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LETTER TO THE EDITOR

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Sequential combination therapy with parenteral prostacyclin in BMPR2 mutations carriers

We read with interest the manuscript entitled "BMPR2 mutations and response to inhaled or parenteral prostanoids: a case series" published in by Scelsi et al.[1] in a recent issue of *Pulmonary Circulation*. The authors reported a small series of 13 patients (6 with idiopathic or anorexigen-induced PAH and 7 with heritable PAH due to *BMPR2* mutation) in whom treatment escalation consisted in adding an inhaled or a parenteral prostacyclin. It was intriguing that *BMPR2* negative patients achieved a greater hemodynamic improvement than *BMPR2* positive patients (−10.1 vs. −2.4 WU), more than 1 year after initiation of prostacyclin.

On the basis of these findings, we analyzed from the French referral Pulmonary Hypertension center database the effects of treatment escalation with a parenteral prostacyclin in all idiopathic, heritable, and anorexigen-induced PAH patients receiving a background oral combination therapy with an endothelin-receptor antagonist and a phosphodiesterase type-5 inhibitor. We identified 24 patients between 2007 and 2020. All were sequenced for *BMPR2* mutations and other predisposing PAH genes.[2] There were 15 idiopathic PAH, 2 anorexigen-induced PAH and 7 heritable PAH due to *BMPR2* mutations. Intravenous epoprostenol was initiated in 7 *BMPR2* positive and 6 *BMPR2* negative patients, and subcutaneous treprostinil was initiated in the remaining 11 nonheritable PAH patients. The first hemodynamic reassessment was performed 6 ± 3 months after initiation of prostacyclin. Cardiopulmonary haemodynamics improved after prostacyclin initiation in almost all patients (Figure 1). Pulmonary vascular resistance decreased from 13.4 ± 5.5 to 8.9 ± 3.8 WU ($p = 0.02$), in the same proportion than previously described.[3] There was no significant difference according to *BMPR2* status with a decrease by 5.9 WU (interquartile range: 4.5–9.0) and 3.1 WU (1.2–6.7) in *BMPR2* positive and BMPR2 negative patients, respectively ($p = 0.21$). In addition, after prostacyclin initiation all patients carrying a *BMPR2* mutation achieved a low-risk status according to COMPERA methodology.[4]

Our results in a larger series of idiopathic and heritable PAH do not validate the conclusions of a lower response to prostanoids in PAH patients carrying a *BMPR2* mutation as suggested by Scelsi et al.[1] In an international meta-analysis of 1550 PAH patients, Evans et al. reported that PAH patients carrying a *BMPR2* mutation present at a younger age with more severe disease, and are at increased risk of death or transplantation, compared with those without *BMPR2* mutations.[5] However, a recent study on long-term outcomes of PAH according to initial treatment strategy has shown that patients initiated with triple combination therapy including parenteral prostacyclin had an excellent long-term survival (86% at 10 years) despite their clinical and hemodynamic severity.[6] Among the 76 patients initiated with triple combination therapy, 48 had heritable PAH.[6] One can suggest that an ambitious therapeutic approach may counterbalance the natural history of heritable PAH and that these patients respond favorably to combination therapy including parenteral prostanoids.

In this cohort, *BMPR2* mutations carriers, in whom a treatment escalation was performed by adding a parenteral prostacyclin, all achieved a low-risk status and improved their hemodynamics. These results suggest that *BMPR2* status should not be considered as a prognostic factor of poor response to prostanoids.

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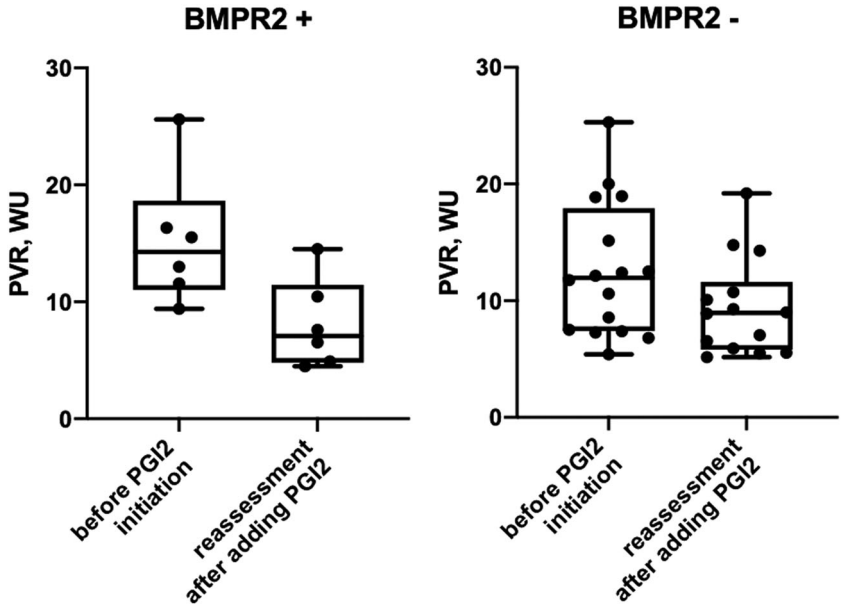

FIGURE 1 Plots of pulmonary vascular resistance before and after addition of parenteral prostacyclin (PGI2) in *BMPR2* mutations carriers and non *BMPR2* mutations carriers receiving background oral combination therapy

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