ABSTRACT

PASS A1501097: Evaluation of the potential association between voriconazole use and squamous cell carcinoma (SCC) of the skin among patients with lung or lung/heart transplants

Background

Voriconazole (Vfend®) is approved for the treatment of invasive aspergillosis (IA) and other invasive fungal infections (IFI). Voriconazole was also approved in June 2014 for prophylaxis of IFI in high-risk recipients of hematopoietic stem cell transplantations (HSCT) in the European Union. In addition to the approved indications, published reports indicate that voriconazole is commonly used as prophylaxis to prevent IA in solid organ transplant (SOT) recipients, primarily in lung or lung/heart transplant (LT) recipients.

Based on published case reports and retrospective observational studies, concerns have been raised about the risk of squamous cell carcinoma (SCC) of the skin with voriconazole administration, particularly in patients with immunocompromised status such as patients with solid organ transplant (SOT). The incidence of SCC of the skin is reported to be 65 to 250 times higher in SOT recipients than in the general population.

An observational study was conducted to evaluate the risk of SCC of the skin associated with voriconazole exposure in patients with LT. This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the European Medicines Agency (EMA).

Objectives

a. Primary objective

To assess the potential association between voriconazole use and the development of SCC of the skin in patients with lung or heart/lung transplant.

b. Secondary objective

To assess the potential association between voriconazole use and the development of melanoma in patients with lung or heart/lung transplant.

Methods

A retrospective cohort study using secondary data sources was designed to address the objectives. Lung or lung/heart transplant recipients constituted the study population. Consecutive patients aged ≥ 18 years that underwent LT between 1 January, 2005 and 31 December, 2008 were identified from 14 LT centres in the EU, North America and Australia.

Study eligible patients were followed from the date of LT to whichever of the following occurred first:

- Occurrence of SCC of the skin or melanoma (for patients developing one endpoint (e.g., SCC), follow up was continued for the occurrence of a second endpoint (e.g., melanoma)
- Death
- Last patient visit or 31 December, 2012, after which all surviving patients not experiencing an outcome were censored.

Patient-level data on voriconazole utilization, biopsy-confirmed diagnosis of SCC of the skin and melanoma, demographic and clinical characteristics including immunosuppressive agents, and underlying diseases at the time of LT were collected from each patient's medical record and entered into an electronic database.

Cumulative (not necessarily consecutive) voriconazole exposure of at least 30 days was considered clinically meaningful for the main analyses; the same criterion was applied to other azoles. Exposure to voriconazole and other azoles (i.e., posaconazole, fluconazole and itraconazole) were considered as time-dependent variables.

At each post-LT time point, an individual patient could be in any one of the following four exposure categories:

1. Totally unexposed to any azole, or exposed to some azole for less than 30 days (hereafter referred to as ***"unexposed"***),

2. Exposed to voriconazole for 30 days or longer but not to any other azole for 30 days or longer (hereafter referred to as ***"exposure to voriconazole alone"***)

3. Exposed to other azole(s) for 30 days or longer but not to voriconazole for 30 days or longer (hereafter referred to as ***"exposure to other azoles alone"***), *or*

4. Exposed to voriconazole for 30 days or longer as well as exposed to some other azole for 30 days or longer (hereafter referred to as ***"exposure to voriconazole and other azole(s)"***).

A patient's follow-up time spent in any of these four exposure status was allocated to the corresponding person-time category. Consequently, a patient may have contributed person-time in more than one exposure categories.

Incidence rates (number of events per 1000 person-years) of SCC of the skin and melanoma were estimated by the four treatment exposure categories. A multivariate Cox regression analyses was conducted to assess the risk of SCC of the skin with voriconazole exposure controlling for confounding variables including age, gender, history of malignancy pre-LT, confounding by indication (by using underlying diseases), patients' immune status and immune intensity (by using immunosuppressive agents and mean cyclosporine and tacrolimus levels), and exposure to sun light (by using geographical location of transplant centres by latitude).

Results

A total of 900 consecutive patients aged ≥ 18 years undergoing LT were included in the final analysis dataset: 440 (48.9%) from 7 centres in the EU, 430 (47.8%) from 6 centres in North America and 30 (3.3%) from one centre in Australia. More than half of the study patients were males and older than 50 years of age. Patients with ≥ 1 day voriconazole exposure and no exposure to voriconazole were comparable with regards to age and gender.

Incidence rate of SCC of the skin by treatment exposure

Overall, the incidence rate (per 1,000 person-years) of SCC of the skin was 33.4 in the exposure to voriconazole alone category, 10.4 in the exposure to other azoles alone category, 21.7 in the exposure to voriconazole and other azole(s) category, and 13.1 in the unexposed category.

Multivariable analyses to assess the risk of SCC of the skin with voriconazole

In a multivariable Cox regression model analyzing voriconazole, other azoles and immunosuppressive agents as time-dependent variables, exposure to voriconazole alone (adjusted hazard ratio [HR]=2.39, 95% CI: 1.31-4.37) and exposure to voriconazole and other azole(s) (adjusted HR=3.45, 95% CI: 1.07-11.06) were associated with SCC of the skin as compared with the unexposed after controlling for the confounding variables.

Effect of duration of voriconazole exposure on the risk of SC of the skin

A separate multivariable model adjusting for potential confounders suggested gradual increase in the risk with increasing cumulative duration of voriconazole exposure. Compared with no exposure to any azole, cumulative voriconazole exposure of 91-180 days (adjusted HR=2.23, 95% CI: 0.94-5.30) and >180 days (adjusted HR=3.52, 95% CI: 1.59-7.79) showed a higher risk of SCC of the skin.

Effect of dose of voriconazole exposure (measured as DDD) on the risk of SCC of the skin

A multivariable model adjusting for potential confounders suggested that an increase of one defined daily dose (1 DDD = 400 mg daily) in mean daily exposure to voriconazole increased the risk of SCC of the skin by 2.70-fold (adjusted HR=2.70, 95% CI: 1.53-4.78).

Among the 900 patients, one case of melanoma was identified— a male, aged 39 years from The Netherlands. The patient had undergone double LT secondary to interstitial pulmonary fibrosis (IPF) and was not exposed to any azole.

Conclusions

The study data suggest a 2.39-fold increased risk associated with exposure to voriconazole alone for 30 days or longer and a 3.45-fold increased risk associated with exposure to voriconazole and other azole(s) each for 30 days or longer compared with unexposed category. Of 900 patients included in the study, 55 developed SCC of the skin. Overall, median time from LT to the diagnosis of SCC of the skin was 3.3 years (range: 0.23 - 6.7 years). The study attempted to control for all major confounding variables and biases. Voriconazole and other azoles were analyzed as time-dependent variables to account for time-varying exposures. Attempt was made to control for potential confounding by immunosuppression by inclusion of immunosuppressive agents and mean cyclosporine and tacrolimus levels in the final multivariable model. Underlying diseases and transplant rejection episodes were included in the multivariate model to control for confounding by indication. It is well known that it is often impossible to obtain sufficiently accurate estimate of the effect of confounding by indication since "indication" is a complex and multifactorial phenomenon. Although data on underlying diseases, mean levels of cyclosporine and tacrolimus, and transplant rejection episode were used in the multivariable model in an attempt to control for potential confounding by indication, residual confounding by indication cannot be ruled out in this study.

Given that only one case of melanoma was identified among the study patients, analysis using inferential statistics for this endpoint was not possible.

The primary objective of this PASS was to evaluate the risk of SCC of the skin with voriconazole exposure and the study did not assess the effectiveness of voriconazole treatment such as reduction in IA or IFIs and/or all-cause mortality in this special patient population. It is important to carefully weigh the risk of SCC of the skin and benefits of voriconazole when prescribing to patients with LT.