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Endothelin Receptor Antagonists

Updated: September 30, 2017.

OVERVIEW

The endothelin receptor antagonists inhibit the binding of endothelin, a vasoconstrictive peptide, to its receptors on smooth muscle cells which results in vasodilation. Endothelin receptors are relatively enriched in pulmonary vasculature and their inibition results in a decrease in pulmonary vascular pressure. In patients with pulmonary arterial hypertension, (PAH) the endothelin receptor antagonists have been shown to improve exercise tolerance and slow progression of disease. Three endothelin receptor antagonists are currently approved and in use in the United States: bosentan (2001: Tracleer), ambrisentan (2007: Letairis) and macitentan (2013: Opsumit). Sitaxsentan, a forth endothelin receptor blocker, was approved in Europe, but not in the United States, and has subsequently been withdrawn because of cases of severe liver injury linked to its use. While all endothelin receptor antagonists have been associated with occasional transient serum enzyme elevations during therapy, only bosentan and sitaxentan have been clearly linked to instances of clinically apparent, acute liver injury.

Endothelin-1 (ET-1) is a 21 amino acid peptide that acts in a paracrine and autocrine fashion as a potent vasoconstrictor. ET-1 appears to play a key role in regulation of vascular tone and can also induce hypertrophy of myocytes, proliferation of fibroblasts and fibrosis. ET-1 acts by engagement of cell surface receptors that result in activation of intracellular pathways leading to vasoconstriction and proliferation of smooth muscle cells. Two forms of endothelin receptors have been identified – type A (ETA) and type B (ETB). The ETA receptor is found predominantly on smooth muscle cells, whereas the ETB receptor is present on both smooth muscle and vascular endothelial cells. The intracellular signaling pathways and overall effects are somewhat different for the two receptors, and there may be an advantage to specific inhibition of the type A receptor as opposed to bimodal inhibition of both.

The use of endothelin receptor antagonists in pulmonary arterial hypertension (PAH) is based upon the proposed pathogenesis of this disease, which is marked by enhanced synthesis of ET-1 and progressive proliferation and hypertrophy of smooth muscle cells in the pulmonary vasculature. In several randomized controlled trials, endothelin receptor antagonists were shown to decrease pulmonary vascular pressure and improve exercise tolerance and symptoms in patients with PAH. Their efficacy has been best demonstrated in patients with idiopathic PAH (World Health Organization [WHO] group 1 PAH) and less well in the secondary forms due to left heart failure [WHO group 2], lung disease or hypoxemia [WHO group 3], chronic pulmonary thromboembolic disease [WHO group 4] or unclear, multifactorial conditions [WHO group 5].

The endothelin receptor antagonists have been associated with a low, but appreciable rate of serum enzyme elevations during therapy that are generally transient and mild, but can cause mild symptoms and require dose modification or discontinuation. Several endothelin receptor antagonists have been associated with rare, but potentially severe instances of clinically apparent, acute liver injury. In addition, the endothelin receptor

antagonists are teratogenic in animals. For these reasons, these agents are restricted in use and available only in programs that require full disclosure of potential side effects and careful monitoring.

The three endothelin receptor antagonists are discussed separately with references appropriate for each agent. Selected general references are provided below.

Drug Class: Pulmonary Arterial Hypertension Agents

Drugs in the Subclass Endothelin Receptor Antagonists: Ambrisentan, Bosentan, Macitentan

ANNOTATED BIBLIOGRAPHY

References updated: 30 September 2017

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Textbook of hepatotoxicity published in 1999, before the availability of endothelin receptor antagonists).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Textbook on drug induced liver injury; clinical features of liver injury due to the endothelin receptor antagonists are not specifically discussed).

Fattinger K, Funk C, Pantze M, Weber C, Reichen J, Stieger B, Meier PJ. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. Clin Pharmacol Ther 2001; 69: 223-31. PubMed PMID: 11309550.

(Analysis of safety databases from 3 premarketing controlled trials of bosentan showed a dose related rate of ALT elevations [>3 times ULN] from 0% [0-20 mg/d] to 2-4% [100-500 mg/d] to 8-11% [1000-2000 mg/d] and concurrent rise in bile acid levels with minor increase in Alk P, but no change in bilirubin levels or clinically apparent liver injury; similar rate related rise in bile acids [but not ALT] in rats given bosentan).

Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001; 358: 1119-23. PubMed PMID: 11597664.

(Controlled trial of bosentan [250 mg daily] vs placebo for at least 12 weeks in 32 patients with PAH; 2 of 21 patients receiving bosentan developed ALT elevations which resolved without need for discontinuation).

Barst RJ, Rich S, Widlitz A, Horn EM, McLaughlin V, McFarlin J. Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. Chest 2002; 121: 1860-8. PubMed PMID: 12065350.

(Open label study of 12 weeks of sitaxsentan in doses of 100 to 500 mg daily in 20 patients with PAH; during extension phase, ALT elevations occurred in 35% of patients and 2 developed jaundice; both cases were 53 year old women with PAH who developed enzyme elevations between 12 and 18 weeks of therapy [peak bilirubin 8.6 and 45.7 mg/dL; ALT 514 and 1041 U/L, Alk P 620 and 233 U/L], the first recovered within 3 months and the second died of acute liver failure).

Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, McLaughlin V, et al; STRIDE-1 Study Group. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169: 441-7. PubMed PMID: 14630619.

(Controlled trial of 2 doses of sitaxsentan vs placebo for 12 weeks in 178 patients with PAH found ALT elevations [above 3 times ULN] in 3% of placebo, 0% of sitaxsentan [100 mg daily] and 10% [300 mg daily], the latter rates increasing with extended therapy to 5% and 21%; no mention of clinically apparent liver injury or jaundice).

Galié N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46: 529-35. PubMed PMID: 16053970.

(Among 64 patients with PAH treated with 1 of 4 doses of ambrisentan for 12 weeks, 3.1% developed ALT elevations above 3 times ULN and 2 patients discontinued therapy because of ALT values, but none had symptoms or jaundice).

Segal ES, Valette C, Oster L, Bouley L, Edfjall C, Herrmann P, Raineri M, et al. Risk management strategies in the postmarketing period : safety experience with the US and European bosentan surveillance programmes. Drug Saf 2005; 28: 971-80. PubMed PMID: 16231952.

(Description of a US and a European postmarketing system for monitoring safety of bosentan, which allows for estimation of rate of hepatic adverse events and which for serum enzyme elevations was 7.7%).

Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N; STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006; 47: 2049-56. PubMed PMID: 16697324.

(Controlled trial of 18 weeks of sitaxsentan [50 or 100 mg daily] vs open label bosentan [125 mg twice daily] vs placebo in 245 patients with PAH; ALT or AST elevations occurred in 6% on placebo, 3-5% on sitaxsentan and 11% on bosentan, reversing in all with time, stopping or dose adjustment).

Benza RL, Mehta S, Keogh A, Lawrence EC, Oudiz RJ, Barst RJ. Sitaxsentan treatment for patients with pulmonary arterial hypertension discontinuing bosentan. J Heart Lung Transplant 2007; 26: 63-9. PubMed PMID: 17234519.

(Controlled trial of two doses of sitaxsentan in 48 patients with PAH who had discontinued bosentan because of safety problems or lack of efficacy, found that side effects were few, and only 1 of 12 patients who had ALT elevations [above 3 times ULN] during bosentan therapy had similar elevations on sitaxsentan).

Humbert M, Segal ES, Kiely DG, Carlsen J, Schwierin B, Hoeper MM. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 2007; 30: 338-44. PubMed PMID: 17504794.

(Description and analysis of the internet based system of monitoring safety in patients receiving bosentan in Europe; in the first 30 months, 4994 patients were enrolled and annual rate of ALT or AST elevation above 3 times ULN was 10.1% [1.3% were >8 times ULN]; 3.2% of patients discontinued therapy because of enzyme elevations, and 11 of 45 patients redeveloped enzyme elevations with reintroduction of bosentan; no mention of clinically apparent liver injury).

Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. Eur Respir J 2008; 31: 407-15. PubMed PMID: 18238950.

(Review of the mechanism of action and clinical efficacy of endothelin receptor antagonists).

Galié N, Rubin Lj, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008; 371: 2093-100. PubMed PMID: 18572079.

(Controlled trial of bosentan [n=93] vs placebo [n=92] for 6 months; serum ALT rose above 3 times ULN in 13% of bosentan vs 2% of placebo treated patients, mostly in first 20 weeks and resolving spontaneously in many without dose adjustment and without clinically apparent liver injury).

Hrometz SL, Shields KM. Role of ambrisentan in the management of pulmonary hypertension. Ann Pharmacother 2008; 42: 1653-9. PubMed PMID: 18957622.

(Review of the mechanism of action, pharmacokinetics, metabolism, safety and efficacy of ambrisentan).

Galié N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, et al.; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008; 117: 3010-9. PubMed PMID: 18506008.

(Combined analysis of two controlled trials of different doses of ambrisentan vs placebo for 12 weeks in a total of 261 patients found that no patient developed ALT elevation above 3 times ULN).

Hoeper MM, Olsson KM, Schneider A, Golpon H. Severe hepatitis associated with sitaxentan and response to glucocorticoid therapy. Eur Respir J 2009; 33: 1518-9. PubMed PMID: 19483056.

(25 year old woman developed ALT elevations 4 months after starting sitaxsentan [bilirubin 1.8 mg/dL, ALT 1000 U/L, Alk P not given], which responded rapidly to prednisolone therapy).

Lavelle A, Sugrue R, Lawler G, Mulligan N, Kelleher B, Murphy DM, Gaine SP. Sitaxentan-induced hepatic failure in two patients with pulmonary arterial hypertension. Eur Respir J 2009; 34: 770-1. PubMed PMID: 19720812.

(2 cases; 47 year old man developed jaundice 4 months after starting sitaxsentan [bilirubin 21.2 mg/dL, ALT 1550 U/L, INR 1.6], ultimately resolving; 70 year old woman developed jaundice 5 months after starting sitaxsentan [bilirubin 4.0 rising to 25.1 mg/dL, ALT 1198 U/L, INR 1.6], dying of respiratory failure a few months later).

Hoeper MM. Liver toxicity: the Achilles' heel of endothelin receptor antagonist therapy? Eur Respir J 2009; 34: 529-30. PubMed PMID: 19720805.

(Editorial in response to Lavelle [2009] recounting the history of development of endothelin receptor antagonists and the problem of hepatotoxicity, stressing the need for "pharmacovigilance").

McGoon MD, Frost AE, Oudiz RJ, Badesch DB, Galie N, Olschewski H, McLaughlin VV, Gerber MJ, Dufton C, Despain DJ, Rubin LJ. Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. Chest 2009; 135: 122-9. PubMed PMID: 18812445.

(36 patients with PAH who had ALT elevations during bosentan [n=31] or sitaxsentan [n=2] therapy were treated with ambrisentan for average of 2 years and only one had transient ALT elevation [3.2 times ULN] that resolved on stopping, and did not recur upon restarting and long term treatment).

Mathier MA, Ishizawar D. Bosentan. Expert Opin Pharmacother 2010; 11: 1023-34. PubMed PMID: 20307226.

(Review of the mechanism of action, pharmacokinetics, metabolism, safety and efficacy of bosentan; on conventional doses of bosentan, ALT elevations arise in 7.6% of patients and lead to discontinuation in 3.2%).

Lee WT, Kirkham N, Johnson MK, Lordan JL, Fisher AJ, Peacock AJ. Sitaxentan-related acute liver failure in a patient with pulmonary arterial hypertension. Eur Respir J 2011; 37: 472-4. PubMed PMID: 21282815.

(19 year old woman developed jaundice 3 months after starting sitaxsentan [bilirubin 10.1 mg/dL, ALT 1250 U/L, Alk P 188 U/L, protime 16 sec], progressing to hepatic failure and death 13 days after presentation).

Galié N, Hoeper MM, Simon J, Gibbs R, Simonneau G; Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology(ESC) and the European Respiratory Society (ERS). Liver toxicity of sitaxentan in pulmonary arterial hypertension. Eur Heart J 2011; 32: 386-7. PubMed PMID: 21416695.

(Review of reports of hepatotoxicity of endothelin receptor antagonists identified 9 cases of severe liver injury from sitaxsentan, including 4 deaths and one liver transplant, compared to no instances of acute liver failure due to ambrisentan [10,000 patients exposed] or bosentan [80,000 patients exposed]).

Vizza CD, Fedele F, Pezzuto B, Rubin LJ. Safety and efficacy evaluation of ambrisentan in pulmonary hypertension. Expert Opin Drug Saf 2012; 11: 1003-11. PubMed PMID: 22861496.

(Review of the mechanism of action, pharmacokinetics, safety and efficacy of ambrisentan; liver test abnormalities are less common with ambrisentan than bosentan or sitaxsentan therapy).

Macías Saint-Gerons D, de la Fuente Honrubia C, Montero Corominas D, Catalá-López F. [Hepatotoxicity in patients treated with endothelin receptor antagonists: Systematic review and meta-analysis of randomized clinical trials.]. Med Clin (Barc) 2014; 142: 333-42. Spanish. PubMed PMID: 23540381.

(Systematic review of the literature, including 21 trials in 3644 patients, found relative risk of ALT or AST elevations above 3 times ULN to be 2.98 for endothelin receptor antagonists compared to placebo controls).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, one was attributed to bosentan, but none to macitentan, ambisentan or other agents used primarily to treat pulmonary artery hypertension).

Wei A, Gu Z, Li J, Liu X, Wu X, Han Y, Pu J. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. J Am Heart Assoc 2016; 5. pii: e003896. PubMed PMID: 27912207.

(Systematic review of 24 randomized trials of endothelin receptor antagonists indicated higher rates of "abnormal liver function" in patients receiving bosentan and macitentan, but not ambisentan).