A Clinico-mycological, Antifungal Drug Sensitivity and Therapeutic Study of Extensive Dermatophytosis in Coastal Andhra Pradesh

Abstract

**Background:** In India, an increased prevalence of chronic, recurrent, and recalcitrant dermatophytosis is being observed. The present study assesses the clinico-mycological profile, antifungal drug sensitivity and therapeutic efficacy of various systemic antifungal drug regimens, in extensive dermatophytosis patients of coastal Andhra Pradesh. **Materials and Methods:** One hundred and fifty clinically diagnosed cases of extensive dermatophytosis affecting more than one body region were enrolled. Skin samples were taken for direct microscopy and fungal culture. Antifungal drug sensitivity testing was done with broth microdilution test. Therapeutic efficacy of systemic antifungal drug regimens was determined by randomly dividing the patients into 5 groups of 30 each.

**Results:** The most common clinical patterns observed were tinea corporis et cruris (62.7%) followed by extensive tinea corporis (11.3%). KOH and culture positivity were seen in 132 (88%) and 84 cases (56%) respectively. *Trichophyton mentagrophytes* was isolated in 78 cases (92.8%) followed by *Microsporum gypseum* in 6 patients (7.1%). The overall mean minimum inhibitory concentration values for itraconazole (0.04 µg/mL) were low when compared to griseofulvin (4.61 µg/mL) and terbinafine (6.9 µg/mL) (*P* < 0.05). Combination of itraconazole and griseofulvin achieved highest clinical and mycological cure rates (93.1%). Among patients receiving single drugs, itraconazole had higher cure rates (71.4%) compared to terbinafine (59.2%) and griseofulvin (53.8%) (*P* < 0.05).

**Conclusion:** *Trichophyton mentagrophytes* has replaced *Trichophyton rubrum* as the predominant species causing dermatophytosis in Andhra Pradesh, presenting with a severe phenotype. Itraconazole was found to be the most effective drug both *in vivo* and *in vitro*. A combination of systemic drugs should be considered in cases of monotherapy failure and in recalcitrant dermatophytosis.

**Keywords:** Antifungal drug sensitivity, clinico-mycological profile, extensive dermatophytosis, therapeutic study

Introduction

Dermatophytosis is a common superficial fungal infection caused by molds belonging to three genera of fungi imperfecti: trichophyton, microsporum, and epidermophyton.[1] Extensive dermatophytosis is characterized by unusually large areas affected or by unusual number of affected sites.[2] In recent years, in India, there is an epidemiological transformation from Trichophyton rubrum being the most common causative organism to trichophyton mentagrophytes acting as the codominant pathogen that may be the cause for increased prevalence of chronic, extensive, and recurrent dermatophytosis.[3,4] Injudicious use of irrational-fixed drug combinations (FDC) containing steroid-antifungal-antibacterial creams, environmental factors, and probably a growing resistance to antifungal drugs may be responsible for this alarming scenario.[5,6]

There is a paucity of published studies from Andhra Pradesh detailing the clinico-mycological aspects and drug sensitivity patterns in extensive dermatophytosis. In this background, the present study was undertaken to assess the clinical features and mycological profile of patients presenting with extensive dermatophytosis in coastal Andhra Pradesh region. Antifungal drug sensitivity testing of commonly available systemic antifungal drugs was carried out to know the drug resistance patterns in the community and the therapeutic efficacy of various systemic antifungal drug regimens (singly and in combinations) was also assessed.

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Materials and Methods

This study was carried out on 150 patients who attended the outpatient department of dermatology at a suburban medical college hospital in north coastal Andhra Pradesh. It was a prospective hospital-based investigative and open-label interventional study carried out over a period of 18 months from January 2018 to June 2019 after being approved by the Institutional Ethics Committee. The sample size was calculated by difference of means formula. To achieve a power of study of 80% and precision alpha of 0.05 with a 95% confidence interval (CI), the estimated total sample size was determined to be 150.

Clinically diagnosed cases of extensive dermatophytic infection affecting more than one region of the body, between the ages of 18 and 70 yrs and not on topical and systemic antifungal medication for the past six weeks were included in the study. Immunocompromised patients including uncontrolled diabetes, HIV infection, patients on treatment with multiple drugs including glucocorticoids for preexisting ailments, pregnant, and lactating women were excluded.

After taking informed consent, details of demographic data, socioeconomic status, and occupation were noted. Thorough clinical history including onset, duration and progression of skin lesions were noted. Details of recurrences, previous treatment and family history were recorded. A detailed dermatological examination was performed taking note of the number and size of the lesions; patients were classified according to the sites of involvement. The specimens for direct microscopy and culture were collected by scraping the active scaly edge of the affected skin lesions, scraping of affected nails, clipping, and epilation of the affected lusterless hair. Direct microscopic examination was done after treatment of an aliquot of the skin scales with 10% potassium hydroxide (KOH) to detect refractile thready septate hyphae. For primary isolation, Sabouraud’s dextrose agar slopes with cycloheximide (0.05 g/L) and chloramphenicol (0.005 g/L) were used, and dermatophyte test medium was used as selective media. Test tubes were incubated at 28°C for 4 weeks before labeling it as negative. Species identification was done by colony morphology and microscopy on lactophenol cotton blue mount.

Antifungal sensitivity testing was done with broth microdilution test according to the Clinical and Laboratory Standard Institute M38-A standards [Figure 1]. Sensitivity testing was carried out for three commonly used antifungals – Itraconazole, Griseofulvin, and Terbinafine. Drug double dilutions ranged from 0.03 to 16 μg/mL with the help of RPMI-1640 medium (HiMedia) and buffered at pH 7. The cultured fungal colonies were used for in vitro sensitivity testing. The slant was flooded with 1 mL sterile saline and the colony was scraped with a sterile loop. The upper homogeneous suspension containing mixture of nongerminated conidial and hyphal fragments was mixed for 15 s with the vortex. Turbidity was measured using a spectrophotometer at 530 nm and adjusted to visually contain standard 1,000,000 cells/mL of fungi counted on Neubauer’s chamber. Stock inoculum suspension was diluted at 1: 50 dilutions in the RPMI-1640 medium. The test was performed in a round-bottomed 96-well microdilution trays. Columns 1–9 were filled with drug dilutions of 100 μg/mL respective antifungal drugs in rows in each well. Column 10 was sterility control with 200 μg/mL of RPMI-1640 medium and Column 11 was used as growth control well without any drug containing 200 μL of pure conidial suspension. In 1–9 wells of serially diluted drugs, conidial suspension of 100 μL was filled and incubated at 30°C for 48–96 h, and visually read to determine minimum inhibitory concentrations (MIC). The growth in each well was compared with drug-free growth control and negative control. MIC endpoint criterion for fungi was the lowest drug concentration showing 90% inhibition of the growth.[6]

To study therapeutic efficacy, all KOH-positive cases were divided randomly using randomization tables provided by a statistician into five groups of 30 each. Group A, B, and C patients were treated with itraconazole 5 mg/kg, griseofulvin 10 mg/kg, and terbinafine 5 mg/kg body weight (BW) per day, respectively. Group D patients were treated with a combination of terbinafine 5 mg/kg and griseofulvin 10mg/kg BW, whereas Group E patients were treated with a combination of itraconazole 5 mg/kg and griseofulvin 10 mg/kg BW. All the systemic antifungals were prescribed daily in two divided doses for a period of six weeks.

Therapeutic efficacy of the above five regimens was determined based on physician assessment during follow up at two weekly intervals during the treatment period. Physician assessment was based on the clinical and mycological cure. Clinical cure was assessed as improvement/resolution in skin lesions; mycological cure was based on absence of fungal elements on KOH examination. Complete hemogram, liver function tests and
renal function tests were done at each follow-up visit during the treatment period. Adverse effects reported by the patient and abnormalities detected in laboratory investigations if any were noted. After completion of treatment, patients were followed up monthly for three months to detect any recurrences.

Quantitative data collected from all patients in each group were tabulated and statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) trial version 25. To test the statistical difference between proportions, Paired t test and Pearson Chi-square test were used, and P value <0.05 was taken as statistically significant.

**Results**

In the present study, 84 (56%) patients were males and 66 (44%) were females with a male to female ratio of 1.3:1. The majority of the dermatophytosis patients belonged to the age group of 18 to 40 years (64%) and the mean age was 24.12 years (SD = 7.13yrs). The duration of the disease was 3–6 months in 31 patients (46.5%), 6–12 months in 34 patients (22.66%), and more than 1 year in 22 patients (14.66%) with a mean disease duration of 5.8 months (SD = 4.41yrs). Past history of similar lesions was recorded in 84 patients (56%); positive family history was elicited in 64 patients (42.66%), out of which 6 patients (9%) had conjugal transmission.

The most common clinical patterns observed were tinea corporis et cruris in 94 patients (62.7%) followed by extensive tinea corporis (involving more than one region of the body) in 17 patients (11.3%) and tinea capitis et faciei in 13 patients (8.7%). Past history of similar lesions was recorded in 84 patients (56%); positive family history was elicited in 64 patients (42.66%), out of which 6 patients (9%) had conjugal transmission.

Assessment of therapeutic efficacy of the 5 treatment regimens showed that patients who received a combination of itraconazole and griseofulvin achieved the highest remission rate [27 out of 29 patients (93.1%); 1 patient lost to follow-up]. Among the groups of patients who received single drugs, patients who were treated with itraconazole attained the highest remission rate [20 out of 27 patients (74.1%); 2 patients lost to follow-up] compared to patients who received terbinafine (59.2%) and griseofulvin (53.8%). The difference in remission rates between all groups were statistically significant (P < 0.05) with Pearson Chi-square value of 13.355. Highest recurrence rate was seen in patients who received griseofulvin (60.8%)

**Table 1: Clinical profile of dermatophytosis**

| Distribution of dermatophytosis over body sites | No. of cases | Percentage |
|-----------------------------------------------|--------------|------------|
| Tinea corporis et cruris                       | 94           | 62.7%      |
| Extensive Tinea corporis                       | 17           | 11.3%      |
| Tinea capitis et faciei                        | 13           | 8.7%       |
| Tinea corporis et manuum                       | 11           | 7.3%       |
| Tinea corporis et pedis                        | 9            | 6%         |
| Tinea cruris et pedis                          | 6            | 4%         |

**Table 2: Mean MIC values of antifungal drugs determined by antifungal drug susceptibility test for the two isolated species**

| Drug                        | Trichophyton mentagrophytes | Microsporum gypseum |
|-----------------------------|------------------------------|---------------------|
|                            | Range (µg/ml)                | Mean (µg/ml)        | Range (µg/ml) | Mean (µg/ml) |
| Itraconazole                | 0.03-0.06                    | 0.04                | 0.03          | 0.03         |
| Griseofulvin                | 0.25-16                      | 4.22                | 2-16          | 9            |
| Terbinafine                 | 0.03-16                      | 7.13                | 0.5-8         | 4.25         |

**Table 3: Overall comparison of MIC values of Itraconazole, Griseofulvin and Terbinafine determined in antifungal susceptibility test using Paired samples t-test**

|                        | Mean    | Std. deviation | Significance |
|------------------------|---------|----------------|--------------|
| Pair 1                 |         |                |              |
| MIC ITR (µg/ml)        | 0.0432  | 0.01504        | P<0.05       |
| MIC GR (µg/ml)         | 4.6100  | 6.47526        |              |
| Pair 2                 |         |                |              |
| MIC ITR (µg/ml)        | 0.0432  | 0.01504        | P<0.05       |
| MIC TER (µg/ml)        | 6.90680 | 7.658104       |              |
| Pair 3                 |         |                |              |
| MIC GR (µg/ml)         | 4.6100  | 6.47526        | P>0.05       |
| MIC TER (µg/ml)        | 6.90680 | 7.658104       |              |

ITR - Itraconazole, GRI - Griseofulvin, TER - Terbinafine
group B patients who were treated with griseofulvin alone [17 out of 26 patients (65.3%); 4 patients lost to follow-up] followed by group C treated with terbinafine alone (13 out of 27 patients [48.1%]; 3 patients lost to follow up). Lowest recurrence rate was seen in group E who received itraconazole and griseofulvin [3 patients (10.3%)]. The difference in recurrence rates between all groups were statistically significant ($P < 0.05$) with Pearson Chi-square value of 25.728 [Table 4].

Adverse effects detected in laboratory tests and reported by patients in all treatment groups were mild, self-limiting and did not lead to cessation of treatment. Headache and photo dermatitis were predominantly reported by patients who received griseofulvin (group B, D, and E).

**Discussion**

In vitro resistance to commonly used systemic antifungals is assumed to be one of the important reasons for increase in the prevalence of dermatophytosis being witnessed in India. Antifungal drug susceptibility testing, especially for dermatophyte strains isolated from extensive, chronic, and recalcitrant cases or those with atypical clinical patterns, provide valuable information regarding the choice of antifungal drugs to be used. Hence, the current study was undertaken to determine the antifungal drug susceptibility pattern and therapeutic efficacy of three commonly used oral antifungal drugs--itraconazole, terbinafine, and griseofulvin, in north coastal Andhra Pradesh region.

A higher prevalence of dermatophytosis was seen in males, in the age group of 18–40 years with a prolonged disease course: 70 patients (46.66%) had a disease duration of 3–6 months and 56 patients (37.22%) reported a disease duration of 6 months and above which was in accordance with the findings of Mahajan et al. and Pathania et al. Of late, chronic dermatophytosis with disease persisting for more than six months to 1 year is being routinely observed, presumably due to inadequate dose or duration of systemic antifungal use, immunosuppressive conditions such as diabetes, HIV/AIDS and unchecked availability of FDC creams which reduce inflammation and pruritus but help in the proliferation of fungus by changing their microenvironment.

Higher prevalence of tinea capitis in adult immunocompetent patients, seen in 13 patients (8.7%) in our study, is a recent phenomenon, extending from tinea lesions of the face or neck (glabrous type of tinea capitis) [Figure 4]. A similar clinical profile with high incidence tinea corporis et cruris and atypical cases of steroid modified tinea have

| Treatment group | Enrolled cases | Lost to follow up | Clinical and mycological cure achieved | Recurrence |
|-----------------|----------------|------------------|---------------------------------------|------------|
| A (ITR)         | 30             | 2                | 20 (71.4%)                            | 5 (17.8%) |
| B (GRI)         | 30             | 4                | 14 (53.8%)                            | 17 (65.3%) |
| C (TER)         | 30             | 3                | 16 (59.2%)                            | 13 (48.1%) |
| D (TER + GRI)   | 30             | 2                | 22 (78.5%)                            | 7 (25%)    |
| E (ITR + GRI)   | 30             | 1                | 27 (93.1%)                            | 3 (10.3%)  |

ITR, itraconazole; GRI, griseofulvin; TER, terbinafine. Clinical and mycological cure achieved-Pearson Chi-square: 13.355; Significance: $P<0.05$. Recurrence-Pearson Chi-square: 25.728; Significance: $P<0.05$
been reported previously by Poojary et al. and Sharma et al. [Figure 5].

KOH examination for fungal hyphae was positive in 132 cases (88%) and culture positivity was seen in 84 patients (56%) with both KOH and culture being positive in 70 cases (46.66%). Out of 84-positive culture cases, T. mentagrophytes were isolated in 78 (92.8%) cases and M. gypseum in 6 cases (7.2%). The dramatic switch from T. rubrum to T. mentagrophytes observed throughout India including Andhra Pradesh, as confirmed by our study, has been highlighted in a recent study done by Nenoff et al. who identified new Indian genotype of Internal Transcribed Spacer (ITS) region type VII using genomic Sanger sequencing of ITS region and translation elongation factor (TEF) 1 alpha gene. Increasing prevalence of T. mentagrophytes in India has also been reported in previous studies by Mahajan et al., Rudramurthy et al., and Singh et al. and is hypothesized to be due to changed ecological conditions, particularly the local immune system and the skin microbiome of the host, secondary to abuse of irrational FDC creams, altered infectivity and virulence of the organisms.

Antifungal susceptibility testing is difficult as it is expensive and standardization of parameters such as inoculum size, incubation temperature, selection of media and percentage of growth inhibition need to be considered. Minimum inhibitory concentration (MIC) of the drug is the lowest concentration of the antifungal drug that substantially inhibits the growth of the organism. In the present study, MIC values of T. mentagrophytes, M. gypseum and the overall MIC values for itraconazole (0.03–0.06, mean MIC: 0.04 µg/mL) were significantly low when compared to griseofulvin (0.25–16 µg/mL, mean MIC: 4.6 µg/mL) and terbinafine (0.03–16 µg/mL, mean MIC: 6.9 µg/mL) (P < 0.05). Similarly, low MIC values with good antifungal susceptibility to itraconazole had been previously reported by Singh et al., Mahajan et al., and Budhiraja et al. In a large multicenter study conducted in India, the upper limit wild-type (in µg/mL) against T. mentagrophytes-interdigitale complex based on MIC95 for terbinafine and griseofulvin were 8 and 64, respectively. High MIC values for terbinafine and griseofulvin were also reported by Shaw et al. (8,32), Rudramurthy et al. (4,64), Pathania et al. (8,128), and Khurana et al. (32,4). Many previous studies have shown that clinical resistance of many strains of T. mentagrophytes to terbinafine could be due to point mutations in the squalene epoxidase target gene, which is a key step in the ergosterol pathway.

Patients who received combination of itraconazole + griseofulvin and terbinafine + griseofulvin showed high cure rates of 93.1% (27/29 patients) and 78.5% (22/28 patients), respectively. These patients also had lower recurrence rates than patients who were treated with single drug. Among patients who received single drugs, patients who were treated with itraconazole
had significantly high cure rates and lower recurrence (71.4%, 17.8%) compared to terbinafine (59.2%, 48.1%) and griseofulvin (53.8%, 65.3%), respectively. The higher efficacy of the combination of systemic drugs compared to monotherapy may be explained by the synergistic action of the drugs on two different targets of fungal cell metabolism. The superiority of itraconazole in achieving clinical and mycological cure when compared to terbinafine and griseofulvin in coastal Andhra Pradesh region is in consonance with observations of Bhatia A et al. and Acharya KM et al.[20,21] Relatively lower efficacy of terbinafine monotherapy, as seen in our study, had been previously reported by Singh S et al.[22] However, use of terbinafine at 5 mg/kg BW in two divided doses was found to be more efficacious than single OD dose of terbinafine 250 mg, in accordance to the results of Singh A et al.[8] In view of the favorable adverse effect profile, in the current epidemic of recurrent and recalcitrant dermatophytosis, a combination of systemic drugs may be administered in routine clinical practice provided that periodic monitoring of hemogram and serum biochemistry profile is carried out. All systemic drugs should be given for a sufficiently long duration of 6-8 weeks to prevent recurrence.

**Limitations**

Antifungal drug susceptibility testing could not be done for all culture-positive cases because of financial and infrastructural constraints. Susceptibility testing for other systemic antifungals such as fluconazole, ketoconazole and voriconazole could not be performed for the same reasons. A combination of itraconazole and terbinafine was not considered as one of the therapeutic regimens in view of their cumulative hepatotoxicity.

**Conclusion**

In coastal Andhra Pradesh, *Trichophyton mentagrophytes* has replaced *Trichophyton rubrum* as the predominant species causing dermatophytosis presenting with a severe phenotype; itraconazole was found to be the most effective drug both *in vivo* and in vitro. A combination of systemic drugs should be considered in case of failure of monotherapy and in recurrent, recalcitrant dermatophytosis.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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