Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERAs) are a class of medications used for the management of pulmonary hypertension (PH). These drugs are competitive antagonists of endothelin receptors, which inhibits the action of the hormone endothelin-1, a potent pulmonary vasoconstrictor. By doing so, pulmonary vascular resistance (PVR) is decreased, which lessens remodeling of pulmonary arterioles, improves exercise capacity, and decreases clinical deterioration. One example drug is Bosentan. These medications can cause hepatotoxicity, and thus LFTs should be monitored.

PLAY PICMONIC

Indication

Pulmonary Hypertension

Lungs Hiker-BP

Pulmonary hypertension (PH) is classified into five groups depending on the etiology. Group 1 is classified as having pulmonary arterial hypertension (PAH), whereas the remaining four groups are considered to have PH. Patients suspected to have pulmonary arterial hypertension (PAH) should be referred to a specialized center for diagnosis and management, because the administration of PAH-specific therapy can be harmful. PAH-specific therapy is directed at the PAH itself rather than the underlying etiology of the PAH. PAH-specific agents include endothelin receptor antagonists (discussed in this Picmonic), as well as prostacyclin pathway agonists, nitric oxide (NO)-cGMP enhancers, and less commonly, select calcium channel blockers. The diagnosis of PAH should be established prior to initiation of treatment, since PAH-specific therapy has not been found to be beneficial in most other forms of PH and may even be harmful.

Mechanism of Action

Competitive Antagonism of Endothelin Receptors

Competitive Ant-togas on Endothelin Receptor

Endothelin receptor antagonists specifically target endothelin receptors A (ET-A) and B (ET-B) located on endothelium and vascular smooth muscle. Endothelin-1 is an endogenous hormone that binds to these receptors, inducing potent pulmonary vasoconstriction and smooth muscle proliferation, which results in remodeling of pulmonary arterioles. Endothelin receptor antagonists (ERAs) competitively bind to these endothelin receptors, and once bound, block the action of endothelin-1.

Decreased Pulmonary Vascular Resistance

Down-arrow Lungs Vessel with Resistance-bandana

Blocking the action of endothelin-1, a potent pulmonary vasoconstrictor, results in decreased pulmonary vascular resistance (PVR). Decreased PVR leads to less remodeling of pulmonary arterioles and slows disease progression.

Drugs

Bosentan

Booze-n-tan

ERAs target endothelin receptors A and B and include non-selective, dual action ERAs (bosentan and macitentan) and a selective antagonist of endothelin receptor A (ambrisentan). Bosentan (Tracleer) is the first approved blocker of both ET-A and ET-B receptors for the treatment of PAH and has been shown to improve exercise capacity and decrease clinical deterioration. Bosentan works to lower pulmonary arterial pressure and PVR, improving cardiac hemodynamics without significant systemic effects. Bosentan has also been used in combination with prostacyclins or PDE-5 inhibitors to improve hemodynamics, RV function, exercise tolerance, quality of life, and mortality.

Side Effects

Hepatotoxicity

Liver with Toxic-green-glow

Bosentan has a [US Boxed Warning] regarding hepatotoxicity due to its association with transaminase elevations (ALT or AST ≥3 times ULN) and a small number of cases with associated elevations in bilirubin. The combination of hepatocellular injury (transaminase elevations >3 times ULN) and bilirubin increased ≥2 times ULN is an indicator of potential serious hepatotoxicity. In postmarketing surveillance, there have been rare cases of unexplained hepatic cirrhosis after prolonged therapy (>12 months). There have also been cases of hepatic failure.

Monitor LFTs

Monitor Liver-with-test-tubes

LFTs should be evaluated prior to initiating treatment. Measure transaminases at baseline and monitor monthly thereafter. A dose adjustment should be made if elevations in liver enzymes occur without symptoms of hepatic injury or elevated bilirubin. Indications to stop treatment include elevated transaminases either in combination with symptoms of hepatic injury (unusual fatigue, jaundice, nausea, vomiting, abdominal pain, and/or fever) or with elevated bilirubin (≥2 times ULN). Use should be avoided in patients with baseline transaminases >3 times ULN as monitoring for hepatotoxicity may be more difficult.