Upfront triple therapy with parenteral prostanoid as a bridge to balloon pulmonary angioplasty in severe chronic thromboembolic pulmonary hypertension

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To the Editor:

Balloon pulmonary angioplasty (BPA) has emerged as a new therapeutic approach for carefully selected patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1]. Despite highly positive results, concerns have been raised about the safety of BPA [2]. The most frequent BPA-related complication is lung injury, which is considered a consequence of mechanical vascular injury during wire manipulation or balloon overdilation [2]. Haemodynamic severity is associated with a higher rate of BPA-related lung injury [2, 3], and improving haemodynamics with pulmonary hypertension (PH)-targeted treatments prior to angioplasty may reduce this risk. In a recent study of CTEPH patients with moderate haemodynamic impairment, those who received the guanylate cyclase stimulator riociguat prior to angioplasty had fewer BPA-related serious adverse events than those who did not [4]. However, how to manage PH-targeted therapies in patients with very severe CTEPH to reduce the risk of BPA-related adverse events remains unresolved.

For the most severe patients with pulmonary arterial hypertension (PAH), intravenous prostacyclin combined with oral PH-targeted therapies is the regimen that produces the greatest haemodynamic improvement [5]. Although there is no recommendation for the use of epoprostenol in CTEPH patients [6], retrospective analyses in severe CTEPH patients have shown that epoprostenol achieved marked haemodynamic improvements [7].

With that in mind, it was decided after multidisciplinary discussion to introduce combined therapies including prostacyclin in three CTEPH patients considered eligible for BPA but who presented with very severe pulmonary haemodynamics.

A 71-year-old woman with a history of breast cancer considered resolved (patient 1) was diagnosed with severe CTEPH in World Health Organisation (WHO) functional class (FC) IV. Pulmonary artery lesions were considered amenable to BPA but not to pulmonary endarterectomy. Triple therapy with epoprostenol, riociguat and bosentan was initiated. Epoprostenol was rapidly titrated up to 20 $ng \cdot kg^{-1} \cdot min^{-1}$. Evaluation after 169 days of epoprostenol showed a 56% reduction in pulmonary vascular resistance (PVR). The decision was made to start BPA. To prevent complications, angioplasties were performed using 2-mm balloons during the four first sessions, in a maximum of four vessels per session. Nevertheless, the patient developed lung injury after session 1 (desaturation and radiological signs of condensations requiring high-flow oxygen therapy for 48 h). All other BPA sessions were uneventful. Haemodynamic evolution and treatments are detailed in figure 1. Weaning from epoprostenol was carried out as follows: drop to 18 $ng \cdot kg^{-1} \cdot min^{-1}$ after session 2; drop to 16 $ng \cdot kg^{-1} \cdot min^{-1}$ after session 5; complete stop over a 3-day period after session 6. 10 BPA sessions were performed. 1 year after BPA completion, without any PH-targeted therapy, haemodynamics had normalised and the patient was now in WHO FC I.

A 67-year-old woman with a medical history of breast cancer, hypertension and grade 1 obesity (patient 2) was diagnosed with severe CTEPH in WHO FC IV. Pulmonary artery lesions were deemed inoperable. PH-targeted triple therapy with epoprostenol (up to 22 $ng \cdot kg^{-1} \cdot min^{-1}$), riociguat and bosentan was initiated, resulting in a 72% reduction in PVR at 150 days (figure 1). Angioplasties were started. Despite

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In patients with very severe CTEPH eligible for BPA, it is possible to achieve major haemodynamic improvement with upfront triple PH therapy including epoprostenol and then to perform angioplasties https://bit.ly/3vZZvib

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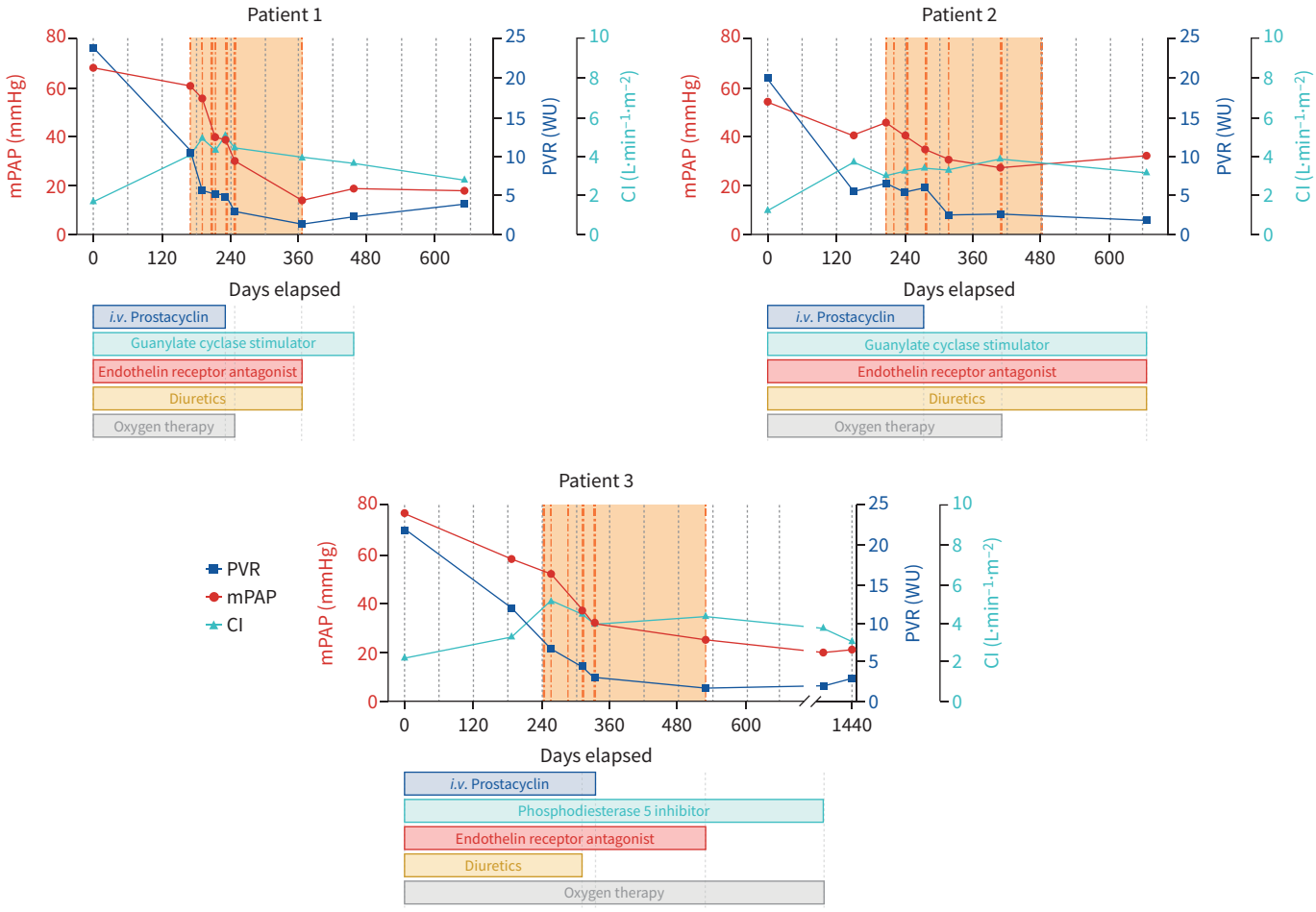

FIGURE 1 Pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP) and cardiac index (CI) as a function of the number of days elapsed since diagnosis of chronic thromboembolic pulmonary hypertension in three patients eligible for balloon pulmonary angioplasty. Orange vertical dotted lines represent angioplasty sessions (one session for a thin line, two sessions for a thick line, with the two sessions performed 2 days apart). *i.v.*: intravenous.

the use of balloons with a maximum diameter of 3 mm and the dilatation of only four segmental arteries during the first five sessions, the patient presented with severe desaturation with radiological condensation requiring high-flow oxygen for 72 h after session 1, and mild haemoptysis during sessions 3, 5 and 6, all of which required oxygen therapy for 24 h. Epoprostenol was reduced to 18 $ng \cdot kg^{-1} \cdot min^{-1}$ after session 3 and stopped over a 3-day period after session 5. At first evaluation after epoprostenol withdrawal, post-capillary PH was found, with pulmonary capillary wedge pressure of 21 mmHg. 11 sessions were performed. Follow-up performed 8 months after BPA completion confirmed post-capillary PH attributed on echocardiography to left ventricular diastolic dysfunction. The patient was now in WHO FC II.

A 58-year-old woman with no significant medical history (patient 3) was diagnosed with severe CTEPH in WHO FC IV. Pulmonary artery lesions were considered distal and accessible to BPA. PH-targeted triple therapy was initiated, combining epoprostenol (up to 16 $ng \cdot kg^{-1} \cdot min^{-1}$), bosentan and tadalafil. Evaluation at 187 days showed a 54% reduction in PVR. BPA was started cautiously, with only four segmental arteries dilated per session and with a balloon diameter <50% of the luminal arterial diameter during the first two sessions. Nine sessions were performed. No complications occurred. Epoprostenol was reduced after session 3 and withdrawn after session 5. Long-term follow-up without PH-targeted therapy revealed near-normal haemodynamics, and the patient was now in WHO FC I.

Our report illustrates that in CTEPH patients with lesions amenable to angioplasty presenting with very severe haemodynamics, BPA is a feasible and effective therapeutic option when initiated after patients have experienced significant haemodynamic improvement with upfront triple PH therapy including epoprostenol.

The haemodynamic effects observed in our patients (decrease of PVR of >10 WU) were of higher magnitude than effects reported in CTEPH patients receiving epoprostenol alone (mean PVR decrease close to 4 WU) [7]. This difference does not seem to be due to differences in baseline haemodynamics or dose of epoprostenol (the latter being lower in our series than in previous series). It is possible that like in other forms of PH [5], the use of a triple therapy (instead of epoprostenol alone) explained at least in part these differences.

We acknowledge that high-dose subcutaneous treprostinil has been shown to be effective in patients with severe CTEPH [8]. Nevertheless, the haemodynamic improvement expected with this therapy (reduction in PVR of <3 WU) would not have allowed our patient's haemodynamic parameters to reach values considered compatible with safe BPA.

The angioplasty strategy in this group, whose haemodynamics were very severe at the time of diagnosis, nevertheless presented a number of specificities. Firstly, there appears to be an increased risk of per-procedural complication during initial angioplasties [1, 2], even when safety precautions are taken, such as using small balloons and limiting the number of arteries dilated per session. Secondly, the number of sessions required to achieve haemodynamic normalisation (9–11 in our series) was greater than the median number of sessions reported in less severe patients (7.7 sessions in the RACE study [4] and 4.7 in the MR-BPA study [9]).

We recognise that the strategy for reducing and discontinuing prostacyclin has been entirely empirical. Dose reduction was initiated once PVR was 5.5–5.8 WU, after only two to three BPA sessions. Prostacyclin was then stopped when PVR was 4.5–6.1 WU, after five to six BPA sessions. The choice of stopping epoprostenol over a short period (3 days) was empirical, but derived from our previous experience of transitioning from epoprostenol to selexipag in patients with PAH [10]. In contrast to what we observed in PAH patients after transition, there was no haemodynamic worsening after weaning from epoprostenol in our CTEPH patients.

In line with what is observed in less severe patients [1, 3], our patients presented a near-normalisation of haemodynamic parameters at the end of BPA, and this situation persisted 8–42 months after the end of BPA.

Although limited to three cases out of 350 patients treated with BPA in our centre since 2013, our observations suggest that in patients with very severe CTEPH eligible for BPA, it is possible with upfront triple PH therapy including epoprostenol to achieve major haemodynamic improvement, thereby drastically improving clinical status, so that angioplasties can be performed. Nevertheless, it seems that precautions must be taken when performing initial angioplasties in these fragile patients.

Nicolas Piliero[1], Muriel Salvat[1], Mathieu Finas[2], Florence Curioz[1], Julie Traclet[3], Kaïs Ahmad[3], Laurent Bertoletti[4,5,6], Estelle Vautrin[1], Hélène Bouvaist[1] and Bruno Degano[7,8]

[1]Service de Cardiologie, CHU Grenoble Alpes, Grenoble, France. [2]Service de Radiologie, CHU Grenoble Alpes, Grenoble, France. [3]Service de Pneumologie, Centre de Référence des Maladies Pulmonaires Rares, Hôpital Louis-Pradel, Université de Lyon, Lyon, France. [4]Service de Médecine Vasculaire et Thérapeutique, CHU de St-Etienne, Saint-Etienne, France. [5]INSERM, UMR1059, Équipe Dysfonction Vasculaire et Hémostase, Université Jean-Monnet, Saint-Etienne, France. [6]INSERM, CIC-1408, CHU Saint-Etienne, Saint-Etienne, France. [7]INSERM U1300, Laboratoire HP2, Université Grenoble Alpes, Grenoble, France. [8]Service de Pneumologie, CHU Grenoble Alpes, Grenoble, France.

Corresponding author: Bruno Degano (bdegano@chu-grenoble.fr)

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