Fungal Infection in Heart-Lung Transplant Recipients Receiving Single-agent Prophylaxis with Itraconazole

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Abstract

Objectives: **Heart and lung transplant recipients are at risk for invasive fungal infections. This study evaluated the affect of single-agent antifungal prophylaxis with itraconazole on the rate of fungal infections after heart or lung transplant.**

Materials and Methods: **An observational, retrospective study was performed to evaluate the rate of fungal infections in heart and lung transplant recipients at the University of Kentucky Medical Center over 4.5 years who received itraconazole as a single therapy prophylaxis.**

Results: **Eighty-three recipients (42 heart, 41 lung) had an overall fungal infection incidence of 16.9% (14/83), while the incidence was 11.9% for heart recipients (5/42), and 22.0% for lung recipients (9/41).**

Conclusions: **Single-agent use with itraconazole in heart or lung transplant recipients did not affect the rate of fungal infection as compared with previous reports. The incidence of fungal infection increased significantly within 3 months after escalation of immunosuppressant for treatment of acute rejection.**

Key words: *Itraconazole, Antifungal prophylaxis, Heart transplant, Lung transplant*

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Acknowledgements: *No funding was required to complete this work. There is no conflict of interest for any of the authors with any companies/organizations whose products/services may be discussed in this article. The work and subsequent manuscript was completed at the University of Kentucky Medical Center, Lexington, Kentucky. This study was approved by the University of Kentucky Institutional Review Board. The authors wish to thank Sue Overman, Srikant Rajan, and Joseph Mueller for their assistance in reviewing the microbiology database, pharmacy database, and the transplant database.*

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Experimental and Clinical Transplantation (2011) 6: 399-404

Introduction

Infectious complications are common after thoracic transplant with fungal infections being less common than bacterial or viral infections. Invasive fungal infection can occur after heart and lung transplant, but typically occur more frequently after lung transplant.[1-11] Despite advancement in thoracic transplant, the susceptibility to fungal infection remains high for heart transplant recipients and lung transplant recipients.[12-13] Fungal infection is associated with a high mortality rate of approximately 60% in lung transplant recipients.[12] The reported highest incidence and attack rate of invasive aspergillosis in solid organ transplant recipients occurs in lung transplant recipients.[13] Subsequently, antifungal prophylaxis is a routinely done after thoracic transplant, including heart and lung transplant recipients, despite a lack of controlled trials.[13-18]

Antifungal prophylaxis has been reported to decrease the incidence and mortality of fungal infections in lung transplant.[13] Despite this widely accepted practice of antifungal prophylaxis after heart or lung transplant, there is no uniform approach because no randomized controlled trials have been done to study the optimal therapeutic agent(s), route of administration, and duration of prophylaxis. Consequently, there are wide variations to antifungal prophylaxis. Recently, a survey of lung transplant centers worldwide identified that 58.6% (34/58) of the 57% centers (58/102) that responded used universal antifungal prophylaxis, with 97.1% targeting *Aspergillus* spp. within the first 6 months after transplant.[14] Beyond 6 months after transplant, 51.8% of centers did not use antifungal prophylaxis.[14] Interestingly, there was a major shift toward of prophylaxis with voriconazole and an increased use of echinocandins, posaconazole, and inhaled lipid formulation amphotericin.[14]

This shift occurred despite voriconazole prophylaxis after lung transplant being associated with a higher incidence of hepatotoxicity and similar clinical effectiveness as compared with itraconazole.[19] Therefore, this study was performed to investigate the outcomes in thoracic transplant recipients (heart or lung) who received single-agent antifungal prophylaxis with itraconazole at our institution.

Materials and Methods

Study design and setting

The study design was an observational, retrospective study performed at the University of Kentucky Medical Center (UKMC) in Lexington, KY, which is an academic medical center with both heart and lung transplant programs. The University of Kentucky Institutional Review Board approved the study.

Subjects and data

All patients undergoing either heart or lung transplant between January 2001 and May 2005 were included in the study. Single-agent antifungal prophylaxis with itraconazole was given to all patients undergoing heart or lung transplant at UKMC during the study period. Itraconazole is a triazole antifungal agent that inhibits cytochrome P450-dependent synthesis of ergosterol in the cell membrane and has activity against *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, dermatophytes, and dimorphic fungi (*Histoplasma, Blastomyces*).[20]

Patients were excluded from the study if they were less than 18 years old at the time of the transplant. Patient medical records, and transplant and pharmacy databases, were used to collect data for the cohort. The hospital pharmacy database was used to identify any thoracic transplant recipient who received fluconazole, itraconazole, voriconazole, caspofungin, or amphotericin B during the study.

Data collected from the cohort included prophylactic itraconazole dosage and date initiated after transplant, duration of antifungal prophylaxis, concomitant medication use, rejection episodes, bacterial/viral infections, and mortality data. If a fungal infection was identified and treated, data was collected that included clinical symptoms, antifungal therapeutic agent, dosage and duration of therapy, and outcome of antifungal therapy.

Preoperative and perioperative immunosuppressive protocol before thoracic transplant

During the study, all heart transplant recipients received muromonab-CD3 (Janssen-Cilag, New Brunswick, NJ) for induction therapy for 5 to 7 days (monitored by muromonab-CD3 antibody panel) along with tacrolimus 1 mg daily, mycophenolate mofetil 1 gram every 12 hours, and methylprednisolone 125 mg every 8 hours beginning postoperative day 1. On the second postoperative day, the methylprednisolone dosage is reduced to 30 mg daily after 3 doses. All of these therapies in the postoperative period were given intravenously. For lung transplant recipients, induction therapy was not given but the same immunosuppressive therapy was given beginning postoperative day 1 as heart transplant recipients.

Definition of fungal infection

For consistency, a predetermined definition of a fungal infection was used for this study. Although there is no published definition of a fungal infection in thoracic transplant, there is a published consensus of the definition of a fungal infection in hematopoietic stem cell transplant recipients.[21] The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group formed a consensus committee that subsequently developed an international consensus on research-oriented definitions for the invasive fungal infections, which are most often seen and studied in immunocompromised patients.[21] The committee used 3 levels of probability for invasive fungal infections, which included "proven," "probable," and "possible."[21] This consensus statement reported that these definitions are intended for use in the context of clinical and/or epidemiologic research and not for clinical decision-making purposes.[21] Therefore, these same 3 levels of probability were used for this study.

Statistical Analyses

Descriptive statistics were used to define the baseline characteristics of the study population, incidence of fungal infection, and trends in both itraconazole use and fungal infections.

Results

A total of 83 thoracic transplants (42 heart transplants and 41 lung transplants) were performed (Table 1 shows the patients' demographics). Of the cohort, 94% of the patients (78/83) received itraconazole 200 mg by mouth daily as the initial dosage for antifungal prophylaxis. The remaining 6% of the patients (5/83) received 200 mg by mouth twice daily for 2 days, followed by 200 mg daily. Itraconazole was started postoperatively, mean time of 3.2 days ± 3.8 days (range, < 24 h and 25 d). The median duration of antifungal prophylaxis was 12 months (range, 6 to 39.5 mo). Itraconazole was well tolerated with no adverse events associated with its use. Tacrolimus dosage had to be adjusted slightly to maintain therapeutic levels when itraconazole was initiated.

During the study, there were 14 fungal infections that met the diagnostic definition according to the published international consensus in hematopoietic stem cell transplant.[21] Table 2 illustrates 14 fungal

Table 1. Patient demographics..

Characteristic	Total (n=83)	Heart transplant (n=42)	Lung transplant (n=41)
Mean age at transplant (y)	51.8 ± 10.9	51.7 ± 12.4	51.9 ± 9.4
Male (%)	60.2	81	39.1
White (%)	96.4	97.6	95.2
Black (%)	3.6	2.4	4.8
Indication for transplant (%)			
Cardiomyopathy (idiopathic or ischemic)		100	
COPD			60.9
Pulmonary fibrosis			26.8
Pulmonary hypertension			9.9
Cystic fibrosis			2.4

Abbreviations: COPD, chronic obstructive pulmonary disease

Table 2. Patient characteristics and outcomes.

Patient No	Age at time of transplant (y)	Ethnicity	Sex	Organ	Positive culture (posttransplant)	Treatment for acute rejection within 3 mo or earlier (therapy given)	Pathogen	Site of infection (source)	Definition criteria[21]	Therapy
1	40	White	Female	Lung	22 mo	Yes (methylprednisolone)	*Aspergillus fumigatus*	Lung (BAL)	Probable	Voriconazole
2[†‡]	64	White	Male	Heart	4 mo	Yes (Muromonab-CD3)	*Mucor* spp.	Brain	Proven by biopsy	Voriconazole, Amphotericin B Caspofungin
3	57	White	Male	Heart	6 d	No	*Aspergillus fumigatus*	Lung (sputum)	Probable	Voriconazole
3	57	White	Male	Heart	5 mo	Yes (muromonab-CD3)	*Candida albicans*	Sternal osteomyelitis	Possible	Fluconazole
4	60	White	Female	Lung	9 mo	Yes (methylprednisolone)	*Aspergillus fumigatus*	Lung (BAL)	Probable	Voriconazole
5	33	White	Female	Lung	3 mo	Yes[#] (methylprednisolone, muromonab-CD3)	*Aspergillus terreus*	Lung (BAL)	Possible	Voriconazole Amphotericin B
6	47	White	Male	Lung	7 mo	Yes (methylprednisolone)	*Aspergillus nidulans*	Lung (BAL)	Probable	Voriconazole
7	68	White	Male	Heart	4 mo	Yes (methylprednisolone)	*Aspergillus fumigatus*	Lung	Proven by biopsy	Amphotericin B
8	61	White	Female	Lung	12 mo	Yes (methylprednisolone)	*Candida glabrata*	Blood	Proven by culture	Caspofungin
8	61	White	Female	Lung	12 mo	Yes (methylprednisolone)	*Aspergillus fumigatus*	Lung (bronchial aspirate)	Possible	Voriconazole
9	57	White	Female	Lung	4 mo	Yes[#] (methylprednisolone, antithymocyte globulin)	*Aspergillus fumigatus*	Lung (BAL)	Probable	Voriconazole Amphotericin B
10	62	White	Male	Heart	11 mo	Yes (methylprednisolone)	*Aspergillus fumigatus*	Lung (sputum)	Possible	Voriconazole Amphotericin B
11	64	White	Female	Lung	10 mo	Yes (methylprednisolone)	*Candida albicans*	Blood	Proven by culture	Fluconazole
12	61	White	Female	Lung	7 d	No	*Aspergillus fumigatus*	Lung	Proven by biopsy	Amphotericin B

Abbreviations: BAL, bronchoalveolar lavage

[†]Strongyloides infection also isolated

[‡]Only death from cohort owing to fungal infection

[#]Initial treatment with methylprednisolone was unsuccessful, so refractory rejection required treatment with 2nd therapeutic agent (patient No. 5 was treated with Muromonab-CD3, and patient No. 9 was treated with anti-thymocyte globulin)

infection episodes in the cohort of 12 patients. For the entire cohort, the fungal infection incidence was 16.9% for both populations (14/83), while it was 11.9% for heart recipients (5/42) and 22.0% for lung recipients (9/41). This internationally accepted diagnostic definition of fungal infection was applied to this cohort and is included in Table 2. Nine fungal infections occurred in 8 lung transplant recipients, and 5 fungal infections occurred in 4 heart transplant recipients. The most-common pathogen was *Aspergillus* spp., which was responsible for 10 of the 14 total fungal infections (71.4%). There were 3 fungal infections caused by *Candida* spp. (21.4%), and 1 fungal infection caused by *Mucor* spp. (7.1%). Two patients had 2 fungal infection episodes. Patient No. 3 had *Aspergillus fumigatus* isolated on respiratory culture 6 days after lung transplant and experienced sternal osteomyelitis owing to *Candida albicans* 5 months later. Patient No. 8 had *Candida glabrata* isolated on blood culture, and *Aspergillus fumigatus* isolated on bronchial aspirate culture 12 months after lung transplant. Based on predefined study definitions, each of these fungal infection episodes was considered individual events, so all episodes were included in the analysis.

A total of 57.1% of the fungal infection episodes (8/14) also had concomitant bacterial infections. The bacterial pathogens included *Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *methicillin-resistant Staphylococcus aureus.* There was 1 patient who had infection with *Strongyloides stercoralis*. There was also 1 patient who had concomitant respiratory syncytial virus pneumonia, which was ultimately fatal. There was only 1 patient who died from a fungal infection during the study (Table 2).

In this cohort, 50% of fungal infections (7/14) occurred at more than 6 months after transplant. In fact, 21.4% of these later fungal infections (3/14) actually did not occur until after 12 months posttransplant. In lung transplant recipients, 67% of fungal infections (6/9) occurred at more than 6 months after transplant compared to 40% in heart transplant recipients (2/5).

During 2001 to 2003, the 1-month, 1-year, and 3-year survival rates were 95%, 85%, and 68%. The 1-month and 1-year survival rates did not significantly change, while the 3-year survival improved to 70% from 2003 to 2005. There was a total of 103 episodes of acute rejection in the entire cohort of 83 patients. This lung transplant recipients had a mean rejection of 0.7 episodes/patient year, while the heart transplant recipients had a mean rejection of 1.8 episodes/patient year. Standard treatment for acute allograft rejection is intravenous methylprednisolone 500 mg daily for 3 days. If acute rejection persists, the patient receives either intravenous Muromonab-CD3 5 mg daily for 10 days or anti-thymocyte globulin 1.5 mg/kg daily for 10 days. A total of 85% of the entire cohort (12/14) experienced a fungal infection after treatment of acute rejection (Table 2). In lung transplant recipients, 100% of patients who developed an acute fungal infection and were more than 6 months out from transplant (6/6) were treated for acute rejection within the last 3 months, compared with 66% of the patients who were less than 6 months out from transplant (2/3) (Table 2). These 2 lung transplant recipients, who underwent transplant earlier than 6 months before developing an acute fungal infection required treatment for refractory rejection that did not respond to high-dose methylprednisolone, with 1 patient being treated with Muromonab-CD3, and the other with anti-thymocyte globulin (Table 2). In the heart transplant recipients, 75% of patients who developed an acute fungal infection earlier than 6 months out from transplant (3/4) had recently been treated for acute rejection (Table 2).

Discussion

We used a diagnostic definition for fungal infection used in hematopoietic stem cell transplant patients published as an international consensus because there is no standard definition in heart or lung transplant. For all solid organ transplant recipients, a complicated postoperative course, repeated bacterial infections, *cytomegalovirus* disease, renal failure, or the need for dialysis, and allograft rejection are known risk factors for fungal infection.[22-23] Reported risk factors specifically for heart transplant include reoperation, *cytomegalovirus* disease, posttransplant hemodialysis, and the existence of an episode of fungal infection in the heart transplant program 2 months before or after the transplant date.[24] Environmental exposures, airway colonization, donor age, ischemia time, profound immuno-suppression, neutropenia, earlier *cytomegalovirus* infection, renal dysfunction, and use of daclizumab versus polyclonal induction are reported risk factors for fungal infection after lung transplant.[25-26]

The incidence rates of fungal infection for this cohort of transplant recipients were comparable to other studies for lung transplant recipients but higher for heart transplant recipients. Minari and associates[27] reported an incidence rate for invasive aspergillosis of 12.8% for lung transplant and 0.4% for heart transplant. An older study in 1995[28] in lung transplant recipients demonstrated an incidence of invasive aspergillosis of 16%, while another study in 2003[29] in heart transplant recipients reported an incidence of 6.6% of invasive aspergillosis infection (2.9% pulmonary and 3.7% extrapulmonary infections). The higher rate for fungal infection in heart transplant recipients in this cohort is likely associated with a more-meticulous method of diagnosis of fungal infection used for the current study.

The primary finding of the current study is the development of fungal infection in heart and lung transplant recipients soon after treatment with high-dose corticosteroids for acute allograft rejection despite single agent antifungal prophylaxis with itraconazole. There is conflicting evidence regarding increased risk of fungal infection after treatment with higher doses of corticosteroids for acute allograft rejection. A case-control study of solid organ transplant recipients, which included 47 heart transplant recipients and 17 lung transplant recipients, reported increased immunosuppression owing to chronic transplant rejection or allograft dysfunction as a risk factor for late-onset *Aspergillus* spp. infections, defined as *more than 3 months after transplant*.[23] In contrast, fungal infections with *Aspergillus* spp. were associated with chronic rejection but not related to treatment with high doses of corticosteroids in a cohort of 251 lung transplant recipients.[30] Allograft rejection, thus, heightened immunosuppressant therapy, was less common in patients with invasive pulmonary aspergillosis than patients with chronic airway colonization, but patients chronically colonized with *Aspergillus* spp. had more-frequent episodes of rejections than did patients with invasive pulmonary aspergillosis.[29]

This study found a total of 50% of fungal infection episodes (7/14) occurring more than 6 months after transplant with 6/7 of these occurring in lung transplant recipients. Typically, fungal infections in thoracic transplant occur 1 to 6 months after transplant.[31-32] These early fungal infections after transplant are related to surgical complications, while infections during the 1- to 6-month postoperative period reflect opportunistic, relapsed, or residual infections.[31] Fungal infections more than 6 months (and thereafter) are typically associated with treatments for chronic rejection or bronchial airway mechanical abnormalities in lung transplant recipients.[31] Previous studies in thoracic transplant recipients report that the most-common fungal pathogens are *Candida* spp. and *Aspergillus* spp.[31-33] In our cohort, *Aspergillus* spp. was the most-common infecting pathogen by far, with 71.4% isolating a species of *Aspergillus* spp. (10/14). Furthermore, *Aspergillus* spp. was isolated in 60% of heart transplant recipients (3/5) and 77.8% of lung transplant recipients (7/9). Moreover, there was a high concomitant infection rate at 57.1% in our cohort with simultaneous bacterial infection occurring more commonly.

The limitations of this study are the small number of patients, with a single-center experience, and the retrospective nature of the study. There also is the lack of a comparison or control group with all patients receiving the same prophylactic therapy. Unfortunately, comparing these outcomes to thoracic transplant recipients before 2001 was not feasible owing to changes in surgical techniques, antimicrobial and antifungal prophylactic strategies, and infection patterns at our institution over the previous 10 years.

This is the first study to use fungal infection definitions in heart and lung transplant recipients, which demonstrates some use for better identification of fungal infections in patients. Based on our findings, single-agent antifungal prophylaxis with itraconazole seems to work as well as other agents historically (just perhaps not in the presence of increased immuno - suppression). There was a high risk for developing fungal infections after treatment for acute rejection with the increase of immunosuppressant therapy; therefore, clinicians should consider intensifying step-up antifungal prophylaxis in this population. Further research is needed to better define fungal infection in heart and lung transplant recipients, as well as to determine ideal antifungal prophylaxis, which includes correct agents, timing for therapy, and need for modifications of therapy.

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