

Perspective

The Treatment of Dermatophyte Onychomycosis and the Three Wise Monkeys

Nardo Zaias* and Gerbert Rebel

Division Dermatology, Mount Saina Medical Center, USA

After attending a symposium on onychomycosis at the latest academy (2013) meeting in my hometown, I decided that as an active veteran and experienced senior, I had the responsibility to speak out. I have the proper credentials on this subject, since in 1959, I was privileged as a second year resident, to be in the team that introduced, Griseofulvin, the first systemic antimycotic [1] and have been an investigator clinically testing antimycotics since. The subject of onychomycosis and its treatment became an interest of pharmaceutical companies who have promoted the clinical research in a marketing strategy, naturally favorably for them. In order to do this, they needed the help of the "Three Wise Monkeys". I must admit I was one of them, until I decided to study instead of just talking. Terbinafine was approved as a 250 mgs capsule, to be taken daily for 3 months, for the treatment of dermatophyte onychomycosis. Innumerable studies followed, showing that the over all cure-rate was not better than 50-60%. An analysis (not a meta-analysis as many like to write about) of the data, quickly showed that the greater percent of failures were in the studies who used subjects with 100% involved nail bed in toes. The Microbiologists assured us that Terbinafine was a "Cidal rather than a Static" drug. I am sure that this may be the case in-vitro.

Most of the younger physicians believe, that terbinafine taken for a 3 month period would kill all the fungus in the entire nail bed of toes and fingers. The marketing strategies of the companies are so sophisticated that the "3 wise monkeys", involved, in the lime light, of the moment, would agree to gather and have a social hour, they call a "Conference" or a "Consensus group" being easier to vote than to study. The subject of onychomycosis has been a windfall to pharmaceutical companies who make systemic, as well as topical antimycotics. None are blind, yet behave as they have not seen a peer reviewed article written in 2004, (1) regarding the treatment of onychomycosis, that resulted in the best cure rates (95%) than any other articles written in the history of onychomycosis. None are mute, since they lecture at national meeting and again say nothing that reflects science. I do believe all are deaf, since they don't respond to their responsibilities as teachers and leaders in dermatology.

Dermatophyte toenail onychomycosis is not a self healing disease

One does not need to do a double blind study, nor mycological

*Corresponding author

Nardo Zaias, Division Dermatology, Mount Saina Medical Center, 4308 Alton rd Suite 750, Miami beach, FL 33141, USA, Email: nardozaia@aol.com

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studies to show the efficacy of an antimycotic drug, topical or systemic (Figure 1), [2]. One only needs to have bonafide cases of proven dermatophyte DSO onychomycosis. There are crucial facts that should be known when launching a new antimycotic drug: 1-The duration of the beneficial "depot" effect the drug (if any) has in preventing the proximal growth of the fungus in the nail bed corneocytes, after a single treatment unit (daily or pulse). For example, when Griseofulvin first came out on 1959, we trialed pulse doses, but only the once daily was effective.

2-How many millimeters of nail bed are infected, (Counting from the Hyponychium proximally). It stands to reason that, if you have a 10 millimeters or greater infected NB, as one sees in 100% infected toe nails, and one takes an effective systemic or topical antimycotic (that does not have a prolonged beneficial depot effect), for a fixed period of 3 months, then, one will clear the 3 months of therapy plus the length of the beneficial depot clinical antimycotic effect. Analyzing, the previous studies with terbinafine, one can deduct that there is a period of clinical antifungal activity. The companies have not attempted to find out how long is this period. I think they were seduced by the CIDAL concept and the lack of understanding on how the disease progresses. Drug companies don't usually do these informative studies, but in the case of systemic terbinafine there is data.

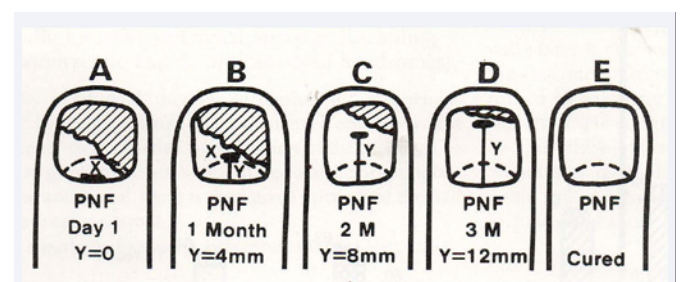


Figure 1 Diagrammatic scheme of what should happen if the drug tested is clinically effective at that dosing schedule. The drug is deposited at the junction of the infected nail bed and if effective will not allow the invading organism continue its movement proximally. This will show as a normal nail bed. In toenails the growth is one mm per month and in finger nails one mm per week. The increase in mms of normal nail bed denotes an effective drug. Any decrease of this progression means the drug is no longer effective. (cortesy Zaias and Drachman).

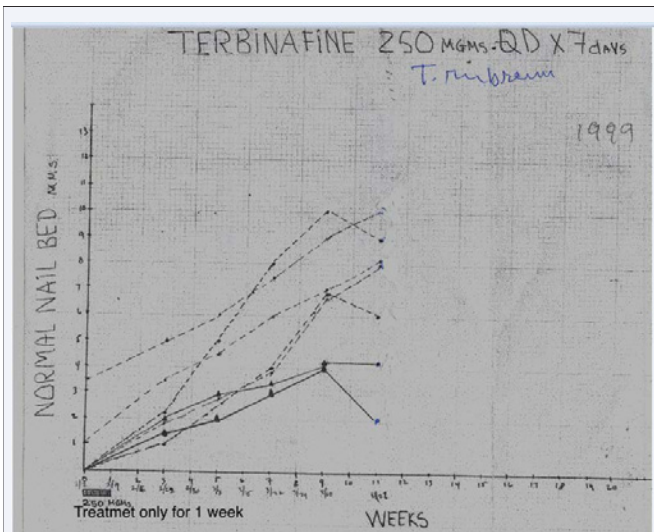


Figure 2 Graph showing the increase in normal nail bed measured in mms and expressed in time. Note that a seven consecutive daily 250 mgs terbinafine (Lamisil) had a beneficial antimycotic effect for approximately 10-12 weeks in 6 volunteers.

(Figure 2), shows the clinical outcome after 7 days of consecutive treatment with oral 250 mgs of Terbinafine HCl (Lamisil). In toes with 100% NB involvement, weekly follow-ups showed new non-infected NB for a period of 10-12 weeks after the single one week pulse. This is my own data, done in 1999. Based on this pilot study we embarked in a more expanded one. With 20 patients, who had their nail bed 100% involved received one week of treatment every month. After approximately one year all patients were cured. This was followed by another set of patients, who

also had 100% of their NB involved and who also received one week of treatment every two months.

All patients were cured again in one year. Another set of patients received the same treatment regimen, one week every 3 months, and 95% of them cured after a year. Fatigued but encouraged, the last set of patients received one week of treatment every 4 months, about 50% were cured. Meaning that the beneficial depot antimycotic effect lasts at least for 3 months. This was published in the Archives of Dermatology, 2004; 140: 1-5. This explains what I mentioned above. If you have a patient with toe onychomycosis, and the hallux measures 12 mms, you treat for 3 months and this clear 3mms, and then the depot effect cures an additional 3 mms, only clearing 6 mms, according to protocol, you still fail. The protocol we used treating for one week every 3 months until cured was 95% effective (some subjects were lost to follow-up) and devoid of side effects. Another way to look at this to better understand what happened, with the conventional protocol the patient took 90 -92 pills. While the other way the patient only took 28 pills. The three wise monkeys are at it again with topical treatments. The cure rates are hilariously low and yet the three wise monkeys keep on meeting and writing on their merits and in combination with systemic therapy. I don't blame the drug companies for doing their job very well, I hope that in time, the wise monkeys will see, hear and talk again.

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