Evaluating the Efficacy and Compatibility of Efinaconazole 10% Solution (Jublia) for the Treatment of Toenail Onychomycosis in Patients Wearing Toenail Polish Compared to Those without Polish

Study Protocol & Statistical Analysis Plan

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Research question

Topical efinaconazole 10% solution is known to be an efficacious and safe treatment modality for toenail onychomycosis. We propose to examine the compatibility of topical efinaconazole and nail polish in patients with distal and lateral subungual onychomycosis (DSLO). We posit that treatment of DLSO with efinaconazole 10% solution will not be adversely affected by the application of nail polish. We will have an interim compatibility analysis at 12 weeks and a final analysis at 52 weeks. We will also look at the efficacy of treating DLSO in patients wearing toe nail polish as compared to no polish when topical efinaconazole 10% (Jublia) solution is applied in the subungual space.

Background

DLSO is a commonly encountered dermatological disease. DLSO, which is caused by a variety of dermatophyte organisms, typically has an indolent and chronic course. Untreated, onychomycosis can pose a potential risk of spreading fungal infection to distant sites, which is especially true for elderly patients with comorbid diseases such as diabetes mellitus, peripheral vascular disease, or immunosuppresion. Traditional therapies for DLSO have been comprised of mainly oral antifungal medications; however many of these treatments have side effect profiles that limit their applicability in this elderly population. Because of the potential toxicities associated with traditional oral therapies for DLSO, there has been great interest in finding safe and efficacious alternatives.

Topical efinaconazole 10% solution (Jublia), which is a new FDA approved treatment for DLSO, has been shown to be efficacious and well tolerated by patients (Elewski, *et al*). In clinical trials, efinaconazole was applied daily to the nail plate, lateral and proximal nail folds, hyponychium and undersurface of the nail. Systemic absorption and associated toxicities are minimized with this topically applied medication. Complete cure and mycologic cure rates using efinaconazole 10% solution were within the range of those seen with oral antimycotic medications (Sporanox and Lamisil package inserts). Because efinaconazole 10% solution was applied in clinical trials directly onto clean, dry toenails that were free of toenail polish, it is not currently known if efficacy may be influenced by the wearing of toenail polish or if toenail polish is adversely modified by application of this medication. Toenail polish is very popular among women, especially during summer months, and wearing toenail polish is currently a major limitation of topical efinaconazole for treatment of DLSO. From our personal experience with efinaconazole solution, our patients have commented their nail polish becomes slightly tacky with daily application to the nail plate, but that application is still possible without discontinuing polish or treatment.

The dermatophytes causing DLSO primarily reside in the nail bed and subungual space, especially early in the disease process. Therefore we posit that application of efinaconazole solution to the nail bed and subungual space (subungual delivery) should be as efficacious as application to the nail plate. In fact, subungual delivery may prove to be more efficacious, as that space harbors the dermatophytes of DLSO.

Methods

We will enroll 20 female subjects who fulfill the inclusion and exclusion criteria for a 52 week study (48 weeks treatment, 4 weeks post treatment follow-up). Ten women who self identify as frequently wearing toenail polish will be placed into the study group, while the control group will be comprised of 10 women who agree to abstain from wearing toenail polish during the length of the study. To avoid having a significant gender difference between both groups, male patients will be excluded since they would likely be exclusively placed into the control group. Because nail size is proportional to body size, with men having larger nails on average, excluding men will prevent introduction of bias in this study. Patients with symptomatic tinea pedis at screening will be treated with Luzu for 2 weeks.

Treatment methods will be similar to those described by Elewski, *et al*. Briefly, all patients will self-apply 1 drop of efinaconazole 10% solution to the hyponychium and undersurface of the nail every night before bed. Patients in the study group will not be restricted with respect to the brand of nail polish, however gel and plastic based polishes that are used in salons and that require curing will be prohibited. Patients in the study group will also be permitted to touch up their polish if needed in the morning without constraint.

Patients will be seen in clinic for this study at screening and then again at baseline. After baseline, patients will be clinically evaluated every month for the first 3 months, followed by 8-week intervals, with the final visit at week 52. Our primary outcome, compatibility of topical efinaconazole solution with wearing polish, will be assessed at every visit.

An interim analysis of our primary outcome will be performed at 3 months and these results will be presented in poster and oral format as well as submitted in manuscript form for publication in a peer reviewed journal. We hope to present these data as oral and poster presentations at the summer AAD, the Fall Clinical Dermatology Conference or other similar national meeting. We will also submit a manuscript regarding the compatibility of treatment with nail polish for publication in an appropriate dermatology journal for US audiences. At the conclusion of this study we will present our findings in poster and oral format, as well as submit a manuscript for publication in the Journal of The American Academy of Dermatology.

Subjective effect of the medication on polish will be assessed with the following series of questions to which patients can answer yes or no:

- Were you able to apply the medication under your nail?
- Are you overall satisfied with Jublia?
- Is your polish tacky in the morning?

Patients will also answer the following question, which will be answered using a Likert or VAS scale where 0 represents no alteration in polish and 10 represents complete destruction of the polish:

- Is the quality of your polish diminished with use of Julia?

We anticipate that some patients may note diminished quality of polish with use of Jublia on a daily bases, however we anticipate that this effect will be minimal.

Secondary outcomes will include efficacy and safety. Using 3rd party blinding, DLSO will be assessed at baseline and at every subsequent visit using the onychomycosis severity index, measuring percent of the target nail involved, and grading the infection from mild to moderate to severe. The target nail will be notched at baseline, thereby allowing overall nail growth to be assessed at each visit and disease free nail growth to be measured every 8 weeks. Photos of the nails will be taken every 8 weeks, including close up photos of the target nail with and without an outline of the onychomycosis. Fungal testing will be done at screening, 3 months, 7 months, end of treatment (48 weeks), and end of study (52 weeks). Clinical and mycologic cure will be evaluated at week 52. Mycology cultures will be processed at the fungal lab of the University of Texas, with whom the UAB Dermatology Research unit has a contract. The following will comprise our inclusion and exclusion criteria:

Inclusion:

- Female age 18-75,
- Clinical diagnosis of DLSO affecting at least 1 great toenail diagnosed with positive potassium hydroxide microscopy. A culture for a dermatophyte will be collected but positive culture is not necessary for inclusion in the study. Cultures for patients with a previous positive culture can be waived at the discretion of the investigator.
- Suitable for application of topical antifungal therapy, in the opinion of the investigator
- Target toenail thickness of 3mm or less as measured by digital caliper, as thickness greater than 3mm may allow inclusion of patients with severe onychomycosis, and this was the criteria used in the pivotal trial using topical efinaconazole for onychomycosis (Elewski BE, *et al.*)
- Women of childbearing potential will be required to use birth control and a negative urine pregnancy test must be documented prior to initiating treatment

Exclusion

- History of immunosuppresion or concurrent use of immunosuppressant drugs
- History of uncontrolled diabetes mellitus
- History of psoriasis or any other condition that might interfere with the toenail evaluation
- Three or more dermatophytomas (streaks) on the target nail
- Severe DLSO of the target nail
- Patients who cannot refrain from wearing gel or plastic based polishes that are used in salons and that require curing

Conclusion

Treatment options for DLSO has until recently been comprised primarily of oral medications that were associated with significant possible toxicities. New research has revealed topical efinaconazole 10% solution (Jublia) to be a promising alternative treatment for DLSO, however it is unknown if this treatment is both compatible and efficacious in persons wearing toenail polish.Our proposal aims to examine the compatibility and efficacy of wearing polish while using efinaconazole 10% solution for DLSO.

Citations

Elewski BE, *et al.* Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol. 2013 Apr;68(4):600-8.

Sporanox (itraconazole) [package insert].Titusville, NJ: Janssen Pharmaceuticals Inc; 2012.

Lamisil (terbenafine HCl) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2012.

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Statistical analysis consisted of 2-tailed T-tests to study associations between continuous variables. P-values less than 0.05 were considered statistically significant.