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Original Research Article

Comparative Efficacy of Terbinafine Monotherapy Versus Combined Terbinafine and Voriconazole in Treating Resistant Fungal Infections

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Abstract: ***Background:*** The rising incidence of resistant fungal infections poses significant therapeutic challenges. This study aimed to compare the efficacy and safety of terbinafine monotherapy versus combination therapy with terbinafine and voriconazole in patients with resistant fungal infections. ***Methods:*** A total of 90 participants were enrolled from June 2022 to May 2024 at Colonel Maleque Medical College, Manikgonj, Bangladesh. Participants were randomly assigned to receive either terbinafine (6 mg/kg, maximum 500 mg/day) alone or in combination with voriconazole (200 mg/day). Outcomes assessed included mycological cure rates, clinical improvement, relapse rates, and adverse events over a 1-year follow-up period. ***Results:*** At 6 weeks, the mycological cure rate was 44% for the monotherapy group versus 78% for the combination group (p=0.001). At 1 year, the rates were 29% and 67%, respectively (p=0.001). Complete clinical improvement was observed in 29% of monotherapy patients compared to 62% in the combination group (p=0.002). Adverse events were more common in the combination group (44% vs. 22%, p=0.03), including higher rates of liver enzyme elevation and visual disturbances. Relapse rates at 1 year were lower in the combination group (27% vs. 44%, p=0.05). ***Conclusion:*** Combination therapy with terbinafine and voriconazole significantly improves mycological cure rates and clinical outcomes in resistant fungal infections compared to monotherapy, despite an increased incidence of adverse events.

Keywords: Terbinafine, Voriconazole, Combination Therapy, Resistant Fungal Infections, Mycological Cure Rates.

INTRODUCTION

Fungal infections particularly those affecting the skin, hair, and nails, are a growing public health concern worldwide [1]. Commonly caused by dermatophytes and occasionally by non-dermatophyte molds, these infections range in severity and are often chronic and difficult to eradicate, particularly in patients with recurrent or resistant infections [2]. Dermatophyte infections, known as dermatophytoses, are the most prevalent fungal infections, impacting millions globally [3]. Despite the availability of various antifungal agents, some infections exhibit significant resistance, posing a treatment challenge and increasing the risk of relapse [4,5]. This issue highlights the need for more effective therapeutic strategies and an improved understanding of resistance mechanisms in fungal infections [6].

Terbinafine an allylamine antifungal is among the most widely prescribed medications for treating dermatophytic and some non-dermatophytic fungal infections [7]. Terbinafine works by inhibiting squalene epoxidase, an enzyme essential for fungal cell membrane synthesis [8]. This drug has been shown to be effective in treating infections of the nails (onychomycosis), skin, and other keratinized tissues [9]. However, emerging resistance to terbinafine has limited its success in some patients. Resistant strains, prolonged infections, and recurrent fungal infections reduce the therapeutic efficacy of terbinafine monotherapy, creating an urgent need to explore alternative or adjunctive treatments [5].

Combination antifungal therapies have emerged as a promising approach to overcoming resistance in difficult-to-treat infections [3]. Voriconazole, a triazole antifungal, is frequently used as a second-line treatment for invasive and resistant fungal infections [10]. Unlike terbinafine, voriconazole targets fungal cytochrome P450 enzymes, which interfere with cell membrane synthesis and fungal growth [11]. Studies have shown that voriconazole may enhance terbinafine's efficacy when used in combination, suggesting a

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synergistic effect that improves outcomes in resistant infections [12]. By combining two drugs with distinct mechanisms of action, there is potential to achieve higher cure rates, prevent relapses, and reduce the risk of resistance development [13].

The efficacy of combination therapy with terbinafine and voriconazole for resistant fungal infections, however, remains understudied. While individual antifungals like terbinafine and voriconazole are well-studied, data on their combined efficacy in resistant infections is limited, especially for cutaneous and nail fungal infections [8]. In addition, potential adverse effects, such as liver enzyme elevation and visual disturbances (associated with voriconazole), may limit the long-term use of this combination [14]. Therefore, a careful examination of both efficacy and safety in a real-world clinical setting is essential to determine the clinical utility of this combination for resistant fungal infections [15].

This study aimed to assess the comparative efficacy of terbinafine monotherapy versus combination therapy with terbinafine and voriconazole in patients with resistant fungal infections, particularly onychomycosis and dermatophytoses. By examining cure rates, relapse rates, clinical improvement, and adverse effects over a one-year follow-up, this study seeks to provide insights into whether combination therapy offers a significant advantage over terbinafine alone. Additionally, it will address the safety profile of combined therapy, particularly regarding hepatic and visual side effects, which are critical concerns for long-term antifungal treatment.

METHODOLOGY & MATERIALS

This prospective study was conducted under the Department of Dermatology at Colonel Maleque Medical College, Manikgonj, Bangladesh, from June 2022 to May 2024. Ninety patients aged 18–65 with clinically and microbiologically confirmed resistant fungal infections (e.g., onychomycosis, dermatophytosis) who had not responded to prior terbinafine therapy were enrolled. Patients were randomized into two groups of 45 each. Group 1 received terbinafine monotherapy at a dosage of 6 mg/kg (up to a maximum of 500 mg/day) for six weeks, while Group 2 received a combination of terbinafine (6 mg/kg, maximum 500 mg/day) with voriconazole (200 mg/day) for six weeks.

Exclusion criteria included known allergies to the study drugs, significant liver or kidney dysfunction, pregnancy, lactation, and concurrent use of medications with known interactions with voriconazole. Baseline assessments included demographic data, infection duration, and laboratory tests such as liver function tests (LFTs). Patients were monitored weekly for adherence, symptom progression, and adverse effects. LFTs and visual acuity assessments were repeated at three and six weeks to ensure safety.

Primary outcomes measured were mycological cure rates at 6 weeks, 6 months, and 1 year, defined by negative culture and microscopy results. Secondary outcomes included clinical improvement (complete and partial), time to symptom relief, and relapse rates at 6 months and 1 year. Adverse events, particularly liver enzyme elevation, visual disturbances, gastrointestinal symptoms, and skin reactions, were tracked throughout treatment and follow-up.

Data analysis was performed using chi-square tests for categorical variables and independent t-tests for continuous variables. Kaplan-Meier survival analysis was used to assess relapse-free survival. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics of Participants (n=90)

Characteristic	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	p-value
Age (years, mean ± SD)	45.2 ± 10.5	46.0 ± 9.8	0.720
Gender (% female)	28 (62%)	30 (67%)	0.600
Duration of infection (months, median [IQR])	10 [6–15]	9 [5–14]	0.650
Prior terbinafine use (%)	45 (100%)	45 (100%)	1.000
Comorbidities (%)			
- Diabetes	15 (33%)	13 (29%)	0.800
- Hypertension	8 (18%)	9 (20%)	0.850

Table 1 summarizes baseline characteristics of the study participants (n=90), with 45 patients each in the Terbinafine Monotherapy and Combination Therapy groups. The mean age was similar between groups (45.2 vs. 46.0 years; p=0.720), as was the gender distribution, with females comprising 62% and 67% of each group, respectively (p=0.600). Both groups had comparable infection durations (median 10 vs. 9 months; p=0.650) and included only participants with prior terbinafine use. Comorbidities were balanced, with no significant differences in diabetes (33% vs. 29%; p=0.800) or hypertension rates (18% vs. 20%; p=0.850).

Table 2: Mycological Cure Rates at 6 Weeks, 6 Months, and 1 Year

Time Point	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	p-value
6 Weeks	20 (44%)	35 (78%)	0.001
6 Months	15 (33%)	32 (71%)	0.002
1 Year	13 (29%)	30 (67%)	0.001

Table 2 shows the mycological cure rates in the Terbinafine Monotherapy and Combination Therapy groups at 6 weeks, 6 months, and 1 year. At 6 weeks, the cure rate was significantly higher in the Combination Therapy group (78%) compared to the Monotherapy group (44%), with a p-value of 0.001. This trend continued at 6 months, where cure rates were 71% for Combination Therapy and 33% for Monotherapy (p=0.002). At the 1-year follow-up, the Combination Therapy group maintained a higher cure rate (67%) than the Monotherapy group (29%), also statistically significant (p=0.001).

Table 3: Clinical Improvement at Key Follow-up Intervals

Follow-up Interval	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	p-value
6 Weeks			
- Complete Improvement	10 (22%)	30 (67%)	0.001
- Partial Improvement	25 (56%)	10 (22%)	0.003
6 Months			
- Complete Improvement	15 (33%)	32 (71%)	0.001
- Partial Improvement	15 (33%)	8 (18%)	0.100
1 Year			
- Complete Improvement	13 (29%)	28 (62%)	0.002
- Partial Improvement	12 (27%)	10 (22%)	0.600

Table 3 outlines clinical improvement rates for the Terbinafine Monotherapy and Combination Therapy groups at 6 weeks, 6 months, and 1 year. At 6 weeks, complete improvement was significantly higher in the Combination Therapy group (67%) compared to the Monotherapy group (22%), with a p-value of 0.001. Partial improvement rates were 56% in the Monotherapy group and 22% in the Combination group (p=0.003). This pattern continued at 6 months, with 71% complete improvement in the Combination group versus 33% in the Monotherapy group (p=0.001). By the 1-year mark, complete improvement was still more frequent in the Combination group (62%) than in the Monotherapy group (29%), with a p-value of 0.002. Partial improvement rates at 1 year were similar between the two groups (27% vs. 22%, p=0.600).

Table 4: Relapse Rates at 6 Months and 1 Year Follow-up

Follow-up Interval	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	p-value
6 Months	18 (40%)	10 (22%)	0.04
1 Year	20 (44%)	12 (27%)	0.05

Table 4 presents relapse rates at 6 months and 1 year for both the Terbinafine Monotherapy and Combination Therapy groups. At 6 months, the relapse rate was significantly higher in the Monotherapy group (40%) compared to the Combination Therapy group (22%), with a p-value of 0.04. By the 1-year follow-up, relapse rates remained elevated in the Monotherapy group (44%) relative to the Combination Therapy group (27%), with a p-value of 0.05.

Table 5: Adverse Events over the Course of Treatment and Follow-up

Adverse Event	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	p-value
Liver enzyme elevation	3 (7%)	10 (22%)	0.05
Visual disturbances	0 (0%)	8 (18%)	0.02
Gastrointestinal symptoms	5 (11%)	7 (16%)	0.6
Skin reactions	4 (9%)	5 (11%)	0.75
Total with any adverse event	10 (22%)	20 (44%)	0.03

Table 5 summarizes adverse events reported in the Terbinafine Monotherapy and Combination Therapy groups throughout treatment and follow-up. Liver enzyme elevation occurred in 7% of patients in the Monotherapy group and 22% in the Combination Therapy group, with a p-value of 0.05, indicating a significant difference. Visual disturbances were reported in 18% of patients in the Combination group but none in the Monotherapy group (p=0.02). Gastrointestinal symptoms were comparable between groups (11% vs. 16%; p=0.6), as were skin reactions (9% vs. 11%; p=0.75). Overall, 22% of patients in the Monotherapy

group and 44% in the Combination group experienced at least one adverse event, with a statistically significant difference (p=0.03).

Table 6: Summary of Efficacy and Safety Outcomes at 1-Year Follow-up

Outcome Category	Terbinafine Monotherapy (n=45)	Combination Therapy (n=45)	Difference (%)	p-value
Overall Mycological Cure Rate	29%	67%	38%	0.001
Overall Clinical Improvement	56%	84%	28%	0.01
Adverse Events	22%	44%	22%	0.03
Relapse Rate	44%	27%	-17%	0.05

Table 6 provides a summary of key efficacy and safety outcomes at the 1-year follow-up for patients in the Terbinafine Monotherapy and Combination Therapy groups. The overall mycological cure rate was significantly higher in the Combination Therapy group (67%) compared to the Monotherapy group (29%), with a 38% difference (p=0.001). Clinical improvement was also greater in the Combination group (84%) versus the Monotherapy group (56%), showing a 28% difference (p=0.01). In terms of safety, adverse events were more frequent in the Combination Therapy group (44%) compared to the Monotherapy group (22%), with a significant difference of 22% (p=0.03). The relapse rate at 1 year was lower in the Combination Therapy group (27%) than in the Monotherapy group (44%), representing a 17% reduction (p=0.05).

DISCUSSION

This study evaluated the comparative efficacy and safety of terbinafine monotherapy versus combined therapy with terbinafine and voriconazole for resistant fungal infections. The findings underscore the significant therapeutic advantage of combination therapy in achieving mycological cure and clinical improvement, while also highlighting an increase in adverse events associated with combination use.

One of the primary findings was that combination therapy resulted in notably higher cure rates and clinical improvement compared to terbinafine alone. At 6 weeks, the mycological cure rate was 44% for the terbinafine monotherapy group compared to 78% in the combination therapy group (p=0.001). By 6 months, these rates were 33% for monotherapy and 71% for combination therapy (p=0.002). Finally, at the 1-year follow-up, the rates were 29% for monotherapy and 67% for combination therapy (p=0.001). These results align with findings from previous studies on combination antifungal therapies, which have demonstrated enhanced efficacy in resistant or refractory fungal infections. Rothe *et al.*, reported successful management of Fusarium infections with a combination of terbinafine and amphotericin B, emphasizing the potential of combining antifungals with distinct mechanisms to overcome resistance and improve clinical outcomes [16] Livengood *et al.*, also reviewed combination therapy for invasive fungal infections, underscoring how such strategies are increasingly used to enhance efficacy when monotherapies fail, particularly against drug-resistant pathogens [17].

The effectiveness of the combination treatment may be attributed to the differing mechanisms of terbinafine and voriconazole, which work synergistically. Terbinafine inhibits squalene epoxidase, interfering with the fungal cell membrane, while voriconazole inhibits fungal cytochrome P450-dependent enzymes, essential for ergosterol synthesis. Combining agents with complementary mechanisms may improve pathogen eradication and reduce the likelihood of resistance. The significant difference in clinical improvement at key follow-up intervals further supports this, with complete improvement at 6 weeks reported at 22% for the monotherapy group versus 67% for the combination group (p=0.001). Similarly, at 1-year follow-up, the complete improvement rates were 29% for monotherapy and 62% for combination therapy (p=0.002).

Nevertheless, the higher adverse event rate associated with combination therapy in this study is a concern. The total incidence of adverse events was 22% in the terbinafine monotherapy group compared to 44% in the combination therapy group (p=0.03). The most common side effects were liver enzyme elevation (7% for monotherapy vs. 22% for combination, p=0.05) and visual disturbances (0% for monotherapy vs. 18% for combination, p=0.02). This is consistent with literature indicating that voriconazole is associated with visual side effects and potential hepatotoxicity, particularly when combined with other agents. Ameen *et al.*, noted that while combination therapy may be necessary in certain cases of onychomycosis and dermatophyte infections, the risks should be carefully weighed, especially in long-term treatments.[18] Similarly, Chen *et al.*, highlighted the need for close monitoring of patients on combination therapy to manage side effects promptly [19].

The observed lower relapse rate in the combination therapy group is another significant outcome of this study. At 6 months, the relapse rate was 40% for the monotherapy group compared to 22% for the combination therapy group (p=0.04), and at 1 year, the relapse rates were 44% for monotherapy and 27% for combination therapy (p=0.05). This finding is crucial

because high relapse rates are a persistent challenge in treating dermatophyte infections, especially with terbinafine-resistant strains. Relapse rates with terbinafine monotherapy alone may be due to incomplete fungal eradication, as resistant strains are less susceptible to the drug's effects, leading to persistent or recurring infections [20]. The combination approach, by exerting dual action on the pathogen, may reduce the fungal burden more effectively and thereby decrease relapse potential [21].

Despite its efficacy, combination therapy raises issues related to treatment cost, duration, and monitoring. Voriconazole, for example, is a more expensive and complex drug to administer than terbinafine, requiring dose adjustments and frequent liver function monitoring. In clinical settings, such as those outlined by Thomas *et al.,* where multidrug-resistant mold infections are increasingly common, combination therapy with systemic terbinafine may offer a viable solution, albeit with increased oversight requirements to manage side effects and ensure patient safety [22].

The findings also bring to attention the need for more comprehensive studies to refine combination protocols, potentially exploring alternative antifungal combinations. As antimicrobial resistance continues to rise, particularly among dermatophytes like Trichophyton indotineae, developing standardized combination treatments is essential. Current guidelines, such as those by the British Association of Dermatologists, recommend terbinafine as a first-line therapy for onychomycosis; however, in recalcitrant cases, alternative regimens including azoles are increasingly considered.[18] Further investigation could explore optimal dosing strategies and adjunct therapies that mitigate side effects while maximizing efficacy.

Limitations of the study

This study has several limitations. Firstly, the sample size of 90 participants, while adequate for showing significant differences, may limit the generalizability of the findings. A larger multicenter study could enhance external validity. Secondly, the one-year follow-up may not capture the long-term efficacy and safety of combination therapy; further studies are needed to assess late-onset adverse effects and treatment durability. Lastly, reliance on clinical and mycological assessments may overlook the subjective aspects of symptom relief and quality of life. Including patient-reported outcomes could provide a more comprehensive understanding of treatment impact.

Recommendations

Based on the study's findings, several recommendations emerge. Healthcare providers should consider using combination therapy with terbinafine and voriconazole for patients with resistant fungal infections, especially after monotherapy failures. Regular monitoring for adverse events, particularly liver function and visual disturbances, is essential for patient safety. Further research should explore alternative antifungal combinations targeting specific resistant strains and investigate adjunct therapies to reduce side effects. Additionally, larger multicenter trials are needed to validate these findings and assess the long-term efficacy and safety of combination therapies.

CONCLUSION

In conclusion, this study demonstrates that the combination of terbinafine and voriconazole offers significant advantages over terbinafine monotherapy in treating resistant fungal infections, with higher mycological cure rates and improved clinical outcomes. However, this comes at the cost of increased adverse events, underscoring the need for careful monitoring. The findings support the rationale for combination antifungal therapy in cases of refractory infections and highlight the importance of ongoing research to optimize treatment protocols. With the rising incidence of antifungal resistance, exploring effective combination therapies will be critical in managing complex fungal infections and improving patient outcomes.

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