Pulmonary Pharmacology & Therapeutics 39 (2016) 21–27

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

Global research trends in the medical therapy of pulmonary arterial hypertension 2000–2014

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ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form
25 May 2016
Accepted 26 May 2016
Available online 1 June 2016

Keywords:
Bibliometric study
Pulmonary arterial hypertension
Clinical science
Basic science

Chemical compounds studied in this article:
Epoprostenol (PubChem CID 5480427)
Sildenafil (PubChem CID 5212)
Bosentan (PubChem CID 104865)

ABSTRACT

Background: Pulmonary arterial hypertension is a progressive disease of the pulmonary vasculature that affects more than 200.000 patients worldwide. Without medical treatment it leads to right heart failure and death. Extensive fundamental and clinical research has been performed throughout the globe to modify the disease and improve survival.
Methods: We performed a bibliometric study on medical treatment for pulmonary arterial hypertension to identify study characteristics, impact factors and the countries of origin of basic and clinical studies that were published between 2000 and 2014. For visualization of the obtained data density equalizing maps were prepared.
Results: A total of 681 studies were eligible, of these 56% were clinical studies that have included a total of 30960 patients. Most studies were performed on endothelin receptor antagonists, followed by prostacyclins and phosphodiesterase type 5 inhibitors. Impact factors did not differ between clinical and basic science studies. The United States for clinical studies, and China for basic science studies were identified as main contributors to the global scientific output.
Conclusions: This first bibliometric study in the field of pulmonary arterial hypertension shows that a significant amount of scientific research was performed within the last 14 years mainly in North America, Asia and Europe. As current trends in this field of research we identified combination therapies and Asian countries being a new hatchery for emerging experimental and clinical studies.

1. Background

Pulmonary Hypertension (PH) is a rare heterogenic disease entity accumulating significant morbidity and mortality among approximately 200.000 patients around the world [1–3]. Among the five WHO classes of PH, class I comprises patients with idiopathic, hereditary, drug induced or associated (connective tissue disease, HIV, congenital heart disease and schistosomiasis) pulmonary *arterial* hypertension (PAH) [4–7]. Whereas in WHO classes II to V therapy of the underlying organ or systemic disease is crucial, for PAH patients the therapeutic options are limited. Since the first pathologic description of PH by Ernst von Romberg in 1891, an enormous knowledge has been gathered [8].

The non-specific medical therapy consists of diuretics, anticoagulants and in a minor subset of patients, if vaso-reactive, calcium channel blockers [9]. The majority of patients needs a specific PAH therapy that interacts with one of the three selective pathways [5,10–12]. The first pathway is the prostacyclin pathway. Epoprostenol, given intravenously in 1984, was the first substance of this group [13]. Subsequent development gave birth to further

Abbreviations: BORG, Rating of Perceived Exertion Scale; DBF, DataBase File, file format used by database software; ERA, Endothelin Receptor Antagonist; EU, European Union; HIV, Human Immunodeficiency Virus; PAH, Pulmonary Arterial Hypertension; PDE5, Phosphodiesterase type 5; PH, Pulmonary Hypertension; U.S./USA, United States of America; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.pupt.2016.05.004
1094-5539/

prostacyclin receptor agonists that can be given either per inhalation (iloprost), subcutaneous (treprostinil), or oral (beraprost, selexipag) [14–19]. The second pathway is the nitric oxide pathway. The first successful use of a selective phosphodiesterase 5 inhibitor was reported in a rat model of monocrotaline-induced pulmonary hypertension in 1996 by a japanese group [20,21]. Since the approval of sildenafil for human PAH in 2005 many studies have shown a significant benefit for the PAH patient [22–24]. New drug formulations (tadalafil, vardenafil) promise less adverse effect and longer half time [25,26]. Recently, a new substance (riociguat) that acts downstream in the nitric oxide pathway was approved [27]. The third pathway is inhibition of endothelin-mediated vasoconstriction. First *in vivo* use of a non selective endothelin receptor blocker (ERA) is documented in a hypoxia rat model by a group in France in 1995 [28]. At the beginning given intravenously, today bosentan, macitentan and the receptor-type A selective successor (ambrisentan) are orally administered and have a leading role in PAH therapy [29–32]. Prior therapeutic concepts considered monotherapy of one of the above mentioned drugs, recent clinical trials focus on combination therapies [33–36]. Experimental and clinical research efforts of the last 30 years have improved the median survival of PAH patients, from 2.8 to 5 years [3,37,38]. With the actual therapy concepts the disease progression is significantly decelerated, but survival rates for PAH patients still remain poor.

In our work we sought to dissect research efforts in the field of PAH during the last 14 years and to identify countries that mainly contributed to the development of major therapy concepts and trends for treatment of PAH.

2. Methods

Bibliometric studies focus on the analysis of research productivity, quality and progress of science in a specific field by using publicly available bibliographic databases (e.g., PubMed or Web of Science).

2.1. Data sources

We extracted all data on published studies for medical therapy for PAH from PubMed maintained by the U.S. National Library of Medicine. Information obtained was collected in a Microsoft Excel database with a spreadsheet file for each year including the time period between 2000 and 2014.

2.2. Search strategy

For our systemic search with used the terms *"therapy OR treatment"* which was combined with the Boolean operator *"AND"* with the terms *"pulmonary arterial hypertension*". Data were acquired between June 1st and November 30th 2015.

2.3. Inclusion criteria

Based on the search term *"therapy OR treatment" AND "pulmonary arterial hypertension*" the title and abstract of 4181 retrieved publications were further screened by hand by six experienced researchers in the field of clinical cardiovascular medicine whether the study addressed the effects of a medical therapy on pulmonary arterial hypertension. Basic science studies, studies investigating animal models as well as human trials were incorporated. Reviews, case reports, diagnostic and epidemiological studies, studies that included a surgical intervention (e.g. ECMO support, atrioseptostomy, pacemaker-implantation) or studies that were conducted in pediatric cohorts were excluded from the study. As accessible via the library data base of the Medical University Vienna or the Paracelsus Medical University Salzburg the original manuscript of selected studies was downloaded and the relevant data extracted. For studies that were not fully accessible title and the abstract were used to excerpt data as far as at hand.

2.4. Statistical analysis

Statistical analysis was performed using Microsoft Excel (Version 2010, Redmond, Washington, USA) and GraphPad Prism (GraphPad Software, USA). Impact factors for publications from 2000 to 2014 were obtained from the year of publication of the respective paper from the Isi Web of Knowledge database (Thomson Reuters, New York, USA). Descriptive statistical methods were used and the Mann-Whitney *U*-test was performed calculating significances. Logistic regression analysis was used to calculate r-values. P-values <0.05 were considered statistically significant.

2.5. Density equalizing mapping

The technique of density-equalizing mapping was applied to illustrate the focus of research activity by using a method for territorial resizing. The method is based on the algorithm by Gastner and Newman for density equalizing mapping and has been used by our group in a prior publication [39,40]. In brief, countries are resized with an area according to a particular variable, in our study the number of publications or the impact factor.

To this purpose a DBF-spreadsheet file from the cumulated data was generated using DBF Viewer 2000 (DBF Viewer 2000, HiBase Group, Vancouver, Canada) and transferred to our database. The World Borders Dataset was obtained from http://thematicmapping.org/ under a creative commons license. For the calculation procedure and illustration of the maps ScapeToad Software (Jacques Lévy, Lausanne, Switzerland, http://scapetoad.choros.ch/) was used [41].

3. Results

Our search term revealed 4181 publications as total. After hand expert selection 685 were suitable according to the predefined inclusion criteria (Fig. 1). Of these we had full access to 551 publications (80.4%). In 19.6% of included studies data was extracted from the title and abstract only.

Over the observation period the mean output was 48.9 publications per year with a mean impact factor of 4.7 (±5.9). The graphic presentation shows a logistic increase with minor fluctuations with an r-value of = 0.93 for total publications per year and 0.86 for total impact factor (Fig. 2). 56% of all publications were

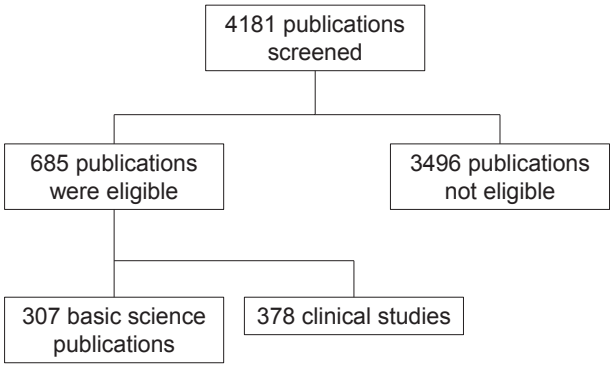

Fig. 1. Flow chart of the study design. 4181 publications were screened, 685 met the inclusion criteria. Basic science and clinical studies were rather equally distributed with a slight advantage for clinical trials (307 vs. 378 publications).