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Research Article

A Study of Oral Terbinafine (Pulse Therapy) In Combination with Topical Amorolfine Versus Oral Itraconazole (Pulse Therapy) In Combination with Topical Amorolfine for the Treatment of Onychomycosis: A Randomized, Open Label, Parallel Group Study

Dr. Laxmikant Kiran Phutane[1], Dr. Avinash V Turankar[2], Dr. Jayesh Mukhi[3], Dr. Bhagyashree Supekar[4], Dr. Sukant Pandit[5], Dr. Gopal Agrawal[6], Dr. Vishal Ubale[7], Dr. Priyanka Kalbhor[8], Dr. Bhushan Dudhe[9]

[1]Senior Resident, Department of Pharmacology, Government Medical College and hospital, Nagpur, Maharashtra - 440003, India
[2]Professor and Head, Department of Pharmacology, Government Medical College and hospital, Nagpur, Maharashtra - 440003, India
[3]Professor and Head, Department of Dermatology, Government Medical College and Hospital, Medical Square, Nagpur, Maharashtra - 440003, India
[4]Assistant Professor, Dermatology OPD, Government Medical College and Hospital, Medical Square, Nagpur, Maharashtra - 440003, India
[5]Assistant Professor, Department of Pharmacology, Government Medical College and Hospital, Medical Square, Nagpur, Maharashtra - 440003, India
[6]Professor, Department of Microbiology, Government Medical College, Gondia, Maharashtra, India
[7]Associate Professor, Department of Pharmacology, Government Medical College, Alibaug, Maharashtra, India
[8]Assistant Professor, Department of Microbiology, Government Medical College and Hospital, Medical Square, Nagpur, Maharashtra, India
[9]Assistant Professor, Department of Pharmacology, Government Medical College and Hospital, Medical Square, Nagpur, Maharashtra, India

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Corresponding Author:

Dr. Laxmikant Kiran Phutane
Senior Resident, Department of Pharmacology, Government MedicalCollege and hospital, Nagpur, Maharashtra - 440003, India

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ABSTRACT

Purpose/Aim: This study was planned to assess efficacy of oral terbinafine (pulse therapy) and topical amorolfine [group AT] versus oral itraconazole (pulse therapy) and topical amorolfine [group AI] for the treatment of onychomycosis. Primary objective was 1) Percentage of participants having achieved mycological cure (defined as no growth on KOH mount) between two groups at the end of 3 months. 2) Percentage of participants having achieved clinical improvement in nail disease (defined as at least 20% reduction in total disease surface area from baseline) between two groups at the end of 3 months. Secondary objective was to assess quality of life between the two groups by mean Dermatology Life Quality Index (DLQI) score at the end of 3 months.

Methods: This was a randomized, open-label, parallel group study conducted in 80 patients of onychomycosis attending dermatology OPD of a tertiary care teaching hospital.

Results: There was significant reduction in percentage area of infected nails from baseline to 3 months in both groups (p-value: <0.0001). Clinical improvement and clinical cure were around 64% and 23% respectively in both groups, and the difference between the two groups was not statistically significant. Mycological cure rate was 78.57% and 88.88% in group AT and group AI respectively at the end of 3 months, with no significant difference between the two groups.

Conclusion: There was no difference in clinical improvement and mycological cure between group AT and group AI. Group AT was found to be similar to group AI with respect to mean DLQI score.

Keywords*: Onychomycosis, Terbinafine, Itraconazole, Dermatology Life Quality Index (DLQI), Mycological cure.*

INTRODUCTION

Onychomycosis is a fungal nail infection, which causes thickening and discoloration of affected nail plate, and is most common infection worldwide. (Gupta et al., 2020a) In India, its incidence ranges from 0.5 to 12%, whereas globally, it is approximately 5%. Yeasts, non-dermatophyte fungi, and dermatophytes (tinea unguium) may cause onychomycosis. Occlusive footwear, humidity, repetitive nail trauma, genetic predisposition, and coexisting conditions like poor peripheral circulation, diabetes, HIV infection, and other immunosuppressive conditions have been some contributing factors that result in this disease. (Welsh, 2010; Elewski, and Charif, 1997; Elewski, 1998)

Therapeutic options for onychomycosis treatment include palliative care, systemic and topical antifungal agents, mechanical or chemical debridement, or a combination of two or more of these modalities. (Faergemann et al., 2005; Evans, 2003, Gupta et al., 2004) Terbinafine is a synthetic allylamine, which inhibits fungal squalene epoxidase, and thereby reduces ergosterol biosynthesis. With an average mycological cure rate of 76%, oral terbinafine is an established treatment for onychomycosis caused by dermatophytes. Itraconazole, which is an oral synthetic triazole, exhibits broad-spectrum antimycotic efficacy against dermatophytes, several nondermatophytic molds, and candida species. It works by preventing the fungal cell membrane's ergosterol from undergoing the cytochrome P450-dependent demethylation step. The topical antifungal drug amorolfine, a morpholine derivative, inhibits 7,8 isomerase and 14-α reductase to prevent ergosterol from being produced in the fungal cell membrane.

Due to the prevalence of relapses and reinfections and the fact that less than 50% individuals achieve disease-free nails with current systemic therapy, onychomycosis is still challenging to treat. Onychomycosis can seriously impair quality of life by causing both physical and psychological issues if left untreated. (Epstein E, 1998; Drake et al., 1999)

Combination therapy of oral and topical antifungals simultaneously or in sequence has several advantages over monotherapy. It has a synergistic antifungal effect since topical antifungals are absorbed through the nail plate and lateral margin of the nail, while oral antifungals act through the nail bed. This increases compliance, thereby improving tolerance and efficacy, and may have a broader spectrum of action. The infection recurs in a significant portion of people who have been cured. Different regimens of already available treatments should be examined to lower recurrence rates, as development of new therapies is infrequent.

Itraconazole treatment, either continuous or pulsed, has been demonstrated to be successful in treating onychomycosis associated with molds, candida species, and dermatophytes. The dose for itraconazole is 200 mg daily for 12 weeks to treat infected toenails. A single pulse consists of 400 mg daily for 1 week, followed by 3 weeks of no drug. Two and three pulses are recommended for treating fingernail and toenail onychomycosis, respectively.(Gupta et al., 2020a) Terbinafine treatment for fingernail and toenail infections is 250mg/day for 6 and 12 weeks, respectively.In treating dermatophyte toenail onychomycosis, a systematic review and network meta-analysis found that the pulse and continuous regimens of itraconazole and terbinafine have similar efficacies and adverse event rates.(Gupta et al., 2020b) Pulse therapy may reduce treatment cost and improve compliance compared to continuous regimens. (Leyden, 1998)

Very few studies comparing oral terbinafine (pulse therapy) and topical amorolfine versus oral itraconazole (pulse therapy) and topical amorolfine were found despite a thorough search. So, this study was planned to assess the effectiveness of oral terbinafine (pulse therapy) and topical amorolfine versus oral itraconazole (pulse therapy) and topical amorolfine in the treatment of onychomycosis.

MATERIALS AND METHODS

It was an open label, randomized, parallel group study carried out in 80 patients of onychomycosis attending the Dermatology OPD. The study wasconducted at a tertiary care teaching hospital from November 2022 to May 2024 (18 months).

The inclusion criteria were -

1. All new cases of onychomycosis diagnosed clinically by dermatologist or on mycological examination by KOH mount
2. Patients between 18 and 75 years (both inclusive) of either gender
3. Patients willing to provide written informed consent

The exclusion Criteria were -

1. Patients who had received any systemic antifungal therapy within preceding 9 months or topical antimycotic treatment within 4 weeks prior to screening
2. Patients with nail diseases other than onychomycosis (e.g, psoriasis) that can impaircorrect interpretation of result
3. Participants with documented history of allergic reactions to any components of terbinafine, itraconazole, or amorolfine

4. Participants with a history of liver or kidney disease
5. Lactating or pregnant women

Primary objective was 1) Percentage of participants having achieved mycological cure (defined as no growth on KOH mount) between two groups at the end of 3 months. 2) Percentage of participants having achieved clinical improvement in nail disease (defined as at least 20% reduction in total disease surface area from baseline) between two groups at the end of 3 months. Secondary objective was to assess the quality of life between the two groups by mean Dermatology Life Quality Index (DLQI) score at the end of 3 months.

The study was initiated after approval from the Institutional Ethics Committee (IEC approval number 1722). It was conducted in accordance with Good Clinical Practice (GCP) guidelines. Patient information sheet was provided to every participant; moreover, the nature of study was elucidated to them. Written informed consent was acquired from every participant prior to enrollment in the study. Patients meeting the inclusion criteria following initial screening were incorporated into the study. Eligible patients had randomly been assigned to the following two treatment groups by using a computer-generated table of random numbers.

Group A: Tab. Terbinafine 250mg BD, for one week per month for 3 months (pulse therapy) with topical Amorolfine 5% nail lacquer applied once a week for 3 months

Group B: Cap.Itraconazole 200 mg BD, for one week per month for 3 months (pulse therapy) with topical Amorolfine 5% nail lacquer applied once a week for 3 months

Each patient was provided with the corresponding tablets/capsules for one week alongside topical amorolfine 5% nail lacquer at the time of recruitment. Tablets/capsules (for one week) were given at first and second follow-up visits, which were in the first and second months, respectively. Reporting of adverse events was recorded in a case record form at each visit. Clinical nail status was recorded by the investigator at the 1st, 2nd and 3rd follow-up visits. Mycological examination status was recorded by the investigator at baseline and third follow-up visit. Quality of life was assessed at baseline and 3 months by avalidated vernacular (in local languages: hindi and marathi) version of DLQI questionnaire. All the drugs were provided by the investigator.

Clinical assessment:
Clinical assessment was conducted by a principal investigator and dermatologist. Efficacy parameters were decrease in number of infected nails and percentage area of nails affected between two groups. The area of nail involvement was calculated by multiplying the longest breadth and the longest length of affected nails. Quality of life was evaluated at baseline and after 3 months in both groups by using a validated vernacular DLQI questionnaire version, comprising 10 questions, each scored between 0 and 3.

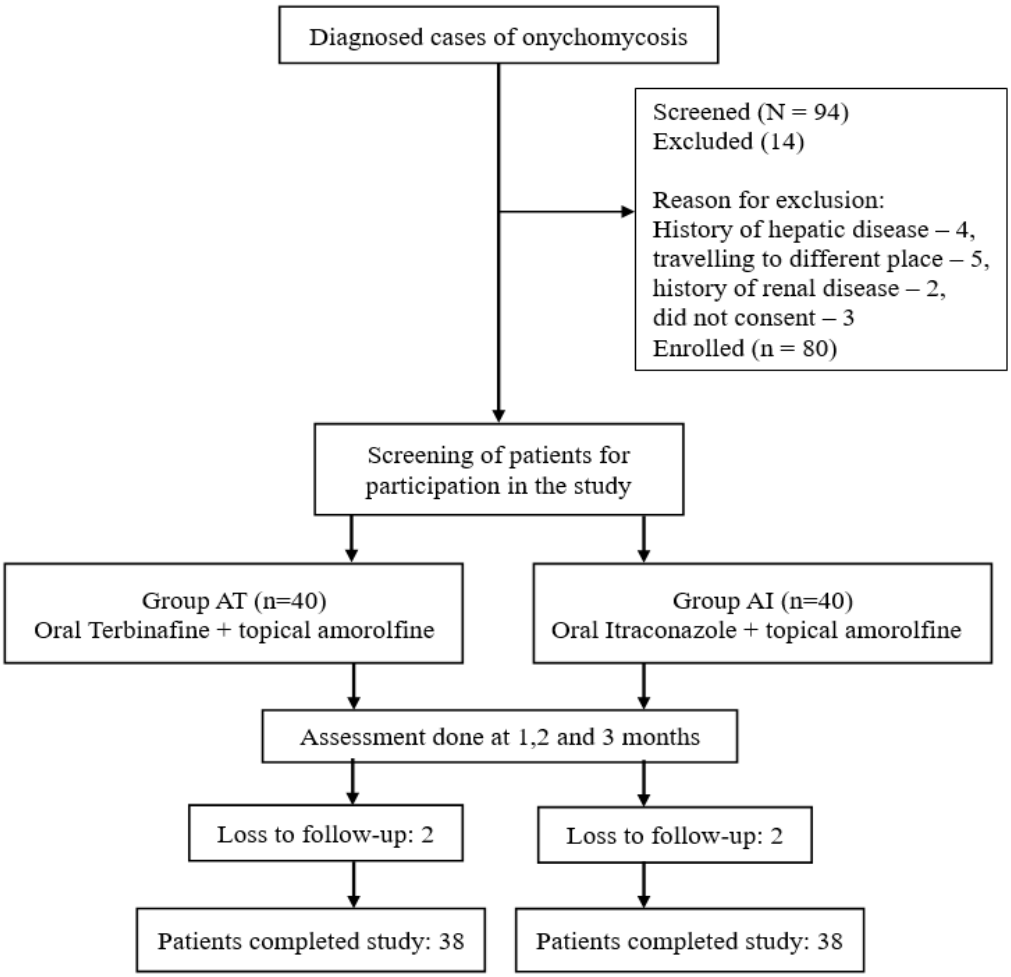
Statistics:
Sample size:
Sample size was computed using a significance level of 5% and power of 80%. Mycological cure of 74% was taken as a cure rate for the standard drug regimen from a previous study. (Rigopouloset al., 2003) Assuming a difference of 25%, the sample size was calculated, which came out to be 36 in each group. So, the total sample size was taken as 80 (40 patients in each group), considering dropout rate of 10%. PS for sample size version 8.4.2 was used for calculation of sample size.

Statistical analysis:
Participants who underwent at least one follow-up were included in the analysis as per modified intention-to-treat analysis. Continuous variables had been denoted as mean ± standard deviation (SD). Categorical variables had been denoted in actual numbers and percentages.

For continuous data, between group analysis was done by Mann-Whitney or unpaired t-test (depending on normality using "Shapiro-Wilk test"). For continuous data, within-group analysis was done by repeated measures ANOVA or Friedman's test (depending on normality using the Shapiro-Wilk test), subsequently, Tukey's or Dunn's multiple comparison test was employed. Categorical data had been assessed by fisher's exact test. P-value of less than 0.05 was considered statistically significant. Statistical analysis had been done using graph pad prism version 8.4.2.

RESULTS
A total of 94 individuals were screened, out of which 14 were excluded. The reasons for exclusion were history of hepatic and renal disease, patients travelling to different places, and those who did not give consent. A total of 80 patients were randomized and allocated to two treatment groups. There were 2 patients each in group AT and group AI who did not return for any of the follow-up visits and were termed as lost to follow-up. Modified intention to treat analysis was followed, and all the patients who did not show up for at least one follow-up had been excluded from the analysis. Figure 1 illustrates patient flow chart during the study.

Figure 1: Patient flow chart



In our study, baseline parameters were comparable between the two groups with respect to age, gender, weight, type of onychomycosis, involvement of fingernail, toenail, or both, and mean duration of onychomycosis (Table 1).

Table 1: Comparison of demographic parameters between two groups

Parameters	**Group AT, N=38**	**Group AI, N=38**	**P-value**	**95% CI**
Age (years)	42.13 ± 15.36	39.15 ± 11.15	0.33	-2.97 (-9.11 to 3.16)
Gender Male Female	 19 19	 19 19	>0.99	0.00 (-0.23 to 0.23)
Male:Female	01	01		
Weight (kg)	59.76 ± 11.63	57.65 ± 8.42	0.36	2.105 (-2.53 to 6.74)
Type of onychomycosis DLSO (Distal and lateral onychomycosis) Total dystrophic onychomycosis WSO (White superficial onychomycosis)	 17 19 02	 19 17 02	 0.818 0.82 >0.99	 0.052 (-0.17 to 0.28) 0.05 (-0.17 to 0.27) 0.00 (-0.42 to 0.42)
Involvement Fingernail	 15 (39.47 %)	 14 (36.84 %)	 >0.99	 0.02 (-0.21 to 0.26)

Toenail Both	10 (02.63 %) 13 (34.21 %)	08 (21.05 %) 16 (42.10 %)	0.78 0.637	0.07 (-0.20 to 0.32) 0.08 (-0.14 to 0.32)
Mean duration of onychomycosis (months)	17.44 ± 30.15	14.40 ± 13.44	0.56	-3.03 (-13.30 to 7.22)

CI: confidence interval

Group AT: Tab. Terbinafine 250 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

Group AI: Cap. Itraconazole 200 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

Percentage area of infected nails at baseline in group AT and group AI were 68.06% and 67.76% respectively. Percentage area of infected nails at the end of 3 months were 36.80% and 38.72% in group AT and group AI respectively. The difference in percentage area of infected nails between the two groups at 3 months was not significant statistically (p-value: 0.76). There was a decrease in percentage area of infected nails by 31.26% and 29.04% from baseline to 3 months in group AT and group AI respectively. The difference in percentage area of infected nails from baseline to 3 months was statistically significant (p <0.0001) in both groups (table 2).

Table 2: Comparison of percentage area of infected nails from baseline to three months

	Baseline	1 month	2 month	3 month	P-value	95% CI
Group AT	68.06 ± 23.84	57.21 ± 21.87* (-10.85)$^{\Delta}$	47.64 ± 23.84$^{*\#}$ (-20.42)$^{\Delta}$	36.80 ± 27.32$^{*\#\$}$ (-31.26)$^{\Delta}$	<0.0001	31.2 (23.6 to 38.8)$^{\wedge}$
Group AI	67.76 ± 19.38	56.93 ± 17.42* (-10.83)$^{\Delta}$	48.23 ± 20.04$^{*\#}$ (-19.53)$^{\Delta}$	38.72 ± 25.14$^{*\#\$}$ (-29.04)$^{\Delta}$	<0.0001	29.0 (20.7 to 37.3) $^{\wedge}$

95% CI: confidence interval, values are denoted as mean ± SD (Standard Deviation)

Repeated measures ANOVA with post hoc Tukey's test applied.

Group AT and AI: *P-value <0.0001 as compared to baseline, $^{\#}$P-value <0.0001 as compared to 1 month, $^{\$}$P-value <0.0001 as compared to 2 month.

$^{\Delta}$Difference between means from baseline.

$^{\wedge}$95% CI (95%) at 3 months as compared to baseline.

Group AT: Tab. Terbinafine 250 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

Group AI: Cap. Itraconazole 200 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

Clinical cure had been denoted as disappearance of all lesions on every nail or residual disease of no more than 10% of original total disease surface area. Clinical improvement was defined as at least 20% reduction in total disease surface area from baseline. Clinical failure was defined as decrease in complete disease surface area by <20% or deterioration of condition from baseline.

Percentage of participants with clinical improvement at the end of 3 months were 65.78% and 63.15% in group AT and group AI respectively. The clinical cure rate at the end of 3 months was 26.31% and 21.05% in group AT and group AI respectively. The difference in clinical cure and improvement between the two groups at 3 months was not statistically significant. Percentage of participants with clinical failure were 7.89% and 15.78% in group AT and group AI respectively. The difference in clinical failure rate in both the groups was not statistically significant (table 3).

Table 3: Comparison of clinical status and mycological status of target nails from baseline to the end of three months between both the groups

	Parameters	Group AT, N=38 n (%)	Group AI, N=38 n (%)	P-value	95% CI
Clinical status	Improvement	25 (65.78)	24 (63.15)	>0.99	0.02 (-0.21 to 0.26)
	Cure	10 (26.31)	08 (21.05)	0.78	0.07 (-0.20 to 0.32)
	Failure	03 (07.89)	06 (15.78)	0.48	0.19 (-0.08 to 0.57)
Mycological	Yes	11 (78.57)	08 (88.88)	>0.99	0.17 (-0.16 to 0.74)

	No	03 (21.42)	01 (11.11)		

CI: confidence interval. Fisher's Exact test applied.
Group AT: Tab. Terbinafine 250 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months
Group AI: Cap. Itraconazole 200 mg BD, for 1 week per month for 3 months (pulse) with] Topical amorolfine 5% nail lacquer applied once a week for 3 months

Mycological cure was defined as percentage area of participants with negative direct microscopy (by KOH mount). Mycological cure rate was 78.57% and 88.88% in group AT and group AI respectively. Difference in mycological cure rate between 2 groups was not statistically significant. However, microscopic examination to know the mycological status could not be done in all participants (table 3).

Complete cure has been implied as percentage of participants with clinical cure and mycological cure. Complete cure rate was 26.31% and 21.05% in group AT and group AI respectively at the end of 3 months respectively. Difference in complete cure rate between the two groups was not statistically significant. (table 4)

Table 4: Comparison of complete cure of target nails between two groups from baseline to the end of three months

Complete cure	Yes, n (%)	No, n (%)	P-value	95% CI
Group AT, N=38	10 (26.31)	28 (73.68)	0.78	0.05 (-0.15 to 0.25)
Group AI, N=38	08 (21.05)	30 (78.94)		

CI: confidence interval, Fisher's Exact test applied.
Group AT: Tab. Terbinafine 250 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months
Group AI: Cap. Itraconazole 200 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

The mean DLQI score in group AT and group AI at the end of 3 months were 3.45 and 3.76 respectively. The difference in mean DLQI score in group AT and group AI at the end of 3 months was not statistically significant (table 5).

Table 5: Comparison of mean Dermatology Life Quality Index (DLQI) score between two groups at the end of 3 months

Parameter	Group AT	Group AI	P-value	95% CI
DLQI score	3.45 ± 2.66	3.76 ± 2.65	0.60	0.32 (-0.89 to 1.52)

CI: confidence interval, values are denoted as mean ± SD (Standard Deviation). Unpaired t-test applied.
Group AT: Tab. Terbinafine 250 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months
Group AI: Cap. Itraconazole 200 mg BD, for 1 week per month for 3 months (pulse) with Topical amorolfine 5% nail lacquer applied once a week for 3 months

No significant difference was observed in the number of patients with adverse effects between the two groups. The adverse events reported were nausea, vomiting, diarrhoea, gastrointestinal distress, abdominal pain and headache. In our study, all the adverse effects were reversible and of mild to moderate severity.

DISCUSSION

A total of 76 patients in both groups were included in research with 38 patients in every group. Baseline demographic parameters and disease characteristics exhibited similarities in both groups. There was a significant decrease in percentage area of infected nails by around 30% from baseline to 3 months in group AT and group AI. However, there was no significant difference in percentage area of infected nails between the two groups at the end of 3 months. During the course of study, percentage area of infected nails in both the groups decreased at each evaluation following baseline, with a statistically significant difference beginning at 1 month. According to a study by R. Baran et al. (in 2007), mean decrease in the percentage of total surface area involved at the end of 18 months was 85.10% in group AT. (Baran et al., 2007)

Clinical cure and clinical improvement rate at the end of 3 months was similar between the two groups. A study by R. Baran et al (in 2007) observed that clinical cure rate and clinical improvement rate were 66.7% and 28.3% respectively in group AT at the end of 18 months. Another study by M Lecha et al observed clinical cure rate of 100% at 6 months in the group of oral itraconazole (given for 12 weeks) in combination with topical amorolfine.(Lecha, 2001) Higher clinical

improvement rate and less cure rate in our study could be due to relapse/reinfection, associated immunosuppressive conditions, and involvement of toenails in many participants which require a little longer treatment period of 3-4 months.

Although the difference in clinical success rate was similar between the two groups, there was higher success rate in group AT. The reported differences between the fungicidal and fungistatic concentrations of terbinafine and itraconazole may be one possible explanation for the higher clinical efficacy of group AT in this study. The concentrations of terbinafine in the nail are 100 times greater than drug's minimum fungicidal concentrations (MFC), whereas documented itraconazole concentrations have been on borderline between fungicidal as well as fungistatic action. (De Doncker P et al., 1996) Terbinafine has primary fungicidal action against dermatophyte fungi, with average minimum fungicidal concentrations (MFC) and minimum inhibitory concentrations (MIC) of about 0.004ug/ml, whereas itraconazole has primarily fungistatic action, with average MFC of about 0.6ug/ml in dermatophytes. (Leyden, 1998)

The difference in clinical failure rate in both groups was similar. A study by M Lecha et al observed a clinical failure rate of 3.2% at 6 months in the group of oral itraconazole (given for 12 weeks) in combination with topical amorolfine. (Lecha, 2001) According to a study by R. Baran et al. (in 2007), clinical failure rate at the end of 18 months was 5 % in group AT. (Baranet al., 2007) Clinical failure in our study may be associated with bacterial coinfection, matrix involvement, age, immunosuppression, systemic disease, mixed infections, resistance to oral antifungal medications, recurrent nail damage, and repeated exposure to pathogens.

No significant difference in mycological cure rate between the two groups was observed. A study conducted by R. Baran et al (2007) observed mycological cure rate (which included negative direct microscopy and negative culture) of 94.2% in group AT at the end of 3 months. Another study conducted by R. Baran et al (in 2000) comparing two different courses of terbinafine treatment combined with amorolfine 5% solution nail lacquer observed the mycological cure rate (which included negative direct microscopy and negative culture) of 27.5% in AT group at the end of 3 months. (Baranet al., 2000) A study carried out by M Lecha et al observed mycological cure rate (which included negative direct microscopy and negative culture) of 82.9% in AI group at the end of 3 months. According to a study by Rigopoulos et al comparing itraconazole (pulse therapy) and topical amorolfine with itraconazole alone in the treatment of candida fingernail onychomycosis, mycological cure rate was 74.4% in AI group at the end of 3 months. (Rigopoulos et al., 2003)

The complete cure rate did not differ significantly between the two groups. In treating candida fingernail onychomycosis, a study by Rigopoulos et al. comparing itraconazole (pulse therapy) and topical amorolfine versus itraconazole alone observed a 93.2% complete cure rate (defined as both clinical cure andimprovement along with mycological cure) at 9 months. (Rigopoulos et al., 2003) At the conclusion of 18 months, a study carried out by Baran et al. (2007) stated that group AT had a complete cure rate (defined as clinical cure along with negative mycology, that includes both negative direct microscopy and negative culture) of 59.2%. However, there is inconsistency in how different studies on onychomycosis define and quantify complete cure.

There are certain limitations of the study. First, the study was an open label and assessor was not blind. Hence the probability of bias cannot be excluded. Second, direct microscopic examination of all participants could not be done due to logistic reasons. Third, larger sample size would be required for meaningful results as the post-hoc power was inadequate.

CONCLUSION

There was significant improvement in efficacy from baseline to 3 months in group AT (oral terbinafine and topical amorolfine) and group AI (oral itraconazole and topical amorolfine). There was no difference in clinical improvement and mycological cure between group AT and group AI; however, conclusions could not be drawn due to the limitation of the lack of complete data regarding mycological cure. Group AT was found similar to group AI with respect to mean DLQI score and adverse events.

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