Thrombosis Research 160 (2017) 83–90

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Assessment of the quality of anticoagulation management in patients with pulmonary arterial hypertension

Tamara Roldan[a], Elena Villamañán[b], Juan J. Rios[c], Aaron B. Waxman[d,*]

[a] Department of Pharmacy, Brigham and Women's Hospital, Boston, MA, USA,
[b] Department of Pharmacy, Hospital Universitario La Paz, Madrid, Spain
[c] Department of Internal Medicine, Hospital Universitario La Paz, Madrid, Spain
[d] Department of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA

ARTICLE INFO

Keywords:
Pulmonary hypertension
Anticoagulants
International normalized ratio
Safety
Hemorrhage

ABSTRACT

Background: Studies assessing the quality of anticoagulation therapy in patients with pulmonary arterial hypertension (PAH) have not been conducted.
Objective: To assess the quality of anticoagulation management, the rate of anticoagulation-related complications in patients with PAH, and to identify risk factors for poor anticoagulation.
Methods: This observational, retrospective cohort study included patients with confirmed PAH taking a regimen of oral anticoagulants from two centers: Brigham and Women's Hospital in Boston, and Hospital Universitario La Paz in Madrid from January 2009 to August 2015. Efficacy of anticoagulation management and time spent within therapeutic range of study participants were assessed.
Results: There were a total of 121 patients with PAH taking oral anticoagulants. Time spent within range (TTR) of those taking vitamin K antagonists (VKAs) was 57.0%. Forty-seven patients (38.8%) had a total of 105 anticoagulation-related events. The odds ratio of having an event in patients with a TTR $<$ 60% was 2.43 (CI 95%, 1.01–5.83; $p = 0.046$). Possible factors that affected the quality of the anticoagulation were the age, sex, functional capacity, atrial fibrillation and certain pulmonary arterial hypertension specific medications.
Conclusion: The quality of targeted anticoagulation in patients with PAH was low. Patients with low TTR were at a higher risk of experiencing anticoagulation-related complications. Specialized anticoagulation centers showed better management of oral anticoagulants.

1. Background

Anticoagulation therapy became widely utilized in the treatment of pulmonary arterial hypertension (PAH) after observational studies demonstrated a high prevalence of vascular thrombotic lesions [1,2].

To date, the anticoagulants of choice in patients with PAH are vitamin K antagonists (VKAs). The use of these agents entails attention due to a narrow therapeutic window, significant variability among patients, unpredictable pharmacokinetics, and multiple drug-drug and drug-diet interactions. The American College of Chest Physicians suggests an international normalized ratio (INR) range of 1.5–2.5 [3,4], while European guidelines recommend an INR range of 2.0–3.0 [5,6]. One study in patients with IPAH established the efficacy of low-intensity warfarin therapy (INR range 1.5–2.5) to decrease thrombin generation, suggesting that low-intensity warfarin therapy could be sufficient in patients with IPAH [7]. However, an INR range of 2.0–3.0 is more frequently used in clinical practice. Henkens et al. reported higher INR target ranges in their study of patients from a Dutch pulmonary hypertension cohort [8]. Most of the patients in this study had target INRs over 2.0–3.0.

Suboptimal anticoagulation management has been associated with poor clinical outcomes in patients with non-valvular atrial fibrillation (AF), even in patients who were routinely monitored with INR readings [9,10,11]. Increased risk of death, myocardial infarction, major

Abbreviations: AF, atrial fibrillation; BWH, Brigham and Women's Hospital; DOACs, direct oral anticoagulants; HULP, Hospital Universitario La Paz; INR, international normalized ratio; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartilic range; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; NSAIDs, non-steroidal anti-inflammatory drugs; PAH, pulmonary arterial hypertension; TTR, time spent within therapeutic range; VKAs, vitamin K antagonists; VTE, venous thromboembolism; WHO, world health organization; 6MWD, six-minute walking distance

* Corresponding author at: Pulmonary Vascular Disease Program, Centre for Pulmonary-Heart Diseases, Brigham and Women's Hospital Heart and Vascular Centre, Harvard Medical School, 75 Francis Street, PBB CA-3, Boston, MA 02115, USA.
E-mail addresses: troldan@bwh.harvard.edu (T. Roldan), elena.villamanan@salud.madrid.org (E. Villamañán), juanj.rios@salud.madrid.org (J.J. Rios), abwaxman@bwh.harvard.edu (A.B. Waxman).

https://doi.org/10.1016/j.thromres.2017.10.024
Received 9 August 2017; Received in revised form 29 October 2017; Accepted 30 October 2017
Available online 02 November 2017

bleeding and stroke or systemic embolization have been linked to poor INR control in patients with AF; thus, effective INR control is paramount to improving patient outcomes [12]. There is increasing evidence that control is difficult to achieve and maintain over long periods of time especially in complex medical patients [11,13]. There are several characteristics of patients with PAH that may possibly increase the risk of bleeding (some PAH etiologies and/or medications), but data on anticoagulation complications in patients with PAH is scarce. The endothelin receptor antagonists bosentan and sitaxsentan (currently withdrawn from the market) moderately interact with warfarin. Nonetheless, it is not a class effect, as no interaction has been found when ambrisentan or macitentan have been used with warfarin. Bosentan induces the CYP enzyme system responsible for the metabolism of coumadin-derived anticoagulants [14]. The clinical relevance of these findings appears to be limited since there were no significant modifications to warfarin regimens or excess in bleeding events in the pivotal Bosentan Randomized Trial [15]. On the other hand, the risk/benefit ratio changes in PAH with approved indications of anticoagulation such us atrial fibrillation (AF) or venous thromboembolism (VTE), in which case the use of VKA demonstrated to be favourable for thrombo-prophilaxys. The proportion of PAH patients using VKAs with a validated indication reported in a recent study rose to 40%. This high percentage is somewhat expected given that PAH patient's profile in the new era is evolving into one with more comorbidities and advanced age.

Achieving successful anticoagulation control in medically complex patients, such as those with PAH, can be challenging. Erratic control of anticoagulation could lead to conflicting clinical benefit, and complications associated with use. Studies assessing the quality of anticoagulation achieved in PAH have not been performed. Given this lack of data, we analyzed the management of VKAs, the rate of associated complications, and potential factors associated with a poor anticoagulation control in patients with PAH.

2. Materials and methods

We performed a retrospective observational cohort study of patients with PAH from two centers: Brigham and Women's Hospital in Boston (BWH), and Hospital Universitario La Paz (HULP) in Madrid. Patients with PAH were followed from January 2009 to August 2015. We collected data from the hospitals' databases, BWH Anticoagulation Management Service (AMS), and primary care institutions where patients were monitored. The study was approved by the HULP Ethics Committee, and underwent classification by the Spanish Medicine Agency. Patients from HULP meeting protocol selection criteria were asked to provide informed consent. Partners Healthcare institutional review board waived the need for informed consent.

2.1. Patients

Patients had a diagnosis of PAH confirmed by right heart catheterization based on a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, and a mean pulmonary artery wedge pressure (mPAWP) ≤ 15 mm Hg. They were followed in one of the two pulmonary hypertension specialized centers for at least a year and started on oral anticoagulation treatment before or throughout the study period. The follow-up time spanned from the beginning of the anticoagulation therapy or from PAH diagnosis if anticoagulation was previously initiated to end of anticoagulation treatment, end of study period or death. Most patients were taking VKAs (warfarin in Boston, acenocoumarol in Madrid) on an individualized dosage regimen as per target INR recommendations. Direct oral anticoagulants (DOACs) were also used to a lesser extent. Pulmonary targeted therapies (prostacyclin analogues, endothelin-receptor antagonists, phosphodiesterase-inhibitors) were prescribed according to recent PAH guidelines.

2.2. Data collection

The following information was obtained from the patient's electronic medical record: demographic variables, clinical variables (PAH etiology and functional capacity), hemodynamic and echocardiographic findings, specific PAH pharmacotherapy, and concomitant medications. Regarding anticoagulation therapy we recorded: anticoagulant agent, target INR, indication for anticoagulation (both approved and off-label), time spent in therapeutic range (TTR), treatment termination, VKA interactions, and anticoagulation-related complications (major hemorrhage, clinically overt and associated with a fall in hemoglobin of at least 20 $g{\cdot}L^{-1}$ (≥ 1.2 $mmol{\cdot}L^{-1}$), resulted in the need for transfusion of at least two units of red cells, involved a critical site, or if it was fatal [16]; minor hemorrhage, all other overt bleeding not meeting the definition for major bleeding; hematomas; thrombosis, every event related to the formation or the presence of a thrombus). To identify risk factors for poor anticoagulation control several patient characteristics and pharmacotherapy variables were evaluated. An anticoagulation therapy was considered poor when the TTR was under 60%. This reference value was stablished in accordance with the criteria used by the HAS-BLED score authors to differenciate poor than adequate anticoagulation control [17].

2.3. Data evaluation

Central tendency measures were used to describe quantitative and ordinal variables. For categorical variables, we calculated absolute and relative frequencies through percentages. We used the Student's *t*-test for independent samples in parametric distributions to analyze differences in TTRs between subgroups, and the Mann-Whitney *U* test to compare groups in non-parametric distributions. Categorical variables were compared using the Pearson's chi-square test for independence. We considered a *p*-value of < 0.05 statistically significant.

The TTR was calculated by the Rosendaal method incorporating the frequency of INR measurements, their actual values, and assuming that changes between consecutive INR measurements are linear over time. The TTRs from BWH AMS patients were directly obtained from DAWN®AC anticoagulation software. TTRs from BWH patients who were not managed by the BWH AMS, and TTRs from HULP patients were manually calculated. Once the TTRs of all the applicable patients were obtained, we measured TTRs by centers. To compare TTRs among centers the cut-off over which anticoagulation was considered successful was 65%, as this value is tipically used by anticoagulation specialty centers as a reference to evaluate the quality of their anticoagulation management [18]. To avoid large differences in anticoagulation lengths between study patients, we calculated the adjusted TTR:

$$TTR(\%) = \frac{TTR_1{}^{*}total\ days_1}{\sum population\ days} + \frac{TTR_2{}^{*}days_2}{\sum population\ days} + \frac{TTR_3{}^{*}days_3}{\sum population\ days} + \ldots + \frac{TTR_n{}^{*}days_n}{\sum population\ days}$$

TTR = time spent in therapeutic range.

To analyze the possible influence of several factors in the control of the anticoagulation therapy with VKAs in patients taking oral anticoagulants we performed a univariate linear regression analysis. The following variables were evaluated: age, sex, years on anticoagulation, target INR > 2.5, world health organization (WHO) functional class, presence of AF, enrollment center,use of combined PAH treatment and specific targeted therapies, number of medications and VKA interactions.

Statistical analysis was performed using SPSS for Windows (version 15.0: SPSS Inc., Chicago, IL, USA) and MedCalc for Windows (version 16.4: MedCalc Software, Ostend, Belgium).