

Assessment of Dermatophytosis Treatment Studies: Interpreting the Data

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ABSTRACT

Antifungal therapy has recently enjoyed a resurgence of interest due to the introduction of a number of new formulations of topical drugs and novel molecules. This has led to a plethora of new publications on management of cutaneous fungal disease. This paper summarizes the various clinical trial factors which may affect the published data regarding how well antifungal drugs work. Understanding these parameters allows the healthcare provider to choose more rationally between available agents based upon an assessment of the evidence.

J Drugs Dermatol. 2015;14(suppl 10):s48-s54.

INTRODUCTION

While difficult to quantify precisely, dermatophyte infections are both common and widely distributed worldwide.[1-7] Estimates based upon epidemiologic data from studies done in a variety of countries and continents suggest that some 20% to 25% of the world's population will be affected by superficial cutaneous fungal infections at least once during their lifetimes. Although fungal infections of the skin, hair, and nails can include those caused by candida species, the yeasts responsible for tinea versicolor, and nondermatophyte molds, the vast majority of such infections are due to dermatophytic organisms.[3,6] Thus, it is further estimated that 10% to 15% of the world's population will acquire at least one dermatophytosis.[6] In the United States, the most recent large scale investigation disclosed that, on average, over 4 million healthcare provider (HCP) visits directly related to cutaneous fungal infection occurred annually (range 3,583,590-6,754,460), the overwhelming majority due to dermatomycoses. This represented some 0.4% of all ambulatory healthcare visits during the time period under study.[5]

It is worth suggesting that this situation will not likely abate in the near future. Well accepted predisposing factors are not likely to decrease in either incidence or prevalence. Consider that onychomycosis is more prevalent among those with diabetes, peripheral vascular disease, and immunocompromise, and amongst the elderly.[8,9] In fact, the changing demographic characteristics of the population living in industrialized countries (mirrored in nations with emerging economies) includes: an increased number of elderly, an increased prevalence of obesity, diabetes, and peripheral vascular disease, a longer survival of those with endogenous immunocompromised conditions, and the commonplace administration of iatrogenic immunosuppression (including for solid organ transplantation). These factors may well lead to even more onychomycosis.[10] Since onychomycosis is frequently associated with tinea pedis, and fungal infections of the foot are often felt to be responsible for dermatophytoses of the groin and/or trunk,[11] it is clear that such fungal infections are not going to diminish in the coming decades.

Moreover, in addition to the foregoing, social mores may lead to expansion of dermatophytoses. For example, earlier and more frequent participation in sports activities and the "workout" craze among young adults could lead to more frequent micro-trauma to the nail unit and the pedal skin; and exposure to common public sports facilities (including showers and locker rooms) are also considered to predispose to onychomycosis.[12] Finally, virtually every factor enumerated above as having the potential to lead to a persistent epidemiologic onychomycosis problem has also, independently, been implicated in the development of tinea pedis, an equally important reservoir of pathogenic fungi.[13]

At present, there is little hope of eradicating dermatophytoses, as is the case with smallpox and nearly the case with polio. Faced with the inevitability of dermatophytosis, it is no wonder that the HCP remains in search of simple, safe, convenient, and reliable therapies. That search has been further complicated by the relatively recent development, approval, and marketing of newer antifungal agents. New formulations of pre-existing molecules (1% econazole nitrate foam and 2% naftifine hydrochloride cream and gel) and novel molecules (10% efinaconazole solution, 1% luliconazole cream, 2% sertaconazole nitrate cream, and 5% tavaborole solution) have recently appeared in the marketplace and re-awakened an interest in clinical mycology.

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and doing a quick comparison of cure rates? The unequivocal answer to this rhetorical question is a resounding "no." Why is this so? Official product information sheets enumerate the results of clinical trials. Such trials demonstrate, to the satisfaction of the Food and Drug Administration (FDA), that an agent is safe and "effective." However, there are marked differences between trials. Limitations inherent to published studies, including those submitted as pivotal trials, include most prominently differences in study design, data collection, and data analysis. Such differences make direct comparison of efficacy across clinical trials nearly impossible, and even preclude reliable systematic reviews and meta-analysis.

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The purpose of this article is to remind the HCP of the various parameters to consider when attempting to assess the data on any of the approved agents for dermatomycoses. While emphasizing recently approved agents, a critical approach to antifungal studies is widely applicable: to new agents as well as old, oral as well as topical, and across all types of dermatophyte infection.

When and Where Study Conducted

There is a rather remarkable disparity regarding which dermatophytes are predominant in differing geographic regions of the globe; and the exact etiologic organisms have indeed undergone dramatic and significant changes during the twentieth century.[3,7] Several well-known examples of this phenomenon include the replacement of *Microsporum audouinii* by *Trichophyton tonsurans* as the leading cause of tinea capitis in the United States, as well as the replacement of *Epidermophyton floccosum* by *T. rubrum* as the leading cause of tinea cruris.

Thus, it is important to consider when and where antifungal studies were performed in order to assess the data. Studies done many years ago may not reflect currently dominant etiologic fungi and, even if comparative in nature, will not include the newer agents enumerated previously. Moreover, as the location of antifungal studies will determine which species are predominant, the results may or may not be relevant to a given clinician. For example, the results of a clinical trial involving tinea capitis done in Iran, Libya, Palestine, Spain, or Sweden would be nearly irrelevant for an American HCP because *Trichosporum violaceum* is quite common in those nations but vanishingly rare in the U.S.[7,14]

Finally, one other point is intuitively obvious. The location of a study may greatly influence the ethnicity of the participants. It may not be possible for an American practitioner, serving a community of Caucasian, Afro-American, Asian, and Hispanic individuals, to extrapolate antifungal treatment decisions based upon the results of a clinical trial done in Iceland, a land of remarkable homogeneity (Norse and Celtic ancestry). There is certainly medical evidence that some drugs have significantly different pharmacokinetic and pharmacodynamic properties in varying racial and ethnic groups.[15] To the extremely limited extent that such knowledge exists relating to antifungal agents, a HCP must consider trial subjects' race and ethnicity when assessing clinical trial data and its relevance to his/her own practice.

Study Design

There are a few critical parameters related to how a study was actually conducted which may impact reported data. These include whether the study was open label or double-blinded, prospective or retrospective, single-center or multi-center, and compared with placebo or another established active agent.

Many initial proof-of-concept and some subsequent trials are open label, especially in Phase 2 investigations. It was admirably demonstrated that, at least for onychomycosis, the efficacy rates of open label studies are substantially higher compared with randomized controlled trials, and may therefore overestimate actual cure rates.[16] This is likely due to bias engendered when both subjects and investigators "believe" that the study agent is effective (or an open label study would not be performed in the first place). A single center study is more likely to have bias (either favorable or unfavorable) than when multiple, geographically diverse centers are involved.

Finally, it has been clearly and repeatedly demonstrated that all approved antifungal drugs are superior to a placebo (including vehicle) control.[17] While this is the traditional standard for conducting antifungal studies, and is still an acceptable manner in which to obtain FDA approval, going forward most impactful antifungal studies should be done as a direct comparison between 2 active agents. In the absence of well-performed and adequately powered head-to-head treatment investigation, the real difference in efficacy between 2 agents designed to treat the same dermatomycosis may not be assessable.[17] Even when head-to-head studies ostensibly compare the same drugs for the same disease, there may be quite different results.[18-20] Such differences may relate to study design features, inherent study flaws, and the manner of efficacy data collection and reporting (discussed below).

Inclusion and Exclusion Criteria

A critical appraisal of antifungal trial data would certainly start with ascertaining who was (and who was not) allowed to enroll,

assuming an unequivocal pre-study demonstration of fungal disease (preferably with speciation to allow post-hoc efficacy data analysis). The first question should be: exactly *what disease* was being treated? Most studies of tinea pedis address only the interdigital form, and FDA approval is based upon this single morphologic type.[21-23] Nonetheless, there are other forms of tinea pedis (moccasin-type and vesiculobullous) for which FDA approval is lacking, even though some degree of efficacy was suggested during clinical trials with naftifine.[24,25] Similarly, clinical trials for oncyhomycosis are conducted on the distal and lateral subungual form of disease (DLSO).[26-32] As is true of tinea pedis, there are other types of onychomycosis aside from the most common: proximal subungual, white superficial, total dystrophic, endonyx, and mixed.[33] However, since the clinical trials address only DLSO, and FDA approval only includes DLSO, there is no way for the HCP to know how likely it is that either any of the older or newer agents will be efficacious for these less common presentations.

Another inclusion criteria of major interest, especially with reference to onychomycosis trials, is the subjects' allowable (and actual) age. Since nails grow more slowly with age, less efficacy might be perceived if a trial enrolled a substantial number of older patients compared with similar studies. As it turns out, although the tavaborole study had the oldest enrollee in any onychomycosis trial (aged 88 years),[27] virtually all the onychomycosis studies to date have had a mean age of study participants within a narrow range (43-53),[26-32] essentially negating this potentially confounding factor.

Another potential problem in the inclusion criteria in onychomycosis is the extent of involvement of the target nail(s). Interestingly, the trials involving oral agents have routinely had a higher percentage involvement (50%-75%) compared with the trials of topical antifungal agents (35%-40%). Since "complete cure" rates are reportedly higher for the oral drugs, apparently this difference in percentage of nail plate involvement does not place the oral antifungals at a major disadvantage.

Aside from inclusion criteria, reported antifungal efficacy may need to be interpreted in terms of exclusion criteria. For example, in onychomycosis studies, the HCP should take note if significant concomitant tinea pedis was sought and, if found, served as an exclusion. It is intuitive that a topical therapy (more so than a systemic one) may not work as well in treating onychomycosis if there is concurrent tinea pedis present to serve as a source of reinfection. Conversely, a pragmatic consideration might be to treat the tinea pedis concurrently with the onychomycosis in the hopes of securing a more beneficial outcome.[34]

Antifungal Studied

It goes without saying that certain studies would be of little value to select audiences. For instance, the American clinician cannot readily use data to facilitate therapeutic choices, when the agents (or one of the agents) being studied is bifonazole, tioconazole, amorolfine, fenticonazole, or flutrimazole, as these drugs are neither FDA-approved nor available over-the-counter in the U.S.

Clinical Trial Methodology

There are many methodological factors that might alter reported efficacy outcomes in antifungal studies. In fact, a classic publication reviewing the general subject of clinical studies provides a quantitative scoring system to assess the quality of randomized controlled trials.[35] It is considerably beyond the intent and scope of this article to apply this scoring system to the vast universe of antifungal studies. Moreover, this has already been done previously, in part, for both onychomycosis and other dermatophytosis clinical trials.[17,36] Suffice it to say that clinical studies involving more recently approved antifungal preparations are, according to the Jadad scale criteria,[35] acceptable, being of medium to high overall quality.[21-28,37,38] Despite the latter, there is at least one methodological feature which may confound the HCP ability to assess efficacy data, and that feature is study duration.

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Consider that during onychomycosis treatment, visible clearance occurs as a healthy nail plate replaces a diseased one. This process requires about 12 to 18 months for a toenail.[36] All American trials involving recently approved topical treatments for toenail onychomycosis were conducted over 48 to 52 weeks.[26-28] By not taking into account the fact that it may well take over 70 weeks to grow out a toenail fully, the roughly 1 year of study may introduce uncertainty into the stated efficacy data. For example, if the drug has a reservoir effect, then the efficacy may actually be better than reported at 48 to 52 weeks because the agent continues to work as the healthy nail finally finishes growing out. Conversely, the drug's effect may be optimized by administration past 48 weeks to insure drug presence as the nail completes its full growth. In the latter case, efficacy results are actually overstated, since residual infection and/or relapse may occur in the time period between study's conclusion (48-52 weeks) and probable date of complete toenail regrowth (up to 72 weeks).

With other dermatomycoses, such as tinea pedis, tinea cruris, and tinea corporis, the longer the interval between cessation of trial drug administration and the final outcome assessment, the more meaningful the result; positive results demonstrated 14 or more days from the conclusion of therapy are considered sustained.[20] The most ambitious attempts to compare efficacy between various topical antifungal drugs, as well as between several classes of topical antifungals, found that: 1) There is no significant difference among classes of antifungal drugs in terms of short term efficacy, safety, and tolerability; and 2) The allylamine agents (and related benzylamine, butenafine) show a higher degree of sustained cure compared with classic imidazoles.[17,20] Of course, these analyses included neither newer formulations of older molecules (such as 2% nafitifine and 1% econazole nitrate foam) nor, and most importantly, new molecules (such as luliconazole); thus, while well done and comprehensive, such systematic reviews are already somewhat outmoded.

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The trend in recent years has been toward shorter treatment durations for non-onychomycosis dermatophytoses. For example, whereas 4 weeks of topical treatment were once considered necessary to achieve clinically meaningful benefits in tinea pedis, newer agents (1% luliconazole and 2% naftifine) prove satisfactory after only 2 weeks of therapy.[21,24,25] Luliconazole cream has even been successfully administered once daily for only 1 week for the treatment of tinea cruris.[37]

Mycological Considerations

Participation as a study patient for all clinical trials involving dermatophytes requires clear proof of pre-treatment fungal infection. This generally requires both a positive potassium hydroxide (KOH) preparation and a positive culture. The latter also delineates which species are being treated. There is little controversy in this aspect of antifungal trials. However, the author foresees a day in the not too distant future where molecular diagnosis will be become the gold standard (eg, real time polymerase chain reaction).[40,41] This may facilitate study recruitment and re-define efficacy results due to the greater sensitivity for dermatophyte detection.

At the conclusion of the study, it is standard to report, either as a primary or secondary end point, mycological cure rates. As pointed out by Gupta and co-workers, this may also be called mycologic success, mycologic response, mycologic efficacy, or even "fungus free" or "eradication."[42] This efficacy parameter typically implies both negative KOH preparation and negative fungal culture. This definition is fairly straightforward in both tinea and onychomycosis trials. Rarely, mycological cure may be defined as negative culture or negative microscopy *alone*, a less stringent standard.[43,44]

It should also be noted clearly that mycologic cure is *not* synonymous with visually determined clinical cure. From the perspective of the patient, a normal appearing nail and lack of pain (if present pre-treatment) are the measures of successful onychomycosis treatment. Similarly, from the patient perspective, normal appearing skin (loss of erythema and scaling) and elimination of bothersome itching are the measures of successful therapy for tinea pedis, tinea cruris, and tinea corporis. From the HCP perspective, however, mycologic cure ensures that once-infected skin or nail has been successfully treated.[42] Thus, it may be advisable to counsel the patient that "successful" therapy, especially of chronic fungal infections such as onychomycosis and tinea pedis, may not result in completely normal appearing nail or skin.

There is a final, perhaps theoretical, issue worth mentioning. In order to achieve mycological cure, both KOH and culture must be negative. How many trial patients fail to achieve this goal because post-treatment specimens fail to grow (negative culture) but still possess demonstrable hyphae microscopically? While this is somewhat speculative, this author suspects that the hyphae which are visible at the end of an antifungal trial may not be viable. In other words, is it possible that the fungal structure is still there, but that the fungus can no longer propagate or cause structural damage? This would lead to lower than real mycologic and complete clinical cure rates. This possibility needs to be addressed in a coherent manner.

Clinical Efficacy Considerations

It is in this realm where assessment of trial results becomes very difficult. There is simply no standardization across antifungal trials as to what parameters are measured, nor as to the terminology used to describe what was, in fact, measured. Unless nomenclature is defined in an unequivocal manner, interpretation of trial results becomes quite precarious.

Complete cure typically means mycological cure (negative KOH and culture) and total absence of signs (onycholysis, subungual debris, discoloration). While this is the most uniform of all criteria, this may be difficult to achieve, as noted in the previous section of this paper. Thus, it is not surprising that investigators have creatively employed a dazzling and bewildering variety of terms or narrative phrases to express the fact that the patient is "better" than before therapy, if not 100% normal. Historically, for onychomycosis, the most common clinical efficacy measurements have included the items listed in Table 1. This is by no means all-inclusive. Even a cursory glance at Table 1

reveals several important items. First, the exact same terms (such as "treatment success") may be defined differently. Secondly, some investigators relied heavily on visual inspection to determine benefit from drug administration. I would submit that the best assessment of onychomycosis response to treatment includes both clinical *and* mycologic parameters, regardless of what terminology is used. Finally, almost all the assessments of the percentage of affected nail infected (both before and after therapy) are based on a subjective, visual inspection. The agreement between objective planimetry and subjective estimation is actually quite good (within 10% in 92% of cases seen by experienced investigators).[47] Nonetheless, a better practice would be routine use of computerized measurement from a photograph or digital image; this would reduce the likelihood of error and promote more accurate efficacy assessments. A final confounding factor is that efficacy assessments measurements are typically performed on a single target nail, usually the great toenail. While there is usually good correlation between the response of the target nail and response of other nails, this is not always the case.

Assessment of data for tinea pedis, tinea cruris, and tinea corporis studies is somewhat more straightforward due to the uniformity of efficacy parameters. Both older and modern studies include complete cure (sometimes called complete clearance) as the primary endpoint. This consists of negative mycology (KOH and culture) and total absence of signs (erythema, scaling) or symptoms (pruritus). Mycologic cure is virtually always shown as a secondary endpoint.

Finally, essentially all studies calculate effective treatment (also known as treatment effectiveness), which consists of negative mycology and no to mild residual signs or symptoms.[21-25,37,38] Several studies allow up to mild erythema and scale, but require no residual pruritus.[21,23,37] The latter seems optimal, since itching is often the factor driving the patient to seek medical attention. With a quick glance at the data, the HCP will note that there is not much variation in rates for these 3 measurements between drug classes. One item to note is how long after the study was the final assessment made; in other words, is there evidence of sustained benefit?

FINAL CONSIDERATIONS

Despite the HCP's careful and individualized selection of treatment options, there will be failures and recurrences of dermatomycoses. Even when the infecting fungus ostensibly has been entirely eradicated by antifungal therapy, patients remain at risk for recrudescence. This phenomenon may be due to genetic predisposition, reinfection from within the household, reinfection from shared facilities, underlying co-morbid diseases (eg, diabetes), endogenous or iatrogenic immunocompromise, or, most rarely, mycological resistance.[48-51] Obviously,

TABLE 1.

Clinical Efficacy Measurements for Onychomycosis			
Terminology	**Definition**	**Synonyms**	**Representative References**
Complete cure	Normal nail Negative mycology	Treatment cure	26-28
Almost complete cure	< 5% residual abnormality Negative mycology		26
Almost complete cure	< 10% residual abnormality Negative mycology	Treatment success	27, 28
Overall success	Clear or Markedly Improved Negative mycology	Overall response	30-32
Almost completely clear nail	< 10% residual abnormality	Treatment success	26, 27, 29
Almost completely clear nail	< 5% residual abnormality		28
Clinical success	Clear or markedly improved (no specified % residual)	Clinical response	30-32
Numerical percent reduction in affected nail	Photography with computerized planimetry		28
Numerical percent reduction in affected nail	Visual assessment		44
Descriptive degree of improvement	Cured, markedly improved, improved, same, worse		45
Number of mm of normal nail outgrowth	Measured from posterior nail fold; 4 mm or 5 mm considered response		19, 26, 46

patients must be warned about the tenacious nature of some dermatomycoses.

DISCLOSURES

Theodore Rosen MD has received honoraria from the following pharmaceutical companies with respect to participation in advisory board meetings: Anacor, Galderma, Merz, and Valeant.

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