Associations Between Sildenafil Use and Changes in Days of Hospitalization in a Population With Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

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ABSTRACT

Purpose: Pulmonary arterial hypertension (PAH) can be a complication in patients with connective tissue disease (CTD). Although the phosphodiesterase-5 inhibitor sildenafil shows evidence of efficacy and tolerability among patients with PAH associated with CTD in clinical trials, no studies have examined the association between its use and health care resource utilization in clinical practice. The objective of this study was to assess the associations between the use of sildenafil and health care resource utilization, specifically days of hospitalization, in a population with PAH associated with CTD.

Methods: A retrospective, matched, case–control analysis was conducted using data from a commercial claims database. Patients with a claim dated between 2003 and 2009 were selected. Cases and controls were matched on age, sex, and baseline total days of hospitalization. A longitudinal, zero-inflated, negative binomial model was used for analyzing the data after control for age, sex, region, Charlson comorbidity score, and use of PAH-specific medication other than sildenafil.

Findings: A total of 420 individuals, 210 cases and 210 controls, were included in the sample. The sample was 85.71% women, and the mean age was 57.6 years. Estimates for variances of an intercept random effect (5.08×10^{-13}) and for a time-variable random effect (2.84×10^{-16}) were both essentially zero. Thus a zero-inflated negative binomial model without random effects was used. When individuals were not using sildenafil, each 1-month interval was associated with a 2.8% increase in the mean number of days of hospitalization. In contrast, when individuals were using sildenafil, each 1-month interval was associated with a decrease of 3.3% in days of hospitalization.

Implications: In this data analysis of the association between sildenafil use and days of hospitalization among individuals with PAH associated with CTD in a large-scale population, sildenafil use in the treatment of PAH associated with CTD was associated with reduced days of hospitalization during the year after the initiation of treatment. (*Clin Ther.* 2015;37:1055–1063)

Key words: connective tissue disease, health care utilization, days of hospitalization, pulmonary hypertension.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disease characterized by elevated mean pulmonary arterial pressure and pulmonary vascular resistance, leading to right heart failure and death.[1] PAH can be a complication in patients with connective tissue disease (CTD), a group of diseases characterized by vascular injury, autoimmunity, tissue inflammation, and organ dysfunction.[2,3] Individuals with PAH associated with CTD account for 25% to 30% of all individuals with PAH,[4,5] the most common group of PAH except for idiopathic PAH. The prognosis of individuals with PAH associated with CTD is poorer than in those with idiopathic PAH.[6–9] In addition, the rate of hospitalization has been reported to be significantly higher in patients with PAH associated with CTD compared with that in patients with idiopathic PAH.[10]

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In the past 2 decades, pharmacotherapy targeted at the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway for PAH has been developed. Therapeutic agents with reported benefits in randomized clinical trials include the phosphodiesterase-5 inhibitors, the endothelin receptor antagonists, and the prostanoids. Among PAH-specific medications, the phosphodiesterase-5 inhibitor sildenafil is the most frequently prescribed medication.[5]

Clinical trials that have reported efficacy and tolerability with sildenafil among patients with PAH associated with CTD have used exercise capacity, hemodynamic measures, World Health Organization functional class, and tolerability as end points.[11] Sample sizes in clinical trials have been relatively small. The number of days of hospitalization has not been included as an end point, and the understanding of the effects of sildenafil use on hospitalization has been limited. Although a recent study by Berger et al[12] investigated the effects of sildenafil on health care resource utilization and costs in clinical practice settings, a single group of patients with PAH without any comparison group was studied, and the study did not focus on patients with PAH associated with CTD. A literature search revealed no studies that have examined the association between sildenafil use and hospitalization days among patients with PAH associated with CTD in clinical practice. The objective of the present study was to compare health care resource utilization, specifically the number of days in-hospital, before and after the initiation of sildenafil treatment in a population with PAH associated with CTD.

MATERIALS AND METHODS

Data Source

An observational data analysis was conducted using data from the MarketScan® Commercial Claims and Encounters database and the MarketScan® Medicare Supplemental and Coordination of Benefits database. These databases capture person-specific enrollment, clinical utilization, and expenditures across inpatient services, outpatient services, and prescription drug services. The institutional review board at Purdue University (West Lafayette, Indiana) approved the study protocol.

Sample Selection

A retrospective, matched, case–control cohort design was used. Data were included in the sample from patients who had at least 1 claim with a diagnosis of CTD identified using *International Classification of Diseases, 9th Revision–Clinical Modification* (ICD-9-CM) codes for systemic lupus erythematosus (710.0), systemic sclerosis (710.1), Sjögren disease (710.2), dermatomyositis (710.3), polymyositis (710.4), or undifferentiated diffuse CTD (710.9) dated from January 1, 2003, to December 31, 2009. Eligible individuals also had at least 1 inpatient claim or 2 outpatient claims with ICD-9-CM–defined diagnoses of PAH (416.0, 416.8) dated between January 1, 2003 and December 31, 2009. Eligible cases had a pharmacy claim for sildenafil after PAH diagnosis, with the date of the first pharmacy claim for sildenafil after PAH diagnosis defined as the *index date*. Eligible individuals also were continuously enrolled in tracked health plans for 390 days pre- and postindex.

Individuals were included in the sample as controls if they met inclusion criteria that were the same as those for cases, except that they did not have a pharmacy claim for sildenafil after PAH diagnosis. Controls were matched to cases based on age, sex, and total number of days of hospitalization within the 360 days preindex (ie, baseline total days of hospitalization). The index date for each case was assigned to its matched control. The case–control matching caliber for age was ± 10 years, and the caliber for baseline total days of hospitalization was ± 1 day. Cases that could not be matched to a control on baseline total days of hospitalization ± 1 day were excluded from the sample.

Individuals with a pharmacy claim for sildenafil before the index date were excluded. Individuals with > 30 baseline total days of hospitalization were excluded from the sample because they might have been considered institutionalized, and the effect of treatment of sildenafil could have been confounded.

Study Variables

A time period starting from 390 days preindex to 390 days postindex was identified as the *study period* for each individual. There were twenty-six 30-day periods, and each 30-day interval was considered a *month* in the analysis.

Total days of hospitalization per month was calculated as the sum of days of hospitalization for each admission that occurred within a 1-month interval.

Predictors in the model included a time variable *month,* indicating the month of the observation described;