Published in final edited form as:

Transpl Infect Dis. 2019 June ; 21(3): e13067. doi:10.1111/tid.13067.

Why Do Lung Transplant Patients Discontinue Triazole Prophylaxis?

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Abstract

Background: Lung transplant recipients are prone to invasive fungal infections prompting many transplant centers to use prolonged triazole antifungal prophylaxis. From a practical standpoint, it is unclear if lung transplant recipients are able to continue prolonged or lifelong prophylaxis without premature discontinuation from side effects, drug interactions, development of fungal disease, or medication cost. We examined the number of patients that are able to reach a prophylactic endpoint and understand the reasons for early termination.

Methods: We conducted a retrospective chart review of all lung and heart-lung transplant patients at Mayo Clinic Rochester from May 1, 2002 to December 31, 2017. Type, duration, and reason for discontinuation of triazole prophylaxis were examined.

Results: During the study period, 193 patients underwent lung or heart-lung transplantation. Itraconazole, voriconazole, and posaconazole were given to 180, 73, and 60 post-transplant patients, respectively. Providers switched itraconazole to another prophylactic antifungal medication for reasons other than prophylactic completion in 61.8% (126 out of 204) of exposure episodes; this was similar with voriconazole (68.8%, 53 out of 77, $p=0.41$). Posaconazole was actively discontinued significantly less often (18.3%, 11 out of 60, $p<0.05$). The most common

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Author contributions:

Concept/design: KMP, CCK, RRR; Data analysis/Interpretation: KMP, CCK, RRR; Drafting article: KMP; Critical Revision of article: KMP, CCK, RRR, SP, JS, HS, MW, RD; Approval of article: KMP, CCK, SP, JS, HS, MW, RD, RRR; Statistical analysis: KMP

Conflict of interest: None of the authors have any conflicts of interest to disclose.

This study was reviewed by Mayo Clinic Institutional Review Board and approved under IRB 18-000712.

All authors have reviewed and contributed to this manuscript. No authors have any financial disclosures or competing interests.

reasons for discontinuing itraconazole were malabsorption (15.5% of exposure episodes) and concern for breakthrough fungal infection (10.2%). In comparison, the most common reason for voriconazole discontinuation was side effect or intolerance (54.5% of VR exposure episodes vs 9.8% of IT exposure episodes, $p<0.05$).

Conclusions: Itraconazole and posaconazole appeared to have fewer side effects prompting discontinuation than voriconazole, but itraconazole was discontinued more often because of malabsorption and clinical suspicion of fungal infections.

Keywords

Prophylaxis; Lung Transplant; Antifungal; Triazole

Introduction

Lung transplant recipients (LT) are particularly susceptible to opportunistic infections. Fungal infections, in particular, have been associated with a nearly three-fold increase in post-transplant mortality¹. Many transplant centers utilize systemic anti-fungal (AF) prophylaxis to prevent invasive fungal infections (IFI)^{2,3}. Itraconazole (IT) was first approved by the United States Food and Drug Administration (FDA) in April 2001; voriconazole (VR) was first approved by the FDA in May 2002. In 2008 (the last survey of AF prophylaxis prescribing patterns in lung transplant) IT and VR were the most commonly used systemic agents, but the duration of prophylaxis was not standardized and varied among transplant programs³. We believe some transplant centers continue to opt for short-term prophylaxis (<12 months post-transplant), while others recommend prolonged prophylaxis (≥ 12 months post-transplant). Because the risk of IFI persists greater than 1 year post-transplant in LT⁴, LT at our institution receive prolonged (for many, anticipated lifelong) triazole prophylaxis.

Several studies have demonstrated the effectiveness at decreasing the cumulative incidence of IFI and the tolerability of short-term VR and IT prophylaxis^{5,6}. From these studies, a theoretical benefit of prolonged prophylaxis may be extrapolated. However, prolonged administration of various AF agents introduces the possibility of a spectrum of side effects that may not be present with shorter durations such as cardiomyopathy, cutaneous cancers, skin reactions, and drug interactions⁷. Secondary to drug interactions with immunosuppressive agents (cyclosporin, tacrolimus, sirolimus, and mycophenolate mofetil), changes in AF prophylaxis may prompt acute rejection episodes or calcineurin inhibitor toxicity if immunosuppressive drug levels are not followed closely. From a practical standpoint, it is unclear if LT are able to continue prolonged or lifelong prophylaxis without premature discontinuation from side effects, drug interactions, development of fungal colonization/IFI, or medication cost. We examined the number of patients that are able to reach a prophylactic endpoint with our prolonged regimen and understand the reasons why prophylactic AF agents are terminated or changed to alternate therapy. We hypothesized that IT or posaconazole (PS) would be discontinued less often than VR, and that side effects and cost would prompt discontinuation most frequently.

Material and Methods

Study population

This single center, retrospective study was approved by the Mayo Clinic Institutional Review Board (IRB 18-000712). Using our transplant database, we identified all patients 18 years and older who underwent lung or heart-lung transplant at Mayo Clinic in Rochester between May 1, 2002 and December 31, 2017. In accordance with the Minnesota statute, only patients who authorized the use of their medical records for research were included in the study. A standardized form was used to retrieve demographic characteristics, post-transplant triazole prophylactic agent, duration of triazole prophylaxis, and the reason for discontinuing triazole prophylaxis as documented by the treating provider. If side effects or intolerances prompted the treating provider to discontinue AF prophylaxis, then the specific side effect/intolerance was recorded. No measures were in place to retroactively ensure the side effects attributed to AF prophylaxis by treating providers were in-fact due to the AF medication. If concern for fungal infection prompted discontinuation, then the type of fungal infection and the serum AF levels within 30-days prior to diagnosis was recorded. Patients were followed until death or last follow-up through October 17, 2018.

Standard protocols

Per protocol, all patients received intra-operative methylprednisolone followed by maintenance immunosuppression consisting of a calcineurin inhibitor, anti-metabolite, and prednisone. Patients received induction therapy with OKT-3 (Muromonab-CD3) from May 2002 to April 2008 or Thymoglobulin from May 2008 to February 2009. Induction immunosuppression was not routinely used from March 2009 onwards. Initial AF prophylaxis included caspofungin (2012 to present) or intravenous fluconazole (2002–2012) post-surgically until the patient was taking oral medications. Once taking oral medications, IT or VR was initiated. PS was reserved for cases of AF intolerance, malabsorption, or fungal airway colonization. IT capsules and PS tablets were used as preferential formulations. Dosing for IT, VR, and PS were based on trough levels. Serum AF trough levels were checked 7 days after initiation, and periodically as deemed necessary by the treating provider. Target trough levels were as follows: 2 ug/mL for IT and hydroxyl-IT, 1 ug/mL for VR, and >700 ng/mL for PS. Systemic triazole therapy was continued as prophylaxis for a minimum of 1 year post-transplant, but most patients received lifelong AF prophylaxis. AF prophylaxis was only discontinued at 1 year if the patient had demonstrated no prior fungal airway colonization and developed intolerance or could not afford the medication. Other antimicrobial prophylaxis included perioperative antibacterial prophylaxis (cefotaxime or cefepime, or tailored to bronchial cultures for cystic fibrosis patients), lifelong trimethoprim-sulfamethoxazole, and at least 6 months of valganciclovir (for cytomegalovirus [CMV] prophylaxis) or at least 4 weeks of oral acyclovir (for herpes simplex virus prophylaxis in LT not at risk for CMV).

Prior to 2009, bronchoscopies were performed only if clinically indicated. Thereafter, bronchoscopies were performed routinely per protocol at one, three, and six months post-transplant and as clinically indicated.

Definitions

Reasons that prompted the treating provider to discontinue a triazole agent (as documented in the electronic health record) were recorded. Liver function test abnormalities were defined as a deviation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase greater than 2 times the upper limit of normal. Gastrointestinal upset included nausea, vomiting, or diarrhea. Hyper-fluorosis was defined as a plasma fluoride levels >4 mmol/L without associated peri-ostitis, and peri-ostitis included hyper-fluorosis with associated bone pain.

Only proven and probable invasive fungal disease based on the revised European Organization for Research and Treatment of Cancer/Mycoses Study group definitions⁸ were considered IFI.

Statistical Analysis

Duration of exposure to IT, VR, or PS is expressed as median values with the interquartile range indicated parenthetically. Statistical comparison for duration of prophylaxis was made using Mann Whitney test. Reasons for discontinuation and side effects were calculated as a percent of the overall exposure episodes and analyzed using Fisher Exact or Chi Square tests, when appropriate. A p value of <0.05 was considered significant. All statistical analysis was performed using GraphPad Prism version 6.04 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

Results

Patient demographics

During the study period, 193 patients underwent lung transplantation at our institution (55 single, 123 bilateral, and 16 heart-lung). Reason for transplantation included: pulmonary fibrosis (72), COPD/ emphysema (47), pulmonary hypertension (21), cystic fibrosis (13), interstitial lung disease (11), alpha-1-antitrypsin deficiency (11), and other (18). The mean age at transplantation was 54.0 years (standard deviation 12.0 years); 47.1% (91) of LT were women and 91.3% (178) were Caucasian. 177 patients survived greater than 1 year post-transplant; 119 patients were deceased at the time of data abstraction with a median post-transplant survival of 3.88 years (1.39; 5.88); the average age at death was 58.1 years (SD 12.1 years).

Triazole prophylaxis

Seven patients were not exposed to IT, VR, or PS following transplant because of a complicated post-transplant course; all 7 patients remained on echinocandin or fluconazole prophylaxis and died during the transplant hospitalization. 180, 73, and 60 patients were exposed to IT, VR, and PS following transplant, respectively. Note some patients were exposed to more than 1 AF agent. More than 1 episode of exposure to IT and VR occurred in 24 and 4 patients, respectively. An episode of exposure was defined as taking an AF agent for greater than 1 day until a discontinuation or change to another AF agent. No patients had repeated episodes of exposure to PS. Duration of IT and PS exposure were similar [537.5 (128.8, 1452.0) and 752.5 (283.5, 1119.5) days, respectively $p=0.82$]. Duration of VR

exposure was significantly less compared to IT [165.0 days (52.0, 47.5), $p<0.05$] and PS ($p<0.05$).

Reason for discontinuation

None of our patients were still taking VR at the end of the study period; whereas 17.0% (31) and 40.0% (24) of patients continued on IT and PS (Table 1). Adequate prophylactic duration, as deemed by treating providers, prompted discontinuation in 3.8% (7), 2.7% (2), and 5.0% (3) of patients receiving IT, VR, and PS, respectively ($p=0.73$). Treating providers considered adequate duration of AF prophylaxis if a LT had received more than 1 year of prophylaxis and did not have any episodes of airway colonization. A similar percent of patients were taking IT (28.9%), VR (27.3%), and PS (36.7%) until death ($p=0.19$).

Providers actively discontinued IT for reasons other than prophylactic completion in 61.8% (126 out of 204) of exposure episodes; this was similar with VR (68.8%, 53 out of 77, $p=0.41$). PS was actively discontinued significantly less often than VR or IT (18.3%, 11 out of 60, $p<0.05$). The most common reasons for discontinuing IT were malabsorption (15.5% of exposure episodes) and concern for fungal infection (10.2%) (Table 1). In comparison, the most common reason for VR discontinuation was side effect/ intolerance (54.5% of VR exposure episodes vs 9.8% of IT exposure episodes, $p<0.05$). Only 19 patients discontinued or changed AF prophylaxis secondary to cost (IT 5.9%, VR 3.9%, PS 6.7%, $p=0.73$).

Side effects and intolerance

The most common side effects prompting IT discontinuation were gastrointestinal upset (3.4%, 7 out of 204 exposure episodes) and LFT abnormalities (2.9%, 6). VR side effects that prompted discontinuation included LFT abnormalities (18.1%, 14), hyper-fluorosis (13.0%, 10), peri-ostitis (10.4%, 8), and photopsia (3.9%, 3). LFT abnormalities were the primary side effect prompting PS discontinuation (3.3%, 2).

Fungal infection

During the study period, AF prophylaxis was changed in 22 patients because of a clinical concern for fungal infection. One patient had AF prophylaxis changed because of proven invasive aspergillus on 2 occasions (IT then PS). This patient was treated for invasive aspergillus and resumed AF prophylaxis after treatment completion. This patient ultimately developed disseminated aspergillus infection. Overall, 2 patients had cutaneous fungal infections, and 15 patients had proven or probable fungal disease (3 fungal sinusitis, 11 pulmonary aspergillosis, and 1 pulmonary *Rhizopus sp.* infection). No episodes of endemic mycoses and no other episodes of disseminated aspergillus infection. The other 5 patients had alternative explanations for their clinical presentations that included bacterial pneumonia (4) and post-transplant lymphoproliferative disease (1).

Sixteen patients with fungal infections received IT prophylaxis; the other patient with IFI was on VR prophylaxis. Serum IT trough levels at steady state were measured within 30 days of fungal infection in 15 of these patients: 1 patient had undetectable serum IT levels; 4 patients had detectable but sub-therapeutic IT levels (< 2 ug/mL for IT and hydroxyl-IT); and 10 patients had therapeutic IT levels (≥ 2 ug/mL for IT and hydroxyl-IT).

Discussion

While we know that short term triazole prophylaxis is safe and effective in LT^{5,6}, no one has previously examined the sustainability and tolerability of long term triazole prophylaxis. We had hypothesized that IT or PS would be discontinued less often than VR, but we found that IT was discontinued for a reason other than prophylactic completion in a similar proportion of exposure episodes as VR. However the reasons for stopping IT or VR were different. IT was discontinued because of malabsorption and concern for fungal infections—many of which were probable or proven IFI. Interestingly, most of these fungal infections occurred in patients with therapeutic serum IT levels. While we have no comparator to group to establish the rate of IFI in patients not on long term triazole prophylaxis, these findings are similar to a previous study conducted at our institution that suggested prolonged IT prophylaxis may not decrease the number of pulmonary or sinus IFI in LT⁹. This may be secondary to lower AF concentrations in the lungs and sinuses. Our rate of IFI, however, remain lower than the rates of IFI previously reported in LT on no or short term AF prophylaxis⁴.

With its unique side effect profile that includes hyperfluorosis, periostitis, and possibly increased risk of skin cancer, it is not surprising that VR was discontinued most often secondary to side effects. The duration of the VR exposure episodes were also much shorter compared to PS or IT indicating that VR was tolerated for shorter periods of time. Some of the discontinuation of VR may be due to hyper-vigilance of the treating providers as reports of VR induced hyper-fluorosis and peri-ostitis¹⁰, and VR associated skin cancer¹¹ occurred during the study period.

Since PS is not a first line AF prophylactic agent at our institution, fewer patients were exposed to PS than IT or VR. Prior studies have demonstrated the tolerability and effectiveness of short term PS prophylaxis^{12,13}. Our data showed that patients on PS had fewer disruptions or changes in AF prophylaxis. Medication sustainability is important with AF prophylaxis as medication alterations require dose adjustments in anti-rejection medications requiring close monitoring. Changes in AF medications may precipitate acute rejection episodes if anti-rejection medication dose adjustments are not completed.

While we hypothesized that cost would be a significant reason for discontinuation of AF prophylaxis, 19 patients discontinued or changed AF prophylaxis secondary to cost. Our study evaluated reasons for discontinuation as documented by the treating provider so patient expense may be under-represented. It is also possible that these patients are hidden in the adequate duration of prophylaxis group. Most patients at our institution receive lifelong prophylaxis so it is conceivable that duration was questioned and considered adequate secondary to patient cost. To our knowledge, no study has evaluated patient perspective and patient barriers to long term AF prophylaxis in lung transplant.

Limitations

The limitations of our study include the inherent bias of a single center, retrospective cohort study. We identified reasons for discontinuation or change in AF prophylaxis from provider documentation; this may under or overestimate the significance of certain side effects as they relate to the patient, such as the financial burden of AF prophylaxis to patients.

Additionally our study evaluated changes in triazole medications so diagnosis of fungal infections may have been missed if it did not prompt a change in the patient's baseline triazole therapy. For this reason, this study should not be used as an epidemiologic estimate of IFI on prolonged triazole therapy, rather an estimation of how frequently suspicion or diagnosis of IFI prompts a change in triazole therapy. Additionally, therapeutic drug monitoring at the time of diagnosis of IFI is not protocolized at our institution. AF troughs that occurred within 30 days prior to IFI diagnosis were used as surrogates.

Conclusion

PS was discontinued or changed prematurely in significantly fewer patients than IT or VR. Both IT and PS appeared to be better tolerated than VR, but IT was discontinued or changed more often because of malabsorption and clinical suspicion of fungal infections. PS appears to be a more sustainable long term AF prophylactic agent in LT than IT or VR.

Financial Support:

KMP and CCK are supported by the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN. CCK is also supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number K23HL128859. The manuscript contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Abbreviations

AF	Antifungal
IFI	Invasive Fungal Infection
IT	Itraconazole
LT	Lung transplant recipients
PS	Posaconazole
VR	Voriconazole

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Table 1:

Outcomes of prolonged triazole prophylaxis and reasons for early discontinuation

	Itraconazole	Voriconazole	Posaconazole	<i>p</i> -value
Number of patients:	180	73	60	
Still taking	31 (17.0)	0	24 (40.0)	<0.05
Adequate duration of prophylaxis	7 (3.8)	2 (2.7)	3 (5.0)	0.73
Taking until death	52 (28.9)	20 (27.3)	22 (36.7)	0.19
Lost to follow-up	7	0	0	n/a
Number of exposure episodes:	204	77	60	
Side effect/intolerance	20 (9.8)	42 (54.5)	4 (6.7)	<0.05
Concern for fungal infection	21 (10.2)	1 (1.3)	1 (1.7)	0.09
Malabsorption	32 (15.7)	2 (2.6)	1 (1.7)	<0.05
Airway colonization	14 (6.9)	1 (1.3)	1 (1.7)	0.09
Expense	12 (5.9)	3 (3.9)	4 (6.7)	0.73
Drug interaction	6 (2.9)	3 (3.9)	0	n/a
Actively discontinued *	126 (61.8)	53 (68.8)	11 (18.3)	<0.05

* Exposure episodes that were stopped by the treating provider for reasons other than adequate duration of AF prophylaxis.

Percentages are indicated parenthetically. Statistical analysis was completed using chi squared test.