

Sodium tanshinone IIA sulfonate for pulmonary arterial hypertension: emerging therapeutic option

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J Thorac Dis 2013;5(2):114-115. doi: 10.3978/j.issn.2072-1439.2013.02.05

Pulmonary arterial hypertension (PAH) is a rare disease characterised by a progressive increase of pulmonary vascular resistance and pulmonary arterial pressure, leading to right ventricle hypertrophy and death (1,2). The last decade has seen major advances in the understanding of the pathobiology of PAH along with discovery of several therapeutic options. Pharmacological agents targeting the endothelin (ET)-1 (ET-1 receptor antagonists, such as bosentan or sitaxentan), the nitric oxide (sildenafil, type 5 phosphodiesterase inhibitor), or the prostacyclin (epoprostenol, iloprost) pathways have shown benefits for patients with PAH (3). However, despite symptomatic improvement these treatments failed to improve the long-term survival and their use is hampered by either side-effects or inconvenient drug administration routes (4). Indeed, none of the currently available therapies is curative, so the search for novel therapeutic strategies continues.

In the current issue of *Journal of Thoracic Disease*, Wang *et al.* report the efficacy of sodium tanshinone IIA sulfonate (STS), a water-soluble derivative of tanshinone IIA isolated as the major active component from Chinese herbal medicine, as a therapeutic option for treating PAH in the clinical setting. Their small pilot study recruiting 5 patients with PAH of varying etiologies and ineffective sildenafil treatment for 3 months showed a beneficial effect of STS infusion at the endpoint of observation for 8 weeks. All five patients experienced reduction of pulmonary artery pressure in the range of 14-45 (mean, 28.6±12.5) mmHg ($P=0.0066$) and right ventricular size in the range of 0-10 (mean, 4.2±1.6) ($P=0.0446$). All patients also exhibited improved exercise capacity with an increase of 6 minutes walking distance from 63 to 268 (mean, 138.4±40.7) meters ($P=0.0192$), significantly reduced Borg dyspnea score from maximum 9 down to 1 or 0

($P=0.1012$), and reduced WHO functional class from III or IV down to II ($P=0.0005$). All the patients tolerated the treatment well throughout the study period.

The study by Wang *et al.* despite its small sample size, non-randomized design and short follow-up deserves credit as the first clinical study evaluating the safety and efficacy of STS as a therapeutic option for PAH. It also provides insight into the potential role of STS as a combination therapy with sildenafil. However, the study also raises questions about the true therapeutic potential of STS owing to flaws in the study design. While the study from Wang *et al.* constitutes a new contribution to the recognition of STS as a promising therapeutic agent, it must be emphasized that only a long-term, adequately powered, prospective, randomized, double-blind, placebo-controlled study would be the only criterion to confirm the safety and the efficiency of any promising new therapeutic option for PAH including STS.

Presently there is paucity of data on effects of long-term STS treatment for PAH. The available evidence from the study by Wang *et al.* contributes to a building sense of excitement that STS may be an effective therapeutic option for PAH. However, the safety and dosage of STS for PAH has still not been established. Moreover, STS therapy in PAH will require continuous exposure to possibly larger doses, suggesting that adverse effects may be an issue.

Because so many novel therapies in the past have not lived up to their initial promise, we should protect our patients (and ourselves) and refrain from empirically administering STS for these emerging indications at present. Several, rigorous, blinded, placebo-controlled, multicenter randomized clinical trials are required to confirm efficacy and establish the safety of long-term STS for these new therapeutic indications (5).

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Submitted Jan 21, 2013. Accepted for publication Feb 20, 2013.

Available at www.jthoracdis.com

ISSN: 2072-1439

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Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Raja SG. Sodium tanshinone IIA sulfonate for pulmonary arterial hypertension: emerging therapeutic option. *J Thorac Dis* 2013;5(2):114-115. doi: 10.3978/j.issn.2072-1439.2013.02.05