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Efficacy of topical resin lacquer, amorolfine and oral terbinafine for treating toenail onychomycosis: a prospective, randomized, controlled, investigator-blinded, parallel-group clinical trial

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Summary

Background Norway spruce (*Picea abies*) produces resin to protect against decomposition by microbial pathogens. *In vitro* tests have shown that spruce resin has antifungal properties against dermatophytes known to cause nearly 90% of onychomycosis in humans.

Objectives To confirm previous *in vivo* observations that a topical resin lacquer provides mycological and clinical efficacy, and to compare this lacquer with topical amorolfine hydrochloride lacquer and systemic terbinafine for treating dermatophyte toenail onychomycosis.

Methods In this prospective, randomized, controlled, investigator-blinded study, 73 patients with onychomycosis were randomized to receive topical 30% resin lacquer once daily for 9 months, topical 5% amorolfine lacquer once weekly for 9 months, or 250 mg oral terbinafine once daily for 3 months. The primary outcome measure was complete mycological cure at 10 months. Secondary outcomes were clinical efficacy, cost-effectiveness and patient compliance.

Results At 10 months, complete mycological cure rates with the resin, amorolfine and terbinafine treatments were 13% [95% confidence interval (CI) 0–28], 8% (95% CI 0–19) and 56% (95% CI 35–77), respectively ($P \leq 0{\cdot}002$). At 10 months, clinical responses were complete in four patients (16%) treated with terbinafine, and partial in seven (30%), seven (28%) and nine (36%) patients treated with resin, amorolfine and terbinafine, respectively ($P < 0{\cdot}05$). Resin, amorolfine and terbinafine treatments cost €41·6, €56·3 and €52·1, respectively, per patient ($P < 0{\cdot}001$).

Conclusions Topical 30% resin lacquer and topical 5% amorolfine lacquer provided similar efficacy for treating dermatophyte toenail onychomycosis. However, orally administered terbinafine was significantly more effective in terms of mycological cure and clinical outcome than either topical therapy at the 10-month follow-up.

What's already known about this topic?

- Treatment of dermatophyte onychomycosis is a clinical challenge.
- Treatment failure is observed in 25–60% of patients with the current gold-standard treatment, orally administered terbinafine.

- When applied as a monotherapy, topical antifungals have shown limited results in treating dermatophyte onychomycosis, with < 30% overall mycological cure rates; however, more than half of patients with onychomycosis are treated with topical preparations.

What does this study add?

- This is the first clinical trial to investigate the efficacy and safety of a 30% lacquer prepared from Norway spruce (*Picea abies*) in the treatment of dermatophyte onychomycosis.
- This treatment was comparable with the most effective topical treatment currently on the market: synthetic amorolfine hydrochloride.
- On the basis of mycological and clinical cures at 10-month follow-up, orally administered terbinafine was significantly more effective against onychomycosis than either topical therapy.

Onychomycosis represents a large burden of workload and costs to increasingly limited healthcare resources worldwide. Its estimated prevalence is 50% in Western countries among the population aged > 60 years.[1–7] Susceptibility to onychomycosis is increased by advanced age, male sex, genetic predisposition, nail trauma, use of occlusive footwear, and some concomitant comorbidities, such as diabetes, decreased peripheral circulation, psoriasis, tinea pedis, hyperhidrosis, acquired or inherited immunodeficiency disorders, and conditions that require permanent immunosuppressive medication.[8–15] In climate conditions like those in Northern and Central Europe, diagnosed cases of onychomycosis are caused by dermatophytes (85–90%), *Candida* yeasts (5–10%) and nondermatophyte moulds (5%). The most frequent anthropophilic dermatophyte species is *Trichophyton rubrum*, which can be cultured from approximately 80% of dermatophyte-positive nail samples.[16–27]

Evidence-based guidelines state that the two most effective antifungals for the treatment of dermatophyte onychomycosis are orally administered fungicidal terbinafine and fungistatic itraconazole. Success rates of these oral medications in monotherapy vary from 20% to 80%. Due to its favourable side-effect profile and lower recurrence rate, terbinafine is currently recommended as the drug of choice for primary treatment of onychomycosis.[6,28–35]

Evidence is scarce regarding the utility of topical treatments for onychomycosis. Current guidelines and recent meta-analyses have concluded unambiguously that topical antifungal monotherapy has limited efficacy for treating onychomycosis.[6,29,36] Nevertheless, over half of patients who seek advice from a general practitioner for first-time treatment of onychomycosis receive a prescription for a topical antifungal preparation.[17] The most effective topical antifungals, based on recent guidelines, are 5% amorolfine hydrochloride lacquer and 8% ciclopirox lacquer.[6] Both topical amorolfine and topical ciclopirox applied for 18 months provided approximately 30% mycological cure rates. However, when the intended outcome included both mycological and clinical cures, successful outcomes with topical treatments alone were < 10%.[37–40]

Both *in vitro* tests and clinical trials have demonstrated that salves and lacquers that comprise purified resin from the conifer Norway spruce (*Picea abies*) are antibacterial and antifungal, particularly against Gram-positive bacteria and dermatophytes.[41–45] Antifungal activity is maximal when the lacquer resin content (w/w) is ≥ 30%.[46] Resin-based preparations have been used for centuries as traditional remedies for various fungal skin and nail disease in Northern Europe, and industrially manufactured resin lacquer has been available in the European Union for 5 years. Nevertheless, only one clinical proof-of-concept study is currently available on the feasibility and clinical efficacy of 30% resin lacquer to treat toenail onychomycosis.[47]

We conducted the current study to corroborate the previous observational clinical trial[47] with more valid methods and a more clinically relevant experimental design. Our aim was to compare the efficacy, safety and cost between topically administered 30% resin lacquer for the treatment of dermatophyte toenail onychomycosis and the current 'best practices': topical 5% amorolfine and systemic terbinafine.

Patients and methods

Study patients

This prospective, randomized, controlled, investigator-blinded, parallel-group clinical trial was designed to compare the clinical efficacy *in vivo* (clinical cure) and the eradication capacity *in vitro* (mycological cure) of three treatments for dermatophyte toenail onychomycosis. These treatments were topical resin lacquer (Abicin® 30% nail lacquer; Repolar Ltd, Espoo, Finland), topical 5% amorolfine hydrochloride (Loceryl® 5% nail lacquer; Galderma Ltd, Amersham, U.K.) and oral terbinafine.

In October 2013 we placed an advertisement in Finnish newspapers in the cities of Lahti and Vääksy to recruit 75 adult volunteers with onychomycosis for enrolment into a clinical study to investigate various treatment options for toenail onychomycosis. Eligible subjects were required to provide toenail samples for screening. The inclusion criteria, based on

the toenail samples, were a positive dermatophyte culture and a positive potassium hydroxide stain. Exclusion criteria were a negative dermatophyte culture or KOH stain; onychomycosis caused by yeasts or nondermatophyte moulds; liver failure, determined by plasma γ-glutamyl transferase levels > 120 U L^{-1} ($2 \times$ upper limit of normal range); kidney failure, determined by plasma creatinine levels > 100 μmol L^{-1} (upper limit of normal range); a known hypersensitivity to resin, amorolfine or terbinafine; potential adverse cross-reactions between resin, amorolfine or terbinafine and any concurrently taken medication; and any prior topical or oral antifungal treatment administered, for any reason, in the year before the beginning of the study.

Study design

The study design and follow-up are shown in Figure 1. Patients received one of three monotherapies: 30% resin lacquer, applied once daily for 9 months; 5% amorolfine lacquer, applied once weekly for 9 months; or 250 mg terbinafine, taken orally once daily for 3 months. Treatment was initiated at the same time in all patients, at the beginning of January 2014. All patients were reviewed at the outpatient department during weeks 20 and 42 and were contacted by phone during weeks 6, 13 and 29. The only exception was the patients on terbinafine treatment, whose plasma γ-glutamyl transferase levels were additionally measured 2 weeks after study initiation for safety reasons. During the control visits, complete clinical examinations were performed by a physician, and toenail samples, sequential digital photographs of the most disfigured and brittle toenails, and a comprehensive panel of laboratory tests were acquired (see Appendix).

In the three phone calls, patients were asked about potential treatment-related side-effects, compliance with treatment, patients' perception of treatment outcome, and their willingness to continue in the study. In each treatment arm, the treatment regimen was discontinued 5 weeks before the last toenail sampling to provide an appropriate washout period before the final culture and KOH analysis.

Clinical responses to treatment were based on the proximal linear growth of healthy nail; thus, the clinical responses were classified as unchanged, partial (evident proximal linear growth of healthy nail) or complete. Partial responses were defined as significant reductions in onycholysis, subungual hyperkeratosis and streaks. A complete response was a fully normal appearance of the toenail.

Evaluation of compliance was based on patient self-reports of whether the treatment protocol was followed 100% (complete), 80% (good), 60% (moderate) or 40% (poor) of the time. Cost analysis was based on the retail price of a 10-mL bottle of Abicin® 30% resin lacquer, a 5-mL bottle of Loceryl® 5% amorolfine lacquer, and 98 tablets of generic 250 mg terbinafine, sold by the University Pharmacy in Finland, January 2014. The cost was expressed as the average treatment cost per patient; for the total cost, this average was extrapolated to the entire study treatment arm.

Safety and tolerability

To ensure safety and to assess potential contraindications for the treatment regimens, all patients included in the study underwent a comprehensive medical interview and physical examination. To identify patients who might develop intolerable adverse events due to drug combinations, all concurrent medications were cross-checked to verify compatibility with the resin, amorolfine and terbinafine regimens at the beginning of the study. All patients were informed of the possibility of developing a hypersensitivity to resin, amorolfine or terbinafine. If patients experienced symptoms that corresponded to any level of hypersensitivity, they were dropped from the study.

Ethics, registration and approval

All patients were orally informed of the study course, and they all provided written informed consent. The European Medicines Agency was duly notified of the study (EudraCT number 2012-004822-48), and the study protocol was approved by the ethics committee of Helsinki University Hospital (clinical trial number 334/13/03/01/12) and registered in the United States ClinicalTrials.gov database (ClinicalTrials.gov identifier: NCT01851590).

Randomization and blinding

This was an investigator-blinded study. Four physicians (T.A., R.T., A.S., J.J.J.) conducted the clinical examinations and collected toenail specimens for KOH staining and mycological

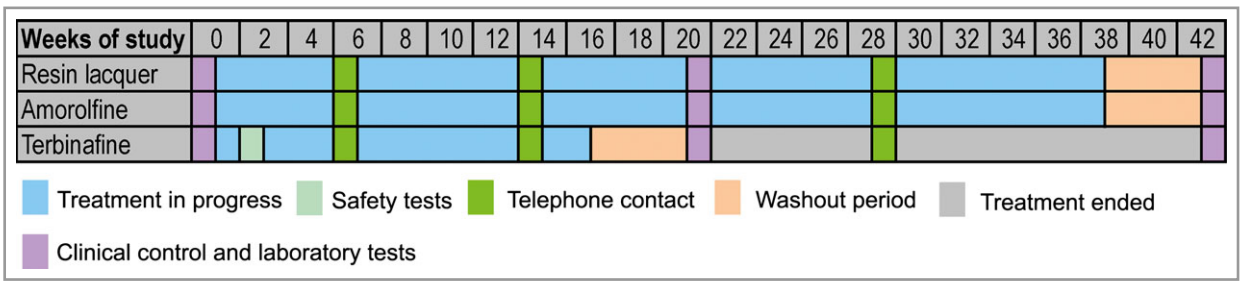

Fig 1. Study design. Resin (once daily) and amorolfine (once weekly) lacquers were applied to the affected nails for 9 months. Terbinafine (250 mg once daily) was taken orally for 3 months.

cultures. After confirming both KOH and culture positivity in toenail samples, the patients were randomly allocated to receive one of the three therapies for onychomycosis. Randomization was in permuted blocks of six with an allocation ratio of 1 : 1 : 1. Treatment was concealed from the investigators; therefore, a research coordinator allocated patients to the three arms according to the randomization list, and delivered the treatments to the patients. At each sampling time, the investigators were thus blinded to the treatment arm.

Grading and classification[6] of onychomycosis and evaluation of outcomes were conducted collectively only at the end of the study: at 10 months, investigators reviewed a series of toenail photographs (three photographs per patient) in random order. The final analysis and assessment of the treatment outcome was carried out in a blinded manner, without the investigators knowing to which treatment arm the patient belonged at any given time.

Estimation of sample sizes

The sample size was estimated according to the primary outcome: complete mycological cure (negative KOH staining and negative fungal culture) at the end of the study (at 10 months). Estimation was based on the design of a binary-outcome head-to-head superiority trial. Orally administered terbinafine treatment was considered the active control. Approximately 25 patients per arm were required to have 80% power ($\beta = 0{\cdot}2$) at a two-sided $\alpha = 0{\cdot}05$ significance level to detect a decrease in primary outcome from 50% in the terbinafine treatment arm to 15% in the amorolfine or resin lacquer treatment arms.

Statistical analysis

All data collection, analyses and reporting were based on the CONSORT statement.[48] Primary and secondary outcome analyses were based on the intention-to-treat population, and missing values were imputed using the last-observation-carried-forward method. Qualitative data are expressed as frequencies and percentages, and differences between parallel groups were compared with the χ^2-test or Fisher's exact test, as appropriate. Normally distributed quantitative data are expressed as the mean ± SD, and skewed data are presented as the median and interquartile range (1st quartile to 3rd quartile). Differences between quantitative data were assessed with one-way ANOVA, and pairwise comparisons were performed with Bonferroni's post hoc test. To assess the mycological treatment outcome, proportions and 95% confidence intervals were calculated for negative KOH staining, negative cultures, and a combination of these at the 4- and 10-month time points. Cochran–Mantel–Haenszel and χ^2-tests were used to analyse efficacy criteria (i.e. clinical and mycological outcomes). All tests were two-sided, and $\alpha = 0{\cdot}05$ was considered statistically significant.

Results

In November 2013, 129 patients were screened for the study. Of those, 48 (37%) were excluded due to negative KOH staining or cultures and eight (6%) were excluded because onychomycosis was caused by nondermatophyte mould or yeast. At baseline, 73 patients (57%) who met the entry criteria were randomized to one of the following three arms (intention-to-treat population): topical resin lacquer (23 patients), topical amorolfine lacquer (25 patients) and oral terbinafine (25 patients) (Table 1). Four patients (5%) discontinued the study; the reasons for dropping out from the terbinafine treatment arm were adverse events in two cases (8%), and one (4%) patient-based refusal without any specific cause. One patient (4%) discontinued amorolfine treatment after 4 months due to subjectively assessed lack of efficacy (Fig. 2).

Outcomes for primary objectives

Figure 3 shows the mycological treatment results, including negative KOH staining, negative cultures and both (i.e. complete mycological cure), at the 4- and 10-month follow-ups. At 4 months, we found significant differences in negative fungal cultures between the groups treated with amorolfine (96% of cultures) and resin lacquer (48% of cultures, $P < 0{\cdot}001$), and between the groups treated with amorolfine and terbinafine (52% of cultures, $P < 0{\cdot}001$).

At 10 months, the treatment outcomes in the resin and amorolfine treatment arms were significantly inferior to the outcomes in the terbinafine treatment arm (Fig. 3). Negative KOH staining was observed in 56% of the terbinafine treatment group, 13% ($P = 0{\cdot}002$) of the resin treatment group and 16% ($P = 0{\cdot}004$) of the amorolfine treatment group. Negative cultures were observed in 52% of the resin lacquer treatment group and 92% of the terbinafine treatment group ($P = 0{\cdot}043$). Complete mycological cure was observed in 56% of the terbinafine treatment group, 13% ($P = 0{\cdot}002$) of the resin treatment group and 8% ($P < 0{\cdot}001$) of the amorolfine treatment group.

Outcomes for secondary objectives

Table 2 and Figure 4 show the clinical responses to treatment at 4 and 10 months. During the 4-month follow-up, all patients reported full compliance, except one patient (4%) in the amorolfine treatment arm. That patient reported moderate compliance (60% of the treatment protocol).

The costs of the resin lacquer, amorolfine lacquer and terbinafine treatment were €41·6, €56·3 and €52·1 per patient, respectively, during the entire treatment period. This represented €0·15, €0·21 and €0·58, respectively, per patient per treatment day. The differences in cost were highly significant among all treatment arms, both per day and per treatment course ($P < 0{\cdot}001$).

Table 1 Baseline demographics and disease characteristics of the patients (intention-to-treat population)

	Resin lacquer	Amorolfine	Terbinafine	P-value
Sex				
Male	21 (91)	20 (80)	17 (68)	
Female	2 (9)	5 (20)	8 (32)	0·14
Age (years)	64 ± 10 (41–87)	63 ± 11 (43–87)	64 ± 9 (38–77)	0·96
BMI (kg m^{-2})	25 ± 3 (20–31)	27 ± 4 (22–38)	27 ± 4 (20–38)	0·17
Dermatophyte species[a]				
T. rubrum	20 (87)	24 (96)	21 (84)	
T. mentagrophytes	3 (13)	1 (4)	4 (16)	0·37
Type of onychomycosis				
WSO	1 (4)	2 (8)	6 (24)	
DLSO	8 (35)	10 (40)	13 (52)	
DO	14 (61)	13 (52)	6 (24)	0·056
Disease history				
1–3 years	3 (13)	4 (16)	4 (16)	
3–5 years	1 (4)	3 (12)	3 (12)	
5–10 years	6 (26)	3 (12)	5 (20)	
10 years	13 (57)	15 (60)	13 (52)	0·87
Previous treatments				
Oral medication	9 (39)	10 (40)	6 (24)	
Topical medication	7 (30)	8 (32)	11 (44)	0·74
Use of podiatrist	2 (9)	3 (12)	2 (8)	0·88
Chronic diseases				
Psoriasis	1 (4)	0	1 (4)	0·58
Rheumatoid arthritis	0	2 (8)	0	0·14
Diabetes (type 1 or 2)	1 (4)	1 (4)	2 (8)	0·79
Hyperlipidaemia	3 (13)	6 (24)	5 (20)	0·62
Hypertension	7 (30)	8 (32)	8 (32)	0·99
Hypothyreosis	1 (4)	2 (8)	4 (16)	0·37
ASO	3 (13)	4 (16)	4 (16)	0·95
Atrial fibrillation	2 (9)	3 (12)	3 (12)	0·92
Plasma creatinine (μmol L^{-1})	76 ± 15 (54–126)	78 ± 13 (57–110)	79 ± 11 (51–98)	0·61
Plasma GGT (U L^{-1})	29 (17–41)	21 (14–41)	27 (18–47)	0·79

Data are number of patients (%), mean ± SD (range) or median [interquartile range]. ASO, arteriosclerosis obliterans; BMI, body mass index; DLSO, distal and lateral subungual onychomycosis; GGT, γ-glutamyl transferase; TDO, total dystrophic onychomycosis; WSO, white superficial onychomycosis. [a]*Trichophyton* spp.

Safety and tolerability

In the terbinafine treatment arm, no patients were excluded due to increased γ-glutamyl transferase at the 2-week laboratory control test. However, two patients experienced adverse events that resulted in treatment discontinuation (8% of patients in the terbinafine arm), and both events were deemed to be due to terbinafine treatment. One patient (4%) experienced a gastrointestinal disorder that manifested as diarrhoea, and the other patient (4%) developed a rash that was potentially related to terbinafine treatment. No patients reported adverse events associated with resin or amorolfine lacquer during the study period.

Discussion

The results of this study indicate that resin lacquer has antifungal efficacy similar to that of amorolfine lacquer, but both topical preparations were significantly inferior to orally administered terbinafine in terms of mycological cure and clinical outcome. To our knowledge, this was the first prospective, randomized, investigator-blinded, controlled clinical study on the effectiveness of a resin-based lacquer in the treatment of dermatophyte onychomycosis. By the end of the study, terbinafine achieved complete mycological cure in 56% of patients; in contrast, resin lacquer and amorolfine achieved mycological cures in only 13% ($P = 0·002$) and 8% ($P < 0·001$) of patients, respectively.

At the beginning of this study, 129 toenail specimens were collected by experienced surgeons to ensure sufficient nail samples for KOH staining and mycological cultures and to reduce the probability of false negatives. No sample was deemed insufficient for fungal diagnostics. Therefore, it was surprising to find that only 73 samples (57%) showed positive KOH staining and cultures for dermatophyte onychomycosis. Nondermatophyte mould or *Candida* was present in eight excluded samples (6%), but 48 samples (37%) did not show any signs of fungal nail infection. The proportion of nondermatophyte onychomycosis was consistent with previous findings, but the rate of negative samples was surprisingly high,

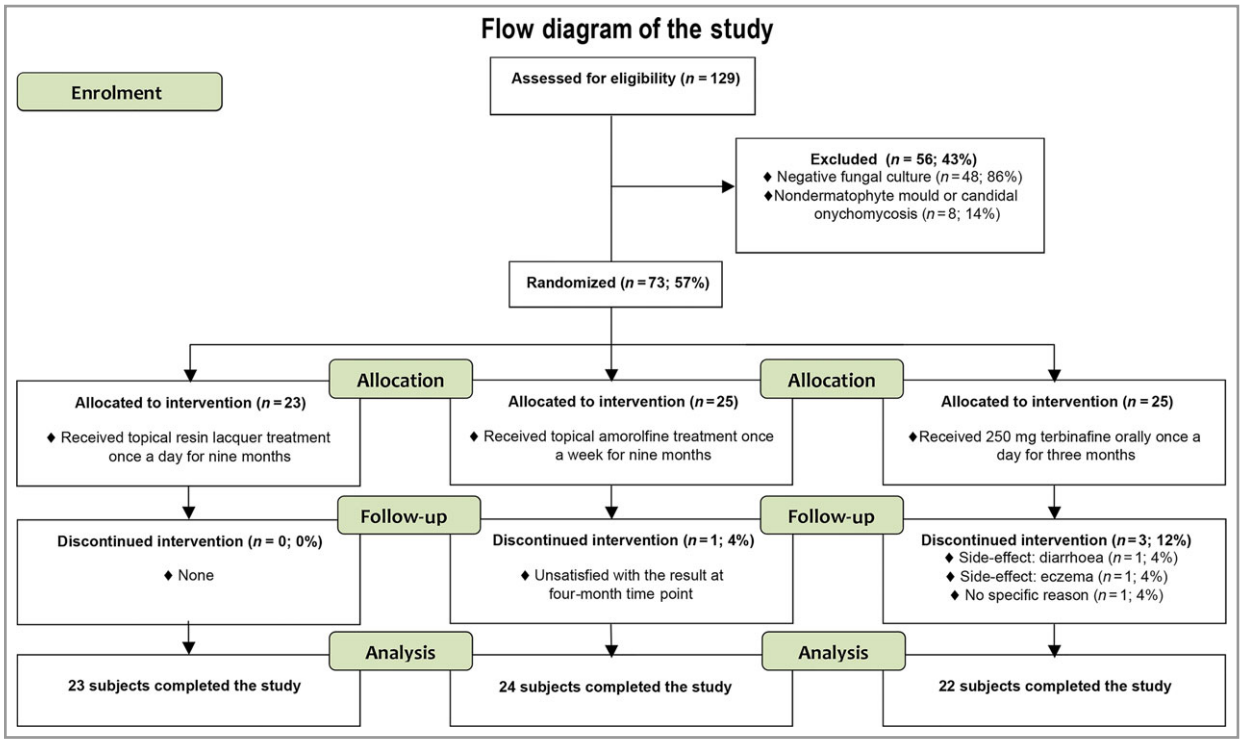

Fig 2. Flow diagram of the study.

even considering the reported 5–15% rate of false-negative findings.[1,11,17,20] This result underlines the importance of a differential diagnosis before initiating antifungal treatment and the need for better diagnostic tools, such as periodic acid–Schiff staining and polymerase chain reaction-based techniques. However, to date, the general availability of these diagnostic techniques is limited.[6,18,29,36]

Clinical and mycological cures require, respectively, at least 80% recovery of disfigured, onychomycotic nail plates to the healthy state, and negative findings in both KOH staining and cultures. A complete cure, which requires both observations, has justly been criticized as too stringent a requirement, because KOH staining does not necessarily correlate with the prevailing outcome at the end of antifungal treatment. It has been shown, particularly with topical treatments, that subungual samples may remain KOH positive, despite a negative mycological culture and clinical evaluation of complete healing. This discrepancy may be explained by retention of the study drug in subungual debris, which could be transferred to the culture medium where it would inhibit fungal growth. To avoid these diagnostic errors, it is recommended that topical treatment administration should continue for at least 1 year and, if necessary, up to 18 months. Moreover, a significantly longer washout period (e.g. 3–6 months) might be necessary to ensure complete removal of nonviable fungal cells, subungual debris and residual topical medication before assessing the final outcome.[49,50] In our study, the lack of a complete washout was the most probable explanation for the significant discrepancy we observed between the rates of negative KOH staining and negative fungal cultures in both topical treatment arms at 10 months. Moreover, we most likely slightly underestimated the rates of complete mycological cure in the resin and amorolfine treatment arms due to positive KOH staining. However, this potential bias was not statistically relevant to the currently observed outcomes.

Because recent guidelines indicate a limited role for topical preparations as a monotherapy for onychomycosis, topical medicines are recommended only for preventing recurrence, as part of a combination therapy,[51–55] or for treating mild, white, superficial onychomycosis and early distal and lateral subungual onychomycosis when < 80% of the distal nail plate is ravaged by a dermatophyte infection.[6] However, topical treatment is the only option for those in whom systemic antifungals are contraindicated (e.g. due to liver or renal failure, hypersensitivity or an adverse interaction with a concurrent medication). Despite generally pessimistic attitudes towards the role of topical treatment in toenail onychomycosis, several well-conducted clinical trials and comprehensive review articles have shown that topical treatment of onychomycosis is feasible and that the clinical outcome is acceptable for mild-to-moderate toenail onychomycosis due to dermatophyte, *Candida* and mixed infections. Mycological cure can be achieved in 6 months, but a clinical cure may require at least 12 months of treatment.[51]

A recent review article by Gupta *et al.*[56] concluded that the most effective topical medication for toenail onychomycosis might be 10% efinaconazole, administered once daily; however, they also observed acceptable outcomes with amorolfine, ciclopirox and tavaborole. In the current study, we compared resin-based lacquer with amorolfine, because abundant, reli-

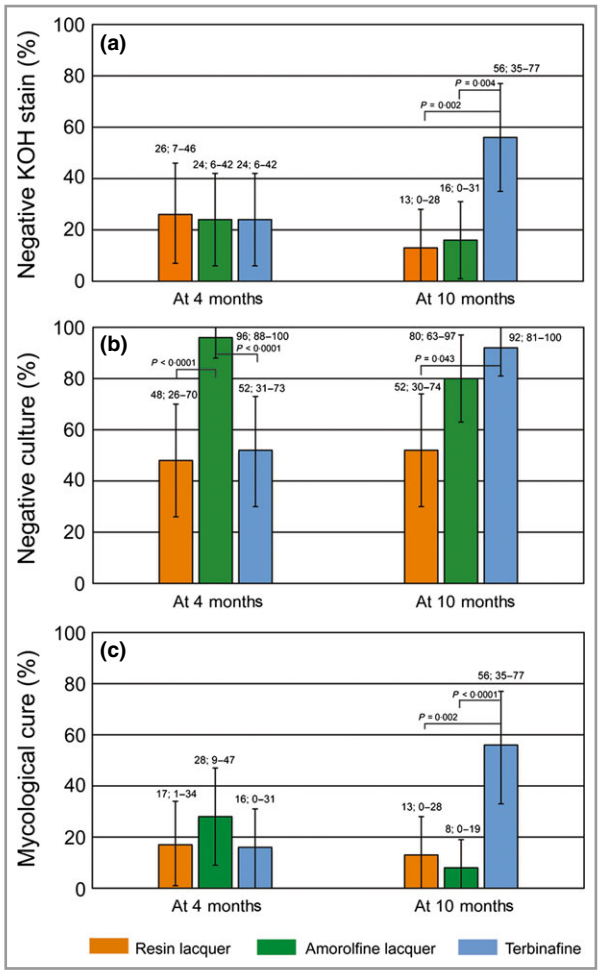

Fig 3. Outcomes at 4 and 10 months of treatment. Test results for (a) negative potassium hydroxide stains and (b) negative fungal cultures. (c) The combination of negative results on both tests, indicating complete mycological cure. Chart labels indicate proportions (%) and 95% confidence intervals (intention-to-treat population, last observation carried forward).

Table 2 Clinical responses to treatments at 4- and 10-month follow-ups (intention-to-treat population, last observation carried forward)

	4 months, partial/complete response	10 months, partial/complete response
Resin lacquer (n = 23)	0/0	7 (30)/0
Amorolfine lacquer (n = 25)	0/0	7 (28)/0
Terbinafine (n = 25)	11 (44)/0	9 (36)/4 (16)

Data are n (%). At the 4- and 10-month time points, the differences between terbinafine and both resin lacquer and amorolfine were statistically significant ($P < 0{\cdot}05$).

able information was available on the feasibility, outcomes and potential side-effects of amorolfine in the treatment of dermatophyte onychomycosis.[6,28,38,39,52,56] We observed no significant differences between the resin and amorolfine treatment arms in terms of mycological and clinical cures, incidence of hypersensitivity, or treatment-related compliance; however, the results of treatment compliance based on patient self-reporting may not be completely reliable. The resin lacquer was significantly more cost-effective than amorolfine lacquer for treating onychomycosis over the study period.

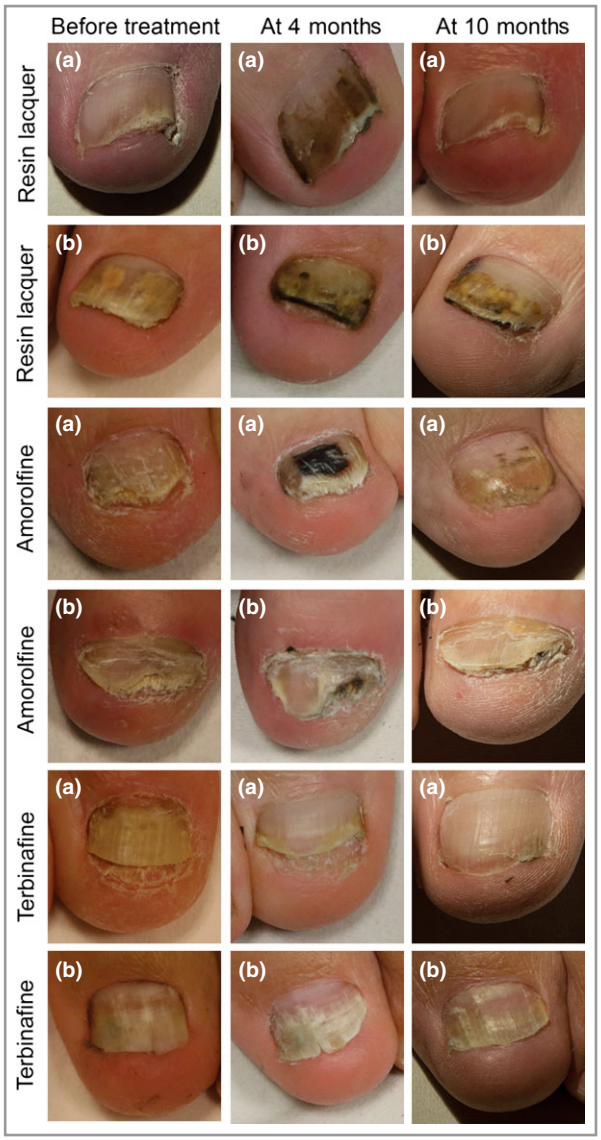

Fig 4. Photographs of affected toenails presented in investigator-blinded settings for objective assessments of the resin, amorolfine and terbinafine treatment arms. Labels (a) and (b) indicate outcome assessments: (a) improved and (b) ineffective. Photographs were taken before treatment (left), at 4 months (centre) and at 10 months (right).

It is known that the hydrophilic nail plate inhibits lipophilic antifungal components from penetrating to the infection site, where biological structures support sporogenesis.[56] Thus, the concentration of a topical preparation on the dorsal nail plate may be 1000 times higher than the concentration of active antifungal molecules that reach the nail bed and matrix.[57] This situation suggests that, rather than developing new topical

antifungal agents, efforts might be better spent in researching, developing and optimizing existing preparations to improve their bioavailability and efficiency. The authors of this study believe that current topical regimens are not utilized to their full potential and many could be developed to optimize their usability and efficacy.[58]

This study had several potential limitations. Firstly, the treatment period was relatively short. However, the treatment periods followed current guidelines for the treatment of toenail onychomycosis. Furthermore, we included patients with severe onychomycosis that might not have been amenable to monotherapy with a topical antifungal treatment. In 46% of diagnosed cases, the clinical pattern was total dystrophic onychomycosis, the most difficult subtype to treat. However, it was very difficult to recruit patients with early-stage onychomycosis from the population of farmers and factory workers who live in rural areas in Finland. Although the difference in the number of cases of total dystrophic onychomycosis was not statistically significant at baseline within the treatment arms, the higher incidence of total dystrophic onychomycosis may have caused bias and led the resin and amorolfine groups to perform less well. Thus, it may be worth repeating the study in the future with larger sample sizes and exclusion of patients who have total dystrophic onychomycosis.

In conclusion, the present clinical study corroborated – in a randomized, investigator-blinded and controlled setting – that 30% lacquer refined from spruce (*Picea abies*) resin had clinically relevant antifungal properties comparable with those of amorolfine hydrochloride lacquer for the treatment of dermatophyte onychomycosis. However, neither topical treatment was as effective as oral terbinafine.

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Appendix

Laboratory tests

During the 42-week study period, laboratory tests were conducted on samples collected before treatment, at 20 weeks and at 42 weeks. The tests included a fungal culture, KOH staining of the toenail sample and blood tests. Cultures and KOH microscopy were performed at an independent, specialized mycology laboratory with standard techniques (Medix Laboratories Ltd, Helsinki, Finland). The blood tests measured plasma γ-glutamyl transferase levels (also at 2 weeks); plasma creatinine levels; the total number of white blood cells, including neutrophils, monocytes, basophils, lymphocytes and eosinophils; the total number of red blood cells, including erythrocytes and haematocrit; erythrocyte indices, including the mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and haemoglobin level; and the total number thrombocytes (initially and at 42 weeks).

