulbs plucked from men applying minoxidil showed a significant increase in proliferation index as measured by DNA flow cytometry. Minoxidil also has been shown to prolong the survival time of keratinocytes in vitro. Finally, minoxidil may oppose intracellular calcium entry. Calcium influx normally enhances epidermal growth factors to inhibit hair growth. Minoxidil is converted to minoxidil sulfate, which is a potassium channel agonist and enhances potassium ion permeability, thus opposing the entry of calcium into cells. Local vasodilatation does not appear to play a primary role in hair growth associated with minoxidil. There are some reports indicating that minoxidil also has some immunosuppressive effects [6,7]. Adverse effects- contact dermatitis can occur in 6%, hypertrichosis (facial hair growth) has been a reported side effect in 3% of patients [8].

Tacrolimus:

Initial trials revealed tacrolimus as a potential tool for treatment of AA [9,10]. The peculiarity of tacrolimus was the induction of anagen and hence hair growth promotion was observed with topical but not systemic route of administration. Topical tacrolimus has been tried in several case series in the treatment of AA, but the results have not been encouraging [11-15]. Price et al, showed no positive result with tacrolimus 0.1% applied twice daily even after 24 weeks in patients with AA [11]. Treatment failure with topical tacrolimus 0.1% may be caused by insufficient depth of penetration of the ointment formulation and less than optimal patient selection. Higher concentrations of tacrolimus ointment and large scale randomized controlled trials are needed.

Material and Methods

Source of Data:

Patients attending skin out patient department in Navodaya medical college hospital and research centre, Raichur from Decemberr 2010 to November 2011 were screened and clinically diagnosed cases of Alopecia Areata were taken for study.

75 cases were included in the study.

Inclusion criteria:

1. All patients with circumscribed, bald patch without any signs of inflammation or scarring.
2. Patients with short, easily extractable broken hair at the margin of a bald patch.
3. Skin within the bald patch being normal.
4. Patients above the age of 12 years.

Exclusion criteria:

1. Patients with re-growing hair.
2. Patients with secondary infection.
3. Patients already on some other medication for AA.
4. Patients having scar over the bald patch.
5. Patients below the age of 12 years.

Method of Collection of Data:

It is a randomized, single blind, intension to treat study. An informed consent was obtained. Relevant history taken and clinical examination including general, systemic and local examinations were made.

The total number of patches and their measurements were noted in all quadrants of scalp.

Alopecia Grading Scale (AGS) was calculated as follows - The percentage of hair loss in each quadrant was added and divided by four to get the average. Presence of exclamationary hairs was noted.

Patients eligible for the study, were randomly allocated into two groups-Group A and Group B. Patients in Group A were treated with 2% Minoxidil solution applied twice daily over the alopecia patch where as Patients in Group B were treated with 0.1% Tacrolimus ointment applied twice daily.

Both the groups were explained about the nature and course of the disease and were followed up at 2,4,6,8,10 and 12 weeks. In each visit- history of any side effects, any new patches and patient compliance were noted. Alopecia Grading Score (AGS) was calculated at baseline and 12 weeks. Regrowth Score (RGS) was calculated at 12 weeks as follows – 0 (regrowth < 10%), 1 (regrowth 11– 25%), 2 (regrowth 26–50%), 3 (regrowth 51–75%) and 4 (regrowth>75%).

Serial photographs were taken in each follow up.

Investigations:

Selected investigations were done only in doubtful cases of AA,

- KOH preparation and fungal culture;
- Hair microscopy;
- Skin biopsy;
- Serology for lupus erythematosus;
- Serology for syphilis.

Statistical Analysis:

The primary efficacy measurement was the mean change in the Alopecia Grading Score (AGS) and to compare the hair regrowth rate by using hair regrowth score (RGS). Chi-square test was used to analyze the data.

Results

	Group A	Group B
Total number of patients	38	37
Remained in study	35 (92.10%)	34 (94.59%)
Study left out	3 (07.89%)	3 (08.10%)
Gender		
Male	23	23
Female	15	14
Mean AGS		
Baseline	9.85	10.08
12 weeks	4.17	4.82

Table I. Patient profile

Grading of the Response

Mean AGS for Group A at baseline was 9.85 and at 12 weeks was 4.17.

Mean AGS for Group B at baseline was 10.08 and at 12 weeks was 4.82 (Tabl. II).

Group A		Group B	
Baseline	12 weeks	Baseline	12 weeks
9.85	4.17	10.08	4.82

Table II. Mean Alopecia Grading Score (AGS)

A RGS of 0 and 1 are taken as Poor, 2 is taken as Moderate improvement, 3 is taken as Good and RGS of 4 as Excellent. From the above graph, it is apparent that the number of patients achieving (Fig. 1). Excellent regrowth was higher in Gr A (23 patients) compared

to Gr B (15 patients). Total 69 patients completed the study (35 in Gr A and 34 in Gr B). Regrowth Score (RGS) more than or equal to 3 at the end of 12 weeks were considered as improved and RGS less than or equal to 2 were considered not improved.

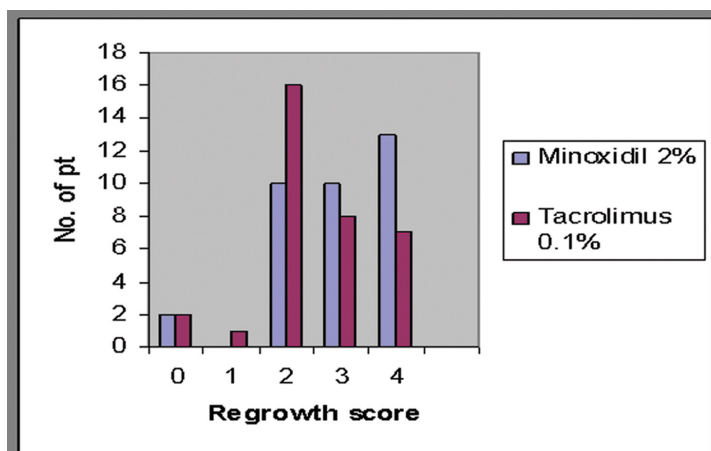


Figure 1. Graph showing regrowth scores for both the groups

Applying Chi-square test to the above Table III.

Chi-Square Test

$$\chi^2 = \sum (O_i - E_i)^2 / E_i,$$

Where O_i is observed frequency and E_i is Expected frequency.

$$\chi^2 = (3.73)^2 / 19.27 + (3.72)^2 / 15.72 + (3.72)^2 / 18.72 + (3.73)^2 / 15.27$$

$$\chi^2 = 3.25$$

	Improved (RGS≥3)	Not improved (RGS≤2)	Total
Gr A	23	12	35
Gr B	15	19	34
Total	38	31	69

Table III. Comparative improvement of both the groups

Side Effects of Treatment

Erythema and scaling were observed in 2 patients and 1 patient respectively each in Minoxidil treated group, whereas tingling

and burning sensation was noticed in 2 patients and 1 patient respectively in Tacrolimus treated group (Tabl. IV).

Side effect	Group A	Group B
Erythema	2	-
Scaling	1	-
Tingling sensation	-	2
Burning sensation	-	1

Table IV. Side effects

Discussion

The earlier trials carried out in alopecia areata, compared single agent such as minoxidil and minoxidil with placebo. This is the first study comparing these two topical agents in AA (Fig. 1-4).

Grading of the Response:

The response was graded by assessment of Alopecia Grading Score (AGS) at baseline and after 12 weeks. Only terminal hair growth was taken into account.

Mean AGS for Goupr A at baseline was 9.85 and at 12 weeks was 4.17

Mean AGS for Goupr B at baseline was 10.08 and at 12 weeks was 4.82.

Total 69 patients completed the study (35 in Goupr A and 34 in

Goupr B). Regrowth Score (RGS) more than or equal to 3 at the end of 12 weeks were considered as “Improved” and RGS less than or equal to 2 were considered “Not improved”.

The data were analyzed using Chi-square test. Group A showed better response then Group B which was found to be of suggestive significance (0.05<P<0.10)

Minoxidil 2% showed significantly better response compared to tacrolimus 0.1% in the treatment of patchy AA.

Side Effects:

Erythema and scaling were observed in 2 and 1 patient respectively in minoxidil treated group, whereas tingling and burning sensation was observed in 2 and 1 patient respectively in patients treated with tacrolimus.

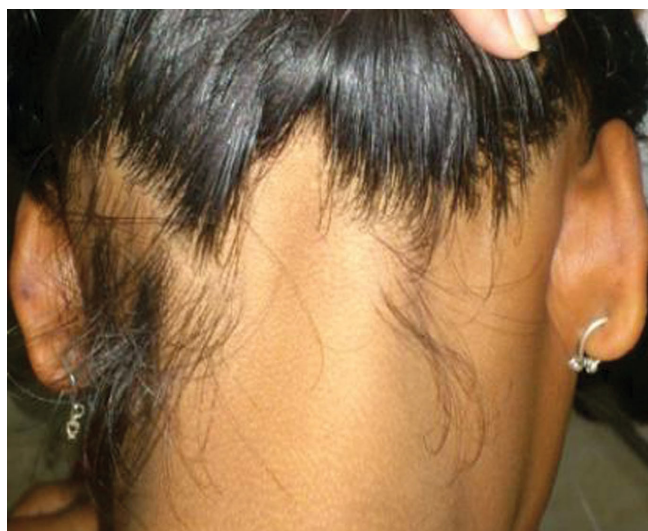


Figure 2. Clinical Photograph showing Alopecia Areata before therapy



Figure 3. Clinical photograph response to treatment with Minoxidil 2% solution



Figure 4. Clinical photograph showing another case of Alopecia Areata (before therapy)



Figure 5. Clinical photograph showing improvement after therapy with Tacrolimus 0.1 %

Conclusion

Total 69 patients completed the study (35 in Gr A and 34 in Gr B).

In our study RGS ≥ 3 was observed in 65.71% of patients treated with minoxidil 2% and 44.12% of patients treated with tacrolimus 0.1%.

Minoxidil 2% showed better response compared to tacrolimus 0.1% in the treatment of patchy AA. Both the treatment modalities showed minimal side effects in the form of mild tingling and burning sensation

Minoxidil 2% has a significant stimulatory effect on hair growth in AA and can be used as in the treatment of AA. Tacrolimus 0.1% is a steroid free topical immunomodulator is safe and well tolerated, but is less efficacious when compared to topical minoxidil. It can be used as an adjuvant therapy. Studies using the combination of topical minoxidil are required to prove if combination is more effective than either alone.

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