

# Treprostinil: Safety Signal Detection Based on Adverse Event Reporting System Database

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## Abstract

**Objective:** To examine the association between treprostinil sodium and pneumonia in patients with pulmonary arterial hypertension, utilizing and analyzing the reports submitted to the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) and the published literature.

**Methods:** A total of 5,332,926 reports of adverse events between January 2006 and June 2012 were downloaded from the FDA AERS. These adverse events were associated with all other drugs inclusive of Treprostinil Sodium. A literature review was conducted on PubMed using the terms treprostinil and pneumonia. Authorized pharmacovigilance tools were used to determine the proportional reporting ratio, the reporting odds ratio, and the information component given by the Bayesian confidence propagation neural network.

**Results:** Based on the numerous adverse event pairs, 144 adverse events were listed as treprostinil sodium associated with pneumonia. The majority of the cases were seen in females (74%) and those between the ages of 51 and 75 years (63%). The most common route of drug administration among the cases was inhalation (73%).

**Conclusion:** This study helps indicate an association between the treatment with Treprostinil sodium and the development of pneumonia in pulmonary hypertensive patients. Additional research is needed to confirm with the medical relevance of the analysis.

**Keywords:** Treprostinil Sodium; Adverse event signals; Pneumonia; Pulmonary Arterial Hypertension; Proportional reporting ratio; Reporting odds ratio

## Introduction

Treprostinil is a prostacyclin analogue and is indicated as an inhalation solution for the treatment of patients with World Health Organization (WHO) Group I Pulmonary Arterial Hypertension (PAH) and New York Heart Association (NYHA) Class III symptoms to increase walking distance [1]. Treprostinil is used to treat pulmonary arterial hypertension, which is a dyspnea - fatigue syndrome that causes vascular resistance and eventually leads to right heart failure [1,2]. PAH is a disease of vasoconstriction and hence vasodilators are usually used to treat this disease. PAH occurs in association with a variety of conditions that include connective tissue diseases, congenital heart diseases, portal hypertension, human immunodeficiency virus infection, and intake of appetite-suppressant drugs [3].

The treatment for PAH has been limited for the past few years. Although the introduction of prostacyclins, endothelin receptor antagonist (ERA), and phosphodiesterase-5 (PDE-5) inhibitors has shown profound effects, the prognosis of PAH remains unfavorable. The medical life time expectancies of 5-6 years, and insufficient clinical improvement in about half of the survivors after 1-2 years were the estimations associated with PAH [4,5]. However, there has been progressive development in the treatment options available for PAH in the recent years, with the approval of two inhaled prostacyclin analogues: iloprost and Treprostinil [6-8]. Treprostinil sodium shows similar pharmacologic actions to epoprostenol with comparable acute hemodynamic effects [9]. Treprostinil has substantially longer half-life (4.5 hrs), can be administered four times a day, with a maintenance dose of 9 breaths per session [10]. A phase III study, examining the addition of inhaled treprostinil to oral bosentan or sildenafil, showed significant improvements in exercise capacity and quality of life [11]. The common adverse events of Treprostinil includes, headache, nausea, flushing and throat irritation or pain [11,12].

The objective of the TRIUMPH study was to examine the long-term efficacy of Treprostinil sodium to bosentan or sildenafil over 24 months used in the management of pulmonary arterial Hypertension. TRIUMPH I, was a 12-week, randomized, double blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group I), nearly all with NYHA Class III symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation [9]. The primary efficacy endpoint of the trial was the change in six-minute walk distance (6 MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6 MWD of 20 meters at Week 12 ( $p < 0.001$ ) [9]. This study confirmed 8 cases of pneumonia [9,13]. The TRIUMPH study open label extension reported over all 14 deaths related to worsening of PAH, septic shock, esophageal tumor, gastrointestinal hemorrhage, right heart failure, post-anoxic encephalopathy drowning, pulmonary embolism and pneumonia [12]. Most of the adverse reactions are associated with prostacyclin class of drugs. Pneumonia is most often characterized by old age, chronic illness such as heart disease, lung diseases, emphysema, smoking and chronic obstructive pulmonary disorder [14]. However the case reports

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	Adverse event of interest	Other adverse events
Drug of interest	a	b
Other drugs	c	d
	Adverse event of interest (Pneumonia)	Other adverse events
Drug of interest (Treprostinil sodium)	144	6579
Other drugs	42174	5332926

Table 1: Calculation of PRR.

of treprostinil induced pneumonia are minimal in published literature. The FDA requires additional investigation to determine the potential association between treprostinil and oropharyngeal and/or pulmonary toxicity given the adverse events reported in the clinical trials.

This study aims to characterize the association of treprostinil with pneumonia in pulmonary hypertensive patients by examining the adverse events reports submitted to the FDA Adverse Event Reporting System (AERS).

## Methods

We accessed the AERS database that includes voluntarily submitted reports of adverse events suspected to be caused by the use of prescription drugs. We downloaded the files and analyzed the data using SAS Version 9.2. We found reports that indicated pulmonary hypertension and for all approved treprostinil sodium using both trade and generic names. (Remodulin, Tyvaso). The preferred term as per the medical dictionary was pneumonia i.e. the adverse event of interest associated with Treprostinil. The reports for the adverse events were confined to severe adverse events leading to hospitalization and death and limited to those listed as primary suspect drug role for Treprostinil. On reviewing the cases, in order to obtain credibility, the duplicate cases were eliminated. The cases were organized based on gender, age, country of reporter, occupation of reporter and the year reported.

There was no known literature based on case reports with treprostinil-induced pneumonia. Hence a brief search was conducted on websites such as www.adverseevents.com, www.druginformer.com and www.fdaable.com to search for cases reported to FDA with regards to treprostinil induced pneumonia.

## Results

Below we examined the association between treprostinil and pneumonia utilizing four classical methods, based on frequentist principles and two methods based on Bayesian approach. Among these, the simplest and commonly used method is known as Proportional Reporting Ratio (PRR). The 2x2 contingency table (Table1) provided below helps in calculating the PRR.

$$PRR = \frac{a/a+c}{b/b+d} = \frac{144/(144+42174)}{6579/(6579+5332926)} = 2.75$$

The PRR can be interpreted as the ratio of the probability of the occurrence of adverse event of interest with treprostinil to the probability of the occurrence adverse event with any other drug. The confidence interval for PRR can be calculated by the method provided below:

$$95\% \text{ CI} = \exp \left( \ln (PRR) \pm 1.96 \sqrt{\left( \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d} \right)} \right)$$

The lower confidence limit of PRR greater than 1 indicates a suggestion of a possible signal.

Similarly, Reporting Odds ratio can also be calculated by the use of Table 1. ROR is interpreted the same way as PRR. However instead of the ratio of probabilities the ROR value gives the ratio of the odds. It can be calculated as follows:

$$ROR = \frac{ad}{bc} = 2.70$$

$$95\% \text{ CI} = \exp \left( \ln (ROR) \pm 1.96 \sqrt{\left( \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d} \right)} \right)$$

The critical value for the signal judgment is the same as PRR.

A Bayesian inferential method provides solutions taking into account all the reported drug-event combination at a time. Moreover the possible dependencies in the dataset can be computed by information component analysis (IC), which utilizes the Bayesian statistical approach.

Calculation for Bayesian Confidence Propagation Neural network (BPCN) =  $\log_2 a(a+b+c+d)(a+c)(a+b)$

In order to make decision about the drug-event combination using this approach, the lower 95% confidence limit of the IC value needs to be monitored. It can be computed as:  $E(IC) - 2\sqrt{V(IC)}$ , and it is denoted by 'IC-2SD'. If the IC value is zero, it indicates independence between the two attributes viz. drug and adverse event. And if the IC-2SD > 0 then it indicates a signal.

We detected the association using the second Bayesian method i.e. Empirical Bayes Geometric Mean (EBGM). This method is based on the concept of Multi-gamma Poisson Shrinkage (MGPS). This method helps examining the posterior distribution of the relative risk (observed / expected). For any (i, j)-th cell, we denote it by  $EB \log 2_{ij}$ .

$$EBGM_{ij} = 2^{EB \log 2_{ij}}$$

The value of EBGM is calculated the same way as relative risk. EB05 and EB95 are the lower and upper bounds of the two-sided 90% credible interval around EBGM.

$$EB05 \approx EBGM_{ij} \exp \left\{ -1.645 / \sqrt{c_{ij} + 1} \right\}$$

$$EB95 \approx EBGM_{ij} \exp \left\{ 1.645 / \sqrt{c_{ij} + 1} \right\}$$

$C_{ij}$  refers to the number of combinations between a specific drug (i) and the suspected AE (j). Data mining threshold using EBGM > 2 i.e. when the drug event combination occurs at least twice as expected.

A total of 6579 cases with treprostinil were initially identified in pulmonary hypertension patients. Among these 144 reports was associated with pneumonia (Table 2). There were (74%) of females and between the age group of 51 and 75 years (63%). Most of the cases were seen for inhalation (73%) route of administration of the drug (Figure 1). Almost all of these reports were from the US, the consumers reported 39% of these reports. We included both initial cases and follow up in our study and 82% of the initial reports stated pneumonia cases.

## Statistical Analysis

We used four different approaches to examine the association of treprostinil with pneumonia. We found the PRR value for treprostinil-pneumonia combination to be 2.75 and the corresponding 95%

Index (Years divided in four quarters)	Frequency Of Pneumonia (%)
200604	1 (0.69%)
200802	1 (0.69%)
200904	1 (0.69%)
201001	1(0.69%)
201002	4 (2.78%)
201003	10 (6.94%)
201004	13 (9.03%)
201101	10 (7.64%)
201102	25 (17.36%)
201103	19 (13.19%)
201104	21(14.58%)
201201	33 (22.92%)
201202	4 (2.78%)
<b>Total</b>	<b>144</b>

Table 2: Index (Year adverse event reported).

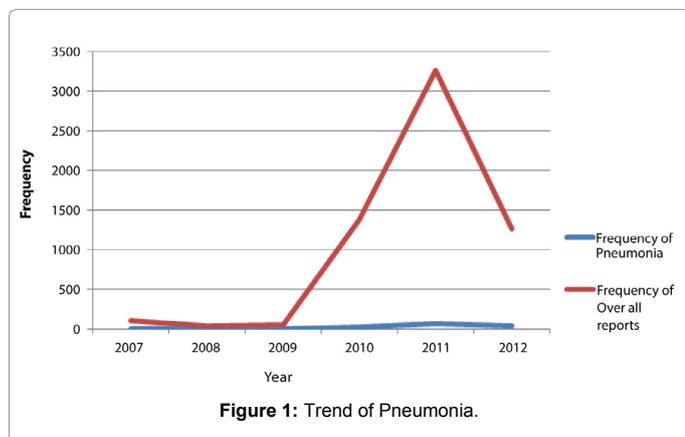


Figure 1: Trend of Pneumonia.

confidence interval as (2.36, 5.00). The value for ROR was found to be 2.00 and the corresponding 95% confidence interval as (1.68, 2.35). Further we examined the association utilizing the Bayesian Propagation Neural Network and found that it to be 1.44 and the value found by MGPS method was found to be 2.72. These results were remarkably similar to those found by PRR. Using the statistical definition of statistical significance of the above methods used, it appears that treprostinil may be associated with pneumonia.

## Discussion

In our analysis we found that in the FDA AERS, we identified 144 cases of pneumonia associated with treprostinil. Pneumonia has been notified as one the severe adverse event for this drug in TRIUMPH study for clinical trials. However, there is not enough published literature to support the findings of the study. Our data was consistent with the available reports found on the website www.adverseevent.com but the results differed from those mentioned on the www.druginformer.com. The difference was mainly due to the search criteria which included oral form of treprostinil i.e. UT-15, and besides PAH it also included cor pulmonale chronic disorder. Females are prone to have a higher risk for PAH and consequently has higher probability for treprostinil induced pneumonia, these findings were consistent with the study results.

PAH is particularly common in interstitial lung disease associated with connective tissue diseases, where the underlying pathology is frequently a non-specific interstitial pneumonia. A research show that PAH is highly prevalent in people with pneumonia, and pneumonia is

Drug Name	Frequency (%)
Remodulin	38 (26.38%)
Tyvaso	106 (73.61%)
Gender	
Male	38 (26.57)
Female	107 (73.43%)
Age of patients (Years)	
1-25	10 (7.19%)
26-50	27 (19.42%)
51-75	87 (62.59%)
76-100	15 (10.79%)
Weight of the patients (Kgs)	
1-50	17 (16.83%)
51-75	34 (33.66%)
76-100	27 (26.73%)
101-125	12 (11.88%)
126-150	8 (7.92%)
151-183	3 (2.97%)
Route of Administration	
Intravenous	26 (18.06%)
Respiratory (inhalation)	105(72.45%)
Retroocular	1(0.69%)
Subcutaneous	12 (8.33%)
Initial reporter's type of occupation	
Consumer (CN)	51 (38.06%)
Physician (MD)	19 (14.18%)
Other health professional (OT)	47 (35.07%)
Pharmacist (PH)	17 (12.69%)
Status of the report	
Initial	118 (81.94%)
Follow up	26 (18.06%)
Country of reporter	
Austria	1 (0.69%)
United States	143 (99.31%)

Table 3: Summary of adverse event cases (pneumonia) associated with treprostinil.

exacerbated in such cases. Studies [15-18] have also stated that PAH increases the mortality in patients with pneumonia. Thus the etiology of pneumonia and its severity could not confirm with the results of our study. This study is exploratory in nature and no adjustments were made for multiple comparisons and hence not confirmatory. There could be an association between treprostinil and pneumonia but needs additional and in-depth- analysis to examine the medical relevance associated with it (Table 3).

There are certain limitations to the study. The AERS database does not receive reports for all the adverse event and medication errors and hence these findings are likely to be underreported. Besides, this study suggests an association between the drug and the adverse event and does not prove any causality related to it. Also, the AERS database does not help in determining the incidence of the adverse event. More research to examine this association of treprostinil and pneumonia is needed to advocate the findings of this study.

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