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Letter to the Editor

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A New Innovative and Transformational Approach to Treatment of Toenail Onychomycosis: An Open Phase 2 Study

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Toenail onychomycosis has long been difficult to treat because many factors affect the treatment outcome: aging patients, long-standing infection, slow growth of thickened nails, co-morbidities, limitations of the treatment (e.g. treatment length, side effects, toxicity, physical limitations of the patient).

Hesitation in using oral medications for a non-life-threatening infection exists due to perceived risk of hepatic toxicity. Hence, physicians continue to prescribe topical drugs that are associated with limited efficacy and poor patient compliance to a daily treatment regimen that can last a year or more.

Hallux Subungual Gel (HSG) is a novel proprietary treatment approach under development that consists of a higher concentration terbinafine gel, prepackaged in prefilled syringes with very fine cannulas, for subungual administration of the drug in the distal spaces between the hard nail plate and the nail bed.

Between January 2022 and August 2024, a Phase 2 open label clinical study was conducted in the USA. The study included 47 patients (13 female and 34 male), aged 22 to 75 years old (mean and median was 56, and 11 of the 47 patients were older than 65 years). KOH and culture positive at baseline, patients received 8 topical applications over 44 weeks, with a final assessment 52 weeks after the start of therapy (which was administered by a podiatrist or a dermatologist). Enrolled patients had between 25 and 75% of the total big toenail infected (mean involved area and length was 47.6% and 72.5%), and an IGA (Investigator Global Assessment or disease severity score) of 3 or 4 (0 being symptom-free and 4 meaning worst symptoms possible). Clinical evaluation was repeated every visit and mycology was tested again at week 52.

Various efficacy and safety parameters were evaluated throughout the study.

The Results at the End of the Study were as Follows:

- Complete cure (0% involved nail, negative KOH and culture): 2/47 or 4.25%
- Mycological cure (negative KOH and culture): 11/47 or 23.4%
- Negative KOH: 11/47 23.4%
- Negative culture: 42/47 or 89.4%
- Clinical cure: 5/47 or 10.6%
- Positive response: (≥80% reduction in nail involvement) 11/47 or 23.4%
- Reduction in nail involvement ≧50%: 16/47 or 34%.
- Four patients (8.5%) were cured or almost cured (IGA 0-1, negative KOH and culture).

Interestingly, 7 of 47 patients were diagnosed with dermatophytoma at baseline (mean involved area and length was 52.4% and 78.2%), a condition that sometimes occurs when dense concentrations of fungal hyphae appear in the onycholytic areas. Considered refractory to oral and topical antifungals, they are always excluded in pivotal clinical trials. At the end of the 52 weeks study period, 4 of these 7 patients were KOH negative, all 7 patients were culture negative (hence 4 had a mycological cure), and 2 of these 7 patients (28.5%) had reduced disease involvement >60%, indicating they were on the road to complete resolution.

During the duration of the study, a total of 1605 toes were treated with HSG (mean affected nails 4.4). Pain was only reported 10 times (0.6%), burning sensation or stinging 4 times (0.2%). No redness, bruising, swelling nor bleeding were reported. Of all adverse experiences reported, only 7 were deemed treatment related. A dose to the target great toe was completed in 60 seconds. Because of the relatively high concentration of terbinafine used locally and in a weaker area of blood perfusion, plasma levels of terbinafine have been monitored in 15 of these patients. The mean peak level of terbinafine was 0.129 ng/ml (i.e. 7,700 times lower than the peak concentrations reported with oral terbinafine).

Several oral and topical drugs have been developed and approved over the past decennia, and overall, oral antifungal medications yielded better outcomes than topical antifungal medications. Traditionally, oral terbinafine and itraconazole have been used for onychomycosis with great therapeutic success but also have concerns of drug interactions and potential liver toxicity. Hence, a renewed interest in topical antifungal drugs emerged for the treatment of fungal toenail infections, resulting in topical terbinafine along with various other topical products, but results have not been as robust as the oral antifungals due to patient compliance and barriers from the nail's pathophysiology.

This Phase 2 study with HSG indicates that monthly or bi-monthly professional application of subungual HSG could become a paradigm shift in the management of fungal infections of the toenails. This approach may help to address issues that have plagued the treatment of toenail onychomycosis for a long time.

Several advantages can be emphasized with this approach:

1. An ideal alternative for older patients who are not able to reach their lower extremities.
2. Monthly or bimonthly application may provide better adherence than daily "at home" applications.
3. Dermatophytomas can be treated with higher expectations of resolution while leaving the nail intact.
4. Podiatrists or dermatologists can visualize where the drug should be applied.
5. Multiple toes can be treated in one session.
6. No risk for significant systemic exposure to the drug.

Although some patients reached study completion with a positive KOH, the majority had negative fungal cultures. This indicates that HSG was fungicidal to dermatophytes, and that it requires a full outgrowth of the nail in 52-weeks before a KOH test would be negative. This may be challenging in older patients with a long history of infection and slower growing nails. A clinically meaningful endpoint for these patients is "Almost Cured" (90% clear nail with negative culture), especially in cases complicated by dermatophytoma.

Conclusion

The topical application of HSG by physician has the potential to simplify the future treatment of onychomycosis. In addition, the dermatophytoma results may show utility to manage a subset of onychomycosis that traditionally has not been formally addressed in a clinical trial.

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