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ORIGINAL ARTICLE

Efficacy of long-term treatment with efinaconazole 10% solution in patients with onychomycosis, including severe cases: A multicenter, single-arm study

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ABSTRACT

We evaluated the efficacy of efinaconazole 10% topical solution in long-term use, for up to 72 weeks, for onychomycosis, including severe cases. Among 605 participants, 219 patients diagnosed as having onychomycosis were evaluated for the efficacy of efinaconazole. The treatment success rate (<10% clinical involvement of the target toenail) at the final assessment time point was 56.6%, the complete cure rate was 31.1% and the mycological cure rate was 61.6%, all of which increased over time, demonstrating that continuous application contributed to the improvement of cure rate. Even in severe cases, reduction of the affected nail area was observed, showing the potential efficacy of the treatment. Responses to a quality of life questionnaire among patients with onychomycosis, OnyCOE-t, suggested that efinaconazole treatment improved the patients' quality of life. The incidence of adverse drug reaction in the patients eligible for the assessment was 6.3%, and this developed only in the administration site in all cases. No systemic adverse event was observed. In addition, no increase in the incidence of adverse drug reaction due to

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long-term use was found. Efinaconazole therapy was proved to exhibit excellent balance between efficacy and safety, and thus may serve as a useful treatment option for onychomycosis.

Key words: efinaconazole, long-term observation, onychomycosis, severe case, topical triazole antifungal.

INTRODUCTION

Onychomycosis is a common disease, with an estimated incidence of approximately 10% in the general population, according to an epidemiological survey conducted in Japan. Onychomycosis incidence is known to increase with age, which has led to the higher prevalence in the elderly.[1]

Subjective symptoms are rare in mild cases. However, once lesions involve ingrown nails, nail hypertrophy or onychogryphosis, the disease leads to physical disorders such as pain and problems with walking and exercise, which then results in decreased quality of life (QOL). In these cases, an appropriate treatment is required. Although severe cases with clinical involvement of more than 50% of the nails or advanced lesions associated with nail deformation are refractory, the appropriate treatment has shown to improve QOL.[2,3]

Treatment for onychomycosis with griseofulvin had long been considered to be the only remedy. However, since the 1990s, when oral antifungals such as itraconazole and terbinafine became available, the cure rate improved. Nevertheless, these oral drugs have some safety problems, including impaired liver function and drug interactions, rendering them unsafe to use in some elderly patients with many comorbidities thus making treatment difficult.

Efinaconazole 10% solution (EFCZ) was approved in July 2014 as the first topical solution for the treatment of onychomycosis in Japan. In a multinational phase III trial conducted in Japan, Canada and the USA, EFCZ showed significant efficacy in patients with mild to moderate (defined as 20–50% clinical involvement of the target nail) distal and lateral subungual onychomycosis (DLSO) when continuously applied for 48 weeks. The complete cure rate was 17.8% in the entire population (656 subjects) and 28.8% in the Japanese population (184 subjects), which successfully led to the approval of EFCZ.[4,5]

However, in clinical practise, EFCZ may be used in cases exceeding the study criteria, namely more severe cases with more than 50% clinical involvement or with long-term use for over 1 year.[6] Therefore, it is meaningful to obtain information on the efficacy and safety of EFCZ when used in severe cases or applied for over 48 weeks to provide findings for clinical medicine.

Our study was conducted to examine the efficacy of EFCZ by daily application for up to 72 weeks in patients with onychomycosis with 20% or more clinical involvement of the nails, including severe cases. As for the impact of EFCZ on patient QOL, only one report so far has used OnyCOE-tTM,[7] which is a QOL questionnaire regarding onychomycosis. So far, no similar study has been conducted in the Japanese population, and thus we decided to include this as one of the aims of our study.

METHODS

Study design

The study was conducted from October 2016 to December 2018 as a multicenter, open-label, single-arm study in 36 facilities nationwide. The purpose of this study was to evaluate patients with severe (>50% clinical involvement) onychomycosis and the efficacy of long-term use of EFCZ for more than 1 year. We also obtained information on patient QOL with EFCZ therapy. The study was conducted in accordance with the study protocol, the Declaration of Helsinki, and the ethical guidelines for medical and health research involving human subjects, with the approval of the appropriate ethics committee. Upon participating in the research, all the patients were given a written explanation of the study before they provided written informed consent.

Subjects

The subjects included in the study were male or female patients aged 20 years or older (at the time of informed consent) who provided written consent and were diagnosed with onychomycosis in either the left or right great toenail (target nail). The lesion should be definitely diagnosed using a potassium hydroxide examination, with 20% or more clinical involvement of the affected great toenail (not reaching the proximal nail fold), and the growth of the target nail (requiring nail clipping at least once a month) should be confirmed by consultation (regardless of the nail thickness). If both the left and right great toenails were affected, the target nail with the larger clinical involvement was selected. In case the clinical involvement was of the same size, then the right nail was chosen.

The following subjects were excluded: (i) patients with either proximal subungual onychomycosis or total dystrophic onychomycosis; (ii) patients with nail psoriasis, lichen planus of the nails, palmoplantar pustulosis of the nails, and complicated nail deformation due to causes other than onychomycosis such as dystrophia unguium; (iii) patients who received EFCZ, oral antifungals or any topical therapeutic drug for onychomycosis within 3 months before the date of informed consent; (iv) patients scheduled to use concomitant medications or combination therapies (oral antifungals, topical therapeutic medicine for onychomycosis other than EFCZ, laser irradiation, occlusive dressing therapy such as urea ointment; removal of nail thickening is allowed) during the period of participation in this study; and (v) patients with negative fungal culture (confirmed at the time of research enrollment after informed consent).

The fungal culture test was outsourced to LSI Medience (Tokyo, Japan). Identification was conducted according to the species; when it was *Trichophyton rubrum* or *Trichophyton interdigitale* (*Trichophyton mentagrophytes*), the name identified was reported. In case of the genus *Trichophyton* other than

T. rubrum or *T. interdigitale*, or the genus *Trichophyton* with its fungal species unidentifiable because of non-typical characteristics, it was reported as the genus *Trichophyton* (*Trichophyton* species). As *T. mentagrophytes* exclusively isolated from humans has been renamed *T. interdigitale* with the recent revision of fungi names, we used both names of the fungi, *T. interdigitale* (*T. mentagrophytes*), in this report.[8]

In this study, 200 subjects met the inclusion criteria and had positive fungus cultures. The rationale was based on the results of the phase III study of EFCZ, which suggested that the proportion of subjects with 10% or less clinical involvement of nails at week 72 after starting the EFCZ application in this study was estimated to be 70%, yielding 165 subjects with a relative accuracy of 10% or less at a 95% confidence interval (CI). Thus, the estimated number of subjects in our study was calculated to be 200 participants, considering a certain number of withdrawal cases.

Efficacy and safety

Efinaconazole was applied over the affected nail once daily. The duration of application was until complete cure, and the observation period in the study was up to 72 weeks. The observation timing of each evaluation parameter was at the start of application, and at weeks 12, 24, 36, 48, 60 and 72 after starting the application (acceptable range, ±4 weeks). The affected nails were visually measured on the basis of the site assumed to be the original location of the nail as 100%.

Primary efficacy end-point

- Changes over time in treatment success rate

Treatment success was defined as a reduction in clinical involvement to ≤10% of the target nail.

Secondary efficacy end-points

- Changes over time in complete cure rate

Complete cure was defined as a 0% clinical involvement of the target nail, with a negative potassium hydroxide examination result.

- Changes over time in mycological cure rate

Mycological cure was defined as a negative result in the potassium hydroxide examination of the target nail.

- Changes over time in the decrease rate of clinical involvement

Calculated using the following formula:

Decreased rate of clinical involvement = (clinical involvement at baseline − clinical involvement after application of EFCZ) / clinical involvement at baseline × 100

As for the analysis items, efficacy was classified as follows to calculate the number of subjects and efficacy rate: 75% or more, "remarkably improved"; 50% or more and less than 75%, "improved"; 25% or more and less than 50%, "moderately improved"; 0% or more and less than 25%, "unchanged"; and less than 0%, "aggravated".

- Changes over time in clinical involvement

Calculated using the following formula:

Changes in clinical involvement = clinical involvement at baseline − clinical involvement after application of EFCZ.

- Changes in the increase rate of the unaffected nail area over time

The change in the increase rate of the unaffected nail area over time was defined as the rate of the "amount of increase in the unaffected nail area from before to after EFCZ application" against "the unaffected area at baseline" of the target nail, calculated with the following formula:

Increased rate of unaffected nail area* = (unaffected nail area after application of EFCZ − unaffected nail area at baseline) / unaffected nail area at baseline × 100

*Unaffected nail area = 100 − clinical involvement

The above-mentioned analysis items were classified into categories (≥75%, ≥50% and <75%, ≥25% and <50%, ≥0% and <25%, and <0%), and the number of subjects and rate were calculated.

- Changes in QOL score at the end (or discontinuation) of treatment

The subjects assessed themselves using the OnyCOE-t questionnaire for onychomycosis,[9,10] and then the results were tallied and used as QOL scores. Changes in the QOL score were calculated with the following formula:

Changes in QOL score = QOL score at the end of treatment − QOL score at study baseline

The OnyCOE-t questionnaire: Patients self-administered the OnyCOE-t questionnaire at the time of enrollment (baseline) and at final assessment. The OnyCOE-t questionnaire comprised 33 items, grouped into multi- or single-item scales, as follows:

- A Toenail Symptom assessment, comprising both symptom frequency and symptom bothersomeness scales
- An appearance problems scale
- A physical activities problems scale
- An overall problem scale
- A stigma scale, and
- A treatment satisfaction scale.

All items in the OnyCOE-t questionnaire were transformed to a 0–100 scale; higher scores indicated better functioning.

Safety

For the subjects who had positive fungus cultures, adverse events (all developed during study participation) were assessed.

Statistical analyses

Population for the analyses

The target subjects in the study were as follows:

- Full analysis set: population excluding subjects without evaluation data after EFCZ application from among the population who met the inclusion criteria and had positive fungus cultures
- Per protocol set: population of target subjects who met the provisions of the clinical study protocol.

Methods of analysis

The primary analysis included the full analysis set, and the supplemental analysis included the per protocol set. The time of the final observation, including the time of discontinuation, was defined as the final assessment time point.

As for each evaluation parameter, the subgroup analysis was set in advance to be performed on the basis of the patient background (sex, age, type of onychomycosis, clinical involvement and causative fungal species).

Hypothesis testing was not performed because the study was a single-group trial. As for the statistical methods, continuous data were represented as summary statistics (number of subjects, arithmetic mean, standard deviation, minimum/median/maximum values, and 95% CI), while categorical data were represented as the number of subjects and proportions. Missing values excluding the QOL scores were supplemented with the last observation carried forward method, while the QOL scores were not supplemented.

Continuous data from the outcomes and discussion of this report are described as mean ± standard deviation unless otherwise noted. Safety analysis was not performed. For the statistical analysis, SAS® System Release 9.4 (32 bit) or the later version was used (SAS, SAS Institute, Cary, NC, USA).

RESULTS

Subjects

Figure 1 shows the disposition of the subjects. Of the 605 subjects who consented to participate in the study, 223 with positive fungal cultures were enrolled. Excluding four subjects who lacked post-EFCZ application data, 219 subjects were included as the full analysis set. Forty subjects (18.3%) discontinued the study because of consent withdrawal in 17 (7.8%), adverse events in 11 (5.0%), loss to follow up in six (2.7%), worsening of primary disease in two (0.9%) and other reasons in four (1.8%).

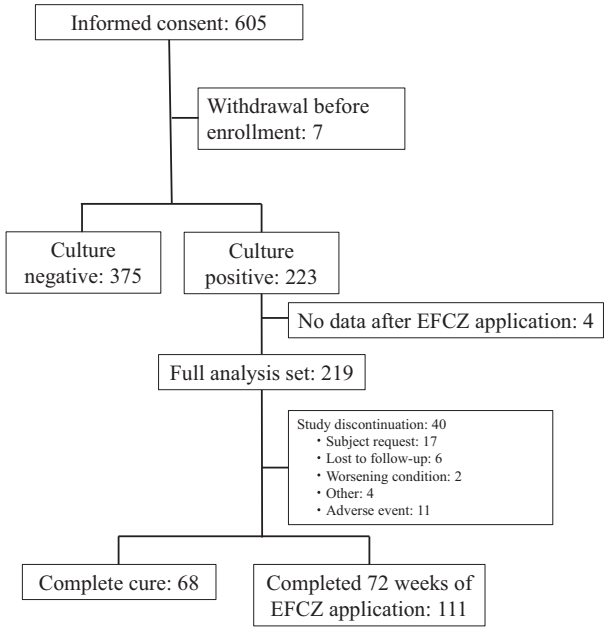

Figure 1. Distribution of the subjects.

Table 1 shows the subjects' baseline characteristics in the full analysis set. Of the subjects, 153 were male (69.9%) and 66 were female (30.1%), with a mean age of 64.3 ± 12.01 years and 101 subjects (46.1%) aged less than 65 years and 118 subjects (53.9%) aged 65 years or more. As for the type of onychomycosis, 203 subjects (92.7%) had DLSO, with 139 (63.5%) and 80 (36.5%) having clinical involvements of 50% or less and more than 50%, respectively. The most common causative fungal species was *T. rubrum* (157 subjects, 71.7%), followed by *T. interdigitale* (*T. mentagrophytes*) (27 subjects, 12.3%), *Trichophyton* species (34 subjects, 15.5%) and *T. rubrum* + *T. interdigitale* (*T. mentagrophytes*) (one subject, 0.5%).

Efficacy

Primary end-point

The changes in treatment success rate (accumulation) in the full analysis set were 9.1%, 27.9%, 39.3%, 47.9%, 51.1% and 53.4% at weeks 12, 24, 36, 48, 60 and 72 after starting the EFCZ application, respectively, showing an increase in efficacy rate over time. The treatment success rate at the final assessment was 56.6% (95% CI, 50.0–63.0%) (Fig. 2).

When comparing this rate to that in the patient populations with 20–50% clinical involvement and more than 50% affected area, the treatment success rate increased with the duration of EFCZ application at any time point of assessment, at 66.9% and 38.8% at the final assessment, respectively.

A subgroup analysis of subjects was also conducted according to the patients' backgrounds other than clinical involvement (sex, age, type of onychomycosis and causative fungal species); results at the time of each final assessment are provided in Table 2. Assessment based on sex revealed treatment success rates of 54.2% in the male patients and 62.1% in the female patients. As for the assessment by age category, the treatment success rate was 54.2% in the elderly (aged ≥65 years) and 59.4% in the non-elderly (aged <65 years). By disease type, the treatment success rate was 54.7% for DLSO and 81.3% for superficial white onychomycosis (SWO). In the evaluation according to the causative fungal species, the treatment success rate was 47.8% for *T. rubrum* and 85.2% for *T. interdigitale* (*T. mentagrophytes*).

Secondary end-points

Changes in the complete cure rate in the full analysis set were confirmed to increase over time until week 72 after starting EFCZ application, like the treatment success rate, achieving 31.1% at the final assessment. Complete cure rate in both patient populations with clinical involvements of 20–50% and more than 50% was also confirmed to increase over time, to 34.5% and 25.0%, respectively (Fig. 3a).

Changes in the mycological cure rate increased earlier than the treatment success and complete cure rates, increasing to 38.8% at week 24, 50.7% at week 36 and 55.3% at week 72

Table 1. Baseline characteristics (full analysis set)

Variables		Full analysis set[†] (n = 219)
Sex	Male	153 (69.9%)
	Female	66 (30.1%)
Age	<65 years old	101 (46.1%)
	≥65 years old	118 (53.9%)
	Mean ± SD (years)	64.3 ± 12.01
Target nail for assessment	Right	121 (55.3%)
	Left	98 (44.7%)
Clinical type of onychomycosis	DLSO	203 (92.7%)
	SWO	16 (7.3%)
Clinical involvement of target nail	≤50%	139 (63.5%)
	>50%	80 (36.5%)
	Mean ± SD (%)	49.1 ± 23.14
Types of causative fungal species	*Trichophyton rubrum*	157 (71.7%)
	Trichophyton interdigitale (*Trichophyton mentagrophytes*)	27 (12.3%)
	Trichophyton species	34 (15.5%)
	T. rubrum + *T. interdigitale* (*T. mentagrophytes*)	1 (0.5%)

[†]Subjects who met the inclusion criteria and had a positive fungus culture. DLSO, distal and lateral subungual onychomycosis; SD, standard deviation; SWO, superficial white onychomycosis.

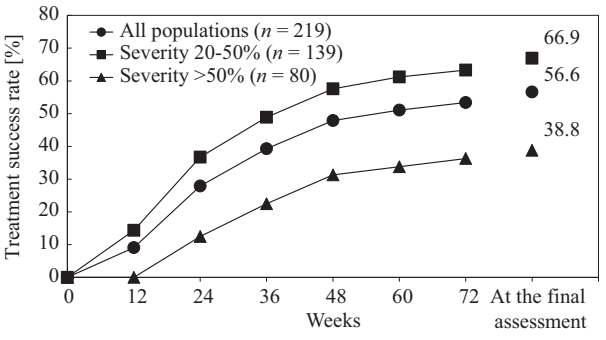

Figure 2. Changes in treatment success rate (full analysis set). The figure shows changes in the treatment success rate according to severity from the start of efinaconazole 10% solution (EFCZ) application to the final assessment. Treatment success was defined as a reduction in clinical involvement to 10% or less of the target nail. Treatment success rate showed a trend of improvement over time regardless of severity.

after starting EFCZ application. The mycological cure rate at the final assessment was 61.6%. The same trend was observed in the patient populations with clinical involvements of 20–50% and more than 50%, with increases of up to 66.9% and 52.5%, respectively, at the final assessment (Fig. 3b).

Changes in clinical involvement started to increase to 11.1% ± 13.27% (clinical involvement, 49.1% ± 23.14% at the start of EFCZ application) from week 12 after starting EFCZ application, reaching up to 21.0% ± 18.40% at week 24 and then 31.9% ± 24.32% at week 72. In the subject population with a clinical involvement of 20–50%, the clinical involvement when starting the EFCZ therapy was 33.6% ± 9.98%, and the change in clinical involvement was 21.6% ± 16.90% at week 72. In the subject population with more than 50% affected nail area, the clinical involvement at the start of EFCZ therapy was 75.9% ± 12.27%, showing greater increases in clinical involvement area of 17.1% ± 15.16% at week 12, 32.7% ± 19.08% at week 24 and 49.9% ± 24.88% at week 72 (Fig. 3c). Table 2 shows the results of subgroup analysis of the complete cure rate, mycological cure rate and changes in clinical involvement.

Regarding the decreased rate of clinical involvement, the proportion of subjects with improvement (reduction of involvement area by ≥50%) was 74.9% at the time of final assessment. By severity, the rate was 75.5% in the patient population with a clinical involvement of 20–50% and 73.8% in the population with more than 50% clinical involvement, showing a consistent trend of improvements without depending on disease severity (Fig. 3d). The increased rate of unaffected nail area also showed a trend of improvement similar to that of the decreased rate of clinical involvement (Fig. 3e).

When evaluating the domain scores in the OnyCOE-t questionnaire for the day of initiation and the end (discontinuation) of EFCZ therapy based on the subjects' responses to the questionnaire, a trend of improvement was observed in the scores for symptom frequency, symptom bothersomeness, appearance problems, physical activities problems, overall problem and stigma. The treatment satisfaction score was 77.0 ± 24.4 at the end (discontinuation) of treatment (Table 3).

Safety

Within 72 weeks, 30 patients exhibited serious adverse events, which had no causal relationship with EFCZ therapy. Of the 128 adverse events observed, 14 occurring in 14 subjects (6.4%) were adverse drug reactions, confirming a causal relationship with EFCZ therapy. Of these events, 11 cases (5.0%) were of contact dermatitis, two cases (0.9%) were of application site irritation and one case (0.5%) was application site erythema, without any systemic adverse drug reactions observed. All of these events were not serious, with resolution or recovery as the final outcome (Table 4).

Table 2. Subgroup analysis on efficacy end-points at the final assessment (full analysis set)

		Sex		Age		Clinical type		Causative fungal species			
	Male (n = 153)	Female (n = 66)	<65 years (n = 101)	≥65 years (n = 118)	DLSO (n = 203)	SWO (n = 16)	*T. rubrum* (n = 157)	*T. interdigitale* (n = 27)	*T.* species (n = 34)	*T. rubrum* + *T. interdigitale* (n = 1)
Treatment success rate (%)	54.2 (83) (46.3, 61.9)	62.1 (41) (50.1, 72.9)	59.4 (60) (49.7, 68.5)	54.2 (64) (45.3, 63.0)	54.7 (111) (47.8, 61.4)	81.3 (13) (57.0, 93.4)	47.8 (75) (40.1, 55.5)	85.2 (23) (67.5, 94.1)	73.5 (25) (56.9, 85.4)	100.0 (1) (20.7, 100.0)
Complete cure rate (%)	26.1 (40) (19.8, 33.6)	42.4 (28) (31.2, 54.4)	28.7 (29) (20.8, 38.2)	33.1 (39) (25.2, 42.0)	29.1 (59) (23.3, 35.7)	56.3 (9) (33.2, 76.9)	22.9 (36) (17.0, 30.1)	63.0 (17) (44.2, 78.5)	44.1 (15) (28.9, 60.5)	0.0 (0) (0.0, 79.3)
Mycological cure rate (%)	60.1 (92) (52.2, 67.5)	65.2 (43) (53.1, 75.5)	63.4 (64) (53.6, 72.1)	60.2 (71) (51.2, 68.5)	60.6 (123) (53.7, 67.1)	75.0 (12) (50.5, 89.8)	55.4 (87) (47.6, 63.0)	85.2 (23) (67.5, 94.1)	73.5 (25) (56.9, 85.4)	0.0 (0) (0.0, 79.3)
Changes in clinical involvement (%)	32.3 (28.3, 36.4)	31.1 (25.8, 36.3)	30.7 (25.8, 35.5)	33.0 (28.7, 37.4)	31.6 (28.2, 35.0)	36.2 (25.0, 47.4)	32.0 (28.2, 35.8)	29.1 (20.7, 37.6)	34.1 (24.7, 43.6)	25.0 (–, –)

Data shows "% (subjects) (lower/upper limits of 95% confidence interval)" or "mean value (lower/upper limits of 95% confidence interval)". Treatment success: a reduction of clinical involvement of target nail to ≤10%. Complete cure: 0% of the clinical involvement of the target nail, with negative potassium hydroxide examination result. Mycological cure: the negative result of the target nail by potassium hydroxide examination. Changes in clinical involvement: defined as "clinical involvement at baseline" – "clinical involvement after application of EFCZ". DLSO, distal and lateral subungual onychomycosis; EFCZ, efinaconazole 10% solution; SWO, superficial white onychomycosis.

DISCUSSION

Once onychomycosis occurs, it is generally a chronic disease requiring specialized and long-term therapy to cure. Treatment includes oral therapy, topical therapy and surgical treatment (e.g. cutting of the nail plate, laser therapy and nail ablation), but topical therapy has an insufficient therapeutic effect due to the low concentration of the fungal agent and the low permeability of the nail plate. No topical drug has been approved for the treatment of onychomycosis in Japan for this reason. Although nail lacquers are available overseas, the complete cure rate ranges 5.5–8.5% for ciclopirox at 48 weeks and 0.96% for amorolfine at 52 weeks of treatment, indicating limited efficacies.[11,12] Therefore, the development of a topical product with adequate efficacy as monotherapy is expected.

Under such circumstances, the first topical triazole antifungals solution exclusively formulated for onychomycosis, 10% efinaconazole, was approved in Japan in July 2014. Efinaconazole is an ingredient discovered in Japan that has low affinity to keratin, the main component of nails. This means that EFCZ has superior nail permeability and antifungal activity in the nail plate and nail bed.[13,14] In a multinational phase III study conducted in subjects with mild to moderate onychomycosis having a 20–50% area of nail involvement, the complete cure rate was significantly greater than that in the vehicle group (study 1, 17.8% vs 3.3%; study 2, 15.2% vs 5.5%; $P < 0.001$).[4]

In our study, the treatment success rate in terms of the primary end-point (≤10% clinical involvement) was 56.6% in the eligible patients after applying EFCZ for up to 72 weeks. In the multinational phase III study for EFCZ in subjects with onychomycosis who had 20–50% area of nail involvement, the treatment success rate was defined as the percentage of subjects with less than 10% area of nail involvement. Treatment success rate was 31.0%, and in the subgroup analysis in the Japanese population, this rate was 46.7% (48 weeks of application and assessed at week 52).[4,5] Considering that the definitions of treatment success are slightly different in a precise sense and that our study included not only patients with DLSO but also those with SWO, an equable comparison is not possible. However, when comparing only with the population with an affected area of 20–50%, a similar trend of 57.6% (at week 48) was obtained in our study.

One of the new findings of our study is the evaluation of the complete cure rate in patients with long-term treatment for more than 48 weeks. Severe cases have been reported to require a longer treatment duration, but the evaluation of EFCZ use for more than 48 weeks had been unclear.[15,16] Considering that the treatment success rate increased until week 72 after starting EFCZ application, the clinical significance of continuing the application beyond 1 year was indicated. The complete cure rates at weeks 48 and 52 in the Japanese group in the multinational phase III study were 20.1% and 28.8%, respectively, which were almost the same as our results of 19.6% and 26.5% at weeks 48 and 60, respectively. Moreover, the rate in our study increased to 31.1% at week 72, indicating the benefit of continuing EFCZ application for more than 1 year. In fact, 121 subjects (55.3%), more than half of the enrolled

subjects, continued EFCZ application to week 72, of whom 10 achieved complete cure. Generally, the factors associated with complete cure included not only fungal infection in the nail but also the growth rate of the nail. Considering that the duration until toenails are completely replaced with new growth is mostly 1 year or even longer for elderly or thickened nails, it is not an easy goal to achieve. Nevertheless, we observed many patients who attained cure after using EFCZ for over 1 year, which suggests that more patients would achieve complete cure with longer therapy. Improvement of the mycological cure rate was observed earlier than that of the treatment success rate, reaching 50.7% at week 36 and even 55.3% at week 72. In the patient population with an affected area of more than 50%, mycological cure was obtained in 47.5% of the subjects at week 72, which is expected for high antifungal activity, even in severe cases. Mycological cure in severe cases was newly achieved even at week 72, suggesting the possible efficacy by further long-term treatment. However, outcomes from our study are limited and thus future reports are expected.

Another finding in our study is that the therapeutic effect was examined for severe cases with an affected area of more than 50%, which was not sufficiently evaluated in the multinational phase III clinical study. The treatment success rate in the subjects with severe onychomycosis with more than 50% affected area was 31.3% at week 48 and 36.3% at week 72, showing continuous improvement over time. Changes in the affected area started to increase from week 12 after starting the application, and at the final assessment, the changes in the affected area from the start of application was 49.7%. This indicates that the affected area in the subjects with more than 50% affected area continuously improved over time with EFCZ application. As for the decreased rate in the affected area, the proportion of subjects in whom the treatment was determined to be effective or better was almost the same in the group with affected areas of 20–50% and the group with affected areas of more than 50% at week 72, indicating the high efficacy of EFCZ regardless of severity. Limited to severe cases, the treatment success rate was 36.3% at week 72, but considering the 47.5% mycological cure rate and changes in nail growth, further improvement can be expected by continuous application. Noguchi *et al*.[6] also reported that efinaconazole was effective regardless of age, disease severity and clinical type when administrated alone in patients with onychomycosis, including severe cases, consistent with the conclusions in our study.

As described earlier, the results of our study suggest the solutions for the two issues with EFCZ therapy, namely longer application for over 1 year and application to severe cases with more than 50% affected area.

In guidelines related to the treatment of onychomycosis, the use of topical drugs at the early stage of DLSO or SWO is recommended.[17,18] Although oral therapy is recommended for severe cases, it is difficult to apply to patients with severe onychomycosis who are much older or with underlying diseases that are typically associated with drug interactions and polypharmacy. Consequently, in clinical practise, topical drugs are often administrated to severe cases. Our study outcomes prove the possibility of EFCZ as a new treatment option available for severe cases.

In our study, analysis by clinical type was also performed. Unlike DLSO, in which the fungus enters underneath the distal part, the causative fungus grows on the surface layer of the nails in SWO; thus, topical treatment on the nail surface has a higher efficacy rate in SWO cases than in DLSO cases. In SWO, where the fungus locally exists on the surface layer of the nail, it is estimated that localization of fungus is more likely affected by the topical application of EFCZ. However, efinaconazole was developed on the basis of the concept that it permeates the nail plate, a property that facilitates its action, and for its application on nails.[14] In this study, like in SWO, a high efficacy rate was also observed in DLSO, indicating the high permeability of EFCZ in the nail plate. *T. interdigitale* (*T. mentagrophytes*) is the major causative fungal species of SWO and reported to be localized in the surface layer, making the disease likely treatable with topical preparation.[19] On the other hand, DLSO, the most commonly observed type of onychomycosis, is mainly due to the fungal species *T. rubrum*, which is often localized on the nail bed. As EFCZ is superior in terms of permeability to the nail plate, it is effective in such cases as well (Table 2).

As for the safety in this study, among the 40 subjects (18.3%) who discontinued EFCZ therapy during the entire study period, only 11 (5.0%) discontinued the treatment owing to particular adverse events and two (0.9%) discontinued because of aggravation of the underlying disease. The incidence of adverse drug reactions was 6.4%, all of which were local site reactions, and all of the symptoms were resolved or recovered after discontinuation or during application. No increase was observed in the incidence of adverse drug reactions during long-term use, indicating the potential for long-term treatment without concern for safety.

The prevalence of onychomycosis in the elderly population is well known to be high; thus, attention for safety is needed. Elderly patients aged 65 years or more were included in our study at a proportion of 53.9%, higher than the elderly population rate of 23.4% in the Japanese population in the multinational phase III study.[5] This is because our study was conducted under comparable conditions to that of actual clinical practise. In the subgroup analysis in our study, the outcome for non-elderly patients aged less than 65 years and that for elderly patients aged 65 years or more were almost the same, indicating the similar efficacy expected for both elderly and non-elderly patients. As mentioned earlier, many elderly patients often take multiple drugs in general due to complications; thus, it may be difficult to select oral treatment because of drug interactions and adverse drug reactions. In such cases, EFCZ can be expected to have the same effect in patients aged less than 65 years, and is thus likely to be a treatment option with excellent safety.

Decrease in QOL due to onychomycosis is considered to be caused by not only a disadvantage in terms of appearance but also by large mental and physical burdens. In our study, we evaluated the extent at which reduced QOL could be improved by EFCZ application, as many subjects with severe disease who showed various symptoms were included. From the results of the OnyCOE-t questionnaire survey,[9,10] we found that

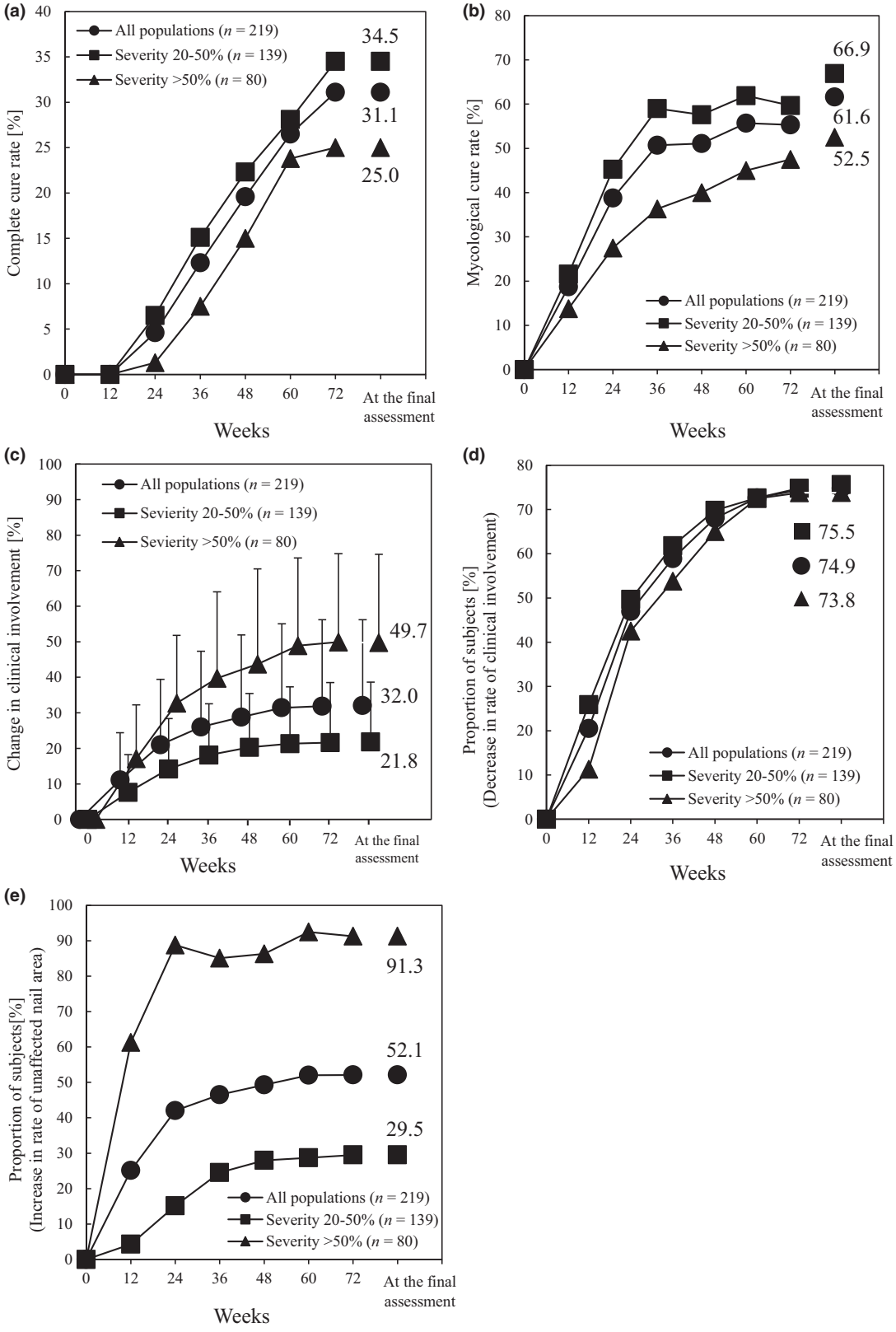

Figure 3. Changes in secondary end-points (full analysis set). (a) Complete cure rates. Changes in complete cure rate are shown according to severity from the start of efinaconazole 10% solution (EFCZ) application to the final assessment. Complete cure was defined as 0% clinical involvement of the target nail, with a negative potassium hydroxide examination result. Complete cure rate showed a trend of improvement over time regardless of severity. (b) Mycological cure rate. Changes in mycological cure rate are shown according to severity from the start of EFCZ application to the final assessment. Mycological cure was defined as the negative result in the potassium hydroxide examination of the target nail. Mycological cure rate showed a trend of improvement over time regardless of severity. (c) Changes in clinical involvement over time. Changes in clinical involvement are shown according to severity from the start of EFCZ application to the final assessment. The changes in clinical involvement showed a trend of improvement over time regardless of severity. (d) Decrease rate of clinical involvement (improved and more). Changes in the decrease rate of clinical involvement for the patients with improvement and more (reduction of clinical involvement by ≥50%) are shown according to severity from the start of EFCZ application to the final assessment. The decrease rate of clinical involvement was defined as the rate of "the amount of decrease in clinical involvement from baseline to post-application" against "the clinical involvement before EFCZ application" of the target nail. The decrease rate of clinical involvement for the patients who attained more than just an improvement showed a trend of improvement over time regardless of severity. (e) Increase rate of the unaffected nail area. Changes in the increase rate of the unaffected nail area for the patients who showed 50% or more increase rates of unaffected nail area are shown according to severity from the start of EFCZ application to the final assessment. The increase rate of the unaffected nail area was defined as the rate of "the amount of increases of the unaffected nail area from baseline to post-application" against "the unaffected nail area before EFCZ application" of the target nail. As for the increase rate of the unaffected nail area, the proportion of patients with 50% or more showed a trend of increase over time regardless of severity, particularly in the severe cases.

Table 3. Changes in QOL score (OnyCOE-t)

Category		Subjects (*n*)	Mean ± SD	Amount of changes (95% CI, lower limit, upper limit)
Symptom frequency score (0–100)	Start of the study	219	64.2 ± 20.0	–
	End (or discontinuation) of treatment	202	86.5 ± 16.3	21.9 (18.8, 25.0)
Symptom bothersomeness score (0–100)	Start of the study	219	77.7 ± 22.7	–
	End (or discontinuation) of treatment	196	92.2 ± 13.8	14.7 (11.4, 18.0)
Appearance problems score (0–100)	Start of the study	219	67.2 ± 26.7	–
	End (or discontinuation) of treatment	202	84.3 ± 21.0	17.2 (13.4, 21.0)
Physical activities problems score (0–100)	Start of the study	219	75.9 ± 25.9	–
	End (or discontinuation) of treatment	202	88.3 ± 20.6	12.8 (9.3, 16.3)
Overall problem score (0–100)	Start of the study	219	55.6 ± 34.1	–
	End (or discontinuation) of treatment	202	74.4 ± 30.3	18.8 (14.0, 23.6)
Stigma score (0–100)	Start of the study	219	71.4 ± 28.4	–
	End (or discontinuation) of treatment	202	82.3 ± 23.3	11.0 (7.5, 14.5)
Treatment satisfaction score (0–100)	Start of the study	0	–	–
	End (or discontinuation) of treatment	201	77.0 ± 24.4	–

The table showed quality of life (QOL) scores at the start of the study and the end (or discontinuation) of treatment. For six categories of scores excluding treatment satisfaction scores, scores for the end (or discontinuation) of treatment tended to be higher than those for the start of the study. Each score was calculated from the mean value of the scores for corresponding items in the questionnaire converted to a 0–100-point scale. Calculation formulas are as follows: symptom frequency score, symptom bothersomeness score, treatment satisfaction score = 100 × (5 − score) / 4; appearance problems score, physical activities problems score, overall problem score = 100 × (score − 1) / 3; stigma score = 100 × (4 − score) / 4. The higher the score is, the better the QOL is. CI, confidence interval; SD, standard deviation.

domain scores increased after EFCZ was used as compared with those on the day of initiation and the end of the application. Our outcome was consistent with the results of improved domain scores reported by Tosti *et al.*,[7] which suggests an increase in QOL. Moreover, this indicator was shown to be useful for QOL evaluation in the treatment of onychomycosis in Japanese patients.

The study clarifies the new efficacy of EFCZ in subjects with onychomycosis and warrants higher safety. These properties may possibly expand the potentiality of EFCZ as a good treatment option for patients with various lesions and backgrounds.

On the other hand, a certain number of patients are resistant to treatment with EFCZ; thus, combination therapy with oral drugs or other surgical treatments would be considered. In fact, reports have described improved cure rates after using a topical preparation in combination with an oral drug or nail debridement,[20–22] and that EFCZ in combination with laser therapy enhances the therapeutic efficacy.[23] Further studies on such cases will be expected. Topical treatment of onychomycosis may be currently at a turning point in the world. From the results of this study, we predict EFCZ to become a practical option for the treatment of onychomycosis.

Limitations

Our study was an open-label, single-arm study. A simple comparison in terms of efficacy with the multinational phase III

Table 4. Incidence of adverse drug reactions

Case	Adverse drug reaction	No. of days to onset	Severity	Outcome
1	Contact dermatitis	64	Non-serious	Recovered
2	Application site irritation	84	Non-serious	Recovered
3	Contact dermatitis	104	Non-serious	Recovered
4	Contact dermatitis	142	Non-serious	Resolved
5	Contact dermatitis	187	Non-serious	Recovered
6	Application site irritation	189	Non-serious	Recovered
7	Contact dermatitis	214	Non-serious	Recovered
8	Contact dermatitis	215	Non-serious	Recovered
9	Application site erythema	399	Non-serious	Resolved
10	Contact dermatitis	415	Non-serious	Recovered
11	Contact dermatitis	471	Non-serious	Recovered
12	Contact dermatitis	–	Non-serious	Resolved
13	Contact dermatitis	–	Non-serious	Resolved
14	Contact dermatitis	–	Non-serious	Recovered

Adverse drug reactions were defined as adverse events in which causality was not denied. There were 128 adverse events observed. Thirty events were observed as serious adverse events, none of which had a causal relationship.

study (randomized, double-blind, placebo-controlled parallel-group study) may cause misjudgment; thus, caution is necessary. However, the evaluation parameters for efficacy in our study had similar results as those in the Japanese group in the multinational phase III study. As for the subgroup analysis, data from the full analysis set were categorized according to patient background. Their uniformity and appropriateness were not examined; thus, the interpretation of the results should be made carefully.

As no control group was included in our study, objective information on the incidence of adverse drug reactions was not obtainable. However, the incidence of adverse drug reactions was low, and compared with the multinational phase III study, our study had a higher proportion of elderly patients. Therefore, we consider that the findings obtained in this study were comparable with that in the actual clinical setting.

This study was conducted at the 36 sites listed below: Department of Dermatology, Tokyo Metropolitan Police Hospital; Sapporo Skin Clinic; Ito Skin Clinic; Uesugi Dermatology Clinic; Asanuma Dermatology Clinic; Eniwa Station Dermatology Clinic; Kato Dermatology Clinic; Megumino Dermatologic Clinic; Takagi Dermatological Clinic; Takeda Dermatological Skin Care Clinic; Nopporo Dermatology Clinic; Showa Skin Clinic; Department of Dermatology, Asahikawa Medical University Hospital; Chitose Dermatology and Plastic Surgery Clinic; Shinoro Dermatology Clinic; Fukuzumi Dermatology Clinic; Yamanaka Skincare Clinic; Atago Dermatology Clinic; Department of Dermatology, Kitasato University Kitasato Institute Hospital; Department of Dermatology, Tokyo Medical University; Naoko Dermatology Clinic; Maruyama Dermatology Clinic; Queen's Square Medical Center; Department of Dermatology, Teikyo University Mizonokuchi Hospital; Nemunoki Dermatology; Department of Dermatology, Saiseikai Kanagawa Hospital; Department of Dermatology, Kanazawa Medical University; Department of Dermatology, Ina Central Hospital; Department of Dermatology, Gifu University Graduate School of Medicine; Department of Dermatology, Fujita Health University School of Medicine; Department of Dermatology, Osaka University; Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Tottori University Faculty of Medicine; Department of Dermatology, National Hospital Organization Hamada Medical Center; Kiryu Dermatology Clinic; Kusuhara Dermatology Clinic; and Department of Dermatology, Nagasaki University Hospital.

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REFERENCES

1 Watanabe S, Harada T, Hiruma M *et al*. Epidemiological survey of foot diseases in Japan: results of 30,000 foot checks by dermatologists. *J Dermatol* 2010; **37**(5): 397–406.
2 Schein JR, Gause D, Stier DM, Lubeck DP, Bates MM, Onychomycosis Fisk R. Baseline results of an observational study. *J Am Podiatr Med Assoc* 1997; **87**(11): 512–519.
3 Wang J, Wiznia LE, Rieder EA. Patient-reported outcomes in onychomycosis: a review of psychometrically evaluated instruments in assessing treatment effectiveness. *Skin Appendage Disord* 2017; **3**(3): 144–155.
4 Elewski BE, Rich P, Pollak R *et al*. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol* 2013 Apr; **68**(4): 600–608.
5 Watanabe S, Igarashi A, Katoh T, Matsuda T, Yamada K, Nishimoto K. Efficacy and safety of efinaconazole shown in Japanese patients

with onychomycosis in the phase III global clinical trial. *Nishinihon J Dermatol* 2015; **77**: 256–264.
6 Noguchi H, Matsumoto T, Hiruma M *et al*. Topical efinaconazole: a promising therapeutic medication for tinea unguium. *J Dermatol* 2018; **45**(10): 1225–1228.
7 Tosti A, Elewski BR. Treatment of onychomycosis with efinaconazole 10% topical solution and quality of life. *J Clin Aesthet Dermatol* 2014; **7**(11): 25–30.
8 de Hoog GS, Dukik K, Monod M *et al*. Toward a novel multilocus phylogenetic taxonomy for the dermatophytes. *Mycopathologia* 2017; **182**(1–2): 5–31.
9 Potter LP, Mathias SD, Raut M, Kianifard F, Tavakkol A. The Ony-COE-t questionnaire: responsiveness and clinical meaningfulness of a patient-reported outcomes questionnaire for toenail onychomycosis. *Health Qual Life Outcomes* 2006 Aug; **15**(4): 50.
10 Potter L, Mathias SD, Raut M, Kianifard F, Landsman A, Tavakkol A. The impact of aggressive debridement used as an adjunct therapy with terbinafine on perceptions of patients undergoing treatment for toenail onychomycosis. *J Dermatolog Treat* 2007; **18**: 46–52.
11 Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. *J Am Acad Dermatol* 2000; **43**: S70–S80.
12 Elewski BE, Ghannoum MA, Mayser P *et al*. Efficacy, safety and tolerability of topical terbinafine nail solution in patients with mild-to-moderate toenail onychomycosis: results from three randomized studies using double-blind vehicle-controlled and open-label active-controlled designs. *J Eur Acad Dermatol Venereol* 2013; **27**: 287–294.
13 Sugiura K, Sugimoto N, Hosaka S *et al*. The low keratin affinity of efinaconazole contributes to its nail penetration and fungicidal activity in topical onychomycosis treatment. *Antimicrob Agents Chemother* 2014; **58**: 3837–3842.
14 Matsuda Y, Sugiura K, Hashimoto T, Ueda A, Konno Y, Tatsumi Y. Efficacy coefficients determined using nail permeability and antifungal activity in keratin-containing media are useful for predicting clinical efficacies of topical drugs for onychomycosis. *PLoS ONE* 2016; **11**: e0159661.
15 Elewski BE, Cantrell W, Lin T. Is severity of disease a prognostic factor for cure following treatment of onychomycosis? *J Drugs Dermatol* 2018; **17**: 175–178.
16 Rodriguez DA. Efinaconazole topical solution, 10%, for the treatment of mild and moderate toenail onychomycosis. *J Clin Aesthet Dermatol* 2015; **8**: 24–29.
17 Ameen M, Lear JT, Madan V, Mohd Mustapa MF, Richardson M. British association of dermatologist' guidelines for the management of onychomycosis 2014. *Br J Dermatol* 2014; **171**: 937–958.
18 Gupta AK, Paquet M. Management of onychomycosis in Canada in 2014. *J Cutan Med Surg* 2015; **19**: 260–273.
19 Jillson OF, Piper EL. The role of saprophytic fungi in the production of eczematous dermatitis. I. The location of fungi within human nails. *J Invest Dermatol* 1957; **28**(2): 137–145.
20 Rigopoulos D, Katoulis AC, Ioannides D. A randomized trial of amorolfine 5% solution nail lacquer in association with itraconazole pulse therapy compared with itraconazole alone in the treatment of Candida fingernail onychomycosis. *Br J Dermatol* 2003; **149**(1): 151–156.
21 Lecha M. Amorolfine and itraconazole combination for severe toenail onychomycosis; results of an open randomized trial in Spain. *Br J Dermatol* 2001; **145**(Suppl. 6): 21–26.
22 Malay DS, Yi S, Borowsky P, Downey MS, Mlodzienski AJ. Efficacy of debridement alone versus debridement combined with topical antifungal nail lacquer for the treatment of pedal onychomycosis: a randomized, controlled trial. *J Foot Ankle Surg* 2009; **48**(3): 294–308.
23 Bonhert K, Dorizas A, Sadick NS. Efficacy of combination therapy with efinaconazole 10% solution and 1064 nm Nd:YAG laser for treatment of toenail onychomycosis. *J Cosmet Laser Ther* 2018; 1–5.