An upcoming drug for onychomycosis: Tavaborole

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ABSTRACT

Fungal infection of the nail as well as nail bed is termed as 'onychomycosis'. It is caused by dermatophytes, non-dermatophytic fungal species and yeasts like *Candida albicans*. It is traditionally treated by topical antifungals, systemic agents like ketoconazole, griseofulvin, itraconazole, fluconazole, etc. Chemical avulsion or surgical removal of nail can also be tried to treat this disease. In spite of all these treatment options available, podiatrists were always in search of an ideal drug molecule with lesser side effects and which may improve the patient compliance. This exhaustive search led to the discovery of a better antifungal agent, known as "Tavaborole." A systematic literature search was carried out using databases such as PubMed, Cochrane Reviews, Google Scholar, etc. Detailed information about onychomycosis and tavaborole was gathered. Tavaborole is the first oxaborole antifungal agent approved by FDA in July 2014. It is marketed under the trade name "Kerydin." It acts by inhibiting protein synthesis in the fungus. It inhibits an enzyme known as cytosolic leucyl-transfer RNA synthetase, or LeuRS, which plays a key role in fungal essential protein synthesis. Dermatitis at the site of topical application, erythema, exfoliation and ingrowing toe nail has been reported in 1% of subjects. Tavaborole may offer a promising role in the treatment of onychomycosis and may compell podiatrists to offer its use in onychomycosis. The present study describes about chemical nature, mechanism of action and two completed phase 3 clinical trial findings of Tavaborole.

Key words: Clinical trial, onychomycosis, tavaborole

INTRODUCTION

A non-dermatophytic infection of the nail which was traditionally termed as "onychomycosis" has now become a general term to denote any fungal nail infection.[1] Onychomycosis is mainly caused by the dematophytes, specially *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Non- dermatophytes species of fungus and yeasts also possess potential to infect nail.[1,2]

It affects patients' emotional, social, and occupational functioning and imposes financial burden to them. But, in immunocompromised patients, it can result in serious life-threatening conditions.[2] Onychomycosis accounts for about 20–40% of onychopathies and about 30% of all mycotic cutaneous infections. Overall it affects 5% of world population. Most of the patients are treated by topical antifungal agents. Systemic antifungal drugs and chemicals as

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well as surgical debridement are the other treatment options available.[3]

But, unfortunately none of these proved to be satisfactory by the podiatrists in treating onychomycosis and most of the patients remained untreated. In spite of all these treatment options available, podiatrists were always in search of an ideal drug molecule with lesser side effects, which may improve the patient's compliance. This exhaustive search led to the discovery of a better antifungal agent, known as "Tavaborole." A systematic literature search was carried out using databases such as PubMed, Cochrane Reviews, Google Scholar, etc. Detailed information about onychomycosis and tavaborole was gathered.

What is tavaborole?

Tavaborole is the first oxaborole antifungal agent approved by FDA in July 2014. It is marketed under the trade name "Kerydin" and is used to treat a fungal infection of the nail as well as nail bed that is termed as onychomycosis of the toe nail. Tavaborole with the molecular formula $C_7H_6BFO_2$ has a molecular weight of 151.930743 g/mol.[4,5]

Chemical structure of tavaborole has been depicted in Figure 1.

Mechanism of action of tavaborole

It acts by inhibiting protein synthesis in the fungus. It inhibits an enzyme known as cytosolic leucyl-transfer RNA synthetase, or LeuRS, which plays a key role in fungal essential protein synthesis. Termination of protein synthesis leads to inhibition of fungal cell growth which ultimately leads to death of fungus.[6]

Efficacy of tavaborole in treating onychomycosis

The efficacy and safety was based on two randomized, double-blind, vehicle-controlled, multi-centere trials to evaluate the efficacy and safety of AN2690 topical solution 5%, versus solution vehicle in the treatment of onychomycosis of the toenail in adults. It has completed phase 3 clinical trial that was sponsored by Anacor Pharmaceuticals. In this study the study drug AN2690 topical solution, 5% was applied once daily for 48 weeks among the clinically diagnosed cases of distal subungual onychomycosis (DSO) affecting at least one great toenail with 20% to 60% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement and who were KOH positive at the time of screening.[7]

A total of 1194 subjects (795 Kerydin, 399 Vehicle), 18 to 88 years of age, participated in these two trials. Out of 1194 patients, 795 patients were treated with Kerydin (Tavaborole) while 399 patients received vehicle.[5,7] It has been shown in Figure 2.

Primary efficacy endpoints

The primary efficacy endpoint was taken as "Completely Clear Nail" that means 0% clinical involvement of the target toenail plus "Mycological Cure" which indicates negative KOH wet mount and negative fungal culture. The primary efficacy endpoint of trials 1 and 2 has been depicted in Figure 3.

Secondary efficacy endpoints

Secondary endpoints has been depicted in Figures 4 and 5 and included "Complete or Almost Complete Cure" (≤10% affected target toenail area involved plus "Mycological Cure") and "Mycological Cure."

Side effects

Dermatitis at the site of topical application, erythema,

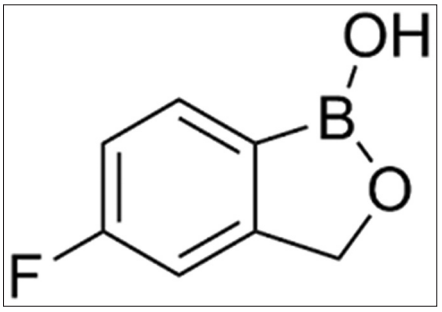

Figure 1: Chemical structure of tavaborole containing 1 boron atom

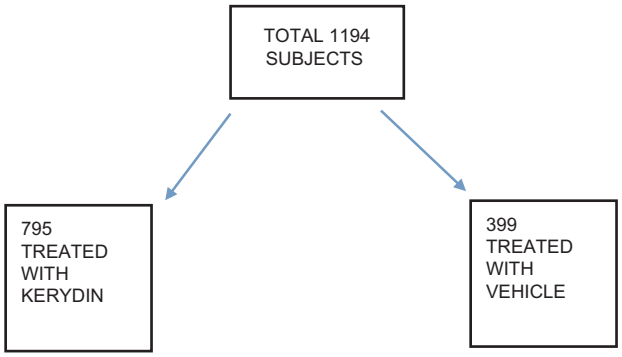

Figure 2: Recruited 1194 patients in two clinical trials

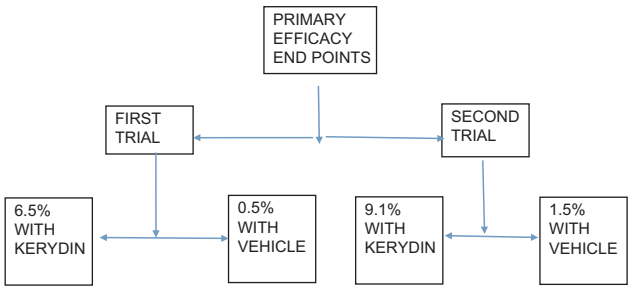

Figure 3: The primary efficacy endpoint of trials 1 and 2

exfoliation and ingrowing toe nail has been reported in 1% of subjects.[4,6,8]

Existing treatment options available for onychomycosis

Treatment of onychomycosis is very difficult because of high recurrence rates with limited treatment options available. Other factors are slow growth of toenail and anatomic nature of nail plate that hinders the nail bed access of topical antifungal agents.[9]

Systemic antifungal agents

Terbinafine (250 mg daily for 12 weeks) and itraconazole "pulse" therapy (200 mg given twice daily for 1 week per month) are the most effective oral drugs available for treating onychomycosis. Griseofulvin and ketoconazole are not used nowadays due to safety concerns. Hepatotoxicity and drug interactions are the two most common limiting features of oral drug therapy.[9] Oral drugs are more effective but patients usually prefer topical agents because of adverse effects and long duration of therapy of oral agents.[10]

Topical antifungal agents

Ciclopirox olamine 8% lacquer is the most commonly used topical agent for toenail onychomycosis. Ciclopirox is a synthetic hydroxypyridone antifungal agent which is metabolized by glucuronidation which leads to lesser chances of drug interactions.[11-13] In a study, treatment with ciclopirox olamine 8% lacquer has resulted in clinical improvement in 63.4% of patients with mycologic cure in 54.3% of patients.[14] Amorolfine 5% nail lacquer (unavailable in North America) is another agent for topical application.[15] Efinaconazole 10% solution was approved on June 9, 2014 by FDA for the treatment of onychomycosis. It has shown complete and mycologic cure rates of 15% to 25% and 53% to 87%, respectively.[16]

Comparison of complete cure and mycological cure rates of efinaconazole and tavaborole has been elaborated in Table 1. More studies on the comparison of efficacy of these two newly approved topical agents are suggested.

Current status

The new drug candidate tavaborole has been approved by US FDA in July 2014. It has been marketed under the trade name Kerydin by Anacor Pharmaceuticals. It is not available in India. The present study describes about chemical nature, mechanism of action and two completed phase 3 clinical trial findings of tavaborole.

The advantage of tavaborole over other older drugs is that it can be used topically so lesser chances of systemic side effects. Debridement of the affected toenail is not required with this drug. Tavaborole has shown negligible inhibition of cytochrome P450 enzyme so there are least chances of drug–drug interactions. In addition to that, its safety and efficacy is comparable to other available topical antifungal agents.[15]

Ongoing trials

After the convincing results of two clinical trials that has been documented by Ancor Pharmaceuticals, results of several other multicentric similar arms trials are also eagerly awaited. These clinical trials have additional benefits of evaluation of systemic doses, different doses apart from topical application. Some of them have completed phases I and II.[5]

A transfersome formulation containing 1.5% of the antifungal terbinafine (TDT-067) and newer laser therapies are also under trial for targeted drug delivery of an antifungal drug.[15] Luliconazole 10% nail solutions and another topical antifungal agent of benzoxaborole derivative, AN7718, are also under testing.[15]

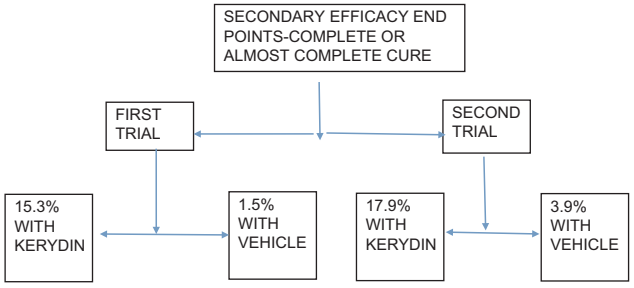

Figure 4: Complete or almost complete cure as the secondary efficacy endpoint of trials 1 and 2

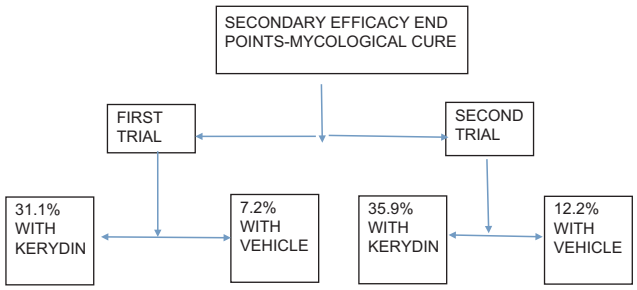

Figure 5: Mycological cure as the secondary efficacy endpoint of trials 1 and 2

Table 1: Comparison of mycological and complete cure of efinaconazole and tavaborole

Cure rate	Study 1		Study 2		Study 1		Study 2	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle	Tavaborole	Vehicle	Tavaborole	Vehicle
Complete cure	17.8	3.3	15.2	5.5	15.3	1.5	17.9	3.9
Mycological cure	55.2	16.8	53.4	16.9	31.1	7.2	35.9	12.2

CONCLUSION

Tavaborole may offer a promising role in the treatment of onychomycosis. The presence of a very small element of Boron in its structure is conferring a strong antifungal action to this drug. It may result in improved patient compliance because of its topical application with minimized side effects. More exhaustive studies are required to establish the efficacy of this boron-containing new topical antifungal candidate against other topical agents available.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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