Topical and Oral Combination Therapy for Toenail Onychomycosis

An Updated Review

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Although effective, oral antifungal therapy is still not completely successful. Recent studies have shown that combination therapy with oral and topical agents offers an increased cure rate for patients. We review the main drug combinations that have been tested. Additional measures, such as mechanical intervention, may help improve response rates further. (J Am Podiatr Med Assoc 96(2): 116-119, 2006)

Recent large, population-based studies have illustrated the high prevalence of onychomycosis across Europe,[1] which has been shown to adversely affect patients' quality of life.[2, 3] Despite effective systemic antifungal drugs and transungual delivery systems, there is still an incompressible failure rate when treating onychomycosis.[4] Olafsson et al[5] showed that 23% of terbinafine-treated patients and 53% of itraconazole-treated patients experienced a relapse or reinfection after 5 years of treatment despite mycologic cure at 12 months.

Combination therapy is a well-established principle in mycology[6, 7] and can result in increased efficacy and rapidity of effects, a broader spectrum of activity, and better tolerability for the patient. These benefits can be the result of drug synergy, that is, the combination is more effective than the additive effects of each drug alone.[8]

The rationale for the combination of topical and oral therapy for onychomycosis is that the systemic antifungal agent reaches the infection area through the nail bed and the topical agent is absorbed through the nail surface by means of a transungual antifungal delivery system. Synergy between amorolfine and other antifungal drugs has been demonstrated *in vitro*.[7] Subsequent studies have focused on clinical trials to test the effectiveness of combination therapies, especially for onychomycosis with involvement of the nail matrix area.

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Combination Studies

Tioconazole and Griseofulvin

Hay et al[9] demonstrated the efficacy of tioconazole used topically in combination with oral griseofulvin. Ten patients receiving 1 g of oral griseofulvin daily for 1 year were treated topically with 28% tioconazole nail solution (29 nails) or placebo (31 nails). The results showed a clinical and mycologic remission rate of 69% in the combination group, compared with 41% in the oral griseofulvin group.

Ciclopirox and Itraconazole

Because ciclopirox nail lacquer is a relatively new formulation, its use in combination with oral antifungal agents has not been well documented. Nevertheless, encouraging results have been reported by Nolting[10] in an open study in which 117 patients with onychomycosis were treated with 8% ciclopirox nail lacquer combined with itraconazole for 3 months. At the end of the study, 41% of the patients were cured (negative mycologic findings with 100% clearance of the nail plate) and 47% had therapeutic success (negative mycologic findings with incomplete clearance

of the nail plate). Although randomized controlled comparative studies are necessary to confirm the effects of such a combination, studies by Gupta and Kohli[11] and Baran et al[12] have suggested that there are no antagonistic effects with the combined use of ciclopirox and systemic antifungal agents.

Amorolfine in Combination

Improvements in fungistatic activity have been demonstrated for amorolfine combined with either griseofulvin, terbinafine, itraconazole, or fluconazole against a variety of dermatophytes implicated in superficial infections. In clinical trials, amorolfine has been combined with several oral drugs used to treat nail infections, with the aim of improving the efficacy and cost-effectiveness of the single agents.

Amorolfine and Griseofulvin. Griseofulvin has been widely used in antifungal drug therapy for more than 40 years, but cure rates tend to be low, and adverse effects, such as headache and gastrointestinal upset, are common. Preliminary data from Lauharanta et al[13] indicate that the combination of topical amorolfine nail lacquer applied twice weekly for 6 months and griseofulvin, 1,000 mg/day, for the first 2 months of therapy has a clinical effect similar to that of 6 months of griseofulvin monotherapy and allows more rapid sterilization of the infectious foci. After 2 months of treatment, 42% of the patients in the combination group had negative cultures and microscopic findings, compared with 13% in the griseofulvin group. After 6 months, the figures were 67% and 45%, respectively. In addition, 90% of the patients who received combination treatment were clinically cured or improved, compared with 84% of those treated with griseofulvin alone.

Zaug[14] compared griseofulvin alone and combined with 5% amorolfine nail lacquer in an open, comparative, 15-month study of patients with severe onychomycosis (affecting the lunulae/matrices in most cases). One group of patients applied amorolfine nail lacquer twice weekly for 12 months, accompanied by twice-daily use of griseofulvin, 500 mg, for the first 2 months. The other group was given griseofulvin, 500 mg, twice daily for 2 months and once daily for the next 10 months. Three months after the end of treatment, clinical and mycologic assessments were performed on 59 and 57 patients in the combination and griseofulvin groups, respectively. Clinical cure rates were 45% in the combination group and 42% in the griseofulvin group. Mycologic cure rates were 63% in the combination group and 50% in the griseofulvin group. Safety profiles for the two treatment groups were similar, but adverse events were more frequent in the first 2 months, suggesting an association with the higher griseofulvin dose.

Amorolfine and Terbinafine. The efficacy of treatment with amorolfine combined with oral terbinafine was investigated in an open, multicenter study of 147 patients with toenail onychomycosis with involvement of the matrix area by Baran et al.[15] Subjects applying 5% amorolfine once weekly for 15 months were given 250 mg of terbinafine daily for either the first 6 or 12 weeks; patients taking terbinafine alone for 12 weeks served as controls. Subjects were followed for up to 18 months. At the last visit, mycologic cure was highest after 12-week combination therapy (89%) and lowest after terbinafine monotherapy (66%). Likewise, end-point global cure rates (clinical cure plus mycologic cure) were much higher for the 12-week combination group (72%) than for either the 6-week combination group (44%) or the terbinafine alone group (38%). Adverse effects were similar for all treatment groups (overall, 22% were assessed as drug related) and decreased after the first 6 weeks, indicating that they were probably caused by terbinafine. According to Szepietowski and Roiycka,[16] the assembled available data show that amorolfine nail lacquer combined with either oral terbinafine or itraconazole is always more efficacious than the systemic drug alone; faster and better curative effects can be obtained, especially in very severe nail infections.

In a multicenter study by Baran et al,[17, 18] 157 patients received amorolfine once weekly for 12 months and an oral antifungal agent (terbinafine, 50 mg/day, for 3 months; itraconazole, 400 mg/day, 1 week per month for 3 months; or fluconazole, 300 mg, once per week for 6 months). There was a 71.3% global cure rate, independent of the oral antifungal agent used.

Amorolfine and Itraconazole. Lecha et al,[19] in an open, randomized, multicenter study, recruited 131 patients to evaluate combined amorolfine and oral itraconazole therapy for the treatment of severe toenail onychomycosis. Patients applied 5% amorolfine lacquer once weekly for 6 months, accompanied by itraconazole, 200 mg/day, for the first 6 or 12 weeks; another group received itraconazole monotherapy for 12 weeks. By 6 months, 90% or more of the patients treated with either of the amorolfine and itraconazole combination regimens had negative mycologic findings, compared with less than 69% of those who received monotherapy ($P < .001$). The combined mycologic-clinical cure rate at 6 months for the amorolfine combined with 12-week itraconazole regimen was 94%, and that for 6-week combination therapy was 84%. Both cure rates were considerably higher than the 69% observed with itraconazole

therapy alone. No serious adverse events were reported during the trial, and the distribution and number of events were similar for the three treatment groups. In another study, Maleszka et al[20] assessed 3 months of itraconazole pulse therapy combined with 6 months of amorolfine administered once weekly in patients with extensive dermatophyte onychomycosis and in a group of patients with recurrent onychomycosis. Cure was achieved in 21 (78%) of 27 patients with extensive onychomycosis and in 12 (75%) of 16 patients with recurrent onychomycosis. A further study was conducted by Adaskevich and Evseenko[21] in 73 patients with onychomycosis of the fingers and toes. The patients were divided into two groups, with 32 patients receiving itraconazole according to a pulse regimen for 3 to 4 months and 41 patients receiving combined therapy of itraconazole and amorolfine lacquer. The combination treatment was highly effective and well tolerated, with all of the patients demonstrating clinical and mycologic recovery.

Amorolfine and Fluconazole. A small study was performed by Sergeev and Sergeev[22] to assess the combination of fluconazole, 150 mg, used once weekly and 5% amorolfine nail lacquer applied once weekly. Fluconazole, 150 mg, was used once weekly until the Scoring Clinical Index for Onychomycosis scores decreased to 3 to 6, and then 5% amorolfine lacquer was given once weekly. Complete clinical and mycologic cure was noted in 19 of 23 patients (83%). Another, smaller study by Sergeev and Sergeev[23] (n = 12) was used to test the effectiveness of a combination of fluconazole and amorolfine. In this study, nine patients (75%) achieved complete clinical cure, and all of the patients showed mycologic cure. This combination was preferred to a terbinafine and amorolfine combination and was found to be well tolerated, effective, and convenient because of its once-weekly application.

The data from these trials, therefore, suggest that combination therapy using the antifungal nail lacquer offers significant clinical benefits over monotherapy for the treatment of onychomycosis. All of the discussed studies assessed combination regimens in which drugs are prescribed in parallel from the start. A different approach has recently been suggested in which oral and topical agents are prescribed sequentially, the topical agent being prescribed immediately after oral treatment is stopped.[5]

Traditionally, nail presentations that are likely to respond less readily to monotherapy include those with lateral nail involvement and those with dermatophytoma, a subungual mass of debris that contains keratin and fungal elements.[24] Because these fungal masses are not in contact with surrounding nail keratin, it is difficult for traditional antifungal therapy to reach these areas. Dormant spores (arthrospores) may remain viable in these areas and out of the reach of therapeutic agents for many months.

In such cases, atraumatic nail removal has been suggested as an adjunct to drug therapy[25] in an attempt to expose fungal particles. Removal of the diseased nail has been demonstrated to improve success rates in treating onychomycosis in a variety of small-scale studies.[26-28] Removal of the diseased nail section is combined with oral and topical antifungal treatment (and has been termed *triple therapy*).[29] After exposure, application of antifungal nail lacquer is continued on the remaining normal-looking part of the nail keratin because some fungi may be left beneath its lateral margin and on the newly growing nail.

Suggested mechanisms of nail removal include clipping and curetting,[24] drilling/grinding,[25] and application of medicaments such as urea paste.[30] The value of total surgical removal before therapy is unclear; however, many researchers have suggested that this is not necessary in most cases[31] and that the procedure risks potential damage to the nail unit.[25]

The Effect of Mechanical Intervention

The effect of modifying foot mechanics in reducing recurrence and improving the outcome of therapy for toenail mycosis has not been formally tested, although it has been implied.[31-33] Physical trauma to the toenails resulting from faulty foot mechanics or interaction with poorly fitting footwear may precipitate treatment failure. Appropriate assessment and treatment of foot faults and correction of inappropriate footwear should help improve treatment outcomes further.

Long-term Therapy

Onychomycosis is frequently secondary to tinea pedis[34]; therefore, long-term intermittent traditional topical therapy should prevent the reestablishment of tinea pedis and limit the possibility of nail reinfection. In addition, the periodic use of amorolfine (eg, twice a month) seems to be a logical and safe method of preventing recurrences[35] because the drug remains in nail keratin (up to 14 days) after the weekly active therapy has been interrupted.

Conclusion

Although several topical agents can be prescribed as monotherapy for mild-to-moderate onychomycosis, amorolfine and ciclopirox nail lacquers are generally considered the most cosmetically convenient. Use of

these agents in combination with a systemic antifungal drug increases the number of patients cured of onychomycosis compared with oral therapy alone. Triple therapy using mechanical intervention should further improve these encouraging results. In addition, appreciable cost savings can result from using oral and topical agents together.

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