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Iranian Pulmonary Arterial Hypertension Registry

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Background: Idiopathic pulmonary arterial hypertension (IPAH) is a fatal disorder with a prevalence of 8.6 per million. We introduce a registry website for IPAH and PAH patients (**www.**IPAH**.ir)** for access and efficient delivery of government-aided and subsidized antihypertensive medications.

Materials and Methods: The IPAH registry was opened in November 2009. Information of IPAH and PAH patients with a username and password were uploaded in the site. Data entry was possible only via the physicians and healthcare organizations via internet that were given a personalized username and password for entry. Following the patients' profile submission, a scientific committee composed of a cardiologist and a pulmonologist who were selected by the Ministry of Health of Iran (MOH), evaluated the data. The eligibility of the patient to receive the medications was confirmed after evaluation. If the patient was eligible, 82% of the Bosentan cost was paid by MOH.

Results: To date, one hundred and sixteen patients (82 females, 34 males) have been registered. The mean pulmonary artery pressure by right heart catheterization was 69.24±17 mmHg (ranging from 35 to 110 mmHg).

Conclusion: The first online Iranian registry program for IPAH and PAH patients is believed to supply essential information for health care providers in the field.

Key words: Iran; Hypertension, Pulmonary; Registries

INTRODUCTION

Pulmonary hypertension has been defined as an increase in the mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (1, 2). This value has been used for selecting patients in all randomized clinical trials and registries of pulmonary arterial hypertension (3, 4).

Pulmonary artery hypertension (PAH) is a fatal disease with a prevalence of 15.5 per million. The prevalence of PAH is about 8.6 per million. The incidence of PAH is 1.2 per million (5). According to the above-mentioned data, the number of cases with this disorder in Iran is estimated to be more than 137.

Pulmonary artery hypertension was a disease with low survival before the new generation of drugs; the mean survival in the afflicted subjects was 2.8 years, with one and three-year survival rates of 68% and 48%, respectively (1). Substantial improvements obtained in survival rates in the past 20 years since institution of the NIH registry, due mainly to changes in treatment, improved patient support plans (6).

Novel anti-hypertensive therapies have improved quality of life, exercise capacity and survival of PAH patients in the recent two decades. The main category of drugs used in PAH treatment are prostanoids, phosphodiestrase inhibitors and endothelin receptor

antagonists (7). These drugs have provided a new horizon in PAH remedy. Since the introduction of intravenous epoprostenol in 1995, the one and three-year survival rates have increased to 88% and 68%, respectively (8). Although the new marketed class of medications in the treatment of PAH over the past years, i.e. endothelin receptor antagonists, have significantly improved patient survival, these drugs are not affordable by most patients. The cost of therapy with newer medications for PAH is up to 100,000$ per year (Table 1)(9).

Bosentan, an endothelin receptor antagonist, costs about 44,878 USD per year for a PAH patient in Iran. Due to the duration of the disease and its high cost, the role of supportive organizations, insurance companies and charities in this regard is very important.

Considering the aforementioned facts, it would be justifiable to present a national data registry system for PAH to prevent inappropriate prescribing in order to ensure that the best possible care is delivered to those with this disease. It is worthy to note that the global trend is now moving towards a system of nominated centers for PAH care, with multidisciplinary teams working in a shared-care approach to patient supervision.

Registry systems are organized not only to acquire a definite and standard approach to the diagnosis of the disease and creation of a database, but also updating the knowledge of managing physicians. Prompt diagnosis and patient identification in the preliminary stages of the disease can result in a more effective treatment. Since no regular and defined procedure for PAH recording existed in Iran, demographics, definite diagnosis and even the exact number of the patients were unknown. Drug treatment choices are few; the drugs are very expensive and out of patients' affordability. Thus, it is reasonable to propose a PAH registry system which can be extended to those with PAH referred to pulmonary vascular centers throughout the country.

The French (3), US (10), Spanish (11), UK and other registries (12), data extrapolation and other PAH populations are affected by factors such as study population characteristics, treatment modalities, methods and strategies for registration of the patients.

A website (http://www.IPAH.ir) was developed for IPAH and PAH registration in which the information of the patients collected was updated by using the latest guidelines such as European Respiratory Society (ERS), European Society of Cardiology (ESC), International Society of Heart and Lung Transplantation (ISHLT)(13), and American College of Cardiology Foundation (ACCF).

Table 1. Comparison of treatment of pulmonary arterial hypertension with regard to drug characteristics [9]

Medication	Class	Route of administration	Comments	Price
Remodulin®(treprostinil)	Prostacyclin	Subcutaneous or IV infusion dose- titrated	Patient must carry pump at all times.	$100,000+
Folan®(epoprostenol)	Prostacyclin	IV infusion dose- titrated	Patient must carry pump with ice at all times and mix under sterile conditions	$50,000-150,000
Tracleer®(bosentan)	Dual Endothelin Receptor Antagonist	Oral, twice daily	Twice –daily pill; patients must undergo monthly liver monitoring.	$35,000
Ventavis®(inhaled iloprost)	Prostacyclin	Inhaled, 6-9 times daily	6-9 inhalation – each one taking 15-20 minutes.	$50,000
Revalto®(sildenafil)	Phosphodiesterase Type 5 Inhibitor	Oral, thrice daily	Thrice daily pill	$15,000-20,000
Inhaled Remodulin®(treprostinil)	Prostacyclin	Inhaled	Four daily inhalations	N/A
Cialis®(tadalafil)	Phosphodiesterase Type 5 Inhibitor	Oral, once daily	Once daily pill	N/A

The validated information and diagnoses were needed by the MOH to subsidize the cost for the patient.

We assess a registry site as a database for IPAH and PAH patients, for a better delivery of subsidized antihypertensive medications and to evaluate prognosis and survival in the future. Currently, the only medication for which the registry is used is Bosentan.

MATERIALS AND METHODS

The registry was opened in Iran since November 2009 and a tutorial article was published in a nationally distributed medical journal to inform clinicians on how to use the registry system at www. IPAH.ir. In the first step, IPAH and PAH patient information is added to the registry. Data entry was allowed for physicians and other healthcare organizations that were qualified to log-in to the registry via Internet with a personalized username and password. Physicians could access patient data entered by them. The most important stage of adding the information was entering the average pulmonary artery wedge pressure, which was obtained by right heart catheterization. The PAH was defined as the presence of a mean pulmonary arterial pressure of more than 25 mm Hg at rest and a pulmonary artery wedge pressure (PAWP) less than 15 mm Hg at right heart catheterization (14).

Following the patient's profile submission at the website, a scientific committee composed of a cardiologist, and one pulmonologist selected by the MOH of Iran, evaluated the data. The eligibility of the patient to receive the medications was announced in the website after evaluation. If a patient was eligible, 82% of the Bosentan cost was paid by MOH. Only the PAH patients were candidates for the named drug. The available dosage forms of Bosentan in Iran are 62.5 mg and 125 mg tablets. Due to the vast geographical extension of our country, in every province a pharmacy was selected and announced by the MOH for dispensing the drug. Registry by the physician in charge via PAH site made the patient able to receive Bosentan by MOH financial support through the selected pharmacies. Also, the information of each patient was available for the physician in charge for further evaluation.

Data collected in PAH registry forms consisted of date of birth, age, sex, type of PAH, diagnosis method (e.g. right heart catheterization), functional class and treatment plan (15). The PAH registry was an online system composed of six pages. In the first page, demographic data such as name, sex, phone number and city of residence were recorded. In the other pages, data regarding the patient's medical history, results of physical examination, radiology, electrocardiogram, echocardiogram, right heart catheterization and six-minute walking distance test (6-MWD) were recorded.

There was no limitation for physicians and medical centers in terms of personal or geographical situations. The PAH registry was open to any of the colleagues who visited these patients in Iran.

The patients should be monitored for hepatic enzyme levels in the first month for treatment complications and then titrate-up the dosage from 62.5 mg twice daily to 125 mg twice daily. Thereafter, routine follow up visits were performed by the responsible physician including cardiopulmonary examinations, echocardiography, and 6-MWT and checking serum pro-BNP (brain natriuretic peptide) every two to three months after initiation of Bosentan. In cases of patient deterioration or no response to Bosentan, right-sided catheterization was done again for the patients. Finally, according to this protocol all registered patients with IPAH and PAH were re-evaluated annually by the National Research Institute of Tuberculosis and Lung disease (NRITLD).

RESULTS

One hundred and sixteen patients (82 females, 34 males) were included in this report. The mean age was 36.69±14 years. The mean weight of the patients was 63.57±16.47 kg (BMI: 28.07±3.48). Of the total, 9 (7.80%) were in New York Heart Association (NYHA) class IV, 60(52.20%) NYHA class III, 43(37.04%) NYHA class II and

2(1.70%) NYHA class I; 114(98.30%) had dyspnea on exertion (DOE) and 107 (92.20%) complained of extreme fatigue. The number of patients with syncope and chest pain was 39 (33.60%) and 65 (56.00%), respectively. At least one of the major systemic signs of pulmonary hypertension was present in 28 (24.10%) of the patients. None of them had collagen vascular disease.

All right ventricular enlargement signs (RVH, RVD, tall R in V1-V4) were present in 70 (60.30%) of the cases, while 9 (7.80%) of them had only one sign of right ventricular enlargement in ECG. Increase in the main pulmonary artery diameter and right ventricle size was seen in 101 (91.80%) and 63 (58.30%) of the subjects, respectively.

The measured mean pulmonary artery pressure by RHC was 69.24±17 mmHg (ranging from 35 to 110 mmHg). The mean systolic pressure was 90.27±21.63 (ranging from 45 to 137 mmHg).

The mean 6-MWT was 331.79±122.25 meters. Arterial oxygen saturation measured at the beginning and at the end of the test was 91.65% and 86.88%, respectively. The least walking distance was 87 meters with O2 saturation of 78% and 67%, at the beginning and at the end of the test, respectively. The mean difference in the mean O2 saturations at the beginning and at the end of the test was 5.7%.

DISCUSSION

The present study summarizes the national registry of IPAH and PAH patients since November 2009. Using the 6-MWT allows us to compare our registry data with the results of other studies and/or registries in the field. In contrast to typical clinical trials, every patient with PAH can be included in the registry regardless of the existence of accompanying diseases.

All patients included in our registry had a diagnosis of IPAH but it should be mentioned that in the vast majority of other PAH reports, secondary pulmonary hypertension cases were also included. We are to start registry on patients with PH secondary to diseases such as Eisenmenger and connective tissue disorders.

The registry is done for almost all IPAH and PAH patients, if they are candidates to receive Bosentan as part of their therapy. This is mandatory in order to receive the subsidized drug. Among new medications for PAH only Bosentan tablets are subsidized by the government and thus, available to patients via this system. The future goal of this registry is to cover other PAH treatments (e.g. prostaglandins).

On the other hand, over 90% of our patients were in NYHA class II and III, while most other registries classified patients as being more severe cases of PAH (3). In the French one-year registry, 674 adult patients (121 novel "incident" cases and 553 known "prevalent" cases) were included. Prevalent cases of PAH correspond to survivors; this may therefore poorly represent PAH all together since the most severe patients were lost in the prevalent subgroup. In fact, 75% of patients registered were in NYHA functional class III or IV.

The number of patients in our registry is acceptable and justifiable since this is a recently installed program. Besides, we only included PAH patients and it is possible that due to the availability of oral drugs for PAH treatment with more affordable price many physicians may tend to treat their patients without registration. Though, at the time of the introduction of the French registry, Sildenafil was not approved in France for PAH, and Bosentan had just been approved for PAH only in NYHA class III with restricted prescription to related specialists.

Our definition for PAH was different from that of others e.g. REVEAL Registry for US PAH patients (10), which enrolled a larger group of patients with broader criteria for a longer duration (March 2006- September 2007). The US registry included less than 200 in 32 clinical centers between 1981-1985. China gathered data from only 72 patients (between 1999-2004) who received medications other than Bosentan and prostaglandins since the newer medications were not available at the time of registry (16). The SNAP study patients were from registered patients with both IPAH and secondary PH visited from September 1996 to December 1997, at 12 referral centers in North

America. The study included 579 patients (205 with IPAH)(17).

Our registry showed a female patient predominance. This is in accordance with data gathered by other registry programs. The patients of the current registry had a mean age of 35.15±13.21 years. Wilkens et al. reported a mean age of 55 year among their PAH patients who were evaluated in 10 hospitals in Germany (18). In a similar study in Scottish hospitals, Peacock et al. reported a mean age of 47±12 years in IPAH cases (4). It seems that the patients included in this registry are younger, compared to similar studies.

It was previously stated by Abenhaim and colleagues (19) that obesity is not considered a confounding factor explaining appetite suppressant exposure in PAH patients, similar to that of the adult French registry (20).

Presenting a model like PAH registry in a national frame seems effective. Benefits of this model could be: Increment of physician knowledge for standard diagnosis, prompt diagnosis, supporting drug supply for the patient and registration of data in a database.

This is of great importance for the health budget by avoiding unnecessary and inappropriate resource consumption. Also, mentioned protocols for PAH patients enable physicians to provide the best available treatment regimens.

In conclusion, the Iranian registry for PAH patients has just started and it is believed that nationwide registry of these patients supplies essential information for health care providers in the field through a web-based program.

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Conflict of interest

The authors declare that they have no conflict of interest.

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