Clinical Infectious Diseases

VIEWPOINTS

Food and Drug Administration (FDA) Public Workshop Summary—Addressing Challenges in Inhaled Antifungal Drug Development

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Allergic bronchopulmonary aspergillosis and invasive fungal diseases represent distinct infectious entities that cause significant morbidity and mortality. Currently, administered inhaled antifungal therapies are unapproved, have suboptimal efficacy, and are associated with considerable adverse reactions. The emergence of resistant pathogens is also a growing concern. Inhaled antifungal development programs are challenged by inadequate nonclinical infection models, highly heterogenous patient populations, low prevalence rates of fungal diseases, difficulties defining clinical trial enrollment criteria, and lack of robust clinical trial endpoints. On 25 September 2020, the US Food and Drug Administration (FDA) convened a workshop with experts in pulmonary medicine and infectious diseases from academia, industry, and other governmental agencies. Key discussion topics included regulatory incentives to facilitate development of inhaled antifungal drugs and combination inhalational devices, limitations of existing nonclinical models and clinical trial designs, patient perspectives, and industry insights.

Keywords. antifungal agents; asthma; rare diseases; drug development.

Limited efforts have been directed towards developing inhaled antifungal agents for prophylactic or therapeutic use. The lack of approved antifungal drugs for inhalational use constitutes an unmet medical need for patients with allergic bronchopulmonary aspergillosis (ABPA) and invasive fungal diseases (IFDs).

On 25 September 2020, the US Food and Drug Administration (FDA) convened a public workshop composed of experts in pulmonary medicine and infectious diseases from academia, industry, government agencies, and patient representatives to discuss existing barriers to developing inhaled antifungal agents and potential benefits of administering inhaled agents as

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monotherapy or in combination with currently approved systemic drugs. This paper provides a high-level overview of the key topics discussed. Readers may refer to the workshop webpage for further details [1].

SESSION 1: BACKGROUND AND NONCLINICAL CONSIDERATIONS

Is There a Role for Inhaled Antifungals in Pulmonary Fungal Diseases?

Patients with pulmonary fungal diseases represent a heterogenous population with a spectrum of disease manifestations and differences in underlying host immunity [2, 3]. For example, in healthy humans, inhaled *Aspergillus* conidia are cleared from the airways via various mechanisms, which may be impaired in lung transplant recipients and patients with muco-obstructive lung disease—for example, asthma, cystic fibrosis (CF), non-CF bronchiectasis, and chronic obstructive pulmonary disease. Germination of conidia can lead to atopic sensitization and respiratory diseases such as severe asthma with fungal sensitization (SAFS) and ABPA [4, 5].

Invasive fungal diseases can induce inflammation and airway invasion, leading to life-threatening disease(s) such as invasive pulmonary aspergillosis (IPA). Patients at high risk include immunocompromised patients with hematologic malignancies or neutropenia, particularly in patients who have undergone allogenic stem cell transplantation (ASCT), solid-organ transplant (SOT) recipients, and intensive care unit patients experiencing post–viral-associated pulmonary aspergillosis—for example, following acute influenza or coronavirus disease 2019 (COVID-19) [6, 7]. Mortality among ASCT and SOT recipients who develop invasive aspergillosis (IA) remains high [8, 9].

To combat the risk of increased morbidity/mortality, nebulized amphotericin B, including lipid formulations, and inhaled voriconazole have long been used off-label, either as monotherapy or in combination with other antifungals as prophylaxis against pulmonary fungal diseases [10–14]. Moreover, some antineoplastic agents (eg, venetoclax, ibrutinib) complicate concurrent azole use due to drug–drug interactions [15]. Inhaled antifungal therapies are often used adjunctively with systemic treatments, particularly against multidrug-resistant pathogens (eg, *Scedosporium*, mucormycetes, and *Fusarium* species) [16].

Nonclinical studies, both in vitro and animal infection models, are useful in evaluating the activity of antifungals administered individually or in combination with other drugs. For example, studies in mice with acute IPA suggest that inhaled drugs combined with systemic therapies may be more effective in improving animals' survival compared with systemic or inhaled monotherapy [17]. Such nonclinical findings bolster support for the study of inhaled products in clinical settings.

Pharmacology/Toxicology Considerations

Animal and in vitro studies are crucial to obtaining pharmacological and toxicological data in support of human trials. Factors considered when administering an aerosolized drug to animals include route of exposure, estimation of the delivered drug dose in the appropriately selected species, calculation of the pulmonary deposition of the delivered dose according to the species deposition factor, and the drug particle size. Repeat inhalation toxicity animal studies should be conducted [18].

Determining the appropriate dosimetry, however, can be challenging. The delivered dose of an aerosolized drug refers to the amount inhaled by the recipient based on the drug concentration, respiratory minute volume, duration of exposure, inhalable fraction, and body weight. To convert the delivered dose into the deposited dose to the lungs, one must know the deposition factor, which varies by species [19]. Disposition data in larger animals are similar to humans.

Clinical Pharmacology Considerations

Drug-, device-, and patient-related factors impact the pharmacokinetics of a drug's lung distribution, deposition, and exposure. Lung distribution and deposition of an inhaled drug are negatively impacted by poor coordination between a patient's breathing pattern, including factors associated with the underlying disease, and the device used [20]. Such factors affect inter- and intrasubject variability, intrapulmonary drug distribution, and drug deposition patterns.

Nonclinical studies can provide estimates on initial clinical dosing regimens. There remain translational gaps between nonclinical lung pharmacokinetic-pharmacodynamic targets and achieving clinically efficacious human dosing. Information critical to pharmacokinetic-pharmacodynamic targets includes knowing whether the adopted sampling approach (eg, bronchoalveolar lavage [BAL], expectorated sputum) adequately measures total drug concentrations and/or reflects unbound drug concentrations that ultimately impact a drug's activity at the site of action. Having appropriate proof-of-concept studies and dose-response/dose-regimen findings are integral to any phase 2 drug development program and subsequent phase 3 trial designs.

Regulatory Perspectives on Combination Products and Human Factors Considerations

Combination products require 2 or more different regulated components to achieve the intended use (eg, a drug and an inhaled drug device). Devices that deliver a drug via the inhalation route are regulated under 3 risk-based classifications (eg, low, moderate, and high risk). There are 2 classes of inhaled devices: (1) nebulizers for liquid drug formulations and inhalers co-packaged with the drug (eg, metered dose inhalers [MDIs]) or (2) dry powder inhalers. The 510(k) pathway is the most common regulatory pathway for clearance of any orally inhaled drug-device product [21]. Review of a combination product requires coordination between multiple centers within

the FDA. The Office of Combination Products determines which center will assume the lead based on the product's primary mode of action [22].

The human-factor engineering process should be used when designing and developing an antifungal inhalational product to ensure safe and effective use of the product and to reduce the occurrence of medication errors. Underlying comorbidities should be considered since they can impact users' needs, capabilities, and limitations. Some inhalational delivery device platforms (eg, MDIs) may not deliver the necessary high drug doses, whereas other device platforms optimize drug delivery to central regions of the lung but fail to deliver drug to peripheral regions. Formulation challenges, such as stability and storage space (eg, at home or an outpatient center), may require additional tasks from users and should be considered in the overall product design.

Considerations for Clinical Outcome Assessment Development

Clinical outcome assessments (COAs) are based on patient-, observer-, and/or clinician-reported outcomes, and performance outcomes. COA development should include understanding of the natural history of the disease/condition, patient/caregiver perspectives of the disease/condition and clinical benefit, and the intended context of use (COU). Principles of COA development and validation are described in FDA guidance documents [23–25].

SESSION 2: CLINICAL TRIAL DESIGN CONSIDERATIONS FOR INHALED ANTIFUNGAL DEVELOPMENT

Regulatory Perspectives

The statutory standard for approval of a drug includes demonstration of substantial evidence of effectiveness based on adequate and well-controlled investigations [26]. The FDA may exercise flexibility in defining "substantial evidence" and may consider information from studies of other dosage forms, endpoints, or populations. Additionally, evidence from nonclinical studies (eg, relevant animal infection models and in vitro investigations) and/or from another indication may be considered supportive.

An antifungal drug can gain marketing approval in the United States by either a traditional or an accelerated pathway. Traditional approvals are based on an endpoint measuring clinical benefit—that is, how a patient feels, functions, or survives. Accelerated approvals are based on surrogate endpoints that are reasonably likely to predict clinical benefit; the intended clinical benefit of the drug must be verified in a confirmatory trial postapproval (21 CFR 314.510).

The FDA offers qualified infectious disease product (QIDP) designation and expedited programs for serious conditions [27, 28]. Antifungal drugs intended to treat serious or life-threatening infections may be eligible for QIDP designation, which provides an additional 5 years of marketing exclusivity, priority review for the first application, and fast-track designation [27, 28]. The limited population pathway for antibacterial and antifungal drugs (LPADs) is intended for drugs that treat a serious or life-threatening infection in a limited patient population with unmet medical needs. Such development programs may follow a streamlined approach involving smaller, shorter, or fewer clinical trials while still meeting the statutory standards of approval [29].

Developers have encountered several challenges in conducting trials for inhaled antifungal products, such as addressing heterogenous patient populations with diverse underlying conditions, defining clinically meaningful endpoints, and designing effective inhalational devices [30]. Device design considerations should include any user comorbidities that limit user impact and capabilities. Developers are encouraged to utilize human-factor engineering to minimize potential medication errors, accommodate higher doses, and deliver drug to the desired lung region(s).

The European Medicines Agency and the European Medicines Regulatory Network generally share FDA's regulatory perspectives in the approval of antifungal drugs. Continued collaboration and discussions with these regulatory agencies are encouraged.

Clinical Trial Design and Endpoint Considerations

Role of Inhaled Antifungals in Allergic Bronchopulmonary Aspergillosis/Asthma

Disease heterogeneity and severity (eg, mild, moderate, and severe) among ABPA/SAFS populations present challenges when designing clinical trials and selecting endpoints for inhaled antifungals [5, 31–33]. Eligibility criteria, including the use of prohibited medications (eg, long-term oral corticosteroids and immunomodulators commonly administered to this population), complicate patient recruitment efforts. Investigators have adopted several primary endpoints for efficacy determinations in fungal asthma studies, including the evaluation of lung function (eg, walking distance and forced expiratory volume in 1 second [FEV_1]); utilization of patient-reported outcomes (PROs) to assess quality of life (QoL) and safety; and assessment of clinical outcomes, such as exacerbations. While several PRO instruments exist for asthma, there are no clinically validated PRO instruments for ABPA. Several randomized controlled trials have utilized composite endpoints that incorporate pulmonary function, radiology, and reductions in biomarker measurements (eg, serum total IgE and sputum eosinophils). The PRO should be fit-for-purpose and carefully defined for the intended COU (eg, treatment or prophylaxis).

Time to exacerbation or frequency of exacerbations may not be optimal primary endpoints. Exacerbations can be infrequent, require long observation periods, and may be difficult to distinguish among different disease states (eg, asthma, ABPA, or

bacterial exacerbations). Each type of exacerbation may require different treatment modalities and durations. Secondary endpoints can include resolution of radiologic findings, sputum markers (eg, eosinophil count, detection of organism by culture or quantitative polymerase chain reaction [PCR], total and antigen-specific IgE antibodies). Microbiologic endpoints are commonly secondary endpoints but may not correlate with clinical outcomes. Different treatment-response patterns are observed in a variety of patient subgroups of ABPA/SAFS, making a singular "one-size-fits-all" endpoint challenging for these heterogeneous populations. Therefore, defining the target population and outcome measures for patients with active disease is important. Patient-relevant outcomes, such as reduction in cough and improved breathing, may differ from investigator-prioritized clinical outcomes.

Role of Inhaled Antifungals in Invasive Fungal Diseases and Solid-Organ Transplant Recipients

There has been a longstanding interest in administering inhaled antifungals for the prevention of IFDs in patients with hematologic malignancies, a subset of whom undergo ASCT, where the type and severity of immunosuppression may result in host and infection heterogeneity. The goal of airway drug delivery (prophylaxis or treatment) is dependent on the host and the disease stage [13, 14, 34, 35].

Among SOT recipients, lung and heart recipients are at highest risk of developing IA [36, 37]. When devising trial endpoints, the risk period for IFDs posttransplantation is an important factor in trial design considerations. Mold infections occur among 60% of lung transplant recipients within the first 12 months posttransplant, with most infections peaking 6 months posttransplant [38, 39]. In the immediate posttransplant period, most lung transplant patients receive aerosolized antifungal prophylaxis, especially those with *Aspergillus* colonization [40–42]. Mold colonization, tracheobronchitis, bronchial anastomotic infections, and the development of chronic lung allograft dysfunction (CLAD) are unique clinical presentations of IFDs in lung transplant recipients [43, 44].

When evaluating strategies against IFDs in the post–lung transplant population, pertinent primary trial endpoints may include the proportion of patients with probable or proven IFDs (eg, pulmonary or systemic fungal disease) or the proportion of patients with mold colonization 6 months posttransplant. Potential endpoints when evaluating pre-emptive therapies include the proportion of patients with proven or probable IFDs or mycological evaluation (eg, BAL fluid galactomannan or microorganism by culture and/or PCR for diagnosis of IA) at the end of therapy. Relevant secondary safety endpoints may include the frequency of adverse effects (eg, headache, wheezing, cough, bronchospasm) either during or 30 days post-therapy. Suggested longer-term secondary efficacy endpoints may include all-cause mortality at 1 year, emerging resistance, proportion of subjects with IFDs (proven vs probable) or mold colonization 1 year post-initiation, rates of CLAD, and proportion of patients requiring adjustments to their therapeutic regimen.

Perspectives and Lessons Learned From Industry

Drug developers of IPA and ABPA products expressed difficulties with patient recruitment efforts and found conducting large, randomized clinical trials nearly infeasible. A lack of patient registries or advocacy groups adds to recruitment challenges.

PC945 (opelconazole) nebulizer suspension (Pulmocide, Ltd) and voriconazole powder formulation for inhalation (TFF Pharmaceuticals) are being developed for IPA [10]. Sponsors encountered trial design challenges when selecting eligibility criteria and endpoints for heterogeneous patient populations, when study populations carried different mortality risk scenarios, and when disparate approaches were used to define standard of care (SoC), the underlying disease, and the duration of therapy. Additionally, it is unclear whether inhaled antifungal agents should be administered as monotherapy or as adjuncts to systemic SoC. Potential antifungal drug–drug interactions (additive, synergistic, or antagonistic) should be evaluated.

Two dry powder triazole formulations, Edry (voriconazole; Zambon SpA) and PUR 1900 (itraconazole; Pulmatrix), are under development for the treatment of ABPA. Development challenges included estimating the true prevalence of ABPA, defining and diagnosing the most appropriate ABPA treatment stage to study (eg, stable disease, acute ABPA exacerbations), ascertaining how best to apply the International Society for Human and Animal Mycology staging criteria towards achieving homogeneity in patient populations, and generating appropriate endpoint measures [4]. Potential surrogate endpoints included laboratory biomarkers (eg, IgE levels and sputum eosinophils); radiologic imaging, including high-resolution computed tomography; pulmonary function assessments; or reductions in the time to or frequency of exacerbations. Other challenges included the absence of a standardized definition of ABPA, determining optimal timing of exacerbation assessments, and distinguishing ABPA exacerbations from asthma, CF, or bronchiectasis exacerbations. Determining the need for alternate or adjunctive treatments, such as dosage reductions or corticosteroid withdrawal, or addition of azole therapy posed additional challenges as different exacerbation types may require different treatment modalities. Uncertainty remained around which tools were most suitable for evaluating patient QoL or functionality. Selecting experienced trial sites proved difficult, as was devising eligibility criteria that were not so narrow that they limited subject enrollment but not so wide that recruitment of a homogenous population became infeasible.

Developers struggled with balancing prolonged periods of risk while ensuring the long-term safety of inhaled

antifungals and the impact of prolonged antifungal exposures on pulmonary microflora potentially leading to the emergence of resistant pathogens or replacement with microorganisms refractory to standard therapy [45].

While insights gained from inhaled antibacterial drug trials may be applicable to antifungal development programs, work is needed in determining key design elements for future trials, including phase 2 trials. ABPA trials may require complex designs and may be difficult to conduct with limited numbers of centers specializing in the care of these patients.

PANEL DISCUSSION: NEXT STEPS

Panelists discussed several key topics, including a need for robust animal models and selecting appropriate endpoints, follow-up periods, SoC therapies, and PROs.

Need for Robust Animal Models

Animal models that better reflect each disease entity and affected populations are needed to optimize and streamline clinical trial designs. This is particularly true of ABPA and chronic pulmonary aspergillosis where suitable models are lacking. Animal models can aid in defining relevant pharmacokinetic-pharmacodynamic targets for inhaled drug development. The emergence of resistant fungi and the inability to achieve and/or measure adequate drug concentrations in the lung and other sites of infection, where there is angioinvasion and necrosis, remain unresolved issues.

Endpoints Selection and Follow-up Period

Challenges associated with comparator selection, primary or composite endpoints, and determination of appropriate follow-up intervals for inhaled antifungal trials were discussed. While there was agreement on the appropriateness of composite endpoints for ABPA, consensus was not achieved on component elements comprising composite endpoints and follow-up intervals. While patients may either be infected de novo with a resistant strain or have resistance develop during therapy, there is limited experience in determining and selecting adequate intervals for monitoring resistance development. Robust observational studies may help define future clinical trial endpoints and design feasible clinical trials.

Key discussion points included incorporation of radiologic outcomes (demonstrating resolution or no further progression of bronchiectasis), patient-centered endpoints (eg, an improvement in cough or exercise capacity), and/or more traditional endpoints (eg, monitoring the frequency of exacerbations, steroid utilization, and/or FEV_1). Graft survival was discussed as a potential endpoint for lung transplant recipients.

Challenges Finding an Acceptable Standard of Care

Complicating antifungal trial design is the lack of standardized drug regimens used among major medical centers when determining acceptable SoC. In the absence of FDA-approved inhaled antifungal therapies, investigators must use active comparators unapproved for the target population. When determining the acceptability of unapproved therapies as SoC, FDA considers the proposed trial design (eg, superiority vs noninferiority designs) and whether the investigational drug is being developed for treatment or prophylaxis. The use of a historical control as the chosen comparator may require multiple considerations; therefore, discussions with the Agency are encouraged. Additionally, it is important to consider the underlying disease pathophysiology. Aerosolized drugs may be more appropriate in ABPA and CF, whereas a combination of systemic and inhaled delivery may be more appropriate in invasive pulmonary fungal disease.

Use of Patient-Reported Outcome Measures in Facilitating Drug Development

The role of PROs as clinical endpoints was discussed, including challenges arising from heterogeneity of patient populations and the lack of validated PROs designed specifically for ABPA and CF. However, existing asthma PROs were considered potentially useful in capturing relevant clinical endpoints in patients with ABPA. Most panelists agreed that PROs would prove most helpful in evaluating patient functional capacity for the intended COU, QoL measures, and drug safety and tolerability assessments.

KEY MESSAGES AND CONCLUSIONS

Standard management of patients with pulmonary diseases using available systemic antifungal therapies is associated with suboptimal clinical outcomes. Overcoming barriers to inhaled antifungal drug development will require collaboration from regulatory agencies, industry, academia, clinicians, and patients. Uncertainties related to patient eligibility, clinical trial endpoints, duration of therapy, and resistant pathogens persist and require openness to various trial design strategies. Regulatory agencies are cognizant of these challenges. The FDA has the QIDP designation, expedited programs for serious or life-threatening infections, and the LPAD pathway, and may exercise flexibility when considering acceptable trial designs. Standardization of diagnostic criteria may improve the understanding of IFDs, including pulmonary diseases. Data from nonclinical and clinical studies will assist in refining trial design approaches and optimizing the clinical application of inhaled antifungals.

Notes

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