Treating allergic bronchopulmonary aspergillosis: the way forward

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Allergic bronchopulmonary mycoses are an endotype of allergic lung disease, similar to but more severe than uncomplicated asthma, caused by a Th2-dominated immune response and a bronchocentric granulocytic inflammation provoked by endobronchial growth of filamentous fungi in individuals with innate host defence defects (primarily people with severe allergic asthma or cystic fibrosis); untreated, it leads to progressive structural damage [1–3]. The scope of this problem, however, has only been recognised recently [4, 5].

In >90% of cases, *Aspergillus fumigatus* is the causative fungal agent; allergic bronchopulmonary aspergillosis (ABPA) has been recognised as a distinct clinical entity since the 1950s [6]. For over 35 years, months-long courses of oral glucocorticosteroids (OGCS) have been the mainstay of ABPA treatment, based on early uncontrolled studies demonstrating near-universal clinical, radiographic and immunological responses [7–9]. However, no controlled studies have ever been performed on this primary treatment modality, and so dose and duration of OGCS courses have been left to clinical trial-and-error and accumulated experience [10].

For reasons that remain unclear, ABPA appears to be more prevalent in south Asia than in many other regions of the world [11]; recently, investigators led by Ritesh Agarwal of the Postgraduate Institute of Medicine Education and Research in Chandigarh, India, who care for a uniquely large cohort of people with ABPA, employed a OGCS regime with higher doses and longer exposures than that commonly used, hoping to lengthen the duration of the remission stage of ABPA [6, 12]. Now, Agarwal *et al.* [13] have completed a randomised, controlled, open-label trial of two OGCS regimes in ABPA, as reported in this issue of the *European Respiratory Journal*.

Beyond praise for conducting one of the few controlled trials published on ABPA treatment, several cautionary aspects of this trial merit comment. First, only new, treatment-naïve cases presenting with acute ABPA were studied, so the applicability to relapsed or chronic (steroid-dependent) ABPA is unclear. Second, concomitant therapy with other agents potentially active in ABPA was excluded (more on this topic shortly). Third, collection of data on adverse effects of OGCS was included but not comprehensive in scope. Fourth, only ABPA in asthmatics was studied, so results cannot necessarily be applied to cystic fibrosis. Finally, selection criteria restrict the overall generalisability of the study, as does the underpowering of the sample size, driven by both study subject attrition and design overestimation of the treatment effect difference between the two OGCS regimes, which was derived from two prior studies of the prevalence of steroid-dependent ABPA that were published 20 years apart from centres on different continents. Nevertheless, the main finding, that the efficacy of the lower dose regime was similar to that of the higher dose regime, while steroid side-effects were lessened, is important, in that harm from overtreatment of ABPA can be reduced based on the results of this study. The lower dose regime employed by Agarwal *et al.* [13] is very similar to that widely employed in Europe, North America and elsewhere.

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This study raises the important question of how further progress in treating ABPA is to occur, given the large number of case reports and series but paucity of controlled trials. First, better case ascertainment is needed, particularly in patients with asthma who are often managed without an appropriate index of suspicion for ABPA risk [14]. As diagnosis remains a complex process [6, 15], a simpler diagnostic approach remains an unmet need. Recently, an *A. fumigatus*-specific basophil activation assay has been found to be a robust diagnostic test in ABPA associated with cystic fibrosis, but it requires specialised flow cytometry expertise and expedited processing, as well as further study of utility in asthmatic ABPA [16, 17]. Even with improved diagnostic methods, pooling of patients *via* multicentre studies seems a needed component to improve feasibility as well as generalisability of controlled trials.

Other approaches to ABPA treatment to complement or replace OGCS have been the subject of increasing interest and scrutiny but more controlled trials are clearly needed. Can monthly high-dose "pulse" intravenous GCS further reduce steroid toxicity while maintaining or even improving efficacy over conventional OGCS [18, 19]?

What about antifungal therapy? The use of oral antifungal azole agents with high activity against *A. fumigatus* has gained widespread use in ABPA and is recommended as second-line treatment in both asthma and cystic fibrosis [6, 15]. However, reviews have emphasised the weakness of the evidence for safety and efficacy of azoles, with only two small, short-term, randomised, double-blind, placebo-controlled trials in asthmatic ABPA, and none in cystic fibrosis ABPA [20, 21]. Can azole monotherapy be considered a viable alternative to OGCS? How long should azoles be used? In what stage(s) of ABPA? Is therapeutic drug monitoring necessary? How dangerous are cytochrome P450 3A4-mediated drug–drug interactions, particularly with certain systemic and inhaled glucocorticosteroid agents [22–24]? How ominous is the emerging problem of *Aspergillus* azole resistance [25, 26]? Fortunately, some of these issues are now being addressed in ongoing controlled trials of ABPA azole treatment by the Chandigarh group. One randomised, open-label trial is comparing OGCS to oral itraconazole monotherapy (www.clinicaltrials.gov identifier number NCT01321827), another OGCS to oral voriconazole (NCT 01621321) and a third OGCS monotherapy to combination OGCS–itraconazole therapy (NCT0244009). These studies should greatly contribute to understanding the proper role of azoles in ABPA.

Are there potential alternative approaches to antifungal treatment that avoid systemic effects, azole resistance and drug–drug interactions? Inhaled amphotericin B has been explored as an ABPA treatment with varying results in uncontrolled studies [27–29]. The lack of controlled trials is also being tackled in a Chandigarh study comparing nebulised amphotericin B deoxycholate combined with an inhaled GCS to inhaled GCS monotherapy in the maintenance of ABPA remission (NCT01857479); a randomised, single-blind, controlled trial of nebulised liposomal amphotericin B in maintaining remission is also underway in France (NCT02273661).

Finally, the success of omalizumab (anti-IgE monoclonal antibody) in improving control of moderate–severe allergic asthma has led to great interest and rapidly increasing usage in ABPA, usually undertaken as a steroid-sparing agent, with virtually unanimous reporting of reduced steroid requirements and exacerbations in published uncontrolled studies [30–33]. However, a recent Cochrane review rightly concluded that omalizumab use cannot be comfortably recommended in the absence of valid controlled trial data [34]. Unfortunately, an industry-sponsored, multicentre attempt at a double-blind, placebo-controlled, randomised trial in cystic fibrosis APBA (NCT00787917) was terminated early due to enrolment and retention issues, almost certainly related to a preposterously unrealistic dose regime (600 mg injected daily for 6 months). Actually, real-world omalizumab dosing in ABPA can be addressed by using a dose calculation resulting in a near-conventional treatment regime [31]. Accordingly, a randomised, double-blind, placebo-controlled omalizumab trial in adult asthmatics with ABPA using a cross-over design and dose regime of 750 mg monthly was recently published, validating the uncontrolled literature: omalizumab works [35]. Validation of similar efficacy in a cystic fibrosis ABPA controlled trial is warranted.

Due to its complexity of diagnosis and treatment, ABPA remains a difficult disease to control and entails troubling steroid toxicity. As is common in medicine, adventures in alternatives have long peppered the scene, with an expected publication bias towards favourable results and weak standards of evidence, and so the solidity of well-designed controlled trials is still where, as Willie Sutton said of banks, you need to go to get the money.

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