An exploration of the optimum dosage and number of cycles of itraconazole pulse therapy for severe onychomycosis

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Summary
Although standard itraconazole pulse therapy is a well-established regimen for toenail onychomycosis, the cure rate for onychomycosis remains low. To evaluate the efficacy and safety of different cycles of itraconazole pulse therapy, determine the optimal dosage and number of cycles for onychomycosis. A total of 90 outpatients of our hospital with onychomycosis were randomised into three treatment groups: (1) standard itraconazole pulse therapy (200 mg twice per day, 1 week each month for three pulses); (2) long-term pulse therapy (200 mg twice per day, 1 week each month for six pulses); (3) low-dose and long-term pulse therapy (200 mg/d, 1 week per month for six pulses) and were followed up for 15 months. Of the initial patients, the trial was completed by 81 patients. The complete cure rates were 32.43% for three cycles and 75% for six cycles \((P < .001)\). For six cycles, despite the administration of half-dose for patients weighing no more than 55 kg, there was no statistical difference in the complete cure rate \((P = .862)\). Long-term therapy is effective and safe for the treatment of toenail onychomycosis. For patients weighing no more than 55 kg, long-term half-dose itraconazole pulse therapy is recommended.

KEYWORDS
itraconazole, onychomycosis, pulse therapy, weight

1 INTRODUCTION

Onychomycosis is a common fungal infection of the nails, accounting for 50% of all nail disorders and an estimated global prevalence ranging from 2% to 18%. There are different species of fungi responsible for this disease, including dermatophyte, yeasts and nondermatophyte moulds. Due to the diversity of the causative pathogens and unique physical properties of nails, it is difficult to treat onychomycosis with topical agents. Fortunately, the cure rate has improved in recent years with the use of fluconazole, terbinafine and itraconazole. However, a meta-analysis indicated that the mycotic cure rate was only 76% for terbinafine, 63% for itraconazole with pulse dosing, 59% for itraconazole with continuous dosing, and 48% for fluconazole. Although onychomycosis is not a life-threatening condition, its psychosocial impact is greater than the physical damage it causes. Patients with onychomycosis feel socially excluded, upset, embarrassed and stigmatised by the infected nails. Therefore, more effective methods to improve the cure rate for onychomycosis are urgently sought.

Itraconazole is one of the most commonly used agents in clinical practice and is active against a range of fungal species, including yeasts, dermatophytes and some nondermatophyte moulds. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously or alternatively at a dose of 400 mg daily for 1 week per month. It is recommended that two of these weekly courses are given for fingernail infections and three courses for toenail disease.

Although itraconazole pulse therapy has proven to be more effective and acceptable than most of the other onychomycosis therapies, the...
complete cure rate remains unsatisfactory, indicating that three cycles of pulse therapy for toenail onychomycosis might be inadequate for severe cases of onychomycosis. In addition, terbinafine, another oral antifungal drug, is recommended to adjust the dosage regimen by body weight.6 However, to the best of our knowledge, adjusting the dose of itraconazole based on individual differences (i.e. body weight) has not been previously reported. Thus, the development of a more effective and suitable therapeutic regimen to improve the complete cure rate is necessary.

In this study, outpatients with onychomycosis presenting to our hospital were treated with standard itraconazole pulse therapy (twice per day, for three pulses), long-term therapy (twice per day, our hospital were treated with standard itraconazole pulse therapy (twice per day, for six pulses), low-dose and long-term therapy (once per day, for six pulses) and followed up for 15 months to evaluate the treatment results.

2 | PATIENTS AND METHODS

A total of 90 patients were included in this study (40 men; 50 women; 18-70 years old; mean age of 38) were recruited from the Shanghai Tenth People’s Hospital, Tongji University School of Medicine from December 2014 to October 2015. The study was a randomised, prospective, open clinical trial. All included patients were consecutively recruited from the outpatient clinics of our hospital after they provided informed consent. The study complied with all international ethical standards.

2.1 | Inclusion criteria

The patients’ age ranged from 18 to 70 years old with typical clinical features of onychomycosis, characterised by crumbling nail plates, thickened nail beds and yellow nails. The patients were positive for fungus via direct microscopy due to the identification of hyphae or blastospores on the target toenail and a positive fungal culture. Moreover, at least one great toenail capable of regrowth and more than 50% of the nail plate of the great toenail was involved. None of the patients had applied a topical agent onto the target nail within 1 month prior to the administration of medication during the study nor had they taken systemic antifungal drugs within the previous 6 months. If the patient was of childbearing potential, she was required to have a negative urine pregnancy test and pledge to use effective methods of contraception until the first menses off of the study medication. The participants voluntarily signed informed consent and agreed to be followed-up.

2.2 | Exclusion criteria

The following patients were excluded from the study: patients with poor adherence, including failing to complete the follow-up, those terminating their treatment on their own, or changing the dosage regimen; subjects who were pregnant, lactating or planning to be pregnant during the study; patients whose affected nails were caused by nail plate psoriasis, atopic dermatitis or lichen planus, in addition to mycotic infections; persons who were previously allergic to imidazole or azole; those taking any medications known to affect the bioavailability of oral itraconazole or metabolised by the CYP3A4 enzyme or have potential drug–drug interactions (e.g. statins and opioids); patients with baseline liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) elevated to more than twice the upper limit of normal or a history of renal disease; those who were unresponsive to systemic antifungal therapy within the past year; patients who were immunocompromised or used systemic immunosuppressants; and subjects exhibiting evidence of ventricular dysfunction (e.g. congestive heart failure [CHF]) or a history of CHF.

2.3 | Patient information and interventions

A total of 40 patients were randomly allocated to Group A (18 men; 22 women; weight range: 43-70 kg; 60 kg mean weight; age range: 24-68 years; mean age: 38 years), which received three pulses, each consisting of 200 mg itraconazole twice per day after a full meal for 1 week each month. The remaining patients were designated to Group B (22 men; 28 women; weigh range: 44-75 kg; 58 kg mean weight; age range: 23-70 years; mean age: 39 years), which was treated with six pulses. There were two subgroups in Group B; (1) Group B1, comprised of patients who weighed more than 55 kg and were treated with each pulse consisting of 200 mg itraconazole twice a day; and (2) Group B2, which included patients weighing less than or equal to 55 kg treated with 200 mg itraconazole once per day, immediately after lunch.

The patients were informed of the aim of the study and signed the informed consent. At the baseline visit, we informed all patients of the risks of itraconazole, noted the involved area of nails and referred them back to our hospital every month for dispensing and assessing. Photographs were taken at each visit. The efficacy of itraconazole pulse therapy was evaluated at 3, 6, 9, 12 and 15 months.

2.4 | Primary and secondary outcome measures

The primary efficacy measures consisted of clinical cure (totally normal-looking nails), mycological cure (negative fungal direct microscopy and negative fungal culture) and complete cure (consisting of a clinical cure and a mycological cure). The secondary outcome measure was clinical improvement defined as a mycological cure plus either a clinical cure or target toenail plate involvement of 10% or less.

2.5 | Safety assessment

For safety reasons, we reviewed the liver function test before the treatment and monitored liver function every 2 months. We discontinued treatment if abnormal liver function tests developed. The patients’ adverse reactions, including gastrointestinal disturbances, skin reactions, and headaches, their duration, extent and prognosis were recorded in detail.
2.6 | Statistical analysis

The analysis was performed using descriptive statistical methods. The chi-square test and a Student’s t test were involved in the statistical analysis. A chi-square test was used to assess the rates and percentages, where relevant and the observed differences between two groups. A threshold of \( P < .05 \) was taken to represent statistical significance. Statistical software package SPSS 20.0 and Microsoft Excel were used for the analysis.

3 | RESULTS

3.1 | Cure rate

Of the 90 patients initially enrolled, 81 completed the study. There were two patients who refused to sign the informed consent, five patients lost to follow-up, and two patients who violated the inclusion criteria. All the baseline personal and clinical conditions of the enrolled patients are presented in Table 1. The average weights of Group A, Group B1 and Group B2 were 60.8, 64.0 and 51.7 kg, respectively. The average amounts of toenail involvement were 5.2 for Group A, 5.1 for Group B1 and 5.5 for Group B2. Patients in Group A and Group B were well-matched for age, sex, the number of infected toenails, and extent of nail involvement. No statistically significant difference between the two groups was noted. There were significantly differences in gender and average weight between Group B1 and Group B2.

The cure rates at 15 months are presented in Table 2. There was a significantly higher complete cure rate for six cycles of itraconazole pulse in Group B compared to the regimen administered to Group A (12 of 37 (32.43%) patients in Group A and 33 of 44 (75%) patients in Group B [\( P < .001 \)]. Similarly the clinical and mycological cure rate for six cycles of itraconazole pulse in Group B were also significantly higher compared to Group A (clinical cure rate: \( P < .001 \), mycological cure rate: \( P < .001 \)). There was no difference in the complete cure rates between the long-term group and the low-dose and long-term group in Group B (17 of 23 patients in Group B1 and 16 of 21 patients in Group B2 [\( P = .862 \]), and so were the clinical improvement cure rates [\( P = .605 \)]. At 15 months, the clinical improvement cure rates were 49% for Group A, 93% for Group B, 91% for Group B1, 95% for Group B2. Compared with three cycles of treatment, all comparisons of clinical improvement demonstrated dramatically higher cure rates with six cycles.

The cure rates are presented in Figure 1. Compared to three cycles of itraconazole therapy, there was a substantial increase at 6 months for six cycles and the efficacy peaked at 9 months, with a complete

### Table 1 | Baseline personal and clinical conditions of the patients enrolled according to treatment group

| Parameter                        | Group A | Group B | \( P \) value | Group B1 | Group B2 | \( P \) value |
|----------------------------------|---------|---------|---------------|---------|---------|---------------|
| No. of patients                  | 37      | 44      | 23            | 21      |         |               |
| Sex: male/female                 | 16/21   | 18/26   | .832          | 15/8    | 3/18    | .001          |
| Age (y), mean ± SD               | 37.8 ± 13.8 | 38.9 ± 13.7 | .725          | 38.1 ± 13.8 | 39.7 ± 13.8 | .714          |
| No. of infected toenails, mean ± SD | 5.2 ± 1.4 | 5.3 ± 1.3 | .921          | 5.1 ± 1.3 | 5.5 ± 1.2 | .320          |
| Weight (kilograms), mean ± SD    | 60.8 ± 8.7 | 58.1 ± 7.6 | .150          | 64.0 ± 5.6 | 51.7 ± 2.4 | <.001         |

### Table 2 | Overall cure rates for toenail onychomycosis in each group at 15 mo

|                     | Clinical cure | Mycological cure | Complete cure | Clinical Improvement |
|---------------------|---------------|------------------|---------------|----------------------|
| Group A             | 13/37 (35%)   | 15/37 (41%)      | 12/37 (32%)   | 18/37 (49%)          |
| Group B             | 36/44 (82%)   | 40/44 (91%)      | 33/44 (75%)   | 41/44 (93%)          |
| \( P \) value       | <.001         | <.001            | <.001         | <.001                |
| Group B1            | 19/23 (83%)   | 21/23 (91%)      | 17/23 (74%)   | 21/23 (91%)          |
| \( P \) value       | <.001         | <.001            | <.001         | <.001                |
| Group B2            | 17/21 (81%)   | 19/21 (90%)      | 16/21 (76%)   | 20/21 (95%)          |
| \( P \) value       | .887          | .924             | .862          | .605                 |

Patients in Group A received three pulses, each consisting of 200 mg itraconazole twice per day for 1 wk each month; patients in Group B received six pulses, there were two subgroups in Group B: Group B1 and Group B2. Patients in Group B1 weighing more than 55 kg, were treated with each pulse consisting of 200 mg itraconazole twice per day for 1 wk each month; patients in Group B2 weighing less than or equal to 55 kg, were treated with each pulse consist of 200 mg itraconazole once per day for 1 wk each month.
cure rate of 82.61% for Group B1 and 85.71% for Group B2; clinical cure rate of 86.96% for Group B1 and 85.71% for Group B2; and mycological cure rate 95.65% for Group B1 and 95.24% for Group B2. There was approximately a 10% decrease in the complete cure rates 6 months later. The clinical manifestations at each of the different time points in Group A, Group B1, and Group B2 are listed in Figure 2.

3.2 | Safety

A total of 23 patients reported experiencing at least one adverse event (10 in Group A, 7 in Group B1, and 6 in Group B2). Nine patients (four for three cycles and five for six cycles) experienced a transient increase in conjugated bilirubin, which all returned to the normal range 1 month later. Two patients experienced irregular menstrual periods. Gastrointestinal discomfort and headache were reported to be the most common adverse events and considered to be mild and transient by the specialist. There was no significant difference in adverse events between the three treatment regimens.

4 | DISCUSSION

Itraconazole is a triazole agent, which functions as a broad-spectrum antifungal drug. Mechanically, itraconazole has been
reported to inhibit the activity of cytochrome P450 (CYP)3A4, resulting in impaired sterol synthesis in fungal cell membranes, therefore inhibiting fungal growth and eventually leading to cell death.\(^7,8\)

Moreover, itraconazole pulse therapy was proven to be more effective and safer than continuous therapy.\(^9,10\) In addition, randomised controlled trials have shown that the cure rate for toenails varied among individuals with three pulses of itraconazole therapy, ranging from 35% to 100%, and the rates of severe onychomycosis were low.\(^11-13\)

Furthermore, another study reported a complete cure rate of 53.1% for three pulses of itraconazole in patients with toenail onychomycosis whose average area of baseline toenail involvement was 74.1%, compared to an 83.3% complete cure rate for two pulses of itraconazole for patients with fingernail onychomycosis patients involving 78% of the fingernail plate, caused by candida,\(^14\) which was substantially higher (21%) than our results. In another study, despite a lower involved area and longer course of treatment, toenail onychomycosis was associated with a lower efficacy compared to fingernails. This is likely because toenail growth rates are estimated to be one-third to one-half that of the fingernails (0.07-0.17 mm/d); however, the growth rates slowed when the nails were affected by fungi.\(^15\) Therefore, it is considered inappropriate to treat patients with three cycles, when nails are totally dystrophic. However, the suitable number of cycles and dosage of itraconazole for severe toenail onychomycosis remains unknown. In this study, all parameters demonstrated six cycles of itraconazole pulse therapy to be superior to three cycles, suggesting that it is a more effective treatment strategy for onychomycosis than standard itraconazole pulse therapy.

According to reports, many people attempt to extend the course of treatment to improve the complete cure rate. A study by Ingber\(^16\) treated 87 patients diagnosed with subungual onychomycosis with a low daily-dose of itraconazole pulse therapy (200 mg/d for six cycles) and found that 88.5% patients exhibited both a microscopical and cultural cure after 6 months of treatment, and only 6.5% relapsed during the first year after treatment. However, Watanabe compared a low daily-dose of pulse therapy (200 mg/d for 6 cycles) with the international standard regimen of itraconazole pulse therapy (400 mg/d for 3 cycles), and found the latter to be more effective, with 25.5% and 32.7% clinical response rate, respectively, at 24 weeks.\(^17\) There are many reasons that could account for the different results of the same dosage regimen, including individual differences (i.e. body weight) and the affected area of the nails. Ramos-e-Silva’s trial supports this opinion, as he treated toenail onychomycosis patients with four cycles of itraconazole pulse therapy; this strategy was sufficient for an involvement smaller than 6 mm, but additional cycles of pulse therapy were required for an area greater than 6 mm.\(^18\)

In our study, since all of the participants were severely affected (more than 50% of the great toenail plate was involved), there was no difference in the affected area among the three groups and all patients were treated with cycles of itraconazole pulse therapy. Considering that the patients’ body weight may affect the blood concentration of itraconazole, we separated the patients according to their weight. Patients with a body weight over 55 kg were treated with a long-term therapy (400 mg/d for six cycles), whereas patients weighing less than or equal to 55 kg were treated with a low-dose and long team therapy (200 mg/d for six cycles), after the 15-month follow-up, the complete cure rates were 74% for Group B1 and 76% for Group B2, and the incidences of adverse effects were 30% and 29%, respectively, suggesting that half of the dose could also be effective at a lower body weight.

For itraconazole pulse therapy, Kyriakidis is concerned with potential adverse effects\(^19\); however, in our opinion, such concerns are not a cause for great concern. One meta-analysis that included 20,000 patients demonstrated that immunocompetent patients...
treated with pulse itraconazole exhibited a very low incidence of adverse events (approximately 2.58%). Moreover, due to the low affinity of itraconazole to human cytochrome P450, it is uncommon for hepatic enzymes to increase or severe liver injury to be observed in patients undergoing itraconazole treatment. Itraconazole pulse therapy was proven to be well-tolerated and the incidence of side effects was no higher than that of placebo therapy.

Nevertheless, hepatotoxicity is still considered to be a risk factor during treatment, especially for the long-term usage of itraconazole. Indeed, there is one reported case of a 61-year-old woman, who developed fatal hepatitis after receiving six cycles of pulse itraconazole. The patient did not present with any risk factors of liver injury and her physician considered it unnecessary to monitor her liver function. Unfortunately, she eventually died of hepatitis. In addition, Srebrnik et al reported a 25-year-old woman with a 13-year history of drug treatment for hypothyroidism underwent severe liver crisis 3 weeks after completing a four-pulse course of itraconazole for toenail onychomycosis. Based on these cases, it can be considered necessary to regularly monitor liver parameters before and during prolonged pulse therapy. In addition, particular attention should be paid to potential drug–drug interactions. However, another study suggested that there was no monitoring requirement for the pulse regimen unless the patient had been previously affected by a hepatic disease, the liver function test was abnormal at baseline, or there were the signs or symptoms of liver dysfunction. According to reports, hepatotoxicity resulted from cholestasis rather than cytolysis, and thus, ceasing the use of drugs was the complete resolution.

To avoid severe adverse effects in this study, we enquired regarding the patients’ disease history in detail, reviewed the patients’ liver function before and 2 months after treatment to ensure the normal metabolism of drugs and advised our patients coming to our hospital every month. At the same time, the patients were advised to come to the hospital immediately if they felt abdominal pain, nausea, vomiting or had a change in urine colour. As a result, most adverse events were mild or moderate, and no treatment-related serious adverse hepatic or cardiac events were observed.

The recurrence of fungal nail infections is common, for which there are several reasons. To reduce the recurrence rate, multiple measures have been proposed. It has been suggested that the feet should be kept clear and the sharing of nail clippers or nail files should be avoided, and footwear should be used in all public areas. It was also reported that the recurrence rate decreased following the prophylactic use of topical antifungals. In our study, compared with the peak of cure rate, there was approximately a 10% decrease in the complete cure rates at 15 months; however, the reasons remain unknown. For patients with severe toenail onychomycosis, the long-term use of antifungals may be effective on increasing the cure rate and reducing the recurrence rate.

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