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Sitaxentan in Pulmonary Arterial Hypertension

A Viewpoint by Marius M. Hoeper

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The dual endothelin $(ET)_A$ and ET_B receptor antagonist bosentan was the first oral drug approved by the US FDA and its European counterpart, the European Medicines Agency, for the treatment of pulmonary arterial hypertension (PAH). Sitaxentan, a selective ET_A receptor antagonist, is also now approved in Europe for use in this patient population and an application is currently under review with the FDA.

It has been claimed that the introduction of sitaxentan is a major advancement for the management of PAH patients; however, scientific evidence to support this claim is limited. A major advancement would require that the drug show higher efficacy than existing treatment options, a better safety profile, or both. To date, there is no conclusive data to show that any of this is true for sitaxentan relative to bosentan, the only other agent in this class of drugs that is currently approved for use in PAH patients. From a theoretical viewpoint, there are strong arguments in favour of a selective ET_A receptor blockade, but equally strong points may be made for blocking both types of endothelin receptors. Clinical efficacy, as measured by improvement in 6 minute walk distance (a surrogate clinical endpoint), appeared to be similar with both drugs in a placebo-controlled trial of 18 weeks' duration, although this study was not designed to evaluate the comparative efficacy of these two agents. Robust data on the long-term effects on 'hard' clinical endpoints, such as time to clinical worsening or mortality, are not yet available for sitaxentan, rendering any comparison speculative.

Concerning safety, by far the most important aspect is hepatotoxicity, which appears to be a class effect of endothelin receptor antagonists. The available data suggest that liver aminotransferase elevations may be less common with sitaxentan than with bosentan treatment. However, what matters more is the freedom from serious liver damage with long-term administration of these drugs. A large, as yet unpublished, European database of nearly 5000 patients treated with bosentan for up to 30 months identified not a single case of permanent liver damage. Although there is nothing to suggest that sitaxentan treatment is associated with serious liver injury when used at the recommended dosage of 100mg once daily, the long-term safety of the drug, particularly in the clinical practice setting (i.e. outside the protected setting of clinical trials), remains to be established.

Taken together, for the time being there are no data to support the superiority of one endothelin receptor antagonist over the other. Currently, only a single group of patients has been identified as clear candidates for sitaxentan treatment, that is, patients who fail bosentan treatment due to hepatotoxicity. There is convincing evidence that many of these patients may be safely exposed to sitaxentan. For all other PAH patients, it remains to be determined which drug is better in the long run. ▲