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Effectiveness of Topical Tazarotene 0.1% Gel Versus Oral Fluconazole in Treatment of Onychomycosis

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ABSTRACT

Objective: The objective of this study was to assess the comparative effectiveness of topical Tazarotene 0.1% gel and weekly oral Fluconazole in the treatment of onychomycosis.

Study Design: Comparative prospective study.

Place and Duration of Study: Pak-Emirates Military Hospital, Rawalpindi, Pakistan, from July 2023 to Dec 2023.

Methodology: A total of 114 patients fulfilling the inclusion criteria were included in the research. A detailed history, dermatological examination, dermoscopy, and calculation of the Onychomycosis Severity Index (OSI) were employed in each patient to record the severity of their disease. The patients were randomized into two groups, i.e., Group-A, where twice daily application of topical Tazarotene 0.1% gel was applied for three months, and Group-B, where weekly oral Fluconazole tablet of 150mg was administered for three months. The Potassium Hydroxide mounts from nail material was performed at the end of treatment period in all the patients.

Results: Of the total, 53(46.5%) were male and 61(53.5%) were female. Following the comparison between two groups, a statistically significant difference was observed, suggesting that treatment with weekly oral Fluconazole (Group-B) had higher effectiveness and better treatment success compared to topical Tazarotene 0.1% gel (Group-A) in terms of the fall in the degree of OSI, dermoscopic findings, clinical evaluation, and potassium hydroxide (KOH) mount after treatment.

Conclusions: The effectiveness of Oral weekly Fluconazole is significantly higher than topical Tazarotene 0.1% gel in onychomycosis.

Keywords: Antifungal therapy, Fluconazole, Onychomycosis, Tazarotene, Treatment effectiveness.

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INTRODUCTION

Onychomycosis (OM) is a chronic fungal infection brought about by various types of dermatophytes, non-dermatophyte molds, or yeasts, with the most common presentation of nail yellowing, onycholysis, and subungual hyperkeratosis.[1] Trichophyton species accounts for most cases of both toenail and fingernail onychomycosis, with Trichophyton rubrum being the predominant pathogen.[2] Yeasts such as Candida albicans, Candida tropicalis, and Candida parapsilosis are also common, while other less frequent causes include Epidermophyton floccosum and Trichophyton tonsurans.[3,4] While the most common species for non-dermatophyte molds causing onychomycosis are Aspergillus, Fusarium, Scopulariopsis, Alternaria, and Scytalidium, etc.[5,6] Yeasts are a further uncommon cause of onychomycosis, in immunocompromised patients, with majority of infections caused by Candida albicans.[7] The current evidence reports an increase in its prevalence, due to several reasons, namely the use of modern occlusive footwear, increased urbanization, a longer life expectancy, rising incidence of obesity, and metabolic syndrome.[8]

While oral antifungal therapy with Terbinafine, Itraconazole, and Fluconazole remains the gold standard for onychomycosis in all ages.[9] This strategy has its fair share of demerits, such as a higher incidence of adverse effects (anorexia, headaches, taste disturbance, vomiting, epigastric pain, dermatitis, diarrhea, and deranged liver and renal function tests, etc.), poor patient compliance due to a prolonged treatment duration, increased cost, a higher treatment failure rate, and frequent recurrences.[10] However, there is an ongoing search for optimal treatment modalities that are devoid of such demerits, such as the employment of topical treatment modalities.

Of late, Tazarotene, a topical retinoid, has garnered interest for its use in the treatment of onychomycosis. It exerts its antifungal effects by decreasing the rate of hyperkeratinization through a fall in the hyperproliferation of keratin 6 and 16. This study aimed to explore the use of a novel agent, like

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topical Tazarotene, against the popularly used oral treatment option, like Fluconazole.

METHODOLOGY

This comparative prospective study was conducted in the outdoor department of dermatology, Pak-Emirates Military Hospital, Rawalpindi, Pakistan, from July 2023 to Dec 2023, following due approval from the institutional ethical committee (A/28/21 a (1)/EC/495/2023 dated 26 Jan 2023). The non-probability consecutive sampling technique was employed in the study, and sample size was calculated using the WHO calculator, with a 95% confidence level, with power of the study being 90%. By using the anticipated population proportion of 8%,[11] the estimated sample size came out to be n=114. Following an explicit informed written consent from all patients, 114 patients fulfilling the inclusion criteria from the department of dermatology were included in the research.

Inclusion Criteria: Male and female patients of age 15-65 years, suffering from onychomycosis with a duration of > 3 months, who did not receive any topical or systemic anti-fungal therapy in the preceding 2 weeks and 3 months, respectively, and willing to undergo a follow-up were included in the study.

Exclusion Criteria: Patients having dermatological ailments that mimicked or presented with onychomycosis, such as psoriasis, lichen planus, alopecia areata, nail dystrophy of various local and systemic causes other than onychomycosis, were excluded from the study. Individuals with a history of active systemic ailments like ischemic heart disease, diabetes, endocrinopathies, hypertension, immunosuppression, positive pregnancy on laboratory test, and those unable to maintain a follow-up were also excluded from the study.

A detailed history of all the volunteers and their general physical as well as dermatological examination was conducted. Dermoscopy was performed on each patient, and the Onychomycosis Severity Index (OSI) was employed to assess the severity of the condition in each patient.[12] OSI is obtained by scoring the area of involvement (range, 0-5) and multiplying it by the score for the proximity of onychomycosis to the nail matrix (range, 1-5). In case of the presence of greater than 2 mm of subungual hyperkeratosis or a longitudinal streak/patch (i.e., dermatophytoma), ten points are added. OSI was recorded as mild OM (1-5), moderate (6-15), and severe (16-35). At each visit, potassium hydroxide stains were also conducted on the nail scraping or clipping. Randomization was conducted through sequentially numbered opaque envelopes generated from a random numbers table into two groups (Group-A & Group-B) of 57 patients each. Each patient was assigned a number at enrolment, which defined a study drug assignment (Topical Tazarotene or Oral Fluconazole). In Group-A, 57 patients received Topical Tazarotene, while in Group-B, 57 patients received oral Fluconazole. Topical Tazarotene 0.1% gel was applied to affected nail twice daily in Group-A for 3 months, while in Group-B, a single 150mg Fluconazole tablet was administered orally once weekly for 3 months. The patient flow diagram is given as per Figure-1. Each patient was followed up for another 3 months every month to evaluate any evidence of nail discoloration, dystrophy, onycholysis, subungual hyperkeratosis, the resolution of the presenting symptoms and signs of OM, and a fall in OSI by trained researchers on a specially designed proforma. The comparison of dermoscopic findings after treatment between the two groups of patients was also carried out.

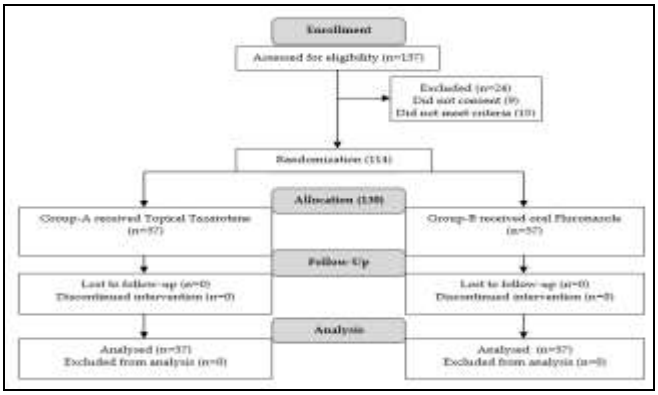

Figure-1: Patient Flow Diagram (n=137)

Data was analyzed by using Statistical Package for the Social Sciences (SPSS) version 23.00. Baseline variables were analyzed descriptively using frequencies and percentages for qualitative variables, and the Mean±SD was calculated for quantitative variables. Chi-Square test was used to compare the effectiveness of both the drugs, with a *p*-value of ≤0.05 taken as significant.

RESULTS

Our study comprised a total of 114 individuals. Of the total, 53(46.5%) were male with the mean age of 46.47±10.60 years, and 61(53.5%) were female with the

mean age of 46.08±10.16 years. The comparison between two groups of patients with Onychomycosis treated either with topical Tazarotene (Group-A) or oral Fluconazole (Group-B), focusing on the degree of Onychomycosis Severity Index (OSI) and clinical response after treatment, is shown in Table-I. A statistically significant difference was indicated by the p-value, suggesting that the two treatment groups differ significantly in terms of the OSI and clinical evaluation after treatment.

Table-I: Comparison of Onychomycosis Severity Index Scores and Clinical Response Following Treatment with Topical Tazarotene Versus Oral Fluconazole (n=114)

		Drugs Groups		Total	*p*-value
		Topical Tazarotene (Group-A)	Oral Fluconazole (Group-B)		
Degree of OSI	Cured	17(31.5%)	37 (68.5%)	54(47.4%)	< 0.01
	Mild	6(35.5%)	11 (64.7%)	17(14.9%)	
	Moderate	27(81.8%)	6(18.2%)	33(28.9%)	
	Severe	7 (70.0%)	3 (3.0%)	10 (8.8%)	
Total		57(50.0%)	57(50.0%)	114(100.0%)	
Clinical Evaluation	Complete Cure	17(31.5%)	37(68.5%)	54(47.4%)	0.001
	Mild Response	23(62.2%)	14(37.8%)	37(32.5%)	
	No Response	17(73.9%)	6(26.1%)	23(20.2%)	
Total		57(50.0%)	57(50.0%)	114(100.0%)	

**OSI = Onychomycosis Severity Index*

The comparison of dermoscopic findings after treatment between two groups of patients with onychomycosis is shown in Table-II, where Group-A received topical Tazarotene, and Group-B received oral Fluconazole.

Table-II: Comparison of Dermoscopic Findings Following Treatment with Topical Tazarotene Versus Oral Fluconazole

Dermoscopic Features		Drugs Groups		Total	*p*-value
		Topical Tazarotene (Group-A)	Oral Fluconazole (Group-B)		
Spiked Pattern	Absent	44(46.3%)	51(53.7%)	95(83.3%)	0.065
	Present	13(68.4%)	6(31.6%)	19(16.7%)	
Total		57(50%)	57(50%)	114(100%)	
Linear Edge	Absent	48(50%)	48(50%)	96(84.2%)	0.601
	Present	9(50%)	9(50%)	18(15.8%)	
Total		57(50%)	57(50%)	114(100%)	
Longitudinal stria	Absent	41(47.1%)	46(52.9%)	87(76.3%)	0.189
	Present	11(40.7%)	27(23.7%)		
Total		57(50%)	57(50%)	114(100%)	
Distal Irregular Term	Absent	42(47.2%)	47(52.8%)	89(78.1%)	0.183
	Present	15(60.0%)	10(40.0%)	25(21.9%)	
Total		57(50%)	57(50%)	114(100%)	
Jagged Proximal Edge	Absent	32(39.5%)	49(60.5%)	81(71.1%)	<0.0001
	Present	25(75.8%)	8(24.2%)	33(28.9%)	
Total		57(50%)	57(50%)	114(100%)	

A comprehensive comparison of outcomes assessed through KOH testing and culture results between two groups of patients with Onychomycosis who underwent different treatments is shown in Table-III. The *p*-value < 0.001 indicated that there was a significant difference between the outcomes of both the drugs, with oral Fluconazole showing more effectiveness than topical Tazarotene.

Table-III: Comparison of Potassium Hydroxide Findings and Culture Results Following Treatment with Topical Tazarotene Versus Oral Fluconazole (n=114)

		Drugs Groups		Total	*p*-value
		Topical Tazarotene (Group-A)	Oral Fluconazole (Group-B)		
KOH after Treatment	Negative	26(35.1%)	48(64.9%)	74(64.9%)	<0.01
	Positive	31(77.5%)	9(22.5%)	40(35.1%)	
Total		57(50.0%)	57(50.0%)	114(100.0%)	

**KOH = Potassium Hydroxide*

DISCUSSION

Our study included a total of 114 individuals. The comparison between two groups of patients with onychomycosis treated either with topical Tazarotene (Group-A) or oral Fluconazole (Group-B), focusing on the degree of the Onychomycosis Severity Index (OSI) and clinical response after treatment, is shown in Table-I. A statistically significant difference indicated by the *p*-value suggests that the two treatment groups differ significantly in terms of OSI and clinical evaluation after treatment. In our study, most patients presented with the distolateral subungual type of onychomycosis, followed by the total dystrophic onychomycosis (TDO) type. This pattern was consistent with a Middle Eastern study. The most common dermoscopic findings in our research were a linear edge and a spiked pattern, followed by longitudinal streaks. Other findings included distal irregular tips and jagged proximal edges. The study by El-Salam *et al.*, reported a treatment success rate of 25.0%, with a mild clinical response in 30.0% of patients in the Tazarotene-only arm. However, the same study found a statistically significant response in the Tazarotene combined with Tioconazole arm, where a complete cure was achieved in 50.0% of patients, and 30.0% showed a mild clinical response.[13]

The study by Cosio *et al.*, contrasted with literature, as this study emphasizes the use of retinols for the treatment of chronic OM in nails. This study also reported jagged proximal edges with spikes, longitudinal streaks, and brown-black pigmentation as the most common dermoscopic features, but the underlying causative species observed were Candida Albicans.[14] Our study showed the effectiveness of topical Tazarotene in 17(31.5%) patients, while a mild clinical response was observed in 23(62.2%) patients. These results differ from previous studies by

Campione *et al.,* who reported an effectiveness of 40% in patients using topical Tazarotene over four weeks. The results documented a good clinical outcome using topical Tazarotene 0.1% gel in distal and lateral subungual onychomycosis and its fungistatic activity of Tazarotene in vitro.[15]

Aslam *et al*., reported efficacy of oral weekly Fluconazole combined with daily topical Tazarotene 0.1% gel is significantly higher than that of weekly Fluconazole monotherapy in the treatment of OM.[16] The findings of this study are consistent with current literature, indicating similar effectiveness of Tazarotene. Falotico *et al*., highlighted that Oral Fluconazole is used by clinicians in various European countries for OM treatment; it is also used off-label in countries like the USA and Australia, especially where patients have tolerability issues with Itraconazole or Terbinafine.[17]

Similarly, Axler *et al*., emphasized the importance of tailoring onychomycosis therapy to individual patient characteristics, comorbidities, preferences, extent of nail involvement, and fungal species, such that physicians may optimize treatment outcomes, patient satisfaction, and safety.[18] In Pakistan, the study reported by Usman *et al*., the weekly dosage of Oral Fluconazole is frequently employed for both adults and children due to its simple weekly regimen and relatively low cost. To our knowledge, there are limited or no local studies on its effectiveness as a single-dose regimen. Comparative data on its effectiveness versus established drugs, such as Tazarotene 0.1% gel, are even scarcer. To date, no clinical studies in Pakistan have examined this comparison. The use of oral antifungal medications for treating onychomycosis, especially when 50% or more of the nail is involved, makes Fluconazole an appropriate choice.[19]

Studies like Nickles *et al*., also suggested that combining oral antifungals with topical agents increases treatment success rates.[20] Our study indicates that Fluconazole is far more effective than topical Tazarotene 0.1% gel in treating onychomycosis. However, since OM is rarely treated with monotherapy in clinical practice, the 31% response rate to Tazarotene suggests it can be a useful adjunct to oral therapy, potentially enhancing the antifungal effects and leading to higher cure rates when used in combination. This hypothesis is supported by previous studies reporting higher effectiveness of topical antifungal therapies when combined with Tazarotene. It also underscores the need for further research, particularly on combined oral and topical treatments, to evaluate their clinical and mycological cure rates. Based on our findings, we recommend this combination as an effective and rapid treatment strategy, as numerous studies indicate it can increase treatment success.[21]

To the best of our knowledge, this study is the first in Pakistan to clinically evaluate and compare the efficacy of oral Fluconazole and topical Tazarotene 0.1% gel in the management of onychomycosis. Our findings provide valuable evidence for clinicians managing this chronic and challenging condition. Nonetheless, larger randomized clinical trials at both national and international levels are warranted to further validate the safety and effectiveness of these therapeutic modalities.

LIMITATIONS OF STUDY

Our study lacked access to a microbiology facility, preventing pre- and post-treatment fungal cultures on nail clippings; this was partly addressed through detailed clinical, dermoscopic, and KOH assessments. We were also unable to systematically record adverse effects of either treatment, although no major complaints were reported during verbal inquiries, and both Fluconazole and topical Tazarotene are generally well tolerated. Additionally, pediatric patients may show faster responses due to thinner, rapidly growing nails, but safety and tolerability of topical Tazarotene in this population require confirmation through pilot and larger-scale studies.

CONCLUSION

Oral Fluconazole in a weekly oral dose is far more efficacious than topical Tazarotene 0.1% gel in the treatment of onychomycosis of toes and fingers in a Pakistani cohort. It is also pertinent that the combination of the two agents may result in a rapid clinical response and higher treatment success rates in onychomycosis than when either of the agents is used alone.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MAK & MA: Data acquisition, data analysis, critical review, approval of the final version to be published.

LH & SN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SN & UA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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