mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Treatment of distal subungual onychomycosis with a topical preparation of urea, propylene glycol and lactic acid: results of a 24-week, double-blind, placebo-controlled study

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Summary

Onychomycosis is difficult to cure as this requires eradication of the primary infection and protection of new areas of growth from reinfection. A new topical treatment (K101) has been developed. The aim of this study was to assess the efficacy, safety and tolerability of K101 treatment of distal subungual onychomycosis. This was a 24-week (plus 2-week washout), multicentre, randomised, double-blind, placebo-controlled study in 493 patients with distal subungual onychomycosis (K101, $n = 346$; placebo, $n = 147$), stratified according to degree of nail involvement. More patients with ≤50% nail involvement achieved the primary endpoint (mycological cure after 26 weeks) in the K101 group (27.2%) than placebo (10.4%; $P = 0.0012$). Proportions for patients with 51–75% involvement were 19.1% for K101 and 7.0% for placebo (not significant). More patients applying K101 than placebo judged that their condition had improved from week 2 ($P = 0.0148$) to week 24 ($P = 0.0004$). No safety issues were identified. K101 provides early visible improvements in nail appearance and a clinically meaningful antifungal activity.

Key words: K101, onychomycosis, placebo.

Introduction

Fungal infection of the finger and/or toe nails, onychomycosis affects from 2% to 13.8% of adults.[1–3] Prevalence of onychomycosis increases with age reaching 25–30% in the elderly,[2] immunocompromised patients and in patients with diseases that affect the peripheral circulation, such as diabetes mellitus.[4] Approximately 90% of infections are caused by the dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*,[5] which typically invade the nail and nail bed via the distal or lateral margins causing distal subungual onychomycosis, the most frequently observed manifestation. Infections can be painful, have negative cosmetic consequences on a patient's self-image and are associated with increased risk of secondary infection.[6]

Onychomycosis can be treated both systemically and topically. Systemic antimycotic drugs, such as terbinafine and itraconazole are effective treatments for onychomycosis. However, use of systemic treatments must be balanced against the risk of adverse effects, the most frequent of which are gastrointestinal effects, headache and minor rashes.[6] Serious adverse events occur rarely (0.7% for terbinafine[7]), but can include serious liver toxicity. Topical treatments are generally formulated as lacquers containing antifungal agents, including amorolfine and ciclopiroxolamine. Lacquers allow concentrated antifungal agents to be applied directly to the site of infection avoiding systemic exposure to active compounds. Establishing topical treatment as a clinical option for treatment of onychomycosis has been challenging because of the questionable quality of some published studies. A lack of control groups in some studies has been cited as a serious limitation and other

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Submitted for publication 9 October 2011
Revised 9 April 2012
Accepted for publication 11 May 2012

doi:10.1111/j.1439-0507.2012.02215.x

studies have been published in non-peer-reviewed supplements.[6] A Cochrane review stated that there is little evidence that topical antifungals are effective against onychomycosis, and recommends that large randomised controlled trials be conducted to establish alternatives to systemic treatments.[8]

A new topical preparation containing propylene glycol, urea and lactic acid (K101), has been developed for the treatment of nails affected by onychomycosis. Urea has a nail dissolving effect when applied in solutions containing more than 20% urea.[9,10] Propylene glycol has humectant and keratolytic effects as well as certain antibacterial and antimycotic properties.[11–16] Lactic acid is a common additive to dermatological products where it is included mainly for its exfoliating and hydrating properties. The antimicrobial activity of lactic acid and other organic acids is also widely used in the food industry. When used in combination, urea and propylene glycol have a softening and keratolytic activity on the nail.[17] During the development of K101, a number of studies were undertaken to determine the minimum inhibitory concentration for *T. rubrum* and several other common microorganisms. The three active components of K101 were tested individually, as binary and tertiary mixtures and as the final K101 solution. The final K101 solution provided the highest level of activity. The concept of treating onychomycosis with a combination of urea, propylene glycol and lactic acid was previously tested in a small study of 23 patients that confirmed its efficacy in the treatment of onychomycosis.[18] The mode of action is not fully known, but may be mainly attributable to the osmotic effect of propylene glycol[11] and to the effects exerted by the other ingredients, urea and lactic acid [J. Faergemann, personal communication]. We report here on a randomised, placebo-controlled trial intended to assess further the efficacy, safety and tolerability of K101 in the topical treatment of onychomycosis.

Materials and methods

Study population

The study population comprised men and women (including fertile women) aged 18 years or older with distal ungual onychomycosis of the finger(s) and/or toe(s) affecting ≤75% of the nail bed according to a subjective assessment by the Investigator. Infection with dermatophytes (e.g. *T. rubrum* or *T. mentagrophytes*) was to be confirmed following culture of nail samples collected at screening. Patients were not considered eligible to take part in the study if they were found to have proximal subungual onychomycosis, if their distal subungual onychomycosis had extended into the proximal portion of the nail or if it affected >75% of the nail. Patients with conditions known to cause abnormal nail appearance, immunosuppression and signs of severe peripheral circulatory insufficiency were excluded, as were patients who had used topical antifungal nail treatment within 1 month or systemic antifungal treatment within 3 months of screening. Patients were not permitted to have participated in another clinical nail study during the previous 3 months or to have a known allergy to any of the study treatments.

This study was conducted under the ethical principles in the Declaration of Helsinki and according to International Conference on Harmonisation-Good Clinical Practice. Local ethics committees approved the study protocol and all patients provided written informed consent to participate in the study.

Study design

This was a randomised, double-blind, placebo-controlled Phase III study conducted in Sweden (28 centres) and Poland (10 centres) to assess the efficacy, safety and tolerability of topical treatment K101 (propylene glycol, urea and lactic acid) in adults with distal subungual onychomycosis. Eligible patients were randomised to receive either K101 or matching placebo according to a computer-generated randomisation schedule stratified according to the percentage of target nail involvement (defined as either ≤50% or 51–75%). The placebo was considered to be indistinguishable from K101. Patients with nail involvement ≤50% were allocated to the active treatment (K101) or placebo following a 3 : 1 allocation ratio, whereas the allocation ratio was 1 : 1 for patients with nail involvement of 51–75%. The 3 : 1 ratio was used in the ≤50% stratum to increase the chance of patients receiving active treatment, thereby facilitating patient recruitment. Patients applied their allocated treatment to the surface of all affected nails and under the free edge drop-wise (3–5 drops per nail), topically at bedtime every day for 24 weeks. A single affected nail with confirmed onychomycosis was identified as the target nail for all assessments. Target nails had to fulfil the study's inclusion and exclusion criteria and harbour dermatophytes as confirmed by positive nail culture results. During the initial 4-week treatment phase, patients wrapped surgical tape (Micropore™; 3M, Sollentuna, Sweden) around the treated nails; no occlusion was used during the following 20-week treatment phase. Patients attended visits at screening, baseline, and at weeks 2, 4, 8, 12 and 26. Adherence

was assessed by recording responses to 'On average, how many days per week have you applied the study treatment since last visit?'. 'Good' adherence was defined as applying the once-daily study treatment on ≥80% of treatment days.

Efficacy assessments

Subungual debris for mycological assessments was collected from beneath the nail plate of the target nail at the most proximal part of the infection that could be reached using a sterile curette. The material was studied with direct fluorescence microscopy using Blancophor and potassium hydroxide. Subungual material was also cultured on routine media and dermatophytes were identified according to standard criteria.[19]

Patient subjective score assessments

Patients evaluated the treatment efficacy using the following scores: (1) no improvement (no signs of improvement/worsening); (2) some improvement (some improvement but not of any relevance for the patient); (3) improvement (substantial improvement and reduction in patient's symptoms); (4) almost cured (most symptoms had disappeared) and (5) cured (completely cured without any symptoms left).

Subjective scores for ease of treatment application were based on a scale to 1–5, where one was 'Very easy' and five was 'Very difficult'. Patients were asked, 'Besides having to bend down to reach your toes, how did you find it to apply the study product?' and 'How did you find it to apply the occlusive surgical tape?'

Safety assessments

Adverse events were recorded from the start of the first treatment period to the end of the study. At each study visit, investigators asked patients how they were feeling using open questions and rated any reported events for intensity and relationship to study treatment.

Statistical methods

Power calculations indicated that 70 patients receiving placebo and 210 patients receiving K101 would have a 94% power to detect a difference in the proportion of patients with mycological cure, using Fisher's test with a 5% two-sided significance level, and assuming that 10% of patients in the placebo group and 30% in the K101 group would achieve mycological cure. We planned to recruit sufficient patients to provide at least 300 evaluable patients who received K101, allowing for dropouts.

The full analysis set of patient data was based on the intention-to-treat principle and comprised all randomised patients who had applied at least one dose of the study medication and for whom at least one post dose observation was recorded for the primary endpoint. The per protocol set was a subset of the full analysis set consisting of patients who had not experienced major protocol violations and who had a measure of the primary endpoint. The safety analysis set comprised all randomised patients who applied study medication at least once.

The primary efficacy endpoint was the proportion of patients with mycological cure for K101 treatment compared with placebo after 24 weeks of treatment plus a 2-weeks washout. Mycological cure was defined as negative fungal culture and negative direct microscopy. The primary analysis was conducted with logistic regression and was performed on the patient group with ≤50% nail involvement at baseline.

The secondary endpoints mycological cure at 8 weeks, negative direct microscopy and fungal culture were analysed with logistic regression. Patients' subjective score was analysed with the proportional odds model. If the assumptions of the model were not fulfilled, the Cochran-Mantel-Haenszel model was used. Ease of application was summarised with descriptive statistics. There was no formal statistical comparison of safety data. Adverse events were classified according to the Medical Dictionary for Regulatory Activities.

Results

Patient disposition and baseline characteristics

Three hundred and forty-six patients were randomised to receive K101 and 147 placebo (Fig. 1). Of this total, 433 patients completed the study (K101, $n = 304$: placebo, $n = 129$). The most frequent cause of withdrawal was 'Patient's wish'. The two treatment groups were well balanced in terms of age, gender and ethnic origin (Table 1). Target nails identified for assessment during the study were predominantly toenails, mainly Digit one of the left or right foot (Table 1); finger nails were chosen for 15 (4%) patients in the K101 group and 4 (3%) patients in the placebo group. The predominant fungal species isolated from target nails at baseline was *T. rubrun* (93.5% of samples), followed by *T. mentagrophytes* (6.1%) and other *Trichophyton spp.* (0.4%). Most patients ($n = 429$, 87%) were judged to have 'good' adherence to treatment throughout the study.

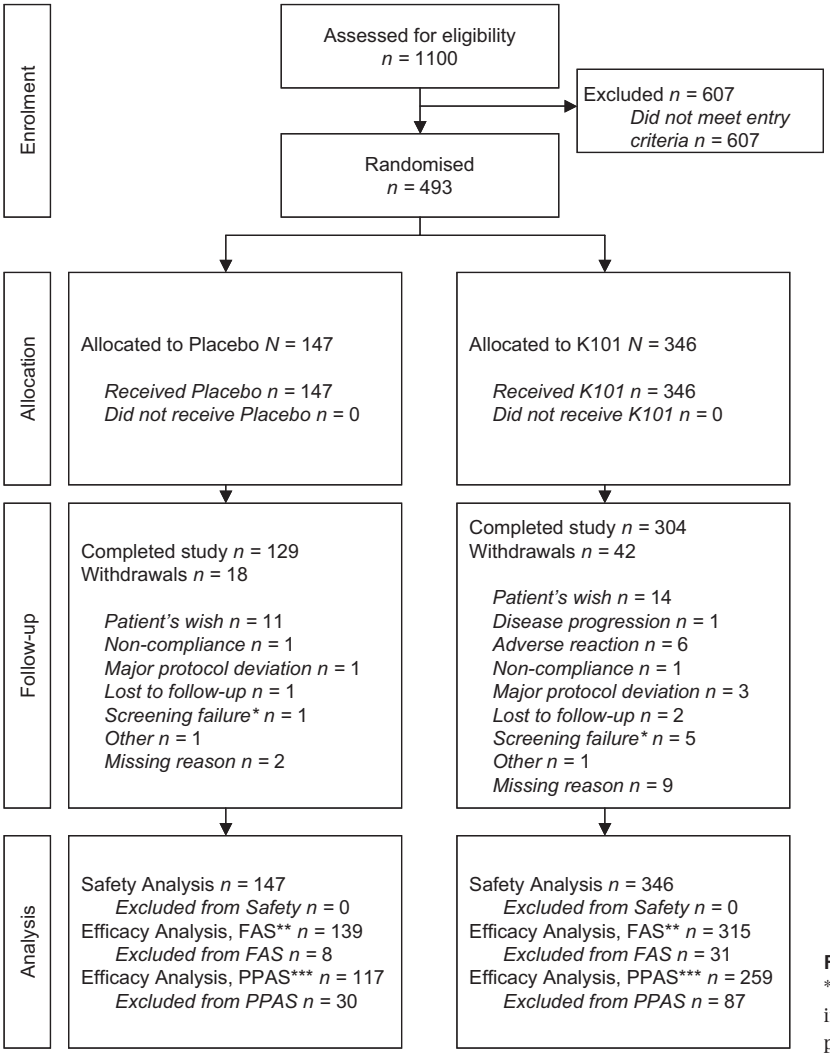

Figure 1 Flow chart of subject disposition. *The screening failures were discovered after inclusion. **FAS = full analysis set. ***PPAS = per protocol analysis set.

Efficacy results

The proportion of patients with mycological cure was higher in the K101 group than for placebo: 27.2% (73 patients) compared with 10.4% (10 patients; full analysis set; Table 2) after 24 weeks of treatment (+2 week washout). This difference achieved statistical significance ($P = 0.0012$). Similar results were obtained for the per protocol data set (Table 2). For the subpopulation of patients with 51–75% nail involvement, more patients who received K101 achieved mycological cure at 24 weeks (+2 week washout) than those who received placebo, although this difference did not reach statistical significance: 19.1% (9/47 patients) versus 7.0% (3/43 patients; full analysis set; $P = 0.1024$). After 24 weeks of treatment (+2 week washout), more patients who received K101 lacked visible fungal elements by direct microscopy than those who received placebo (Fig. 2b; full analysis set). This difference was most notable for patients with ≤50% nail involvement, where the difference was statistically significant ($P = 0.0059$, full analysis set). No statistically significant difference was observed for patients with 51–75% nail involvement. After 8 weeks of treatment, more patients lacked visible fungal elements by direct microscopy after receiving K101 than placebo (Fig. 2a; full analysis set), although these differences did not achieve statistical significance. Similar results were obtained for the per protocol set.

Seventy-nine percent of patients with ≤50% nail involvement and 81% of patients with 51–75% nail involvement had negative fungal nail cultures after 24 weeks of treatment (+2 week washout) with K101 (Fig. 3b, full analysis set). Statistically significant differ-

Table 1 Baseline characteristics.

	Treatment group	
	Placebo (*N* = 147)	K101 (*N* = 346)
Age; years		
Median [range]	58.0 [22–83]	59.0 [22–85]
Gender; *n* (%)		
Male	116 (79)	262 (76)
Female	31 (21)	84 (24)
Ethnic origin; *n* (%)		
Caucasian	146 (99)	338 (98)
Asian or Pacific Islander	0	3 (1)
Other	1 (1)	5 (1)
Target nail location; *n* (%)[1]		
Right foot digit 1	56 (38)	115 (34)
Left foot digit 1	51 (35)	99 (29)
Left foot digit 3	10 (7)	17 (5)
Left foot digit 2	3 (2)	29 (9)
Right foot digit 3	9 (6)	15 (4)
Right foot digit 4	4 (3)	18 (5)

[1]Data presented only for nails affected in >5% of patients in either group.

Table 2 Mycological cure following 24 weeks of treatment (+2 week washout).

	Treatment group		
Mycological cure	Placebo *n* (%)	K101 *n* (%)	*P*-value[1]
Full analysis set	*N* = 96	*N* = 268	
Yes	10 (10.4)	73 (27.2)	0.0012
No	86 (89.6)	195 (72.8)	
Per protocol set	*N* = 80	*N* = 221	
Yes	9 (11.3)	61 (27.6)	0.0042
No	71 (88.8)	160 (72.4)	

[1]Logistic regression comparison of K101 and placebo.

ences between K101 and placebo were observed both for patients with ≤50% nail involvement ($P < 0.0001$, full analysis set) and those with 51–75% nail involvement ($P = 0.0018$, full analysis set). After 8 weeks of treatment, percentages of patients with negative fungal nail cultures had been higher (approximately 95%) than at the end of the study, and differences between the two treatment groups were statistically significant for both patient strata (Fig. 2a; both $P < 0.0001$).

Patient subjective score assessments

More patients receiving K101 judged that their condition had improved versus those on placebo; these differences were statistically significant from 2 weeks ($P = 0.0148$) until the end of the study ($P = 0.0004$)

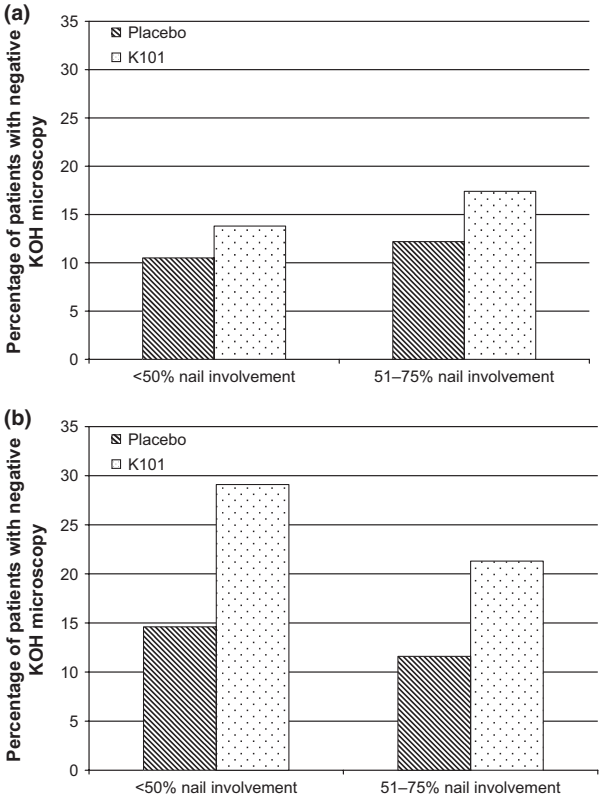

Figure 2 Percentage of patients with negative direct microscopy results at 8 weeks (Panel a) and at 24 weeks (+2 week washout; Panel b).

for those with nail involvement ≤50% (full analysis set). Similar results were observed for the per protocol set. For patients with 51–75% involvement, statistically significant differences were observed between K101 and placebo at week 2 ($P = 0.0069$), week 12 ($P = 0.0253$) and 24 weeks (+2 week washout; $P = 0.0008$; full analysis set). The proportions of patients recording 'Improvement', 'Almost cured' and 'Cured' increased throughout the study (Fig. 4a and b). For patients who received K101, combined percentages for 'Improvement', 'Almost cured' and 'Cured' increased from 14.1% at week 2 to 42.9% at week 26; percentages for placebo at these time points were 6.3% and 27.1%, respectively.

The following percentages of patients considered the study treatment to be 'Easy' or 'Very easy' to apply, K101: 83.5% at week 2 and 84.6% at week 26; placebo: 80.2% and 85.8%, respectively. Percentages considering K101 to be 'Somewhat difficult' or 'Very difficult' were less than 5% throughout the study: 3.8% at week 2 and 4.3% at week 26; values for placebo at these time points were 8.3% and 3.3%, respectively.

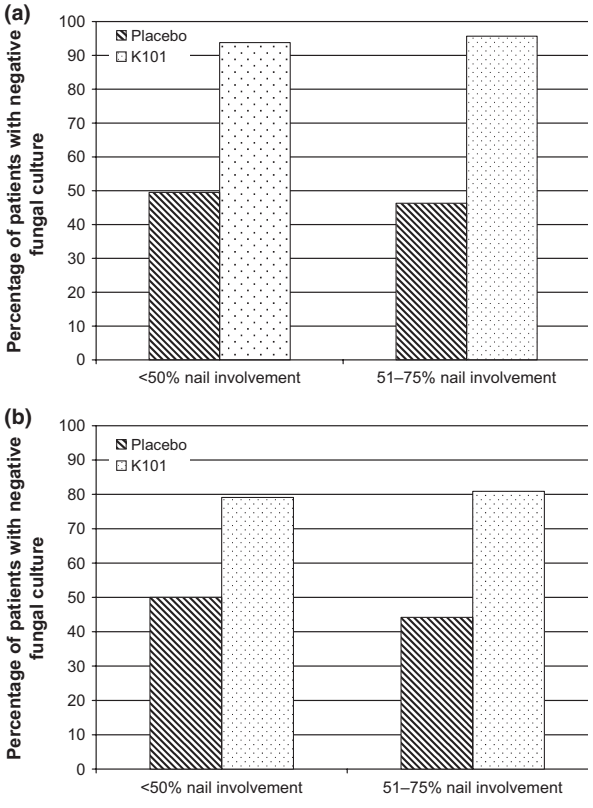

Figure 3 Percentage of patients with negative fungal culture results at 8 weeks (Panel a) and at 24 week (+2 week washout; Panel b).

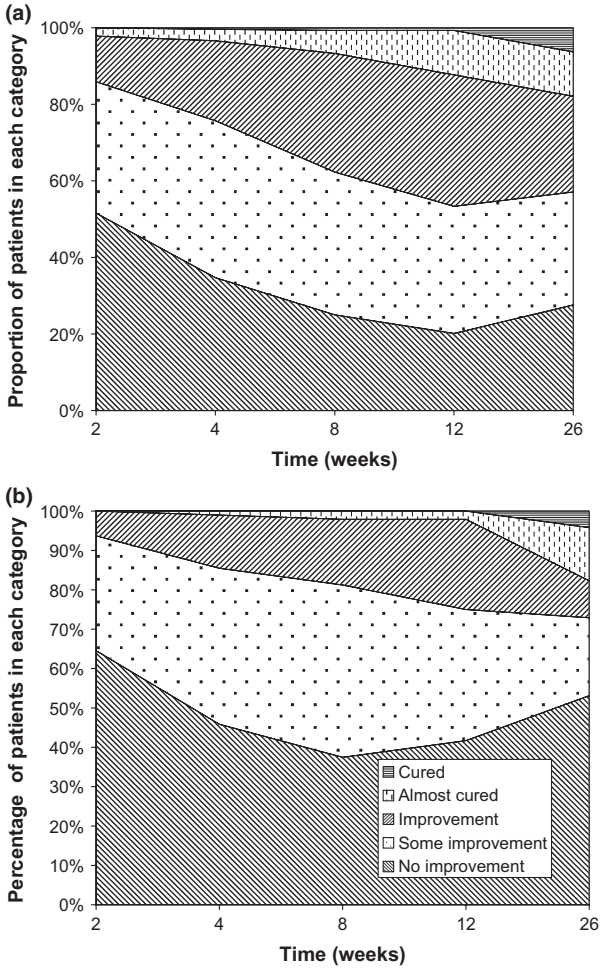

Figure 4 Patients' subjective scores of treatment for K101 (Panel a) and placebo (Panel b) (≤50% nail involvement; full analysis set).

Safety results

K101 was generally well tolerated; 162 (46.8%) patients in the K101 group and 50 (34.0%) patients in the placebo group experienced adverse events. Most events were mild in intensity, transient and did not require specific therapy. Nail discolouration was the most frequently reported; most frequently in the K101 group (Table 3). The nails of affected patients became white in colour with increasing opacity (Fig. 5). This typically involved the infected part of the nail, and occasionally included part of the nail that had previously been judged to be healthy. In some cases, changes in nail curvature were observed combined with separation of the nail plate that started at the distal free margin and progressed in the proximal direction (onycholysis) leading to nail detachment. Onycholysis and irritation, pain and erythema around the application site were also more frequently reported for K101 than for placebo. Eight (2%) patients reported events that were judged to be severe in intensity and related to K101. These were either irritation around the site of application or opacity of the target nail. Six (1.7%) patients in the K101 group and none in the placebo group discontinued the study because of adverse events. Five of the patients discontinued because of irritation and pain in the area of the treated toe and one discontinued because of nail detachment and softness.

Five patients reported adverse events that were considered serious by the investigator: pneumonia, arrhythmia, dyspnoea (all placebo), myocardial infarction and prostate cancer and operation (both K101). None was considered likely to be related to study treatment.

Discussion

K101 is a topical treatment composed of propylene glycol, urea and lactic acid that has been developed for the treatment of discoloured and deformed nails result-

Table 3 Most frequently reported adverse events (≥2.5% of either group; safety set).

	Treatment group	
	Placebo (N = 147) n (%)	K101 (N = 346) n (%)
Nail discolouration	9 (6.1)	48 (13.9)
Onycholysis	1 (0.7)	27 (7.8)
Application site irritation	1 (0.7)	22 (6.4)
Application site pain	1 (0.7)	21 (6.1)
Application site erythema	0	16 (4.6)
Skin irritation	0	15 (4.3)
Nasopharyngitis	3 (2.0)	10 (2.9)
Erythema	0	11 (3.2)
Headache	5 (3.4)	5 (1.4)
Application site pruritus	0	9 (2.6)

ing from onychomycosis. We showed K101 to be an effective and relatively rapid treatment considered by patients to cause significant improvements in their condition. Approximately half the patients felt that their condition had shown at least some improvement after only 2 weeks of treatment; this was significantly more than those who applied placebo. Significantly more patients with nail involvement up to 50% who received K101 achieved mycological cure at 24 weeks (+2 week washout) than with placebo. K101 was also demonstrated to have an early onset of antifungal activity by fungal culture of nail samples, which showed that approximately 95% of patients who received K101 had negative samples after 8 weeks of treatment. In patients with more advanced onychomycosis (51–75%), K101 displayed antifungal activity similar to that in patients with lower levels of nail involvement (≤50%). Although more patients in the 51–75% stratum, who received K101, achieved mycological cure than placebo, this difference did not achieve statistical significance.

The rate of mycological cure observed at 24 weeks (+2 week washout) in this study is similar to those seen at 48 weeks in two pivotal, vehicle-controlled US studies of ciclopirox nail lacquer (8% solution), where 29% and 36% of patients had mycological cure compared with 27.2% in this study,[20] and it exceeds the mycological cure rate reported for amorolfine following 48 weeks of application (15.7%; n = 522).[21] Rates of mycological cure in the placebo groups in these studies were similar to that in the current study. A study of amorolfine nail lacquer applied once weekly for up to 6 months reported complete cure rates of 12% for a 2% amorolfine solution and 38% for a 5% solution.[22] However, the study did not include a control group and the definition of complete cure was not fully defined, thereby limiting interpretation of the results.

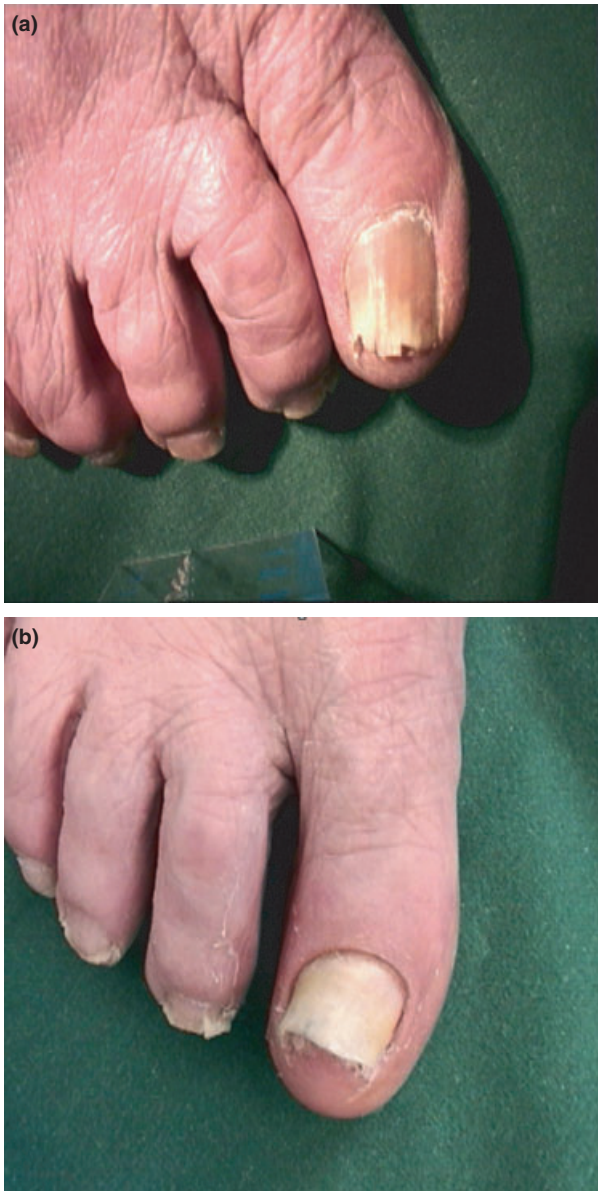

Figure 5 Photographs of a patient's nail at baseline (Panel a) and at Week 12 following treatment with K101 (Panel b).

Systemic treatments for onychomycosis have shown higher levels of mycological cure than antifungal nail lacquers[23–27]; however, there are circumstances where the use of systemic agents may be contraindicated. Systemic agents are not recommended in patients with liver disease and are contraindicated in those with congestive heart failure (itraconazole). Interaction with other drugs is also a problem, especially with itraconazole. Mycological cure rates for systemic treatments have varied, but the highest rates have been observed for treatment with terbinafine, where mycological cure

rates have been 75–87% after treatment periods of 12–24 weeks.[23,24] The LION study of terbinafine and itraconazole, each administered for 12 or 16 weeks,[24] found mycological cure rates at 24 weeks ranging from 25% to 45% for both treatments.

At the same time point, rates of complete cure (defined as mycological cure plus 100% toenail clearing) were <10% for both treatments. Despite no further treatment being administered, the rates of both mycological and complete cure increased over the remainder of the study. At the end of the study (week 72), with no further treatment administered, mycological cure rates had increased to approximately 40–80% and complete cure rates had increased to approximately 25–55%. Similarly, in the North American multicentre trial on oral terbinafine (23), the time course of mycological response (% of patients with negative microscopy or negative culture) points to a mycological cure rate under 50% at 24 weeks and indicates a longer response time for negative microscopy to be achieved. The latter is also evident from the data in this study (see Fig. 2a and b). Increases in mycological cure rates with time, even after stopping treatment imply a lag between achievement of negative culture and negative microscopy. This could be attributable to the well-known high affinity and long-lasting binding of terbinafine to keratin and/or the longer response time to achieve negative microscopy. As the treatment period in our study was short (24 weeks) compared with treatment with ciclopirox nail lacquer and the post-treatment follow-up period only 2 weeks, one may speculate that longer follow-up times, based on the experiences from the LION study, would confirm increasing numbers of patients attaining complete and mycological cure after cessation of treatment with K101.

As approximately 30% of cultures for dermatophytes are associated with false negative results and 25–80% displayed varying sensitivity,[28] we defined mycological cure as the combination of negative fungal culture and negative direct microscopy. We combined the two tests to increase the predictive outcome of our assessments. It has been argued that a preferable endpoint for assessment of onychomycosis treatments is the disease-free nail, defined as a normal appearing nail that is also mycologically negative.[29] Although the 26-week study duration provided sufficient time for many patients to achieve mycological cure, it was not long enough to determine how many patients ended the study with disease-free nails (i.e. mycological cure and normal appearance). Most patients had onychomycosis of the big toe nail which requires 12–18 months to regrow.[6] The 2-week follow-up period in this study was considered sufficient as K101 does not contain a specific antifungal substance and the ingredients of K101 are readily biodegradable and endogenous.

One possible explanation for the nail opacity and tendency for increased onycholysis observed in the study may be the relative concentrations of the components of K101. Urea-containing ointments previously used under occlusion for non-traumatic removal of dystrophic nail often contained urea at a concentration of 40–50%, although a treatment containing 22% urea has also accomplished chemical avulsion.[10,30] Inclusion of propylene glycol and lactic acid in K101 contributes to the keratolytic and hydrating effect of urea,[10,30] possibly explaining the changes in nail appearance. Nail occlusion during the first 4 weeks of treatment may have been another possible cause of the change of appearance. Occlusion enhances the keratolytic effect of K101.

K101 was generally well tolerated by the patients and adverse effects could mostly be allocated to one of three categories: nail discolouration, onycholysis or irritation/pain, typically in the periungual skin. The latter symptoms were probably due to application of excessive amounts of K101. To address this, it is planned in future studies to use a different applicator: a tube with a silicon tip that enables K101 solution to be easily spread over the nail surface, minimising any spillage over adjacent skin.

The current study demonstrated that K101 provides early visible improvements in nail appearance and clinically meaningful antifungal activity. Further studies should determine the clinical response to treatment with K101 beyond 26 weeks, providing data on the proportions of patients mycologically cured, who regrow healthy new nails.

Acknowledgments

The authors would like to thank all the patients and study staff who participated in this study.

Funding

This study was wholly funded by Moberg Derma AB.

Conflict of interest

Lennart Emtestam reports having received consulting fees and grants for this study from Moberg Derma AB. Taavi Kaaman reports having received consulting fees from Moberg Derma AB. Kjell Rensfeldt is an employee of Moberg Derma AB, the manufacturer of K101 and sponsor of this study.

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