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Sitaxentan in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) causes significant functional limitations and an increased risk of death. Endothelin (ET)-1 is increased both locally and systemically in patients with PAH. The ET_A receptor mediates many of the adverse effects of ET-1, whereas the ET_B receptor is thought to trigger the release of vasodilator substances.

Bosentan blocks both of the ET receptors and was the first ET receptor antagonist to be approved for PAH. Sitaxentan preferentially blocks the ET_A receptor, which is theoretically more desirable. Randomised clinical trials (RCTs) have shown the benefits of sitaxentan compared with placebo in terms of haemodynamics and distance walked in 6 minutes, with low rates of adverse effects, the most pertinent being elevation in liver transaminase levels. Other studies have suggested that the drug is effective in various PAH subtypes and after cessation of treatment with bosentan.

Advantages of sitaxentan include efficacy that is comparable with that of bosentan, with possibly a better adverse-effect profile than bosentan. Once-daily administration is another plus with sitaxentan. A drawback of sitaxentan is its action on the metabolism of warfarin, which is commonly used to treat patients with PAH. Considering the inherent complexity of PAH management, however, the requirement for warfarin dose adjustment should not be a significant deterrent to its use by health professionals experienced in caring for this group of patients. To date, neither sitaxentan nor any other oral PAH therapy has been shown to prolong the time to reaching 'hard' clinical endpoints.

Sitaxentan is an important new therapy and future RCTs and clinical experience will elucidate the optimal setting for its use. The addition of this drug of a distinct class to the armamentarium currently used to treat patients with PAH is an important step towards the ultimate goal of medical cure for this currently treatable but chronic disease. ▲