VORICONAZOLE THERAPEUTIC DRUG MONITORING AMONG LUNG TRANSPLANT RECIPIENTS RECEIVING TARGETED THERAPY FOR INVASIVE ASPERGILLOSIS

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Abstract

Background: Invasive aspergillosis (IA) is the most important fungal infectious complication after lung transplantation. Voriconazole with regular therapeutic drug monitoring (TDM) is its recommended treatment. No studies have assessed the use of TDM in treatment of IA in lung transplants recipients. We aimed to determine if TDM was predictive of clinical outcome.
Methods: Retrospective chart review was performed for all lung transplant recipient from January 2013 to December 2015 at the Montreal University Health Center (CHUM). All patients with probable or proven IA, treated with voriconazole and TDM were included in the study. Population characteristics, TDM level, and outcome and toxicity at 6 and 12 weeks were recorded. Voriconazole levels of 1 to 5.5 µg/mL were considered therapeutic. CART regression tree analysis was used to find the most predictive voriconazole level thresholds for successful outcome at 12 weeks.
Results: In total, 111 lung transplantations were performed, and 12 fit inclusion criteria. Included and non-included patients had similar profile (age, type and urgency of transplants, underlying lung disease). All aspergillosis were pulmonary. A median of 4 voriconazole levels were obtained per patients: the overall median level was 1.1 µg/mL (min: 0.05, max: 7.3). Five out of the 12 patients had a median TDM higher than recommended therapeutic level. CART analysis cutoffs for median and minimum TDM were 0.645 and 0.415, respectively, and their corresponding fisher exact tests were close to or achieved statistical significance (p-values 6.06% and 1.52%). None of our patients died.
Conclusion: Our study supports the use of voriconazole TDM for IA treatment in lung transplant recipients. However, our data suggests that lower voriconazole level than currently recommended could be appropriate, and more research is required to arrive at definite conclusions regarding how to best monitor drug level and its optimal cutoffs.

Introduction

- Invasive aspergillosis (IA) is the most important fungal infection complication following lung transplantation **[1]**
- Voriconazole is the recommended treatment **[2]**
- There is conflicting evidence on the benefit of voriconazole therapeutic drug monitoring (TDM) **[3][4]**
- No study has assessed the utility of voriconazole TDM among lung transplant recipients (LTRs) receiving targeted therapy for proven or probable IA.
- Our aim was to determine if voriconazole TDM is predictive of clinical outcome in this patient group.

Methods

Retrospective review between Jan 2013 and Dec 2015
Inclusion criteria: - Probable or proven IA as defined by the ISHLT criteria**[5]**
- Treated with voriconazole monotherapy
- Underwent at least one voriconazole TDM

Population characteristics, TDM level, toxicity and outcome at 6 and 12 weeks of therapy, were recorded.
Clinical outcome were defined using the EORTC response to therapy definition**[6]**
Patients who did not complete the 12 week course due to toxicity were not included in the final analysis.

RESULTS

Table 1: Population characteristics

Characteristics	N =12 (%)
Age at transplant (median, IQ)	55 (46.8, 60.8)
Gender (male)	6/ 12 (50)
Underlying disease	
•Cystic Fibrosis	4/12 (33)
•Emphysema/COPD	4/12 (33)
•Idiopathic Pulmonary Fibrosis	2/12 (16.7)
•Interstitial Lung Disease	1/12 (8.3)
•Pulmonary Hypertension	1/12 (8.3)
Proven infection	0/12 (0)
Probable infection	12/12 (100)
Pulmonary involvement	12/12 (100)
Extra-pulmonary involvement	0/12 (0)
Time of onset after transplantation (d) (median, IQ)	194.5 (118, 259.5)

Table 2. Voriconazole therapy

Voriconazole formulation at initiation of therapy	N=12 (%)
•Intravenous	3/12 (25)
•Oral	9/12 (75)
Daily dose (mg) (median, IQ)	456.9 (400, 527.1)
Weight-adjusted daily dose (mg/kg) (median, IQ)	7.71 (6.29, 8.44)
Treatment duration (weeks) (median, IQ)	12 (12, 12)
Number of weeks until first TDM (median, IQ)	2 (1.75, 4)
Number of TDM performed per patient (median, IQ)	3 (2, 4.25)

Figure 1. Clinical outcome at 12 weeks

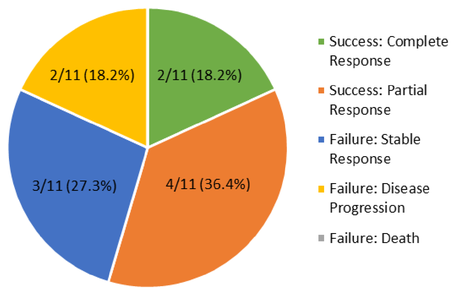


Table 3. Toxicities during therapy

Characteristics	N = 12 (%)
Toxicity	
•Hepatotoxicity	8/12 (66)
•Cutaneous reaction	1/12 (8.3)
•Musculoskeletal	1/12 (8.3)
Discontinuation of therapy due to toxicity	1/12 (8.3)

CART Decision Tree-Analysis

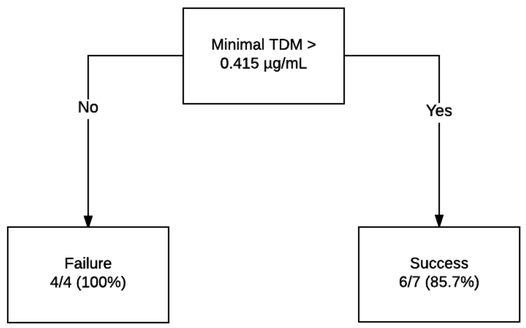


Figure 2A. Minimal TDM cut-off and clinical outcome at 12 weeks

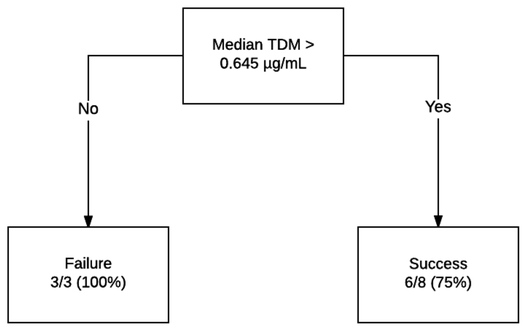
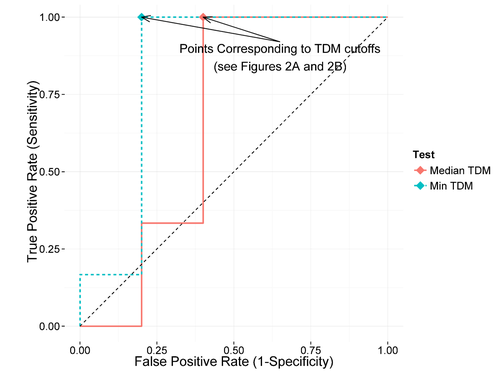


Figure 2B. Median TDM cut-off and clinical outcome at 12 weeks

RESULTS

Figure 3. Comparison of minimum and median TDM value and their relationship with outcome at 12 weeks

Figure 4. Comparison of minimum and median TDM value and their predictive value for outcome at 12 weeks, ROC analysis



Discussion

Limitations:
- Small sample size
- Retrospective design
- Voriconazole TDM measured at inconsistent intervals

Conclusion
- Among LTRs receiving voriconazole monotherapy for targeted therapy, those who achieve a minimal TDM value of **> 0.415ug/mL** were more likely to achieve successful outcome at 12 weeks of therapy
- Performing voriconazole TDM during therapy for IA among LTR may be useful to improve outcome
- TDM levels lower than the currently recommended ones could be appropriate in this patient population

References: **[1]** Neofytos TID. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. 2010; 12:220-9 **[2]** Walsh et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. CID 2008; 46:327-60 **[3]** Racil et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. Mycoses. 2012; 55:483-92 **[4]** Chu et al. Voriconazole therapeutic drug monitoring: retrospective cohort study of the relationship to clinical outcomes and adverse events. BMC Inf Dis. 2013; 13:105 **[5]** Husain et al. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. JHLT. 2011; 30:361-374 **[6]** Segal et al. Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria. Clin Infect Dis. (2008) 47 (5): 674-683