How Often Does Oral Treatment of Toenail Onychomycosis Produce a Disease-Free Nail?

An Analysis of Published Data

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Objective: To analyze studies on oral treatment of toenail onychomycosis so as to aid clinicians and patients in making informed decisions.

Data Sources: Studies dealing with treatment of toenail onychomycosis were identified by means of 2 MEDLINE search strategies. One was a title search using the word “toenail”; the other search used the combined Medical Subject Headings “onychomycosis” and “therapy.”

Study Selection: Articles were read to ascertain that they (1) described results in toenails, (2) used both culture and microscopy, and (3) included a clinical evaluation. Not included were case reports, series of fewer than 15 subjects, reports that combined fingernail onychomycosis and toenail onychomycosis in their statistics, and articles reporting only the total number of toenails cured without providing data as to how many subjects were cured.

Data Extraction: This elimination process left 26 articles, which were then analyzed by means of a checklist that included a morphologically normal nail, mycological findings, and methodological items including recurrence rate, intent-to-treat analysis, placebo group, and whether terms were defined.

Data Synthesis: When there was sufficient data, the frequency with which the treatment achieved normal mycological results, a clinically normal nail, and a disease-free nail (normal-appearing nail plus normal mycological results) was calculated. Confidence intervals were calculated for disease-free nail results.

Conclusions: Standard courses of terbinafine achieved a disease-free nail in approximately 35% to 50% of patients. For itraconazole, the relevant disease-free nail rate was about 25% to 40%. Disease reappearance is an important issue; unfortunately data are lacking as to its frequency.

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TREATMENT OF toenail onychomycosis has been a vexing problem. Topical preparations are generally ineffective, and griseofulvin has had a dismal record in treating toenail onychomycosis.1 The introduction of the antifungal agents fluconazole, itraconazole, and terbinafine led to an avalanche of reports with “cure” rates for toenail onychomycosis ranging from about 35%2 to more than 80%.3,4

This article analyzes studies on the efficacy of itraconazole, terbinafine, and fluconazole in the treatment of toenail onychomycosis. Studies dealing with treatment of toenail onychomycosis were identified by means of 2 MEDLINE search strategies. One was a title search using the word “toenail”; the other search used the combined Medical Subject Headings “onychomycosis” and “therapy.” Articles were read to ascertain that they (1) described results in toenails, (2) used both culture and microscopy, and (3) included a clinical evaluation. Not included were case reports, series of fewer than 15 subjects, reports that combined both fingernail onychomycosis and toenail onychomycosis in their statistics, and articles reporting only the total number of toenails cured without providing data as to how many subjects were cured.

Emphasis was placed on the ability of treatment to produce a disease-free nail (DFN), defined as a clinically normal nail with negative results of potassium hydroxide (KOH) microscopy and culture. Total cure has been used to denote a nail free of disease on both gross and mycological examination; however “cure” has been interpreted in so many ways that this article will use DFN.

I also sought to determine how long the DFN remained disease free. There is concern—but very few data—as to how often, and when, a successful result turns into a failure. Depending on the investigator, such failures have been labeled relapse, recurrence, or reinfection. However, for both patient and physician, the important aspect is the reappearance of nail dystrophy,
irrespective of its mechanism. Disease reappearance describes the failure to maintain the disease-free state without implying the mechanism responsible.

**INDUCTION OF A DFN**

Only 7 of 26 studies identified by MEDLINE search provided results in terms of the DFN. While 14 studies used a normal-appearing nail as an end point and all provided mycological results, morphological results and mycological findings were combined in only 7 studies. The other 7 studies, while providing data as to the percentage of patients who achieved a normal nail and the percentage who achieved negative mycological results, did not combine these to provide DFN data.

The DFN results for treatment with itraconazole and terbinafine are shown in the Table. Seven reports covered 11 trials, 3 with itraconazole and 8 with terbinafine. There have been a number of reports on fluconazole treatment of toenail onychomycosis. Unfortunately, none satisfied the inclusion criteria.

For itraconazole, 3 months of treatment produced a DFN in about 35% irrespective of whether the treatment was given continuously, at 200 mg/d, or as a 1-week pulse each month of 400 mg/d. Although there are only 3 studies with itraconazole that reported DFN rates, and 1 of these involved only 20 patients, the multicenter study by Elewski et al provides additional evidence that the DFN rate with itraconazole is not significantly above 35%. In that study of 110 patients, itraconazole, 200 mg/d for 12 weeks, achieved an “overall success” of 35%. Overall success referred to mycologically negative patients whose nails had “cleared or markedly improved.” Consequently, fewer than 35% would have achieved a DFN.

Terbinafine achieved DFN status in about 40% to 50% of subjects, except for the 76% DFN rate achieved by Tosti et al in 17 subjects. While the usually recommended schedule for terbinafine treatment of toenails is 250 mg for 12 weeks, in 5 of the 8 trials terbinafine was prescribed for 16 weeks or longer.

The study by Brautigam et al supports DFN ranges of 40% to 50% with terbinafine and 30% to 40% with itraconazole. They found a morphologically normal nail in 49% of 86 terbinafine-treated subjects and 36% in 86 of those treated with itraconazole.

**FREQUENCY OF DISEASE REAPPEARANCE**

Only 1 study provided adequate results to assess the frequency of disease reappearance. Heikkila and Stubb examined itraconazole-treated patients 1 year and 2 years after treatment was initiated. Of 31 patients who achieved a normal-appearing nail at 1 year, 5 showed recurrent nail dystrophy at the 2-year evaluation, for a reappearance rate of 17%. This applied only to the appearance of the nail; there was a much greater mycological failure rate. At 1 year, cultures were negative in 95% for organisms, but at the 2-year evaluation only 55% of cultures were negative. A startling 42% of subjects showed mycological failure during a 1-year period.

**COMMENT**

Whereas both patient and physician desire a normal-appearing nail, physicians also aim for a nail free of fungal disease, ie, negative results of direct microscopy and negative fungal culture. The assumption behind this goal of negative mycology is that failure to clear the fungal infection will sooner or later result in a dystrophic nail. On the assumptions that the purpose of treatment is to satisfy the patient and the patient’s goal is a normal-appearing nail, a normal-appearing nail would be a logical clinical end point. Unfortunately, only a minority of studies used a normal-appearing nail as an end point. The appearance of the nail was usually described as a “clinical” result. While one might assume that “clinical cure” refers to a normal nail, it is not necessarily so. One study stated, “clinical cure was defined as patients who were cured without or with nail malformation.” “Clinical success” was a popular end point and was defined as “patients with a 90-100% clear nail” or “cleared or mark-

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**Induction of Disease-Free Nails by Oral Treatment of Toenail Onychomycosis**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Medication</th>
<th>Dose, mg/d, and Duration of Treatment</th>
<th>Disease-Free 1 y After Start of Treatment, No. (%)</th>
<th>95% Confidence Interval, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baudraz-Rosselet et al</td>
<td>130</td>
<td>Terbinafine</td>
<td>250, up to 24 wk</td>
<td>60 (46)</td>
<td>38-55</td>
</tr>
<tr>
<td>De Backer et al</td>
<td>186</td>
<td>Terbinafine</td>
<td>250, 12 wk</td>
<td>76 (41)</td>
<td>34-48</td>
</tr>
<tr>
<td>Faergemann et al</td>
<td>186</td>
<td>Terbinafine</td>
<td>250, 12 wk</td>
<td>62 (33)</td>
<td>27-39</td>
</tr>
<tr>
<td>Herranz et al</td>
<td>43</td>
<td>Terbinafine</td>
<td>250, 16 and 32 wk†</td>
<td>18 (42)</td>
<td>27-57</td>
</tr>
<tr>
<td>Heikkila and Stubb</td>
<td>88</td>
<td>Itraconazole</td>
<td>200, 12 wk, or three 1-wk pulses of 400†</td>
<td>31 (35)</td>
<td>25-45</td>
</tr>
<tr>
<td>Svejgaard et al</td>
<td>48</td>
<td>Terbinafine</td>
<td>250, 12 wk</td>
<td>11 (52)</td>
<td>31-74</td>
</tr>
<tr>
<td>Tosti et al</td>
<td>26</td>
<td>Terbinafine</td>
<td>250, 12 wk</td>
<td>11 (42)</td>
<td>23-61</td>
</tr>
<tr>
<td>Hetz et al</td>
<td>17</td>
<td>Terbinafine</td>
<td>500 for 1 wk</td>
<td>13 (76)</td>
<td>56-97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>each mo ×4</td>
<td></td>
<td>10 (50)</td>
<td>28-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>400 for 1 wk each mo ×4</td>
<td>7 (35)</td>
<td>14-56</td>
</tr>
</tbody>
</table>

* Nine patients failed to respond by 16 weeks; they were given an additional 16 weeks of treatment with terbinafine.
† Half received continuous therapy; half, pulse therapy. Only combined results were given.
edly improved. 7–9 Similar lumping together of normal appearing nails and those that have only improved was termed “effective treatment.” 28 A number of studies did not define their end points of “clinical remission,” “clinical success,” and “favorable clinical response.” Of the 26 studies analyzed, only 14 presented results in terms of achieving a normal-appearing nail.

At least 3 11–13 of the 7 DFN studies summarized in the Table based their clinical and mycological results on a single “target nail.” While such restriction simplifies the mycological and morphological assessments, it adds uncertainty to the clinical relevance of their data. Patients want all their toenails to appear normal, not just the target nail.

It seems reasonable to select a target nail for periodic mycological assessment. This should be the most severely affected nail, as was specified in 1 study. 31 However, if the target nail achieves normal morphological findings, and another nail remains abnormal, mycological sampling should include the dystrophic nail. While 3 of the 7 DFN studies explicitly describe the use of a target nail, it is uncertain whether target nails were used in the other 4 studies. Furthermore, these 4 studies did not describe the criteria for choosing the nail(s) for mycological sampling.

Most of the published studies I analyzed failed to provide accurate, clearly stated information regarding the efficacy of treatment schedules in achieving a DFN. Too often, the ability of a treatment to achieve a DFN was obscured by the data reported. A common problem was lumping together morphologically normal with improved nails into a single category of “successful outcome.” Such lumping made it impossible to determine the frequency of DFN. Data were often selectively reported, with only 8 of 26 reviewed studies reporting results in terms of a DFN.

Summaries often failed to accurately reflect the data in the body of the article. A common practice was to provide only “mycological cure” rates in the summary, with data regarding nail morphological findings being restricted to the body of the article. In most studies, the percentage of nails becoming mycologically negative significantly exceeded the percentage of nails achieving a normal appearance. Enthusiastic endorsements of therapy in the summary were sometimes contradicted in the body of the article. Elewski et al 8 in their summary stated that “12 weeks of continuous itraconazole, 200 mg once daily, is a highly effective, well tolerated therapy for the management of toenail onychomycosis.” However, in the body of the article, “overall success” (negative mycological findings plus “clinical success”) was 35%.

In contrast, Heikkila and Stubb 1 presented results directly. They calculated that, in their 88 patients, a single course of itraconazole would have produced, at 2 years, a DFN in only 27%. They concluded that the long-term treatment results of onychomycosis with itraconazole “are not very encouraging.” They also emphasized that total cure of all nails, rather than improvement, should be used as an end point.

There is the question of the significance of negative results of culture in the face of positive microscopic findings. When the results of culture are negative, but hyphae are still visible, are we dealing with dead remnants of fungi waiting to be shed? How often are false-negative cultures inflating the cure statistics? These issues have been ably summarized by Shuster. 28 Once achieved, how long is the DFN maintained? There is surprisingly little information on this crucial point. Gupta and Shear 37 in their recent update on terbinafine stated that patients examined at least 1 year after completing therapy had “a clinical relapse rate of approximately 15%.” Villars and Jones 38 in their 1992 review cited a relapse rate of 18%, 12 months after successful treatment with terbinafine. De Doncker et al 39 in their overview of itraconazole pulse therapy stated that the relapse rate “twelve months after starting therapy was 10.4%.” Unfortunately, these 3 relapse figures were reported without supporting data.

The data presented by Drake et al 6 do not support their conclusion that “approximately 11% of terbinafine responders showed evidence of relapse 18–21 months after cessation of treatment.” A relapse rate is meaningful only in terms of length of follow-up. It is not possible to determine their median time of follow-up; however, the maximum possible follow-up was 1 year, not 18 to 21 months. Drake et al 6 did not follow up all 358 terbinafine-treated patients, but only 167 who at 1 year had achieved negative mycological findings and at least 5 mm of normal nail growth. These 167 patients were then followed up for an additional year. Consequently, even with 100% follow-up, the follow-up period could not exceed 1 year. (For convenience, I have rounded off their intervals measured in weeks to intervals of months and years.)

What do Drake et al mean by the phrase “evidence of relapse,” used in their summary? Relapse is generally accepted to mean return of a disease after its apparent cessation. Their relapse rate, “estimated” to be approximately 11%, was apparently estimated solely on the basis of gross morphological characteristics of the nail, and not mycological findings. They stated, “In terms of clinical response . . . 11% exhibited evidence of relapse during the follow-up period.” Elsewhere, Drake et al stated, “of those patients with negative KOH and negative culture at the beginning of the extended observation, 95% and 88%, respectively, were still negative at their last evaluation.” A 12% culture failure rate and 5% KOH microscopy failure rate mean that the mycological failure rate was at least 12%, since positive results of culture and KOH examinations do not always overlap. Since negative mycological findings were part of their criteria for entry into the follow-up part of their study, it is puzzling that this criterion was not used in their definition of relapse. It is not possible to calculate the relapse rate, as it is generally defined, from the data presented by Drake et al).

A further problem with both the Drake et al 6 and the Elewski et al 8 studies is their end point criterion of a 90% to 100% normal nail. Suppose a nail, previously evaluated as 90% clear (a “successful outcome”), is evaluated as only 80% clear by a subsequent observer. By the above authors’ criteria, this subject has had a relapse. Yet, would not most of us consider this only as a worsening
of disease? Aside from this matter of definitions, there is the issue of the reproducibility of visual estimates of percentage of nail involvement.

Although itraconazole and terbinafine have been in clinical trials for more than 8 years, I was able to find only 1 study2 that provided data both 1 year and 2 years after treatment. I well remember the enthusiasm that greeted the introduction of griseofulvin; here we finally had a “cure” for dermatophytosis and onychomycosis. We painfully learned that the fungal infection almost always recurred. Considering the numerous published clinical trials of itraconazole and terbinafine, it is difficult to believe that no one has looked at the results 2, 3, or more years after completing a course of the new antifungal drugs. Is the lack of data an example of selective reporting?

Both itraconazole and terbinafine are expensive medications, costing the patient between $600 and $1000 for the medications alone. While generally well tolerated, both may cause significant side effects, and itraconazole interacts with a number of commonly used medications. To realistically advise our patients, we need to know not only how often the infection can be cleared, but how long the nails remain free of disease. If we are to practice evidence-based medicine, authors must clearly present all their evidence!

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REFERENCES