ORIGINAL ARTICLE

The Positive Impact of Combined Treatment of Tazarotene and Systemic Antifungal on Onychomycosis

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ABSTRACT

Background: *Onychomycosis is a nail plate fungal infection with low initial cure rates and high relapse. Current treatment choices consist of topical and oral therapies. Tazarotene is a synthetic retinoid, with anti-inflammatory activities.* ***Objectives:*** *to investigate the effect of topical Tazarotene with and without systemic antifungal as a treatment of onychomycosis.* ***Methodology****: This work is a prospective, comparative, observational study. Thirty onychomycosis patients (with nail changes) were recruited out of 300 patients admitted to the dermatology clinic at Fayoum University Hospital , they were divided into three groups, group I: 10 patients treated with topical Tazarotene, group II: 10 patients treated with systemic antifungals, and group III: 10 patients treated with both. The groups were evaluated clinically by onychomycosis severity index (OSI) and laboratory by direct film and fungal culture of nail samples taken by scraping or clipping before and after treatment of all patients.* ***Results****: Trichophyton mentagrophyte (20%), was the commonest isolated fungus followed by Epidermophytone floccosum and candida species (13.3% each). After 3 months of treatment: (group I) showed improvement clinically with no lesion within 30% of patients (especially lesions of mild and moderate cases). Also (group II) showed improvement in cases cured with 50% of patients with no lesion. Group III showed 70% of patients (all cases especially severe cases) clinically no lesion.* ***Conclusion****: Combined treatment of Tazarotene and systemic antifungal has a worthy clinical effect on all onychomycosis especially severe cases also Tazarotene alone is a safe and effective cure choice for mild and moderate onychomycosis.*

INTRODUCTION

Onychomycosis accounts for 50% of all onychopathies and one-third of fungal infections of skin. It leads to the gradual destruction of the nail. Onychomycosis is presented by hyperkeratosis, thickening, and nail discoloration[1]. There is a wide variation of fungi causing onychomycosis. The commonest causative agents are dermatophytes, especially *trichophyton ruburm* and *tricophyton mentagrophytes*, which account for 50%-90% of cases. Onychomycosis is also caused by yeasts and non dermatophyts molds. Yeasts infection like *Candida parapsilosis*, *Candida albicans*, *Candida tropicalis*, and *Candida krusei* [2]. Non-dermatophytes molds account for 2% to 12% of onychomycosis patients, mainly *Scopulariopsis brevicaulis* and Aspergillus [3]. There are different clinical types of onychomycosis: distal and lateral subungual onychomycosis (DLSO) which the plate of the nail appears yellow-white with distal subungual hyperkeratosis[4]. White superficial onychomycosis (WSO) is less common than DLSO [5]. Proximal subungual onychomycosis (PSO) is uncommon. PSO presents as leukonychia, proximal onycholysis, and subungual hyperkeratosis [3]. Endonyx subungual onychomycosis is characterized by massive nail plate invasion in the absence of nail bed involvement**.** Total dystrophic onychomycosis **(**TDO) is the most severe stage of onychomycosis due to the destruction of the nail plate [6]. Microscopic examination and mycological culture are the gold standard methods for the diagnoses of onychomycosis, but high false-negative degrees have forced for added precise techniques, like histology and molecular methods [7]. Numerous factors have been presented to raise the onychomycosis risk as systemic disorders like diabetes mellitus, infections (AIDS), and age (due to decreased the nail growth, poor peripheral circulation, and defective immune function). Also, Local factors such as reduce blood flow peripherally due to atherosclerosis, and repeated trauma increase the onychomycosis risk. Consideration of these factors is important when selecting the appropriate onychomycosis therapy [8]. Treatment choices for onychomycosis range from palliative care, mechanical or chemical debridement,

topical and systemic antifungal drugs to a mixture of two or more of these modalities [9]. Systemic antifungal drugs like terbinafine, itraconazole, fluconazole, ketoconazole, and griseofulvin are considered as the gold standard for all types of onychomycosis [10]. Because of the potential systemic adverse effects of oral antifungals, an increased demand for topical options with minimal side effects and no drug–drug interactions have been required [11]. Numerous topical treatments are accessible in the form of nail lacquers or solutions, but the effectiveness of these treatments remains low [12]. Tazarotene is a third-generation retinoid (vitamin A derivative). Tazarotene inhibits excess keratinocyte proliferation, and decreases the expression of inflammatory cytokines. Moreover, it can exert a defensive action against infection[13]. Tazarotene is slowly absorbed through healthy skin and the concentration of plasma reaches 18.6 hours after application and a mean absorption time of 28.8 hours. Tazarotene is applied in psoriasis, and acne treatment. The topical delivery of Tazarotene helps to minimize systemic exposure to the drug and thus helps to promote a safety profile that is higher than orally administered retinoid [14]. Dual therapy of topical and oral drugs is beneficial because therapy with only topical drugs is frequently not entirely active as well hazard of side effects by oral medications. This work aimed to investigate the effectiveness of tazarotene alone, systemic antifungal alone, and compared to the combination of both in the treatment of onychomycosis patients.

METHODOLOGY

A prospective comparative study was conducted on thirty patients recruited from 300 Outpatients of the Dermatology Clinic of Fayoum University Hospital from first of December 2021 to 30 June 2022, after the approval of the Research Ethical Committee no. M464. The study is in line with the Declaration of Helsinki, written informed consents were obtained from all patients.

Patient's inclusion criteria:

Adult participants with nail changes who were highly indicative of onychomycosis of toes and-or fingers were enrolled in the study. While **exclusion criteria** involved patients with systemic and other cutaneous diseases, pregnancy, lactation, autoimmune disease, history of drug reactions, severe allergic reactions, and psychiatric illness. Age, sex, onset, course, duration of the onychomycosis, and response to previous treatment were recorded for each patient. Clinical evaluation was performed on the basis of general, local examination, and Onychomycosis Severity Index (OSI). Mild Onychomycosis matches a score of (1-5), moderate (6-15), and severe (16-35).[4] The patients were divided into three groups each group included 10 patients, Group I: was treated with topical Tazarotene 0.1% gel daily applied on the affected nail for 3 months. Group II: treated with systemic antifungal (Itraconazole 100 mg cap), were taken by the patient for a week every month, for 3 months. Group III: treated with both systemic antifungal and topical Tazarotene for 3 months.

A total of 120 finger and toe-nail clipping samples were collected from all patient groups as described by Lawry et al. [15] before treatment and after one month, two months, and three months of treatment**.** The Specimens were placed in a folded square of paper, labeled, and transferred to the Department of Medical Microbiology and Immunology, Faculty of Medicine, Fayoum University for microbiological analysis. The samples were directly mounted with potassium hydroxide (KOH) 20% wet-mount preparation and examined with x10 and x40 objective lenses of the light microscope for the recognition of fungal hyphae, or spores**.** The culture was done for the samples regardless of the microscopic examination results. Samples were cultured in screw-capped bottles (slopes) containing Sabouraud Dextrose agar media (Oxoid, LTD, England) supplemented by chloramphenicol (50mg/liter) and cycloheximide (500mg/liter) (Hi-media supplements, India), and incubated at 26-30 °C for 2-4 weeks. The culture was examined periodically for evidence of fungal growth. Identification was approved using conventional techniques for color, morphology, and texture of growth from the top and reverse sides (surface pigmentation) and for identification of the presence of septate or non-septate hyphae, macroconidia, microconidia, and other structures needed for identification of different species, microscopic investigation of film stained by lactophenol cotton blue was done. Urea hydrolysis was used to further distinguish *T. mentagrophytes* from *T. rubrum* [16]. The assessment of the therapy response was evaluated clinically and microbiologically before treatment (week 0), every month during the 3 months of the therapy. The clinical remedy is well-defined as a 100% visually clear nail, while a fungal cure is well-defined as a nail that results in negative KOH preparations and no growth of fungal culture[11].

Statistical analysis:

Information was collected and coded to enable data handling, double entered into Microsoft Access, and data examination was completed using the Statistical Package of Social Science (SPSS) software version 22 in Windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive examination for numbers and percentages of qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion of quantitative parametric data. One-Sample Kolmogorov-Smirnov test, the Kruskal Wallis test, Chi-square test. MC-Nemartest was

performed for paired dependent qualitative data. The p-value≤ 0.05 was considered **statistically** significant.

RESULTS

Demographic, clinical, and microbiological data of the studied groups:

Among 30 onychomycosis patients, females were more than males (63.3% versus 36.6 % respectively). A high percentage of finger-nail lesions than toe-nail lesions (80% versus 20% respectively) were reported. In addition, the commonest lesion type was DLSO (66.7%), while the least common form was TDS (6.7%) (Table 1). Regarding the fungal type, *Trichophyton mentagrophytes* was the prominent species isolated (20%), followed by *Epermophytone floccosum (*13.3%) (Table 2). Microscopic examination of fungal cultures are shown in (Figure 1 a, b,).

Table 1: The demographic and clinical data among the studied groups

Variables		Total (N=30)	Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)	*p-value*
Age	(Mean /SD)	35.6±9.6	35.6±9.6	32±7.5	39.4±7.8	0.159
Sex	Female (N %)	**19(63.3%)**	7(36. 8%)	6(31.6%)	6(31.6%)	0.866
	Male (N %)	**11(36.6%)**	3(27.3%)	4(36.4%)	4(36.4%)	
Site of lesion	Finger-nail (N %)	**24(80%)**	7(70%)	8(80%)	9 (90%)	0.535
	Toe-nail (N %)	**6(20%)**	3(30%)	2(20%)	1(10%)	
Onychomycosis Subtypes	DLSO	**19(66.7%)**	7(70%)	7(70%)	5(50%)	0.918
	PSO	**5(16.7%)**	1(10%)	1(10%)	3(10%)	
	WSO	**3(10%)**	1(10%)	1(10%)	1(10%)	
	TDS	**3(6.7%)**	1(10%)	1(10%)	1(10%)	
The severity of onychomycosis by OSI	Mild	**5(16.7%)**	2(20%)	2(20%)	1(10%)	0.953
	Moderate	**18(60%)**	6(60%)	6(60%)	6(60%)	
	Severe	**7(23.3%)**	2(20%)	2(20%)	3(30%)	

(OSI): Onychomycosis Severity Index, **DLSO:** distal-lateral subungual onychomycosis; **PSO:** proximal subungual onychomycosis; **WSO:** White superficial onychomycosis**, TDS:** total onychodystrophy. P-value≤ 0.05.

Table 2: Fungal type's distribution among the studied patients

Fungal type	N (%)
Trichophyton mentagrophytes	**6(20%)**
Epermophytone floccosum	**4(13.3%)**
Candida spp.	**4(13.3%)**
Trichophytone rubrum	**3(10%)**
Trichophyton megnini	**3(10%)**
Trichophyton tonsurans	**2(6.7%)**
Trichophyton violaceum	**2(6.7%)**
Trichophyton schoenleinii	**2(6.7%)**
Aspergillus spp	**2 (6.7%)**
No growth	**2(6.7%)**
Total	**30(100%)**

N%: number, percentage

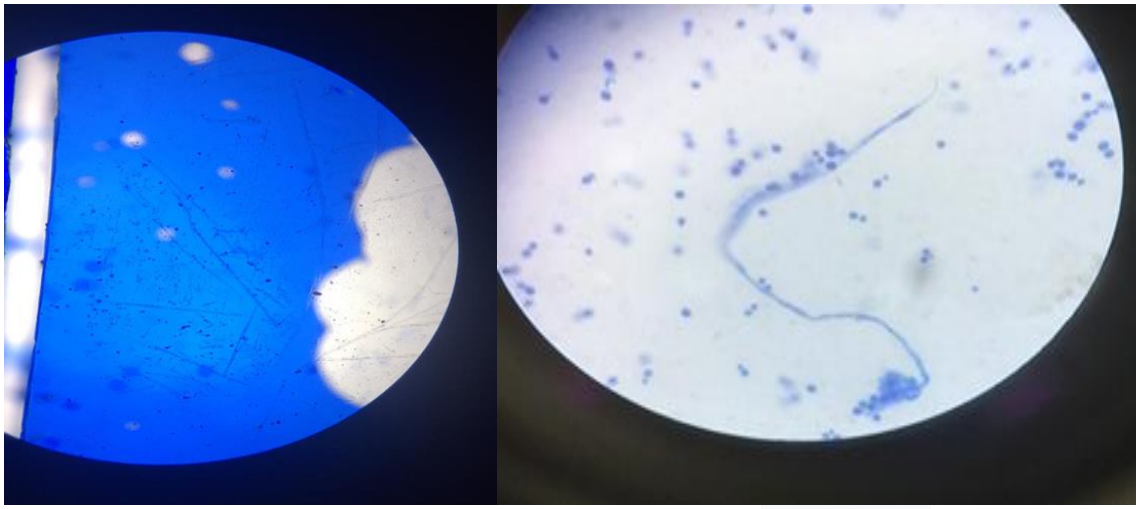

Fig. 1a: Microscopic examination of *Trichophyton mentagrophytes*

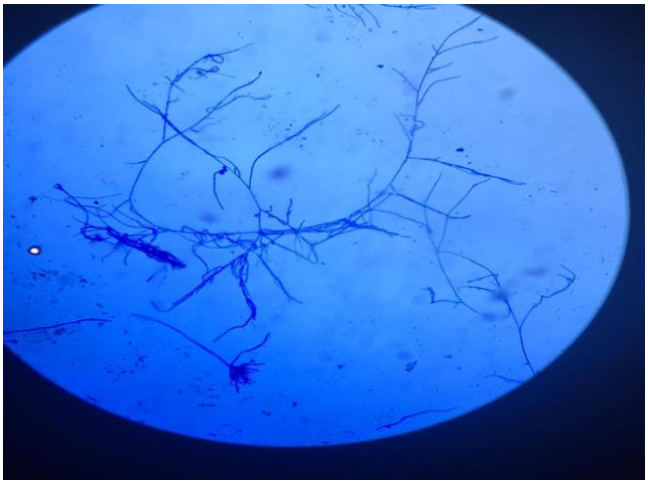

Fig. 1b: Microscopic examination of *Aspergillus spp*

Treatment assessment (clinically, microbiologically) of the studied groups:

Treatment with topical Tazarotene gel alone in group I showed improvement of cases cure after 3 months with thirty percent of patients clinically showing no lesion and fifty percent of patients' cultures showing no growth (especially cases of mild and moderate lesions) (Figure 2: a). While systemic antifungal treatment alone in group II showed improvement in cases cured after 3 months with fifty percent of patients clinically showed no lesion and seventy percent of patients' cultures showing no growth (Figure 2: b). And in group III with combined treatment after 3 months eighty percent of patients' cultures showed no growth, and seventy percent of patients clinically showed no lesions (all cases especially severe cases) (Figure 2: c), (Tables 3) .

Table 3: Treatment assessment (clinically, microbiologically) of the studied patients' groups

Follow up	Group I (N=10)		Group II (N=10)		Group III (N=10)		*P-value*
	No.	%	No.	%	No.	%	
Pre-treatment							
Clinically							
No lesion	**0**	**(0%)**	**0**	**(0%)**	**0**	**(0%)**	
Mild	**2**	**(20%)**	**2**	**(20%)**	**1**	**(10%)**	
Moderate	**6**	**(60%)**	**6**	**(60%)**	**6**	**(60%)**	
Severe	**2**	**(20%)**	**2**	**(20%)**	**3**	**(30%)**	0.83
Culture							
No growth	**2**	**(20%)**	**1**	**(10%)**	**0**	**0(0%)**	0.39
growth	**8**	**(80%)**	**9**	**(90%)**	**10**	**10(10%)**	
1 month treatment							
Clinically							
No lesion	**0**	**(0%)**	**0**	**(0%)**	**0**	**(0%)**	
Mild	**5**	**(50%)**	**5**	**(50%)**	**2**	**(20%)**	0.287
Moderate	**4**	**(40%)**	**4**	**(40%)**	**6**	**(60%)**	0.585
Severe	**1**	**(10%)**	**1**	**(10%)**	**2**	**(20%)**	0.749
Culture							
No growth	**6**	**(60%)**	**3**	**(30%)**	**4**	**(40%)**	0.387
Growth	**4**	**(40%)**	**7**	**(70%)**	**6**	**(60%)**	
2 month treatment							
Clinically							
No lesion	**1**	**(10%)**	**2**	**(20%)**	**1**	**(10%)**	
Mild	**6**	**(60%)**	**4**	**(40%)**	**7**	**(70%)**	0.749
Moderate	**2**	**(20%)**	**3**	**(30%)**	**1**	**(10%)**	0.387
Severe	**1**	**(10%)**	**1**	**(10%)**	**1**	**(10%)**	0.535
Culture							
No growth	**5**	**(50%)**	**5**	**(50%)**	**7**	**(70%)**	0.581
Growth	**5**	**(50%)**	**5**	**(50%)**	**3**	**(30%)**	
3 month treatment							
Clinically							
No lesion	**3**	**(30%)**	**5**	**(50%)**	**7**	**(70%)**	0.202
Mild	**5**	**(50%)**	**4**	**(40%)**	**3**	**(30%)**	0.659
Moderate	**1**	**(10%)**	**0**	**(0%**	**0**	**(0%)**	0.355
Severe	**1**	**(10%)**	**1**	**(10%)**	**0**	**(0%)**	0.585
Culture							
No growth	**5**	**(50%)**	**7**	**(70%)**	**8**	**(80%)**	0.350
Growth	**5**	**(50%)**	**3**	**(30%)**	**2**	**(20%)**	

P-value≤ 0.05

Fig. 2: Assessment of onychomycosis treatment clinically in the studied groups

DISCUSSION

Onychomycosis is defined as a chronic infection of fungal nails, the treatment possibilities include systemic and topical remedies. Systemic antifungal agents offer better effectiveness and shorter treatment durations than topicals but are restricted by the dangers of drug-drug interactions, and systemic toxicity. Topical antifungals are well endured and safe, with only possible local side effects. Combination therapy for Onychomycosis may theoretically result in greater cure rates than monotherapy, by providing broader spectrum antifungal activity and drug synergy, but this remains unclear because of the lack of trials on combination treatments for onychomycosis, which tests assessments of efficiency and safety [10]. Tazarotene is a synthetic retinoid derived from vitamin A. Its antifungal activity might be related to its immunomodulatory and anti-inflammatory effects [17]. The current study aimed to investigate the efficiency of Tazarotene alone compared to its combination with the systemic antifungal drug in the onychomycosis treatment. Out of thirty onychomycosis patients, fingernail infection was higher compared to toenail infection (63.3% versus 36.6%). This is comparable with other studies which reported that fingernail infection was the most recurrently in onychomycosis infection[17, 18] . The low incidence of toenails onychomycosis could be due to open footwear and less concern for toenails appearance. *Garg et al.* [19] stated that the distolateral type was higher than other types of onychomycosis, this coincides with our finding which (66.7%) of our patients were diagnosed as DLSO, only 3 patients (6.7%) have DS. Dermatophyte fungi (*Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans,* and *T. mentagrophytes interdigitale*) are the highest causes of nail plate invasion in most countries [20]. In our study, *Trichophyton mentagrophytes in (20%), Epermophytone floccosum* in (13.3%). *Elewski et al.*[21] reported that DSO is usually produced by *Trichophyton. rubrum, and Trichophyton. tonsurans* that are in the USA and is emerging in Europe. Also, *Bunyaratavej et al.* [22] reported that *Trichophyton tonsurans* has been implicated to cause lateral and distal subungual onychomycosis.

Abdelhamid et al. [23] recognized the quick effectiveness and safety of Tazarotene topical treatment on onychomycosis, the exact mechanism underlying the antifungal activity of Tazarotene might be attributed to a modulatory effect on keratinocyte proliferation,

differentiation, and normalization of the atypical keratinization. In the current study, treatment with Tazarotene 0.1% gel alone (group 1) showed improvement of cases cure during the follow- up period after 3 months, fifty percent of patient's cultures showed no growth, and thirty percent of patient's clinical showed no lesion .

These results were comparable with the results of *El-Salam et al.* [17] who reported that Tazarotene exerts an antifungal activity against species causing onychomycosis if applied for three months once daily . Also, *Abdelhamid et al.* [23] who found that Tazarotene 0.1% gel achieved a mycological cure in one-fourth of the treated cases (25.7%) with a moderate capacity, they found that that Tazarotene could significantly reduce the onychomycosis severity by reducing for the OSI, which reflects improvement in the size of the infected area, the load of mycological infection, and the subungual hyperkeratosis. In addition to, *Campione et al.* [24] proposed Tazarotene as a new possible therapeutic for the onychomycosis therapy and showed a complete clinical and fungal remedy for all onychomycosis cases.

Our findings revealed that: systemic antifungal therapy alone (group 2) showed improvement of in cases cured after 3 months, seventy percent of patients' cultures showed no growth and fifty percent of patient's clinical showed no lesion. Also, combined treatment of Tazarotene and systemic antifungal showed high improvement in cases cure, after 3 months, eighty percent of the patients' cultures and seventy percent of clinical showed no lesion. Systemic antifungal agents are suggested for lesions of moderate to severe disease. Instead, topical antifungal treatments may be considered for lesions of mild to moderate disease. Topical antifungals with systemic antifungal dual therapy may be used to diminish the therapy duration and raise the cure rate due to synergistic antifungal action of the drugs [25]. Our results are comparable with *Campione et al.* [24] who reported that the dual therapy of topical and systemic antifungals improves the cure rates and gives better results than systemic treatment alone. Positive cultures growth were found in a lower number than the clinical cases almost in all groups that may be clarified by that greatest of the patients regularly apply oils with anti-fungistatic oils [16].

CONCLUSION

Tazarotene showed better antifungal activity when added to systemic antifungal drugs especially in severe lesions which act as an adjunct to the systemic antifungal agent. It might be used alone for treatment of mild and moderate onychomycosis patients.

Ethics approval and consent to participate

The present work was approved by the Ethics Committee of Fayoum University NO: D234. Written informed consent were obtained from all participants after a clear explanation of the study's objectives, and in accordance with the Declaration of Helsinki ethical principles and guidelines.

Competing interests

No conflict of interests.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

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-All methods were performed in accordance with relevant guidelines and regulations.

The author(s) read and approved the final manuscript.

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