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Therapeutic Outcomes in Patients With *Trichophyton indotineae*: A Systematic Review and Meta-Analysis of Individual Patient Data

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ABSTRACT

Background: *Trichophyton indotineae* has emerged as a significant global dermatophyte, associated with recalcitrant dermatophytosis and increasing antifungal resistance.

Materials and Methods: This study evaluates therapeutic outcomes in *T. indotineae* infections. We conducted a systematic review and meta-analysis of individual patient data adhering to PRISMA guidelines, including studies published before December 2023 from six electronic databases. Only studies with confirmed *T. indotineae* by rDNA sequencing and therapeutic outcome data were included.

Results: A total of 27 publications with 81 cases were included. *T. indotineae* infections affected both genders equally, with 25% having prior steroid use, which was significantly associated with non-improvement. Resistance to terbinafine was observed in 85.3% of cases. Oral itraconazole was significantly associated with a cure. The restricted median time to complete clinical cure was 11.50 weeks, with a recurrence rate of 19.7%.

Conclusions: The effective management of *T. indotineae* infections is essential, given the significant challenges posed by antifungal resistance.

1 | Introduction

Over the past few decades, dermatophytosis has globally increased, affecting up to 20%–25% of the population worldwide [1]. Symptoms of dermatophytosis, particularly itching, could potentially cause a negative effect on the patient's quality of life (QoL) [2, 3]. The emergence of chronic, difficult-to-treat or recalcitrant widespread dermatophytosis was initially emphasised in India [4–6]. Subsequently, this phenomenon has been reported worldwide, extending beyond India, including Asia, Europe and North America [7–9].

While *Trichophyton rubrum* was the dominant species of dermatophytosis for many years, there has been an epidemic shift in dermatophytosis from *T. rubrum* to *Trichophyton mentagrophytes*. This shift was attributed to its tendency to probably cause multidrug-resistant dermatophytosis [10, 11]. This recalcitrant *T. mentagrophytes* was molecularly identified through ribosomal

deoxyribonucleic acid (rDNA) sequencing as *T. mentagrophytes* Internal Transcribed Spacer (ITS) genotype VIII. Later on, it was proposed as a new species under the name *Trichophyton indotineae* (*T. indotineae*) in 2020 [12, 13].

T. indotineae infections often manifest as a widespread form of tinea cruris, tinea corporis and tinea faciei with intense itching [14] Elevated minimal inhibitory concentrations (MICs) against terbinafine have been reported among *T. indotineae* infections [15, 16]. Various single-point mutations in the squalene epoxidase (SQLE) gene, associated with terbinafine resistance, have been reported in *T. indotineae* [17]. This resistance has significantly impacted therapeutic strategies. While oral terbinafine (250 mg daily for 4–8 weeks) was previously recommended as the first-line treatment for dermatophytosis due to its lower potential for drug interactions and fewer side effects [18, 19], recent evidence suggests this approach may no longer be suitable. The emergence of *T. indotineae*, which frequently exhibits resistance to terbinafine, has necessitated a shift in treatment recommendations [20]. Current guidelines for resistant dermatophytosis advocate itraconazole as the preferred first-line therapy [20]. Additionally, in cases refractory to itraconazole, newer-generation antifungal drugs such as posaconazole and voriconazole have been reported to be effective in managing recalcitrant infections [21, 22]. However, it is important to note that these medications are not currently approved by the FDA for the treatment of superficial fungal infections or onychomycosis [22].

The effectiveness of treatment outcomes and the optimal therapeutic approach for patients with *T. indotineae* dermatophytosis still remains inconclusive [16, 23]. This systematic review and meta-analysis of individual patient data aimed to review therapeutic outcomes for patients with *T. indotineae* dermatophytosis. The demographic and clinical characteristics of the patients were also evaluated.

2 | Methods

2.1 | Protocol and Registration

This systematic review and meta-analysis of individual patient data adhered to the guidelines outlined in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) Statement and PRISMA for individual patient data systematic reviews (PRISMA-IPD) [24]. The research protocol was officially registered in PROSPERO (International Prospective Register of Systematic Reviews, http://www.crd.york.ac.uk/PROSPERO/, registration number CRD42024499989).

2.2 | Search Strategy

We conducted a systematic search across six databases, including Scopus, Embase, MEDLINE (via Ovid), PubMed, Cochrane Controlled Trials Register and ClinicalTrials.gov. We included studies published before December 2023. The search strategy is outlined in Table S1. Additionally, the reference lists of all identified studies were reviewed for relevance. Abstracts without full-text articles were excluded. Studies were included without language restrictions. Non-English studies were translated into English using Google Translate.

The search terms were ("*Trichophyton indotineae*" OR "*T. indotineae*" OR "*Trichophyton mentagrophytes*" OR "*T. mentagrophytes*") AND ("Dermatophytosis" OR "Dermatomycoses" "Tinea" OR "Superficial fungal infection" OR "Fungal skin infection") AND ("Antifungal Agents" OR "Itraconazole" OR "Terbinafine" OR "Griseofulvin" OR "Voriconazole" OR "Ketoconazole" OR "Miconazole" OR "Posaconazole" OR "Fluconazole" OR "Bifonazole" OR "Ciclopirox" OR "Clotrimazole"). Specific controlled vocabularies, such as Medical Subject Headings (MeSH) for PubMed, were used where feasible.

2.3 | Eligibility Criteria for Systematic Review

This study includes both clinical trials and observational studies including case-control, cohort and case series or case reports of patients with *T. indotineae* dermatophytosis at any sex, race, age and disease severity. The inclusion criteria comprised (1) published studies of patients with *T. indotineae* confirmed by rDNA sequencing and (2) the availability of viable data on therapeutic outcomes. The exclusion criteria were (1) in vitro-based studies without clinical outcomes, (2) unavailability of full text or abstract, (3) conference abstracts and (4) articles that were not derived from primary data comprising meta-analysis, systematic review, review article, guideline and commentary.

2.4 | Screening and Study Selection

After conducting a systematic search obtaining from each database, duplicates of records were excluded. Two authors (C.L. and P.S.) independently screened those titles and abstracts through Covidence, an online web-based systematic review software. Subsequently, the full text of potentially relevant articles was reviewed. Eligibility criteria were employed to obtain the viable articles for further data extraction. Any conflicts at either stage were resolved through consensus and consultation with a third author (S.B.). The screening and study selection process is demonstrated with a PRISMA flow diagram (Figure 1).

2.5 | Data Extraction

Two authors (C.L. and P.S.) independently extracted details of the following: first author's name, study type, number of patients, comorbidities, duration since onset, clinical manifestation, MICs, antifungal susceptibility, SQLE mutation, treatments and duration, clinical response and the time to a complete response. Any disagreements of extraction by the two authors (C.L. and P.S.) were resolved through consensus and consultation with a third author (S.B.).

2.6 | Quality Assessment

Two authors (C.L. and P.S.) independently evaluated the bias risks and disagreements resolved through consensus and

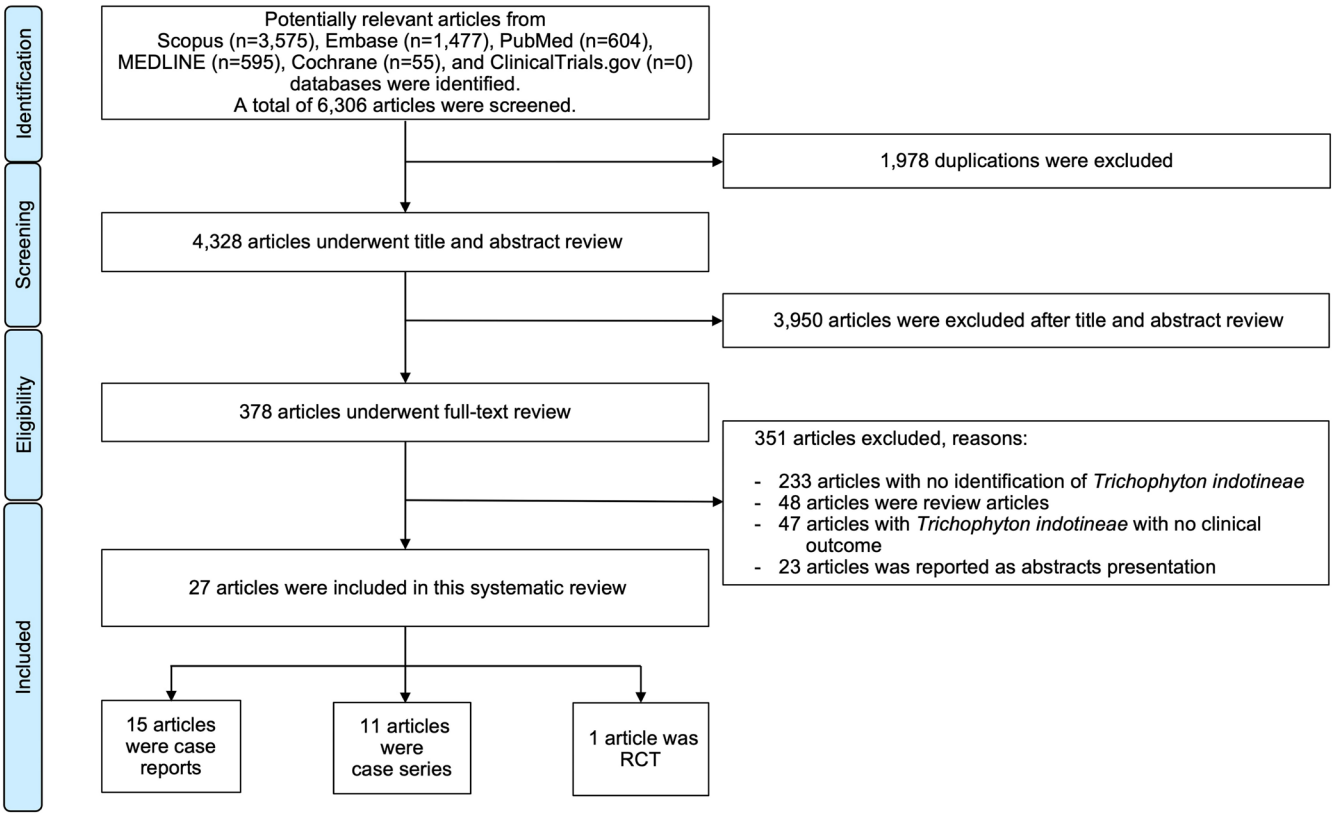

FIGURE 1 | Flow of study review and selection process.

consultation with a third author (S.B.). Risk-of-Bias 2 (RoB2) assessment tools by the Cochrane Collaboration were used to assess the quality of randomised controlled trials (RCTs) across five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. Quality of RCT was defined as "low risk of bias," "high risk of bias" or "some concerns" [25]. Moreover, methodological quality and synthesis for case series and case reports were employed for the evaluation of quality assessment for case series and case reports comprising eight items across four domains: selection, ascertainment, causality and reporting [26].

2.7 | Defining Outcomes

The main focus of this study included two key outcomes. The primary outcome was the complete clinical cure rate, defined as the rate of clinically complete resolution of cutaneous or nail lesions after each treatment. The secondary outcome was the time to complete the clinical cure, determined by the duration from the initiation of each treatment to the clinically complete resolution of all cutaneous or nail lesions. Another secondary outcome was the improvement rate, defined as the rate of clinical improvement marked by a decrease in erythema, scale, extension or pruritus.

The initial treatment was defined as the therapy course from the initiation of treatment to the point of documented response.

Regarding MICs determination, MIC50 refers to the minimal inhibitory concentrations at which growth is inhibited in 50% of isolates, while MIC90 indicates the minimal inhibitory concentrations at which growth is inhibited in 90% of isolates. Additionally, the geometric means (GMs) of MICs are calculated as the average of all available MICs, and the distribution of MICs is depicted by their range.

2.8 | Statistical Analysis

Descriptive analysis was used to describe demographic data, clinical manifestations, laboratory results and treatments. Normally continuous data are presented by the mean ± standard deviation, non-normally distributed continuous data as the median and interquartile range, and categorical data as the number and percentage. Categorical data underwent comparison through both the Chi-square test and Fisher's exact test, while continuous variables were assessed using an independent t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. To evaluate time-to-event outcomes, we employed multivariable flexible parametric survival regression with cluster variance correction to estimate the restricted mean survival time (RMST). The RMST represents the average survival time from the start of observation (time 0) to a specified time point [27, 28]. In our study, RMST refers to the average time from the initiation of treatment to the achievement of either a complete response or initial improvement. We reported the RMST for each treatment group and compared the treatment effects between

them. Analyses were performed with IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, N.Y., USA), MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium) and Stata software version 17.0 (StataCorp, College Station, TX, USA).

3 | Results

3.1 | Characteristics of Included Studies

In all, 6306 publications were identified. After excluding 1978 duplicates, we screened 4328 abstracts to eliminate unrelated articles, leaving 378 articles for full-text review. Only 27 publications (15 case reports [29–43], 11 case series [17, 44–53] and 1 RCT [54]) with a total of 81 patients met inclusion criteria. The characteristics of each study were demonstrated in Table 1. Certain studies did not provide specific clinical and therapeutic information for each patient, including details such as age, sex, onset duration and the duration of antifungal medication. This study review and selection process are demonstrated in Figure 1.

3.2 | Quality Assessment

The quality assessments of each study are listed in Table S2. The overall bias of the RCT was assessed as low risk. Assessments for case series and case reports in each domain are defined as shown in Table S3. All patients adequately determined outcomes, and the follow-up periods were long enough to determine outcomes.

3.3 | Demographic Data of Patients

Demographic data of all 81 patients, confirmed with *T. indotineae* infection via rDNA sequencing, was demonstrated in Table 2. Among those with available data, males were affected in 50.0% of cases, and the mean age was 34.6 ± 14.2 years old. Only 4.9% of cases were immunocompromised hosts, with diabetes mellitus being the underlying cause. Interestingly, among all provided travelling history, India was visited the most (48.6%). About a quarter of patients revealed a history of steroid use, with almost exclusively topical forms (90.5%). Patients presented with a chronic onset, with a median duration of 8.9 weeks (IQR 2.5, 10.5). The most common morphologies were scale (86.0%) and plaque (86.0%), with an annular configuration of 80.0%. Tinea corporis (88.3%) and tinea cruris (80.0%) were frequently observed in this review, with almost every case (96.7%) suffering from widespread dermatophytosis (≥ 2 regional areas). Besides cutaneous lesions, tinea ungium, both on fingernails and toenails, was observed in a case with widespread *T. indotineae* infection presenting in combination with tinea corporis.

3.4 | Antifungal Susceptibility and Drug Resistance

GMs of MICs, MIC ranges, MIC_{50} and MIC_{90} of each antifungal agent against *T. indotineae* isolates are demonstrated in Table 3. Regarding susceptibility to itraconazole, GM of MIC and MIC_{50} are 0.526 and 0.06 μg/mL, respectively (MICs range = 0.014–16 μg/mL). Itraconazole resistance (MIC ≥ 0.25 μg/mL) was observed in 21.9% of the cases. Whereas, in the aspect of susceptibility to terbinafine, GM of MIC and MIC_{50} are as high as 12.168 and 4 μg/mL, respectively (MICs range = 0.014 to > 32 μg/mL). Terbinafine resistance (MIC ≥ 0.125 μg/mL) was predominantly reported in 85.3% of the cases. Moreover, SQLE mutation was described in 84.8%. In addition, patients with SQLE mutation presented with a longer median duration of clinical cure compared to those without mutation (16.0 weeks vs. 8.0 weeks; $p = 0.038$).

3.5 | Treatment and Outcome of *T. indotineae*

Regarding initial treatment, among 37.0% of patients initially prescribed oral itraconazole, 80.0% received monotherapy of oral itraconazole. Whereas, out of 44.4% of patients were initially prescribed oral terbinafine, and among those, 47.2% received a combination of oral terbinafine and topical antifungal treatment. Focusing on the treatment regimen, we considered patients who received oral antifungal drugs without switching to avoid the effects of prior medications. Nine cases received only topical antifungal treatment, of which only one (11.1%) showed improvement. The results show that initial treatment with oral itraconazole was significantly associated with improvement, whereas initial treatment with oral terbinafine was significantly associated with non-improvement.

After evaluating the response to initial treatment, the therapeutic course was altered in a number of patients. Focusing on the overall treatment, among those who started with oral terbinafine, the regimen was mostly switched to oral itraconazole (58.6%). Systemic treatment with itraconazole was statistically significantly associated with cure, while monotherapy with topical antifungals was significantly associated with non-cure.

Only 40.7% of patients achieved clinical improvement with initial treatment with restricted mean time to initial improvement = 11.11 weeks (95% CI, 6.85–15.37; Figure 2). Associated factors regarding clinical improvement in initial treatment are summarised in Table 2. Among patients with a history of steroid use, only 9.1% showed clinical improvement compared to 37.5% who did not experience improvement ($p = 0.004$). Complete clinical cure was reported in 75.3% with restricted mean time to complete clinical cure =11.50 weeks (95% CI, 6.85–16.15; Figure 3). There were no statistically significant associated factors to complete clinical cure, including sex, age, comorbidities, immune status, past history, morphology, location of lesion and susceptibility. Furthermore, there was no significant difference in the RMST among the treatment groups, both for initial improvement and complete clinical cure (Figures 4 and 5). Recurrence was reported in 19.7% of patients with a median duration of 14.0 weeks (IQR 8.0, 45.0).

4 | Discussion

Trichophyton indotineae infections are a growing concern due to their potential to cause multidrug-resistant dermatophytosis, particularly as the prevalence of recalcitrant dermatophytosis increases globally [7–9]. This scoping review aims to examine demographic data, clinical manifestations, antifungal

TABLE 1 | Characteristics of included studies.

Study number	Author (year of publication)	Article type	Country	Study period	Number of included cases	Sex	Median age (years), (min-max)
1	Süß et al. (2019) [29]	Case report	Germany	2019	1	1 Female	0.5
2	Kakurai et al. (2020) [30]	Case report	Japan	2020	1	1 Male	47
3	Kimura et al. (2020) [31]	Case report	Japan	2017	1	1 Female	27
4	Nenoff et al. (2020) [44]	Case series	Germany	2016–2020	3	2 Males 1 Female	31 (28–32)
5	Khurana et al. (2021) [54]	RCT	India	2021	21	NA	NA
6	Brasch et al. (2021) [45]	Case series	Germany	2011–2019	3	1 Male 2 Females	29 (20–38)
7	Fattahi et al. (2021) [46]	Case series	Iran	2021	4	1 Male 3 Females	30.5 (4–64)
8	Gawaz (2021) [32]	Case report	Germany	2019–2020	1	1 Male	21
9	Siopi (2021) [47]	Case series	Greece	2010–2019	2	1 Male 1 Female	55.5 (42–69)
10	Dellière et al. (2022) [48]	Case series	France	2018–2019	7	3 Males 4 Females	44 (20–57)
11	Gueneau et al. (2022) [33]	Case report	France	2017–2018	1	1 Male	28
12	Jabet et al. (2022) [17]	Case series	France	2019–2021	7	NA	30 (16–53)
13	Khurana (2022) [34]	Case report	India	2022	1	1 Male	24
14	Moreno-Sabater et al. (2022) [49]	Case series	France	2021	1	NA	NA
15	Ngo et al. (2022) [35]	Case report	Vietnam	2021	1	1 Male	27
16	Posso-De Los Rios (2022) [50]	Case series	Canada	2021	8	4 Males 4 Females	33.5 (26–78)
17	Bortoluzzi et al. (2023) [51]	Case series	Italy	2019–2022	4	4 Males	44 (32–59)
18	Caplan et al. (2023) [36]	Case report	USA	2021–2022	2	2 Males	37.5 (28–47)
19	Dashti et al. (2023) [37]	Case report	Kuwait	2022	1	1 Female	33
20	Durdu et al. (2023) [38]	Case report	Turkey	2022	2	1 Male 1 Female	26 (25–27)
21	Jia et al. (2023) [52]	Case series	China	2017–2022	2	1 Male 1 Female	26 (20–32)
22	Kong et al. (2023) [39]	Case report	China	2022	1	1 Male	47

(Continues)

TABLE 1 | (Continued)

Study number	Author (year of publication)	Article type	Country	Study period	Number of included cases	Sex	Median age (years), (min-max)
23	Messina et al. (2023) [40]	Case report	Argentina	2023	1	1 Female	21
24	Russo (2023) [53]	Case series	Switzerland	2021	2	1 Male 1 Female	29 (26–32)
25	Villa-Gonzalez et al. (2023) [41]	Case report	Spain	2023	1	1 Female	17
26	Thakur (2023) [42]	Case report	India	2022	1	1 Male	42
27	Crotti et al. (2023) [43]	Case report	Italy	2023	1	1 Female	42

Abbreviation: RCT, randomised controlled trial.

susceptibility and therapeutic outcomes associated with *T. indotineae*. The findings of this study will provide valuable information and contribute to raising awareness of the challenges posed by *T. indotineae* infections.

Our findings revealed that *T. indotineae* infections affected both males and females equally. Among patients with a history of travel, India was the most frequently visited country, comprising 48.6% of cases, in accordance with previous studies by Bishnoi A. et al. and Verma SB, which reported the emergence of recalcitrant widespread dermatophytosis in India [5, 6]. Importantly, a history of steroid use was associated with a significantly lower rate of clinical improvement (9.1% vs. 37.5%, $p = 0.004$). This finding aligns with the known risks associated with corticosteroid use in dermatophytosis, which can exacerbate the infection and complicate treatment [55].

Based on a previous study in France by Jabet A. et al., *T. indotineae* infection is often presented as a widespread form of dermatophytosis [14]. Similarly, in this study, almost all cases involved an extensive form of cutaneous fungal infection, accounting for 96.7%. In addition to cutaneous lesions, tinea unguium was observed in a case with widespread *T. indotineae* infection, presenting in combination with tinea corporis, highlighting the importance for physicians to conduct thorough whole-body examinations. These infections typically had a chronic onset, with a median disease duration of 8.9 weeks (IQR 2.5, 10.5).

A significant finding of our study was the high level of resistance to terbinafine among *T. indotineae* infections. Resistance to itraconazole (MIC $>0.25\,\mu g/mL$) was observed in 21.9% of the cases, while resistance to terbinafine (MIC $>0.125\,\mu g/mL$) was predominant, reported in 85.3% of cases. Regarding terbinafine susceptibility, the GM of MIC and MIC_{50} were as high as 12.168 and $4\,\mu g/mL$, respectively. These findings are consistent with studies from Singh A. et al. and Verma SB et al. in India, which also reported elevated MICs against terbinafine among *T. indotineae* infections [15, 16]. In comparison, the GM of MIC and MIC_{50} for itraconazole were significantly lower at 0.526 and $0.06\,\mu g/mL$, respectively. This resistance presents a challenge for treatment, as terbinafine is typically the first-line therapy for dermatophytosis [18]. Therefore, itraconazole may need to be considered as an alternative treatment option for *T. indotineae* infections.

Data from Jabet A et al. reported terbinafine-resistant *T. indotineae* isolates in India and Germany harbouring SQLE single amino acid substitutions [17]. Interestingly, our study found that SQLE mutations were present in as many as 84.8% of cases. Furthermore, patients with these mutations had a longer median duration to clinical cure compared to those without mutations (16.0 weeks vs. 8.0 weeks; $p = 0.038$), suggesting that these mutations may influence the clinical course of the infection, potentially leading to delayed resolution of symptoms. A study by Ananta K et al. [56] and Avrom C et al. [57] reported that patients with SQLE mutations had higher MICs for terbinafine compared to those without these mutations. However, the clinical significance of SQLE mutations requires further investigation, as other factors may also contribute to treatment outcomes.

In terms of treatment, focusing on regimens without drug switching, patients prescribed oral itraconazole as initial therapy demonstrated a markedly higher improvement rate compared to those who received oral terbinafine, with the difference being statistically significant (75.8% vs. 18.2%; $p < 0.001$). This suggests that itraconazole may be a more effective initial treatment option, especially in regions with prevalent terbinafine resistance. These results are consistent with earlier studies conducted in the United States [58] and China [20, 59] and a global retrospective review [60], which also reported that itraconazole was generally more effective against *T. indotineae* infections than terbinafine. Additionally, our study showed that topical antifungal monotherapy is less effective, with a lower improvement rate observed among patients using this regimen compared to those who experienced no improvement. These findings emphasise the necessity for clinicians to consider systemic therapies more carefully, particularly in cases of *T. indotineae* dermatophytosis.

Interestingly, with regard to overall treatment, a significant number of patients required alterations to their therapeutic course following initial treatment. Among those who initially received oral terbinafine, more than half (58.6%) had their

TABLE 2 | Demographic data of *Trichophyton indotineae* and associated factors on clinical improvement in initial treatment ($n = 81$).

	Total *n* (%)	Improve (%) ($n = 33$)	Not improve (%) ($n = 48$)	*p*
Sex ($n = 52$)				
Male	26/52 (50.0)	4/9 (44.4)	22/43 (51.2)	1.000
Mean age ± SD (year) ($n = 59$)	34.6 ± 14.2	34.3 ± 16.3	34.7 ± 13.8	0.840
Comorbidities[a]	9/81 (11.1)	2/9 (22.2)	7/48 (14.6)	0.598
Diabetes mellitus	4/9 (44.4)	0/2 (0.0)	4/7 (57.1)	1.000
Hypertension	1/9 (11.1)	0/2 (0.0)	1/7 (14.3)	1.000
Dyslipidemia	3/9 (33.3)	0/2 (0.0)	3/7 (42.9)	1.000
HBV infection	2/9 (22.2)	1/2 (50.0)	1/7 (14.3)	0.268
Others	3/9 (33.3)	1/2 (50.0)	2/7 (28.6)	0.377
Immune status				
Immunocompromised host	4/81 (4.9)	0/33 (0.0)	4/48 (8.3)	1.000
History of travelling from India ($n = 37$)	18/37 (48.6)	3/6 (50.0)	15/31 (48.4)	1.000
Family history of tinea infection ($n = 18$)	12/18 (66.7)	2/3 (66.7)	10/15 (66.7)	1.000
History of steroid use	21/81 (25.9)	3/33 (9.1)	18/48 (37.5)	0.004*
History of topical steroid	19/21 (90.5)	2/3 (66.7)	17/18 (94.4)	0.041*
History of systemic steroid	1/21 (4.8)	0/3 (0.0)	1/18 (5.6)	
History of systemic and topical steroid	1/21 (4.8)	1/3 (33.3)	0/18 (0.0)	
Lesion characteristics[a] ($n = 50$)				
Annular	40/50 (80.0)	5/8 (62.5)	35/42 (83.3)	0.331
Patch	9/50 (18.0)	0/8 (0.0)	9/42 (21.4)	0.322
Papule	6/50 (12.0)	0/8 (0.0)	6/42 (14.3)	0.572
Plaque	43/50 (86.0)	8/8 (100.0)	35/42 (83.3)	0.580
Vesicle	7/50 (14.0)	0/8 (0.0)	7/42 (16.7)	0.580
Pustule	1/50 (2.0)	0/8 (0.0)	1/42 (2.4)	1.000
Scale	43/50 (86.0)	7/8 (87.5)	36/42 (85.7)	1.000
Location of lesions[a] ($n = 60$)				
Tinea corporis	53/60 (88.3)	13/14 (92.9)	40/46 (87.0)	1.000
Tinea cruris	48/60 (80.0)	10/14 (71.4)	38/46 (82.6)	0.448
Tinea facei	14/60 (23.3)	3/14 (21.4)	11/46 (23.9)	1.000
Tinea pedis	2/60 (3.3)	1/14 (7.1)	1/46 (2.2)	0.415
Tinea manuum	2/60 (3.3)	1/14 (7.1)	1/46 (2.2)	0.415
Tinea barbae	1/60 (1.7)	1/14 (7.1)	0/46 (0.0)	0.233
Tinea capitis	1/60 (1.7)	0/14 (0.0)	1/46 (2.2)	1.000
Tinea ungium	1/60 (1.7)	1/14 (7.1)	0/46 (0.0)	0.233
Investigation				
SQLE mutation ($n = 46$)	39/46 (84.8)	9/13 (69.2)	30/33 (90.9)	0.087
Antifungal susceptibility testing				

(Continues)

TABLE 2 | (Continued)

	Total *n* (%)	Improve (%) (*n* = 33)	Not improve (%) (*n* = 48)	*p*
Resist to terbinafine (*n* = 68)	58/68 (85.3)	25/31 (80.6)	33/37 (89.2)	0.494
Resist to itraconazole (*n* = 64)	14/64 (21.9)	6/30 (20.0)	8/34 (23.5)	0.771
Resist to voriconazole (*n* = 54)	1/54 (1.9)	1/30 (3.3)	0/24 (0.0)	1.000
Treatment (without switching regimen) (*n* = 72)				
Topical antifungal alone	9/72 (12.5)	1/33 (3.0)	8/39 (20.5)	0.033*
Oral itraconazole base	30/72 (41.7)	25/33 (75.8)	5/39 (12.8)	< 0.001*
Oral terbinafine base	31/72 (43.1)	6/33 (18.2)	25/39 (64.1)	< 0.001*
Oral fluconazole base	2/72 (2.8)	1/33 (3.0)	1/39 (2.6)	1.000

Abbreviations: HBV, hepatitis B virus; IQR, interquartile range; SQLE, squalene epoxidase.
[a]One patient can have more than one comorbidity, lesion characteristics and location of the lesion.
*Significantly different at *p*-value < 0.05.

TABLE 3 | MIC values (μg/mL) of each antifungal agent against *Trichophyton indotineae* isolates.

	TRB (*n* = 64)	ITC (*n* = 60)	VOR (*n* = 50)	ISZ (*n* = 29)	POS (*n* = 30)	FLZ (*n* = 32)	STZ (*n* = 21)	GRE (*n* = 26)	AMB (*n* = 33)
MIC_{GM} (95% CI)	12.168 (8.911–15.426)	0.526 (0.100–1.114)	0.295 (0.136–0.453)	0.342 (0.069–0.615)	0.154 (0.022–0.286)	33.000 (18.372–47.628)	4.140 (1.105–7.180)	2.920 (1.870–3.976)	0.233 (0.166–0.300)
MIC_{50} (95% CI)	4.000 (2.000–16.000)	0.060 (0.060–0.125)	0.125 (0.125–0.250)	0.125 (0.125–0.250)	0.125 (0.060–0.125)	16.000 (8.000–32.000)	2.000 (2.000–4.000)	2.000 (1.000–2.000)	0.250 (0.125–0.250)
MIC_{90} (95% CI)	32.000 (32.000, 32.000)	0.500 (0.240–7.580)	0.500 (0.250–0.500)	0.500 (0.250–4.000)	0.125 (0.125–2.000)	128.000 (54.400–128.000)	8.000 (3.600–32.000)	8.000 (2.600–8.000)	0.500 (0.250–0.800)
MIC_{range}	0.0140–> 32.000	0.0140–16.000	0.025–4.000	0.015–4.000	0.150–2.000	2.000–128.000	1.000–32.000	1.000–8.000	0.010–1.000

Abbreviations: AMB, amphotericin B; FLZ, fluconazole; GRE, griseofulvin; ISZ, isavuconazole; ITC, itraconazole; POS, posaconazole; STZ, sertaconazole; TRB, terbinafine; VOR, voriconazole.

regimen switched to oral itraconazole, reflecting the suboptimal response to terbinafine. This underscores the importance of monitoring treatment response closely and being prepared to adjust therapy when necessary [14, 16].

The time to clinical improvement with initial treatment was relatively prolonged, with a restricted mean time of 11.11 weeks (95% CI, 6.85–15.37), which exceeds the guideline-recommended treatment duration of 4–8 weeks [18]. Complete clinical cure was achieved in 75.3% of patients, with a restricted mean time to complete clinical cure of 11.50 weeks (95% CI, 6.85–16.15), indicating the chronic and recalcitrant nature of *T. indotineae* infections, consistent with previous studies [14, 17]. However, no significant differences were observed in the RMST among the treatment groups, both for initial improvement and complete clinical cure, and no statistically significant factors were associated with complete clinical cure.

The recurrence of *T. indotineae* infections was reported in 19.7% of patients. This high recurrence rate highlights the persistent and challenging nature of this infection, particularly in the context of multidrug resistance. Long-term follow-up and possibly extended antifungal therapy may be required to manage and prevent recurrence effectively.

This study had some limitations, as the treatment outcomes in some studies were evaluated solely based on clinical resolution without assessing mycological cure. This may have contributed to the observed high recurrence rate of T. *indotineae* infections.

5 | Conclusion

T. indotineae dermatophytosis presents significant challenges and emphasise the need for increased awareness regarding treatment, particularly in the context of antifungal drug resistance, especially terbinafine resistance, which is associated with prolonged time to improvement and clinical cure. The recurrence rate of this infection is notably high. Clinicians

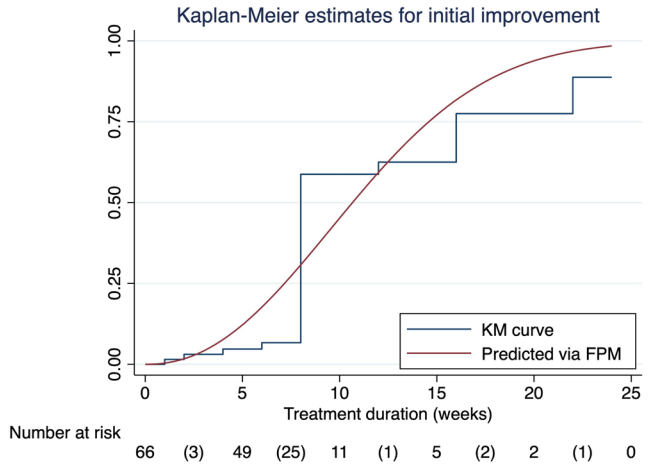

FIGURE 2 | Overall time to initial improvement. FPM, flexible parametric model; KM, Kaplan–Meier.

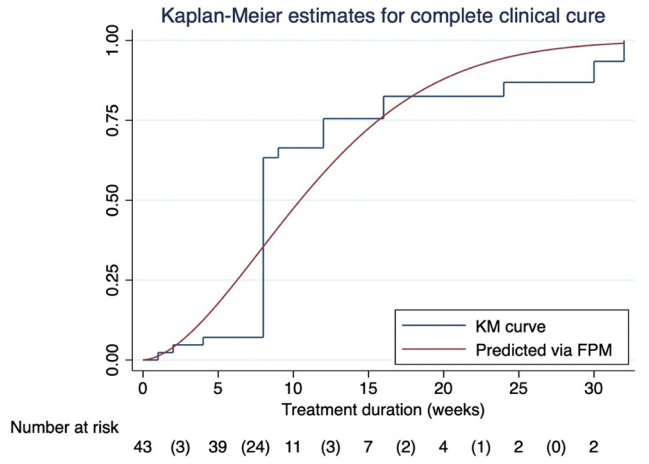

FIGURE 3 | Overall time to complete the clinical cure. FPM, flexible parametric model; KM, Kaplan–Meier.

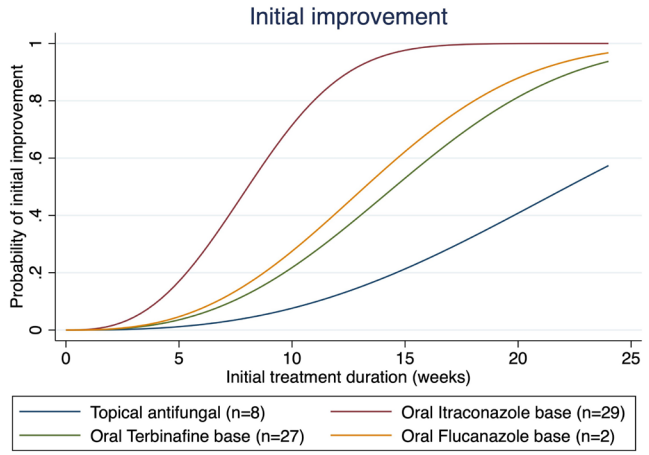

FIGURE 4 | Time to initial improvement by treatment groups ($N = 66$).

must carefully consider treatment regimens, closely monitor treatment responses and be prepared to adjust therapy as needed.

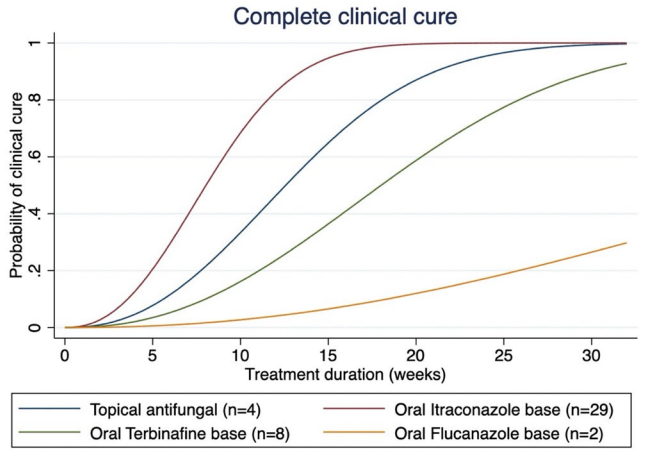

FIGURE 5 | Time to complete clinical cure by treatment groups ($N = 43$).

Author Contributions

Charussri Leeyaphan: conceptualization, data curation, methodology, supervision, writing – review and editing, project administration. **Phuwakorn Saengthong-aram:** data curation, formal analysis, writing – original draft, validation. **Jomgriditip Laomoleethorn:** formal analysis, validation, writing – original draft. **Phichayut Phinyo:** supervision, investigation, methodology, formal analysis, visualization. **Lalita Lumkul:** methodology, investigation, formal analysis, visualization. **Sumanas Bunyaratavej:** conceptualization, methodology, investigation, data curation, writing – review and editing, supervision, project administration.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

References

1. B. Havlickova, V. A. Czaika, and M. Friedrich, "Epidemiological Trends in Skin Mycoses Worldwide," *Mycoses* 51, no. Suppl 4 (2008): 2–15.

2. S. Mushtaq, N. Faizi, S. S. Amin, M. Adil, and M. Mohtashim, "Impact on Quality of Life in Patients With Dermatophytosis," *Australasian Journal of Dermatology* 61, no. 2 (2020): e184–e188.

3. S. Verma, R. Vasani, R. Reszke, Ł. Matusiak, and J. C. Szepietowski, "Prevalence and Clinical Characteristics of Itch in Epidemic-Like Scenario of Dermatophytoses in India: A Cross-Sectional Study," *Journal of the European Academy of Dermatology and Venereology* 34, no. 1 (2020): 180–183.

4. S. Dogra and S. Uprety, "The Menace of Chronic and Recurrent Dermatophytosis in India: Is the Problem Deeper Than We Perceive?," *Indian Dermatology Online Journal* 7, no. 2 (2016): 73–76.

5. A. Bishnoi, K. Vinay, and S. Dogra, "Emergence of Recalcitrant Dermatophytosis in India," *Lancet Infectious Diseases* 18, no. 3 (2018): 250–251.

6. S. B. Verma, "Emergence of Recalcitrant Dermatophytosis in India," *Lancet Infectious Diseases* 18, no. 7 (2018): 718–719.

7. N. P. Madarasingha, S. Eriyagama, P. I. Jayasekera, et al., "Characterization of Recalcitrant Dermatophytosis in a Multicenter Study in Sri Lanka," *American Journal of Tropical Medicine and Hygiene* 107, no. 1 (2022): 117–121.

8. D. M. L. Saunte, M. Pereiro-Ferreirós, C. Rodríguez-Cerdeira, et al., "Emerging Antifungal Treatment Failure of Dermatophytosis in Europe: Take Care or It May Become Endemic," *Journal of the European Academy of Dermatology and Venereology* 35, no. 7 (2021): 1582–1586.

9. D. Gu, M. Hatch, M. Ghannoum, and B. E. Elewski, "Treatment-Resistant Dermatophytosis: A Representative Case Highlighting an Emerging Public Health Threat," *JAAD Case Reports* 6, no. 11 (2020): 1153–1155.

10. P. Nenoff, S. B. Verma, R. Vasani, et al., "The Current Indian Epidemic of Superficial Dermatophytosis due to *Trichophyton mentagrophytes*-A Molecular Study," *Mycoses* 62, no. 4 (2019): 336–356.

11. H. Hanumanthappa, K. Sarojini, P. Shilpashree, and S. B. Muddapur, "Clinicomycological Study of 150 Cases of Dermatophytosis in a Tertiary Care Hospital in South India," *Indian Journal of Dermatology* 57, no. 4 (2012): 322–323.

12. R. Kano, U. Kimura, M. Kakurai, et al., "*Trichophyton indotineae* sp. nov.: A New Highly Terbinafine-Resistant Anthropophilic Dermatophyte Species," *Mycopathologia* 185, no. 6 (2020): 947–958.

13. P. Nenoff, S. Uhrlaß, S. B. Verma, and S. Panda, "*Trichophyton mentagrophytes* ITS Genotype VIII and *Trichophyton indotineae*: A Terminological Maze, or Is It?," *Indian Journal of Dermatology, Venereology and Leprology* 88, no. 5 (2022): 586–589.

14. A. Jabet, A. C. Normand, S. Brun, et al., "*Trichophyton indotineae*, From Epidemiology to Therapeutic," *Journal of Medical Mycology* 33, no. 3 (2023): 101383.

15. A. Singh, A. Masih, A. Khurana, et al., "High Terbinafine Resistance in *Trichophyton interdigitale* Isolates in Delhi, India Harbouring Mutations in the Squalene Epoxidase Gene," *Mycoses* 61, no. 7 (2018): 477–484, https://doi.org/10.1111/myc.12772.

16. S. B. Verma, S. Panda, P. Nenoff, et al., "The Unprecedented Epidemic-Like Scenario of Dermatophytosis in India: III. Antifungal Resistance and Treatment Options," *Indian Journal of Dermatology, Venereology and Leprology* 87, no. 4 (2021): 468–482.

17. A. Jabet, S. Brun, A. C. Normand, et al., "Extensive Dermatophytosis Caused by Terbinafine-Resistant *Trichophyton indotineae*, France," *Emerging Infectious Diseases* 28, no. 1 (2022): 229–233, https://doi.org/10.3201/eid2801.210883.

18. M. Rajagopalan, A. Inamadar, A. Mittal, et al., "Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India)," *BMC Dermatology* 18, no. 1 (2018): 6.

19. B. Dogan, D. Akpolat, and Z. Kutlubay, "Current Approaches in the Treatment of Superficial Fungal Infections," *Journal of the Turkish Academy of Dermatology* 17 (2023): 83–86.

20. G. Liang, X. Li, R. Li, et al., "Chinese Expert Consensus on Management of Antifungal-Resistant Dermatophytoses," *Mycoses* 67, no. 9 (2024): e13785.

21. A. Firooz, E. Lotfali, M. Fattahi, M. Fattahi, A. Miramin Mohammadi, and M. Shahrzad Kavkani, "A Case of Terbinafine-Resistant Tinea Cruris Caused by *Trichophyton tonsurans*," *Case Reports in Dermatological Medicine* 2021 (2021): 9611072.

22. A. K. Gupta, M. Talukder, A. Shemer, and E. Galili, "Safety and Efficacy of New Generation Azole Antifungals in the Management of Recalcitrant Superficial Fungal Infections and Onychomycosis," *Expert Review of Anti-Infective Therapy* 22, no. 6 (2024): 399–412.

23. S. Singh, U. Chandra, V. N. Anchan, P. Verma, and R. Tilak, "Limited Effectiveness of Four Oral Antifungal Drugs (Fluconazole, Griseofulvin, Itraconazole and Terbinafine) in the Current Epidemic of Altered Dermatophytosis in India: Results of a Randomized Pragmatic Trial," *British Journal of Dermatology* 183, no. 5 (2020): 840–846.

24. L. A. Stewart, M. Clarke, M. Rovers, et al., "Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data: the PRISMA-IPD Statement," *JAMA* 313, no. 16 (2015): 1657–1665, https://doi.org/10.1001/jama.2015.3656.

25. J. A. C. Sterne, J. Savović, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *BMJ* 366 (2019): l4898.

26. M. H. Murad, S. Sultan, S. Haffar, and F. Bazerbachi, "Methodological Quality and Synthesis of Case Series and Case Reports," *BMJ Evidence Based Medicine* 23, no. 2 (2018): 60–63.

27. P. Royston and M. K. Parmar, "Restricted Mean Survival Time: An Alternative to the Hazard Ratio for the Design and Analysis of Randomized Trials With a Time-To-Event Outcome," *BMC Medical Research Methodology* 13 (2013): 152.

28. P. Royston, "Estimating the Treatment Effect in a Clinical Trial Using Difference in Restricted Mean Survival Time," *Stata Journal* 15, no. 4 (2015): 1098–1117.

29. A. Süß, S. Uhrlaß, A. Ludes, et al., "Extensive Tinea Corporis due to a Terbinafine-Resistant *Trichophyton mentagrophytes* Isolate of the Indian Genotype in a Young Infant From Bahrain in Germany," *Der Hautarzt* 70, no. 11 (2019): 888–896.

30. M. Kakurai, K. Harada, T. Maeda, J. Hiruma, R. Kano, and T. Demitsu, "Case of Tinea Corporis due to Terbinafine-Resistant *Trichophyton interdigitale*," *Journal of Dermatology* 47, no. 4 (2020): e104–e105.

31. U. Kimura, M. Hiruma, R. Kano, et al., "Caution and Warning: Arrival of Terbinafine-Resistant *Trichophyton interdigitale* of the Indian Genotype, Isolated From Extensive Dermatophytosis, in Japan," *Journal of Dermatology* 47, no. 5 (2020): e192–e193, https://doi.org/10.1111/1346-8138.15300.

32. A. Gawaz, P. Nenoff, S. Uhrlaß, and M. Schaller, "Treatment of a Terbinafine-Resistant *Trichophyton mentagrophytes* Type VIII," *Der Hautarzt* 72, no. 10 (2021): 900–904.

33. R. Gueneau, B. Joannard, N. Haddad, et al., "Extensive Dermatophytosis Caused by Terbinafine-Resistant *Trichophyton indotineae*, Successfully Treated With Topical Voriconazole," *International Journal of Antimicrobial Agents* 60, no. 5–6 (2022): 106677.

34. A. Khurana, A. Agarwal, D. Agrawal, K. Sardana, A. Singh, and A. Chowdhary, "Multidrug Resistant Tinea Corporis/Cruris: Response to Voriconazole," *Journal of Medical Mycology* 32, no. 4 (2022): 101306.

35. T. M. C. Ngo, P. A. Ton Nu, C. C. Le, T. N. T. Ha, T. B. T. Do, and G. Tran Thi, "First Detection of *Trichophyton indotineae* Causing Tinea Corporis in Central Vietnam," *Medical Mycology Case Reports* 36 (2022): 37–41.

36. A. S. Caplan, S. Chaturvedi, Y. Zhu, et al., "Notes From the Field: First Reported U.S. Cases of Tinea Caused by *Trichophyton indotineae* - New York City, December 2021-March 2023," *MMWR. Morbidity and Mortality Weekly Report* 72, no. 19 (2023): 536–537.

37. Y. Dashti, K. Alobaid, S. Al-Rashidi, et al., "Autochthonous Case of *Trichophyton indotineae* in Kuwait," *Journal of Medical Mycology* 33, no. 4 (2023): 101432.

38. M. Durdu, H. Kandemir, A. S. Karakoyun, M. Ilkit, C. Tang, and S. de Hoog, "First Terbinafine-Resistant *Trichophyton indotineae* Isolates With Phe(397)Leu and/or Thr(414)his Mutations in Turkey," *Mycopathologia* 188, no. 1 (2023): 2.

39. X. Kong, G. Song, H. Mei, et al., "The Domestic Isolation of Terbinafine- and Itraconazole-Resistant *Trichophyton indotineae* in Chinese Mainland," *Mycopathologia* 188, no. 4 (2023): 383–393.

40. F. Messina, G. Santiso, M. Romero, A. Bonifaz, M. Fernandez, and E. Marin, "First Case Report of Tinea Corporis Caused by *Trichophyton indotineae* in Latin America," *Medical Mycology Case Reports* 41 (2023): 48–51.

41. J. M. Villa-Gonzalez, M. Pascual Ares, L. M. López-Soria, M. R. Gonzalez-Hermosa, J. Gardeazabal García, and O. Lasa Elgezua, "Extensive Tinea Corporis Caused by *Trichophyton indotineae*: Report of a Case in Spain," *Journal of the European Academy of Dermatology and Venereology* 38, no. 1 (2024): e22–e23.

42. R. Thakur, P. Kushwaha, and A. S. Kalsi, "Tinea Universalis due to *Trichophyton indotineae* in an Adult Male," *Indian Journal of Medical Microbiology* 46 (2023): 100476.

43. S. Crotti, D. Cruciani, S. Spina, et al., "A Terbinafine Sensitive *Trichophyton indotineae* Strain in Italy: The First Clinical Case of Tinea Corporis and Onychomycosis," *Journal of Fungi* 9, no. 9 (2023): 865.

44. P. Nenoff, S. B. Verma, A. Ebert, et al., "Spread of Terbinafine-Resistant *Trichophyton mentagrophytes* Type VIII (India) in Germany-'The Tip of the Iceberg?'," *Journal of Fungi* 6, no. 4 (2020): 207, https://doi.org/10.3390/jof6040207.

45. J. Brasch, Y. Gräser, V. Beck-Jendroscheck, et al., "'Indian' Strains of *Trichophyton mentagrophytes* With Reduced Itraconazole Susceptibility in Germany," *Journal der Deutschen Dermatologischen Gesellschaft* 19, no. 12 (2021): 1723–1727, https://doi.org/10.1111/ddg.14626.

46. A. Fattahi, F. Shirvani, A. Ayatollahi, et al., "Multidrug-Resistant *Trichophyton mentagrophytes* Genotype VIII in an Iranian Family With Generalized Dermatophytosis: Report of Four Cases and Review of Literature," *International Journal of Dermatology* 60, no. 6 (2021): 686–692, https://doi.org/10.1111/ijd.15226.

47. M. Siopi, I. Efstathiou, K. Theodoropoulos, S. Pournaras, and J. Meletiadis, "Molecular Epidemiology and Antifungal Susceptibility of Trichophyton Isolates in Greece: Emergence of Terbinafine-Resistant *Trichophyton mentagrophytes* Type VIII Locally and Globally," *Journal of Fungi* 7, no. 6 (2021): 419.

48. S. Dellière, B. Joannard, M. Benderdouche, et al., "Emergence of Difficult-To-Treat Tinea Corporis Caused by *Trichophyton mentagrophytes* Complex Isolates, Paris, France," *Emerging Infectious Diseases* 28, no. 1 (2022): 224–228, https://doi.org/10.3201/eid2801.210810.

49. A. Moreno-Sabater, A. C. Normand, A. L. Bidaud, et al., "Terbinafine Resistance in Dermatophytes: A French Multicenter Prospective Study," *Journal of Fungi* 8, no. 3 (2022): 220.

50. C. J. Posso-De Los Rios, E. Tadros, R. C. Summerbell, and J. A. Scott, "Terbinafine Resistant *Trichophyton indotineae* Isolated in Patients With Superficial Dermatophyte Infection in Canadian Patients," *Journal of Cutaneous Medicine and Surgery* 26, no. 4 (2022): 371–376.

51. P. Bortoluzzi, A. Prigitano, A. Sechi, et al., "Report of Terbinafine Resistant Trichophyton spp. in Italy: Clinical Presentations, Molecular Identification, Antifungal Susceptibility Testing and Mutations in the Squalene Epoxidase Gene," *Mycoses* 66, no. 8 (2023): 680–687.

52. S. Jia, X. Long, W. Hu, et al., "The Epidemic of the Multiresistant Dermatophyte *Trichophyton indotineae* has Reached China," *Frontiers in Immunology* 13 (2022): 1113065, https://doi.org/10.3389/fimmu.2022.1113065.

53. G. Russo, L. Toutous Trellu, L. Fontao, and B. Ninet, "Towards an Early Clinical and Biological Resistance Detection in Dermatophytosis: About 2 Cases of *Trichophyton indotineae*," *Journal of Fungi* 9, no. 7 (2023): 733, https://doi.org/10.3390/jof9070733.

54. A. Khurana, A. Agarwal, A. Singh, et al., "Predicting a Therapeutic Cut-Off Serum Level of Itraconazole in Recalcitrant Tinea Corporis and Cruris-A Prospective Trial," *Mycoses* 64, no. 12 (2021): 1480–1488.

55. D. Meena, N. Hazarika, P. Chauhan, and P. Goyal, "Steroid Abuse, Quality of Life, and Various Risk Factors in Dermatophytosis: A Cross-Sectional Observational Study From a Tertiary Care Center in Northern India," *Acta Dermatovenerologica Alpina, Panonica et Adriatica* 31, no. 4 (2022): 135–140.

56. A. Khurana, A. Masih, A. Chowdhary, 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," *Antimicrobial Agents and Chemotherapy* 62, no. 12 (2018): e01038-18, https://doi.org/10.1128/aac.01038-01018.

57. A. S. Caplan, G. C. Todd, Y. Zhu, et al., "Clinical Course, Antifungal Susceptibility, and Genomic Sequencing of *Trichophyton indotineae*," *JAMA Dermatology* 160, no. 7 (2024): 701–709, https://doi.org/10.1001/jamadermatol.2024.1126.

58. T. S. Bui and K. A. Katz, "Resistant *Trichophyton indotineae* Dermatophytosis—An Emerging Pandemic, Now in the US," *JAMA Dermatology* 160, no. 7 (2024): 699–700.

59. W. Xie, X. Kong, H. Zheng, et al., "Rapid Emergence of Recalcitrant Dermatophytosis Caused by a Cluster of Multidrug-Resistant *Trichophyton indotineae* in China," *British Journal of Dermatology* 190, no. 4 (2024): 585–587.

60. G. Song, X. Kong, X. Li, W. Liu, and G. Liang, "Prior Selection of Itraconazole in the Treatment of Recalcitrant *Trichophyton indotineae* Infection: Real-World Results From Retrospective Analysis," *Mycoses* 67, no. 1 (2024): e13663.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.