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End points in pulmonary arterial hypertension: the way forward

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End points in pulmonary arterial hypertension: the way forward. A. Peacock, R. Naeije, N. Galié, J.T. Reeves. ©ERS Journals Ltd 2004.

ABSTRACT: Pulmonary arterial hypertension is a rare disease of poor prognosis.

Despite its rarity >1,000 patients have been randomised in placebo-controlled trials using novel therapies, including prostacyclin analogues, endothelin receptor antagonists and, most recently, phosphodiesterase 5 inhibitors. Nearly all of these trials have used exercise capacity, measured by the unencouraged 6-min walking distance, as the primary end point and a variety of other measurements as secondary end points. This approach has been productive, leading to the licensing of a number of effective treatments. Future clinical trials, however, will probably assess drug combinations, make comparisons between drugs and include less severely ill patients. It is, therefore, timely to examine the end points used.

The authors discussed the various end points that have been used in the past and possible end points that might be used in the future. End points considered included measurements of: exercise capacity, haemodynamics, quality of life, imaging of the right heart and circulation, and chemical markers of pulmonary hypertension.

Many of these show promise but will have to be used in parallel and compared with conventional end points such as the 6-min walking distance before their value can be demonstrated convincingly to the regulatory authorities.
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Pulmonary arterial hypertension (PAH) is a disease of the peripheral pulmonary arteries of varying patho-aetiology. Interestingly, whatever the aetiology, the histology of the vessels is similar, prompting a unified approach to treatment. Initial success was achieved with anticoagulants and calcium channel blockers [1], but calcium channel blockers are effective in <10% of patients. Later, it was found that continuous intravenous epoprostenol was effective even in those who could not use the calcium channel blockers [2]. In 2001 and 2002, >1,000 patients with PAH were entered into placebo-controlled trials [3–7]. Nearly all of these trials have used the unencouraged 6-min walking distance and resting haemodynamics as end points. Results were significant, but not dramatic in physiological terms, with mean increases in 6-min walking distance ranging 17–72 m, and decreases in mean pulmonary artery pressure (Ppa) never exceeding a few millimetres of mercury. Although patients reported improvement, survival remains limited, and none of the newly introduced therapies has yet been shown to reverse the pathological process.

Some physicians monitoring clinical trials consider that the end points used may not best adequately represent the effectiveness of therapy. It is likely that placebo-controlled trials will become unacceptable and, in the future, more back-to-back comparisons of different therapies and also comparisons of different combinations of therapy will be introduced. In order to convince patients, physicians, funding agencies and regulatory bodies of the value of treatments which are often expensive, it is worth considering whether other end points should be examined that more adequately describe the changes that occur. From the patients′, and increasingly also the regulatory agencies′, perspective, quality of life is one of

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For editorial comments see page 799.

the most important measures of the success or failure of a new treatment. However, physicians treating PAH will not be satisfied with improvements in quality of life alone, and a specific questionnaire has not been validated in PAH patients. The physicians will require to see physiological changes accompanying the change in quality of life, whether these be changes in pulmonary haemodynamics, exercise physiology, biological markers or cardiopulmonary morphology. At the End Points Meeting held in Gleneagles, UK, May 1–4, 2003, experts on quality of life, imaging, exercise physiology, pulmonary haemodynamics and the hormonal changes associated with PAH were collected together from all over the world. There were also contributions from the regulatory bodies. The aim of the meeting was to consider the end points that have been used in the past and also to consider end points that might be used in the future. The definition of "end point" used was "a measurement used by investigators conducting a drug trial to determine whether patients with pulmonary arterial hypertension were benefited by drug administration". The following is a summary of the conclusions of the workshops that considered each of these topics.

Regulatory issues

The decision on appropriate end points for clinical trials in PAH needs to take into account the requirements of the regulatory agencies that are the ultimate referees for the approval of a treatment for a given indication.

In the process of decision-making for the implementation of new trials for PAH, the two main points are trial design and choice of appropriate primary and secondary reinforcing end points [7, 8].

Trial design

Following approval of an oral drug (bosentan) for the treatment of New York Heart Association Functional Class (NYHAFC) III PAH patients and the availability of new oral compounds to be tested, a range of questions need to be addressed. 1) Are placebo-controlled studies still possible in PAH? 2) Are noninferiority studies feasible in PAH? 3) Are withdrawal studies ethical in PAH?

Placebo-controlled studies

Currently four treatments for PAH patients are officially approved by regulatory agencies, the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA): intravenous epoprostenol for NYHAFC III and IV primary pulmonary hypertension (FDA and EMEA) [2]; subcutaneous treprostinil in NYHAFC II [3], III and IV PAH (FDA); oral bosentan in NYHAFC III PAH (FDA and EMEA) [6]; and inhaled iloprost in NYHAFC III PAH (EMEA) [5]. Only epoprostenol treatment has been shown, in a controlled clinical trial, to improve survival [2]. Treprostinil, iloprost and bosentan treatments have reduced the rate of clinical events but not mortality in the 3–4 months of the randomised trials [3, 5, 6]. The patient population enrolled in these last three studies was less compromised as compared to that in the epoprostenol study, but the reduced rate of events, small sample size and short duration of the studies have clearly underpowered these trials in detecting effects on mortality.

From the ethical and methodological point of view, experts now believe that a mortality study in PAH (NYHAFC III and IV) can be performed only with intravenous epoprostenol as comparator in countries in which this treatment is approved and available.

It is less clear whether a placebo-controlled study whose primary end point is exercise capacity assessed after 3 months of a randomised treatment would be acceptable. The points in favour of the continuation of the use of placebo include the following: 1) no prognostic superiority has been demonstrated by any new drug over the 3–4-month randomised trial periods (mortality ranging 1–3%, corresponding to 4–12%·yr^{-1}); 2) the setting of a controlled clinical trial "protects" patients who can be shifted to already approved treatments in case of deterioration; 3) NYHAFC II patients have been involved only marginally in clinical trials in PAH and may be included in placebo-controlled studies; and 4) a consistent proportion of patients with PAH fail to respond to the currently available treatments, and, therefore, it is not desired that hurdles be too high for the investigation of "new" drugs.

In contrast, arguments against the continuation of placebo-controlled studies include the following: 1) it is not ethical to expose patients to a 3-month period of placebo that has been shown to produce, in some cases, symptomatic and clinical deterioration; 2) NYHAFC II patients are a "minority" in the population observed in clinical practice; and 3) the current priority should be the comparison of new treatments with approved ones, and noninferiority studies should be implemented

Noninferiority studies

Noninferiority comparative studies can be an alternative to superiority placebo-controlled studies if the latter are considered inappropriate for ethical reasons. Superiority comparative studies between active therapies would be difficult to perform in a rare disease such as PAH because the sample size needed is usually quite large. The objective of a noninferiority study is the demonstration that there is no significant difference between the two compounds for a given end point. The feasibility of noninferiority studies in PAH is related to the following points. 1) Noninferiority studies can be performed only using the primary end points already investigated. In the case of PAH, this would be the 6-min walking distance if the comparator is bosentan. This would seem to restrict the use of new end points, but these could be used in parallel with the 6-min walking distance. 2) Noninferiority studies require an identical setting (inclusion criteria, exclusion criteria, patient population, study protocol, *etc.*) to the pivotal study of the "comparator". 3) The sample size would need to be quite high (>500 patients) if the end point is the six-min walking distance and the comparator is bosentan. 4) The risks and costs for a pharmaceutical company are much higher compared to a superiority study.

Withdrawal studies

Withdrawal studies are suggested by regulatory agencies for different reasons, *e.g.* when the pivotal trials have not shown a "clinically relevant" benefit or more consistent proof of efficacy is required. However, in a life-threatening disease such as PAH, a withdrawal study seems to be inappropriate for the following reasons: 1) in PAH, no drugs have been shown to induce a consistent modification of the disease process and therefore there is no reason to believe that the withdrawal of an effective drug would not induce a deterioration; 2) as a consequence, the end point of this study would be an assessment of deterioration and this could be considered to be against basic medical principles (*primum non nocere*); 3) nobody can guarantee the reversibility of deterioration in patients with PAH, even after the reinstitution of a previous

treatment; and 4) the approval of institutional review boards, for ethical reasons, and patients' acceptance of such trials are questionable

Primary and secondary reinforcing end points according to the requirements of the regulatory agencies

Regulatory agencies currently accept as "primary" only clinical end points such as exercise capacity, time to clinical worsening and mortality. Usually, pathophysiological parameters such as haemodynamics are considered "secondary".

In PAH, the assessment of exercise capacity using the 6-min walk test may still be the "best option" for the primary end point, especially since it allows comparison with results from previous trials. The 6-min walking distance could be improved by utilisation of an index that includes the distance walked and the Borg dyspnoea index or the level of arterial desaturation during the exercise. A correction for age and body weight could prove useful. Obviously, these new indices and other end points should be validated in prospective studies that investigate their superiority compared to simply the walked distance. It is important that the "clinical relevance" of a given improvement in the distance walked is defined *a priori* in the protocol of a study to avoid inconclusive discussions at the end of the trial. As the "clinical relevance" of a given improvement is somewhat arbitrary, it can be defined according to the treatment effect obtained with treatments already approved.

The use of quality-of-life questionnaires as "primary" end point has been proposed, but there are several doubts as to their applicability in PAH, in particular because no validation has been provided in this specific clinical setting.

Time to clinical worsening as a combined end point requires standardisation to make it more objective and comparable. This parameter is usually defined by a combination of death, hospitalisations due to worsening of PAH and escalation of treatments (need for epoprostenol or transplantation). The latter two events are influenced by the judgement of the attending physician and should be supported by some "objective" findings, such as predefined cut-off levels for exercise capacity and haemodynamic parameter deterioration.

Haemodynamic parameters have been considered traditionally as "secondary" reinforcing end points, based on their prognostic value [9], and this concept has been accepted by regulatory agencies, but resting haemodynamics are likely, at best, to give an incomplete picture of the damaged pulmonary vessels in PAH. Haemodynamics under conditions of stress, such as exercise, dobutamine or leg raising, are likely to be more useful. The possibility of using selected echocardiographic parameters as a substitute for invasive haemodynamic measurements should also be explored. Indeed, some echocardiographic and Doppler parameters, such as Doppler-derived cardiac output, right ventricular (RV) (Tei) index, pericardial effusion size, *etc.*, have been shown, in recent studies, to be of value prognostically [10] and in assessing therapeutic changes in patients with PAH [11, 12].

The usefulness of biological end points, such as levels of B-type natriuretic peptide (BNP), troponin, endothelin, *etc.*, in clinical trials have still to be tested and validated in clinical studies before they can be proposed to regulatory agencies.

Possible ways forward

Imaging

Magnetic resonance imaging (MRI) has been introduced, in recent years, for the assessment of ventricular mass and cardiac volumes and measurements of absolute flow and velocity in the pulmonary circulation [13–17]. Although more expensive and complex than echocardiography, MRI may ultimately reduce the number of observations needed to verify a research hypothesis. This is because of the improved (over echocardiography) reproducibility of its results. However, new generations of software need to be developed, permitting semiautomatic evaluation of acquired data, in order to reduce the excessive time currently needed for even relatively simple measurements. In addition, costs and the time required for the procedure need to be considered in the comparison with established methods.

Spiral computerised tomography using recent multi-element technology provides the highest resolution of all the imaging methods. However, it gives less insight into haemodynamics, and is likely to be superseded by MRI, which provides both structural and functional information.

The evaluation of imaging in assessing pulmonary hypertension has come almost entirely from echocardiographic studies in primary pulmonary hypertension [10–12, 18–25]. The data indicate that some variables potentially useful as end points reflect chronic consequences of PAH, rather than being measurements of instantaneous haemodynamics. The following are examples of this. 1) Elevation of right atrial pressure by assessment of the presence and score of pericardial effusion, as well as measurement of right atrial area/volume or the dimensions of the inferior vena cava. 2) RV dysfunction assessed by calculating Doppler indices of ventricle performance or, alternatively, measuring the duration and flow velocity pattern of RV ejection. Surrogate assessment of RV ejection fraction by tissue Doppler imaging or M-mode assessment of tricuspid annular systolic motion could be of value. 3) Decreased left ventricular preload by assessment of left ventricular diastolic eccentricity index or end diastolic area/volume, as well as by decreased left ventricular early diastolic filling velocity. Interestingly, it was the improvement in left ventricular early diastolic filling which seemed best to reflect the effects of treatment of patients with PAH according to existing evidence [12].

Tissue Doppler imaging may further simplify assessment of the dynamics of the heart and may provide assessment of indices of RV function from a single trace. Recent experimental data suggest that myocardial acceleration during isovolumic RV contraction is load-independent and strongly correlated with end-systolic RV elastance, the best available measure of its contractility

Haemodynamics

Right heart catheterisation measurements of $P\mathrm{pa}$, pulmonary artery occlusion pressure ($P\mathrm{pa,occ}$) and blood flow (Q'), with calculation of pulmonary vascular resistance, are correlated to clinical state, NYHAFC, exercise capacity and prognosis [2, 9, 26–28], but these correlations are rather loose when the measurements are performed only at rest. A single point measurement may under- or overestimate changes in the functional state of the pulmonary circulation, primarily because the inherent assumptions of zero crossing of the $(P\mathrm{pa}\text{-}P\mathrm{pa,occ})/Q'$ relationship are not met [29, 30, 31]. This error can be minimised by defining resistance from a multipoint pressure/flow line [29]. For example, recent studies showed that improvement in exercise capacity with prostacyclin therapy in PAH patients may not be associated with significant changes in pulmonary haemodynamics at rest, whereas resistance defined by a multipoint $(P\mathrm{pa}\text{-}P\mathrm{pa,occ})/Q'$ plot shows a significant decrease [30]. Multiple points can be

obtained by increasing cardiac output with exercise [30] or a low-dose infusion of dobutamine [31].

In addition, mean P_{pa} and Q' determinations may be insufficient to measure RV afterload [32], since, in addition to vascular resistance, afterload involves elastance and wave reflection. Although afterload can be estimated by pulmonary arterial input impedance (the ratio of pulsatile P_{pa} to pulsatile Q'), impedance determination requires spectral analysis, complicated mathematics and high-fidelity technology [32, 33], which is unavailable in most catheterisation laboratories. Therefore, the clinical relevance of impedance determinations is unclear. RV afterload can be indirectly evaluated by P_{pa} and Q' waveform analysis [34–36], but its diagnostic value remains controversial [37].

Continuous 24-h monitoring of P_{pa} shows the effects of daily life (postural changes, exercise and sleep) on pressure [38], and therefore provides a novel index of afterload. However, the method uses micromanometer-tipped catheters and is expensive and invasive, and requires a high level of expertise. Therefore, it can be considered only in a limited number of reference centres, where results can be correlated with other, more available, techniques.

With the addition of these newer techniques and methods of analysis, the current tendency to omit invasive haemodynamics, even as a secondary end point, appears premature.

Exercise capacity

The most common symptoms of patients with PAH, namely shortness of breath and fatigue, occur predominantly during exercise. These symptoms result from the combined effects of decreased oxygen delivery to the tissues, increased physiological dead space and arterial hypoxaemia, together causing a decreased peak or maximum oxygen consumption, an early anaerobic threshold and increased ventilatory equivalents. Accordingly, the physiological severity of PAH can be quantified by measurements of ventilation, oxygen consumption and carbon dioxide production at progressively increased workload. Several such cardiopulmonary exercise testing (CPET)-derived measurements have been shown to be correlated to outcome [39–42]. One of the best indicators of disease severity in PAH patients appears to be elevation of ventilation/carbon dioxide production, measured at the anaerobic threshold [39–43].

The 6-min walking distance, used as primary end point in randomised controlled trials, is nothing more than a simpler, cheaper and better-tolerated submaximal exercise surrogate of CPET for evaluating exercise capacity. However, there is very little experience with CPET in randomised controlled trials in PAH patients. In a recent trial of the oral prostacyclin derivative beraprost in PAH, the 6-min walking distance improved at 3 and 6 months, whereas there were no concomitant significant changes in CPET indices [44]. Similar results have been preliminarily shown in a randomised study with the endothelin receptor antagonist sitaxentan [45]. These surprising results, which might be related to unknown causes, including insufficient quality control in participating centres, deserve further investigation.

Quality of life

Until now, the impact of PAH on quality of life has been evaluated by generic health status measures such as the 36-item Short-Form Health Survey [46], Nottingham Health Profile [47], European quality of life [scale] [48] and Living with Heart Failure Minnesota questionnaire [49]. Although the results of these measures improve or deteriorate along with changes in clinical condition, functional state and exercise capacity [2, 3, 5], there is a concern about validation, sensitivity and possible failure to assess those issues that are of major concern to the patient [50]. Accordingly, efforts are being made to collect, directly from patients, information on impairments (symptoms), disability (functioning), handicap and utility [50, 51]. It is important to be clear about how these items differ, how they relate to each other and their relative value in determining the impact of disease [52–57]. The availability of a PAH-specific quality-of-life instrument would provide the patient-relevant end point that is currently lacking.

Biological markers

Markers of endothelial cell and/or platelet dysfunction in PAH include endothelin-1 [58–62], prostaglandins, thromboxanes [63, 64], nitric oxide [65, 66], von Willebrand factor [67, 68], D-dimers [69], serotonin [70, 71], adhesion molecules, cytokines and chemokines [72]. Although these markers probably have pathophysiological or prognostic relevance in PAH, the trials suffer from small study populations and thus require confirmation. Furthermore, interventions which directly alter levels of endothelins, prostaglandins, or their receptors, reduce their interest as markers for monitoring treated patients.

Markers of heart failure (A-type natriuretic peptide, BNP and cyclic guanosine monophosphate (cGMP)) may be more relevant to addressing prognosis and improvements with therapy [73, 74] than assessing disease state. Interestingly, N-terminal pro-BNP (the biologically inactive alternative) is more stable than is plasma BNP, and is a potentially useful marker. Whether heart failure markers are useful early in the natural history of the disease remains to be demonstrated.

Chronic leakage of troponin T (presumably from RV myocytes) is a high-sensitivity test indicative of ongoing damage to the right ventricle and is related to poor survival in PAH [75].

Serum uric acid levels correlate inversely with cardiac index and positively with total pulmonary resistances. The levels correlate inversely with survival and fall with haemodynamic improvement [76]. However, uric acid is affected by variables including drugs, tissue perfusion, decreased glomerular filtration and hypoxia.

Markers of the effects of PAH which can be measured in urine (*i.e.* cGMP, prostaglandins, thromboxanes and isoprostanes [77]) or in exhaled air or its condensate (nitric oxide) are potentially useful, although validation studies are needed.

Clinical end points

Signs and symptoms in PAH are well defined and limited in number, and, accordingly, a 15-item clinical score has been developed, and implemented in one clinical trial of PAH treatment [3]. This score proved to be as sensitive to the active treatment as the 6-min walking distance [3] and would be worth considering in future clinical studies.

Clinical events such as death, hospitalisation for right heart failure and the requirement for alternative treatments have been used as secondary, often combined, end points. In three different trials, the active treatment led to a reduction in these clinical events after 3–4 months [2, 5, 6]. A combined end point of clinical events has the potential of a primary end point.

Conclusions and recommendations: the end point

The present working group on end points, with participants from Belgium, the UK, France, Germany, Ireland, Italy, Switzerland and the USA, drew conclusions and made recommendations relative to the evaluation of patients with PAH.

Perhaps the main result of the present conference was that those evaluating the treatment of PAH were not completely satisfied with the current end points. For example, a given end point was: 1) insensitive (poor signal-to-noise ratio), 2) inaccurate (did not reflect the status of the disease), 3) incomplete (ignored important components of the disease), 4) expensive/time-consuming/complicated (not generally applicable to a population of patients, could not be frequently repeated and/or not appropriate for use by many clinicians), 5) transient (reflected a moment in time and was too labile to represent the overall picture), 6) subjective (sensitive to mood or bias of patient or investigator), and 7) required a longer evaluation period than was practically available during the trial.

Conversely, for broad application to a population, characteristics of an "ideal" marker for PAH might include the following: 1) it should be heart- or lung-specific, 2) it should be abnormal in PAH, 3) sample collection should be simple, 4) the marker should be easy to measure (ideally bedside measurement), 5) values should be reproducible, 6) values should follow the course of the disease (*i.e.* increasing if patients deteriorate and falling if patients improve), and 7) abnormal values should be indicative of poor survival.

In the absence of an "ideal end point/marker", recommendations for improvement of future studies could involve the following items. 1) Validation studies might include longitudinal analyses in stable and unstable patients with or without targeted therapies. 2) Strategies should be devised to improve the sensitivity of given end points, and consideration should be given to the analysis of several markers in parallel, which might also improve sensitivity. 3) More emphasis should be placed on the early stages of disease, with end points/markers tailored to this stage. 4) Strategies which give rapid results and allow immediate use of the information should be emphasised. 5) There should be continued development of new technologies and methods of analysis, with emphasis on sensitive predictors of prognosis. 6) If legally possible, plasma and other biological samples should be stored, with the patient's consent, in well-characterised PAH populations to be available for tests devised in the future. 7) More individual data should be shared among investigators to facilitate more rapid progress.

General recommendations are as follows. 1) Working groups should be convened regularly because they are effective in clarifying and discussing the problems, proposing possible solutions and developing collaboration to bring about solutions. 2) Small subgroups of experts dealing with specific problems result in conclusions, which are then brought back to the general group. 3) Publication of the result of deliberations provides broader dissemination of information and a benchmark for the future.

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