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Tailored Treatment of Recalcitrant Tinea Cruris and Tinea Corporis: Insights from Antifungal Susceptibility Testing

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Running title: Antifungal susceptibility-guided personalized treatment of recalcitrant tinea infections

Abstract

Antifungal resistance in dermatophytes is an emerging global concern. This study evaluated a treatment protocol for recalcitrant tinea corporis/cruris using antifungal susceptibility testing (AST). 20 patients with *Trichophyton indotineae* were enrolled and categorized into resistant, tolerant, and clinically recalcitrant groups based on AST results. Treatment was tailored per protocol. Mean age was 37.65 years, 85% had infection ≥ 1-year, average number of used systemic antifungals was 1.9, median past therapy was 14 weeks, 40% had a MIC above 1 μg/mL (resistant), 7 were terbinafine-resistant. 65% had an MIC ≥0.5 μg/mL (tolerant). 2 patients had simultaneous tolerance and resistance. 80% reached complete cure. The average time of therapy for the cured patients was 6.6 weeks. The overall response was calculated as 75%, 75%, 100%. Our study demonstrated that the management of the tolerant patients was similar to the resistant patients. Currently there are no defined MIC cut-off in AST for dermatophytes. Our study suggests a need for lowering the traditionally used cut-off of 1 μg/mL to 0.5 μg/mL among itraconazole-recalcitrant patients with *T. indotineae*. Meanwhile, we believe the resistance cut-off of 1 μg/mL for terbinafine-recalcitrant patients is suitable.

Keywords: Tinea corporis. Tinea cruris. Recalcitrant dermatophytosis. Antifungal susceptibility test

Introduction

Tinea corporis, also known as ringworm disease, is the most common dermatophyte infection [1]. The common age for this disease is classically during the post-pubertal period and at the beginning of the sex life, especially, at adolescence and early adulthood with a similar prevalence pattern in both genders [2-4]. The classic presentation of tinea corporis infection is a circular erythematous lesion with an inflamed rim and a hypopigmented center which usually involves the torso, neck, upper extremities and/or lower extremities [2,5]. *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Microsporum canis* are the most frequent causative pathogens of tinea corporis infection [5]. Tinea cruris, on the other hand, is a form of dermatophytosis that particularly affects perineal area, groins and hypo-abdomen. The major causative agents of tinea cruris are *T. rubrum, T. mentagrophytes,* and *M. canis* [2,5]. It impacts men more often than women and generally is more commonly seen among sexually active individuals. Transmission in both infections classically happens through contact with infectious materials, whether directly from the patients or indirectly from their contaminated belongings. Furthermore, it could be transmitted from domestic pets and animals, or, ground soil. Autoinfection is another mode of transmission [2]. Additionally, clinical observations of dermatophytosis show that, in general, zoophilic and geophilic species induce more severe inflammatory reactions than anthropophilic species [2]. Traditional available treatments for dermatophytosis include: Terbinafine, imidazoles (e.g., clotrimazole, miconazole) and triazoles (e.g., fluconazole, itraconazole); which can be used as mono or combination therapy [6].

At this day and age, antifungal drug resistance is becoming a global health issue on rise, since the recent reports present and warn the higher rates of treatment failure and the need for change in protocols of therapy; whether longer durations of treatment or choosing alternative medications. Moreover, the available treatment options remain limited and there has not been any approved new antifungal drug classes in the past two decades. Only one new agent, isavuconazole from a known antifungal class,

azoles, has been clinically approved over the last ten years; while all the newly proposed options remain in line to be evaluated by trials and are not at disposal .The emergence of this resistance has been traditionally contributed to selective pressures from increased consumptions of antifungals for prophylaxis (such as in cancer settings and among immune-deficient patients), empiric therapy approaches and agriculture. Additionally, recent manifestations of fungal infections during the coronavirus pandemic in the past 4 years, such as COVID-19 associated aspergillosis and mucormycosis, demanded broad implication of antifungals, which may have had a role to do with further aggravation of resistance; possibly due the extensive exposure of the susceptible fungi to these chemicals [7]. These limitations are challenged even more by drug–drug interactions, adverse toxicities, and impediments in administration routes [7]. Subsequently, it is no surprise to mention that dermatophyte species have also been influenced by these alterations. Terbinafine-resistant dermatophytes isolates have been recently described globally [8-10]; meanwhile, azole formulation resistance rates have been reported to become as frequent as 19% worldwide [11]. These epidemiological changes have even highlighted the need for new terminologies to better describe the recent observations. In this study recalcitrant tinea disease was defined as an infection that has failed to respond to the chosen treatment in spite of receiving the right dose and duration of therapy for the mycologically identified species. This terminology includes two forms of tolerant and resistant, based on the report of the antifungal susceptibility test (AST) and minimum inhibitory concentrations (MIC).

In our belief, this change in antifungal infections' epidemiology requires special attention; meaning that contemporary treatment protocols should be addressed and examined in order to prolong and maintain the antifungal activity of the available but limited treatment options. This would provide adequate time to restrict and control the on-going resistance until new therapeutic agents would become approved and accessible.

In this context, documenting and analyzing cases of recalcitrant dermatophytosis is essential for understanding resistance patterns and guiding evidence-based therapeutic approaches. Herein, we report two cases of chronic and recurrent tinea corporis and cruris caused by *T. mentagrophytes* complex, refractory to conventional antifungal therapy, but successfully managed with oral itraconazole after discontinuation of topical steroids and implementation of patient education and supportive measures.

Materials and Methods

Patient Selection

This was a prospective cross-sectional study. Patients were selected among confirmed cases of tinea corporis and tinea cruris infection, who were referred to the dermatology clinic of Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), Tehran, Iran, and medical mycology laboratory at Immunology, Asthma and Allergy Research Institute, Tehran, Iran from August 2021 to October 2023. Confirmation was previously done via clinical evaluation by a dermatologist and mycological testing with direct potassium hydroxide (KOH) smear microscopy and culture on Mycosel™ Agar media (Quelab, Canada). For species from *Trichophyton mentagrophytes* complex, additional Polymerase chain reaction (PCR) assay and genomic sequencing were performed in order to differentiate the precise sub-species [12]. In this study we selected only patients with *Trichophyton Indotineae* infection to inhibit fungal subtype as a possible confounding factor for evaluation of our protocol. Thereafter, those of patients were selected that had received one or more lines of antifungal therapy for at least 6 weeks with one medication prior to this study, and who had little to poor response to those treatments. Subjects were interviewed in their first visit at our center in order to make sure that they had full compliance in their previous therapy and that they had taken the treatment with the standard dose and duration. This verified that the reason behind the treatment failure was due to recalcitrance. Patients were then asked to stop any antifungal treatments for at least 2 weeks in order to be prepared for the

AST testing. Thereafter, AST was performed in order to distinguish resistant species from the tolerant (Tolerance was defined as MICs of 0.5-1 µg/mL, while resistance was defined as MICs higher than 1 µg/mL). Additionally, culture reports were collected in the data registry. Detailed inclusion and exclusion criteria of the study are demonstrated in Table 1.

Treatment Protocol

Included patients were divided into three major groups of a) Drug resistant, and b) Drug tolerant, c) Clinically recalcitrant patients with normal AS, based on the report of the AST test. Individualized treatment protocol was chosen for each of the patients regarding the causative dermatophyte, previous drug history and MIC level. The standard treatment duration for tinea corporis and tinea cruris is usually considered 4 to 6 weeks. In this study we defined one cycle of treatment as 4 weeks of therapy, in order to have a tighter control over the process. Drug doses were as follows: Terbinafine (adult: 250mg daily- max dose of 250 mg/day), itraconazole (adult:100 mg BD-max dose of 400 mg/day), fluconazole (adult:250 mg daily-max dose of 250 mg/day) and voriconazole (adult: 200 mg twice daily). Renal adjustment was calculated as follows: Terbinafine (50% of standard dose for creatine clearance (CrCl) < 50 mL/min), itraconazole (non-dialyzable, dose adjustment needed based on multidisciplinary expert opinion), fluconazole (50% of standard dose for CrCl< 50 mL/min) and voriconazole (not needed for oral treatment).

Figure 1 demonstrates the treatment algorithm of the study. Alternative therapy was implicated for the drug-resistant patients early from the beginning. Drug-resistant patients were divided into two subgroups of a) Terbinafine-resistant, and b) Itraconazole-resistant. Itraconazole was generally the first alternative option for terbinafine-resistant patients, except for special cases who had used itraconazole beforehand and did not meet cure. For the latter patients, next-line alternative treatment, voriconazole, was chosen as the method of treatment. As for itraconazole-resistant patients, voriconazole or terbinafine was chosen as alternative treatment. Patients must have used the treatment for at least 4

weeks before their scheduled visits at our center; if the lesions faded away sooner than 4 weeks and before their appointment, they must have informed the medical team and reschedule was done for them. At the end of each 4 weeks, if the lesions were still present, subject must have repeated the treatment, if not, he/she must have stopped the treatment for 2 weeks. This step helped to rule out any false negative results in the mycological evaluation (ME), since it takes at least 2 weeks for the drug to be fully cleared from the serum and keratinoid layer of skin, and during this time, its therapeutic effects continue, and may hide the infection presentation. After this period, patients underwent ME with KOH microscopy. If no mycelium was detected under the microscope, the subject was considered as cured. On the other hand, if mycelium was detected, the subject was recommended to repeat the treatment for another 4 weeks. This repetition could go for up to 12 weeks (except for voriconazole that could be used for longer times, since it was the last available choice). Eventually, if mycelium was still detected after 12 weeks with alternative therapy, voriconazole 200mg daily, would have been chosen for the subject according to the expert opinion and the patient was asked to repeat the rest of the protocol accordingly.

As for drug-tolerant patients, we had hypothesized that a possible approach to bypass the antifungal tolerance is to use the medication for longer durations. We considered a 12 weeks interval (the standard treatment duration included) in order to examine this idea. In the first step, a thorough evaluation of drug history was performed. If the patient was not cured and had not continued the indicated drug for at least 12 weeks, it was recommended to do so (e.g., if patient was itraconazole-tolerant and had used the therapy for only 2 weeks and was ended up with no cure, it was recommended to repeat the treatment cycle with itraconazole, have monthly reevaluations with the same protocol as drug-resistant patients and reassess the cure status, for maximum 12 weeks). If the patient had already received 12 weeks of therapy with the tolerant drug and did not meet cure, or, did not respond to the therapy after the 12 weeks interval of this study, alternative treatment with other available drug (voriconazole or

terbinafine) was recommended with the same protocol of drug-resistant patients. All of the included patients were followed until mid-January 2023, minimum defined time of follow up was considered 16 weeks.

Ethical Statement

The present study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.MEDICINE.REC.1401.587). The authors attest that the process of this study followed the ethical standards of the Helsinki Declaration. All patients had been informed about the different treatment plans for their disease and were part of the decision making process. All the patients signed a written consent form prior to participating in this study. Patients were informed about the photo documentation and gave their consent for the photos to be used in case their identities remain sealed.

Results

A total of 20 patients (11 males and 9 females) were included in this study, out of which 14 participants had tinea corporis and 6 had tinea cruris. The mean age of subjects was 37.65 years old (18-60). Eighty-five percent (17/20) of the patients had the infection for more than 12 months with one patient being affected for 48 months continuously, prior to this study. The median for duration of therapy among the patients before the study was calculated 14 weeks (5-192), with an Interquartile range (Q1 and Q3) of 28 weeks; Patients used an average of 1.9 types of systemic antifungal drugs before this study and almost all patients (18/20) also had used one or two lines of topical antifungal treatments. A comprehensive review of patients' demographic data and past drug history is demonstrated in Table 2 and Table 3.

The findings of the AST were as follows. 8/20 (40%) of the patients had antifungal resistance (1 μg/mL ≤ MIC for one drug or more); these included one itraconazole-resistant patient [patient ID: 4] and seven

terbinafine-resistant patients [patient IDs: 1, 2, 3, 6, 7, 11, 20]. 13/20 patients had antifungal tolerance (MIC of 0.5-1 μg/mL for one drug or more); these included ten itraconazole-tolerant patients [patient IDs: 9, 10, 11, 12, 14, 16, 17, 18, 19, 20] and three voriconazole-tolerant patients [patient IDs: 10,11,18]. No terbinafine-tolerant patients were identified. There were two patients who had simultaneous resistance and tolerance to more than one medication [patient IDs: 11, 20]. Case 11 was terbinafine-resistant, itraconazole-tolerant and voriconazole-tolerant. Case 20 was terbinafine-resistant and itraconazole-tolerant. There were two patients who had simultaneous tolerance to more than one medication [patient IDs: 10, 18]; these two patients were both itraconazole-tolerant and voriconazole-tolerant. There were 4 patients who had normal range AST results despite their clinical recalcitrant outcome [patient IDs: 5, 8, 13, 15].

To better classify the evaluation of our treatment protocol and avoid overlap, we considered the patients who demonstrated both resistance and tolerance in the AST [patient IDs: 11, 20], as resistant. Overall, 16/20 (80%) reached complete cure. The average time of therapy for the cured patients who implicated the medication continuously (whether starting from prior this study with the target drug or started by the beginning of this study) and based on the protocol of this study was 6.6 weeks. None of the 4 uncured recalcitrant patients had normal range MICs.

The overall response rate in the resistant group was calculated as 75% (6/8). The response rate in the terbinafine-resistant group was 71.4% (5/7). All the cured patients responded to the therapy with itraconazole. The average time of therapy for the cured patients in this group was 5.6 weeks (4-8). The two unresponsive patients were treated with voriconazole as they were both itraconazole-tolerant in their AST and had long history of itraconazole consumption prior to this research [case 11: 12 weeks, case 20: 20 weeks]. Case 11 has received voriconazole for 4 weeks in our setting (and 16 weeks prior to this study) and has not responded yet, but is being followed. Case 20 had an initial response after 4 weeks of treatment with voriconazole, but then had a relapse with a new lesion on the neck and has not

responded ever since, the case discontinued the treatment at the present time due to lack of access to the medication. Our only itraconazole-resistant patient responded to treatment with terbinafine after only 2 weeks. This patient had received itraconazole for 192 weeks prior to this study.

The overall response rate in the tolerant group was estimated as 75% (6/8). As mentioned above, all the voriconazole-tolerant patients were also itraconazole-tolerant [patient IDs: 10, 18], so the overall response rate was the same for itraconazole-tolerant group (75%). None of the itraconazole-tolerant patients did not respond to the longer treatment with same dose itraconazole (100mg BD) with our experimental protocol. These all needed to shift medication into either voriconazole (6/7) or terbinafine (1/6, patient ID: 12). Cases 10 and 18 started their treatment with voriconazole in the first place as they had already taken the defined duration of treatment with itraconazole before taking part in this research (case 10: 3 cycles of pulse-therapy with itraconazole, case 20: 20 weeks of therapy with itraconazole). Case 10 responded to this treatment after 16 weeks, on the other hand, case 18 reached complete cure after 24 weeks of treatment with voriconazole; the reason for such long duration was that terbinafine was not accessible for these two patients. 1/8 itraconazole-tolerant patients responded to the maximum dose itraconazole (200mg BD) in 2 weeks [patient ID: 16]; the clinical progress of this case is further discussed in the discussion section. The mean duration of therapy with voriconazole for the 4 cured itraconazole-tolerant patients was 12 weeks (4-24).

The overall response rate in the group of patients with normal AST was 100%, an alternative medication was chosen for these patients based on their past drug history. Average duration of therapy was calculated as 6.5 weeks. A detailed description of subjects´ clinical follow-ups is demonstrated in Table 3.

Discussion

Dermatophytosis has undergone a significant epidemiological transformation in India, with an alarming increase in chronic, recurrent, and treatment-resistant cases. This shift, often termed "recalcitrant dermatophytosis," is multifactorial in origin. A major contributor is the widespread misuse of over-the-counter topical corticosteroid-antifungal combinations, which suppress local immunity, alter lesion morphology, and promote fungal persistence.

Since early 2018, the emergence of antifungal resistance has become a prominent subject in the list of potentially threatening global issues. The number of clinical and laboratory-evaluated terbinafine resistant cases are on rise. A total of 548 cases of terbinafine-resistant *T.mentagrophytes / T.interdigitale* complex has been reported since early 2019 [8].Azole resistance in dermatophytes is also reported by several studies [11,13,14]. Therefore, suggesting novel diagnostic and therapeutic approaches are of paramount importance. In this study we suggested an AST-based strategy to diagnose and treat recalcitrant dermatophyte patients with *T.indotineae* infection and evaluated possible therapeutic responses among three study-defined groups of resistant in AST, tolerant in AST and clinically recalcitrant patients with normal AST.

The Importance of AST for Management of Recalcitrant Dermatophyte Infection

The rising incidence of recalcitrant dermatophyte infections, particularly in South Asia, necessitates a paradigm shift in diagnostic and therapeutic approaches. In our study, we used an AST-guided protocol that led to an overall cure rate of 80%. It also showed that 80% (16/20) of our patients had an evident defect in their susceptibility to available antifungal options. These results are compatible with the traditionally used rule of 90/60 for susceptibility tests [15]. We also had a mycological resistance percentage of 40% (8/20) [MIC cut-off for this was considered as 1 µg/mL]. This can potentially mean that clinical recalcitrance and laboratory-identified recalcitrance overlap in many cases. AST is usually performed in laboratory settings in order to aid clinicians to make the appropriate decisions in the

clinical setting, should recalcitrance be detected, or as a supplementary testing to determine possible reasons for treatment failure. Despite the fact that AST is not yet a routine step of fungal dermatophytosis management, it is strongly believed that it can provide valuable information on guiding the clinicians and potentially decrease the duration of treatment via providing a targeted therapeutic approach [13]. Hence, using AST seems to be a catalyzing method among the recalcitrant patients, in order to reach the proper therapeutic choice sooner than anticipated, and to potentially avoid longer treatments with the inappropriate medication, that can possibly reduce further exposure of the susceptible fungi to the unneeded antifungals and thus avoid further genetic and molecular alterations that lead to drug resistance. A growing number of studies are now recommending AST-guided approaches for management of recalcitrant tinea infection [16-18], nonetheless, some important key points should not be overlooked. Although antifungal susceptibility kits are available commercially, disparities and considerable variability have been reported in case of dermatophytes, therefore, evidence suggests that in case of dermatophytes it is more reliable to use more surveyed guidelines such as EUCAST (European committee on antimicrobial susceptibility testing) and CLSI (clinical and laboratory standards institute) for performing AST.

Although our study's findings were in favor of clinical and mycological recalcitrance compatibility, it is important to note that however AST provides helpful measurements of the *in vitro* behavior of the infectious agent, the currently known MIC values are not adequate alone to establish definite interpretations of susceptibility and resistance in the manner that the clinicians are accustomed to, and based on which clinical plannings are made by bedside. It is important to note that a susceptible MIC does not guarantee a successful clinical outcome, nor a resistant MIC indicates clinical failure. The reason behind that is that AST result is only one of the contributing factors to clinical outcome and the final result roots also in certain other elements such as host factors (e.g., Immune status), extent and severity of the underlying infection, other medical comorbidities, presence of arthroconidia [19],

pharmacokinetics and pharmacodynamics of the antifungal agent, drug-drug interactions (e.g., change in drug metabolism) and patient´s compliance to the treatment. On top of that, despite there are certain defined clinical breakpoint for several fungal subtypes such as *Aspergilloses* and *Candida* spp. By CLSI and EUCAST, there are still no defined clinical cut-offs of MIC for dermatophytes. Moreover, no epidemiological cut-off values (ECVs) are also determined for any medications against this group of fungi. All of this suggests that AST, could be a potential great help, and that despite there may be other contributing factors that define the final clinical outcome of the patients, chances are in favor of the fact that a poor clinical outcome is more likely when *in vitro* resistance is detected. Also, that AST is by nature, a highly operator dependent technique, as it has different interpretations based on the types of the antifungals, the causative fungal strains and patients' history. At the time being, we believe that in order to achieve the optimal results, it is necessary that the test is performed by an expert mycologist with sufficient expertise in dermatophyte infections.

Concise Evaluation of the Protocol of this Study and Prospect of Future Strategies

As mentioned before, so far there has not been any determined MIC cut-offs for any drugs against dermatophytes by the two major guidelines. Although, multiple studies have made consensus on MIC level of 1 µg/mL to be a reliable clinical break-point for *Trichophyton* spp.. Several studies had suggested the same cut-off for the more recent terbinafine-resistant species [20,21],nonetheless, these values are different based on the country of origin and the method of testing; for example, a French study had used cut-off of 2 µg/mL with EUCAST method for *Trichophyton* spp. [22],meanwhile several American studies had used cut off of 0.5 µg/mL with CLSI method for *T. rubrum* [23,24], In this paper, we considered a MIC level of 1 µg/mL as a base point for definition of resistance in the AST and proceeded with assessment of MIC level of 0.5 µg/mL as another cut-off for those of species that we named "tolerant". We recruited 20 patients with confirmed clinical recalcitrant *T. indotineae* tinea

corporis/cruris infection. We first investigated their mycological susceptibility with consideration of their previous drug history in order to evaluate the comparability of clinical and mycological recalcitrance for each of the subjects. Thereafter, we suggested a personalized treatment protocol with assistance from AST results (Figure 1). We followed our patients' progress for a duration of at least 16 weeks (the first cases were followed for up to 24 weeks). Among the resistant group, we had 7 terbinafine-resistant patients (both clinical and mycological), our protocol reached an impressive cure rate of 71.4% in 5 patients in duration of 5.7 weeks. One of the interesting findings was that 5/7 patients reached complete cure (CC) by more accessible and more traditional antifungal, itraconazole. Similar responsiveness to azoles among terbinafine-resistant patients has been mentioned by other studies as well. In a study of 580 *Trichophyton* induced tinea infection patients, Moreno-Sabater *et al.* demonstrated that there was no significant correlation between MIC level changes of azoles and terbinafine in the identified terbinafine-resistant patients [22].Other recent studies have also shown that itraconazole remains an effective treatment against terbinafine-resistant strains in many cases and its therapeutic capacity should not be overlooked [21,25,26]. As for the tolerant patients, we figured that none of our 10 itraconazole/tolerant patients responded to the same dose itraconazole for longer durations (12 weeks). 9/10 patients needed to shift medication, either to terbinafine or voriconazole, and eventually were treated similar to the resistant group. Based on these findings we believe that the MIC cut-off of 1 μg/mL was not the most inclusive for the itraconazole recalcitrant target group, and we suggest the cut-off to be lowered to 0.5 μg/mL and that these patients would possibly benefit more from an early shift of medication. 5/10 patients reached CC, 4 of which with voriconazole with a mean duration of 12 weeks and 1 of which with terbinafine after 2 weeks, which further confirms the effect of shift in drug therapy. In a summarized point of view, the average time of therapy for the cured patients was 6.6 weeks. The overall cure rates were calculated as 75%, 75%, 100%, and the average time of therapy for the cured patients was calculated 5.6 weeks, 12 weeks, 6.5 weeks for the resistant, tolerant and susceptible groups, respectively. As mentioned above, all the cured terbinafine- resistant

patients were treated with itraconazole over a duration of 5.7 weeks. Also, all the itraconazole-tolerant patients of this study were treated with voriconazole with a mean duration of 12 weeks. These observations suggest that as for the time being, the duration of therapy of 8 weeks with itraconazole seems more reasonable as the primary end-point for the recalcitrant patients, rather than the 12 weeks that was primarily considered by our pilot protocol. But in case of voriconazole, we had response rates even after 12 weeks of therapy, besides voriconazole does not have many alternatives, thus longer treatments are suggested at the time being, if terbinafine is not available or if simultaneous terbinafine-resistance exists. As for terbinafine we could not find additional evidence in this study to support longer treatment durations rather than the standard 6 weeks and further studies are needed for such assumption. Figure 2 demonstrates the final suggested treatment protocol of this study based on the clinical findings. 1/10 itraconazole-tolerant patients had sought consult elsewhere as well and had increased the dose of itraconazole to 400 mg/ day and showed clinical improvements after 2 additional weeks. This was a coincidental finding in this study but we find worthy of reporting, as it can also be a hypothetical solution for management of recalcitrant patients. an Australian case report has reported one similar recalcitrant patient to be treated with the same method [25]. In one study Khurana *et al.* have compared the response rates of three different doses of 100 mg/day, 200 mg/day and 400mg/day of itraconazole among 126 tinea corporis/cruris patients. This study found that cure rates between the 100 and 200 mg groups was not statistically significant, whereas the statistical differences between the 100 and 400 mg groups and the 200 and 400mg groups were significant [27]. However, relapse rates were the same for all three groups and that this study only assessed this among treatment-naïve patients. Hence, it seems that more evidence is needed to consider max-dose itraconazole therapy as reassuring for recalcitrant cases.

Here, we have reported 4 cases with resistance/tolerance to more than one drug [patient IDs: 10,11,18,20]. All of these patients were eventually put on treatment with voriconazole. Two of these

patients reached CC with a late response [IDs: 10,18], interestingly these two patients had higher MIC levels for voriconazole in their AST assay, compared to the other two who did not meet CC. Given the fact that the remaining alternative options for multiple drug resistant (MDR) patients are intensely limited at the time, we still believe that voriconazole is a good alternative MDR patients; also, for those who fail to respond to other antifungals. Ever since the emergence of terbinafine resistance in early 2018, several studies have reported voriconazole to be an effective alternative against MDR strains [12,28,29]. An important notion on this matter is the importance of timely prescription by preferably using AST, case selection and precise follow up. Voriconazole is currently used mostly for invasive fungal infection and is one of the limited options for disseminated fungal infection, a broad implication of this medication without the proper follow-up may lead to further resistance that this time will not affect the patients with superficial mycoses but also many intense hospitalized patients. Certain studies have also introduced lasers, photodynamic therapy as adjuvant therapy. One recent study has performed surgical pairing on the site of infection and replaced it with tissue auto-implantation [30], but all of these methods are poorly backed up with evidence. Eventually, the future visionary for treatment of recalcitrant dermatophytosis relies on introduction of new antifungal agents beside monitoring treatment guideline to avoid resistance repetition.

Based on the findings of this study, we believe that AST is a helpful step for strategic treatment of recalcitrant dermatophytosis, if performed by an expert mycologist and according to surveyed guidelines protocols. We also believe that voriconazole is an appropriate alterative choice for terbinafine and itraconazole resistant patients, however case selection and attention to the report of AST seems necessary. To our belief and based on the findings of this study, MIC level of 0.5 µg/mL seems to be a better cut-off value for itraconazole resistance, nonetheless we suggest further focus on this matter for precise definitions of clinical breakpoint. We suggest our protocol as a bench method for treatment of recalcitrant tinea infection at the time, however the future visionaries for treatment of

MDR cases relies on global strategies to control further antifungal resistance, help accessibility of drugs for all the patients and development of new antifungal agents.

Study Limitations

This study only recruited 20 patients; larger sample size may be needed to repeat the method of this study. This study did not make any head-to-head comparisons, future studies must focus on designing comparative methods. Many of our patients did not have access to terbinafine, further data is needed for making comparison between voriconazole and terbinafine and also longer durations of treatment with terbinafine for those with MICs lower than 0.5 µg/mL. Also, the findings of this study could not suggest any definite treatment plans for those recalcitrant patients with normal AST.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Author Contribution

Study concept, design and technical supervision: M. F; Obtaining the specimens from patients and interpretation, physical examination: M.F and A. A; Acquisition of data and drafting of the manuscript: M. F and E. L,Technical support: M. F and A. A and E.L; Critical revision of the manuscript: M .F and F. A.

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

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References

1. Poudyal Y, Joshi SD. Medication practice of patients with dermatophytosis. Journal of Nepal Medical Association 2016;55(203):07-10
2. Leung AK, Lam JM, Leong KF, Hon KL. Tinea corporis: An updated review. Drugs Context 2020;9(

3. Ely JW, Rosenfeld S, Seabury Stone M. Diagnosis and management of tinea infections. Am Fam Physician 2014;90(10):702-10
4. Hsu S, Le EH, Khoshevis MR. Differential diagnosis of annular lesions. Am Fam Physician 2001;64(2):289-96
5. Yee G, Syed HA, AM AA. Tinea corporis. StatPearls [Internet]: Treasure Island (FL): StatPearls Publishing; 2025 Jan.
6. Panackal AA, Halpern EF, Watson AJ. Cutaneous fungal infections in the united states: Analysis of the national ambulatory medical care survey (namcs) and national hospital ambulatory medical care survey (nhamcs), 1995-2004. Int J Dermatol 2009;48(7):704-12
7. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R, et al. The antifungal pipeline: Fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. Drugs 2021;81(15):1703-29
8. Shen JJ, Arendrup MC, Verma S, Saunte DML. The emerging terbinafine-resistant trichophyton epidemic: What is the role of antifungal susceptibility testing? Dermatology 2022;238(1):60-79
9. Posso-De Los Rios CJ, Tadros E, Summerbell RC, Scott JA. Terbinafine resistant trichophyton indotineae isolated in patients with superficial dermatophyte infection in canadian patients. J Cutan Med Surg 2022;26(4):371-76
10. Saunte DML, Pereiro-Ferreirós M, Rodríguez-Cerdeira C, Sergeev AY, Arabatzis M, Prohić A, et al. Emerging antifungal treatment failure of dermatophytosis in europe: Take care or it may become endemic. J Eur Acad Dermatol Venereol 2021;35(7):1582-86
11. Ghannoum M. Azole resistance in dermatophytes: Prevalence and mechanism of action. J Am Podiatr Med Assoc 2016;106(1):79-86
12. Fattahi A, Shirvani F, Ayatollahi A, Rezaei-Matehkolaei A, Badali H, Lotfali E, et al. Multidrug-resistant trichophyton mentagrophytes genotype viii in an iranian family with generalized dermatophytosis: Report of four cases and review of literature. Int J Dermatol 2021;60(6):686-92
13. Gupta AK, Venkataraman M. Antifungal resistance in superficial mycoses. J Dermatolog Treat 2022;33(4):1888-95
14. Noguchi H, Matsumoto T, Kubo M, Kimura U, Hiruma M, Tanaka M, et al. Effective response of dermatophytoma caused by terbinafine-resistant trichophyton interdigitale solely to topical efinaconazole. Mycopathologia 2022;187(4):421-22
15. Rex JH, Pfaller MA. Has antifungal susceptibility testing come of age? Clin Infect Dis 2002;35(8):982-9
16. Dogra S, Shaw D, Rudramurthy SM. Antifungal drug susceptibility testing of dermatophytes: Laboratory findings to clinical implications. Indian Dermatol Online J 2019;10(3):225-33
17. Rezaei-Matehkolaei A, Khodavaisy S, Alshahni MM, Tamura T, Satoh K, Abastabar M, et al. In vitro antifungal activity of novel triazole efinaconazole and five comparators against dermatophyte isolates. Antimicrob Agents Chemother 2018;62(5):
18. Badali H, Mohammadi R, Mashedi O, de Hoog GS, Meis JF. In vitro susceptibility patterns of clinically important trichophyton and epidermophyton species against nine antifungal drugs. Mycoses 2015;58(5):303-7
19. Khurana A, Sardana K, Chowdhary A. Antifungal resistance in dermatophytes: Recent trends and therapeutic implications. Fungal Genet Biol 2019;132(103255
20. Khurana A, Masih A, Chowdhary A, Sardana K, Borker S, Gupta A, et al. Correlation of in vitro susceptibility based on mics and squalene epoxidase mutations with clinical response to terbinafine in patients with tinea corporis/cruris. Antimicrob Agents Chemother 2018;62(12):
21. Hiruma J, Noguchi H, Hase M, Tokuhisa Y, Shimizu T, Ogawa T, et al. Epidemiological study of terbinafine-resistant dermatophytes isolated from japanese patients. J Dermatol 2021;48(4):564-67

22. Moreno-Sabater A, Normand AC, Bidaud AL, Cremer G, Foulet F, Brun S, et al. Terbinafine resistance in dermatophytes: A french multicenter prospective study. J Fungi (Basel) 2022;8(3):
23. Chen E, Ghannoum M, Elewski BE. Treatment-resistant tinea corporis, a potential public health issue. Br J Dermatol 2021;184(1):164-65
24. Gu D, Hatch M, Ghannoum M, Elewski BE. Treatment-resistant dermatophytosis: A representative case highlighting an emerging public health threat. JAAD Case Rep 2020;6(11):1153-55
25. Jones CME, Blaya Alvarez B, Polcz M. Multi-drug resistant dermatophyte infections in western sydney: A retrospective case series. Australas J Dermatol 2022;63(4):e360-e62
26. Dellière S, Joannard B, Benderdouche M, Mingui A, Gits-Muselli M, Hamane S, et al. Emergence of difficult-to-treat tinea corporis caused by trichophyton mentagrophytes complex isolates, paris, france. Emerg Infect Dis 2022;28(1):224-28
27. Khurana A, Agarwal A, Agrawal D, Panesar S, Ghadlinge M, Sardana K, et al. Effect of different itraconazole dosing regimens on cure rates, treatment duration, safety, and relapse rates in adult patients with tinea corporis/cruris: A randomized clinical trial. JAMA Dermatol 2022;158(11):1269-78
28. Ahmed SS, Ahmed SS, Haque MM, Tabassum FJSJM. Efficacy and safety of oral voriconazole in refractory and recurrent cases of dermatophytosis: A prospective study in a tertiary care hospital in bangladesh. 2022;7(11):591-97
29. Khurana A, Agarwal A, Agrawal D, Sardana K, Singh A, Chowdhary A. Multidrug resistant tinea corporis/cruris: Response to voriconazole. J Mycol Med 2022;32(4):101306
30. Kumar S, Kaur A, Kaur S. Autoimplantation therapy in extensive and recalcitrant dermatophytosis: A case series. J Clin Aesthet Dermatol 2021;14(1):34-37

500 **Table 1:** Inclusion and exclusion criteria

501

Table 1.A. Inclusion criteria
1. *Confirmed tinea corporis and tinea cruris by KOH microscopy and culture.* 2. *Confirmed recalcitrance defined as no response to each of the chosen treatments for at least 6 weeks, considering that the medications have been correctly used.* 3. *Confirmed culture and PCR of T. Indotineae.*
Table 1.B. Exclusion criteria
1. History of previous allergic reaction to the chosen antifungal. In case of azole, allergic reaction to each of the drugs is also considered as a contraindication for others due to cross-reaction. *2. Active or chronic hepatic disease* *3. Liver enzyme elevation (x3 times more than the normal range).* *4. Acute kidney injury, end stage renal disease (ESRD) or renal failure (patients with CrCl<50 mL/min are not excluded but will receive 50% of therapeutic standard doses according to the expert opinion).* *5. Females with pregnancy, breast feeding or plans for pregnancy.* *6. Past drug history of medications with significant interaction with either terbinafine or azoles.*

504 **Table 2:** Demography of dermatophytosis cases

Characteristics	**No. of Patients with Positive Dermatophytes (%)**
Gender (Total)	20(100%)
Male	11 (55%)
Female	9 (45%)
Age Groups (Total)	20 (Mean=37.65)
1-9	0 (0%)
10-19	1 (5%)
20–29	5 (25%)
30–39	7 (35%)
40–49	1 (5%)
50–59	4 (20%)
60≤	1 (5%)
Type of Infection	
Tinea Corporis	14 (70%)
Tinea Cruris	6 (30%)
Tinea Duration	
< 1 Year	3 (15%)
≥ 1 Year	17 (85%)

505

506 **Table 3.** Antifungal treatment, and outcome in recalcitrant cases

Patient' s ID			1	2	3	4	5
Sex/Year			F/26	M/34	F/33	M/48	F/29
Type of Infection	**Tinea Corporis**			*		*	*
	Tinea Cruris		*		*		
Duration			1Y	1Y	1Y	4Y	2Y
Previous Antifungal Exposure		**Topical**	CTZ 1%	CTZ 1%	NU	CTZ 1%	NU
		Systemic	TRB 250 mg/d	TRB 250 mg/d	TRB 250 mg/d FCZ 150 mg/d	KTZ 200 mg/d ITZ 100 mg/d	FCZ 150 mg/d
Year of First Terbinafine Exposure and Duration (Year/Duration Weeks)			2020/6W	2020/6W	2020/6W	NU	NU
Year of First Itraconazole Exposure and Duration (Year/Duration Weeks)			NU	NU	NU	2018/ 192W	NU
Year of First Voriconazole Exposure and Duration (Year/Duration Weeks)			NU	NU	NU	NU	NU
Year of First Fluconazole Exposure and Duration (Year/Duration Weeks)			NU	NU	2021/4W	NU	2019/16W**
Alternative Antifungal Treatment			ITZ 100 mg/d + CTZ 1% for 6 W	ITZ 100 mg/d+ CTZ 1% for 4 W	ITZ 100 mg/d + CTZ 1% for 4 W	TRB 250 mg/d + CTZ 1% for 2 W	ITZ 100 mg/d+ CTZ 1% for 4 W
Outcome			CC	CC	CC	CC	CC

6	7	8	9	10	11	12	13	14
M/29	M/56	M/51	M/50	F/30	M/32	F/32	F/22	F/54
	*	*	*	*	*	*	*	*
*								
9M	1Y & 6M	1Y & 6M	1Y & 6M	1Y & 6M	1Y	1Y	1Y & 6M	9M
CTZ	CTZ 1%	CTZ 1%	CTZ 1%	CTZ 1%	CTZ 1%	CTZ 1%	CTZ 1%	CTZ 1%
TRB 250 mg/d	TRB 250 mg/d	TRB 250 mg/d FCZ 150 mg/d	ITZ 100 mg/d	TRB 250 mg/d FCZ 150 mg/d ITZ 100 mg/d VCZ 200 mg/d	TRB 250 mg/d ITZ 100 mg/d VCZ 200 mg/d	ITZ 100 mg/d	TRB 250 mg/d KTZ 200 mg/d FCZ 150 mg/d	TRB250mg/d FCZ 150 mg/d ITZ 100 mg/d
2021/12W	2020/12W	2020/6W	NU	2020/6W	2021/16W	NU	2019/6W	2021/12W
NU	NU	NU	2022/8W	2020/3W P*	2021/12W	2022/5W	NU	2022/16W
NU	NU	NU	NU	2022/12W	2022/16W	NU	NU	NU
NU	NU	2021/4W	NU	2021/4W	NU	NU	2019/1W	2021/4W
ITZ 100 mg/d +TRB (T) 1% for 8W	ITZ 100 mg/d +TRB (T) 1% for 6W	ITZ 100 mg/d +CTZ 1% for 4 W	VCZ 200 mg/d + CTZ 1 % for 4 W	VCZ 200 mg/d + CTZ 1 % for 4 W	VCZ 200 mg/d + CTZ 1% for 4 W	TRB250 mg/d +KTZ 2% For 2 W	ITZ 100 mg/d+ CTZ 1% for 2 months	VCZ 200 mg/d + CTZ 1% for 4 W
CC	CC	CC	CC	CC	Not completely cured	CC	CC	CC

15	16	17	18	19	20
M/60	M/34	M/18	M/37	F/28	F/50
*	*		*	*	*
		*			
1Y	8M	1Y & 3M	2Y	7M	3Y
CTZ 1%	CTZ 1%	NU	CTZ	CTZ 1%	CTZ 1%
ITZ 100 mg/ BD*	ITZ 100 mg/d	FCZ 150 mg/d ITZ 100 mg/d VCZ 200 mg/d	ITZ 100 mg/d VCZ 200 mg/d	TRB250 mg/d ITZ 100 mg/d	TRB 250 mg/d FCZ 150 mg/d ITZ 100 mg/d
NU	NU	NU	NU	2022/16W	2019/20W
2021/8W	2022/8W	2021/24W	2020/20W	2022/12W	2020/20W
NU	NU	2022/6W	2021/20W	NU	NU
NU	NU	2021/4W	NU	NU	2020/12W
TRB250 mg/d+ CTZ 1% for 2 W	ITZ 400 mg/d + CTZ 1% for 2 W	VCZ 100 mg/d + CTZ 1% for 8W and after the visit at the clinic, VCZ was continued for another month	VCZ 200 mg/d + CTZ 1% (T) after the visit at center the VCZ was continued for a month again (20W+ 4W)	VCZ 200 mg/d + CTZ 1% (T) for a month	VCZ 200 mg/d + CTZ 1% for 4 W
CC	CC	Not completely cured treatment was continued	CC	Not completely cured treatment was continued	CC after 4 W antifungal therapy with VCZ then a eritmatous, purpuric plaque was emerge

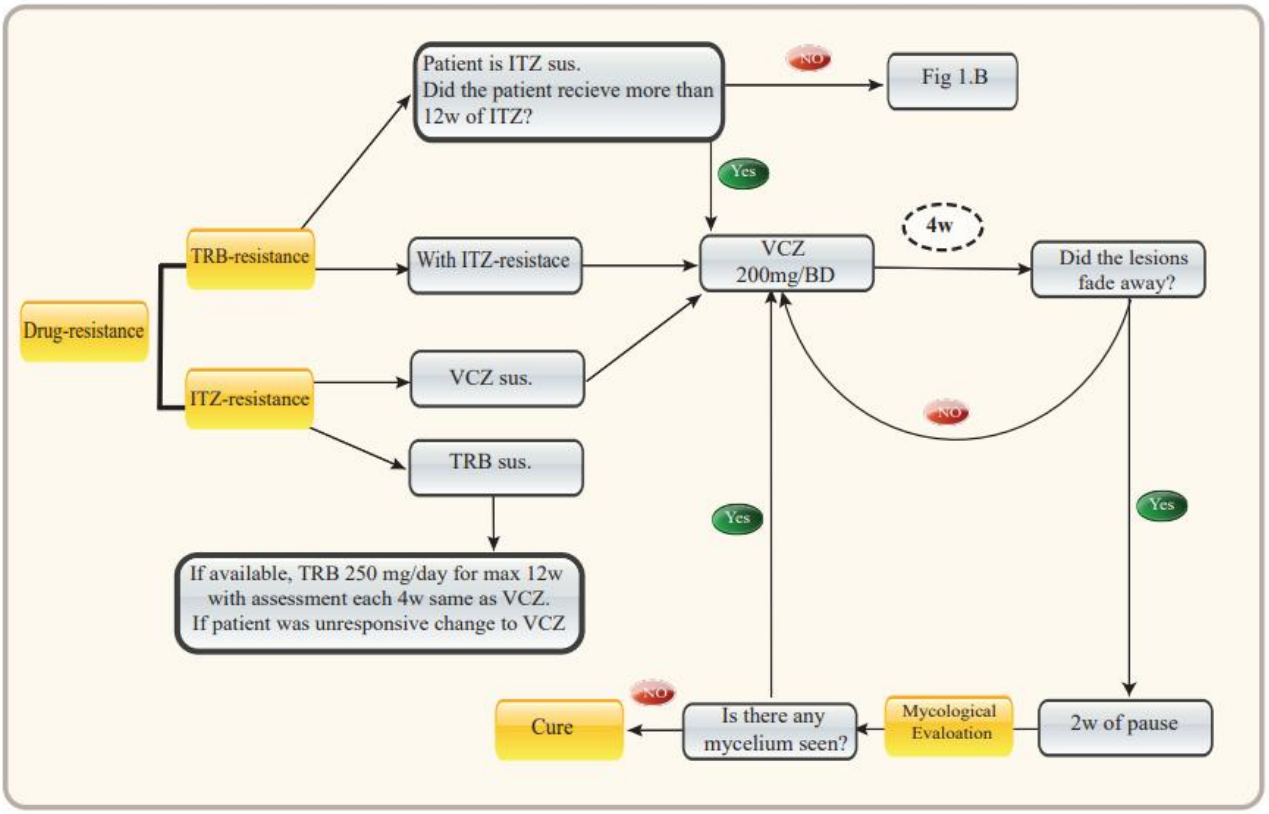
*Systemic antifungal consumption; No: number; NU; Not Used. F; Female. M; Male. BD; Twice daily. M; Month. P; period

*CTZ; Clotrimazole, TRB: Terbinafine, FCZ: fluconazole, KTZ: Ketoconazole, ITZ: Itraconazole, VCZ: Voriconazole, STZ: Sertaconazole, MCZ: Miconazole, SeS: Selenium sulfide

** Pulse therapy

*** Pulse therapy and continuous treatment

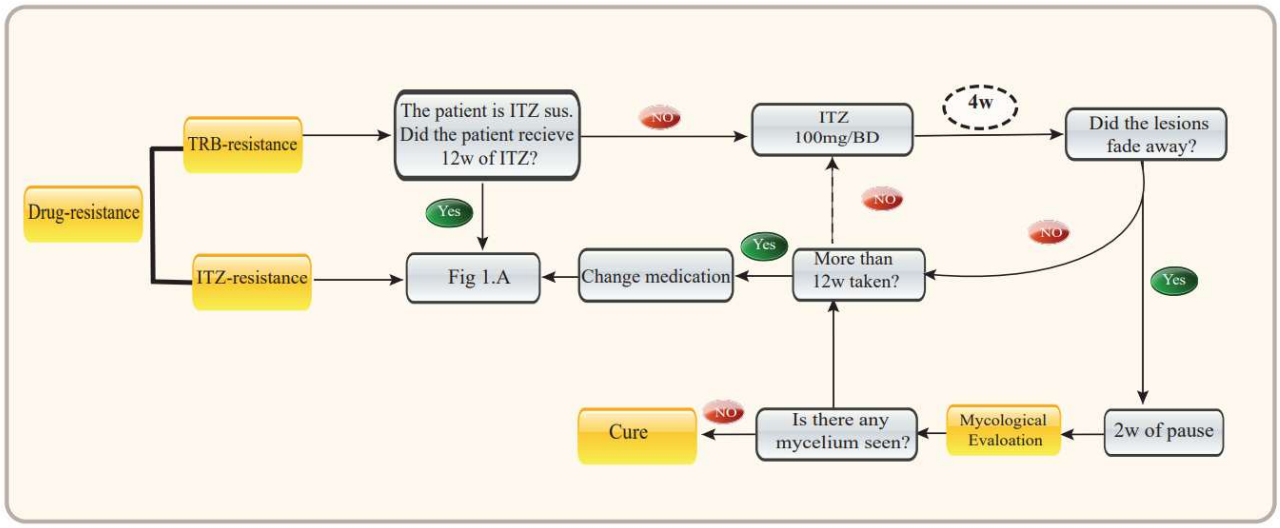
**** Intermittent treatment



515

516 **Figure 1 (A)**; Demonstrates the study´s primary treatment algorithm with voriconazole or terbinafine
517 for the drug resistant patients. Terbinafine resistant who had received itraconazole for more than 12
518 weeks but were not cured, or, those of itraconazole-resistant who had not access to terbinafine, were
519 eligible candidates for voriconazole. There was no defined limitation for duration of therapy for
520 voriconazole, mostly due to the fact that voriconazole was the only available option for these
521 candidates.Those of itraconazole-resistant patients who had access, terbinafine could be chosen as an
522 alternative therapy.

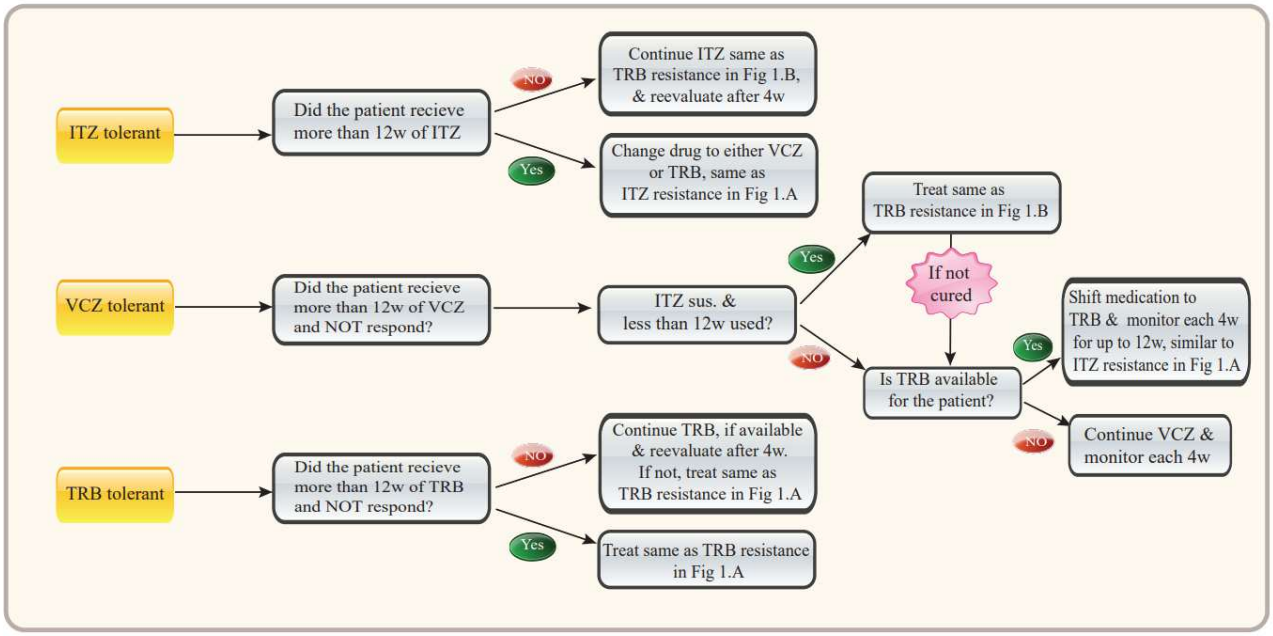
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524

525 **Figure 1 (B);** Demonstrates the study´s primary treatment algorithm with itraconazole for terbinafine-
526 resistant patients that had not received itraconazole for 3 months, and who were susceptible to
527 itraconazole in the AST assay.

528



529

530 **Figure 1 (C);** Demonstrates the study´s primary treatment algorithm for drug-tolerant study group.
531 This part was one of the hypothetical ideas of this paper that was evaluated.

532 ----------

533 *Tolerance was defined as MIC: 0.5-1 µg/mL. Resistance was defined as MIC: 1 µg/mL ≤.

sus.: Susceptible, w: Weeks, VCZ: Voriconazole, ITZ: Itraconazole, TRB: Terbinafine, BD: Twice daily, MIC: Minimum inhibitory concentration, KOH: Potassium hydroxide

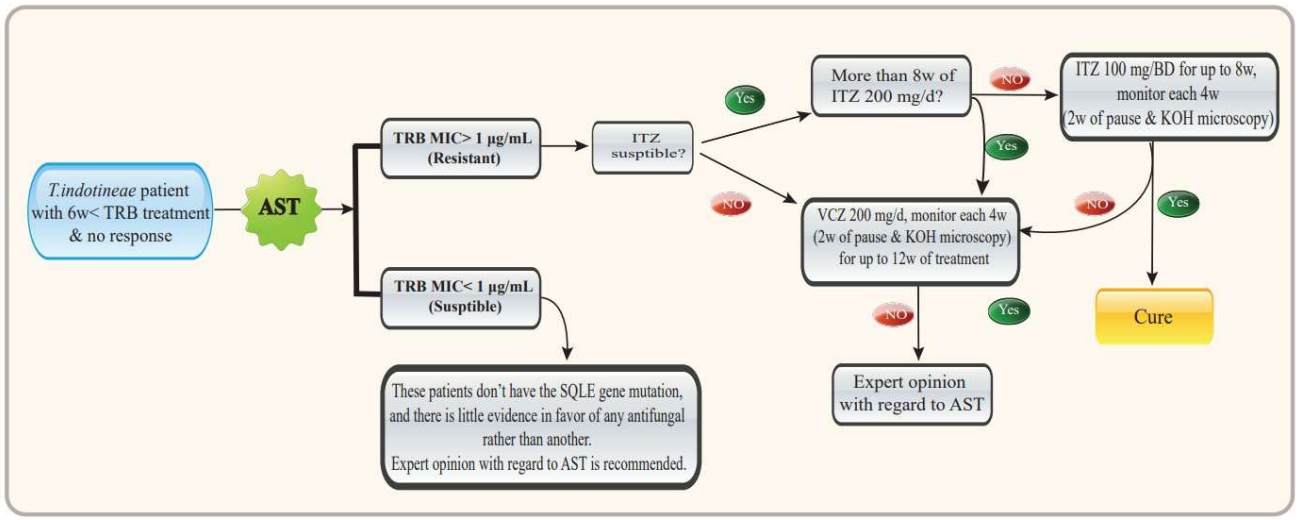


Figure 2 (A); Demonstrates the study´s suggested treatment algorithm for the Terbinafine resistant patients, based on the clinical results.

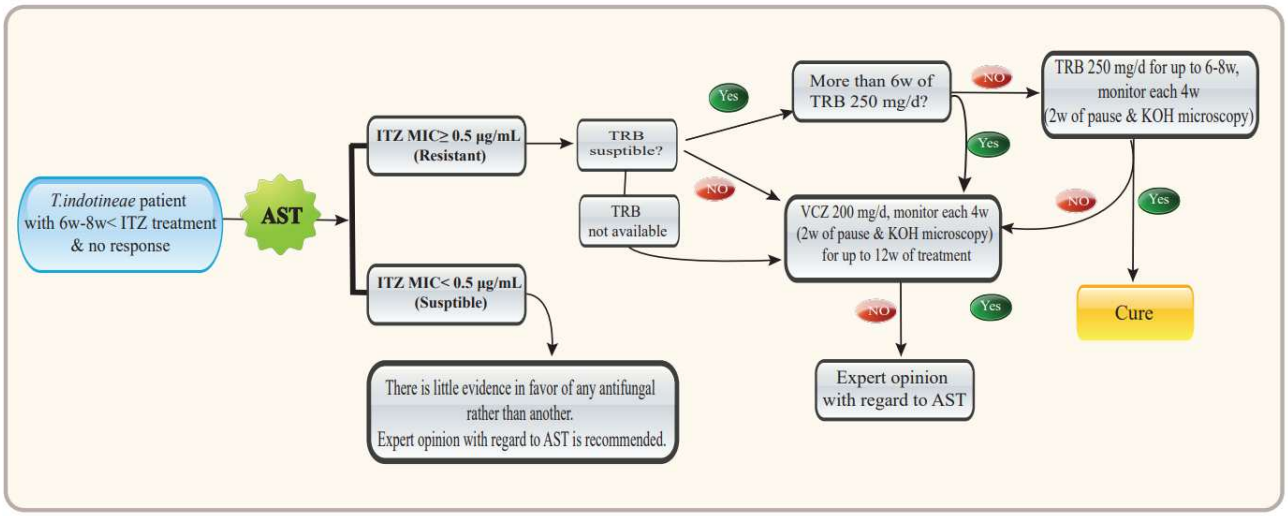


Figure 2 (B); Demonstrates the study´s suggested treatment algorithm for itraconazole-resistant patients. In the final algorithm we defined itraconazole-resistance as MIC ≥ 0.5 µg/mL in the antifungal susceptibility test based on the clinical findings.

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w: Weeks, , VCZ: Voriconazole, ITZ: Itraconazole, TRB: Terbinafine, BD: Twice daily, , AST: Antifungal susceptibility test,