Bronchopulmonary complications therapy

Allergic bronchopulmonary aspergillosis (abpa) in cystic fibrosis

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Background

Aspergilli are saprophytic, spore-forming, filamentous fungi found ubiquitously in the environment. Aspergillus fumigatus (AF) is the most prevalent species isolated from the respiratory secretions of CF patients.

Several distinct clinical phenotypes are observed in CF (King J et al, 2016):

1. Aspergillus can persist without respiratory decline (Aspergillus colonization);
2. Aspergillus may develop a localized infection, associated to mucosal inflammation and worsening respiratory disease without allergic responses (Aspergillus bronchitis);
3. Aspergillus may trigger an IgE-mediated hypersensitivity response either with or without respiratory exacerbation, airway inflammation, and the development of bronchiectasis and fibrosis (Aspergillus sensitization and ABPA respectively).

Allergic Broncho-Pulmonary Aspergillosis (ABPA) is the result of a Th2-mediated hypersensitivity response to colonisation with the fungus AF (Janahi IA et al, 2017). ABPA usually occurs in susceptible individuals suffering from bronchial asthma and in people with CF and is generally associated with an accelerated decline in lung function. Comparable ABPA prevalences in paediatric and adult CF patients range from 1 up to 20%, although huge variations are observed between countries. Prevalence of ABPA in children with CF and the potential predisposing factors to Aspergillus infection (AI) and ABPA (Walicka-Serzysko K et al, 2015) have been evaluated in a care CF centre.

ABPA manifests clinically with respiratory exacerbations, especially wheeze, positive antibodies against Aspergillus and characteristic radiological abnormalities. Since the clinical features of this condition overlap significantly with that of CF, ABPA remains underdiagnosed in a lot of patients. Diagnosis of ABPA in CF patients should be sought in those with evidence of clinical and radiologic deterioration that is not attributable to another etiology, a markedly elevated total serum IgE level (while off steroid therapy) and evidence of AF sensitization.

A consensus statement for diagnosis and management of ABPA in current practice is still debating, thus accounting for the ongoing variation in reported prevalence. Previously the Cystic Fibrosis Foundation Consensus Conference laid down criteria for either diagnosis or screening for ABPA in CF (Stevens DA, 2003).

The use of multiple recombinant antigens may improve the diagnostic accuracy in CF complicated with ABPA or AB. Asp f1 reactivity may relate to the presence of actively growing Aspergillus spp., which might be a useful marker for guiding antifungal therapy in ABPA (Alghamdi Ns et al, 2019).

Recently (Aqarwal R et al , 2015) it has been evaluated the performance of serum galactomannan (GM) in patients with ABPA as a diagnostic criteria. The results of this study suggested that serum GM estimation has a limited role in the diagnostic workup of patients with ABPA. New commercially available tools (Barrera C et al, 2016) might accelerate diagnosis of ABPA in patients with CF.

It is still debated what is the ideal antifungal therapy for ABPA and other fungi. High doses of corticosteroids as oral prednisolone are suggested as the treatment of choice for ABPA (Smith AR et al , 2014). However, their long-term benefits are unclear, while their side effects are well documented.

More data are in favour of treatment with antifungal therapy.

Issues

1. To assess the optimal type, duration and dose of antifungal therapy;
2. to test the hypotheses whether antifungal therapy:
   - may improve clinical status compared to placebo or standard therapy;
   - is devoid of any unacceptable adverse effect.

What is known

Azoles compounds have been proposed as an alternative treatment to corticosteroids for ABPA, as they are endowed with activity against AF. Itraconazole is the most active one, whereas a few data are available on the efficacy of voriconazole. Amphotericin B has been employed in aerosolized form to treat invasive infection with A fumigatus.

1 CDSR (Jat Kana R et al, 2018) compared anti-IgE therapy to placebo or other therapies for ABPA in CF patients. Authors considered all doses of anti-IgE therapy in the review. People with CF and ABPA (diagnosed using the Rosenberg-Patterson criteria, Nelson'
criteria, Greenberger's criteria or the Cystic Fibrosis Foundation Consensus Criteria) were included. No limit to age or disease severity for participants were included in the review. Only one study enrolling 14 participants was eligible for inclusion in the review. The double-blind study compared a daily dose of 600 mg omalizumab or placebo along with twice daily itraconazole and oral corticosteroids, with a maximum daily dose of 400 mg. Treatment lasted six months, but the study was terminated prematurely and complete data were not available. There is lack of evidence for the efficacy and safety of anti-IgE (omalizumab) therapy in people with CF and allergic bronchopulmonary aspergillosis.

In a retrospective analysis of 32 patients Aspergillus-specific IgE was evaluated as an outcome for the use of triazoles. Main results showed that there was a significant reduction in Aspergillus IgE with posaconazole but not with other triazoles (P?=0.026). Aspergillus IgE levels were inversely correlated with the therapeutic drug level of posaconazole, suggesting that posaconazole is better than comparator azoles at decreasing serological response to Aspergillus and that this response was better with therapeutic levels of posaconazole (Periselneris J et al, 2019).

Clinical trials

A study (Gilchrist FJ et al, 2013) reported a suppression of adrenal glucocorticoid synthesis in 11 out of 25 people with CF treated with both itraconazole and budesonide.

A retrospective study (Lehman S, 2014) of six patients with CF and ABPA treated with omalizumab within an observation period of 7.5 years showed that Omalizumab has the potential to be an additional and solitary treatment option in patients with CF and ABPA. Early onset treatment may be beneficial and patients with early stage of lung disease seem to benefit more. In a review study (Tanou K, 2014) including eight case reports, 13 children with CF and ABPA received anti-IgE resulting in improved FEV1, fewer respiratory symptoms and decreased corticosteroid use.

In a small population of 6 CF patients with omalizumab the treatment decreased IgE levels, and improved respiratory symptoms, suggesting that omalizumab may be an alternative therapy for ABPA in CF patients who fail to respond to systemic corticosteroids or have serious adverse effects (Emirlioglu N, 2016).

A Canadian randomized, double-blind, placebo-controlled trial (NCT00528190, 2007-2011; 60 enrolled patients) aimed to determine whether itraconazole could be effective at preventing respiratory exacerbations and improving pulmonary function in patients with CF who are chronically colonized/infected with AF. Main results published (Aaron SD et al, 2012) failed to show evidence supporting clinical benefits from itraconazole treatment in CF patients. Limitations of this pilot study were mainly due to the small sample size, as well as to the inability to achieve therapeutic levels of itraconazole in many patients.

A multicenter RCT study (NCT00787917) regarding the efficacy of Omalizumab (subcutaneous injections of maximum 600mg daily dose) in severe ABPA versus conventional therapy as itraconazole (twice daily with a maximum daily dose of 400 mg) and oral corticosteroids has been terminated prematurely for side effects and difficulty to enroll patients. No published results are available.

Another clinical trial (NCT00585364) have been proposed to unravel the pathogenic mechanisms of immune tolerance and inflammation in CF patients with ABPA versus CF patients without ABPA in order to identify the immunological factors that influence patient's responsiveness to AF in the lungs.

A clinical trial (Lynat G et al, 2014) designed to evaluate the effect of duplication in Chitotriosidase (CHIT1) gene on the risk for ABPA in patients with CF with and without ABPA did not found any significant correlation between Aspergillus positive sputum and CHIT1 duplication.

An open-label phase I observational trial showed that daily Vitamin D3 supplementation over a 24-week period was associated with reduced Aspergillus induced IL-13 responses from periphera, CD4+ T cells and Aspergillus-specific IgE levels, as well as increased serum vitamin D levels (Nguyen NL et al, 2015).

Unresolved questions

The review on antifungal therapy of ABPA did not find any completed RCT on this topic. Screening for early detection of Aspergillus colonization in the annual assessment of CF patients who are over 6 years old is suggested. Due to the small sample size and retrospective design of available studies, the identification of risk factors of ABPA in CF requires further prospective studies.

While data are already available from studies regarding people with ABPA but without CF, diagnosis of ABPA is quite difficult in CF, as
many of their findings overlap with common manifestations of the lung disease. No RCT data support the evidence of patients responsiveness to corticosteroid therapy on disease evolution. An improvement in symptoms associated to decrease of exacerbations, and increase of lung function has been reported in more studies and was more common with oral azoles. Antifungals also had a positive impact on biomarkers and radiological pulmonary infiltrates, but adverse effects were also common.

Data supporting the use of Omalizumab are still inconclusive, however its indication is only for selected cases.

The quality of evidence supporting these results was low or very low due to a shortage of controlled studies, heterogeneity between studies, and potential bias. The recommendation for their use is weak and clinicians should therefore weigh up desirable and undesirable effects on a case-by-case basis. More studies with a better methodology are needed to increase confidence in the effects of antifungal treatments in ABPA.

The last CDSR review to 2018 concluded that there is a need for large prospective randomized controlled studies of anti-IgE therapy in people with CF and ABPA with both clinical and laboratory outcome measures such as steroid requirement, number of allergic bronchopulmonary aspergillosis exacerbations and lung function profile.

Keywords

Allergic Bronchopulmonary Aspergillosis -ABPA--; Aspergillus;