Original Article

A Comparative Study between only oral Corticosteroid (OCS) versus a combination of Oral corticosteroids and antifungal therapy in acute Allergic Bronchopulmonary aspergillosis (ABPA)

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Abstract

Background: Allergic bronchopulmonary aspergillosis, a well-known entity in today's era, is an idiopathic inflammatory condition characterized by an allergic inflammatory reaction to Aspergillus fumigates colonization of the airways. Both OCS and antifungal therapy have been found to be effective in the treatment of ABPA, but the efficacy of combining the two groups has recently attracted attention. In this article, we report the findings of comparing the effectiveness of OCS in combination with antifungal medications to OCS monotherapy in ABPA. **Material and Methods:** All the patients with ABPA attending the Respiratory Medicine OPD were enrolled. Clinical History, Spirometry, absolute eosinophil count, serum IgE (both total and specific against Aspergillus fumigatus, and radiographic evidence were analyzed to arrive at the diagnosis of ABPA. Patients enrolled were randomized to either of the arms – steroid only vs steroid and antifungal combination arm. Patients were followed up for a period of 1 year and response and relapse were recorded. **Results:** After meeting inclusion and exclusion criteria, 64 patients were randomized either to receive steroid monotherapy or a combination of steroids and antifungals. Both arms experienced a statistically significant decrease in clinical symptoms as well as serum total IgE during the 8-week assessment. None of the arms had any statistically significant adverse drug reaction leading to the termination of therapy. The combination therapy arm resulted in less number of exacerbations, although this data was not statistically significant. Another additional finding seen was that smokers had a higher mean level of total serum IgE than non-smokers. Discussion: It has been mentioned in the literature that azoles reduce the fungal colonization burden of the airway and reduce antigenic stimulation resulting in decreased inflammation, disease severity, and progression. This evidence is supported by this RCT showing addition of itraconazole to the standard oral steroids results in an increased fall in serum total IgE as compared to single oral steroids treatment along with improvement in symptoms and decreasing the risk of future exacerbation in a follow-up period of 1 year. **Conclusion:** Adding azoles to oral steroids in ABPA improves the outcome of treatment in terms of symptomatology and future risk of exacerbations.

Keywords: Aspergillosis, Steroids, Itraconazole.

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Introduction

Hinson et al., in 1952, published the first report on ABPA and defined it as an idiopathic lung inflammation secondary to an allergic inflammatory response to the colonization of the Aspergillusfumigatus in the airways.[1] Literature shows that around 7-14% of poorly controlled asthmatics met the diagnostic criteria of ABPA.[2] The most common presentation includes difficult-to-control asthma, and other non-specific complaints of dyspnea, wheezing, cough, expectorating brown-colored mucus plugs, malaise, fever, and hemoptysis.[3] Though historically monotherapy with steroids was the benchmark for the treatment of ABPA, until a few decades ago, the development of oral antifungal agents bought new hope.[4] Both oral steroids and triazoles have been proven to be successful in studies on monotherapy for the treatment of ABPA, albeit more adverse medication reactions have been recorded with oral corticosteroids than with azoles. A combination of both classes of drugs (Oral corticosteroids and antifungals) is the need of the hour to be studied. Here, we report the findings of an RCT assessing the effectiveness of OCS in combination with antifungal therapy in ABPA.

Materials and Methods

We enrolled all the patients with a confirmed diagnosis of ABPA attending the Respiratory Medicine OPD. For labeling them as

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ABPA, clinical history, lung functions, absolute eosinophil count (AEC > 1000 µL−1), total IgE (>1000 IU/ml), Specific IgE against aspergillus Fumigatus (>0.35 KuA/L), and radiological Findings consistent with ABPA (based on ISHAM criteria) were analyzed.[5] Approval was taken from ethics committee of the institute and informed consent was taken from all enrolled patients.

The following protocol was followed in treating the study subjects. The allocations were put in sealed, opaque envelopes, and the computer-generated randomization sequence was used. The study was not blinded. The oral prednisolone was administered to subjects in the prednisolone monotherapy group sequentially at 0.5 mg/kg/day in OD dosing for 4 weeks, followed by 0.25 mg/kg/day for 4 weeks. It was subsequently tapered by 5 mg every 2 weeks and terminated at the completion of 4 months. In a similar manner, subjects in the prednisolone-itraconazole combination group received oral prednisolone and itraconazole was given at 200 mg twice daily for 6 months. Inhaled corticosteroids (ICS), long-acting beta 2-agonists, leukotriene receptor antagonists, and antihistamines were continued as prescribed by the treating physicians in both groups.

Patients less than 18 years of age, with any prior history of anti-tubercular treatment, any structural lung damage, any recent history of steroid intake (within the last 1 month), pregnancy/ lactation, or unable to take antifungals due to deranged Liver function tests were excluded from the study.

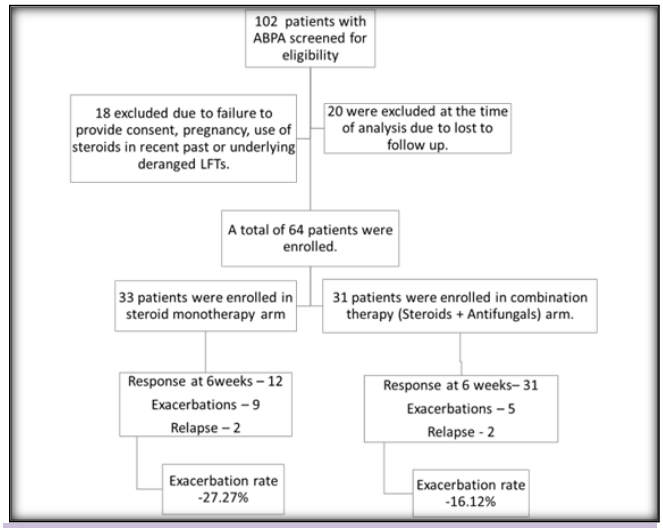

Figure 1: Flow Chart of Study

Statistical Analysis: It was a single-centered, hospital-based follow-up study. Study population descriptive analytics is presented as the "mean ± standard deviations" for continuous variables and percentage frequencies for categorical variables. The Chi-square test was used to compare the discrete variables and the student's t-test was for comparing means in two arms. A two-tailed probability and an alpha level of 0.05 were used to determine statistical significance.

Outcomes: Relapse and exacerbation rates within 12 months of treatment start, response and percentage decrease in serum total IgE at 6 weeks of treatment, and treatment-emergent adverse events (TEAEs) are the outcomes measured.

Definitions: The response was defined as improvement in clinical symptoms (including all symptoms that were present at the time of presentation) of all patients compared to the baseline and a minimum 25% or more fall in total IgE compared to baseline values.

The exacerbation/relapse was labeled among study participants when there is almost a doubling of baseline IgE levels irrespective of clinical or radiological worsening.

Results

A total of 102 patients were screened, out of which 18 were excluded due to various reasons - not giving consent, underlying deranged LFTs, Pregnancy, or use of steroids in the past 1 month. A number of 20 patients failed to follow up, so were excluded at the time of analysis. So, a final number of 64 patients were enrolled and randomized either to receive steroid monotherapy or a combination of steroids and antifungals. [Figure 1]

The mean age (standard deviation) of the patients involved in prednisolone arm and combination therapy of antifungal agent and oral steroids was 33.4(16.07) and 34.9(14.6) years respectively. There were 72.7 % (n=24) and 45.1% (n=14) of males in prednisolone and combination therapy arms respectively. The most common symptom at the time of presentation was productive cough (100%) followed by dyspnea (93.7%), hemoptysis (21.8%), and fever (14%). Among the patients studied, 15.6% (n=10) were either current or former smokers.

The mean value of baseline serum total IgE in steroid-only and combination arms was 6100 and 6189 IU/ml (p-value=0.165). The mean value (S.D.) of specific IgE levels in the steroid-only arm was 7.53 (16) and in the combination (steroid & antifungal) arm was 14.4 (16.1) in the present study (p-value = 0.049).

The mean level of specific IgE against Aspergillusfumigatus was 11.84 in smokers and 12.25 in non-smokers (p-value=0.952). Fall in serum total IgE in both arms at 8 weeks, when compared to baseline was statistically significantly declined [Table no. 1].

The first outcome measured was the proportion of subjects experiencing exacerbation at 1 year. Although the steroid-only arm had a slightly higher percentage of subjects experiencing exacerbation (27.27%) compared to the steroid and antifungal combination arm (16.12%), however the data was statistically non-significant (p=0.281). The second outcome measured was the response after 6 weeks of treatment. The steroid and antifungal combination arm had a significantly higher response rate (100%), according to the definition of response as mentioned in the methodology, compared to the steroid-only arm (69.7%; p=0.0009).

The third outcome measured was the mean decline in Serum total IgE after 6 weeks of treatment. The steroid and antifungal combination arm had a significantly higher mean decline in Serum total IgE (55.61%) compared to the steroid-only arm (28.06%; p<0.001).

Similarly, at 8 weeks, the mean decline in serum total IgE in the oral steroids arm vs steroid and antifungal arm (36.21% versus 69.64%). [Table 2].

One of the extra findings seen in our study is that the mean level of total serum IgE was higher in smokers (9773.4) as compared

to non-smokers (4554.04) and this data was statistically significant (p-value = 0.007).

Finally, adverse events were measured, including weight gain, hyperglycemia, hypertension, cushingoid facies, and deranged liver function tests. No statistically significant differences seen in the occurrence of the adverse events between the two treatment arms. However, a slightly higher percentage was seen in the steroid and antifungal combination arm experiencing hyperglycemia (45.1% vs. 30.3%) and deranged LFTs (6.4% vs. 0%).

Discussion

Allergic Broncho Pulmonary Aspergillosis an allergic inflammation in response to fungal colonization, especially by aspergillus in the airways. All past studies are evident towards oral corticosteroids being the cornerstone for treating ABPA. Among antifungals, we have azoles including itraconazole and voriconazole in the treatment of ABPA. Few studies have been conducted on the use and efficacy of posaconazole,[6] and Omalizumab,[7] for ABPA treatment. However, there are no well-defined guidelines describing the exact duration of antifungals. In a 131-patients RCT comparing the effectiveness of steroids vs. Itraconazole in patients with acute ABPA, it was shown that the overall response was substantially greater in the prednisolone group (100%) as compared with the itraconazole group (88%).[8] Other RCTs also showed beneficial effects of antifungals in the improvement of symptoms, lung function improvement, radiology, and Serum IgE levels.[2,9] In a recent RCT study by Agarwal R et al,[10] prednisolone-itraconazole combination therapy and prednisolone monotherapy both demonstrated a drop in ABPA exacerbations at one year. Although this data was not statistically significant but they met their primary assumptions. Likewise, the proportion of patients experiencing exacerbation in our study at 1 year was comparatively lower in the combination arm, although this data was also not statistically significant.

For monitoring ABPA patients, Serum total IgE has been used in monitoring the response to the treatment, in contrary, Specific IgE - Aspergillusfumigatus has restricted utility as evidenced by studies in the past.[11] ABPA is treatable with timely diagnosis and appropriate therapy though it is also troublesome as it usually recurs, causing acute or subacute exacerbations, and therefore needs long-term vigilance.

Additional finding of higher levels of serum total IgE in smokers in our study was similar to the previous studies done.[12,13] Glucocorticoids taken orally reduce pulmonary inflammation, whiletriazolesaid in lowering the fungal load in the airways.[14,15] The clinical response and decline in IgEafter 6 weeks in both the groups in our study demonstrated potent anti-inflammatory effect of glucocorticoids and an additional boost in efficacy with the addition of itraconazole. This hypothesis can explain the findings of our study and is supported by previous studies in the literature.[10] This can also be explained by the hypothesis that itraconazole in the combination arm is a cytochrome 3A4 (CYP3A4) inhibitor and hence, increases the levels of inhaled steroids along with the decrease in fungal load in airways.[16] The fall in serum total IgE at 6 weeks was statistically significant in the combination arm (100%) compared to steroid monotherapy arm (69.7%). At 6 weeks, the mean reduction in serum total IgE was more in combination therapy (55.61% vs 28.06%) and this data was statistically significant.

Among adverse drug reactions (ADRs), the proportion of ADR events related to treatment experienced in both groups was almost similar, except for deranged Liver functions which were more commonly seen in the combination arm. However, there was no withdrawal from the study due to ADRs.

Conclusion

Overall, the data suggest that both treatment options can be effective in reducing the risk of exacerbation and improving symptoms in patients with elevated Serum Total IgE levels. However, the steroid and antifungal combination treatment seems to be more effective in producing a response and reducing Serum total IgE levels compared to steroid-only treatment, potentially at the expense of some additional potential adverse effects. Ultimately, treatment decisions should be tailored to individual patient needs and based on careful consideration of the potential benefits and risks of each approach. We found and added to the literature that adding antifungal medications to oral steroids led toa decline in the number of ABPA exacerbations at 1 year compared to steroid monotherapy. Adding azoles led to an improved response in terms of symptoms and reduction in serum total IgE. Additional studies are needed to add strength to these findings and determine the efficacy of these treatments over the long haul.

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Conflicts of interest

There are no conflicts of interest.

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