

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Efficacy and safety of posaconazole for chronic pulmonary aspergillosis: next strategy against the threat of azole-resistant *Aspergillus* infection

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Chronic pulmonary aspergillosis (CPA) is a complex and slowly progressive inflammatory disease caused by *Aspergillus* spp. There are three major unsolved issues regarding this disease: 1) the complexity of the disease entity; 2) the scarcity of clinical evidence for management; and 3) the drug resistance of *Aspergillus*.

The pathophysiology of CPA ranges widely from aspergilloma to semi-invasive types, such as chronic necrotizing pulmonary aspergillosis (CNPA), as well as chronic cavitary pulmonary aspergillosis (CCPA) or chronic fibrosing pulmonary aspergillosis (CFPA). These subtypes of CPA have recently been proposed and the recommendations for treatment of each type are outlined in the latest guidelines from the Infectious Diseases Society of America (IDSA) [1,2]. However, Hope et al. reported that apparent distinct entities do not exist for this syndrome and these subtypes usually overlap [3].

This causes difficulties in comparing more recent efficacy results for antifungal drugs with previous data regarding CPA management. It is difficult to establish a simple disease entity for this disease due to the complex backgrounds of CPA patients, such as existence of chronic pulmonary underlying diseases (e.g., tuberculosis sequelae, bronchiectasis, chronic obstructive pulmonary disease, and pulmonary fibrosis) with mild immunosuppression (e.g., low-dose steroid administration, diabetes, collagen diseases, or alcohol) as well as co-infection with other microorganisms. Thus, it is also difficult to conduct large-scale randomized clinical trials for CPA cases.

In this issue of *Clinical Infectious Diseases*, Felton et al. reported the efficacy and safety of posaconazole in CPA cases, showing 61% and 46% response rates at 6 and 12 months, respectively, with a relatively low incidence of side effects [4]. The study evaluated a total of 79 CPA patients who were administered posaconazole, and the definition of CPA was as follows: (a) presence of progressive pulmonary cavitation with associated cavity wall or pleural thickening on chest radiograph or cross-sectional imaging; (b) positive *Aspergillus* antibody titer or isolation or visualization on biopsy of *Aspergillus* species from the lung or pleura; (c) constitutional or pulmonary symptoms for at least 3 months; (d) exclusion of other causes that may mimic this syndrome (e.g., pulmonary malignancy); (e) or significant systemic immunosuppression. Both clinical and radiological data were used to assess the response to therapy. Denning et al. previously proposed enrollment criteria for prospective clinical studies of CPA [1], and the criteria of CPA in the study by Felton et al. [4] basically follow this criteria. The definition proposed by Denning is simple and practical for

conducting studies. This criterion, however, possess some difficulties for clear interpretation in details. For example, co-infection with other bacteria, such as *Pseudomonas aeruginosa* or mycobacterium is not uncommon in many CPA cases and it would be very difficult to confirm that only *Aspergillus* is involved in each case. It is also difficult to distinguish significant and mild systemic immunosuppression, as there are no good tools for assessment. It is, however, reasonable to evaluate overall clinical efficacy by both clinical and radiological data, since other serological and microbiological data, such as *Aspergillus* antigen or antibody, (1,3)- β -D-glucan and the results of culture are not typically correlated with the strength of response to antifungal drugs.

We assumed that many of the cases investigated in Felton's study were CCPA cases; however, there may be cases more accurately characterized as CNPA or aspergilloma. Questions remain over that the differences of the radiological appearance of CPA on chest X-ray films, and their correlation with the effectiveness of posaconazole. It is difficult to compare Felton's results directly with previous data of other azoles, such as itraconazole (ITCZ) and voriconazole (VRCZ). It is apparent that even the newer azole, posaconazole possesses low efficacy rates in the treatment of CPA. The reported efficacy of oral ITCZ varied widely, with an approximate range of 30-82%, and that of oral VRCZ ranges from 53-65% with several months' administration [5]. The efficacy of ITCZ and VRCZ in these studies was mostly assessed by clinical, radiological and mycological improvement at the end of treatment or a regular interval, regardless of whether there was a partial or complete response. These wide ranges of efficacy are due to the differences in the definition of CPA, evaluation methods, endpoints of each study and duration of treatment. However, it is apparent that oral azole formulations, including posaconazole do not possess sufficient efficacy for CPA.

Azole-resistant *A. fumigatus* is reported to be increasing mainly in the U.K and the Netherlands, and is becoming major clinical concern [6]. Unlike to bacterial or *Candida* infections, drug resistance in *A. fumigatus* has not been paid attention in the last decade. One of the major reasons is that there was no standardized drug susceptibility test. However, in the last few years, universal methods for drug susceptibility testing, such as the Clinical and Laboratory Standards Institute (M38-A2) and the European Committee on Antimicrobial Susceptibility Testing, as well as tentative clinical breakpoints, have become available [7]. It is very important that we realize that some azole-resistant strains have been isolated from CPA cases, and many of these cases had been exposed to azoles for an extended

duration (1-30 months) [6, 8]. Although oral administration of azoles is the mainstay of treatment of CPA, long-term administration potentially induces azole resistance. This means that the more we use azoles in CPA patients, the fewer treatment options we will have. As Felton et al. noted in this issue [4], there were four isolates that showed a minimum inhibitory concentration of >8mg/L for posaconazole, and treatment failure with posaconazole was observed in all cases. Although Felton et al. did not describe in detail how they treated these patients, possible options in such cases would be intravenous amphotericin B or intravenous echinocandins, both of which are unavailable in oral formulations. Using other azoles such as ITCZ or VRCZ is another option, but cross-resistance among azoles is carefully considered before administration.

We recently published the first large scale prospective study comparing intravenous MCFG and intravenous VRCZ in CPA [9]. There was a favorable response rate with both MCFG (60.0%) and VRCZ (53.2%) with fewer side effects for MCFG (26.4% vs. 61.1% for VRCZ) [9]. Originally, the study was conducted because intravenous antifungal agents may have an important role as induction therapy for CPA cases, or may be required if the patients are refractory to oral antifungal drugs or develop severe disease. The utility of intravenous antifungal drugs has not been evaluated for CPA, as they are very expensive and require hospital admission. Azole-resistance in *Aspergillus*, however, needs to be considered as cases refractory to oral antifungal drugs, and such trials would be useful. We are also currently conducting a comparative study between liposomal amphotericin B and intravenous voriconazole for CPA. We believe such data on intravenous antifungal drugs will be important for future clinical management of CPA, but it would be only a temporarily treatment option (at most a month), and the problems related to maintenance therapy using oral antifungal drugs still remain. Thus, it is very important to minimize the production of azole-resistant strains in clinical settings.

As there may be a relationship between drug exposure and the emergence of drug resistance, the appropriate application of drugs based on pharmacokinetics/pharmacodynamics properties and TDM is important, particularly in CPA patients. Felton et al. reported that they maintained serum posaconazole concentrations over 0.5 mg/L, but no data of the interactions between adverse effects and serum posaconazole concentrations were discussed in the study. We believe that TDM for azoles may have an important role in achieving maximum efficacy with minimum side effects. Furthermore, it will be necessary to prevent the development of drug resistance. Importantly, urgent studies on drug exposure and azole

resistance are required.

In conclusion, Felton's article provided new evidence for posaconazole in the management of CPA; however, efficacy remains unsatisfactory. There is a clear need for the development of better antifungal drugs and studies regarding drug resistance.

Acknowledgements

Potential conflicts of interest. S.K. and K.I.: No conflicts.

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