Evaluating the safety and long-term efficacy of triple vasodilator therapy for pulmonary arterial hypertension associated with congenital heart disease

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Background: Pulmonary arterial hypertension (PAH) affects 5-10% of congenital heart disease (CHD) patients, but there is limited information on the safety and efficacy of triple combination therapy for PAH-CHD. The aim of this study was to assess the long-term effects of triple therapy (TT) with prostacyclins on PAH-CHD patients.

Methods: A retrospective, longitudinal, cohort study of patients with PAH-CHD under active follow-up in our center. All patients were receiving baseline dual therapy at maximum doses. Clinical characteristics, including functional class (FC), 6-minute walk test distance (6MWTd), and NT-ProBNP were recorded before initiating TT and during annual follow-ups during 2 years.

Results: 60 patients were included (median age 41, 31 women 61%). 32 had Eisenmenger syndrome, 9 had coincidental shunts, 18 had postoperative PAH, and 1 had a significant L-R shunt. TT was initiated based on the clinical situation, existence of shunt and ease of administration (epoprostenol 20%, treprostinil 41%, selexipag 32%, iloprost 7%). A significant improvement in the 6MWTd was observed one year after the initiation of TT (p<0.05), which was maintained at two-year follow-up, with an average improvement of 44 metres. An improvement of FC was observed in 79% of patients at one year, maintained at 2 years in 76%. A NT-ProBNP levels decreased from the start, and reached significance two years after the initiation of TT, with an average decrease of 199 ng/l (Figure 1). Twenty patients (33.3%) experienced side effects after drug initiation. Most were mild and well-controlled with symptomatic treatment. Only 3 (5%) had to change the administration route (Figure 2). By subgroups, patients without Eisenmenger and with pre-tricuspid defects had a more marked benefit.

Conclusions: TT has been shown to be safe and effective in patients with PAH-CHD, improving FC, 6MWTd, and NT-proBNP levels, particularly in pre-tricuspid defects and non-Eisenmenger PAH-CHD.
Changes after initiation of TT

**Prostacyclin**

- **Iloprost**: 32%
- **Epoprostenol**: 41%
- **Treprostinil**: 7%
- **Selexipag**: 20%

**Type of treatment and side-effects**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Maximum doses achieved</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Selexipag</td>
<td>1200 (1000-1400) mcg</td>
<td>2 mild (11%) 5 moderate (26%)</td>
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<tr>
<td>Treprostinil</td>
<td>37 (30-49) ng/kg/min</td>
<td>7 mild (27%) 1 severe - repeated puncture site infections (4%)</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>30 (27-32) ng/kg/min</td>
<td>2 mild (17%) 2 severe - catheter infection (17%)</td>
</tr>
<tr>
<td>Iloprost</td>
<td>All patients on 5 mcg/6 times/day</td>
<td>1 mild (25%)</td>
</tr>
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