Characteristics and Efficacy of Two Topical Therapeutic Agents for Onychomycosis: Efinaconazole 10% Solution and Luliconazole 5% Solution

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ABSTRACT

Tinea pedis and tinea unguium are the most common dermatophytoses seen in the daily practice of dermatology. According to a report in Japan Foot Week 2006, it is estimated that about 1 in 5 Japanese have tinea pedis and that about 1 in 10 have tinea unguium. Thus far, use of oral antifungal agents has been the first-line therapy for onychomycosis. Many patients with onychomycosis, however, are elderly and have concomitant diseases as well as liver function disorder. Moreover, oral medications are reportedly associated with risks of impaired liver function and interactions. Due to such risks, therefore, treatment with topical agents is the only applicable therapy for most patients with onychomycosis. Recently, two topical agents (efinaconazole in 2014 and luliconazole in 2016) have been approved for the treatment of onychomycosis in Japan. Efinaconazole 10% solution is a triazole antifungal drug developed in Japan. Due to its low keratin affinity, efinaconazole shows high transungual penetration into nails and retains a high antifungal activity in the nail plate and the nail bed. Luliconazole 5% solution is an imidazole antifungal agent that has high keratin affinity. Luliconazole has also been shown in vitro to permeate from the superficial to the deep layers of the nail and to achieve concentrations above the MIC in all layers of the nail. Both efinaconazole 10% solution and luliconazole 5% solution have high antifungal activities for Trichophyton species. These two topical agents, therefore, have certainly increased treatment options for onychomycosis in the daily practice of dermatology.

Keywords: efinaconazole, luliconazole, onychomycosis, topical agents, treatment

Introduction

Tinea pedis and tinea unguium are the most common dermatophytoses seen in the daily practice of dermatology. According to a report in Japan Foot Week 2006, it is estimated that about 1 in 5 Japanese have tinea pedis and that about 1 in 10 have tinea unguium. According to the same report, 49% of the foot diseases of new dermatological outpatients were tinea pedis and/or tinea unguium. Another study indicates that patients with occult athlete’s foot account for 25% of all new dermatological outpatients in Japan. According to the large-scale European study, Achilles Foot Screening Project, the incidence rates of both tinea pedis and tinea unguium were each approximately 20%. Onychomycosis involves fungal infection of the nail bed, matrix or plate and represents about 50% of all nail disorders. It is caused by dermatophyte fungi in about 90% of cases, but can also be caused by yeast and mold. Onychomycosis is clinically classified into the following five types based on fungal invasion routes to nail plate: distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), total dystrophic onychomycosis (TDO), and dermatophytoma (yellow spikes) (Fig. 1). The clinical symptoms of tinea unguium are primarily subungual hyperkeratosis, with the end nail plate becoming rough and fragile, finally leading to deformity and destruction of the nail. Worsening of tinea unguium can cause pain while walking, leading to a significant deterioration of the quality of daily life. Risk factors associated with onychomycosis include advanced age, tinea pedis, psoriasis, diabetes, immunodeficiency, and others.

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diseases as well as liver function disorder. Moreover, oral medications are reportedly associated with risks of impaired liver function and interactions. Not all patients with onychomycosis, therefore, can take internal drugs for onychomycosis. Thus, in order to avoid various risks, most patients with onychomycosis are only treated with topical agents. Two topical agents (efinaconazole in 2014 and luliconazole in 2016) recently have been approved for treatment of onychomycosis in Japan. These two topical agents have certainly increased treatment options for onychomycosis in the daily practice of dermatology, wherein many clinics in Japan are already using these two topical agents.

**Efinaconazole 10% solution (Clenafin®)**

Efinaconazole is a triazole antifungal drug developed in Japan. Due to its having a lower keratin affinity compared with existing drugs, efinaconazole shows higher transungual penetration into human nails and retains a higher antifungal activity in the nail plate and the nail bed. Efinaconazole (Clenafin®) was first marketed in Japan in September 2014. Two identical, multicenter, randomized, double-blind, and vehicle-controlled studies were conducted in patients with tinea unguium showing moderate DLSO type (20% < affected nail area < 50%) [Study 1: N = 870, Study 2: N = 785] to investigate the efficacy and safety of efinaconazole 10% solution. Patients were randomized to efinaconazole or vehicle, once daily use for 48 weeks, with a 4-week post-treatment follow up. At week 52, complete cure (0% clinical involvement of target toenail, and negative for both potassium hydroxide examination and fungal culture) rates were significantly greater with efinaconazole (Study 1: 17.8%, Study 2: 15.2%). Also, mycological cure rates were greater with efinaconazole (Study 1: 55.2%, Study 2: 53.4%). Treatment success (percent affected target nail ≤10) was 44.8% in Study 1 and 40.2% in Study 2. Adverse events associated with efinaconazole were local site reactions.

A single-arm open study (N = 219) including severe cases (affected nail area > 50%) was also conducted in Japan to evaluate the efficacy and safety of long-term use (up to 72 weeks) of efinaconazole 10% solution. According to the report, at week 72, complete cure rate was 31.1%, mycological cure rate was 61.6%, and treatment success (< 10% clinical involvement of the target nail) was 56.6%. Another open study (N = 484) including long-term use reported that in 30% of the patients, achieving complete cure required more than one-year treatment. The results of these studies demonstrate that continuous application contributes to the improvement of cure rate. No increase in the incidence of adverse drug reaction due to long-term use was found. Clinical course of a 61-year-old man with DLSO type onychomycosis is shown in Fig. 2.

**Luliconazole 5% solution (Luconac®)**

Luliconazole 5% solution is an imidazole antifungal agent that has high affinity for keratin. Luliconazole 1% cream for tinea pedis had been applied for the treatment of onychomycosis. Luliconazole 5% solution has been shown in vitro to permeate from the superficial to the deep layers of the nail and to achieve concentrations above the MIC in all layers of the nail. A multicenter, double-blind, randomized phase III study
was conducted in Japanese patients with DLSO type onychomycosis affecting the great toenails (affected nail area < 50%) to investigate the efficacy and safety of luliconazole 5% solution. At week 48 after continuing once daily use, complete cure (clinical cure plus mycological cure) rate was 14.9%, and mycological cure (negative results for direct microscopy and culture) rate was 45.4%. Treatment success (reduction of the affected nail ≥ 50%) was 32.8% at week 48. There were no serious adverse drug reactions.

Clinical course of an 81-year-old man with SWO type onychomycosis is shown in Fig. 3. Table 1 shows comparative characteristics of efinaconazole 10% solution and luliconazole 5% solution.
Conclusion

Both efinaconazole 10% solution and luliconazole 5% solution have high antifungal activities for Trichophyton species, which are the main causative pathogens of onychomycosis. These two agents bring substantial benefits to patients who cannot take oral antifungal agents due to liver dysfunction or other reasons. Treatment success rates of these two topical agents, however, are generally lower than those of internal drugs for onychomycosis. These topical agents are therefore mainly applied to patients with moderate onychomycosis (affected nail area < 50%). Treatment success for onychomycosis is deeply dependent on the patient’s proper adherence to daily drug application. Nail clipping and scraping at each visit would be helpful to improve the patient’s adherence. The need for long-term use of topical agents should be adequately explained to the patients before the start of treatment.

Understanding the efficacy and safety of efinaconazole 10% solution and luliconazole 5% solution will need further data on long-term use and on application to severe cases (affected nail area > 50%). Treatment of tinea pedis and daily foot care are also very important for preventing recurrences of tinea unguium.

Conflicts of interest

None.

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