Combination therapy for onychomycosis

J.H. OLAFSSON, B. SIGURGEIRSSON* AND R. BARAN†
Department of Dermatology, Landspitali University Hospital, Tverholt 18, 105 Reykjavik, Iceland
*Hudlaeknastodin, Smaratorg 1, 200 Kopavogur, Iceland
†Nail Disease Centre, Le Grand Palais, 42 rue des Serbes, 06400 Cannes, France

Summary
Combination therapy is one way of improving the cure rate of onychomycosis. The LION Study examined the efficacies of terbinafine and itraconazole. The Icelandic cohort of the study reported that after 5 years only 46% of the terbinafine-treated patients and 13% of the itraconazole-treated patients were still disease-free, suggesting that relapses and reinfections were common in the long term treatment of onychomycosis with monotherapy. Combination therapy is a well-established principle in mycology; the current strategy involves the combination of oral and topical antifungal treatments. A number of specific drug combinations have proved to be useful in the treatment of onychomycosis: tioconazole and griseofulvin, amorolfine and griseofulvin, amorolfine and terbinafine, and amorolfine and itraconazole. However, comparison of the combination trials can be difficult because of the short duration of some of the studies and variation in global cure rates. Although it is necessary to consider these factors it is clear that combination therapy offers advantages when compared with monotherapy. Combination therapy can be administered sequentially or in parallel. Parallel therapy is recommended for patients who are likely to fail therapy (e.g. patients with diabetes), whereas sequential therapy is recommended for patients who show a poor response to initial treatment.

Key words: combination, onychomycosis, trials

Introduction
Combination therapy is one way of improving the speed of cure and the overall cure rate of onychomycosis, a common and persistent fungal infection of the nail unit. Although monotherapy has proven effective in the short term, a substantial proportion of patients does not experience a complete and lasting cure. Treatment strategies include topical and systemic antifungal therapies, and surgical and chemical nail avulsion. This paper summarizes the clinical studies investigating the efficacy of therapy combining oral and topical antifungal agents, and considers situations in which combination therapy may lead to better outcomes.

Efficacy of monotherapy
In the largest study of the treatment of toenail onychomycosis, the LION Study, the efficacies of terbinafine and itraconazole were compared in patients with mild to moderate onychomycosis. After 72 weeks of follow-up, 75–80% of terbinafine recipients and 38–49% of itraconazole recipients were classified as mycologically cured.1,2 The long-term efficacy and treatment failure rates for the Icelandic cohort within this multinational study were then followed for a further 5 years. At endpoint, only 46% of the terbinafine-treated patients and 13% of the itraconazole-treated patients were still disease-free, suggesting that relapses and re-infections were common in patients who received monotherapy.3 In fact, 23% of terbinafine-treated patients and 53% of the itraconazole-treated patients experienced a relapse or re-infection after 5 years of treatment despite being mycologically cured at 12 months.

The rationale for combination therapy
The use of combination strategies and the exploitation of antifungal drug synergy is a well-established principle in mycology. The combination of two or more drugs can result in increased efficacy and rapidity of effects, a broader spectrum of activity and better patient tolerability. These benefits can often be the result of drug synergy, that is, the combination is more effective than the additive effects of each drug alone.
The current strategy for combination therapy involves combining oral and topical antifungal agents. The different modes of drug administration allow for complementary drug penetration into areas of infected tissue where each drug alone does not accumulate in effective concentrations; oral drugs rapidly suffuse and accumulate in the nail bed, while topical therapies effectively penetrate the nail plate and may be effective in preventing reinfection of the nail itself. As detailed below, a number of reports have described the successful combination of topical nail lacquers and oral antifungals in the treatment of severe onychomycosis.

**Combination studies**

The benefits of combination therapy were first shown with griseofulvin, the standard therapy for onychomycosis due to dermatophytes for the last 30 years. More recently, combinations with amorolfine have been shown to have even greater efficacy than griseofulvin.

**Griseofulvin or itraconazole combination therapy**

An open, randomized trial compared griseofulvin and itraconazole for the treatment of onychomycosis of the foot. Patients received griseofulvin or itraconazole plus either placebo, 1% isoconazole (antimycotic cream) or 40% urea (keratolytic cream). The itraconazole groups showed better results compared with the griseofulvin group; when itraconazole was combined with isoconazole cream, keratolytic cream or placebo, the number of patients showing complete clearance was 73.3%, 78.5% and 91.6%, respectively. The griseofulvin group showed complete clearance in combination with isoconazole cream in 46.1% of patients, in combination with keratolytic cream in 26.6% of patients, and in combination with placebo cream in 26.6% of patients.

**Griseofulvin and tioconazole**

Tioconazole 28% solution was compared with placebo in patients receiving 1 g daily oral griseofulvin over a 1-year period. All the patients in the study had bilateral toenail *Trichophyton rubrum* infections. Seventy nails were treated in total; each patient received active treatment on the nails of one side and placebo on the other. In total, 69% of nails treated with griseofulvin and tioconazole achieved clinical and mycological remission, compared with 41% of nails receiving oral griseofulvin and placebo solution. The results of this study suggest that combination therapy of griseofulvin and 28% tioconazole topical therapy is more effective than oral treatment alone in managing onychomycosis.

**Amorolfine and griseofulvin**

The efficacy and tolerability of combination therapy with amorolfine and griseofulvin was compared with that of griseofulvin monotherapy in the treatment of onychomycosis with or without matrix involvement. A total of 233 patients were given either oral griseofulvin treatment for 2 months plus amorolfine nail lacquer for 12 months or the standard 12-month griseofulvin treatment. At 6 months, mycological cure had occurred in 67% of patients in the combination group and 45.3% of the griseofulvin group; positive cultures were obtained from 7.4% of patients receiving combined therapy and 34.7% of patients treated with griseofulvin alone. After 6 months of treatment, the number of toenails and fingernails cured in the combination group was approximately double that seen in the griseofulvin group.

**Amorolfine and terbinafine**

The efficacy of combined amorolfine and terbinafine therapy for severe dermatophyte toenail onychomycosis was investigated in an open study by Baran and colleagues. A total of 147 patients were randomized to three treatment arms: terbinafine was given orally for 6 (AT-6 group) or 12 (AT-12 group) weeks and amorolfine nail lacquer was applied weekly for 15 months. A control group received terbinafine alone for 12 weeks (T-12). The global cure rate was markedly better in the AT-12 combination group (72.3%) in comparison with the AT-6 combination group (44%) and the T-12 group (37.5%; Fig. 1). The majority of patients in all groups had visible clearing of the clinical signs of infection within 24 weeks. A typical example of the improvement in nail appearance during combination therapy of a patient in group AT-12 is illustrated in Fig. 2.

**Amorolfine and itraconazole**

Two alternative regimens of topical amorolfine and oral itraconazole therapy were compared with itraconazole
monotherapy in an open study of toenail onychomycosis with matrix involvement. A total of 131 patients were randomized to treatment. Patients in combination groups received amorolfine 5% nail lacquer once weekly for 24 weeks and 200 mg itraconazole once daily for 6 weeks (AI-6) or 12 weeks (AI-12). A control group received itraconazole monotherapy for 12 weeks (I-12). The global cure rate at study endpoint was highest for the AI-12 group (93.9%). Compared with itraconazole monotherapy, the difference was statistically significant (P < 0.05). Furthermore, while improvement of the toenail was visible at 6 months, the result was still unclear regarding a cure. These results indicated that amorolfine and itraconazole combination therapy may be an improved treatment strategy for patients with severe onychomycosis.

Methodological considerations of combination studies

Comparison of the combination trials can be difficult because of the short duration of some of the studies and the variation in global cure rates. Some of these studies lacked an observation period after the final treatment, and a study length of 6 months is not considered sufficiently long to determine whether a patient is cured of severe onychomycosis. Cure rates may also vary, reflecting the use of different definitions of cure. While it is necessary to consider these factors, it is clear that combination therapy offers potential advantages compared with monotherapy.

Which onychomycosis treatment?

In our group in Iceland, current choices for treating onychomycosis include topical monotherapy with amorolfine, or a combination of oral and topical therapy using amorolfine and terbinafine. In our experience, amorolfine monotherapy is effective in mild cases of onychomycosis without matrix involvement and in children, who normally have thin, quick-growing nails. Monotherapy can also be used as a prophylactic. In patients who have been successfully treated but are at risk of recurrence, amorolfine can be used prophylactically, being applied once or twice a month.

Combination therapy may be of benefit in patients who are likely to fail monotherapy. For example, a patient who had been treated with terbinafine in 1995 and was cured both mycologically and clinically within a year quickly relapsed. In 1998, the patient was again treated with terbinafine and remained disease-free for 4 years. However, the same patient recently presented with another reinfection of onychomycosis with lateral and matrix involvement. This patient represents a perfect case for the use of combination therapy comprised of oral and local agents, which might have prevented the recurrences.

Frequent swimmers are another group that may benefit from the combination of oral and topical therapy. An Icelandic cohort study found that onychomycosis of the toenail is at least three times more prevalent in swimmers than in the rest of the population: one-third of male swimmers and one-fifth of female swimmers had onychomycosis. Such frequent swimmers are candidates for prophylactic therapy.
Parallel or sequential therapy?

The combination regimens can be administered sequentially or in parallel. When therapy is sequential, the oral agent alone is administered for a period of time that is then followed by a further period of treatment with the topical agent alone. When treatment is used in parallel, the topical and oral antifungal agents are used simultaneously. Parallel treatment is recommended when patients are likely to fail therapy, for example, patients with diabetes or patients with yellow spikes in the nail. Sequential treatment is recommended when patients show a poor response to treatment. A response is considered poor when the microscopy is still positive after 3–6 months of treatment. A patient who shows a positive culture at these times is unlikely to be cured. For example, in Iceland, terbinafine is first administered for 3 months, after which the mycology is tested. If the mycology is negative, the treatment can be stopped. However, if the mycology is positive, the patient can be treated with amorolfine once weekly until they are cured.

Conclusions

Combination therapy has resulted in the marked improvement of mycological and clinical outcomes associated with onychomycosis. Combination therapy is useful in selected patient populations: in parallel, it can be used in patients who are likely to fail therapy; in sequence, it can benefit patients who show a poor response to treatment.

References