Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy

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ABSTRACT

Background Onychomycosis is a relatively common disease accounting for up to 50% of all nail disorders and its prevalence rises with age. As onychomycosis is an important medical disorder affecting both patient’s health and quality of life, it requires prompt and effective treatment.

Objective Topical antifungal nail lacquers have been formulated to provide efficient delivery to the nail unit. As both amorolfine and ciclopirox have proved useful as monotherapy for onychomycosis that does not involve the nail matrix area, the purpose of this article is to check if, when combined with oral agents, the effectiveness and scope of treatment can be improved further.

Methods Combining data for mycological cure with clinical success (nail morphology) provides a more exacting efficacy measure.

Results Clinical investigations have shown that the combination of oral therapies with antifungal nail lacquer can confer considerable advantage over monotherapy with either drug type.

Conclusion The improved effectiveness and economic advantages of combined topical/oral therapies benefit both patients and health providers; these treatment regimens therefore have an important role to play in the modern management of onychomycosis.

Key words: Onychomycosis, antifungal nail lacquers, combination therapy

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Onychomycosis: the nature and causes of the disease

Onychomycoses are fungal infections of both the fingernails and toenails.1–2 Toenails are 4–10 times more frequently affected than fingernails, probably because of their slower growth and increased exposure to injury and infecting organisms.3–4 Onychomycosis is a relatively common disease accounting for up to 50% of all nail disorders.5–6 Typically, 2–3% of the adult population are affected but, in some countries, this figure approaches 10%.1–4 The prevalence of onychomycosis rises with age, and as many as 14–28% of > 60-year-olds suffer from the condition.1,7 Diabetes, psoriasis and other diseases may also increase the risk of infection.1,8,9 Even otherwise healthy individuals engaged in sporting activities, involving shared bathing and changing facilities, are prone to the disease (Table 1).1–4

Table 1 Risk factors for onychomycosis

<table>
<thead>
<tr>
<th>Predisposing factor</th>
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<tbody>
<tr>
<td>Increased age</td>
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<tr>
<td>Genetic and atopic tendencies</td>
</tr>
<tr>
<td>Family history</td>
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<tr>
<td>Poor general state of health</td>
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<tr>
<td>Frequent nail trauma</td>
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<tr>
<td>Environmental contact with pathogens</td>
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<tr>
<td>Warm and humid climates</td>
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<tr>
<td>Sports activities</td>
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<tr>
<td>Shared bathing facilities</td>
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<tr>
<td>Occlusive clothing and footwear</td>
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<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Prevalence of tinea pedis (athlete’s foot)</td>
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<tr>
<td>Diabetes</td>
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</tbody>
</table>

Modified from Ref. 1.
Dermatophytes, which are related fungi of the genera *Trichophyton*, *Epidermophyton* and *Microsporum*, are the most likely causes of onychomycosis, and are responsible for 90% of toenail infections. However, non-dermatophytic moulds such as *Scytalidium*, *Acremonium*, *Fusarium* spp. and *Aspergillus* spp. can also cause the disease. Yeasts, notably *Candida albicans*, may also give rise to nail infections, although fingernails are more likely to be affected than toenails. Although care must be taken to ensure that fungus is the cause of the nail dystrophy to avoid unnecessary treatment, it is also important to clinically assess the degree and type of involvement, together with the mode and site of invasion, using a fourfold classification.

The most common type of fungal nail infection is distal lateral subungual onychomycosis (DLSO). With proximal subungual onychomycosis (PSO), fungi (usually *trichophyton rubrum*) invade the nail from beneath the proximal fold resulting in nail discoloration. This is the least common form of onychomycosis, but frequently occurs in AIDS patients and is thus considered indicative of HIV infection. Paronychia may be associated with secondary PSO, which is due to some moulds or *Candida* spp. Superficial white onychomycosis (SWO), representing about 10% of all cases, occurs following direct fungal invasion of the dorsal nail plate. Recently, a more comprehensive classification scheme has been proposed to accommodate current advances in the study of the disease; for example, it identifies endonyx onychomycosis, where the core of the nail plate is infected. Moreover, this new classification system also introduces a novel distinction between primary and secondary total dystrophic onychomycosis. Thus, primary total dystrophic onychomycosis constitutes the simultaneous involvement of all tissues of the nail apparatus during chronic mucocutaneous candidiasis, whereas secondary total dystrophic onychomycosis is the culmination of any of the different types of destructive nail dystrophy (i.e. DLSO, PSO, white superficial onychomycosis (WSO) or endonyx onychomycosis), and both primary and secondary totally dystrophic onychomycosis require combination therapy.

While it is evident from these descriptions that the most obvious impact of onychomycosis is visual, it should not be assumed that this condition is a minor and primarily cosmetic problem. For older patients, and those with other underlying disease, there is a risk of serious complications or disability; for example lower limb amputation in diabetics. Furthermore, even during the normal course of the disease, the effects can be considerable.

As onychomycosis is an important medical disorder affecting both patients’ health and quality of life, it requires prompt and effective treatment. Moreover, early treatment before disease progression to total dystrophic onychomycosis can also increase the cure rate and therefore avoid prescription of systemic treatments. Early medications used for onychomycosis and superficial fungal infections were mainly non-specific ointments and disinfectants, which proved relatively ineffective. Antifungal drugs provided more effective treatments, but, when used systemically, also increased the risk of side-effects. Newer systemic agents, such as itraconazole and terbinafine, are safer, although even with these treatments, failure rates can be as high as 30–50%. Topical agents have generally been perceived as ineffective, mainly because of poor penetration into the nail. However, newer topical agents, such as ciclopirox and amorolfine, have been formulated to provide efficient delivery to the nail unit. Both these agents have proved useful as monotherapy for onychomycosis that does not involve the nail matrix, and, when combined with oral agents, the effectiveness and scope of treatment can be improved further.

**Drug penetration as a factor in onychomycosis treatment**

Nail keratin is both compact and hard, and as such, is somewhat impermeable, thus restricting drug access to the organisms causing onychomycosis. Although topical agents allow greater proximity to the infection site, some areas may still prove relatively inaccessible and maintaining effective drug concentrations can be difficult. Moreover, topical solutions and creams are easily removed by washing or wiping, which further reduces delivery of the drug to the subungual tissue. The effectiveness of topical antifungals can be enhanced when applied as a nail lacquer, as is the case with amorolfine and ciclopirox. Volatile vehicles, used to deliver the drug, evaporate leaving an occlusive film, thus concentrating the drug on the nail surface. This film then acts as a drug depot and, by increasing hydration of the nail, enhances drug diffusion. The effectiveness of nail lacquer-formulated agents in penetrating the nail unit is outlined in the following sections.

**Penetration of ciclopirox**

The penetration of $C_{14}$-labelled ciclopirox nail lacquer was assessed *in vitro* following a single application to nails avulsed as a result of onychomycosis. After 24 h an antifungal concentration gradient was apparent, with mean concentrations ranging from 7.8 µg/mg in the uppermost layer to 0.034 µg/mg in the deepest layer. Crucially, even the concentrations of ciclopirox achieved in the nail bed exceeded the minimal fungicidal concentration (MIC) for most fungal organisms responsible for onychomycosis.

The penetration of ciclopirox into and through the nail unit has also been investigated in preliminary studies involving small numbers of healthy volunteers. In the first study, five subjects applied ciclopirox nail lacquer 8% daily for 45 days, with the lacquer removed once a week. The mean concentration of ciclopirox increased throughout the treatment phase, and by day 45 had reached 6.8 µg/mg. Interestingly, although residual amounts of ciclopirox remained in the nail 14 days after treatment, mean concentrations were reduced significantly. In a similar study, nine healthy volunteers applied ciclopirox nail...
Penetration of amorolfineln
Results from a study in which 5% amorolfineln, in either ethanol or methylene chloride, was applied to a range of nail types of varying hardness and morphology for 24 h demonstrated that exponential penetration kinetics were followed; concentrations of the drug in the uppermost layer were 100-fold higher than in the deepest layer. Drug levels in the uppermost layer ranged from 1 to 6.7 µg/mg nail tissue. Importantly, concentrations of amorolfineln achieved at the nail bed exceeded those needed to prevent the growth of most fungi responsible for onychomycosis. In a further in vitro study by Franz, a 48-h treatment with 3H-labelled 5% amorolfineln in methylene chloride and ethanol lacquers resulted in concentrations of 2.9 and 1.2 µg drug/mg nail tissue, respectively. Franz also demonstrated in several experiments that amorolfineln in ethanol or methylene chloride penetrates rapidly into the nail, with rates ranging from 20 to 100 ng/cm²/h and peaking between 5 and 25 h, before declining slowly. These data indicate that amorolfineln lacquers should be able to deliver effective levels of antifungal drug to onychomycosis infection sites.

The effectiveness of penetration of amorolfineln into subungual tissues has been confirmed in patients with onychomycosis. Two groups of patients applied 5% amorolfineln lacquer in ethanol or methylene chloride to infected nails twice weekly for 4 weeks. Subungual material was subsequently removed after 3, 7, 10 and 14 days, and tested for both mycological cultures and and its ability to inhibit growth of fresh T. rubrum inocula (i.e. indicating the presence of active drug). Three days after treatment, 94% of samples had negative cultures; even after 14 days at least 82% of samples still had negative cultures. Furthermore, >97% of subungual samples taken between 3 and 10 days inhibited growth of T. rubrum cultures and 91% still prevented growth 15 days after discontinuing treatment. These results demonstrate that amorolfineln lacquer not only penetrates into subungual debris but also maintains effective antifungal drug concentrations for at least 2 weeks after termination of treatment.

Overall, results from these in vitro and in vivo studies indicate that, when formulated as lacquers, amorolfineln and ciclopirox can effectively penetrate nail tissue. In addition, active concentrations of amorolfineln have been shown to persist for up to 2 weeks in subungual debris. However, these studies do not demonstrate whether these agents subsequently achieve clinical cures. The overall efficacy and wider applications of antifungal lacquers and other topical agents are considered in the following sections.

Limitations of clinical trials
Judging the efficacy of treatments for onychomycosis is made difficult, especially when comparing different studies, by the varying criteria used to define clinical cure or improvement (sometimes called clinical success). Cure does not always indicate a disease-free normal nail, but may be a nail that is mycologically cured, even if it is still malformed. Similarly, clinical success could be assessed as a 90–100% clear nail, or as one that simply shows marked improvement. A residual affected area smaller than 10% may correspond to residual onychomycosis not yet completely cured but is more likely to include previous nail dystrophy of unknown aetiology. Combining data for mycological cure with clinical success (nail morphology) provides a more exacting efficacy measure. Indeed, following extensive analysis of several published clinical studies, Epstein concluded that for the newer oral agents, terbinafineln and itraconazoleln, disease-free toenails (i.e. clinically normal nails with negative microscopy and fungal culture) were achieved in only 35–50% and 25–40% of cases, respectively. Complete replacement of a fingernail takes 4–6 months and that of a toenail 12–18 months. Although studies involving only distal onychomycosis can be relatively short, for severe onychomycosis a study length of 6 months is not sufficient. Even longer follow-up periods are warranted for recurrence assessment.

Topical monotherapy for onychomycosis without matrix involvement
Oral antifungals often give rise to side-effects and may interact with other medications, which can reduce patient compliance. Although these problems have been overcome to some extent with newer drugs, such as itraconazoleln and terbinafineln, there is clearly a place for topical agents in the management of fungal nail diseases. Topical agents have generally been regarded as rather ineffective, but the development of novel agents and formulations offers the prospect of more successful topical therapies, provided that the affected nail area is restricted to the distal two-thirds.

Imidazoles
In onychomycosis, imidazoleln are generally given systemically, but some have been used topically as monotherapy. For example, Hay et al. investigated the efficacy of topical tioconazoleln 28% solution in a small-scale, open study involving 27 patients with
onychomycosis.\textsuperscript{27} The results suggested that topical tioconazole achieved a cure (defined as a completely normal nail and negative direct microscopy) in 22% of patients (six – five having only fingernails – involved patients). It was subsequently suggested that combination therapy might improve the cure rate with topical tioconazole.\textsuperscript{27} As mentioned previously, the efficacy of topical solutions and creams may be hindered by their poor penetration of the nail unit. Consequently, many are used in combination with chemomechanical nail avulsion. Indeed, Rollman demonstrated the efficacy of a topical miconazole solution following nail avulsion in 13 patients with DLSO. Six months after treatment, 42% of treated nails were cured (cure was defined as no subungual hyperkeratosis, negative microscopy and negative fungal culture).\textsuperscript{28} Similarly, topical treatment of onychomycosis with a combination of 1% bifonazole and 40% urea, followed by 1% bifonazole cream alone (i.e. once the nail is removed), has, in a number of clinical trials, repeatedly shown efficacy in the treatment of onychomycosis.\textsuperscript{29–33}

Ciclopirox

Ciclopirox has proven effective in the treatment of superficial dermatomycoses.\textsuperscript{34} In fact, two double-blind, vehicle-controlled, multicentre studies have recently demonstrated the efficacy and safety of ciclopirox nail lacquer 8% monotherapy in the treatment of a total of 460 patients with mild to moderate onychomycosis.\textsuperscript{35} Ciclopirox or vehicle lacquers were applied once daily to all (even unaffected) toenails and any affected fingernails. At treatment end (48 weeks), combined results showed that patients treated with ciclopirox had significantly higher mycological cure rates (defined as the percentage of patients with negative culture and negative KOH microscopy) compared with those treated with the vehicle lacquer (Table 2). Clinical assessments also demonstrated the efficacy of ciclopirox nail lacquer over vehicle (Table 2). Safety profiles in the two studies were similar, with no serious adverse events reported in any patient. The ciclopirox-treated patients did show a slightly higher incidence of erythema in the skin adjacent to the nail plate, but this was generally mild in severity.\textsuperscript{35}

The efficacy of ciclopirox has also been assessed in a variety of clinical trials (most of which were open-label) conducted in Europe, South America and Asia.\textsuperscript{36} Patients with mild to moderate onychomycosis were treated with ciclopirox nail lacquer 8% for periods of 6–12 months. Mycological cure rates of 47–67% were reported; no data was available regarding clinical success or clinical cure rates. In some of these studies ciclopirox nail lacquer was applied less frequently (e.g. three times a week instead of once a day), particularly towards the end of the treatment phase. Whether less frequent ciclopirox applications are as effective as the recommended once-daily regimen needs confirmation with more strictly controlled studies.

Amorolfin

The efficacy and safety of amorolfiné lacquer for the treatment of fungal nail infections has been assessed in a number of clinical studies with overall encouraging results. For example, Lauharanta compared amorolfiné nail lacquer 2% (77 patients) with amorolfiné nail lacquer 5% (80 patients) for the treatment of onychomycosis (predominantly the toenail) in a double-blind, randomized, multicentre trial.\textsuperscript{37} Lacquers were applied weekly on affected nails only. Throughout the 6-month treatment period there was a steady clinical improvement, and 3 months after stopping medication, combined mycological and clinical response data showed that onychomycosis had improved or was cured in 67% and 70% of assessments following application of the 2% and 5% formulations, respectively. The cure rate was, however, higher in the 5% amorolfiné group; 38% vs. 12% (Table 2). Another multicentre, randomized, parallel group study compared once- and twice-weekly applications of 5% amorolfiné lacquer for 6 months.\textsuperscript{38} A total of 317 patients were included in the efficacy analysis with 326 assessments performed (nine patients had both affected fingernails and toenails). Three months after cessation of therapy, onychomycosis had improved or was cured in 69% of assessments and cured in 46% of assessments following once-weekly applications; results for the twice-weekly dosing regimen were similar (Table 2).\textsuperscript{4} Importantly, in both studies the medications were

<table>
<thead>
<tr>
<th>Study</th>
<th>Active ingredient concentration</th>
<th>Dosing frequency</th>
<th>Mycological cure (%)</th>
<th>Overall cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauharanta\textsuperscript{37}</td>
<td>Amorolfiné 2%</td>
<td>Once weekly</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Reinel and Clarke\textsuperscript{38}</td>
<td>Amorolfiné 5%</td>
<td>Once weekly</td>
<td>60</td>
<td>38</td>
</tr>
<tr>
<td>Gupta and Joseph\textsuperscript{39}</td>
<td>Ciclopirox 8%</td>
<td>Once daily</td>
<td>76</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Ciclopirox vehicle</td>
<td>Once daily</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

\*Cure = mycological cure with a normal nail or a nail with ≤ 10% still affected.

\textsuperscript{2} ‘Clinical cure’ was defined as a normal nail or a nail with ≤ 10% still affected; ‘clinical improvement’ was defined as a nail with ≥ 20% reduction of total affected area compared with baseline.

\textsuperscript{a}
well tolerated, with all reported side-effects being minor and confined to the application site. Similar findings were reported in a more detailed and comprehensive analysis of a large number of onychomycosis patients \((n = 727)\) treated with amorolfine lacquer once- or twice-weekly for 6 months.\(^3\) A total of 379 assessments were made with the recommended doses where clinical cure/ improvement (definition as in footnote) with associated negative culture was observed in 56% of assessments. Importantly, < 1% of patients \((7/727)\) reported adverse events linked to medication; these included burning, itchiness, or redness near the application site.

When evaluating results from these clinical trials it is important to consider that the criteria used to gauge efficacy can also influence estimates of success with topical agents. Indeed, a recent pharmacoeconomic meta-analysis, performed using intent-to-treat estimates of success with topical agents.\(^3\) In addition, the criteria used to define therapy failure may significantly influence the cure rates. For example, a study reported that microscopic cure rates were < 20%,\(^4\) compared with clinical cure rates of 50%.\(^5\) The criteria used to define success are, therefore, critical to the interpretation of the results of this study. Proximal half of the nail is involved. Potential advantages of this approach include: antimicrobial synergy; wider antifungal spectrum; improved fungicidal activity; suppression of resistant mutants; increased cure rates; and enhanced tolerability and safety.\(^6\) In addition, combination therapy provides effective oral therapy against tinea pedis, which usually precedes and accompanies toenail onychomycosis.

Chances of clinical success are increased with combination therapies if the drugs have distinct mechanisms of action. For example, although both itraconazole and amorolfine block fungal ergosterol biosynthesis, they have different target enzymes,\(^5,6\) There may also be advantages in using drugs with separate administration routes because they can access the infection site from different directions.\(^2\)

### Limitations with monotherapy

The reasons why monotherapy for onychomycosis may fail are not completely understood, especially as antifungal drugs are often very active against the causative organisms in vitro. However, several factors can influence the success of the chosen monotherapy. For example, antifungal resistance, a less severe problem compared with antibacterial resistance, may result in some fungi that cause nail infections falling outside the spectrum of any one drug. Moreover, monotherapy may fail because of the difficulty in achieving biologically effective drug concentrations in the infected tissue, a particular problem with more severe forms of onychomycosis (dermatophytoma). Additionally, some patients may not show any improvement despite clearing of infection owing to pre-existing nail dystrophy. Finally, failure of monotherapy may be due to the fact that nails, particularly those on the toe, grow very slowly, which can make them vulnerable to reinfection, especially from the surrounding tissue (other superficial fungal diseases often accompany nail infections).\(^2,10\)

### Combination therapies for onychomycosis with matrix involvement

When presented with non-responders who have received 6 months of monotherapy with topical treatment, the clinician should recommend the second therapeutic stage, which is a combination of treatments. However, double-pronged therapy, involving a combination of a topical and an oral antifungal, should also be considered as a first step, particularly when the proximal third of the nail is involved. Potential advantages of this approach include: antimicrobial synergy; wider antifungal spectrum; improved fungicidal activity; suppression of resistant mutants; increased cure rates; and enhanced tolerability and safety.\(^6\) In addition, combination therapy provides effective oral therapy against tinea pedis, which usually precedes and accompanies toenail onychomycosis.

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### Imidazoles in combination

Hay et al. demonstrated the efficacy of tioconazole used topically in combination with oral griseofulvin.\(^43\) Ten patients receiving 1 g oral griseofulvin daily over 1 year were treated topically with tioconazole 28% nail solution (29 nails) or placebo (31 nails) and the results showed a clinical and mycological remission of 69% in the combination group compared with 41% in the oral griseofulvin group.\(^43\) Similarly, in a comparative, open-label single-blind study of 90 patients with onychomycosis, clearance of infecting fungi from toenail onychomycoses by oral griseofulvin rose from 27% to 46% when it was combined with isoconazole cream, and to 43% when given with a keratolytic cream.\(^44\) The activity of itraconazole was not improved in combination with these topical agents, presumably because of its high cure rate alone (73% in this trial).

### Ciclopirox in combination

As a relatively new formulation, the use of ciclopirox nail lacquer in combination with oral antifungals has not been well documented. Nevertheless, encouraging results have been reported from a recent open study in which 117 onychomycosis patients were treated with ciclopirox nail lacquer 8% in combination with itraconazole for 3 months.\(^45\) At the end of the study, 41% of patients were cured (negative mycology with 100% clearance of the nail plate) and 47% had therapeutic success (negative mycology with incomplete clearance of the nail plate). Randomized, controlled comparative studies are, however, necessary to confirm the effect of such a combination.

### Amorolfine in combination

Improvements in fungistatic activity have been demonstrated for combinations of amorolfine with griseofulvin, terbinafine, itraconazole or fluconazole, against a number of dermatophytes implicated in superficial infections.\(^46\) In clinical trials, amorolfine has been combined with several oral drugs used to treat nail
infections, with the aim of improving both the efficacy and the cost-effectiveness of the single agents (Table 3).47–49

**Amorolfine with griseofulvin**
Griseofulvin has been widely used in antifungal therapy for over 40 years, but cure rates tend to be low, and side-effects, such as headache and gastrointestinal upset, are fairly common.2,15,16 Its activity alone and in combination with 5% amorolfine nail lacquer has been compared in an open-comparative 15-month study of patients with severe onychomycosis (affecting lunulae/matrices in most cases).47 One set of patients applied amorolfine nail lacquer twice weekly for 12 months, accompanied by twice-daily griseofulvin 500 mg for the first 2 months. The other group were given griseofulvin 500 mg twice daily for 2 months, and once daily for the following 10 months. Three months after the end of treatment, clinical and mycological assessments were performed on 59 and 57 patients in the combination and griseofulvin alone groups, respectively. Clinical cure rates were 45% and 42% in the combination and griseofulvin treatment groups, respectively. Mycological cure rates were 63% in the combination and 50% in the griseofulvin group (Table 3).5 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.47

**Amorolfine with terbinafine**
The efficacy of amorolfine combined with oral terbinafine has been investigated in an open, multicentre study enrolling 147 patients with toenail onychomycosis with matrix involvement.48 Subjects applying 5% amorolfine once a week for 15 months were given 250 mg of terbinafine daily for either the first 6 or 12 weeks (groups AT6 and AT12, respectively); a group taking terbinafine alone for 12 weeks served as controls (T12). Subjects were followed for up to 18 months. At the last visit, mycological cure was highest following AT12 combination therapy (89%) and lowest after T12 monotherapy (66%) (Table 3). Similarly, end-point global cure rates (clinical cure plus mycological cure)6 were much higher for the AT12 group (72%) than either the AT6 (44%) or T12 groups (38%). Side-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 most probably caused by terbinafine.

**Amorolfine with itraconazole.**
A further open, randomized multicentre study recruited 131 patients to evaluate combined amorolfine/oral itraconazole therapy for the treatment of severe toenail onychomycosis.49 Patients applied 5% amorolfine lacquer once a week for 6 months, accompanied by itraconazole 200 mg daily for either the first 6 or 12 weeks; a further group received itraconazole monotherapy for 12 weeks. By 6 months, ≥ 90% of patients treated with either of the amorolfine and itraconazole regimens had negative mycology4, compared with < 69% of those receiving monotherapy (P < 0.001) (Table 3). The combined mycological–clinical cure4 rate at 6 months for the amorolfine/12-week itraconazole regimen was 94%, and 84% for 6-week combination therapy. Both cure rates were considerably higher than the 69% rate observed with itraconazole alone. No serious adverse events were reported during the trial, and the distribution and number of events were similar for the three treatment groups. Another study assessed a combination of 3-months’ itraconazole pulse therapy with 6 months’ amorolfine once weekly in patients with extensive dermatophyte onychomycosis and a group of patients with recurrent onychomycosis. Cure was achieved in 21/27 patients (77.8%) with extensive onychomycosis and in 12/16

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**Table 3 Combined amorolfine/oral antifungal therapy for severe onychomycosis: responses at last reported visit**

<table>
<thead>
<tr>
<th>Study</th>
<th>Oral drug and duration of dose</th>
<th>≥5% Amorolfine (%)</th>
<th>Mycological cure (%)</th>
<th>Clinical response (%)</th>
<th>Overall cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaugg47</td>
<td>Griseofulvin 12 months</td>
<td>–</td>
<td>50</td>
<td>42</td>
<td>–</td>
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<tr>
<td></td>
<td>Griseofulvin 2 months</td>
<td>12 months</td>
<td>63</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td>Baran et al48</td>
<td>Terbinafine 3 months</td>
<td>–</td>
<td>66</td>
<td>42†</td>
<td>38*</td>
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<tr>
<td></td>
<td>Terbinafine 1.5 months</td>
<td>15 months</td>
<td>73</td>
<td>46†</td>
<td>44*</td>
</tr>
<tr>
<td></td>
<td>Terbinafine 3 months</td>
<td>15 months</td>
<td>89</td>
<td>75†</td>
<td>72*</td>
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<tr>
<td>Lecha49</td>
<td>Itraconazole 3 months</td>
<td>–</td>
<td>69</td>
<td>90</td>
<td>69†</td>
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<tr>
<td></td>
<td>Itraconazole 1.5 months</td>
<td>6 months</td>
<td>≥ 90</td>
<td>88.1</td>
<td>84†</td>
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<tr>
<td></td>
<td>Itraconazole 3 months</td>
<td>6 months</td>
<td>≥ 90</td>
<td>100</td>
<td>94†</td>
</tr>
</tbody>
</table>

*Combined clinical response and negative mycology at 6 months.
†Unpublished data.
‡Global cure assessment at 6 months.

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patients (75%) with recurrent onychomycosis. A further study was conducted in 73 patients with onychomycosis of the fingers and toes. The patients were divided into two groups with group I (32 patients) receiving itraconazole according to a pulse regime over 3–4 months and group II (41 patients) receiving a combination of itraconazole with amorolfine lacquer. The combination treatment was highly effective and well tolerated, with all patients demonstrating clinical and mycological recovery.

**Amorolfine with fluconazole**

A small study was performed by Sergeev and Sergeev to assess the combination of fluconazole 150 mg once weekly with amorolfine nail lacquer applied once weekly. This combination was preferred over a terbinafine/amorolfine combination, and was found to be well tolerated, effective, and convenient because of its once-weekly application. Another study in 23 patients started with fluconazole 150 mg once weekly and, as soon as the Scoring Clinical Index for Onychomycosis scores had decreased to 3–6, amorolfine lacquer 8% was started once weekly. Complete clinical and mycological cure was noted in 19 patients (82.6%). Another, smaller study (n = 12) was used to test the effectiveness of fluconazole/amorolfine combination. In this study, nine patients (75%) achieved complete clinical cure and all patients showed mycological cure. A study was also conducted in 157 patients treated with amorolfine once weekly for 12 months and an oral antifungal of the investigator’s choice: either terbinafine once daily for 3 months, itraconazole pulse therapy for 3 months or fluconazole once weekly for 6 months. Cure rates were similar in all groups (71–73%).

The data from these trials therefore suggest that combination therapy using amorolfine nail lacquer offers significant clinical benefits for the treatment of onychomycosis.

The use of combination therapy of onychomycosis might also decrease costs per cure by 16–23%. As financial considerations often dictate prescribing practices as much as clinical efficacy, combined therapy is clearly an attractive option from more than one viewpoint.

When there is a risk of failure because of interruption in the transport of the drug from the nail into the nail bed, immediate eradication of the pathogen is indicated. In triple therapy, mechanical or chemical removal of the diseased nail is combined with oral and topical antifungal therapy. Application of antifungal nail lacquer is continued on the remaining, normal-looking part of the nail keratin, as some fungi may be left beneath its lateral margin and on the newly growing nail. Although current combination therapies have proven effective in the treatment of onychomycosis, it also remains to be established whether it is possible to formulate a combination of different antymycotics in a single lacquer, and if such a combination will result in increased cure rates.

All the studies described above assessed combination regimens in which drugs are prescribed in parallel from the start. A different approach has been suggested recently in which oral and topical agents are prescribed sequentially, with the topical prescribed immediately after the oral treatment is stopped.

**Long-term therapy**

Assessment of disease recurrence in patients 2 years after itraconazole therapy showed recurrent dystrophy in 17% of nails assessed. Long-term results from a recent 5-year blinded follow-up study also show significant recurrence rates, with approximately 20% of terbinafine-treated patients and 50% of itraconazole-treated patients.

Long-term intermittent traditional therapy should prevent the re-establishment of tinea pedis and limit the possibility of reinfection. In addition, periodic use of amorolfine (for instance, twice a month) appears to be a logical and safe method for preventing recurrences, as it remains in nail keratin (up to 14 days) after the weekly active therapy has been interrupted.

**Summary and conclusions**

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. However, although current monotherapy recommendations suggest applying ciclopirox to all nails, once daily, amorolfine nail lacquer has an advantage in that only once-weekly applications to affected nails are required.

Recent clinical investigations have shown that the combination of oral therapies with a topical agent, such as amorolfine or ciclopirox, can confer considerable advantages over monotherapy with either drug type. Co-administration of amorolfine with an oral antifungal drug can result in dose-sparing effects and can increase the number of patients cured from onychomycosis compared with oral therapy alone. In addition, appreciable cost savings can be made by using oral and topical agents together.

The improved effectiveness and economic advantages of combined topical/oral therapies benefit both patients and health providers; these treatment regimens therefore have an important role to play in the modern management of onychomycosis.

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