The Key Role of PH Patients in Guiding Research

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In pulmonary hypertension (PH), the ultimate goal of new drugs is to prolong survival and improve patients' quality of life. However, in the context of a clinical trial, it is difficult to demonstrate that new treatments reduce the risk of mortality. Indeed, due to the availability of rescue treatments in the event of clinical deterioration, deaths are, fortunately, infrequent in clinical trials. Consequently, it is practically impossible to demonstrate that the number of deaths is lower in the group of patients that receive a new treatment compared to the group of patients receiving only the standard treatment. Similarly, current tools to assess quality of life have not been able to detect significant changes in PH clinical trials. Thus, for several years, clinical trials primarily aimed to demonstrate that the new treatment under study improved the distance covered during the six-minute walk test more than its comparator as an indirect measure of the well-being of patients. More recently, to consider other consequences of PH on the life of patients, the effect of new treatments on the occurrence of a "group of events"—called a. composite endpoint—has been evaluated. With a composite endpoint, we compare the proportion of participants treated with the new drug in whom one of these events occurred versus its comparator.

Unlike a study that would compare the occurrence of death only, the use of a «composite» criterion takes into account a greater number of events occurring during the study and, therefore,the power of the study (i.e., the ability to demonstrate that the treatment is effective if it is). However, this approach can complicate the interpretation of the results. Let's take a concrete example to understand the issues fully.

When shopping, the informed buyer will focus on several characteristics they think are important. For example, when buying a vehicle, a buyer will likely be interested in safety, energy savings, passenger space, price, and colour. The rational buyer will choose the vehicle that best meets their needs. A simple way to do this would be to compare, among the possible vehicles, the one that fulfills the greatest number of desired characteristics. However, among the selection criteria, it is possible that some aspects are more important than others and that these priorities differ from those of another client. Thus, parents of young children may prioritize safety and space, while the single environmentalist may place more importance on purchasing an electric vehicle. By comparing only the number of characteristics satisfied by each vehicle, the colour of the vehicle—which has less importance in their final choice—will count as much as safety or energy saving.

This problem can also arise when using composite endpoints in a clinical trial. A composite criterion commonly used in PH is called «clinical worsening." Generally, it includes death or hospitalization, the need for a transplant, the progression of symptoms, or the need to start a new treatment. We then compare the proportion of participants receiving the new treatment in whom one of these events occurs compared to those who do not. Using a composite criterion does not pose a problem if the new treatment comparably prevents all these events and if these events are considered to be of similar importance for the participants. However, like the vehicle's characteristics, preventing some of these events will be more important than others.

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In this context, our team at Laval assessed the relevance of the «composite» criteria used in clinical trials in PH. Our team first listed, through an exhaustive search of the literature (a systematic review), all the PH studies that had used a «composite» efficacy endpoint over the past decades. In the 35 studies listed, the occurrence of death or hospitalization was commonly included in the definition of the composite endpoint used. However, the way of defining the progression of symptoms or the need for additional therapy was very heterogeneous between studies. Thus, it became difficult to compare the results of the different studies with each other. Unsurprisingly, most «clinical worsening» events were related to hospitalization or symptom progression, while deaths and transplants, which are significant events, were rare. In addition, for each patient, only the first event of «clinical worsening» is documented during an event-driven study, and subsequent events are rarely reported. Thus, for a patient hospitalized for deterioration of their disease (as a first event), a subsequent hospitalization, transplant, or even death will not necessarily be reported. Our analysis also demonstrated that the effect of the new treatment on the occurrence of «clinical worsening» was a poor predictor of its impact on future mortality amongst patients under study. Similarly, a new medicine's effect on each event defining «clinical worsening» was inconsistent in the studies. In some cases, the new treatment could prevent the worsening of symptoms while increasing hospitalizations.

Next, we questioned how important preventing these events was to patients. We conducted an extensive survey of Canadian PH patients and their caregivers regarding the importance they placed on preventing the various events used to define «clinical worsening.» It revealed several interesting findings. First, about one-third of the events used in clinical trials to define «clinical worsening» were considered unimportant by patients. Thus, in several clinical trials, preventing the occurrence of events of limited importance to patients had a similar weight to the prevention of other events considered critical (such as when the colour of the vehicle has the same influence as safety in the purchase of a vehicle described in the previous example).

The importance of preventing these events among patients with PH also varied. For example, older patients tended to place less importance on preventing death than younger ones. Finally, caregivers generally overestimated the importance placed by patients on preventing many events defining «clinical worsening.» For example, the prevention of hospitalization was considered essential for most caregivers, while its importance appeared significant but to a lesser extent for patients. This phenomenon is not unique to PH and has been noted in various diseases. Nevertheless, this observation reminds us that PH patients are probably best able to define what matters to them and how the success of a pharmacological approach should be defined.

Using «composite» criteria in clinical trials in PH has made it possible to demonstrate the effectiveness of several treatments, allowing for their approval and access to patients. It seems essential to involve representative patients in designing and implementing clinical trials to ensure that PH research meets patients' needs. More broadly, patients and their advocates have a key role in guiding research priorities.

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