THE KEY ROLE OF PH PATIENTS IN GUIDING RESEARCH

In pulmonary hypertension (PH), the ultimate goal of new drugs is obviously to prolong survival and improve the quality of life of patients. 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 possibilities of having access to 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 in whom a new treatment is added 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 so far. Thus, for several years, clinical trials aimed to demonstrate that the new treatment under study improved the distance covered during the walk test more than its comparator as an indirect measure of the well-being of patients. More recently, in order to take into account other consequences of PH on the life of patients, the effect of new treatments on the occurrence of a group of events (called composite endpoint) has been evaluated. We thus compare the proportion of patients in whom one of these events occurred among the participants treated with the new drug 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. its ability to demonstrate that the treatment is effective if it really is). However, this approach can complicate the interpretation of the results. Let's take a concrete example to fully understand the issues. When shopping, the informed buyer will focus on several characteristics that seem important to him. When buying a vehicle, for example, he is likely to be interested in safety, energy savings, passenger space, price and color of the vehicle. The rational buyer will choose the vehicle that best meets all of his 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 will place more importance on the purchase of an electric vehicle. By comparing only the number of characteristics satisfied by each of the vehicles, the color 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. In PH, this composite criterion is commonly called “clinical worsening” and generally includes the occurrence of either 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 in whom one of these events occurs among those receiving the new treatment compared to those not receiving it. The use of a composite criterion does not pose a problem if the new treatment prevents all of these events in a comparable way, and that these are considered to be of similar importance for the participants. However, much like the characteristics of the vehicle, it is likely that preventing some of these events will be considered more important than others.

It is in this context that our team assessed the relevance of the "composite" criteria used in clinical trials in PH. Our team first listed, through an exhaustive search of the literature (what is called a systematic review), all of the PH studies that had used a “composite” efficacy endpoint over the past decades. In the 35 studies listed, while the occurrence of death or hospitalization was commonly included in the definition of the composite endpoint used, 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, the vast majority of “clinical worsening” events were related to hospitalization or symptom progression, while deaths and transplants, which are major 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 being hospitalized for a deterioration of his disease (as a first vent), a subsequent hospitalization, transplant or even death will not necessarily be reported. Our analyzes also demonstrated that the effect of the new treatment on the occurrence of “clinical worsening” was a poor predictor of its effect on the future mortality amongst patients under study. Similarly, in each of the studies, the effect of the new medicine on each of the events defining “clinical worsening” was not necessarily consistent. In some cases, the new treatment could prevent worsening of symptoms while tending to increase hospitalizations.

We then questioned how important preventing these events were important for patients. In a large survey of Canadian PH patients and their caregivers regarding the importance they placed on preventing the various events used to define "clinical worsening", several interesting findings were made. First, about one-third of the events used in clinical trials to define “clinical worsening” were considered to be of limited importance by patients. Thus, in several clinical trials, preventing the occurrence of events of limited importance had a similar weight to the prevention of events considered critical by patients (such as the color of the vehicle which would have a similar influence on safety in the purchase of a vehicle described in the previous example). Among patients with PH, the importance given to the prevention of these events was also variable. 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 the prevention of many events defining “clinical worsening”. For example, the prevention of hospitalization was considered essential for a majority of 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 patients suffering from PH are probably the best able to define what matters to them and how the success of a pharmacological approach should be defined.

Thus, although the use of "composite" criteria in clinical trials in PH has made it possible to demonstrate the effectiveness of several treatments in order to allow their approval and make them available to patients, it seems essential to involve representative patients in the design and implementation of clinical trials to ensure that PH research meets patients’ needs. More broadly, patients and their associations have a key role to play in guiding research priorities.