Clinical effectiveness of efinaconazole 10% solution for treatment of onychomycosis with longitudinal spikes

Shinichi Watanabe1 | Ken Iozumi2 | Masatoshi Abe3 | Yoshiko Ito4 | Takashi Uesugi5 | Takashi Onoduka6 | Ichiro Kato7 | Fumihiro Kato8 | Kazuo Kodama9 | Hidetoshi Takahashi10 | Osamu Takeda11 | Koki Tomizawa12 | Yasuki Tateishi13 | Mizue Fuji14 | Jun Mayama15 | Fumio Muramoto16 | Hidemi Yasuda17 | Kiyomitsu Yamanaka18 | Tsunao Oh19 | Hiroko Kasai20 | Ryoji Tsuboi21 | Naoko Hattori22 | Ryuji Maruyama23 | Tokuya Omi24 | Harunari Shimoyama25 | Ichiro Nakasu26 | Emiko Watanabe-Okada27,28 | Shuhei Nishimoto29 | Takashi Mochizuki30 | Masao Fukuzawa31 | Mariko Seishima32 | Kazumitsu Sugiura33 | Osamu Yamamoto34 | Masahisa Shindo35 | Hiroe Kiryu36 | Masahiro Kusuhara37 | Motoi Takenaka38

1Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan
2Department of Dermatology, Tokyo Metropolitan Police Hospital, Tokyo, Japan
3Sapporo Skin Clinic, Sapporo, Japan
4Ito Skin Clinic, Sapporo, Japan
5Uesugi Dermatology Clinic, Sapporo, Japan
6Asanuma Dermatology Clinic, Chitose, Japan
7Eniwa Station Dermatology Clinic, Eniwa, Japan
8Kato Dermatology Clinic, Sapporo, Japan
9Megumino Dermatologic Clinic, Eniwa, Japan
10Takagi Dermatological Clinic, Obihiro, Japan
11Takeda Dermatological Skin Care Clinic, Sapporo, Japan
12Nopporo Dermatology Clinic, Ebetsu, Japan
13Showa Skin Clinic, Hakodate, Japan
14Department of Dermatology, Asahikawa Medical University Hospital, Asahikawa, Japan
15Chitose Dermatology and Plastic Surgery Clinic, Chitose, Japan
16Shinoro Dermatology Clinic, Sapporo, Japan
17Fukuzumi Dermatology Clinic, Sapporo, Japan
18Yamanaka Skincare Clinic, Sapporo, Japan
19Atago Dermatology Clinic, Tokyo, Japan
20Department of Dermatology, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
21Department of Dermatology, Tokyo Medical University, Tokyo, Japan
22Naoko Dermatology Clinic, Tokyo, Japan
23Maruyama Dermatology Clinic, Tokyo, Japan
24Queen’s Square Medical Center, Yokohama, Japan
25Department of Dermatology, Teikyo University Mizonokuchi Hospital, Kawasaki, Japan
26Nemunoki Dermatology Clinic, Kawasaki, Japan

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. The Journal of Dermatology published by John Wiley & Sons Australia, Ltd on behalf of Japanese Dermatological Association
INTRODUCTION

Onychomycosis is a common disease in daily medical practice, and affects approximately 10% of the population in Japan.¹ The disease types of onychomycosis are classified by the fungal entry route; as per the Japanese guidelines,² they are classified into the following five types: (i) distal and lateral subungual onychomycosis (DLSO); (ii) superficial white onychomycosis; (iii) proximal subungual onychomycosis (PSO); (iv) endonyx onychomycosis; and (v) total dystrophic onychomycosis (TDO). In addition, there may be specific disease types such as onychomycosis with longitudinal spikes (yellow or white linear affected area) or onychomycosis with dermatophytoma (round circumscribed yellow or a white patch) in the nail plate. Recently, DLSO with a V-shaped affected area at the tip of the nail are called “wedge shape” in Japan. However, it is a normal manifestation in DLSO; thus, it is different from longitudinal spikes.

In daily clinical practice, oral antifungal drugs are effective in many cases. However, longitudinal spikes or dermatophytoma have been reported to be refractory to oral drugs.³⁻⁶ Therefore, in previous clinical trials for onychomycosis, these disease types were excluded.⁷⁻⁹ However, after launching 10% efinaconazole solution (EFCZ) as the first topical therapeutic agent for onychomycosis in Japan, some cases with longitudinal spikes responded to EFCZ.

METHODS

2.1 Study subjects

This was a retrospective study to investigate the data from the study conducted by Iozumi et al.¹⁰ where longitudinal spikes were not excluded, we conducted a post-hoc analysis of the efficacy of EFCZ in onychomycosis with longitudinal spikes.
the study by both the medical expert and the investigator of the study site were included.

2.2 | Assessment and fixation of onychomycosis with longitudinal spikes

In this study, onychomycosis with a yellow or white linear affected area was defined as onychomycosis with longitudinal spikes. We defined longitudinal spike as a clinical manifestation of longitudinal linear opacity; however, the fungal histological findings, such as a dense mass of dermatophytes, were not confirmed. The medical expert evaluated whether or not the masked images of onychomycosis at the start of the study corresponded to the definition. After this, the investigator at each site assessed whether the image at the start of the study corresponded to the definition of patients at their site. When the assessments by the medical expert and the investigator were the same, it was placed as the assessment result. If the assessments of the medical expert and the investigator were different, the two parties discussed and the agreed assessment was placed as the assessment result. When multiple longitudinal spikes were observed in the study nail, the one with a higher opacity ratio was evaluated.

The opacity ratio and width ratio of the longitudinal spike were calculated. The opacity ratio was defined by the following formula: \[
\frac{X}{Y} \times 10,
\]
where \(X\) and \(Y\) represented the length of the longitudinal spikes and the length of the entire toenail (distance between free edge and posterior nail fold), respectively. The width ratio was the ratio of the widest of the longitudinal spike to the width of the posterior nail fold. Disappearance was assessed at the time point when the opacity ratio of the longitudinal spike was zero. Each length was measured using Image J (version 1.53a/Java 1.8.0_112).

2.3 | Primary end-point

The primary end-point was change in longitudinal spike opacity ratio and disappearance rate over time.

2.4 | Secondary end-points

Evaluation of the complete cure rate, mycological cure rate, and treatment success rate were for the entire infected area, not for longitudinal spikes.

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

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

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

Other secondary end-points were changes over time in the opacity area and in the decrease of the affected nail area.

2.5 | Evaluation time points

The evaluation time points were at the start of application, weeks 12, 24, 36, 48, 60, and 72, and the final evaluation (week 72 or the date of completion of administration).

In the data to be evaluated in this study, the data from the study conducted by Iozumi et al. were used for the following:

- Study nail (left or right first toenail): if the right and left first toenails were affected, the one with a larger opacity area was evaluated. If the areas were the same, the right toenail was evaluated.
- Opacity area (%): the opacity area was measured by visual measurement for the percentage of the opaque area (including the area of opacity lost due to nail cutting) with the nail area assumed to be 100%.
- KOH examination: results of the target nail on the evaluation time point after the start of application.
- Fungal culture test: results of the target nail at the start of application.
- Background information: sex, age, opacity area, and causative fungal species.

2.6 | Statistical analysis

For each end-point, the number of subjects and proportion (%) were obtained for nominal variables, and summary statistics were calculated for continuous variables. The statistical analysis software R version 3.6.2 (R Core Team) was used. Missing data were imputed using the last observation carried forward method.

3 | RESULTS

Figure 1 shows the disposition of the subjects. Of the 223 subjects enrolled in the clinical research of EFCZ (UMIN000024268), 83 patients (37.2%) had longitudinal spikes. Excluding one subject who lacked post-EFCZ application data, 82 subjects were included as the analysis population. Table 1 shows the subjects’ baseline characteristics. Of the subjects, 49 were male (59.8%) and 33 were female (40.2%), with a mean age of 61.7 ± 11.5 years and 46 subjects
TABLE 1 Baseline characteristics

| Variables                  | n = 82 |
|----------------------------|--------|
| Sex                        |        |
| Male                       | 49 (59.8) |
| Female                     | 33 (40.2) |
| Age                        |        |
| <65 years old              | 46 (56.1) |
| ≥65 years old              | 36 (43.9) |
| Target nail for assessment |        |
| Right                      | 46 (56.1) |
| Left                       | 36 (43.9) |
| Causative fungal species   |        |
| Trichophyton rubrum        | 51 (62.2) |
| Trichophyton interdigitale | 19 (23.2) |
| Trichophyton species       | 12 (14.6) |

Note: Data are presented as means (upper and lower limits of 95% confidence interval) or proportions (%) (number of subjects). The complete cure rate, mycological cure rate, and treatment success rate are for the entire infected area, not for longitudinal spikes.

TABLE 2 Results of each end-point

| End-point                              | n = 82 |
|----------------------------------------|--------|
| Longitudinal spike width ratio         |        |
| At baseline                            | 2.0 (1.7–2.2) |
| Longitudinal spike opacity ratio       |        |
| At baseline                            | 8.1 (7.8–8.4) |
| At final assessment                    | 0.9 (0.4–1.3) |
| Longitudinal spike disappearance rate  | 81.7 (67) |
| Complete cure rate                     | 41.5 (34) |
| Mycological cure rate                  | 72.0 (59) |
| Treatment success rate                 | 64.6 (53) |

Note: Data are presented as means (upper and lower limits of 95% confidence interval) or proportions (%) (number of subjects). The complete cure rate, mycological cure rate, and treatment success rate are for the entire infected area, not for longitudinal spikes.

(56.1%) aged less than 65 years and 36 subjects (43.9%) aged 65 years or more. The causative fungal species were Trichophyton rubrum in 51 subjects (62.2%), Trichophyton interdigitale (Trichophyton mentagrophytes) in 19 subjects (23.2%), and Trichophyton species in 12 subjects (14.6%). The width ratio of the longitudinal spike at baseline was 2.0 (95% confidence interval [CI], 1.7–2.2).

Table 2 shows the results of each end-point at the final assessment. Figure 2 shows changes over time in the opacity ratio of the longitudinal spike and changes in the disappearance rate of the longitudinal spike over time. The opacity ratio of the longitudinal spike was 8.1 (95% CI, 7.8–8.4) at baseline, decreasing from the early stage of treatment. It decreased to 2.5 (95% CI, 1.9–3.1) at week 24, which was approximately 30% of the baseline value, and decreased to 0.9 (95% CI, 0.4–1.3) at the final assessment (Figure 2a). The disappearance rate was 41.3% (nearly half disappeared) at week 24, and 81.7% at the final assessment (Figure 2b).

In addition to the evaluation of the longitudinal spike, changes over time in the complete cure, mycological cure, and treatment success rates of the entire opaque part of the target nail are shown in Figure 3. The complete cure rate at the final evaluation was 41.5% (Figure 3a). The mycological cure rate and treatment success rate at the final evaluation were 69.5% and 64.6%, respectively (Figure 3b,c). The total opacity area was 42.5% at baseline and decreased to 11.3% at the final assessment (Figure 3d,e).

Representative changes in symptoms after application of EFCZ are presented in Figure 4. Marked improvement was observed; longitudinal spike had disappeared at week 24, and onychomycosis was completely cured at week 36 (subject 1) or week 48 (subjects 2 and 3).

Subgroup analysis was performed for the primary and secondary end-points. The results are shown in Table 3. In all subgroup analyses, the disappearance rate of the longitudinal spike at the final assessment was comparable to the entire achievement rate. In addition, the rates of complete cure, mycological cure, and treatment success for the entire opacity part of the target nail were all comparable to those of the entire achievement rate.

4 | DISCUSSION

Ten percent efinaconazole solution has been shown to be effective for various types of onychomycosis and has been prescribed as a treatment option for onychomycosis. In a global phase 3 study, EFCZ was shown to be effective for mild to moderate DLSO. Iozumi et al. evaluated the efficacy of long-term use of EFCZ for onychomycosis, including severe cases. The complete cure rate at the final evaluation was 31.1%. In another study, Noguchi et al. reported an efficacy rate of 65.4% in patients with an infected area exceeding 50%. In 2020, randomized controlled trials of EFCZ with a high level of evidence were cited in the review of local treatment and device treatment for onychomycosis in the Cochrane Library.

In our study, the opacity ratio of the longitudinal spike decreased over time to approximately 1/10th of the baseline value at the final assessment. The disappearance rates were 40.2% at week 24 and 79.3% at week 48, reaching approximately 80%, showing early cure of longitudinal spike. EFCZ was suggested to be a useful option for longitudinal spikes, which had been considered intractable. We consider that EFCZ was effective because a sufficient amount reached the lesion site of longitudinal spikes. Three characteristics of EFCZ can be considered as the reason why a sufficient amount reaches the nail bed: (i) high fungicidal activity in the nail plate and nail with low keratin affinity and excellent nail penetration; (ii) low surface tension with the inclusion of surfactant; and (iii) increased drug delivery into infected nails due to low surface tension.
Dermatophytoma is characterized by white or yellow opacities in the center of the nail plate, with the lesion present in the lower layer of the nail plate. Histologically, the lo-
of dermatophyte hyphae, which are thick-walled and somewhat abnormally presented. The nail plate is cavitated and the cavity becomes semi-anaerobic, with fungal elements forming a thick pellicle, which inhibits drug penetration and becomes resistant to treatment. Longitudinal spikes and dermatophytoma are closely related pathologies, and the major difference is whether they are vertically linear or have a wide cavity, which is difficult to distinguish in many cases. Thus, as with dermatophytoma, longitudinal spikes have been reported to be refractory to oral drugs. One of the reasons is that a sufficient amount of the drug does not reach the site of fungal infection.

Ten percent efinaconazole solution has been reported to be effective for dermatophytoma. Wang et al. applied EFCZ to 19

---

**FIGURE 4** Changes over time in symptoms after application of 10% efinaconazole solution

**TABLE 3** Subgroup analysis on efficacy end-points at the final assessment

| Sex          | Age          | Causative fungal species |
|--------------|--------------|--------------------------|
|              | Male (n = 49) | Female (n = 33) | <65 years (n = 46) | ≥65 years (n = 36) | Trichophyton rubrum (n = 51) | Trichophyton interdigitale (n = 19) | Trichophyton species (n = 12) |
| Longitudinal spike disappearance rate | 79.6 (39) | 84.8 (28) | 76.1 (35) | 88.9 (32) | 82.4 (42) | 73.7 (14) | 91.7 (11) |
| Complete cure rate | 28.6 (14) | 60.6 (20) | 34.8 (16) | 50.0 (18) | 27.5 (14) | 63.2 (12) | 66.7 (8) |
| Mycological cure rate | 69.4 (34) | 75.8 (25) | 65.2 (30) | 80.6 (29) | 64.7 (33) | 78.9 (15) | 91.7 (11) |
| Treatment success rate | 61.2 (30) | 69.7 (23) | 65.2 (30) | 63.9 (23) | 52.9 (27) | 78.9 (15) | 91.7 (11) |

Note: Data are presented as percentage (%) (number of subjects). Evaluation of the complete cure rate, mycological cure rate, and treatment success rate are for the entire infected area, not for longitudinal spikes.
patients with onychomycosis complicated by dermatophytoma and reported that all patients resolved and did not recur during the study. They believe that an effective therapeutic agent must be able to diffuse through the nail plate and remain at high enough antimicrobial concentrations in the subungual space. Shimoyama et al. reported that the complete cure rate of dermatophytoma with EFCZ was 60% (3/5). They stated that the reason for the efficacy was that a sufficient concentration of the drug reached the fungal elements in the infected nail due to the specific characteristics of the drug.

According to the data obtained from the study by Iozumi et al., the frequency of DLSO with longitudinal spikes was as high as 37.2%. Moreover, part of the infected area remains as longitudinal spikes in many cases when DLSO is treated with oral drugs. EFCZ will also be useful in such cases. As the application of EFCZ can eliminate longitudinal spikes in a short period of time (~6 months), combination therapy with oral drugs will enable complete cure of DLSO in a short period of time.

In the study by Tsunemi, the selection of drugs for each type and severity of onychomycosis was investigated. As the drug most frequently prescribed for onychomycosis with wedge-shaped lesions, topical drugs accounted for 54.1%, which was higher than that of oral drugs. However, this selection was based on therapeutic experience, and the efficacy of topical agents for wedge-shaped lesions was not clear. Strictly speaking, wedge-shaped lesions are different from longitudinal spikes, but our study results demonstrated that EFCZ is the first-line therapy for onychomycosis with these lesions based on evidence. On the other hand, since it takes time to cure PSO or TDO with topical agents, treatment should be selected according to the disease type and severity.

Among cases of onychomycosis with longitudinal spikes in this study, 51 (62.2%) of the 82 were caused by T. rubrum. There was no significant difference in the fungal species reported in the epidemiological studies of onychomycosis in Japan, and it was found that the main causative fungal species was T. rubrum. For the causative species of dermatophytoma, although the sample size was only seven patients, a study reported that T. rubrum was detected in three of the seven. This is the first report on causative fungal species of longitudinal spikes, providing new findings. However, in this study, the sampling site was not limited to the longitudinal spikes, and we cannot rule out the possibility that the causative fungal species of the longitudinal spike were different from those collected from other lesions. Therefore, examination of the causative species localized to the longitudinal spike will be needed in the future.

In conclusion, this study clarified the clinical effectiveness of EFCZ for the treatment of onychomycosis with longitudinal spikes. Since this is a multicenter study with a sample size of over 80 subjects, it will provide important findings to clarify the therapeutic effect. Although data on the efficacy of longitudinal spikes have been insufficient, the results of our study showed that EFCZ has a high therapeutic effect and can be the first-line therapy.

ACKNOWLEDGMENTS
We sincerely appreciate the cooperation of the medical staff of institutions that participated in the study. This study was funded by Kaken Pharmaceutical.

CONFLICT OF INTEREST
S.W. received a consultancy fee from Kaken Pharmaceutical, and T.O. has stock in Kaken Pharmaceutical.

ORCID
Shinichi Watanabe https://orcid.org/0000-0001-8216-9237
Masatoshi Abe https://orcid.org/0000-0002-8863-9428
Hirotoshi Takahashi https://orcid.org/0000-0001-5375-3266
Ryoji Tsuboi https://orcid.org/0000-0002-1047-0351
Takashi Mochizuki https://orcid.org/0000-0002-3793-980X
Mariko Seishima https://orcid.org/0000-0003-0007-3632
Motoi Takenaka https://orcid.org/0000-0002-7045-2518

REFERENCES
1. Watanabe S, Harada T, Hiruma M, Iozumi K, Katoh T, Mochizuki T, et al. Epidemiological survey of foot diseases in Japan: results of 30,000 foot checks by dermatologists. J Dermatol. 2010;37:397–406.
2. Mochizuki T, Tsuboi R, Iozumi K, Ishizaki S, Ushigami T, Ogawa Y, et al. Guidelines for the management of dermatomycosis. J Dermatol. 2020;47:1343–73.
3. Roberts DT, Evans EG. Subungal dermatophytoma complicating dermatophyte onychomycosis. Br J Dermatol. 1998;138:189–90.
4. Gupta AK, Konnikov N, Lynde CW, Summerbell RC, Albreysi D, Baran R, et al. Onychomycosis: predisposed populations and some predictors of suboptimal response to oral antifungal agents. Eur J Dermatol. 1999;9:633–8.
5. Sigurgeirsson B. Prognostic factors for cure following treatment of onychomycosis. J Eur Acad Dermatol Venereol. 2010;24:679–84.
6. Bennett D, Rubin AI. Dermatophytoma: a clinicopathologic entity important for dermatologists and dermatopathologists to identify. Int J Dermatol. 2013;52:1285–7.
7. Elewski BE, Rich P, Pollak R, Pariser DM, Watanabe S, Senda H, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol. 2013;68:600–8.
8. Watanabe S, Kishida H, Okubo A. Efficacy and safety of luliconazole 5%nail solution for the treatment of onychomycosis: a multicenter, double-blind, randomized phase III study. J Dermatol. 2017;44:753–9.
9. Watanabe S, Tsubouchi I, Okubo A. Efficacy and safety of fosparaconazole L-lysine ethanolate, a novel oral triazole antifungal agent, for the treatment of onychomycosis: a multicenter, double-blind, randomized phase III study. J Dermatol. 2018;45:1151–9.
10. Iozumi K, Abe M, Ito Y, Uesugi T, Onoduka T, Kato I, et al. Efficacy of long-term treatment with efinaconazole 10% solution in patients with onychomycosis, including severe cases: a multicenter, single-arm study. J Dermatol. 2019;46:641–51.
11. Noguchi H, Matsumoto T, Hiruma M, Asao K, Hirose M, Fukushima S, et al. Topical efinaconazole: a promising therapeutic medication for tinea unguium. J Dermatol. 2018;45:1225–8.
12. Tschen EH, Bucko AD, Oizumi N, Kawabata H, Olin JT, Pillai R. Efinaconazole solution in the treatment of toenail onychomycosis: a phase 2, multicenter, randomized, double-blind study. J Drugs Dermatol. 2013;12:186–92.
13. Foley K, Gupta AK, Versteeg S, Mays R, Villanueva E, John D. Topical and device-based treatments for fungal infections of the toenails. Cochrane Database Syst Rev. 2020;1:CD012093.

14. Sugiura K, Sugimoto N, Hosaka S, Katafuchi-Nagashima M, Arakawa Y, Tatsumi Y, et al. The low keratin affinity of efinaconazole contributes to its nail penetration and fungicidal activity in topical onychomycosis treatment. Antimicrob Agents Chemother. 2014;58:3837–42.

15. Bhatt V, Pillai R. Efinaconazole topical solution. 10%: Formulation development program of a new topical treatment of toenail onychomycosis. J Pharm Sci. 2015;104:2177–82.

16. Kircik LH. Enhancing transungual delivery and spreading of efinaconazole under the nail plate through a unique formulation approach. J Drugs Dermatol. 2014;13:1457–61.

17. Harada T. Tinea unguium. Med Mycol J. 2011;52:77–95.

18. Wang C, Cantrell W, Canavan T, Elewski B. Successful treatment of dermatophytomas in 19 patients using efinaconazole 10% solution. Skin Appendage Disord. 2019;5:304–8.

19. Shimoyama H, Kuwano Y, Sei Y. Retrospective survey of treatment outcomes of efinaconazole 10% solution and luliconazole 5% solution for onychomycosis in our facility. Med Mycol J. 2019;60:95–100.

20. Tsunemi Y. A questionnaire survey on drug selection by subtype and severity of onychomycosis and drug evaluation. J Jpn Organization Clin Dermatol. 2016;33:630–6.

21. Martínez-Herrera E, Moreno-Coutiño G, Fernández-Martínez RF, Finch J, Arenas R. Dermatophytoma: description of 7 cases. J Am Acad Dermatol. 2012;66:1014–6.

How to cite this article: Watanabe S, Iozumi K, Abe M, Ito Y, Uesugi T, Onoduka T, et al. Clinical effectiveness of efinaconazole 10% solution for treatment of onychomycosis with longitudinal spikes. J Dermatol. 2021;48:1474–1481. https://doi.org/10.1111/1346-8138.16035