Reply to Jin *et al.* and to Sun *et al.*

From the Authors:

We are grateful for the positive comments in the two letters from Jin and colleagues and Sun and colleagues. Our data suggested that initial triple combination therapy including a parenteral prostacyclin could be a promising therapeutic strategy in patients with pulmonary arterial hypertension (PAH), especially for intermediate- and high-risk patients (1). They have several suggestions for future analyses; however, these were not part of our statistical plan described in the article or the peer-review process. We do agree, and have discussed in our manuscript, that prospective multicenter trials are needed to determine the optimal triple combination regimen and to definitively examine whether initial triple therapy is superior to dual therapy. In rare diseases like PAH, observational data from registries often guide clinical decision making, inform guidelines, and are often necessary to establish the need for larger prospective trials, as well as to inform their hypotheses and design (2, 3). Furthermore, registry-based data may complement the results of clinical trials in real-world populations (1, 4–8). Registry-based observational studies further supported the concept of initial oral dual combination therapy in PAH (8), which was studied in the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial (5). Initial data supporting the potential of initial triple combination therapy targeting the three pathways (7) ultimately supported the need for a trial of initial triple therapy versus dual oral therapy, the TRITON (Efficacy and Safety of Initial Triple versus Dual Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension) trial (9). Although TRITON was a negative study with respect to the effect of initial triple oral therapy with macitentan, tadalafil, and selexipag on pulmonary vascular resistance, we contend that further long-term studies are needed to evaluate the effect of an initial triple therapy regimen on clinical outcomes. Moreover, parenteral prostacyclin derivatives should also be considered in future studies of initial triple therapy regimen, as supported by our registry data (1). Our recent study will help support new hypotheses and justification for such studies and will inform perspectives on treatment strategies in PAH (1).

Although we agree that prospective and, ideally, randomized trial data are needed to confirm our results, we do contest the claim by Sun and colleagues that the study by Stubbe and colleagues (10) raises "a little controversy" about whether triple therapy affects prognosis. In this cited study from Germany, there were only 131 patients, of whom 45 were "atypical," and only 1 atypical patient received initial triple combination therapy within the first 3 months. Thus, comparisons were effectively between initial mono versus dual therapy and they were underpowered to look at survival differences in these subgroups. It should be emphasized that there are other observational data on triple therapy with intravenous or subcutaneous prostacyclins (7, 11, 12) that underline the probable interest of this therapeutic approach in the most severe patients, as discussed in the 2015 European guidelines and sixth World Symposium on Pulmonary Hypertension (13, 14). We do agree with both groups of authors that more data are needed on this therapeutic approach in other types of PAH, such as connective tissue disease and congenital heart disease. As both letters point out, the use of complex parenteral medications such as epoprostenol and treprostinil may not be possible in all intermediate- and high-risk patients for a variety of reasons, including long-term side effects and patient preference. The nature of data collection in the French Pulmonary Hypertension Registry does not permit a comparison of side effects between treatment strategy groups. Our registry data with a large number of patients do, however, provide novel hypothesis-generating information that can be tested prospectively in future studies to evaluate efficacy, safety, and tolerability.

Of course, in certain countries a more aggressive approach with triple therapy may not be feasible or possible because of restricted or limited access to parenteral therapies, as they state is currently the case in China. There are economic and technical obstacles to implementation of triple therapy in many countries, underlining the importance of setting up networks of expert centers benefiting from multidisciplinary teams, therapeutic education, and dedicated funding (15). Our goal as a global community of clinicians treating PAH should be to advocate that all patients have access to the most effective medications and access to combination therapy strategies to achieve optimal outcomes. Last, drug discovery and development should also help define if novel approaches targeting more recently identified pathways may provide added benefit on top of the currently available drug armamentarium (16). ■

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