**ORIGINAL ARTICLE**

# Comparison of Efficacy of Continuous Terbinafine versus Intermittent Itraconazole in the Treatment of Toenail Onychomycosis

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## ABSTRACT

**Aim:** To compare the efficacy of continuous terbinafine with intermittent itraconazole in patients with toenail onychomycosis.
**Study Design:** Randomized control trail
**Place and Duration of Study:** Department of Dermatology, Multan Medical and Dental College Multan, DHQ Hospital Multan and Bahawal Victoria Hospital Bahawalpur from 1st January 2017 to 31st May 2018.
**Methods:** One hundred and seventy patients were enrolled in this study. Patients were randomly divided into two groups one receiving terbinafine while other group receiving intermittent itraconazole. Each group contained 85 patients each. Efficacy of the two drugs was assessed on the basis of mycological cure at the end of the follow up without the requirement of secondary intervention. Secondary outcomes for efficacy were clinical cure, complete cure, mycological or clinical relapse over time, mycological and clinical cure over time and effect of terbinafine as a secondary intervention in mycological and clinical cure.
**Results**: Seventy (82.35%) and 40(47.06%) showed mycological cure (p<0.001); 64(75.29%) and 33(38.82%) showed clinical cure (p<0.001); and 61(71.76%) and 25(29.41%) showed complete cure (p<0.001) without second course of antifungal medication, in the Terbinafine group and Itraconazole group, respectively. Relapse rate was higher in the Itraconazole group. At the end of study, 56 (65.88) and 22 (25.88) showed mycological cure (p<0.001); 53(62.35) and 21(24.71) showed clinical cure (p<0.001); and 50 (58.82) and 18 (21.18) showed complete cure (p<0.001) without second course of antifungal medication, in the Terbinafine group and Itraconazole group, respectively.
**Conclusion:** Continuous terbinafine is superior to intermittent terbinafine in the treatment of toenail onychomycosis.
**Key words:** Terbinafine, Itraconazole, Onychomycosis

## INTRODUCTION

Onychomycosis has a prevalence of 3% in general population as it has been shown by recent studies[1]. It is a very common disease and its prevalence is higher in elder populations as compared to the younger population and aslo in certain population groups like, diabetics, swimmers and people suffering from psoriasis[2,3]. In certain dermatomycoses, a reservoir may be left in the adjacent skin which can be termed as onychomycosis, such as in tinea pedis, plantar and interdigital (moccasin type)[4]. This disease has severe lifestyle impact in lives of the patients as shown in certain studies.[5] Griseofulvin was the main stay of treatment for onychomycosis in the past but it has lower treatment efficacy and takes longer duration of therapy to have its effect[5]. In recent times treatment approach has been changed and antifungal drugs such as terbinafine and itraconazole are much more effective in treating this ailment and have much shorter duration of time to treat.[7] Previous studies have been performed to compare the efficacy of continuous terbinafine with intermittent itraconazole and results were in favor of continuous terbinafine in terms of overall cure rate, mycological and clinical[8].

Both drugs are effective in treating toenail onychomycosis but it requires further study to establish which one of these drugs is superior to the other especially in this community. No studies like this have been done in this region of the world to compare these two modalities of the treatment which makes it important so that proper recommendations can be made by judging the superiority of the one drug over the other. In this study not only definite cure rates of the two antifungal drugs will be compared but their long-term efficacy will also be assessed on basis of clinical and mycological relapse rates.

## MATERIALS AND METHODS

The study was a randomized control trail, performed in Department of Dermatology, Multan Medical and Dental College Multan, DHQ Hospital Multan and Bahawal Victoria Hospital Bahawalpur from 1st January 2017 to 31st May 2018. A total number of 170 patients were enrolled in this study. Patients belonging to any gender with age ranging from 18 to 75 years and diagnosed clinically as toenail onychomycosis, diagnosis was confirmed with the help of mycological culture and dermatophyte seen under microscopic examination and follow was done on prospective basis were included. Pregnant patients, breast

feeding patients, patients suffering from psoriasis, patients with severe renal, hepatic or endocrinal impairment, patients using concomitant drugs like cyclosporine, digoxin, rifampin, oral anticoagulants and phenytion or patients allergic to azoles or antifungal drugs were excluded.

Patients were randomly divided into two groups one receiving terbinafine 250mg\dl for a duration of twelve or sixteen weeks while other group receiving intermittent itraconazole at a dose of 400mg\dl one week every four for twelve or sixteen weeks. Each group contained 85 patients each. Comparison between the groups was made at baseline and at four, eight, twelve, sixteen, thirty two, forty eight and seventy two weeks. All the microbiological or mycological examinations took place in one laboratory.

Efficacy of the two drugs was assessed on the basis of mycological cure at the end of the follow up without the requirement of secondary intervention. Secondary intervention was done with terbinafine. If results of both mycological culture and microscopy came out negative, it was stated as mycological cure i.e. primary outcome. Secondary outcomes for efficacy were clinical cure, complete cure, mycological or clinical relapse over time, mycological and clinical cure over time and effect of terbinafine as a secondary intervention in mycological and clinical cure. Clinical cure can be defined as completely normal appearance of the nail at the end of the follow up. If both clinical and mycological cure was observed it was termed as complete cure. If a patient was mycologically cured at duration of twelve months but had a relapse later on, it was termed as mycological relapse. Similarly if it happened in terms of clinical cure after achieving clinical cure at 18 months follow up and then developing clinical symptoms and signs later one, it was termed as clinical relapse. Clinical cure assessment requires at least 18 months follow up while mycological cure can be assessed at 12 months or less.

The data was analyzed by SPSS-23. P value less than or equal to 0.005 was considered significant statistically.

## RESULTS

Both the groups were comparable in terms of age (p=0.492), male percentage (0.538), incidence of trichophyton rubrum (0.231), average weight (0.752), mean number of infected toenails (0.650), time since the onset of onychomycosis (0.611) and number of patients presenting with nail involvement (0.075) [Table 1]. After eighteen months of treatment, 70 (82.35%) and 40 (47.06%) showed mycological cure (p<0.001); 64 (75.29%) and 33 (38.82%) showed clinical cure (p<0.001); and 61 (71.76%) and 25 (29.41%) showed complete cure (p<0.001) without second course of antifungal medication, in the Terbinafine group and Itraconazole group, respectively. Relapse rate was higher in the Itraconazole group. At the end of study, 56 (65.88) and 22 (25.88) showed mycological cure (p<0.001); 53 (62.35) and 21 (24.71) showed clinical cure (p<0.001); and 50 (58.82) and 18 (21.18) showed complete cure (p<0.001) without second course of antifungal medication, in the Terbinafine group and Itraconazole group, respectively (Table 2).

The number of patients who had to receive additional course of Terbinafine were significantly higher in the Itraconazole group (p<0.001) as compared to the Terbinafine group. The duration of second Terbinafine course was much longer in the Itraconazole group as compared to Terbinafine group (p=0.006). The outcome in the form mycological cure, clinical cure and complete cure after second course of Terbinafine was not significantly between the two groups (p>0.05) [Table 3].

Table 1: Demographic information of patients

| Variable | Terbinafine | Itraconazole | P value |
|---|---|---|---|
| Age (years) | 42.68±8.55 | 43.69±10.51 | 0.492 |
| Male | 48 (56.47%) | 44 (51.76%) | 0.538 |
| Incidence of trichophyton rubrum | 81 (95.29%) | 77 (90.59%) | 0.231 |
| Weight (kg) | 55.21±12.71 | 54.57±13.42 | 0.752 |
| No. of infected toenails | 5.07±1.55 | 4.93±2.40 | 0.650 |
| Duration of onychomycosis, years | 8.13±2.94 | 7.91± 2.77 | 0.611 |
| Nail involvement | 59 (69.41%) | 69 (81.18%) | 0.075 |

Table 2: Mycological and Clinical cure rates

| Time period | Cure | Terbinafine | Itraconazole | p-value |
|---|---|---|---|---|
| Month 18 | Mycological | 70 (82.35) | 40 (47.06) | <0.001 |
| | Clinical | 64 (75.29) | 33 (38.82) | <0.001 |
| | Complete | 61 (71.76) | 25 (29.41) | <0.001 |
| End of study without 2nd intervention | Mycological | 56 (65.88) | 22 (25.88) | <0.001 |
| | Clinical | 53 (62.35) | 21 (24.71) | <0.001 |
| | Complete | 50 (58.82) | 18 (21.18) | <0.001 |

Table 3: 2nd intervention with Terbinafine at month 18

| Variable | Terbinafine | Itraconazole | p-value |
|---|---|---|---|
| Additional Terbinafine course | 35 (41.18%) | 67 (78.82%) | <0.001 |
| Duration of Terbinafine course m | 3.47±0.91 | 3.84±0.81 | 0.006 |
| Mycological cure | 31 (36.47%) | 61 (71.76%) | 0.690 |
| Clinical cure | 28 (32.94%) | 57 (67.06%) | 0.514 |
| Complete cure, n (%) | 26 (30.59) | 53 (62.35) | 0.580 |

## DISCUSSION

In meta-analysis comparing terbinafine with itraconazole, it was found that recurrence rate were higher among the patients receiving treatment with itraconazole as compared to the patients administered with terbinafine. It was predicted from the fact that overall combined risk ratio of terbinafine with itraconazole was very high for mycological care (0.44 with CI=95%, 0.29 to 0.66)[10]. Similarly another study comparison was made between three groups' one receiving terbinafine alone, one receiving itraconazole and one receiving combined therapy with both itraconazole and terbinafine and results were in the favor of monotherapy with terbinafine. Combined therapy did not affect the outcome and recurrence was more in itraconazole group as compared to terbinafine group as it is also evident in our study. They also suggested that there might be some difference between the continuous or intermittent modes of antifungal drugs but our study suggests otherwise as continuous terbinafine is still better than intermittent itraconazole[11]. Long term treatment efficacy can be better

provided with the use of systemic terbinafine when patient presents with first episode of onychomycosis. Dermatophyte strain, nail lacquer use as prophylaxis or other predisposing factors did not influence the relapse rate, as shown by a previous study[12].

In our study conclusion is that, continuous terbinafine is significantly more effective than intermittent itraconazole, similarly a previous study also states that even though both forms of therapy are almost equally tolerable and are highly effective, continuous terbinafine is slightly better in terms of achieving the definite mycological cure of toenail onychomycosis[13]. In a meta-analysis conducted to compare the continuous and intermittent regimens of terbinafine alone and results showed that continuous regimen was superior to intermittent regimen in terms of achieving mycological cure. But pulsed terbinafine was better in some studies as compared to continuous regimen for obtaining the complete cure.[14] In contrast to the results of our study a previous study has suggested that both modalities of treatment of toenail onychomycosis in elderly patients were equally effective. Continuous terbinafine was as effective and safe as intermittent itraconazole and both drugs were associated with high rate of compliance[15]. Multiple previous studies provide evidence of the fact that terbinafine is superior to itraconazole and recommended that initial or primary treatment of onychomycosis should with be four month continuous terbinafine[16-18].

## CONCLUSION

Continuous terbinafine is superior to intermittent terbinafine in the treatment of toenail onychomycosis in terms of achieving mycological as well as clinical cure or both (complete cure). Relapse rate was also lower in group of patients receiving continuous terbinafine.

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