Pulmonary Arterial Hypertension Associated With Connective Tissue Disease and Immunosuppressive Therapy

Kazuhiko Takeuchi, MD, PhD; Hiroshi Watanabe, MD, PhD

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The treatment for PAH including CPAH has undergone a remarkable evolution in the recent decade after the advent of the intravenous prostacyclin analog, epoprostenol. New pulmonary vasodilators for PAH, such as the prostacyclin analog, endothelin receptor antagonists and phosphodiesterase type 5 (PDE5) inhibitors, significantly improve patients’ symptoms and slow the rate of clinical deterioration. A meta-analysis performed on 23 randomized controlled trials (vs. placebo) in PAH, including CPAH (retrieved from the Medline database from 1990 to 2008), showed a 43% reduction in mortality in patients treated with these new pulmonary vasodilators (RR, 0.57; 95% confidence interval, 0.35–0.92; P=0.023).

Despite these positive clinical trial results, PAH remains a chronic disease without a cure.

It is currently accepted that the genesis and progression of PAH are attributable to the immune and/or inflammatory system in CPAH and IPAH patients. Macrophages and lymphocytes have been detected in perivascular and plexiform lesions of the pulmonary artery of CPAH patients and deposits of antinuclear antibodies, rheumatoid factor, gamma globulins and complement have been identified in the pulmonary vascular wall in lung biopsies of these patients.

Sanzhe et al reported that immunosuppressive therapy comprising cyclophosphamide (600mg/m² IV monthly for at least 3 months) and glucocorticosteroids without pulmonary vasodilators (prostacyclin analog, endothelin receptor antagonists or PDE5 inhibitors) could improve the symptoms and prognosis of CPAH patients with SLE or MCTD, but not those of CPAH patients with SSc. A responder in their study was defined as a patient in NYHA functional class I or II with sustained hemodynamic improvement after at least 1 year of immunosuppressive therapy without additional pulmonary vasodilators; 8 of 21 CPAH patients with SLE or MCTD responded to the immunosuppressive therapy and those responders were characterized by a lower NYHA functional class, lower pulmonary vascular resistance and a higher cardiac index at baseline, which indicates that diagnosis and treatment for CPAH in an earlier phase of pathological pulmonary vascular changes may be linked to better outcomes.

Jais et al described the effect of additional pulmonary vasodilators on non-responders to immunosuppressive therapy among CPAH patients with SLE or MCTD, according to their retrospective analysis; 8 non-responders to immunosuppressive therapy were subsequently treated with pulmonary vasodilators 6 months later, and 6 of the 8 non-responders responded to the pulmonary vasodilators.

In this issue of the Journal, Miyamichi-Yamamoto et al report the effectiveness of intensive immunosuppressive therapy (IIT) combined with pulmonary vasodilators (IIT group: mean age, 45±8 years) on pulmonary hemodynamics and prognosis in patients with CPAH. The IIT was a combination therapy with cyclophosphamide (500mg IV, 10 times in a year) and glucocorticosteroids (1 mg/kg PO daily in the first month, followed by gradual tapering afterward by 5–10 mg/day every 2–4 weeks with a maintenance dose of 5–10 mg/day). The authors compared these patients with a historical control group treated with only pulmonary vasodilators (mean age, 52±18 years) regarding pulmonary hemodynamics and prognosis. Although mean pulmonary arterial pressure (mPAP) remained unchanged in the control group, IIT with pulmonary vasodilators significantly decreased mPAP (40±9 to 29±11 mmHg, P<0.01). Intriguingly, in approximately half of the patients in the IIT group, mPAP was almost normalized (<25 mmHg). Furthermore, the IIT group showed a significantly better prognosis compared with the control group (P<0.01). It should be taken into consideration that there were differences in the baseline characteristics of the 2 groups. For example, no PDE5 inhibitors were given to patients in the historical control group and 6 patients were administered PDE5 inhibitors in the IIT group, there were different proportions of underlying CTD and WHO functional class, and the 6-min walking distance was...
84 m longer in the IIT group than in the control group. However, the data from this study suggest some potential CPAH treatments. The CPAH patients with SSc did not respond to the IIT, which is consistent with previous reports that showed that CPAH patients with SLE or MCTD respond well to immunosuppressive therapy but not patients with SSc. CPAH patients with SSc may be resistant to the present immunosuppressive therapy, and, therefore, an immunosuppressive therapy appropriate to each underlying CTD with CPAH should be examined in future studies. Moreover, in most of the CPAH patients of the present study, IIT with pulmonary vasodilators was initiated within a few months after the diagnosis and indicated good outcomes regardless of the immunological activity of the underlying CTD. Sanchez et al also showed that patients who responded to immunosuppressive therapy had less severe NYHA functional class and pulmonary hemodynamics at baseline than those patients who did not respond. Immunosuppressive therapy for CPAH may be less effective in patients with longstanding PAH because their pulmonary arteries have already sustained irreversible pathological damage. Initiation of treatment in an earlier phase of pathological pulmonary vascular changes could be important for achieving good improvement of pulmonary hemodynamics and long-term prognosis.

IIT with pulmonary vasodilators could be a promising therapy for CPAH. However, more reliable data from larger randomized clinical trials are required to establish appropriate therapy for CPAH. CPAH is such a rare disease that cooperation is required in recruiting a sufficient number of patients to reliably estimate the efficacy of therapy for each underlying CTD.

References