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ORIGINAL ARTICLE

Evaluating the combined efficacy of oral isotretinoin and topical tacrolimus versus oral finasteride and topical tacrolimus in frontal fibrosing alopecia—A randomized controlled trial

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Abstract

Objective: Treatment of frontal fibrosing alopecia (FFA) is complicated and challenging. In this study, we evaluated the efficacy of combining topical tacrolimus with isotretinoin versus finasteride in patients with FFA.

Methodology: Thirty-one patients with FFA were divided randomly into two groups. Therapeutic regimen of the first group (group A, $n = 16$) was isotretinoin and tacrolimus (Capsule isotretinoin 20 mg daily and topical tacrolimus 0.1% BD). The second group (group B, $n = 15$) was given finasteride and tacrolimus (Tablet finasteride 2.5 mg daily and topical tacrolimus 0.1% BD). Patients were treated and followed up periodically for 12 weeks. Evaluation of the treatment efficacy was based on Patient Global Assessment and Physician Global Assessment scales. Objective evaluation was based on improving the severity of skin lesions by viewing serial images taken from the affected areas.

Results: Physician Global Assessment (PGA) was significantly better in the group A as compared with the group B at 4 weeks ($p = 0.038$). Physician satisfaction in the group A was better than the group B at 12 weeks, but this was not statistically significant ($p > 0.05$). Patient Global Assessment and patient satisfaction in the group A was better than the group B at 8 and 12 weeks, but it was not statistically significant ($p > 0.05$).

Conclusion: Although both therapeutic regimens were effective in the treatment of FFA, treatment with tacrolimus and isotretinoin is significantly more effective than tacrolimus and finasteride.

KEYWORDS
cicatricial alopecia, finasteride, frontal fibrosing alopecia, isotretinoin, tacrolimus

1 | INTRODUCTION

Frontal fibrosing alopecia (FFA) is a subtype of cicatricial alopecia that causes hair loss and scarring over the forehead, the temporoparietal region, or other parts of the body. It was first described by Kossard in 1994 and is considered as a subtype of lichen planopilaris.[1,2] The prevalence of this disease is higher in postmenopausal women and Caucasians than the normal population.[3,4] The most common clinical findings are recession of the frontal hairline, scarring alopecia, eyebrow alopecia, and perifollicular and facial papules. Axillary alopecia, pruritus, follicular hyperkeratosis, lichen planus, and androgenic alopecia are other manifestations of the disease.[5,6] Most cases of FFA are diagnosed clinically; however, trichoscopy and histopathology can be employed to help us for an exact diagnosis.

There is a wide spectrum of diseases as differential diagnoses for FFA, including lupus erythematosus alopecia, traction alopecia, non-scarring patterned alopecia, and even alopecia areata.[1] The exact pathogenesis of FFA is unknown. Despite the existence of various therapeutic modalities, including finasteride (or dutasteride), retinoids, prostaglandin analogues, topical formulations, (tacrolimus, vitamin D analogues, minoxidil, anthralin), and procedures (laser therapy, phototherapy, and platelet rich plasma), there is still no definitive treatment for it.[7–12] FFA wields a profound psychosocial impact on the affected patients. Most often, these patients require chronic treatment regimens. The authors evaluated the efficacy of combination therapy with isotretinoin and topical tacrolimus in comparison with finasteride and topical tacrolimus in this randomized clinical trial.

2 | METHODS

This was a multi-center single blinded, randomized, active controlled trial study on 31 FFA patients from June 2018 to June 2020. The diagnosis of FFA was made by dermatologist, on the basis of clinical manifestations or patient's medical history. For randomization process, patients were randomly numbered from 1 to 31 in a list, in the order of patients' visits. Odd-numbered individuals were treated with isotretinoin and tacrolimus (group A); and even-numbered individuals were treated with finasteride and tacrolimus (group B). Assignment of patients in groups was done by numbering and the type of medication was given to the executor of the project (dermatologist) in an envelope. The dermatologist, patient, and project partner, who is responsible for measuring outcomes and statistical analysis, were unaware of the grouping and type of medication.

The study was approved by ethic committee of Mazandaran University of Medical Sciences. Written consent was obtained from all the patients. The exclusion criteria included subjects less than 18 years, pregnant or breastfeeding mothers, and drug reaction to the prescribed treatment. Patients were randomly divided into two groups. Isotretinoin and tacrolimus (Capsule isotretinoin 20 mg daily and topical tacrolimus 0.1% BD) was given to the first group (group A, $n = 16$), whereas finasteride and tacrolimus (Tablet finastride 5 mg 1/2 daily and topical tacrolimus 0.1% BD) to the second group (group B, $n = 15$). Patients were followed up for 12 weeks. The blood lipids, blood glucose level, and liver function tests of the patients were checked regularly (monthly). Daily use of sunscreens, lip moisturizers, and artificial eye drop was prescribed for the patients in the group A, due to the fame of isotretinoin in increasing eye dryness, skin sensitivity to the sun and causing cheilitis. Evaluation of the treatment efficacy was based on both objective and subjective variables. Patient Global Assessment and Physician Global Assessment scales (severe = 0–24%, moderate = 25–49%, mild = 50–74%, almost clear = 75–99%, and clear = 100%) were employed. Objective evaluation was based on improving the severity of skin lesions including the severity of pigmentation, extent and distribution of the lesions, forehead hairline receding, eyebrows alopecia, and perifollicular papules, by viewing serial images taken from the affected areas (photographic documentation). Baseline photography was done prior to initiating therapy with a digital single lens reflex camera (Canon EOS D4000). Serial photography was performed at subsequent follow-ups. (4, 8, and 12 weeks).

Patients were also questioned about complications after treatment. We used the Treatment Satisfaction Questionnaire for Medication (TSQM) to evaluate the efficacy and adverse effects of the mentioned therapeutic regimens, and to record patient satisfaction with the treatment process.

2.1 | Statistical analysis

Fisher's exact test, Chi-Square test, Spearman or Pearson correlation coefficient, and independent *t*-tests were used for statistical analysis, and a p value ≤0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (version 22.0).

3 | RESULTS

Thirty-one patients (2 men and 29 women) with FFA were evaluated in our study. Sixteen patients with a mean age of 39.19 ± 11.26 years were recruited in the group A, and 15 patients with a mean age of 41.47 ± 7.51 years in the group B (Figures 1 and 2). The mean disease duration of the groups was 21.94 ± 17.48 and 21.93 ± 17.46 month, respectively. 12.9% of patients were single and 87.1% of patients were married in the cumulated sample. Fisher's Exact Test and Pearson Chi-Square Test showed that the study groups were not significantly different in terms of menopausal status, disease pattern, and disease severity (p-value >0.05). Due to the normality of the data, independent *T*-test was used to compare Physician Global Assessment (PGA) and Physician satisfaction (Ps) of patients at any time, which showed PGA in group A was significantly better than the group B at 4 weeks (p-value = 0.038) (Tables 1–3). Physician satisfaction was better in the group A than the group B at 12 weeks, but it was not statistically significant (p-value >0.05). Patient Global

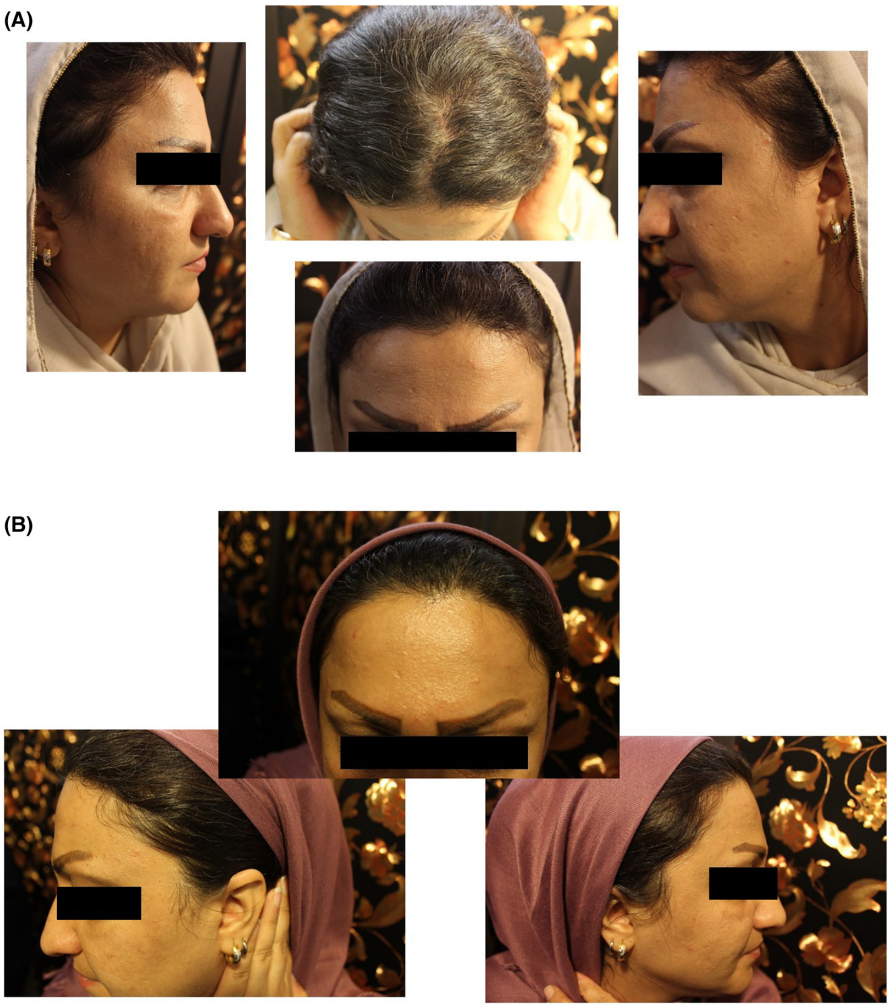

FIGURE 1 Facial inflammation and papules before study (A) and 12 weeks after study (B) in group A

Assessment (PtGA) and Patient Satisfaction (PtS) in the group A were better than the group B at 8 and 12 weeks, but this difference was not statistically significant (p-value >0.05) (Tables 4 and 5). After 12 weeks of follow-up, no serious adverse effects were reported.

4 | DISCUSSION

Frontal fibrosing alopecia is a type of alopecia causing hair loss and scarring on the forehead and is classified as a subtype of lichen planopilaris.[1] Although hormonal changes or an autoimmune response may cause FFA, the exact cause of the disease is still unknown.[4,13]

It is proven that hair follicle inflammation causes alopecia in FFA patients. According to this fact, therapeutic regimens of FFA are almost consisted of medications whit anti-inflammatory, immunosuppressive, or immuno-modulatory mechanisms.[5,14] Finasteride is a 5-alpha-reductase enzyme inhibitor. The 5-alpha-reductase enzyme converts testosterone to the dihydrotestosterone (active form of testosterone).[10] Drugs that halt the production of male hormones (such as finasteride) have been reported to arrest the progression of alopecia.[5,14] Tacrolimus is a calcineurin inhibitor that reduces the symptoms of FFA by down-regulating the proliferation of T-cells and inhibiting the cellular and humoral immune responses.[9] Isotretinoin, a derivation of vitamin A, inhibits sebaceous gland functions, promotes differentiation of keratinocytes, and prevents hyper-keratinization.[11,12]

Mahmudi et al. studied on the efficacy of monotherapy with topical medications (clobetasol 0.05% and tacrolimus 0.1%) versus the combination therapy with topical medications (clobetasol 0.05% and tacrolimus 0.1%) and isotretinoin for FFA treatment. In this study, 28 patients with FFA were treated and were followed up for 6 months. They concluded that combination therapy with isotretinoin and topical medications is more effective than monotherapy with topical clobetasol and tacrolimus for FFA treatment (p-value <0.001).[2] The results were concordant with our study, in terms of efficacy of isotretinoin for FFA treatment. Rakowska et al. studied on the efficacy of isotretinoin and acitretin for FFA treatment, in a retrospective analysis of 54 FFA patients. All the patients were female, who underwent treatment with oral isotretinoin 20 mg daily (n–29), oral acitretin 20 mg Daily (n = 11), and oral finasteride 5 mg Daily (n = 14) for 24 months. They found that isotretinoin was more effective than other modalities for FFA treatment (p-value <0.05).[7] The results were concordant with our study, in terms of higher efficacy of isotretinoin in comparison with finasteride, for FFA treatment. Rodrigo et al. studied on the efficacy of isotretinoin for FFA treatment. Three female patients with FFA were entered to the study and

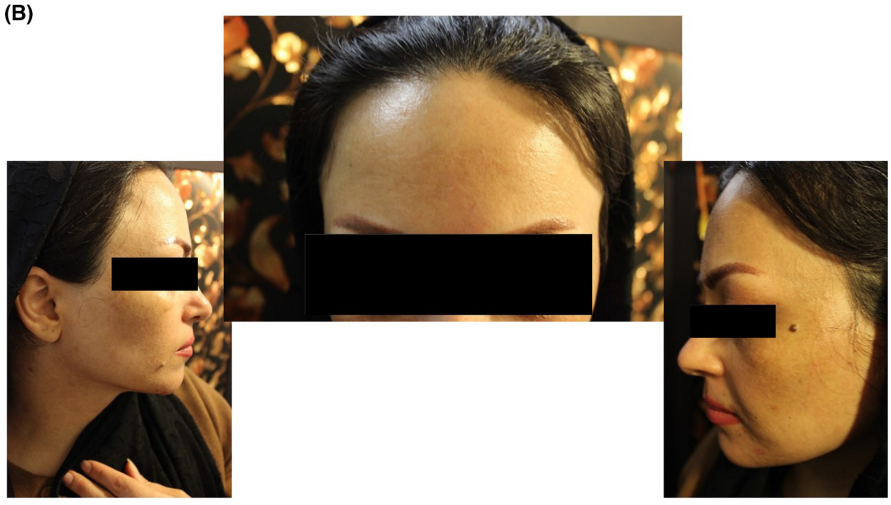

FIGURE 2 Facial inflammation and papules before study (A) and 12 weeks after study (B) in group B

TABLE 1 Frequency of subjects in treatment groups by PGA at first visit

	Therapeutic regimen			
	Isotretinoin + tacrolimus	Finasteride + tacrolimus	Total	*p* value
PGA. Physician Global Assessment				
Almost clear				0.055
Number	2	1	3	
Percent %	6.5	3.2	9.7	
Mild				
Number	3	8	11	
Percent %	9.7	25.8	35.5	
Moderate				
Number	6	6	12	
Percent %	19.4	19.4	38.7	
Severe				
Number	5	0	5	
Percent %	16.1	0	16.1	
Total				
Number	16	15	31	
Percent %	51.6	48.4	100	

Abbreviation: PGA, Physician Global Assessment.

TABLE 2 Frequency of subjects in treatment groups by PGA at Week 4

	Therapeutic regimen			
	Isotretinoin + tacrolimus	Finasteride + tacrolimus	Total	*p* value
PGA (week 4)				
Almost clear				0.038
Number	2	1	3	
Percent %	6.5	3.2	9.7	
Mild				
Number	3	9	12	
Percent %	9.7	29	38.7	
Moderate				
Number	6	5	11	
Percent %	19.4	16.1	35.5	
Severe				
Number	5	0	5	
Percent %	16.1	0	16.1	
Total				
Number	16	15	31	
Percent %	51.6	48.4	100	

TABLE 3 Frequency of subjects in treatment groups by PGA at Week 12

	Therapeutic regimen			
	Isotretinoin + tacrolimus	Finasteride + tacrolimus	Total	*p* value
PGA (week 12)				
Clear				0.296
Number	2	3	5	
Percent %	6.5	9.7	16.1	
Almost clear				
Number	7	10	17	
Percent %	22.6	32.3	54.9	
Mild				
Number	6	2	8	
Percent %	19.4	6.5	25.8	
Moderate				
Number	1	0	1	
Percent %	3.2	0	3.2	
Total				
Number	16	15	31	
Percent %	51.6	48.4	100	

were treated with oral isotretinoin for 3 months. At the end of the third month, significant progress was seen, so that the facial papules completely disappeared, no progression of the disease was seen, and all patients reported decrease of pruritus.[11] The results were concordant with our study, in terms of the efficacy of isotretinoin for FFA treatment. Tosti et al. studied on the efficacy of different therapeutic methods for treating FFA patients. Fourteen women with FFA entered the study. Three patients were treated with systemic steroids (intramuscular), and 8 patients were treated with oral finasteride (therapeutic information of the 3 other patients is not available). They found that finasteride was more effective than systemic steroids for treating FFA patients (p-value <0.05).[15] The results were concordant with our study, in terms of the efficacy of finasteride for FFA treatment. Vano-Galvan et al. studied on the efficacy of different therapeutic methods in treating FFA patients, in a retrospective study. The study included 355 FFA patients (343 females and 12

TABLE 4 Frequency of subjects in treatment groups by PtGA at first visit

	Therapeutic regimen			
	Isotretinoin + tacrolimus	Finasteride + tacrolimus	Total	*p* value
PtGA. Patient Global Assessment				
Almost clear				0.156
Number	2	2	4	
Percent %	12.4	13.3	12.90	
Mild				
Number	5	9	14	
Percent %	31.3	60	45.16	
Moderate				
Number	5	4	9	
Percent %	31.3	26.7	20.03	
Severe				
Number	4	-	4	
Percent %	25	-	12.90	
Total				
Number	16	15	31	
Percent %	51.6	48.4	100	

Abbreviation: PtGA, Patient Global Assessment.

TABLE 5 Frequency of subjects in treatment groups by PtGA at Week 12

	Therapeutic regimen			
	Isotretinoin + tacrolimus	Finasteride + tacrolimus	Total	*p* value
PtGA (week 12)				
Clear				0.639
Number	2	2	4	
Percent %	6.5	6.5	12.9	
Almost clear				
Number	8	10	18	
Percent %	25.8	32.3	58.1	
Mild				
Number	5	3	8	
Percent %	16.1	9.7	25.8	
Moderate				
Number	1	0	1	
Percent %	3.2	0	3.2	
Total				
Number	16	15	31	
Percent %	51.6	48.4	100	

males) with a mean age of 61 years. One hundred eleven patients (31%) were treated with anti-androgen agents such as finasteride and dutasteride, of which 52 patients (47%) obtained complete recovery and 59 patients (53%) experienced stabilization of disease status and no FFA progression was reported.[3] The results were consistent with our study, in terms of the efficacy of finasteride for FFA treatment. Ho-A et al. conducted a review study concerning the therapeutic options and treatment response of FFA patients. Their findings indicated that intra-lesional steroids and 5-alpha reductase inhibitors were the most effective treatments. Oral prednisone was rarely used, and it delayed the hair loss process temporarily without affecting a favorable response.[16] Their results were concordant with our study, in terms of the efficacy of finasteride in treating FFA patients. Also, Zhang et al. conducted a systematic review to study the

effects of topical calcineurin inhibitors on rosacea. They studied 28 articles (published from 2001 to 2016) and reported the noticeable efficacy of both pimecrolimus and tacrolimus on treating rosacea patients.[17] Their results were concordant with our study, in terms of the efficacy of topical tacrolimus as a treatment for an immune-mediated skin disease.

5 | CONCLUSION

Frontal fibrosing alopecia is a psychologically debilitating condition that requires long-term treatment. Although both therapeutic combinations in our study were effective in the treatment of FFA patients, treatment with tacrolimus and isotretinoin is significantly more effective than tacrolimus and finasteride. Further studies with a larger sample size would add to the evidence laid down by this trial.

AUTHOR CONTRIBUTIONS

Ghasem Rahmatpour Rokni contributed in design, methodology, and gathering the data. Seyed Naser Emadi, Abbas Dabbaghzade, Neda Jahantigh, and Amir Mohammad Beyzaee gathered the data. Aseem Sharma involved in design, methodology, review and revising the manuscript, and final proof of the manuscript. Mohamad Goldust contributed in conception, design, methodology, writing, review, and revising the manuscript.

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None.

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CONFLICT OF INTEREST

None.

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENTS

The project was approved by the Ethic committee of Mazandaran University of Medical Sciences.

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