Retrospective audit of outcomes following Allergic Bronchopulmonary Aspergillosis (ABPA) treatment in paediatric patients with Cystic Fibrosis

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INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is caused by an allergy mediated response to the colonisation of opportunistic fungal species *Aspergillus* in the respiratory tract.

Aspergillus is the third most common organism found in Australian Cystic Fibrosis (CF) patients after *P. aeruginosa* and *S. aureus* [1] with the fumigatus species being the most common causative agent of ABPA [2]. These fungal spores trigger the release of pro-inflammatory cytokines which can result in pulmonary infiltrates, impaired mucocilliary clearance and obstructed airways.

TABLE 1: FAST FACTS ON ABPA

Prevalence in CF Population	Up to 15% [1]
Age of Onset	6 years and older
Causative Organism	Aspergillus
Risk Factors	Poorly established, has been linked with Inhaled Dornase and Inhaled Corticosteroids [3]
Dominant clinical symptom(s)	Wheeze

Combination therapy of glucocorticoids and azole antifungals for treatment of ABPA from diagnosis, is thought to be superior to delayed and/or symptomatic treatment for ABPA [4, 5, 6]. Intravenous (IV) methylprednisolone is preferred to oral prednisolone as it is thought to reduce systemic complications and aids compliance.

AIM

To evaluate safety and efficacy of IV methylprednisolone in combination with itraconazole for the treatment of ABPA, in a paediatric CF cohort.

METHODS

PATIENT IDENTIFICATION

Patients with CF dispensed itraconazole from the hospital pharmacy from 1/6/2017 to 1/12/2020. A total of 24 patients were identified.

PATIENT INCLUSION & EXCLUSION CRITERIA

Only 10 patients of the 24 identified patients were included in the audit based on the following criteria:

Inclusion Criteria: CF patients were diagnosed with ABPA if they had the following:

- ✓ **Clinical features** of ABPA (i.e. wheezing)
- ✓ Elevated total Immunoglobulin E (IgE) **>500kU/L or >2SD for age**
- ✓ Positive skin prick tests or Radioallergosorbent Test **(RAST) positive** for *Aspergillus fumigatus* (AF)
- ✓ Positive Aspergillus specific **IgE**
- ✓ **Radiographic changes** from baseline
- ✓ **Eosinophils** >400m^3
- ✓ Positive **sputum culture** of AF

Exclusion criteria: Of the above;

- ✓ If they were using itraconazole for another indication
- ✓ If they had started on treatment prior to 1/6/2017
- ✓ If they had an identified drug interaction with itraconazole (i.e. Rifampicin)
- ✓ If the patient/family was known to be non-compliant
- ✓ If this was not a first diagnosis of ABPA

TABLE 2: PATIENT CHARACTERISTICS

Mean Patient Age	12.07 years (SD 2.47)
Assigned Female at Birth	70%
Most Common CF Genotype	Homozygous F508del (60%)
Patients with Wheezing	30%
Concurrent Pseudomonas Infection	0%

THE TREATMENT- As per the Women's and Children's Hospital (WCH) protocol;

Glucocorticoid

- Nine patients were prescribed **IV methylprednisolone monthly, at a dose of 20mg/kg.** One patient was prescribed IV methylprednisolone at 10mg/kg.
- Six patients (60%) completed the recommended 6 months of IV methylprednisolone therapy. Mean length of treatment was 5.2 months.

Itraconazole

- All patients were prescribed itraconazole with daily dose ranging from **2mg/kg/day to 5mg/kg/day.**
- Each patient was required to have **therapeutic drug monitoring** and obtain therapeutic levels of 0.5mg/L or above.
- Mean length of treatment was 9.4 months.
- Four patients completed the **recommended 12 months treatment.**

ETHICS APPROVAL *(audit 1171A/07/2023).*

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SCAN TO FIND OUT MORE ABOUT CAREER OPPORTUNITIES

METHODS *(Continued)*

STATISTICAL ANALYSIS

Data were analysed using software package IBM SPSS version 28. To measure changes in IgE and lung function (FEV1 % predicted), student paired t – tests were used with p value of 0.05 denoting statistical significance.

RESULTS

RADIOLOGICAL CHANGES

ABPA related radiological changes **resolved in 85%** of cases post IV methylprednisolone treatment.

CHANGES TO IgE

TABLE 3: CHANGE IN IgE PRE AND POST ABPA TREATMENT

Patient	Number of months of IV methylprednisolone treatment	Initial (pre-treatment) IgE level (KU/L)	IgE level (KU/L) at last steroid dose
1	2	881	454
2	6	1310	212
3	6	617	77
4	6	603	430
***6**	4	506	100
7	3	78	28
8	6	84	108
9	6	1634	64
10	6	228	210

**Patient 5 removed as was prescribed oral prednisolone*

There was a **statistically significant** reduction (p value = 0.042) in IgE levels when comparing –

- Post treatment IgE (KU/L) (Mean 159.5, 95th Confidence Interval (CI) 92.1) as compared to
- Pre-treatment IgE (Mean 660.1, 95th CI 367.2*).*

CHANGES IN LUNG FUNCTION

TABLE 4: CHANGE IN FEV1% PREDICTED PRE AND POST ABPA TREATMENT

Patient	Pre-treatment FEV1% predicted	Number of months of steroid treatment	FEV1% at last steroid dose	Change in FEV1% predicted
1	96.9	2	99.7	+2.8
2	62.3	6	64.5	+2.2
3	85.2	6	80.2	-5.0
4	78.6	6	99.9	+21.3
***6**	107.3	4	111.8	+4.5
7	36.2	3	41.7	+5.5
8	65.4	6	76.2	+10.8
9	91.8	6	90.7	-1.1
10	81.9	6	98.1	+16.2

**Patient 5 removed as was prescribed oral prednisolone*

There was a **near statistically significant** increase in FEV1 % predicted levels (p value = 0.052) when comparing –

- Post IV methylprednisolone FEV1% predicted (Mean 84.7 + 95th CI 12.6) as compared to
- Pre-treatment FEV1 % predicted (Mean 78.4+ 95th CI 12.4).

ADVERSE DRUG REACTIONS (ADRs)

- One patient developed a **dose-related infusion reaction** to IV methylprednisolone and had to be decreased to 10mg/kg/dose.
- Another patient developed **labile blood glucose** and was changed to oral prednisolone.
- Nil ADRs were reported with itraconazole.

CONCLUSION

The results of this audit indicate that itraconazole with IV methylprednisolone therapy results in clinical improvement in ABPA as demonstrated by radiological, IgE and lung function. This treatment combination is also safe, with minimal ADRs.

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