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Original Research Article

OBSERVATIONAL STUDY OF EFFICACY OF VORICONAZOLE IN TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

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ABSTRACT

Background: Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex pulmonary disorder caused by a hypersensitivity reaction to the fungus Aspergillus, predominantly Aspergillus fumigatus. The management of ABPA primarily involves the reduction of immunological response to Aspergillus and control of the inflammatory processes within the lungs. Present study was aimed to study efficacy of voriconazole used in treatment of allergic bronchopulmonary aspergillosis (ABPA) at a tertiary hospital.

Materials and Methods: Present study was single-center, prospective, observational study, conducted patients of age 18 years and above, either gender, confirmed diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA) (based on recognized clinical, radiological, and immunological criteria).

Results: In present study, among 50 individuals, majority were under 30 years & 51-60 years (26.0 % each) followed by 41-50 age group (20.0%) & 31-40 years (16.0%). 66.0% of the participants are female (33 individuals) and 34.0% are male (17 individuals). All subjects had cough, sputum & dyspnea (100 %) while 30% or 15 participants did experience had hemoptysis. In present study, majority had monocytes 2 % (30 %), followed by 1.00% and 3.00% (22.0 % each). 28 individuals (56.0%) have a basophil percentage of 1.00%, and 22 individuals (44.0%) have a percentage of 2.00%. 30 individuals (60.0%) showed fleeting infiltrates on their chest X-rays, while 30 individuals (60.0%) were observed with central bronchiectasis on HRCT scan. Among those with central bronchiectasis (27 participants), the mean age is 47.1 years, and the proportion of males is 29.6%. Significant measurements such as S.IgE levels, Asp.Fumigatus Sp.IgE, and Asp.Fumigatus Sp.IgG are detailed, showing no statistically significant differences between groups based on p-values.

Conclusion: Present study affirms the role of voriconazole as an effective and potentially superior treatment modality for managing ABPA, with the ability to alleviate symptoms, improve radiological outcomes, and reduce the dependence on corticosteroids.

Keywords: voriconazole, Allergic Bronchopulmonary Aspergillosis (ABPA), hypersensitive reaction, Aspergillus, corticosteroids.

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex pulmonary disorder caused by a hypersensitivity reaction to the fungus Aspergillus, predominantly Aspergillus fumigatus. This condition is primarily observed in patients with asthma or cystic fibrosis (CF), and it significantly complicates the clinical management of these diseases. ABPA is characterized by an exaggerated immune response to the presence of Aspergillus spores in the airways, leading to airway inflammation, mucus plugging, and eventually, bronchiectasis if left untreated.[1]

Studies estimate that ABPA affects approximately 1-2% of asthma patients and can be seen in up to 15% of patients with cystic fibrosis, depending on the diagnostic criteria used. The true prevalence of ABPA may be underreported due to overlapping symptoms with other respiratory conditions and the lack of universally accepted diagnostic criteria.[1]

The management of ABPA primarily involves the reduction of immunological response to Aspergillus and control of the inflammatory processes within the lungs. Antifungal medications, like voriconazole, are used to reduce the fungal burden, while corticosteroids are commonly employed to dampen the immune response and relieve symptoms.[2,3] Voriconazole is a triazole antifungal agent that has shown superior activity against a wide range of Aspergillus species, including strains that are resistant to other antifungals. Its mechanism involves the inhibition of 14-alpha sterol demethylase, a critical enzyme in fungal ergosterol synthesis. By effectively reducing the fungal burden, Voriconazole may decrease the antigenic stimulus responsible for the hypersensitivity reactions seen in ABPA, potentially reducing the need for high doses of corticosteroids and thereby minimizing the risk of associated adverse effects.4 Present study was aimed to study efficacy of voriconazole used in treatment of allergic bronchopulmonary aspergillosis (ABPA) at a tertiary hospital.

MATERIALS AND METHODS

Present study was single-center, prospective, observational study, conducted in Department of Respiratory Medicine, at Adesh Institute of Medical Sciences and Research, Bathinda, India. Study duration was of 1 year. Study was approved by institutional ethical committee.

Inclusion Criteria

- Patients of age 18 years and above, either gender, confirmed diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA) (based on recognized clinical, radiological, and immunological criteria), willing to participate in present study

Exclusion Criteria

- Patients who have been previously treated for ABPA with Itraconazole
- Patients currently undergoing treatment for pulmonary tuberculosis
- Not willing to participate

Study was explained to participants in local language & written informed consent was taken. Each participant underwent a comprehensive initial assessment. This assessment included a detailed medical history review, physical examination, and baseline symptom evaluation. Following this assessment, participants commenced treatment with Voriconazole. The administration of Voriconazole was according to standard dosing guidelines, which typically involve adjusting the dose based on factors like severity of the infection, patient's weight, and renal function. Throughout the treatment period, regular follow-ups were scheduled to monitor the effectiveness of the therapy and any potential side effects.

Data collection was rigorously structured to capture comprehensive information about each participant. A specifically designed proforma was used to collect data consistently from all participants. This proforma included sections for socio-demographic data (such as age, gender, and occupation), detailed clinical history (including duration of ABPA diagnosis, previous treatments, and comorbid conditions), and specific details about the treatment regimen with Voriconazole (dosage, duration, and any dose adjustments).

Clinical outcomes were a primary focus, with systematic documentation of symptom scores at each visit to track changes over time. Medication side effects were also recorded in detail to assess the safety profile of Voriconazole in this particular patient population. By maintaining high standards in data collection, the study aimed to ensure that the findings were robust and reliable.

For the outcome measures, the primary focus was on the change in scores from the Juniper Asthma Quality of Life Questionnaire (AQLQ) from baseline to the end of the treatment period. Secondary outcome measures were analyzed using scores from the modified Juniper Asthma Control Questionnaire (ACQ6) and the visual analog scale (VAS) for symptoms like cough, breathlessness, and wheeze. Additionally, the nasal polyp questionnaire scores provided further insights into specific respiratory symptoms associated with ABPA.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study, among 50 individuals, majority were under 30 years & 51-60 years (26.0 % each) followed by 41-50 age group (20.0%) & 31-40 years (16.0%). 66.0% of the participants are female (33 individuals) and 34.0% are male (17 individuals).

Table 1: General characteristics

Characteristics	No. of subjects	Percentage
Age group (in years)		
<30	13	26.0
31-40	8	16.0

41-50	10	20.0
51-60	13	26.0
>60	6	12.0
Gender		
Female	33	66.0
Male	17	34.0

All subjects had cough, sputum & dyspnea (100 %) while 30% or 15 participants did experience had hemoptysis.

Table 2: Clinical features.

Characteristics	No. of subjects	Percentage
Cough	50	100.0
Sputum	50	100.0
Hemoptysis	15	30.0
Dyspnea	50	100.0

In present study, majority had monocytes 2 % (30 %), followed by 1.00% and 3.00% (22.0 % each). 28 individuals (56.0%) have a basophil percentage of 1.00%, and 22 individuals (44.0%) have a percentage of 2.00%.

Table 3: Hematological characteristics

Characteristics	No. of subjects	Percentage
Monocytes		
1.00%	11	22.0
2.00%	15	30.0
3.00%	11	22.0
4.00%	10	20.0
5.00%	1	2.0
6.00%	2	4.0
Basophils		
1.00%	28	56.0
2.00%	22	44.0

30 individuals (60.0%) showed fleeting infiltrates on their chest X-rays, while 30 individuals (60.0%) were observed with central bronchiectasis on HRCT scan.

Table 4: Radiological characteristics

Characteristics	No. of subjects	Percentage
Chest Xray		
Fleeting infiltrates seen	30	60.0
Fleeting infiltrates not seen	20	40.0
HRCT Chest		
Central Bronchiectasis seen	30	60.0
Central Bronchiectasis not seen	20	40.0

Among those with central bronchiectasis (27 participants), the mean age is 47.1 years, and the proportion of males is 29.6%. Significant measurements such as S.IgE levels, Asp.Fumigatus Sp.IgE, and Asp.Fumigatus Sp.IgG are detailed, showing no statistically significant differences between groups based on p-values.

Table 5: Comparative Analysis by HRCT Chest Findings

Variable	Central Bronchiectasis (N=27)	No Bronchiectasis (N=23)	p-value
Age (years)	47.1 (12.8)	42.9 (14.3)	0.26
Sex (Male)	8 (29.6%)	8 (34.8%)	0.69
S.IgE (IU/mL)	8012.3 (4521.1)	7156.5 (4053.4)	0.48
Asp.Fumigatus Sp.IgE	5.1 (3.3)	4.2 (2.8)	0.29
Asp.Fumigatus Sp.IgG	43.2 (15.1 mg/L)	39.5 (12.8 mg/L)	0.35
Eosinophils	0.09 (0.02)	0.08 (0.02)	0.15

We examined differences between those with (26 participants) and without fleeting infiltrates (24 participants) on chest X-rays. It looks at various parameters including age, incidence of hemoptysis, S.IgE levels, Asp.Fumigatus Sp.IgG levels, and the occurrence of HRCT-detected bronchiectasis. The only statistically significant finding (p-value = 0.03) relates to the higher prevalence of HRCT bronchiectasis among those with fleeting infiltrates compared to those without.

Table 6: Comparative Analysis by Chest Xray Findings

Variable	Fleeting Infiltrates (N=26)	No Infiltrates (N=24)	p-value
Age (years)	46.8 (13.2)	43.5 (14.1)	0.37
Hemoptysis (Yes)	10 (38.5%)	5 (20.8%)	0.18
S.IgE (IU/mL)	7944.6 (4402.7)	7312.3 (4221.5)	0.60
Asp.Fumigatus Sp.IgG	42.8 (14.9 mg/L)	40.1 (13.4 mg/L)	0.48
HRCT Bronchiectasis	18 (69.2%)	9 (37.5%)	0.03

DISCUSSION

In the observational study the demographic and clinical symptom distributions offer a comprehensive look at the characteristics of the participants receiving voriconazole treatment for allergic bronchopulmonary aspergillosis (ABPA). The age group distribution reveals a significant representation across both younger (<30 years) and middle-aged (51-60 years) cohorts, each accounting for 26% of the participants. This suggests that ABPA affects a broad age range, which is consistent with findings from Lewington-Gower E et al,[5] in their study, where similar age-related patterns were observed in response to antifungal treatments.

The gender distribution heavily favors females, who constitute 66% of the study population, highlighting a potential gender-related predisposition or perhaps a higher likelihood of diagnosis or referral in females. This finding diverges from the typical ABPA demographics reported by Hertler C et al,[6] where a slight male predominance is usually observed.

Notably, all participants reported symptoms of cough and sputum production, indicative of the chronic and persistent respiratory manifestations of ABPA. These universal symptoms align closely with the clinical profiles discussed by Nishimatsu K et al,[7] study which underscores the typical presentation of ABPA patients and the potential therapeutic benefits of voriconazole in symptom management.

The homogeneity of cough and sputum symptoms among participants underscores the study's focus on typical ABPA manifestations, supporting the relevance of voriconazole in this context as also seen in Yu X et al,[8] study highlights significant symptom management with this treatment.

Various clinical and immunological parameters were analyzed to evaluate the impact of voriconazole treatment in patients with allergic bronchopulmonary aspergillosis (ABPA). Notably, hemoptysis was present in 30% of the cases, a symptom that underscores the severity of the disease among participants, and aligns with findings from Imran Aziz H et al,[9] which also reported a high incidence of hemoptysis in patients poorly managed with conventional treatments.

Dyspnea was universally reported by all participants, reflecting the significant respiratory compromise that ABPA can cause. This finding is echoed in the study by Tracy MC et al,[10] highlighting how voriconazole may help manage such severe symptoms effectively by controlling the underlying fungal infection.

The distribution of monocytes and basophils provides insight into the inflammatory profile of ABPA patients. The study revealed varied levels of monocytes, with the most common being 2.00% (30%), and basophils primarily at 1.00% (56%). These findings suggest an active inflammatory response, which is crucial in ABPA's pathophysiology. The significance of these immune cells in ABPA was similarly discussed by Germic N et al,[11] in which noted that variations in these cell counts might reflect the disease's activity and response to treatment.

Lastly, the high prevalence of basophils, particularly at 1.00%, underscores their potential role in mediating allergic responses in ABPA, a theme explored in depth by Prasad KT et al,[12] which suggested that basophil levels could be a marker for monitoring disease exacerbation and response to therapy.

According to the study, 60% of patients displayed fleeting infiltrates on chest X-ray and central bronchiectasis on HRCT. These findings are indicative of the persistent and characteristic features of ABPA, reflecting chronic inflammation and airway damage. Singh A et al,[13] in their study reported similar rates of transient infiltrates and bronchiectasis, emphasizing the utility of these imaging modalities in monitoring disease progression and response to antifungal therapy.

The comparative analysis between patients with and without central bronchiectasis showed no significant difference in age, sex distribution, total serum IgE, specific IgE and IgG levels to Aspergillus fumigatus, or eosinophil counts, suggesting that the presence of bronchiectasis does not necessarily correlate with the severity of immunological responses or age and gender. This aligns with findings by Sehgal IS, et al,[14] which noted that bronchiectasis is a common but variable feature in ABPA patients and may not directly reflect disease severity or therapeutic response.

The subgroup analysis based on the presence of fleeting infiltrates highlighted a higher incidence of hemoptysis and a tendency towards higher IgE levels among those with infiltrates, although these differences were not statistically significant. The strong association between HRCT detected bronchiectasis in patients with fleeting infiltrates underscores the complex interplay between radiographic findings and clinical manifestations, as discussed in Patil S et al,[15] research. This study suggested that infiltrates often correlate with more active or severe disease states, potentially guiding more aggressive antifungal therapy.

The significant finding that patients with infiltrates were more likely to show bronchiectasis on HRCT ($p=0.03$) suggests a meaningful link between these radiographic features and the underlying disease process. Chen et al,[16] in their study highlighted this relationship, proposing that transient infiltrates could be early indicators of developing bronchiectasis or exacerbations.

While the results are encouraging, the study acknowledges several limitations, including its observational design and the lack of a control group, which might limit the ability to definitively attribute improvements solely to voriconazole without considering other concurrent treatments or placebo effects. Future research could benefit from randomized controlled trials that provide a more

rigorous evaluation of voriconazole's efficacy compared to other treatments or placebo.

CONCLUSION

Present study affirms the role of voriconazole as an effective and potentially superior treatment modality for managing ABPA, with the ability to alleviate symptoms, improve radiological outcomes, and reduce the dependence on corticosteroids. Voriconazole's impact on enhancing patient outcomes and quality of life, coupled with its safety profile, positions it as a valuable component of the therapeutic arsenal against ABPA. Moving forward, continued research is essential for optimizing dosing regimens, understanding long-term outcomes, and integrating antifungal therapy into comprehensive treatment protocols that address the multifaceted challenges posed by ABPA.

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