ORIGINAL ARTICLE

Efficacy and safety of voriconazole in the treatment failure cases of Dermatophytosis

Lubna Khondker, MD

Associate Professor, Dept of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

ABSTRACT

Introduction: A large number of patients receiving treatment of dermatophytosis getting no response or partial response to treatment despite completing the therapy in the recommended dosage and duration. Major limitations of conventional antifungals are narrow spectrum of activity and high resistance rate. So, it demands new antifungal drugs.

Objective: To assess the efficacy and safety of voriconazole in the treatment failure cases of dermatophytosis

Methods and Materials: A prospective, clinical trial was conducted with 81 treatment failure cases of dermatophytosis patients attending outpatient department (OPD) of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The patients received 200 mg of voriconazole 2 times per day for 4 weeks, then 200 mg 1 time per day for next 4 weeks and were followed up for clinical improvement and side-effects of drug therapy.

Results: The age of the patients ranged from 18 to 60 years with the mean age of 32.5(SD ± 10.5) years. Among the 81 patients, tinea corporis was seen in 47(58.0%) patients and tinea cruris in 34(42.0%) patients. On the basis of global response, level of improvement was clear in 55(67.9%) patients, good in 25(30.9%) patients and fair in 55(67.9%) patients. Based on mycological efficacy, eradication was achieved in 80(98.8%) patients and persistence was seen in only 1(1.2%) patient. And, based on clinical efficacy, cure was observed in 55(67.9%) patients, improvement in 25(30.9%) patients and failure in 1(1.2%) patients. According to side effects, 12(14.8%) developed side effects and among them disturbance of vision was found in 4(33.2%) cases, followed by perioral stickiness 3(25%) cases respectively.

Conclusion: On the basis of the results, it can be concluded that voriconazole is highly effective and well tolerated by treatment failure cases of dermatophytosis. Further controlled randomized trials involving multiple centres and large sample size should be carried out to draw final conclusion.

KEY WORDS: voriconazole, treatment failure cases of dermatophytosis

INTRODUCTION

Dermatophytosis is a major health burden worldwide and is now increasing day by day.[1] Systemic antifungals are indicated in case of extensive involvement and patients who fail topical therapy. Out of the various systemic antifungals, terbinafine, and itraconazole are commonly prescribed. Griseofulvin and fluconazole are also effective but require long-term treatment.[2,3] Previously it was simple treatable infection, but now treatment unresponsive cases and recurrence with chronicity is a major concern for dermatologists.[4] Increasing incidence of resistance to conventional antifungal therapy has demanded that novel therapies should be introduced. Voriconazole seems to be better drug in fluconazole-terbinafine-resistant dermatophytes.[3-6] Voriconazole, a new molecule of triazole class, has demonstrated *in vitro*

Correspondence: *Dr. Lubna Khondker, Associate Professor, Dept of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Email: lubnaderma@gmail.com*

activity against a broad spectrum of fungi and clinical activity against various fungal pathogen.[7] Voriconazole was approved by the US FDA in May, 2002 and available in oral and intravenous form.[8] Voriconazole selectively inhibits the fungal cytochrome P450-dependent enzyme 14α-sterol demethylase, thereby interrupting an essential step in ergosterol biosynthesis. It ultimately destroys the fluidity and stability of cell membrane and gives antifungal effect.[9,10] British Association of Dermatologists' guidelines for the dermatophytosis management provide upto-date, evidence-based recommendations for voriconazole, as an alternative treatment option in dermatophytosis, considered for cases refractory to the other regimens and in exceptional circumstances. These guidelines have also demonstrated that voriconazole is more potent against dermatophyte isolates than griseofulvin or fluconazole.[11-14] Voriconazole is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[15] Common adverse effects, occurring in between 1 and 10% of people, include disturbance of vision (like blurred vision, photophobia, visual hallucination, bright spots and way lines), peri-oral stickiness, headaches, diarrhea, vomiting, abdominal pain, nausea, rashes, and fever.[16-19] Our research goal was to find out the efficacy and safety of voriconazole in treatment failure cases of Tinea corporis and Tinea cruris which will help us to reduce the treatment cost and sufferings of patients of our country.

METHODS AND MATERIALS

A prospective, clinical trial was conducted at the department of dermatology and venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. About 81 treatment failure cases of dermatophytosis (Tinea corporis and Tinea cruris) who had taken one complete course of oral fluconazole 100 mg per day for 4 weeks, followed by terbinafine 250 mg daily for 4 weeks and did not either respond completely to therapy (judged on the basis of clinical response) or had a recurrence within 1 month of stopping the therapy, were included. Consecuitive type of non-probability sampling technique was followed.
Complete history, general physical and dermatological examinations was done for all enrolled patients. Data was collected by face to face interview and history and physical findings were recorded in a semi structured questionnaire. Baseline investigations included complete blood count (total count, differential count), platelet count, Hb%, ESR, urine analysis, random blood sugar (RBS), serum creatinine and liver function test (SGPT) were done. Identification of dermatophytes was done by KOH microscopical examination and culture. All investigations were done before starting voriconazole drug therapy, 4 weeks after drug therapy and 8 weeks after drug therapy. Finally those patients, who agreed freely to give their informed consent, were selected for the study. Adverse effects of the drugs among all patients were recorded.

INTERVENTION

Patients received 200 mg of voriconazole 2 times per day for 4 weeks, then 200 mg 1 time per day for next 4 weeks. Patients were followed up for clinical improvement and side-effects of therapy after 4 weeks and then after 8 weeks of drug therapy. In each follow up, the patients were evaluated by microscopic examination (10% potassium hydroxide) of a skin scraping from site

of the lesion and culture. Assessment of clinical improvement, fungal lesions and global response evaluations were performed throughout the course of study. Statistical analysis of the results was obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-23).

Main Outcome Variables

1. Clinical efficacy
2. Adverse effects

Outcome measure

Global evaluation responses of the clinical condition compared to baseline were assessed in accordance to the following criteria:

- Clear: 100% remission of clinical signs and symptoms, except for residual manifestations.
- Excellent: 90-99% improvement of clinical signs and symptoms from baseline.
- Good: 50-89% improvement of clinical signs and symptoms from baseline.
- Fair: 25-49% improvement of clinical signs and symptoms from baseline.
- Poor: <25% improvement of clinical signs and symptoms unchanged from baseline.
- Worse: Clinical signs and symptoms deteriorated from baseline.

Clinical efficacy was categorized as

- Cure (disappearance of all baseline signs and symptoms of infection; negative KOH reading in conjunction with a global response as cleared or excellent).
- Improvement (improvement in or partial disappearance).
- Failure (no change or worsening).
- Relapse (improvement or cure followed by reappearance or worsening).

Mycological efficacy was categorized as

- Eradication (negative KOH reading and culture).
- Persistence (positive KOH reading and culture at follow-up).

ETHICAL CONSIDERATION

Prior to the commencement of this study, approval from Institutional Review Board (IRB) was taken. Before enrollment of the patients into the study, the aims and objectives of the study along with its proper application procedures for the therapy, possible therapeutic outcomes and adverse effect associated with the therapy, alternative methods, risks and benefits of this study were explained to the patients in easily understandable local language, so that they could make independent decision about their participation. Finally, the informed written consent was taken from each of the patient.

RESULT

A prospective, clinical trial was conducted with 81 treatment failure cases of patients with dermatophytosis attending outpatient department (OPD) of dermatology and venereology, BSMMU, Dhaka. Figure 1 shows the distribution of the patients on the basis of age group. There were 29(35.8%) patients in the age group of 21-30 years, 22(27.2%) patients in the age group of 31-41 years, 14(17.3%) patients in the age group of 18-20 years, 11(13.6%) patients in the age group of 41-50 years and 5(6.2%) patients in the age group of 51-60 years.

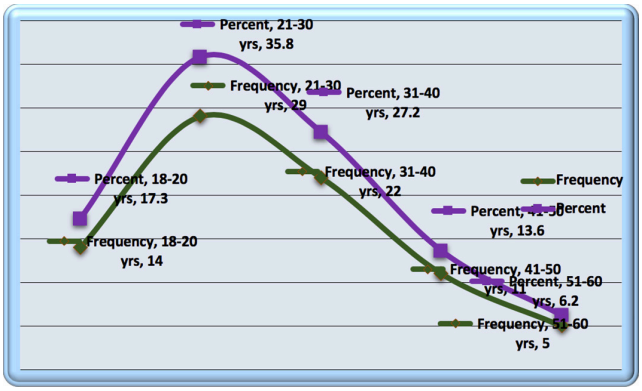

Fig. 1 Distribution of the patients on the basis of age group (n=81).

Figure 2 shows the distribution of the patients by of clinical types of dermatophytosis. Among the 81 patients, tinea corporis in 47(58.0%) patients and tinea cruris in 34(42.0%) patients.

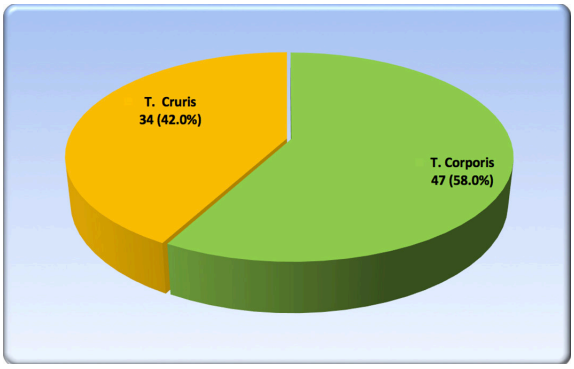

Fig. 2 Distribution of the patients by of clinical types of dermatophytosis (n=81).

Distribution of patients by global response is shown in figure 3. Global response showed that level of improvement as clear in 55(67.9%) patients, good in 25(30.9%) patients and fair in 55(67.9%) patients.

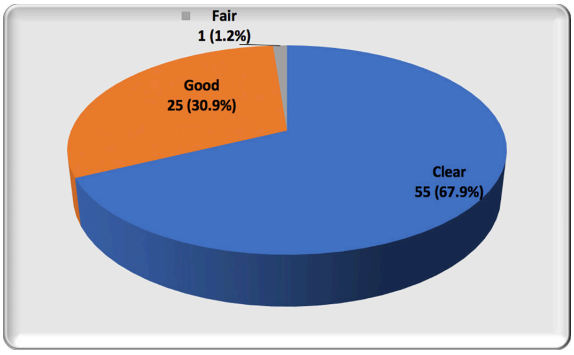

Fig. 3 Distribution of patients by global response (n=81).

Distribution of patients by mycological efficacy is shown in figure 4. Mycological response was eradicated in 80(98.8%) patients and persistent in only 1(1.2%) patient.

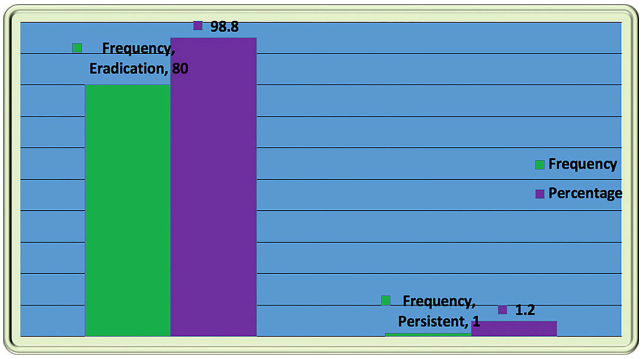

Fig. 4 Distribution of patients by mycological efficacy (n=81).

Distribution of patients by clinical efficacy is shown in figure 5. Clinical efficacy was cure in 55(67.9%) patients, improvement in 25(30.9%) patients and failure in 1(1.2%) patient.

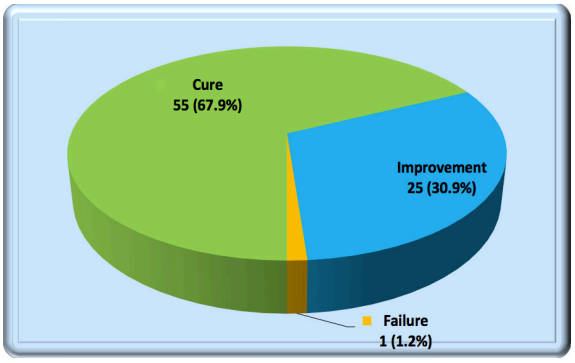

Fig. 5 Distribution of patients by clinical efficacy (n=81).

Table 1 shows the distribution of patient according to side effects associated with voriconazole. About 12(14.8%) developed side effects and among them disturbance of vision was found in 4(33.2%) cases, followed by perioral stickiness 3(25%) cases and diarrhoea, abdominal pain, general weakness, headache and skin rash in 1(8.3%) case for each respectively.

Table 1 Distribution of patients by side effects (n=12)

Side effects	Frequency	Percentage (%)
*Disturbance of vision	4	33.2%
Perioral stickiness	3	25%
Diarrhoea	1	8.3%
Abdominal pain	1	8.3%
General weakness	1	8.3%
Headache	1	8.3%
Skin rash	1	8.3%

*(photophobia, blurred vision, visual hallucination)

DISCUSSION

Patients received voriconazole and were followed up for clinical improvement and side-effects of drug therapy. My study findings were similar to other findings, described as follows. Voriconazole is approved for the treatment of invasive aspergillosis on the basis of the results results of a smaller European open, noncomparative trial. The noncomparative trial enrolled 141 patients, 116 of whom were deemed evaluable; most patients had a hematological malignancy or had received an allogeneic stem cell transplant. The study included patients who had received prior antifungal therapy for aspergillosis as well as those who received voriconazole as primary therapy. The overall rate of complete or partial response was 48%. Of the 60(52%) patients who received primary therapy with voriconazole, 59% had either a complete or a partial response; of the patients who received voriconazole as salvage therapy after failure or intolerance of other antifungal therapy, 38% had either a complete or a partial response. When compared with historical controls, the data from this trial showed that voriconazole therapy had equivalent or improved efficacy for some types of aspergillosis. However, a firm assessment of the role of voriconazole in the treatment of invasive aspergillosis could not be made because of the uncontrolled design of the study and the comparison with outcomes for patients treated 5-10 years earlier.[20]

A multicenter, randomized, double-blind, double-dummy study compared voriconazole with fluconazole for the treatment of esophageal candidiasis in 391 immunocompromised patients, most of whom had AIDS. Patients received either voriconazole 200 mg twice daily, or fluconazole 200 mg daily, for at least 7 days (range, 2-6 weeks) after clinical resolution. There was no difference between the 2 groups with respect to cure, as determined by esophagoscopy (98.3% of patients who received voriconazole and 95.1% of patients who received fluconazole achieved cure).[21] One small open-label, noncomparative study evaluated the efficacy of voriconazole treatment for fluconazole-refractory esophageal candidiasis in 12 patients with AIDS. At day 7, six patients were cured, and the condition of 3 showed marked improvement; 1 other patient was cured after 2 weeks of therapy, and, in 2 patients, there was no response. Thus, voriconazole treatment was efficacious for patients who have esophageal candidiasis, including some who had fluconazole-refractory disease. There are very few available clinical studies with regard to the treatment of other forms of candidiasis.[22]

Voriconazole is generally well tolerated. The most common side effect-one not previously noted with other azoles-is a reversible disturbance of vision (photopsia). This occurs in 30% of patients but rarely leads to discontinuation of the drug. Visual disturbances include altered color discrimination, blurred vision, the appear-

ance of bright spots and wavy lines, and photophobia. Symptoms tend to occur during the first week of therapy and decrease or disappear in spite of continued therapy in most patients. Patients whose therapy is initiated in an outpatient setting should be cautioned that driving may be hazardous because of the risk of visual disturbances. The visual effects are associated with changes in electroretinogram tracings, which revert to normal when treatment with the drug is stopped; no permanent damage to the retina has been noted.[23,24]

Skin rashes are the second most common adverse effect noted with voriconazole therapy. Most of these are mild and constitute no major problem. However, severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in a very small number of patients. Patients should be warned to avoid exposure to direct sunlight, because photosensitivity reactions can occur. Five patients who developed facial erythema and cheilitis have been described; 1 of these patients also developed lesions similar to those characteristic of discoid lupus erythematosus. All of these effects disappeared after voriconazole treatment was stopped, but a direct causal relationship was not clear for all 5 patients.[25]

Elevations in hepatic enzyme levels occur with voriconazole therapy, as they do with other azoles. The usual pattern described has been elevations in the serum levels of alanine aminotransferase and aspartate aminotransferase, but elevations in alkaline phosphatase levels have also been noted. Although most patients have asymptomatic elevation of hepatic enzyme levels, several patients with severe life-threatening hepatitis have been described. The risk of developing hepatitis appears to increase with increased serum voriconazole levels and resolves with discontinuation of treatment with the drug. Patients receiving voriconazole should have liver function tests performed prior to therapy, within the first 2 weeks after the initiation of therapy, and then every 2-4 weeks throughout therapy.[20]

Other less commonly noted side effects include headache, nausea and vomiting, diarrhea, abdominal pain, and visual hallucinations. Visual hallucinations occurred at a rate of 5% in one clinical trial and clearly differed from photopsia.[24]

CONCLUSION

On the basis of the results presented, it can be concluded that voriconazole is highly effective and well tolerated by patients in the treatment failure cases of dermatophytoses. Although, a few patients developed minor adverse effects. But, all were diminished within one week and no patient have to discontinue the drug during study period. Further controlled randomized trial involving multicentre and large sample size should be carried out to draw final conclusion.

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