Assessing response to therapy in idiopathic pulmonary arterial hypertension: A consensus survey of Canadian pulmonary hypertension physicians

Adrienne E Borrie MSc, David N Ostrow MD FRCP, Robert D Levy MD FRCP, John R Swiston MD MPH FRCP

BACKGROUND: Many treatment options are now available for patients with idiopathic pulmonary arterial hypertension (IPAH). Data regarding the optimal combination of therapies are lacking, as is consensus on how to assess response to therapy and when to change therapeutic regimens.

OBJECTIVES: To gather the opinions of Canadian pulmonary hypertension (PH) experts regarding standard practice in the care of IPAH patients after therapy is initiated.

METHODS: Canadian PH physicians were surveyed using short questionnaires to assess their opinions and practices in the care of IPAH patients. A Delphi forecasting approach was used to gain consensus among Canadian physicians on the most important clinical parameters to consider when assessing patients after the initiation of therapy.

RESULTS: Twenty-six of 37 Canadian PH experts who were invited to participate completed the study. All endorsed the use of combination therapy for IPAH patients despite the lack of universal provincial coverage for this approach. By consensus, WHO functional class, 6 min walk distance and hospitalization for right heart failure were the most important clinical parameters. The most highly rated physical examination parameters were jugular venous pressure, peripheral edema, the presence of ascites and body weight.

CONCLUSIONS: The overall approach to care of IPAH patients is similar across PH centres in Canada. A limited number of clinical and physical examination parameters were considered to be most important to reassess patients after therapy is initiated. These parameters, along with definitions of threshold values, will facilitate the development of standard practice guidelines for IPAH patients in Canada.

Key Words: Health survey; Pulmonary hypertension; Therapy

Pulmonary arterial hypertension (PAH) is a condition affecting the lung microcirculation and is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular dysfunction, cardiopulmonary disability and premature death (1-3). PAH is defined hemodynamically as a resting mean pulmonary arterial pressure (mPAP) of greater than 25 mmHg with a pulmonary capillary wedge pressure of lower than 15 mmHg (1,4). When there is no identifiable cause for the development of PAH, the disease is labelled idiopathic PAH (IPAH) (5).

While there is currently no cure for IPAH, medical advances in the field of pulmonary hypertension (PH) have led to the emergence of several treatment options for patients with IPAH aimed at slowing disease progression, improving symptoms and quality of life, and prolonging survival (6). Three classes of medications have now been approved in Canada for the treatment of PAH: prostanoids (7), endothelin-1 receptor antagonists (ERAs) (8) and phosphodiesterase type 5 inhibitors (PDE5is) (6,9,10). With the availability of multiple therapies, treatment of IPAH has become more complex. Attention is now being paid to treating patients earlier in the disease course, considering the use of multiple agents in combination, and changing therapeutic regimens based on clinical status and response to treatment (9). To some degree, the pharmacological advances in the treatment of IPAH have grown faster than our understanding of how to best use these therapies clinically. Data regarding the optimal combination of therapies are lacking, as is consensus on when or how to introduce multiple medications (6). Furthermore, despite the lack of evidence-based guidance, clinicians must decide when and how to re-evaluate patients after the initiation of therapy, define what an adequate response to therapy is, and determine what to do when such a response is or is not achieved. The purpose of the present study was to survey the attitudes of Canadian physicians caring for patients with IPAH, and to generate a consensus opinion with regard to the methods of reassessment and goals after patients have been initiated on therapy.

METHODS

A list of PH experts was generated from a census of Canadian physicians who regularly prescribe bosentan (provided by Actelion Pharmaceuticals, Canada) as well as those known to be PH specialists affiliated with one of the 14 major PH centres in Canada and/or members of the Canadian Thoracic Society’s Canadian Pulmonary Vascular...
TABLE 1
Summary of survey participants

<table>
<thead>
<tr>
<th>Question</th>
<th>Surveys sent, n</th>
<th>Respondents, n</th>
<th>Response rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>37</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>Phase II stem A</td>
<td>37</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>Phase II A1</td>
<td>36</td>
<td>22</td>
<td>61</td>
</tr>
<tr>
<td>Phase II A2</td>
<td>22</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>Phase II stem B</td>
<td>36</td>
<td>22</td>
<td>61</td>
</tr>
<tr>
<td>Phase II B1</td>
<td>22</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>Phase II B2</td>
<td>23</td>
<td>22</td>
<td>96</td>
</tr>
</tbody>
</table>

TABLE 2
Survey question 2: “How soon after initiation of therapy should patients be re-evaluated?”

<table>
<thead>
<tr>
<th>WHO class</th>
<th>Months, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>3.73±1.55</td>
</tr>
<tr>
<td>III</td>
<td>2.23±0.97</td>
</tr>
<tr>
<td>IV</td>
<td>1.36±0.85</td>
</tr>
</tbody>
</table>

RESULTS

Of the 37 PH experts invited, 26 (70%) participated in phase I of the survey and in generating clinical parameters in phase II stem A (Table 1). In the first rating of phase II stem A parameters (phase II A1), 22 of the 36 physicians who were re-contacted (61%) participated. For the second re-rating of phase II stem A parameters (phase II A2), all 22 of the physicians who were re-contacted (100%) participated. In phase II stem B, 22 of 36 physicians who were contacted (61%) participated in the generation of physical examination parameters. All 22 of the physicians contacted (100%) participated in the initial rating of these parameters (phase II B1), and 22 of 23 physicians contacted (96%) participated in the final re-rating exercise (phase II B2). PH physicians from 14 cities in eight provinces across Canada were represented including physicians from Vancouver (British Columbia), Calgary and Edmonton (Alberta), Saskatoon (Saskatchewan), Winnipeg (Manitoba), London, Toronto, Hamilton, Kingston and Ottawa (Ontario), Montreal and Quebec City (Quebec), Moncton (New Brunswick) and Halifax (Nova Scotia). Collectively, this representation encompassed all major PH centres in Canada at the time of the study. The majority of the participating physicians were trained in respiratory medicine; however PH physicians specializing in cardiology, rheumatology and critical care medicine were also represented.

The first question of the survey was a query to determine whether the physician believed that the establishment of a predefined goal-oriented approach to the management of PH was feasible. Of the physicians surveyed, 100% answered ‘yes’. When asked “How soon after initiation of therapy should patients be re-evaluated?” the mean response was 3.73 months for a WHO class II patient, 2.23 months for a WHO class III patient, and 1.36 months for a WHO class IV patient (Table 2). Physicians were asked whether they believed a repeat right heart catheterization (RHC) should routinely be performed after the initiation of therapy: 63% of respondents answered ‘yes’. Of the 37% of respondents who answered ‘yes’, 82% indicated that the RHC should be performed within the first six months after initiation of therapy, while 18% of respondents believed that more than six months should elapse before a repeat RHC is performed.

When a WHO class II patient on oral monotherapy was not regarded to have exhibited an adequate clinical response, 60% of physicians indicated that their preferred approach would be to add an additional oral agent, while 40% would prefer to switch to an alternative oral agent (Figure 1). When a WHO class III patient on oral monotherapy was not regarded to have exhibited an adequate clinical response, 97% of physicians believed that they should add – not switch – medication. Furthermore, for WHO class IV patients, 100% of the PH physicians surveyed believed that they should not switch.
In phase II stem B of the present study, participants were asked to list physical examination parameters they considered to be important in the evaluation of patients after the initiation of therapy. Respondents described a median of three parameters yielding a collective total of 16 (Figure 4). After two rounds of rating, there were no parameters with mean scores of greater than 4. Parameters that had a mean score of greater than 3 included jugular venous pressure (JVP), peripheral edema, ascites and weight. There were six parameters with final scores of between 2.0 and 2.9 (exertional saturation, hepatic jugular reflux, third heart sound, right-sided third heart sound, resting saturation and parasternal heave), and six parameters with scores of less than 2 (Kussmauls sign, hepatic size, fourth heart sound, hepatic tenderness, external jugular vein and hepatic pulsatility). Due to an error in the survey process, the parameter ‘hepatic pulsatility’ was only distributed once.

**DISCUSSION**

The present survey provided an overview of the expert opinions of Canadian PH physicians with regard to their preferred approach to IPAH patients after the initiation of therapy. The use of the Delphi technique enabled physicians to provide dynamic input with modification of their opinion based on the response of others without the negative aspects of group dynamics such as coercion or judgment. To the credit of the Canadian PH community, the response rate of our survey was very high, and participation was sustained through multiple rounds of questioning. There was complete representation of the PH community in Canada, with participation of physicians residing in each of the recognized Canadian PH centres. This is a reassuring indication that the survey results were an accurate reflection of opinions of physicians regarding optimal PH care across Canada.

Aside from calcium channel blockers, three classes of medications targeting the pulmonary vasculature are currently approved for PAH therapy: PDE5is, ERAs and prostacyclins (6). Combination therapy refers to the simultaneous use of more than one of these classes of PAH-specific therapies (usually excluding calcium channel blockers). The use of combination therapy for patients exhibiting an inadequate response to monotherapy is endorsed by several societies and PH treatment guidelines including the European Society of Cardiology, the European Respiratory Society, and the International Society of Heart and Lung Transplantation, as well as the 4th World Symposium on PH and the United Kingdom/Ireland PAH consensus statements (1,6,12). These
recommendations are based on a strong biological rationale for combina-
tion therapy, as well as a growing body of evidence indicating that
combining PH medications is safe and effective (9). Each class of medi-
cation acts on different signalling pathways believed to be dysregulated
in IPAH, and all classes have been shown to independently improve
outcomes (3). However, none are curative therapies, and IPAH remains
a progressive disease with a high mortality rate (13). The paradigm
of simultaneously targeting multiple pathways has been successfully
used in many other diseases such as hypertension, congestive heart
failure and cancer. However, drug therapies for PH are significantly
more expensive than those for more common diseases such as systemic
hypertension. PDE5is and ERAs for PAH cost $10,000 to $40,000
der per year per patient in Canada, while intravenous and subcutaneous
therapies cost $80,000 to $100,000 per year. Therefore, the use of combi-
nation therapy for PAH has significant cost implications that have
resulted in strict control of prescribing by government and private
care in Canada. Recent data from the Registry to Evaluate Early
And Long-term pulmonary arterial hypertension disease management
(REVEAL), a multicentre PAH registry populated from 2006 to 2007,
and containing 2525 PAH patients, indicates that combination ther-
apy is routinely used in the United States (14). Baseline data from the
REVEAL registry found that approximately 65% of PAH patients on
PH-specific medications were being treated with combination therapy
(excluding calcium channel blockers) (14). Our survey indicated that
the majority of PH physicians in Canada support the use of combi-
nation therapy in IPAH patients who do not adequately respond to
monotherapy. However, access to combination therapy is currently not
available to all PH patients in Canada because prescription reimburse-
ment is not universally provided by all provincial health care providers
or private insurers.

With multiple PH medications to choose from and, now the possibil-
ity of combination therapy, the need to monitor disease progression and
response to therapy has become more salient. From this need, the con-
cept of goal-directed therapy has emerged -- the establishment of pre-
defined clinical targets used to make decisions regarding the mainten-
ance and acceleration of therapy for PH. However, the optimal indicators
clinical deterioration, stability or improvement are not known with
certainty. In 2005, Hooper et al (15) published a study evaluating a
protocol for future research and, with the worldwide push for the establish-
ment of disease registries, identify clinically important database components
for surveillance, outcome assessments and future investigation.

**CONCLUSION**

In the absence of clear guidance from the scientific literature, gather-
ing expert opinions and building consensus is necessary to standardize
care and optimize outcomes in IPAH. Collectively, the present survey
provided an overview of the opinions of Canadian PH physicians with
regard to the best approach to the management of IPAH patients after
the initiation of therapy. The identification of key parameters that are
believed to be most important in the assessment of patients on therapy is
the first step in the development of consensus guidelines and care path-
ways. The parameters described in the present study also highlight areas
for future research and, with the worldwide push for the establishment
of disease registries, identify clinically important database components
for surveillance, outcome assessments and future investigation.

**ACKNOWLEDGEMENTS:** The authors thank Actelion Pharmaceuticals
Canada Inc for assistance identifying PH practitioners in Canada. They
thank all Canadian pulmonary hypertension experts who participated in
this survey, because this survey would not have been possible without their ongo-
ing support. They also thank Wendy Lo for preparing the web survey and
managing the e-mail participation requests and responses.

**CONFLICTS OF INTEREST:** Adrienne Borrie has no conflicts of interest to declare. David Ostrow has received honoraria from Abbott
Pharmaceuticals, Actelion Pharmaceuticals, AstraZeneca Pharmaceuticals,
Bayer Pharmaceuticals and GlaxoSmithKline Pharmaceuticals for speak-
ing engagements, as well as participation in Advisory Boards for Actelion,
Pfizer/Encycive Pharmaceuticals and GSK. Robert Levy has participated in
advisory and/or speaker boards for Actelion, GlaxoSmithKline, Encycive,
Pfizer, Lilly and Bayer. John Swiston has received honoraria from Actelion and
Pfizer/Encycive for speaking engagements as well as participation in
advisory boards for GSK, Pfizer, Lilly and Actelion. Assistance for partici-
pation in educational activities has also been received from Actelion and
Pfizer.
APPENDIX 1: PHASE I AND II SURVEY QUESTIONNAIRES

Phase I:
1) Do you think that establishment of a predefined goal orientated approach to the management of pulmonary hypertension is feasible?
   - Yes or No

   If no stop and do not continue with the questionnaire

2) How soon after initiation of therapy should patients be re-evaluated?
   - Answer in months:
     - 0 – 3 months
     - 3 – 6 months
     - >6 months

3) Do you think that repeat right heart catheterization should routinely be carried out after the initiation of therapy?
   - Yes or No

4) If you answered Yes to question 3, how soon after initiation of therapy should right heart catheterization be carried out?
   - 0 – 3 months
   - 3 – 6 months
   - >6 months

   For questions 5 through 7 assume that your local formulary rules did/do not play a role in your decision process:

5) When a patient is on oral monotherapy but is not felt to have had an adequate clinical response, would you routinely switch to an alternate oral agent or add and additional oral agent (assuming that the patient is tolerating the first drug without side effects)?
   - a. Class II add or switch
   - b. Class III add or switch
   - c. Class IV add or switch

6) When patients on oral monotherapy are transitioned to prostacyclin therapy do you routinely continue or discontinue the oral agent?
   - continue or discontinue

REFERENCES