Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France

Caractéristiques et suivi prospectif sur deux ans d’enfants atteints d’hypertension artérielle pulmonaire en France

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KEYWORDS
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Summary
\textit{Background.} — Limited data are available describing paediatric pulmonary arterial hypertension.
Aims. — To characterize the epidemiology, management and impact on quality of life and outcome of paediatric pulmonary arterial hypertension, excluding persistent pulmonary hypertension of the newborn and pulmonary arterial hypertension caused by congenital heart disease.

Methods. — In this multicentre study, children with pulmonary arterial hypertension were included and followed prospectively for two years at 21 referral centres in France. WHO functional class, 6-minute walk distance and quality of life (CHQ-PF50 questionnaire) were evaluated.

Results. — Fifty children were included with a mean age of 8.9 ± 5.4 years from May 2005 until June 2006. The estimated prevalence for pulmonary arterial hypertension was 3.7 cases/million. Patients had idiopathic pulmonary arterial hypertension (60%), familial pulmonary arterial hypertension (10%), pulmonary arterial hypertension associated with, but not caused by, congenital heart disease (24%), pulmonary arterial hypertension associated with connective tissue disease (4%) or portal hypertension (2%). During follow-up, the combination of pulmonary arterial hypertension-specific therapies was increasingly prescribed (44% patients versus 22% at inclusion). Patients remained stable regarding clinical status, 6-minute walk distance and quality of life. Survival estimates after one and two years were 86% (95% CI 76, 96) and 82% (95% CI 71, 93), respectively.

Conclusions. — In children, idiopathic/familial pulmonary arterial hypertension accounts for the majority of cases. A specific pulmonary arterial hypertension group in conjunction with congenital heart disease can be identified that resembles patients with idiopathic pulmonary arterial hypertension. Combined pulmonary arterial hypertension-specific therapies may have contributed to disease stability and favourable survival.

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Résumé

Justification. — Les données décrivant l’hypertension artérielle pulmonaire chez l’enfant sont peu nombreuses.

Objectifs. — L’objectif a été de caractériser l’épidémiologie, la prise en charge, l’impact sur la qualité de vie et les conséquences de l’hypertension artérielle pulmonaire de l’enfant en excluant les patients avec une hypertension pulmonaire persistante du nouveau-né et ceux dont l’hypertension artérielle pulmonaire était causée par une cardiopathie congénitale.

Méthodes. — Dans cette étude multicentrique, des enfants atteints d’hypertension artérielle pulmonaire ont été inclus et suivis prospectivement pendant deux ans dans 21 centres français. La classe fonctionnelle OMS, la distance de marche de sixminutes et la qualité de vie (questionnaire CHQ-PF50) ont été évaluées.

Résultats. — Cinquante enfants ont été inclus avec un âge moyen de 8,9 ± 5,4 ans de mai 2005 à juin 2006. La prévalence de l’hypertension artérielle pulmonaire a été estimée à 3,7 cas/million. Les patients avaient une hypertension artérielle pulmonaire idiopathique (60%), familiale (10%), associée avec une cardiopathie congénitale qui n’était pas la cause de l’hypertension artérielle pulmonaire (24%), associée à une connectivite (4%) ou à une hypertension portale (2%). Pendant le suivi, le nombre d’associations de médicaments spécifiques de l’hypertension artérielle pulmonaire prescrits a augmenté (44% patients contre 22% à l’inclusion). Les patients sont restés stables en ce qui concerne leur état clinique, test de marche de six minutes et qualité de vie. La survie à un et deux ans a été estimée à 86% (intervalle de confiance à 95% : [76,96]) et 82% (intervalle de confiance à 95% : [71,93]).

Conclusions. — Chez l’enfant, dans la majorité des cas, les hypertensions artérielles pulmonaires sont idiopathiques / familiales. Un groupe spécifique d’hypertension artérielle pulmonaire concomitante d’une cardiopathie congénitale a été identifié et ressemble à une hypertension artérielle pulmonaire idiopathique. Les associations de traitements spécifiques de l’HTAP peuvent avoir contribué à la stabilité de la maladie et à une meilleure survie.

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Introduction

PAH is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure [1]. The impact on quality of life is substantial and the prognosis poor [2,3]. The natural history of PAH in adults was described initially by a national registry conducted in the United States in the early 1980s, which included patients with IPAH followed for up to five years [3]. Following subsequent significant advances in the development of PAH-specific therapies (e.g., prostacyclin, endothelin receptor antagonists, and type 5 phosphodiesterase inhibitors), a multicentre registry was initiated in France, in 2002, to collect data on adult patients with PAH treated in the modern era, and to document the evolution of PAH during a 3-year follow-up [4]. However, no such multicentre studies have been performed in children and the current understanding of the epidemiology and natural course of paediatric PAH is consequently limited.

Adults and children with PAH present with the same histopathological lesions [5] and the same abnormalities of vascular and endothelial homeostasis, including imbalance of prostacyclin and thromboxane A2 [6] and abnormal pulmonary clearance of endothelin-1 [7]. The spectrum of associated conditions, clinical presentation, and factors influencing survival, however, may differ between adults and children. Although limited data are available on the clinical responses of paediatric PAH patients, children with severe PAH are currently treated with similar clinical strategies to those applied to adults [8]. Treatment goals for paediatric patients with PAH may require specific adaptations of adult treatments in order to meet a different set of practical, social and therapeutic challenges [9]. There are currently, however, insufficient data to inform treatment objectives and decisions. This prospective, multicentre, non-interventional study was therefore initiated to investigate the specific epidemiology of paediatric PAH. This study also examined the medical management of paediatric PAH in the current treatment era and the impact on quality of life and outcome during a 2-year follow-up period.

Methods

Study design

This multicentre, prospective, non-interventional study was initiated in May 2005 and was based on a previously described method [10]. Enrolled patients either had a known diagnosis of PAH before the beginning of the study or were diagnosed during the recruitment period (cross-sectional phase), from May 2005 until June 2006. All enrolled patients were followed prospectively for two years (longitudinal phase). The protocol did not impose any procedures or therapies. Written, informed consent was obtained from patients or guardians before data collection.

Study patients

Patients aged between 28 days and 18 years were included. Patients with PAH-CHD were only included if the increase in pulmonary vascular resistance could be considered unrelated to the congenital heart defect (i.e. children with PAH related to an atrial septal defect with increased pulmonary vascular resistance from birth or a transposition of the great arteries associated with PAH after an arterial switch operation). These patients were referred to as patients with PAH in conjunction with CHD. Patients with an evolving defect, which could lead to increased pulmonary vascular resistance (either left-to-right shunt or left heart obstructive defect), were excluded. Patients with persistent pulmonary hypertension of the newborn were also excluded because their disease differs from other PAH aetiologies in terms of natural history and treatment.

Diagnosis of PAH

Diagnosis of PAH was established using either right heart catheterization or Doppler echocardiography following the European Society of Cardiology guidelines [11]. Patients were considered responsive to vasodilator testing if inhaled nitric oxide during right heart catheterization-induced reductions in mean pulmonary arterial pressure greater than 10 mmHg, leading to a value less than 40 mmHg, with increased or unchanged cardiac output.

Patient characteristics at inclusion and study assessments

PAH history included date of first presentation, date of diagnosis and World Health Organization functional class at diagnosis. Age, height, weight and functional signs were documented at study inclusion and a complete physical and cardiac examination was performed.

WHO functional class and exercise capacity measured by the 6MWD in patients older than seven years [12] were determined at inclusion and at six months, one year and two years. Haemodynamic parameters were collected at inclusion and at six months, one year and two years. Last assessment was defined as the latest available assessment performed at month 6, Year 1 or 2.

Assessment of quality of life was collected at inclusion, one year and two years, using parent-administered versions of the most appropriate questionnaires for each age group. For children aged less than five years, analyses from the QUALIN [13] and Autoquestionnaire Enfant Image (AUQUEI) instruments [14] planned per protocol [10] were not presented due to the small number of patients. For children over five years, results from the Child Health Questionnaire — Parent. Form 50 (CHQ-PF50) questionnaire [15] at inclusion were compared with those of standard (n = 73; age range 5–7 years) [16] and asthmatic (n = 74; age range 5–12 years) [17] paediatric reference cohorts.

Statistical analysis

Quantitative variables are described as mean ± SD or median (range), when appropriate. For analytical comparisons between two groups of normally distributed quantitative data, Student’s t-test was performed; in case of small samples of patients or not normally distributed variables, the non-parametric Wilcoxon’s test was used. For multiple comparisons of quantitative data, analysis-of-variance or non-parametric tests were used. Qualitative variables are
described using frequencies and percentages. For analytical comparisons between two groups of matched qualitative data, the McNemar’s test was performed. A p value less than 0.05 was considered significant. Statistical analyses were performed using SAS software (version 8; SAS Institute, Cary, NC). Patient height and weight were compared with average values for French children of the same age. Delayed growth was defined as height or weight at least twice the standard deviation below the mean.

Prevalence of PAH was calculated as the ratio between the number of enrolled patients and the number of persons aged between 28 days and 18 years in the French population (excluding overseas territories) in 2006, derived from public data provided by the Institut national d’études démographiques population census [18]. Survival, assessed from study inclusion until death/data cut-off date, was summarized using Kaplan-Meier estimates and 95% confidence interval (CI) of the event-free survival at relevant time points.

Results

Fifty patients (35 with a diagnosis established before study initiation) were included from 21 referral centres with a widespread geographical distribution in France [10]. Five participating centres did not recruit patients. Patients were followed for a median duration of 23.4 months (range 0.1–31).

Diagnosis of PAH

Diagnosis of PAH was confirmed using right heart catheterization in 43 of 50 patients (86%) and was performed a median 2.7 years before study initiation (range 0—15 years). The mean pulmonary artery pressure was $59 \pm 18$ mmHg and the cardiac index was $3.9 \pm 1.8$ L/min/m$^2$. Four of 35 patients evaluated (11%) were responsive to nitric oxide. The remaining seven patients had the diagnosis confirmed by Doppler echocardiography; their mean calculated systolic pulmonary arterial pressure using maximum velocity of tricuspid regurgitation was $87 \pm 18$ mmHg.

Prevalence of PAH

The overall prevalence of PAH (excluding persistent pulmonary hypertension of the newborn and PAH caused by CHD) in paediatric patients in 2005 was estimated to be at least 3.7 cases per million. The prevalence of idiopathic IPAH in paediatric patients was estimated to be at least 2.2 cases per million.

Patient demographics and disease characteristics at inclusion

The characteristics at inclusion of the 50 patients are summarized in Table 1. The male to female ratio was 1.1:1.0. Patients were $4.4 \pm 4.5$ years at first symptoms and $5.1 \pm 4.8$ at diagnosis. They most frequently had IPAH (60%). PAH associated with but not caused by CHD was encountered in 24% of the patients (Table 2).

Low weight and height were reported in 12 (24%) and eight (16%) patients, respectively and nine patients (18%) had a history of premature birth, defined as less than 36 weeks of gestation. Two patients developed PAH shortly after bone marrow transplantation, a procedure which can be associated with chemoradiation-induced lung injury [19]. Both of these patients were responsive to calcium channel inhibitors. One patient had an astrocytoma treated with chemotherapy; no link with the PAH diagnosis was considered. Two patients had major digestive surgery.

Clinical symptoms

The most frequently reported clinical symptoms were dyspnoea and fatigue whereas signs of right heart failure

### Table 1  Patient characteristics at study inclusion (n = 50).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boys / girls</th>
<th>Age, years</th>
<th>Weight, kg</th>
<th>Aetiology of pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys / girls</td>
<td>26 (52) / 24 (48)</td>
<td>8.9 ± 5.4 (0.4—18)</td>
<td>28.3 ± 17.9 (4—70)</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Aetiology of pulmonary arterial hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>30 (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In conjunction with CHD</td>
<td>12 (24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td>5 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>1 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg (n = 43)</td>
<td>59 ± 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min/m$^2$ (n = 30)</td>
<td>3.8 ± 1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed pulmonary vascular resistance, Wood units.m$^2$ (n = 29)</td>
<td>20 ± 19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td>4 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO FC I, II, III, IV (n = 46)*</td>
<td>8, 25, 12, 1 (17, 54, 26, 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number (percentage) of patients or mean ± standard deviation (range).

* Four patients did not have an inclusion assessment (including three patients who died during the first month of follow-up).
Table 2: Characteristics of patients with PAH in conjunction with CHD.

<table>
<thead>
<tr>
<th>CHD/surgery</th>
<th>Age at diagnosis/ inclusion (years)</th>
<th>Premature</th>
<th>Weight (kg)</th>
<th>WHO FC at inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD/SC</td>
<td>5.4 / 13.8</td>
<td>—</td>
<td>41.0</td>
<td>II</td>
</tr>
<tr>
<td>ASD/SC</td>
<td>4.1 / 7.5</td>
<td>+</td>
<td>17.5</td>
<td>III</td>
</tr>
<tr>
<td>ASD/SC</td>
<td>1.1 / 6.9</td>
<td>—</td>
<td>20.0</td>
<td>III</td>
</tr>
<tr>
<td>PDA(^a)/no</td>
<td>0.5 / 05</td>
<td>+</td>
<td>6.2</td>
<td>—</td>
</tr>
<tr>
<td>PDA/SC</td>
<td>0.8 / 16.3</td>
<td>—</td>
<td>42.0</td>
<td>II</td>
</tr>
<tr>
<td>PDA/SC</td>
<td>4.2 / 10.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TGA/ASO</td>
<td>0.1 / 9.4</td>
<td>—</td>
<td>20.0</td>
<td>II</td>
</tr>
<tr>
<td>TGA/ASO</td>
<td>0.2 / 0.4</td>
<td>—</td>
<td>6.9</td>
<td>I</td>
</tr>
<tr>
<td>TGA/ASO</td>
<td>0.9 / 13.3</td>
<td>—</td>
<td>28.0</td>
<td>III</td>
</tr>
<tr>
<td>TGA/ASO</td>
<td>2.0 / 7.8</td>
<td>—</td>
<td>26.5</td>
<td>II</td>
</tr>
<tr>
<td>TGA/ASO</td>
<td>0.3 / 1.5</td>
<td>—</td>
<td>4.2</td>
<td>I</td>
</tr>
<tr>
<td>Scimitar syndrome/no</td>
<td>0 (7 days)b / 7</td>
<td>+</td>
<td>16.0</td>
<td>II</td>
</tr>
</tbody>
</table>

\(^a\) With CHARGE syndrome and no significant left-to-right shunt.
\(^b\) Without persistent pulmonary arterial hypertension of the newborn.

ASD, atrial septal defect; ASO, arterial switch operation; PDA, patent ductus arteriosus; SC, surgical closure; TGA, transposition of the great arteries; WHO FC, World Health Organization functional class.

(hepatomegaly) were rare (Table 3). At the last assessment, no significant changes were observed except for cyanosis with exercise.

WHO functional class, 6MWD and haemodynamics

Of 50 patients, 44 were evaluated for WHO functional class at both inclusion and last assessment (40 patients had a 2-year assessment, two had their last assessment at one year and two at six months). At the last assessment, 11 patients (25%) had improved from inclusion by at least one class (95% CI 12, 38), and 12 patients (27%) had worsened by at least one class (95% CI 14, 40).

The 6MWD performed for children over seven years of age improved non-significantly from 421 ± 65 min at inclusion (n = 22) to 448 ± 108 min at last assessment (n = 25; p = 0.07).

Thirteen patients had a haemodynamic evaluation by right heart catheterization at inclusion and last assessment. This evaluation detected no significant changes in haemodynamic parameters (Table 3).

Impact of PAH on scholarship and quality of life

At inclusion, from a subpopulation of 40 patients over three years of age, 29 (81%) were attending regular school, of which three were experiencing learning disabilities and seven (19%) received tuition in a specialized establishment (the educational establishment was unspecified for four children). These percentages were not different at the last assessment.

The majority of quality-of-life scores from the CHQ-PF50 questionnaire were reduced for paediatric patients with PAH compared with the standard and asthmatic paediatric population.

Table 3: Changes between inclusion and last assessment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inclusion</th>
<th>Last assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameters</td>
<td>(n = 50)</td>
<td>(n = 44)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>38 (76%)</td>
<td>35 (80%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (72%)</td>
<td>25 (57%)</td>
</tr>
<tr>
<td>Cyanosis with exercise</td>
<td>8 (16%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (11%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (7%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>3 (6%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Haemodynamic parameters</td>
<td>(n = 13)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>59.7 ± 14.7</td>
<td>59.6 ± 18.2</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>3.0 ± 1.3</td>
<td>3.1 ± 1.3</td>
</tr>
<tr>
<td>Indexed pulmonary vascular resistance, Wood units.m²</td>
<td>10.6 ± 6.0</td>
<td>7.6 ± 4.3</td>
</tr>
</tbody>
</table>

Values are number (percentage) of patients or mean ± standard deviation.

\(^a\) p = 0.02.
reference cohorts although behaviour and familial cohesion were preserved (Fig. 1). At the last assessment (n=19), the scores were not statistically different except for bodily pain (p = 0.02) and mental health (p = 0.03), which both improved.

Survival

Kaplan-Meier estimates of survival at one and two years were 86% (95% CI 76, 96) and 82% (95% CI 71, 93) (Fig. 2), respectively. Nine patients died during study period. Of these, four (44%) had PAH in conjunction with CHD, two (22%) had IPAH and one (11%) had familial PAH. Of the nine deaths, four resulted from clinical progression of PAH, two from heart failure, two from sudden death and one from pulmonary disease.

Treatment

Monotherapy with a PAH-specific treatment was less frequent at the last assessment than at inclusion. Conversely, bitherapy and tritherapy were increased (Table 4). Bosentan was the most frequently prescribed PAH-specific treatment at inclusion and last assessment, and sildenafil was the most frequently added treatment between inclusion and last assessment.

Discussion

This multicentre study investigated the epidemiology and outcome of PAH in the French paediatric population treated with PAH-specific treatments.
with the strategies developed for adults with IPAH [8]. Until now, few studies have described the course of this devastating disease in children and they have been limited by the inclusion of small numbers of patients or from having been conducted before the availability of PAH-specific therapies [3,20,21]. The present registry was initiated to describe the French paediatric PAH population in the current treatment era when several disease-specific therapies (e.g., prostacyclin, endothelin receptor antagonists, and type 5 phosphodiesterase inhibitors) are commercially available.

Prevalence

The overall prevalence for paediatric PAH (excluding persistent pulmonary hypertension of the newborn and PAH caused by CHD) in France, in 2005, was estimated to be at least 3.7 cases per million and at least 2.2 cases per million for IPAH. The referral centres that participated to the study represent the majority of large University Hospitals in France but these numbers should be regarded as slight underestimates of the true prevalence. The prevalence of IPAH in children was the same as that reported in the adult registry [4].

Clinical presentation

Paediatric PAH has a distinct profile compared with adult PAH [4]. In children, idiopathic / familial PAH and PAH-CHD account for the majority of the PAH cases. There are fewer associations between PAH and portal hypertension or connective tissue disease in paediatric versus adult patients. These differences may result from dissimilar underlying causes of PAH in adult patients, such as PAH resulting from anorexigen intake, or the longer durations of illness associated with portopulmonary hypertension.

Twelve patients (24%) fulfilled the inclusion criteria of PAH in conjunction with CHD. Half of these patients had a transposition of the great arteries or scimitar syndrome, two conditions that have been previously reported to occur in conjunction with PAH [22,23]. The other half had a patent ductus arteriosus or atrial septal defect but the pulmonary vascular resistance increase was considered to occur too early in life to be related to the natural course of the shunt. These patients were therefore considered to have IPAH-like PAH occurring in conjunction with CHD and represent a different population of patients than those having PAH caused by chronic left-to-right shunts or left heart obstruction defects.

At inclusion, the majority of patients recorded in this registry were in WHO functional class II or III (71%). Although this classification can be difficult to apply in young children, it suggests an earlier diagnosis than for the adults included in the French registry [4]. These patients had an elevated pulmonary pressure but their cardiac index was preserved; they had no signs of right heart failure, which is a frequently observed difference with adult patients with PAH [21,24]. Children seem to tolerate the increased right heart workload better than adults for the same degree of disease severity. The children from this cohort were also more likely to respond to acute vasodilator testing than the adults included in the French registry (11% versus 5.8%) [4]. However, there is a wide variability in paediatric patients with numbers of responders to acute vasodilator testing as high as 40% [25]. Most patients with PAH, whether adults or children, will lose their initial acute vasoresponsiveness within several years and need PAH-specific therapy before they begin to deteriorate [26].

Quality of life

Although the assessment of quality of life in children is less straightforward than in adults, the parent administered CHQ-PF50 is considered a valid and reliable instrument for children aged over five years [15]. The CHQ-PF50 scores from this cohort indicate that paediatric PAH patients have a low overall quality of life in comparison with healthy children [16] and children with asthma [17], even though familial cohesion is preserved as seen for many chronic diseases [27]. Nevertheless, the overall quality of life was maintained during the study and some scores even improved (mental health and bodily pain). The majority (81%) of this cohort attended mainstream school at inclusion and last follow-up.

Follow-up and survival

With the development of continuous intravenous epoprostenol in the late 1980s and the more recent availability of bosentan, sildenafil and iloprost, the treatment of children with PAH has considerably evolved in the past few years [24,26,28,29]. Whilst the study was non-interventional, it was observed that a high proportion of patients received targeted therapies for PAH, despite the absence of controlled trials supporting their use in children. Moreover during the 2-year follow-up, patients received an increasing number of combined PAH-specific therapies, which may have contributed to their relative stability regarding clinical status (73% patients presented improvement or no change in functional class), 6MWD, and quality of life. Given the appalling prognosis of this disease, it is encouraging that children presented signs of stabilization or improvement, even at the expense of an increase in medication. The observed survival estimates, 86% at one year and 82% at two years, compare favourably with the median survival of 10 months reported by National Institutes of Health registry in 1991 [3] or with survival estimates of 37% at one year and 12% at 2.5 years observed in a Canadian study [20], before the availability of PAH-specific therapies. Survival as high as 88% at two years with bosentan [24] and 88% at three years with epoprostenol [26] have subsequently been reported for children with IPAH. Our survival figures are very similar to those recently reported by Haworth et al. [86% and 80% at one and three years, respectively] for children with IPAH treated with epoprostenol, sildenafil and/or bosentan [30].

The study findings suggest that an increasing awareness of novel therapeutic options for adolescent and adult patients with PAH may have influenced the decisions of physicians faced with the management of paediatric PAH. The concept of starting treatment with a single PAH-specific therapy, followed by combination therapy has shown benefit in adult trials as well as in a recent paediatric study [30]. This highlights the need for continued evaluation of the treatment of paediatric patients with PAH, to enable clinicians to make informed treatment decisions.
Follow-up of French children with PAH

Limitations

This study was limited by its observational design resulting in the inclusion of children with long-term ongoing disease and children newly diagnosed. A second limitation is the lack of right heart catheterization in seven patients at diagnosis and 37 patients at the last assessment. Finally, the CHQ-PF50 questionnaire could only be used in those children older than five years and this instrument, which is not specific for PAH, may have limited sensitivity in detecting changes in quality of life resulting from PAH progression/treatment over time.

Conclusion

In children, idiopathic/familial PAH and PAH-CHD account for the majority of PAH cases. The present registry provides an overview of the current state of care and management of paediatric PAH in France and supports the use in children of the PAH-specific treatments that have been developed for adults. In addition, we suggest that a particular group of patients with PAH in conjunction with CHD can be identified who are more likely to show signs similar to those of IPAH patients than those who have developed PAH as a consequence of a CHD.

Conflict of interest

Virginie Gressin is an employee of Actelion Pharmaceuticals France, as Medical Director.

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