



Targeting bone morphogenic protein receptor 2 (BMPR2) signalling to treat pulmonary arterial hypertension

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BMPR signalling may be a therapeutic target for PAH, but further studies are needed
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Since the demonstration nearly 20 years ago that mutations of bone morphogenic protein receptor 2 (BMPR2) are associated with heritable pulmonary arterial hypertension [1–4], investigators have postulated that altered BMPR2 signalling, whether inherited or acquired, may be a novel therapeutic target for pulmonary arterial hypertension (PAH) of all aetiologies. Enhancing BMPR2 activity in animal models of pulmonary hypertension attenuates the severity of pulmonary vascular growth and proliferation [5, 6], although these models have not been predictive of responses in human disease. In the current issue of the *European Respiratory Journal*, SPIEKERKOETTER *et al.* [7] report that BMPR2 mRNA expression is attenuated in PAH and that FK506 (tacrolimus), a BMPR2 activator, produced no meaningful effects in a small, single-centre 16-week clinical trial in subjects with PAH due to a variety of aetiologies. While the authors identified several “FK506 responders” in a *post hoc* analysis, they found no difference in BMPR2 expression between “responders” and “non-responders”, nor did they observe any change in serologic biomarkers linked to increased BMPR2 signalling.

The results of the clinical trial reported by SPIEKERKOETTER *et al.* [7] neither confirm nor refute the notion that targeting BMPR2 signalling represents a potentially effective therapeutic approach for PAH. The authors chose to investigate doses of FK506 that produce blood levels below those targeted for immunosuppressive therapy based on their experience with animal experiments and in order to minimise safety concerns: while this approach clearly supported safety and tolerability, the primary objectives of this study, these doses may have been insufficient to produce the desired effect on BMPR2 signalling. Furthermore, the short duration of the trial may have been insufficient to either enhance BMPR2 activity or to observe clinical effects resulting from this drug-induced effect, especially since it took 50 days on average to achieve trough levels that differentiated between the low, medium and high dose treatment arms. A further limitation to the study is its small sample size: while the planned sample size was 40 subjects, only half of this target were enrolled and completed the 16-week study period. It is virtually impossible to demonstrate meaningful treatment effects in such a small study unless their magnitude and consistency are overwhelming. Finally, there is The Goldilocks Principle, which states that something must fall within certain margins, as opposed to reaching extremes; applied to clinical trials, this concept may be used to suggest that the study population was either too sick or not sick enough to manifest a beneficial

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response to the investigational therapy. In this case, the authors suggest that their study cohort, which consisted predominantly of patients who were functional class II and stable on background PAH-targeted therapies, may not have been sufficiently impaired to achieve the desired treatment effect. While this principle may have validity in other serious conditions such as advanced malignancy, there is little evidence to support its applicability in PAH, where the approved medical therapies have been shown to produce clinical improvement, alone or in combination, in patients with disease severity ranging from mild to severe.

Both the prespecified and *post hoc* analyses of this study do not as yet support conducting a large, multicentre phase 3 study. They do, however, provide insight and generate new hypotheses to be tested in a well-designed phase 2 study. Such a study should include a sufficient number of experienced centres to ensure adequate enrolment, and enrol a better defined “at risk” population, such as heritable PAH and idiopathic PAH subjects with reduced or absent levels of normal BMPR2 expression. Study doses of FK506 should be reconsidered, since blood levels in the immunosuppressive range may be necessary to achieve a treatment effect. In light of the serious nature of PAH, patients and their physicians are accustomed to risking serious adverse treatment effects in return for the possibility of a disease-modifying treatment effect. More meaningful and compelling efficacy end-points should be selected, particularly in this era of combination therapy, and analyses should be pre-specified and based on the study’s power to interpret them.

It has now been several years since any new treatment for PAH has received regulatory approval, and a number of novel drug candidates have failed to produce a sufficiently favourable efficacy/safety balance to warrant further development. While we may not know whether enhancing BMPR2 signalling is achievable in PAH, or if such enhancement translates into a clinical benefit, this pathway remains a target worthy of exploration in a well-designed proof-of-concept clinical study.

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