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Topical NEWS

In Onychomycosis

A newsletter devoted to education, discussion and current opinion on the treatment of onychomycosis

Editor:
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EDITORIAL

Onychomycosis with matrix involvement: combined topical and oral treatments or oral treatment alone?

By Osvaldo Correia, MD, PhD, Centro Dermatologia Epidermis, Porto, Portugal.

A recent large European study showed that the prevalence of onychomycosis may be as high as 30%, with dermatophytic infections being the most frequent[1]. Onychomycosis is more than a cosmetic problem: it entails physical and psychological effects and in many instances it is a debilitating disease. Current treatment strategies can include topical, oral and a combination of both treatments. The therapeutic choice depends on various factors: severity, localization and extent of disease and underlying condition of the patient. A consensus guidelines paper has recently been published[2]. These guidelines recommend topical monotherapy when <50% of the nail is affected without matrix area involvement. Oral monotherapy or combination therapy is indicated when >50% of the nail, including the matrix area, is involved. When topical drug transport is suboptimal, as in dermatophytoma, chemical or mechanical removal should be considered.

When topical monotherapy is recommended we should consider that efficacy depends on penetration and persistence of the drug. Amorolfine 5% nail lacquer demonstrated superior fungistatic and fungicidal activity against dermatophytes than ciclopirox 8%[3]. Cure rates (i.e. completely normal nail and negative mycological examination) were disappointing with tioconazole 28% solution, but higher for ciclopirox 8% and higher still for amorolfine 5% nail lacquer. Indeed, the clinical efficacy of the latter drug has been reported to be as high as 80% for fingernails and 76% for toenails (in onychomycosis without matrix involvement)[2] and it has also been proved that is the more cost-effective topical treatment[2,4].

Oral antifungal drugs are more effective than topical treatments; however they are more expensive and carry a higher risk of systemic adverse effects. Terbinafine and itraconazole are the drugs most commonly used in monotherapy for dermatophytic onychomycosis with matrix involvement. Although mycological success is higher, clinical success rates for monotherapy are just 35–50% for terbinafine and 25–40% for itraconazole[2]. Combined topical and oral therapy therefore will most likely improve prognosis and reduce the time of exposure to systemic therapy.

Combination therapy is usually considered when a high proportion

of the nail plate is affected (>50%) and/or when the matrix area is involved; however a recent publication adds credence to the argument for more widespread use of combination therapy[5]. The paper, entitled *"Efficacy and safety of amorolfine nail lacquer with oral terbinafine vs. oral terbinafine alone in the treatment of onychomycosis with matrix involvement"* was an international open-label, multicentre, randomised, parallel group study of 249 patients with a diagnosis of subungual onychomycosis affecting at least one great toenail with matrix involvement. Subjects received randomly either amorolfine 5% nail lacquer once weekly for 12 months in combination with oral terbinafine 250 mg once daily during the first 3 months of the study (120 patients) or oral terbinafine 250 mg alone once daily over a treatment period of 3 months (129 patients). After the treatment period, patients were followed up for 6 months if they were treated with the combination and 15 months if they had received terbinafine as monotherapy. Overall response (success rate), defined as the combination of clinical cure and negative mycology, was 57.5% with the combination treatment at month 15 and 59% at month 18 compared to 46% and 45% for terbinafine alone at months 15 and 18, respectively, and the difference was statistically significant. Two adverse effects were found related to amorolfine and 32 patients (12.9% of the total) of the patients experienced adverse effects related to terbinafine and in 2.8% of them this led to discontinuation of the treatment.

This study is an amorolfine phase IV study and was performed according to both Goodman & Gilman's principles of therapeutics[6] and the methodology recently proposed for clinical trial designs for onychomycosis[7].
Analysis of the randomized study shows that indeed there was careful diagnosis of onychomycosis with matrix involvement and it includes clear definitions and results of mycological, clinical and overall response (success rate), all in favour of combination treatment.

This study confirms previous studies on the efficacy of combination therapy on onychomycosis with matrix involvement: Baran *et al* demonstrated that amorolfine plus terbinafine compared with terbinafine alone gives an overall response of 72.3% for combination treatment compared to 37.5% for oral monotherapy[8] and Lecha *et al* demonstrated higher mycological cure rates in patients treated with itraconazole for 12 weeks plus amorolfine 5% for 24 weeks (93.9%) compared with itraconazole alone for 12 weeks (68.8%). This study showed that combination treatment was more cost-effective than monotherapy.

Indeed, although it may initially appear to be an expensive option because two drugs are prescribed simultaneously, combination therapy is both cost-saving and cost-effective compared to oral treatment alone. This is true for both oral drugs, namely terbinafine or itraconazole pulse therapy[4].

Combination therapy is associated with a wider antifungal spectrum than monotherapy and confers possible synergy. This gives raise to rapid and higher cure rates and

reduction in duration of systemic drug exposure, resulting in fewer side effects. A decreased probability of resistant fungal strains emerging is a further benefit of this approach[2].

It is this author's conviction that combination topical and oral treatments, either oral pulse terbinafine or itraconazole or continuous oral treatment as proposed by Baran *et al*[5,8], will become the gold standard therapy for onychomycosis with matrix involvement. The following examples (Figures 1–6) demonstrate the effect of combined treatment on onychomycosis with matrix involvement by dermatophytic infection.

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Figure 1 - Before treatment: oral: terbinafine 250 mg/day (28 days x 4 months); topical: urea 50%, amorolfine once a week x 1 year

Figure 2 - After treatment: 18 months after the beginning of the treatment

Figure 3 - Before treatment: oral: itraconazole 200 mg/day during 1 week x 4 months; topical: urea 50%, amorolfine once a week x 1 year

Figure 4 - After treatment: 18 months after the beginning of the treatment

Figure 5 - Before treatment: oral: itraconazole 200 mg/day during 1 week x 4 months; topical: urea 50%, amorolfine once a week x 1 year

Figure 6 - After treatment: 18 months after the beginning of the treatment

Topical NEWS
In Onychomycosis

HOT TOPIC

Efficacy and safety of amorolfine nail lacquer in combination with oral terbinafine versus oral terbinafine alone in the treatment of onychomycosis with matrix involvement

By Dr Robert Baran, Nail Disease Centre, Cannes, France

Onychomycosis is the most common of infectious diseases involving nails representing about 15–40% of all nail problems[1]. Although it is not a life-threatening condition it is associated with a significant degree of morbidity for the majority of individuals that require treatment. A number of studies identified that onychomycosis has a significant impact on many aspects of patient quality of life[2,3].

Amorolfine is an antifungal drug (with a dual fungistatic and fungicidal activity) belonging to the class of phenylpropyl-piperadine and -morpholine derivatives that have activity against certain fungi that are pathogenic to plants, animals and humans[4]. Amorolfine 5% nail lacquer is indicated for onychomycosis without matrix involvement. Previous studies have demonstrated a significant clinical response (cure + improvement) in onychomycosis without matrix involvement: 76% in toenails and 80% in fingernail infections[5]. Terbinafine is a systemic treatment for onychomycosis with fungicidal properties, especially on dermatophytes. It is highly effective in the treatment of dermatophyte nail diseases[6–10].

In a pilot-study the combination of terbinafine 250 mg daily for 3 months and amorolfine 5% nail lacquer once weekly for 15 months demonstrated a clear benefit over terbinafine alone for 3 months with complete cure rates of 64% and 42% respectively[11].

Study aims and methods

This was an international open-label, multicentre, randomised parallel-group study with the objective of assessing the efficacy profile of a combination of amorolfine 5% nail lacquer and oral terbinafine 250 mg compared to monotherapy treatment with oral terbinafine in the treatment of dermatophytic onychomycosis. Suitable subjects for the study were aged between 18 and 70 years of age and had been diagnosed with subungual onychomycosis affecting at least one great toenail with matrix involvement.

A total of 249 subjects were randomly assigned to one of two treatment groups - demographic characteristics and history of onychomycosis were similar between the two groups. 120 subjects received amorolfine 5% nail lacquer once weekly for 12 months in combination with oral terbinafine 250 mg once daily during the first three months of the study. The remaining 129 subjects received oral terbinafine 250 mg alone once daily over a treatment period of three months.

The primary efficacy criterion was "overall response" (defined as the combination of clinical cure and negative mycology) at the end of the study (Month 18). Other efficacy parameters were "complete clinical cure" (an entirely grown healthy nail) and "success" (clinical cure with negative direct microscopy and negative mycology). "Failure" was defined as a failure of one of clinical and mycological cures. Evaluation took place at baseline visit and every three months until the end of the study (at Month 18).

After the treatment period, subjects were followed up (without any treatment) for six months if they were treated with the combination, and 15 months if they had received terbinafine as monotherapy. Follow up assessment recorded the incidence of any adverse events and assessed efficacy criteria including clinical response (rated as failure, improvement or cured) and mycological cure (KOH and negative culture).

Results

The demographic characteristics of the 249 subjects were similar between the two treatment groups with 32.1% of females

Table 1 Demographics and baseline disease data

		Terbinafine 250mg/day	Amorolfine 5%/Terbinafine 250mg/day	Total
	N (%)	129 (100%)	120 (100%)	249 (100%)
Gender	Male Female	87 (67.4%) 42 (32.6%)	82 (68.3%) 38 (31.7%)	169 (67.9%) 80 (32.1%)
Age (in years)	Mean ± sd	47.8 ± 12.6	46.8 ± 13.3	47.3 ± 12.9
Race	White/Caucasoid Black/Negroid Yellow/Mongoloid Other or mixed	126 (97.7%) 2 (1.6%) 1 (0.8%) -	115 (95.8%) 2 (1.7%) 2 (1.7%) 1 (0.8%)	241(96.8%) 4 (1.6%) 3 (1.2%) 1 (0.4%)
Culture	Negative Positive	3 (2.3%) 126 (97.7%)	2 (1.7%) 118 (98.3%)	5 (2.0%) 244 (98.3%)
Direct microscopy	Positive	129 (100%)	120 (100%)	249 (100%)
Mycological examination	Positive	129 (100%)	120 (100%)	249 (100%)
% Total diseased surface	Mean ± STD	234 ± 717	253 ± 197	244 ± 184

and a mean age of about 47 years in both groups. More than 95% in both groups were White/Caucasian (Table 1).

In terms of the primary efficacy criterion, overall responses were in favour of the combination therapy by Month 15 (p=0.074) and significantly in favour at Month 18 (p=0.0304). Success rates reached 57.5% with the combination at Month 15 and 59% at Month 18; for terbinafine alone, success rates were 46% and 45% at Months 15 and 18 respectively (Figure 1).

Clinical cure rate was also statistically in favour of combination therapy at Month 18 (p=0.0374) with 66.7% of the subjects being cured, compared to 53.5% of those treated with terbinafine alone (Figure 2).

Direct microscopy did not show any statistically significant difference between the two treatment schemes; however the combination showed that somewhat more subjects had negative results (69.2%) compared to the monotherapy group (61.2%) (Figure 3).

Results for the mycological culture demonstrated significant treatment differences during the whole treatment in favour of the combination of amorolfine and terbinafine. However, after amorolfine was stopped at Month 12, a reappearance of fungi (up to 12% of subjects at Month 18) was recorded (Figure 4).

In the evaluation of treated diseased nail surfaces, both treatment groups showed a high reduction from baseline for each subsequent evaluation (more than 90% from Month 9 onwards). Although there was no statistically significant difference, a numerical superior trend could be demonstrated for the combination with a mean decrease of 85% versus 78.5% for the terbinafine group at Month 18.

Safety

Two (0.8%) subjects experienced two adverse events related to amorolfine in the combination group and a total of 32 (12.9%) subjects experienced 40 adverse events related to terbinafine. Adverse events leading to permanent discontinuation of study medication occurred in seven (2.8%) subjects: three (2.3%) in the terbinafine monotherapy group and four (3.3%) in the combination group.

Conclusions

This study demonstrated that there was an enhanced efficacy in terms of "overall response" when amorolfine 5% nail lacquer is used in combination with terbinafine 250 mg in the treatment of dermatophytic toenail onychomycosis with matrix involvement as compared to terbinafine alone.

Figure 1

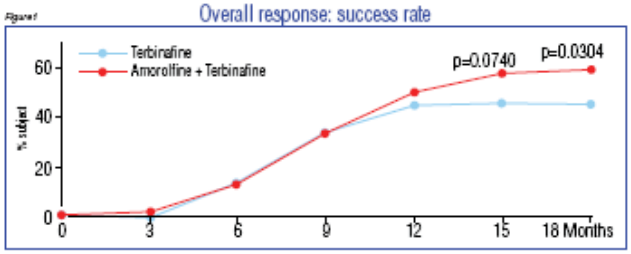


Figure 2

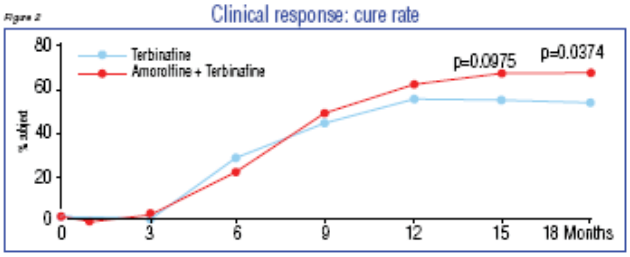


Figure 3

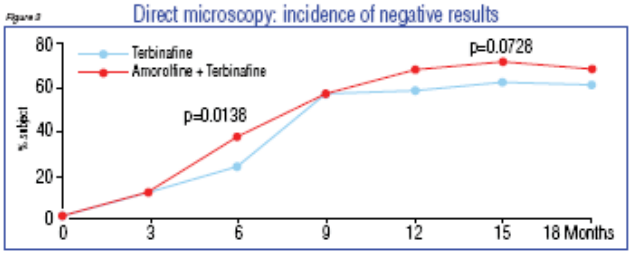
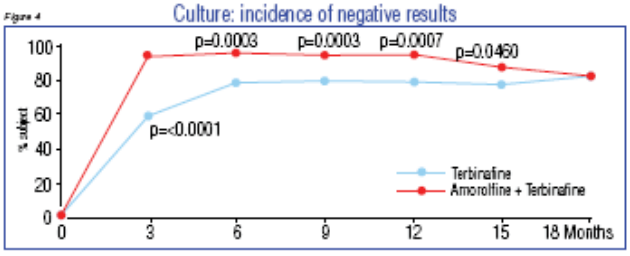


Figure 4



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OBSERVATIONAL STUDY

Amorolfine 5% nail lacquer in the treatment of onychomycosis patients with diabetes mellitus

By Dr Andreas Jäckel and
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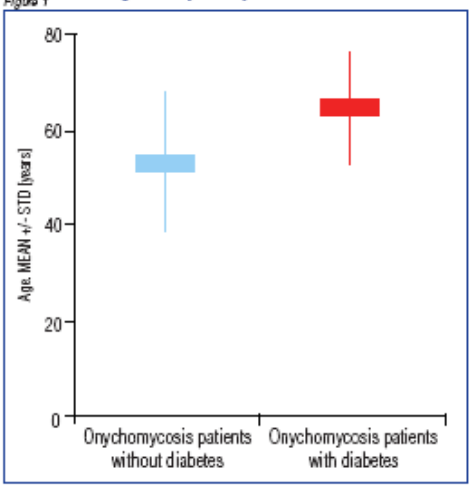
Onychomycosis is a mycological infectious disease of the nail. With no spontaneous remission it needs to be treated with effective local and/or systemic antimycotic drugs. The prevalence of onychomycosis is higher in diabetic patients than in the non-diabetic population. Predisposing factors for onychomycosis are, among others: age, immune situation, trauma, poor peripheral circulation and diabetes.

The aim of a post marketing surveillance study, the results of which were presented at the 14th EADV Congress in London[1], was to evaluate data on the treatment of onychomycosis in diabetic and non-diabetic patients treated with amorolfine 5% nail lacquer in everyday clinical practice. In this large observational, open-label study, a subset of diabetic and non-diabetic patients with onychomycosis received amorolfine 5% nail lacquer for 6 months. The severity of onychomycosis was assessed and stratified into "matrix involvement and non matrix involvement" classes. At the end of the treatment period, patient compliance and efficacy were assessed clinically and categorized into "complete response", "improved" or "no improvement". The variable "clinical response" summarizes the results obtained for "complete response" and "improvement". In addition, the adverse events were recorded.

Figure 1

Age of onychomycosis patients



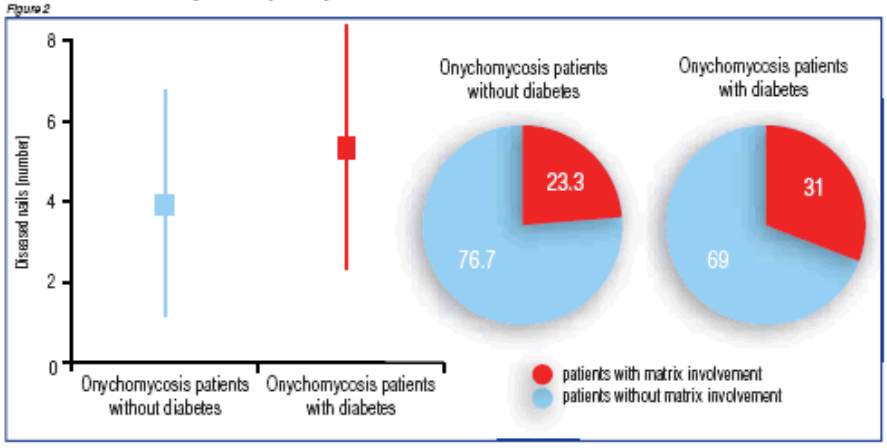
Results

From the 4211 patients treated, 2996 (71.1%) received amorolfine as monotherapy. A total of 339 (11.3%) of these patients were diabetics. Diabetic patients were slightly older (64.6±11.9) than non-diabetic patients (52.8±14.6) (Figure 1).

Furthermore, it was found that diabetic patients had a proportionally higher nail matrix involvement compared to non-diabetics (31.2% vs 23.3%) and presented a higher number of affected nails (5.3±3.0 vs 3.9±2.8) (Figure 2).

Figure 2

Signs of onychomycosis are more severe in patients with diabetes



Global efficacy results showed that patients suffering from diabetes had a slightly lower clinical response (86.1%) and complete response (16.5%) than non-diabetic patients (91.8% and 27.5%, respectively). However, these findings were due to the higher age in the diabetic population and due to the fact that diabetics presented a more severe onychomycosis compared to non-diabetics, both factors resulting in prolonged treatment requirements. When clinical results were stratified by age into quartiles, no significant difference could be demonstrated (Figures 3 and 4).

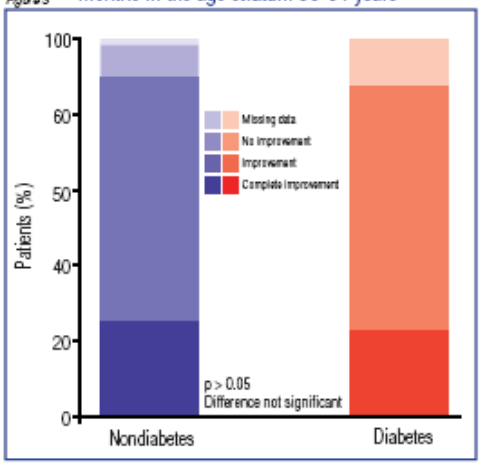
Patient compliance in the diabetic subpopulation was predominantly "very good" (46.6%) or "good" (37.5%). A total of five adverse events in the overall population were recorded, two of these in patients with diabetes (local stinging and burning linked to amorolfine nail lacquer; neither adverse event led to discontinuation of the study).

Conclusions

Patients with onychomycosis and concomitant diabetes mellitus are older and have clinically more severe mycotic infections of the nails than non-diabetic patients. The variable "age" was revealed as a statistically confounding variable. Considering clinical efficacy, drug safety and patient compliance, amorolfine 5% nail lacquer meets all criteria for local treatment of onychomycosis in diabetic patients.

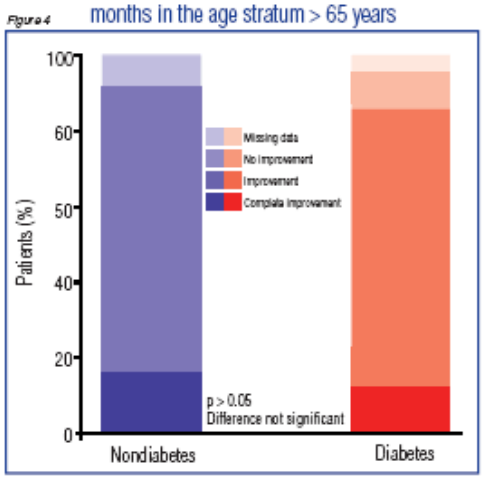
Clinical efficacy of amorolfine 5% nail lacquer after six months in the age stratum 56-64 years

Figure 3



Clinical efficacy of amorolfine 5% nail lacquer after six months in the age stratum > 65 years

Figure 4



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EPIDEMIOLOGY

Onychomycosis in geriatric patients

By Dr Roberto Arenas, Departamento de Dermatologia, Hospital General Dr. Manuel Gea Gonzalez SS, Mexico

Onychomycoses are nail infections caused frequently by dermatophytes. They are rare in children, common in adults with a high frequency in the elderly. In the latter age group few Mexican reports have been published. Peripheral vascular insufficiency has been related to the presence of onychomycosis in patients over 50 years of age[1].

The objective of this paper is to describe the frequency and the epidemiological data of onychomycosis in geriatric patients (65 or more years of age) with the data from a descriptive and transversal study performed during a ten-year period at a General Hospital in Mexico City[2].

Results

The authors found 435 cases of onychomycoses in the elderly with positive mycological test in the decade 1994–2003. Onychomycoses represented 47% of all mycoses in geriatric patients. Females accounted for 60% of the onychomycoses and the age range with the highest incidence was the 65–74 yrs group (73%) (Tables 1 and 2).

Distribution according to sex

Table 1

Cases	Total = 435	%
Female	262	60%
Male	173	40%

Distribution according to age group

Table 2

Age range	Total = 435	%
65-74	316	73%
75-84	100	23%
85 y >	19	4%

Toenails were involved in 71% of cases and fingernails in 6%. Toenail onychomycosis was associated with another dermatophytic infection in 50%, and fingernail onychomycosis only in 3%; the former with tinea pedis in 24% and the latter with tinea manuum in 0.6%. The frequency of two feet one hand syndrome was 8%.

Fingernail onychomycosis due to *Candida*

Toenail onychomycosis in an elderly patient

Total dystrophic onychomycosis was reported in 50%, distal and lateral subungual onychomycosis in 44% and white superficial onychomycosis only in 1%.

The aetiological agent was isolated in 60% of cases. Dermatophytes were isolated in 55% of these, *Candida* sp in 35.5% and non dermatophyte molds in 9.5% (Tables 3, 4 and 5). The causal agent that was isolated most frequently was *T. rubrum*.

Conclusions

Onychomycosis has a high frequency in the elderly (47%). The causal agents are dermatophytes in 55% and *Candida* in one third, and an increased incidence in cases caused by non dermatophyte molds has been observed. Combined treatment of a topical and a systemic antifungal agent is the best option of treatment[3].

Life expectancy has dramatically changed this century. Increased longevity is a result of improved health conditions and lifestyles; however, with a greater proportion of people living beyond 65 yrs old, chronic diseases of the skin and other organs become more prevalent.

For the reasons mentioned above, an understanding of the frequency, diagnostic tools and treatment of onychomycosis, is a useful complement for geriatric medicine.

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Onychomycoses caused by dermatophytes

Table 3

Culture	Total = 70	% of all isolates
T.rubrum	66	52%
T.mentagrophytes	3	2%
Trichophyton sp	1	1%

Onychomycoses caused by *Candida*

Table 4

Culture	Total = 45	% of all isolates
Candida sp	30	24%
C albicans	11	9%
C glabrata (T.glabrata)	4	4%

Onychomycoses caused by non dermatophytes

Table 5

Culture	Total = 11	% of all isolates
Acremonium sp	5	3%
Geotrichum sp	4	3%
Scopulariosis sp	1	1%
Trichosporon sp	1	1%

SURVEY

An international epidemiological survey to improve the understanding and current treatment of onychomycosis

By Dr Robert Baran, Nail Disease Centre, Cannes, France

Onychomycosis is the most prevalent of all nail diseases, accounting for up to 50% of all onychopathies[1,2]. According to population-based studies, the incidence of onychomycosis, mostly involving toenails, in the general population varies between 2 and 8%, but this is undoubtedly an underestimate due to the low level of diagnosis[3,4]. Indeed, the Achilles Project confirmed that the prevalence of onychomycosis in Europe is much higher than previously thought (26.9%)[5]. Furthermore, the incidence of onychomycosis has increased sharply in recent decades, probably due to changes in lifestyle e.g. wearing closed, tight shoes, increasing number of immunosuppressed (HIV-positive) individuals, or increased use of communal locker rooms[1,6]. The aetiology of this condition is multifactorial[7]. The factors that increase the prevalence of onychomycosis include increasing age, male sex, genetic factors, underlying conditions such as diabetes, immunodeficiency, peripheral arterial disease, psoriasis, and environmental and behavioural factors such as sporting and religious practices and certain professions.

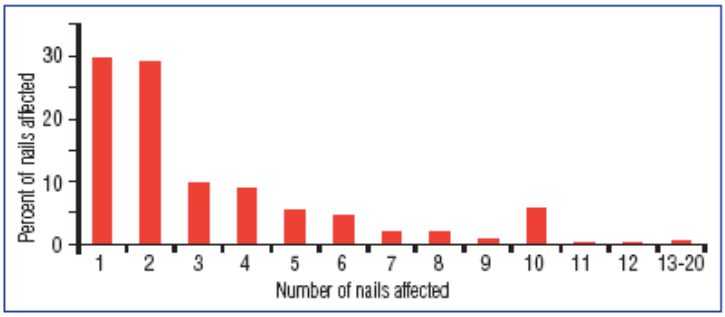
The European Onychomycosis Observatory (EUROO) international epidemiological survey was carried out to assess patient profiles, current status of diagnosis, and treatments to improve the understanding of onychomycosis. The survey was conducted in 16 different countries: South Africa, Saudi Arabia, Belgium, Germany, Denmark, Spain, Finland, France, Italy, Morocco, Norway, Austria, Portugal, Russia, Switzerland and Sweden. Participating general physicians (GP) were asked to provide patient profiles, visual and mycological diagnoses, and details of the treatment prescribed for the onychomycosis, as shown in Table 1.

Table 1

Patient profiling	• Gender • Age • Associated pathologies: diabetes, psoriasis, immunodeficiency, peripheral vascular pathology, and other pathologies • Regular sport practice • First instance of onychomycosis • Presence of infected nails in family members
Visual diagnosis	• Location of the affected nails • Type of onychomycosis: -Distal lateral subungual onychomycosis due to dermatophytes -Distal lateral subungual onychomycosis due to dermatophytes (with broken nail) -Distal lateral subungual onychomycosis due to dermatophytes (lateral involvement) -Superficial onychomycosis due to molds -Proximal onychomycosis due to dermatophytes due to *Candida* (paronychia) proximal or due to mold (paronychia + leuconychia) -Total onychodystrophy due to dermatophytes
Mycological sampling	• Statement that a sample was taken and if yes, what the outcome was
Treatment strategies	• Including amorolfine, bifonazole, ciclopirox, itraconazole, fluconazole, griseofulvin, oral terbinafine, tiacoazole • Confirmation if the treatment was prescribed as monotherapy or in combination

Figure 1

Visual diagnosis: percent distribution of affected nails



Results

Patient profiling

In total, 44972 patient questionnaires (31291 from dermatologists and 13681 from GPs) were completed and returned. The compiled demographics showed that more than half of the patients were aged over 46 years and about 30% were aged over 60 years. Males accounted for 45.2% of the population. A total of 70.7% of the affected population did not practice sports. A considerable proportion of patients were identified as having associated conditions: 13.1% diabetes; 11.7% vascular disease; 3.7% psoriasis, and 1.0% immunodeficiency.

Visual diagnosis

Most patients had one (29.4%) or two (29.1%) affected nails (Figure 1).

In almost 60% of the cases the infected area was distributed across less than 50% of the nail area (Figure 2).

Matrix area involvement was detected in 25.8% of cases. Analysis of the distribution of types of onychomycosis showed that distal lateral subungual onychomycosis was the most frequent form of the disease affecting both finger and toe nails.

In the fingernail section of the population, 44.7% of patients were diagnosed with distal lateral subungual onychomycosis due to dermatophytes; whereas the prevalence of *Candida* onychomycosis was 35.7%; all other types of onychomycosis concerned fewer than 10% of patients.

For the toenail population, distal lateral subungual onychomycosis due to dermatophytes occurred in 71.8% of cases; total onychodystrophy due to dermatophytes was the second most common diagnosis, present in 10.1% of patients; all other types of onychomycosis concerned fewer than 10% of the toenail population (Figure 3).

Mycological sampling

Only 3.4% of GPs and 39.6% of dermatologists requested nail sample analyses, leading to missing information regarding causative agent in a high proportion of cases. When samples were taken, results were positive in 58.0 and 78.1% of cases for requests made by GPs and dermatologists respectively. The fungus strains described the most often by GPs were *Candida albicans* (30%), *Trichophyton rubrum* (25%), *Penicillium spec.* (20%) and *Scopulariopsis brevicaulis* (10%). Other fungus strains represented less than 10% of the nail sample analyses conducted.

Dermatologists rated *Trichophyton rubrum* (44.4%), *Trichophyton mentagrophytes var. interdigitale* (6.6%) and *Trichophyton mentagrophytes var. mentagrophytes* (6.5%) as the most current strains: other fungus strains represented less than 6%.

Treatment strategies

Treatment strategies reported depend largely on the type of treating physician, with GPs preferring monotherapy and dermatologists preferring combination therapy (Figures 4 & 5).

The most frequently prescribed treatment was topical amorolfine (61.8%), followed by oral terbinafine (21.7%) and itraconazole (15.5%).

The prescribed treatment varied depending on whether the treatment was monotherapy or combination (Table 2).

Conclusion

This international epidemiological survey confirmed that regular education on the diagnosing and treatment of onychomycosis remains a major issue. Current practice should include mycological sampling to identify yeasts and strains, allowing for an adequate therapy. Combination therapies such as a combination of systemic fungistatics (i.e. terbinafine) and topical antifungals (i.e. amorolfine nail lacquers) should be the preferred approach to a successful treatment of onychomycosis[8,9].

Figure 2 Distribution of affected nail area of target nails

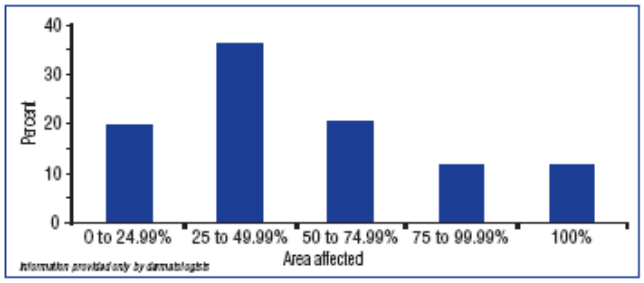


Figure 3 Distribution of types of onychomycosis

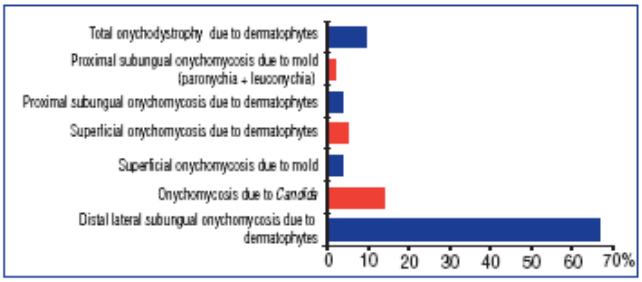


Figure 4 Distribution of treatments as prescribed by general physicians

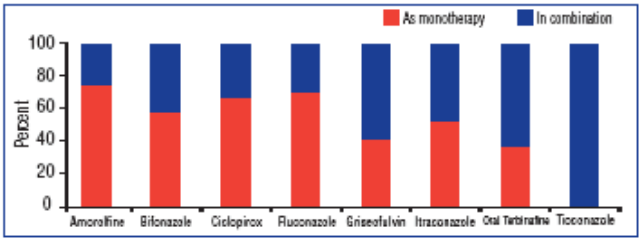


Figure 5 Distribution of treatments as prescribed by dermatologists

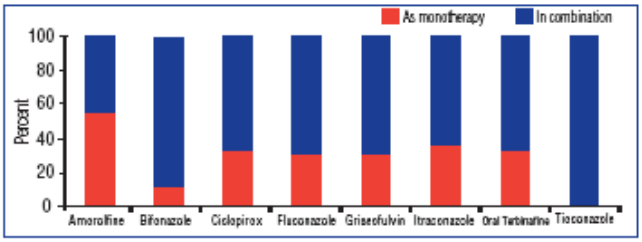


Table 2

	Monotherapy	Combination
Topical amorolfine	58.4%	41.6%
Oral terbinafine	33.9%	66.1%
Topical itraconazole	37.5%	62.5%

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