Inhaled voriconazole: an effective novel antifungal delivery method which reduces systemic absorption and toxicity

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Purpose: Invasive fungal infections remain a significant contributor to morbidity and mortality in immunocompromised patients such as lung transplant recipients. Voriconazole and other newer azole antifungal agents have revolutionized the management of mold infections and have dramatically improved outcomes but are associated with significant short- and long-term toxicities. Inhalation represents a novel route of administration that has successfully been used by many other antimicrobials, which can maximize dosing and efficacy at the site of infection but minimize systemic absorption and therefore adverse effects.

Methods: We describe the first case of inhaled dry powder voriconazole used to treat a pulmonary mold infection in a lung transplant recipient. Outcome assessment was with serial bronchoscopy, CT imaging, lung function, clinical assessment of adverse effects, and serum voriconazole levels.

Results: A 50-year-old man underwent lung transplantation in September 2019 for chronic obstructive pulmonary disease which was complicated by right anastomotic stricture. Shortly post-transplant he developed several fungal infections including *Aspergillus fumigatus*, *Scedosporium apiospermum* and *Lomentospora prolificans*. He was treated with extended courses of oral antifungals including posaconazole, terbinafine and isavuconazole. This was complicated by significant adverse effects including gastrointestinal disturbance, joint pains and multiple skin cancers (melanoma, squamous cell carcinoma). He transitioned to voriconazole 80mg twice daily administered via a handheld single-use powdered inhalation device in February 2022. This was well tolerated, with no adverse effects and trough serum levels below the limit of detection on several occasions. Tacrolimus did not require dose modification. Clinical improvement occurred over the ensuing months with fewer symptoms, improvement in CT changes and stabilization of lung function. FEV1 which was steadily declining from 2.98L to 1.70L plateaued to 1.60L. Similarly, FVC which had decreased from 4.98L to 3.82L, improved to 4.28L. *Lomentospora* was however isolated again on repeat bronchoscopy 3 months after commencement.

Conclusions: Inhaled voriconazole represents a novel therapeutic option for the treatment of pulmonary fungal infections in lung transplant recipients. In our case, it was well tolerated, easy to administer, clinically efficacious and not associated with any significant adverse effects. Unlike systemically administered azoles, drugs interactions were negligible, with no tacrolimus dose adjustment required. This is an attractive option that could offer high-risk patient populations such as lung transplant recipients an alternative for both prophylaxis and treatment. Additional studies are required to further validate the clinical efficacy of this approach.