Treatment Outcome with Fosravuconazole for Onychomycosis

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Received: 4 February 2021 / Accepted: 2 March 2021 / Published online: 22 March 2021
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Abstract Fosravuconazole L-lysine ethanolate (F-RVCZ), a ravuconazole prodrug, is a newly available agent with high expectations for efficacy in the treatment of onychomycosis. However, clinical data regarding the efficacy of F-RVCZ are limited because the drug was launched only in Japan in 2018. Therefore, we analyzed the outcome of F-RVCZ therapy in the treatment of onychomycosis at outpatient dermatology clinics in Japan. We examined data for 109 patients (68 male, 41 female) with varying clinical type, including total dystrophic onychomycosis and dermatophytoma, and a wide range of age groups, including the elderly. The complete cure rate at 12 weeks was 6.4% (7/109) and 67.9% (74/109) at the last visit (mean time to last visit: 32 ± 14.2 weeks). Mean rate of improvement in the affected nail area was 49.1 ± 23.3% at 12 weeks and 86.8 ± 22.4% at the last visit. Efficacy at 12 weeks and the last visit, respectively, was as follows: none, 4 cases and 1 case; slight, 35 cases and 4 cases; moderate, 51 cases and 21 cases; significant, 12 cases and 9 cases; complete cure, 7 cases and 74 cases. There were no serious adverse events. This retrospective survey was the first large-scale analysis of actual clinical practice outcomes and had minimal exclusions. Compared to previous reports, our results demonstrated excellent efficacy of F-RVCZ therapy in a variety of patients. Considering our results and the ease of oral administration (1 capsule/day for 12 weeks) and few adverse events, F-RVCZ therapy appears to be a useful option for the treatment of onychomycosis.

Keywords Onychomycosis · Fosravuconazole L-lysine ethanolate (F-RVCZ) · Dermatophytoma · Total dystrophic onychomycosis · Complete cure

Introduction

Onychomycosis is common nail infection, with an estimated global prevalence in the range of 2%–8% [1, 2]. Although onychomycosis is not life-threatening, nail abnormalities can cause physical and mental distress and lead to impaired quality of life [3, 4]. Therefore, proper treatments that completely cure onychomycosis would improve both clinical findings and patient quality of life. According to several guidelines, systemic therapy is recommended for the treatment of onychomycosis [5–7]. Two oral antifungal
agents, itraconazole and terbinafine hydrochloride, have a long history of use in Japan, and these agents received approval for insurance coverage for the treatment of onychomycosis in the 1990s. However, systemic therapy may not be suitable for all cases due to drug interactions, adverse events associated with oral medications, and/or comorbidities. Since 2010, two topical antifungal agents, efinaconazole 10% solution and luliconazole 5% solution, have been approved for the treatment of onychomycosis in Japan. Compared with systemic therapy, topical agents are not associated with serious adverse events and can be applied safely, but they are not as effective as systemic therapies [8–10]. In addition, complete cure can take considerable time [10]. Fosravuconazole L-lysine ethanolate (F-RVCZ), a prodrug of ravuconazole (RVCZ), was approved for the treatment of onychomycosis only in Japan in 2018 [11–13]. RVCZ exhibits strong antifungal activity against a variety of pathogenic fungi, including the major pathogens causing onychomycosis [11, 14]. The prodrug exhibits improved pharmacokinetics, with the bioavailability after oral administration reaching 100%, and the skin and nail tissue transition as well as tissue retention are excellent [11, 12]. Moreover, F-RVCZ has fewer drug interactions, leading to improved patient medication adherence, as the regimen involves taking only 1 capsule per day (equivalent to 100 mg of RVCZ) for 12 weeks [11–13].

Watanabe et al. reported the results of a phase III, placebo-controlled study of F-RVCZ involving 153 onychomycosis patients ranging in age from 20 to 75 years [13]. In their study, severe cases involving spike or linear lesions, clinical involvement reaching the proximal nail fold, or significant nail thickening or deformities due to onychogryphosis or other conditions were excluded. The average nail lesion involvement area in the first toenail among study participants was 53%. F-RVCZ was orally administered once daily after meals for 12 weeks. The rate of complete cure after 48 weeks was 59.4% (60/101) in the F-RVCZ group and 5.8% (3/52) in the placebo control group. Gastrointestinal symptoms and elevated liver function enzymes were observed in several cases, but in all such cases, the symptoms improved with discontinuation of the drug, and no serious side effects were reported. These data suggest that F-RVCZ would be a useful oral treatment option for onychomycosis. According to Guidelines for the Management of Dermatophytosis (2019) published in Japan, oral F-RVCZ therapy is highly recommended for the treatment of tinea unguium [7]. Although expectations for F-RVCZ are high based on the abovementioned data, few studies have examined the efficacy of F-RVCZ because it has only been available in Japan since 2018 [12, 13, 15]. Moreover, the exclusion criteria of these studies narrowed the scope of participants analyzed. However, in actual clinical care, patients may present with a variety of medical conditions, ranging from mild to severe in scope, and patient ranging in age from the young to the elderly must be treated. Therefore, we analyzed the outcome of F-RVCZ therapy with the aim of contributing to the treatment of onychomycosis in real-world situations at outpatient dermatology clinics.

**Patients and Methods**

A retrospective survey was conducted of patients diagnosed with onychomycosis and started on oral F-RVCZ therapy between March 1, 2018, and August 31, 2020. The treatment regimen for patients was set as administration of 1 capsule per day (equivalent to 100 mg of RVCZ) for 12 weeks. All cases were diagnosed by direct microscopic examination. Patients treated with oral antifungal therapy within the previous 6 months were excluded. Gender, age, clinical type, location (adopting the most severe site), percentage of the affected nail area, and nail thickness were recorded for each patient. The clinical type of onychomycosis was classified as distal and lateral subungual onychomycosis (DLSO), proximal subungual onychomycosis (PSO), total dystrophic onychomycosis (TDO), or dermatophytoma based on clinical findings and direct microscopic examination at the first visit to the outpatient clinic. Dermatophytoma was diagnosed by direct microscopic examination based on the presence of abundant fungal filaments, large spores, or both, which were compacted and formed a mass or fungal ball [16, 17]. When mixed clinical features were present, the most severe nail-affecting type was selected. Superficial white onychomycosis was excluded because this type of infection is easily treated with topical antifungal agents [7, 10]. To evaluate severity before treatment was initiated, we measured the percentage of the affected nail area and the nail thickness at the first visit. Percentage
of the affected nail area was categorized as follows: 0%–25%, 26%–50%, 51%–75%, and 76%–100%. Nail thickness was categorized as < 2 mm or ≥ 2 mm.

Treatment efficacy was evaluated based on clinical photographs taken at each visit, and the percentage of the affected nail area was determined and compared at each visit using PDF software (Foxit PhantomPDF, FoxitJapan, Inc. Tokyo, Japan). Improvement rate was calculated using the following formula:

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\text{Improvement rate} = \left( \frac{\text{Affected nail area at first visit} - \text{Affected nail area at each assessment}}{\text{Affected nail area at baseline}} \right) \times 100.
\]

Efficacy of treatment was classified into five categories according to the improvement rate, as follows: no clearance, 0%–10%; slight clearance, 11%–40%; moderate clearance, 41%–70%; significant clearance, ≥ 71%; and complete cure, clinical cure and negative mycologic test result. The significance of differences in improvement rate at the last visit and time to complete cure was analyzed using BellCurve for Excel (Social Survey Research Information Co., Tokyo, Japan) at a significance level of \( \alpha = 0.05 \) by one-way analysis of variance followed by Tukey’s test.

Adverse events were assessed by determining whether patients had any subjective symptoms or objective findings. In addition, laboratory tests were conducted every 4–6 weeks during the administration period to monitor for abnormal findings.

Patients were observed for at least 12 weeks from the start of oral administration of F-RVCZ, including cases in which treatment was discontinued due to adverse events. This survey was approved by the research ethics committee of Teikyo University (Teirin 18–235-2), and the analyses were performed at Teikyo University Mizonokuchi Hospital, Kanagawa, Japan.

Results

Patients

Patient profiles are shown in Table 1. In total, 109 patients (68 males, 41 females) were diagnosed with onychomycosis and treated with F-RVCZ. Most of the patients (53.2%; 58/109) were in the 60–79 years old age group, and 16.5% (18/109) of the patients were >80 years old. DLSO was the most frequent clinical type, accounting for 70.6% of patients (77/109), followed by dermatophytoma, TDO, and PSO. The most frequently affected location was the nail of the big toe (86.2%; 94/109). With regard to the percentage of affected nail area as determined at the first visit, 26–50% of the nail area was affected in 39.4% of patients (43/109), followed by 51%–75%, 0%–25%, and 76%–100%. Nail plate thickness <2 mm was observed in 77.1% of patients (84/109).

Efficacy

Treatment outcome data are summarized in Table 1. Tukey’s tests revealed a significant difference in time to complete cure between patients with DLSO and TDO and between those with TDO and dermatophytoma. There was a significant difference in the improvement rate between patients with DLSO versus other clinical types. There were also significant differences in improvement rate between patients in the 0%–25% and 75%–100% of the affected nail area groups and between patients in the 25%–50% and 75%–100% of the affected nail area groups.

Analysis results are shown in Table 2. Complete cure at 12 weeks was observed in 6.4% of patients (7/109) and 67.9% of patients (74/109) at the last visit (mean time to last visit: 32 ± 14.2 weeks). The mean improvement rate was 49.1 ± 23.3% at 12 weeks and 86.8 ± 22.4% at the last visit. Efficacy at 12 weeks and the last visit, respectively, was as follows: none, 4 cases and 1 case; slight, 35 cases and 4 cases; moderate, 51 cases and 21 cases; significant, 12 cases and 9 cases; complete cure, 7 cases and 74 cases (Table 3).

Analyses based on clinical type are shown in Table 4. The complete cure rate for DLSO at 12 weeks and the last visit was 9.1% (7/77) and 76.6% (59/77), respectively. For TDO, the complete cure rate at 12 weeks and the last visit was 0% and 30% (3/10), respectively, and for dermatophytoma, the complete cure rate at 12 weeks and the last visit was 0% and 57.1% (12/21), respectively. Only one case of PSO was confirmed, and complete cure could not be achieved. The mean improvement rate at the last visit for each clinical type was as follows: DLSO, 92.5 ± 15.3%; PSO, 43.1%; TDO, 62.3 ± 30.6%; and dermatophytoma, 79.8 ± 28.9%.
Analyses based on patient age are shown in Table 5. The complete cure rate at 12 weeks and the last visit, respectively, was 50% (1/2) and 100% (2/2) in patients aged 20–39 years, 3.2% (1/31) and 71% (22/31) in patients aged 40–59 years; 8.6% (5/58) and 69% (40/58) in patients aged 60–79 years, and 0% and 55.6% (10/18) in patients aged 80–99 years. The mean improvement rate at the last visit for each group was 100% among patients aged 20–39 years, 87.4 ± 22.9% in patients aged 40–59 years, 87.5 ± 21.0% in patients aged 60–79 years, and 82.2 ± 27.4% in patients aged 80–99 years.

There were 4 cases of onychomycosis with tinea corporis among the patients in the study, and all 4 cases were completely cured within 4 weeks (data not shown).

### Adverse Events

In total, there were 6 cases (5.5%) of confirmed adverse events leading to discontinuation of therapy. Three patients (2.8%) discontinued therapy due to increased liver function test values: mean serum γ-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase values were 547.7 ± 679.3 IU/L, 70 ± 15.1 IU/L, and 129.3 ± 59.2 IU/L, respectively. The other 3 patients (2.8%) discontinued therapy due to abdominal discomfort. None of the patients exhibited serious side effects, and their condition improved following discontinuation of therapy. Among the patients who discontinued therapy, the mean oral administration period was 6.3 ± 2.0 weeks, and the mean improvement rate for the affected nail area was 55 ± 17.9% by 12 weeks (data not shown).

## Discussion

This retrospective survey represents the first large-scale analysis of actual clinical practice outcomes. In contrast to previous studies, we were able to analyze the efficacy of F-RVCZ therapy for treating onychomycosis of varying severity and clinical type in...
patients over a wide range of age. In addition, we had minimal exclusions in our survey and thus obtained data that are clinically useful.

Generally, onychomycosis may present as a mixture of clinical types, but the most common type is DLSO [7, 18], and our study found that oral F-RVCZ therapy is effective for treating DLSO. In addition, F-RVCZ therapy exhibited efficacy against dermatophytoma, an intractable clinical feature. Dermatophytoma is a clinical type of onychomycosis typically refractory to systemic therapies and thus can necessitate surgical removal of the diseased nail plate [17]. Although patients with dermatophytomas are often excluded from clinical surveys, we were able to analyze 21 cases. In a previous study in Japan, the complete cure rate for treatment of dermatophytomas with topical agents was 54.5%, and the duration of treatment was > 1 year [10]. In our study, 12 patients (57%) achieved complete cure without any special surgical removal over an average observation period of 34.3 ± 11.1 weeks. More notably, oral F-RVCZ therapy was also effective against TDO (Fig. 1), the most severe form of onychomycosis [5, 7]. In our study, 3 patients (30%) achieved complete cure within an average observation period of 53.3 ± 11.5 weeks, and our results indicated that the time until therapeutic effect against TDO became clear was longer than for the other types of onychomycosis. Therefore, it was considered that continuous, long-term follow-up was necessary. Moreover, similar to previous reports, the complete cure rate several months after the end of oral administration was higher than the complete cure rate at the end of 12 weeks [13]. In 1 patient, clinical findings improved steadily after the start of treatment but worsened 6 months after the end of oral administration.

| Efficacy evaluation category | Number of patients (%) |
|-----------------------------|------------------------|
| At 12 weeks | At last visit |
| No | 4 (3.7) | 1 (0.9) |
| Slight clearance | 35 (32.1) | 4 (3.7) |
| Moderate clearance | 51 (46.8) | 21 (19.3) |
| Significant clearance | 12 (11.0) | 9 (8.3) |
| Complete cure | 7 (6.4) | 74 (67.9) |

Table 3 Five-grade evaluation of efficacy at 12 weeks and at last visit

| Efficacy evaluation category | Number of patients (%) |
|-----------------------------|------------------------|
| At 12 weeks | At last visit |
| No | 4 (3.7) | 1 (0.9) |
| Slight clearance | 35 (32.1) | 4 (3.7) |
| Moderate clearance | 51 (46.8) | 21 (19.3) |
| Significant clearance | 12 (11.0) | 9 (8.3) |
| Complete cure | 7 (6.4) | 74 (67.9) |
regimen, we encourage regular visits once every 1–3 months to evaluate the patient’s nail condition.

In terms of age, the present study examined a wider range of patients compared with previously reported surveys [15]. Due to aging of the Japanese population, the proportion of patients aged >80 years is increasing, which could pose problems in the future [19–21]. Therefore, we conducted a more-detailed age-specific evaluation than previous studies. We found no significant difference in improvement rate or time to complete cure between age groups, suggesting that F-RVCZ is effective for all age ranges.

We focused on the complete cure rate because complete cure is often the treatment goal in daily practice. In previous reports, the clinical and complete cure rates at 72 weeks with terbinafine 250 mg/day administered for 12 weeks were 53.6% and 45.8%, respectively, and 60.2% and 55.1%, respectively, for 16 weeks of administration. For itraconazole pulse therapy (400 mg/day), the clinical and complete cure rates at 72 weeks with 3 courses were 31.8% and 23.4%, respectively, and 32.1% and 25.9% (28/108), respectively, for 4 courses [22]. The reported complete cure rate with topical agents is approximately 30–40%, and a long period of administration is required for achieving complete cure [8–10]. In terms of the complete cure rate, our study achieved excellent results. In terms of efficacy, 76.1% (83/109) of patients were evaluated as having significant clearance or greater. Although further investigations are necessary, these results suggest that oral treatment with F-RVCZ is an important option for the treatment of onychomycosis. Many patients can aim for complete cure with oral F-RVCZ therapy. In addition, the duration of oral administration is short, there are fewer drug interactions, and side effects are typically not severe.

F-RVCZ therapy is reportedly effective for the treatment of various dermatomycoses, and it is also reported to be an effective option for treating terbinafine-resistant dermatophytes, which have recently attracted clinical attention [23–25]. Our study included 4 cases of onychomycosis with tinea corporis. In all 4 cases, the clinical symptoms of tinea corporis were completely cured by at least 4 weeks. Considering the results of previously reported cases and the simple oral administration regimen in conjunction with few adverse events, F-RVCZ therapy appears to

| Clinical type | Number of patients | Mean age, years ± SD | Mean percent-age of affected nail area at first visit, % ± SD | Mean percent-age of affected nail area at 12 weeks, % ± SD | Mean improvement rate of affected nail area at 12 weeks, % ± SD | Complete cure rate at 12 weeks, n/n (%) | Mean percent-age of affected nail area at last visit, % ± SD | Mean improvement rate of affected nail area at last visit, % ± SD | Complete cure rate at last visit, n/n (%) | Mean time to complete cure, weeks ± SD |
|---------------|--------------------|---------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| DLSO          | 77                 | 68.6 ± 13.3         | 46.8 ± 17.7                                     | 23.0 ± 14.5                                     | 20.6 ± 13.0                                     | 0.0                             | 4.1 ± 8.9                       | 92.5 ± 15.3                     | 7/77(9.1)                        | 4.1 ± 8.9                       |
| PSO           | 1                  | 78                  | 68.4 ± 13.0                                     | 90.0 ± 15.0                                     | 35.7 ± 19.4                                     | 0.0                             | 4.1 ± 8.9                       | 92.5 ± 15.3                     | 7/77(9.1)                        | 4.1 ± 8.9                       |
| TDO           | 10                 | 68.4 ± 13.0         | 90.0 ± 15.0                                     | 65.2 ± 21.3                                     | 18.6 ± 13.2                                     | 0.0                             | 0.0                             | 79.8 ± 28.9                     | 12/121(57.1)                     | 33.8 ± 12.9                     |
| Dermatophyt- | 21                 | 60.4 ± 12.7         | 35.7 ± 19.4                                     | 18.6 ± 13.2                                     | 46.2 ± 20.6                                     | 0.0                             | 0.0                             | 79.8 ± 28.9                     | 12/121(57.1)                     | 33.8 ± 12.9                     |

Table 4 Analyses based on clinical type

SD Standard deviation; DLSO Distal subungual onychomycosis; PSO Proximal subungual onychomycosis; TDO Total dystrophic onychomycosis
be an effective option for treating other dermatomycoses, although further research is needed.

This study has some limitations. As this was a retrospective study, we did not have a negative control group. The analyses of PSO type were also limited; as the number of cases of PSO was small, more cases need to be analyzed.

### Table 5 Analyses based on patient age

| Patient age, years | Number of patients | Mean percentage of affected nail area at first visit, % ± SD | Mean percentage of affected nail area at 12 weeks, % ± SD | Mean improvement rate of affected nail area at 12 weeks, % ± SD | Complete cure rate at 12 weeks, n/n (%) | Mean percentage of affected nail area at last visit, % ± SD | Mean improvement rate of affected nail area at last visit, % ± SD | Complete cure rate at last visit, n/n (%) | Mean time to complete cure, weeks ± SD |
|-------------------|--------------------|-------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------|---------------------------------------|
| 20–39             | 2                  | 52 ± 46.7                                                   | 23 ± 32.5                                                | 72.9 ± 38.2                                                  | 1/2 (50)                             | 100 ± 0                                                       | 87.4 ± 22.9                                                  | 2/2 (100)                             | 21.0 ± 12.7                           |
| 40–59             | 31                 | 44.5 ± 22.5                                                | 22.7 ± 14.3                                              | 49.6 ± 19.5                                                  | 1/31 (3.2)                           | 5.1 ± 11.1                                                   | 87.4 ± 22.9                                                  | 22/31 (71.0)                          | 33.5 ± 11.1                           |
| 60–79             | 58                 | 47.9 ± 22.0                                                | 24.6 ± 20.4                                              | 51.4 ± 25.0                                                  | 5/58 (8.6)                           | 8.1 ± 15.7                                                   | 87.5 ± 21.0                                                  | 40/58 (69.0)                          | 34.9 ± 13.9                           |
| 80–99             | 18                 | 59 ± 20.9                                                  | 38.4 ± 20.4                                              | 37.8 ± 19.2                                                  | 0                                    | 12.9 ± 20.4                                                  | 82.2 ± 27.4                                                  | 10/18 (55.6)                          | 39.6 ± 12.4                           |

SD Standard deviation

**Fig. 1** Treatment course in a 64-year-old man with total dystrophic onychomycosis (TDO) in the nail of the right big toe. The patient was on dialysis therapy due to diabetic nephropathy. **a** Clinical findings at first visit showed that the entire nail plate was affected. **b** Direct microscopic examination of nail revealed abundant fungal filaments and spores (×100). We diagnosed dermatophytoma along with TDO. **c** Clinical findings after 12 weeks of oral F-RVCZ therapy. There was no significant change in the affected nail area. **d** Clinical findings at 24 weeks. Improvement rate was 19%. **e** Clinical findings at 84 weeks (last visit in observation period of this survey). Clear nail growth and a decrease in nail thickness were observed. Improvement rate was 85%, and the efficacy of therapy was classified as significant clearance. **f** Clinical findings at 100 weeks. Complete cure was confirmed. This patient experienced no adverse events during the administration period.
Because F-RVCZ has only been available for approximately 2 years and was launched only in Japan, we believe that sharing the actual outcomes of treatment is useful for the treatment of onychomycosis and could aid clinicians worldwide. We hope that our findings prove useful in the actual treatment of onychomycosis.

Acknowledgements The authors thank Koichi Makimura of Teikyo University for contributions based on expertise in mycology. The authors thank Kazuo Satoh of Teikyo University for contributions to the statistical analyses and manuscript revisions.

Author Contributions HS designed the study, carried out the diagnosis, treatment, and data analysis, and drafted the manuscript. YS, AY, and YK participated in the diagnosis and treatment of onychomycosis and revision of the manuscript. All authors read and approved the final manuscript.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with Ethical Standards

Conflict of interest The author declare that they have no conflict of interest.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Consent for publication was obtained from the study participant presented in Fig. 1.

Ethical Approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees (Research Ethics Committee of Teikyo University; Teirin 18–235-2) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Gupta AK, Versteeg SG, Shear NH. Onychomycosis in the 21st century: an update on diagnosis, epidemiology, and treatment. J Cutan Med Surg. 2017;21(6):525–39.
2. Gupta AK, Jain HC, Lynde CW, Macdonald P, Cooper EA, Summerbell RC. Prevalence and epidemiology of onychomycosis in patients visiting physicians’ offices: a multicenter Canadian survey of 15 000 patients. J Am Acad Dermatol. 2000;43(2):244–8.
3. Elewski BE. The effect of toenail onychomycosis on patient quality of life. Int J Dermatol. 1997;36(10):754–6.
4. 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):144–55.
5. Ameen M, Lear JT, Madan V, Mohd Mustafa MF, Richardson M. British Association of Dermatologists’ guidelines for the management of onychomycosis 2014. Br J Dermatol. 2012;171(5):937–58.
6. Seebacher C, Brasch J, Abeck D, Cornely O, Effendi Y, Ginter-Hanselmayer G, et al. Onychomycosis. Mycoses. 2007;50(4):321–7.
7. Mochizuki T, Tsuboi R, Iozumi K, Ishizaki S, Ushigami T, Ogawa Y, et al. Guidelines for the management of dermatomycosis (2019). J Dermatol. 2020;47(12):1343–73.
8. Iozumi K, Abe M, Ito Y, Uesugi T, Onoduka T, Ichiro 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(8):641–51.
9. 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(7):753–9.
10. 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(4):95–100.
11. Yamaguchi H. Potential of ravuconazole and its prodrugs as the new oral therapeutics for onychomycosis. Med Mycol J. 2016;57(4):E93–110.
12. Gupta AK, Leonard C, Stoltz RR, Pierce PF, Conetta B. Ravuconazole Onychomycosis Group A phase II randomised, doubleblind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. J Eur Acad Dermatol Venereol. 2005;19(4):437–43.
13. Watanabe S, Tsubouchi I, Okubo A. Efficacy and safety of fosravuconazole 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(10):1151–9.
14. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Garcia-Effron G, Rodriguez-Tudela JL. In vitro activities of ravuconazole and four other antifungal agents against fluconazole-resistant or –susceptible clinical yeast isolates. Antimicrob Agents Chemother. 2004;48(8):3107–11.
15. Noguchi H, Matsumoto T, Kimura U, Hiruma M, Kano R, Kubo M, et al. 2020 Fosravuconazole to treat severe onychomycosis in the elderly. J Dermatol doi: https://doi.org/10.1111/1346-8138.15651. Online ahead of print.
16. Martinez-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.
17. Burkhard CN, Burkhart CG, Gupta AK. Dermatophytoma: recalcitrance to treatment because of existence of fungal biofilm. J Am Acad Dermatol. 2002;47(4):629–31.
18. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. J Am Acad Dermatol. 2011;65(6):1219–27.
19. Shimoyama H, Sei Y. 2016 Epidemiological Survey of Dermatomycoses in Japan. Med Mycol J. 2019;60(3):75–82.

20. Loo DS. Onychomycosis in the elderly: drug treatment options. Drugs Aging. 2007;24(4):293–302.

21. Reszke R, Pelka D, Walasek A, Machaj Z, Reich A. Skin disorders in elderly subjects. Int J Dermatol. 2015;54(9):e332–338.

22. Sigurgeirsson B, Billstein S, Rantanen T, Ruzicka T, di Fonzo E, Vermeer BJ, et al. LION Study: efficacy and tolerability of continuous terbinafine (Lamisil) compared to intermittent itraconazole in the treatment of toenail onychomycosis Lamisil versus Itraconazole in Onychomycosis. Br J Dermatol. 1999;141(5):5–14.

23. Takeshima R, Asahina Y, Yaguchii T, Sato T. Tinea barbae due to Trichophyton rubrum successfully treated using oral fosravuconazole l-lysine ethanolate. J Dermatol. 2020;47(7):e254–5.

24. Noguchi H, Matsumoto T, Kimura U, Hiruma M, Kano R, Yaguchi T, et al. Fungal melanonychia caused by Candida parapsilosis successfully treated with oral fosravuconazole. J Dermatol. 2019;46(10):911–3.

25. Noguchi H, Matsumoto T, Hiruma M, Kimura U, Kano R, Yaguchi T, et al. Tinea unguium caused by terbinafine-resistant Trichophyton rubrum successfully treated with fosravuconazole. J Dermatol. 2019;46(12):e446–7.

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