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BOSENTAN: A FUTURE DRUG FOR PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Bosentan is a dual endothelin receptor antagonist. It is used in the treatment of pulmonary artery hypertension by blocking the action of endothelin molecules that would otherwise promote the narrowing of the blood vessels and lead to high blood pressure. Bosentan is highly protein-bound, with approximately 98% bound to albumin. Pulmonary arterial hypertension (PAH) is a chronic progressive disease of the pulmonary vasculature, characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. PAH is considered a life-threatening condition unless treated. PAH is caused by numerous disorders. The orally active and non-peptide, dual endothelin receptor antagonist bosentan improves exercise endurance, hemodynamics, and functional class over the short term. Bosentan is an attractive target for the generic industries.

INTRODUCTION

This article provides an overview of understanding pulmonary hypertension (PH) and the role of bosentan in its treatment. The perception that others lack awareness and knowledge about their disease is distressing. In recent years, epidemiological characteristics of paediatric PH in the Netherlands and the United Kingdom showed that paediatric IPAH/HPAH accounted for 46–70 and 35–60% of PAH in children, respectively. Bosentan was approved by the US Food and Drug Administration to treat pulmonary hypertension; it has been reported to improve the function of the right ventricle as well as exercise tolerance of patients. Bosentan is a non-peptidic ET receptor antagonist. Being a low-MW synthetic compound, bosentan could be administered orally. As a result, it has been tested for efficacy not only to inhibit ET-1- induced responses but also in experimental animal models of, for example, hypertension, congestive heart failure, cerebral vasospasm and renal failure. Bosentan is an endothelin-receptor antagonist that reportedly induces both cytochrome P450 (CYP) 3A4 and CYP2C9 enzymes. Bosentan, a non-selective, oral ET-1 receptor antagonist, decreases pulmonary arterial pressure and vascular resistance and improves exercise capacity or quality of life in patients with symptomatic pulmonary arterial hypertension. Bosentan improves ET-1 induced imbalance of oxidative stress and nitric oxide (NO) bioavailability leading to inflammation in pulmonary arteries, which leads to the decrease in pulmonary vascular resistance and amelioration of pulmonary arterial re-modelling[1-6].

HISTORY

In 1994, Martine Clozel and group at Hoffman-La-Roche (Basel, Switzerland) reported the discovery of Bosentan. Bosentan was ready to enter Phase II clinical trials by 1994. However, it

entered Phase III clinical development in 2012, for hypertension and congestive heart failure. The annual World Pulmonary Hypertension Day was first held on May 5, 2012 in Madrid, Spain to raise global awareness and this was adopted by PHA Europe. The World Pulmonary Hypertension Day has gained increasing momentum, with 86 global partner organizations involved in an international awareness campaign in 2018. Through its involvement of national political and health authorities, academia, HCPs, and celebrities, World Pulmonary Hypertension Day has generated media interest and awareness across the world. PH community re-emphasized the need for professional education, including periodic international symposia (e.g. the World Symposia on Pulmonary Hypertension (WSPH) and the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for PH, culminating in publications of state-of-the-art knowledge summaries, management guidelines and, algorithms), web-based educational programs, on-site preceptor ships and PH-focused publications[7-10]. A multidisciplinary steering committee of PAH specialists, including respiratory physicians, internists, rheumatologists, PAH specialist nurses ,and patient group representatives, led the development of the survey content and analysis of results to ensure medical and practical relevance.

DEFINITION OF PH: Pulmonary hypertension (PH) is a severe disease diagnosed when the arteries responsible for transporting blood from the heart to the lungs become constricted. Under normal circumstances, blood is supposed to gather oxygen from the lungs and distribute it to the organs, muscles and body tissue. However, due to the disease, normal blood flow is disrupted and the heart becomes enlarged and weakened, which can lead to right heart failure.

There are three types of pulmonary hypertension,

1. Pulmonary arterial hypertension (PAH),
2. Associated Pulmonary Hypertension and
3. Idiopathic Pulmonary Hypertension.

Pulmonary Hypertension has clinically been defined as a resting mean pulmonary arterial pressure (mPAP) <25 mm Hg, with exercise <30 mm Hg. The subgroup of PH known as pulmonary arterial hypertension (PAH) adds the criterion that the pulmonary arterial wedge pressure must be ≤15 mm Hg.

TYPES OF PULMONARY HYPERTENSION

The World Health Organization (WHO) created five groups to classify various types of pulmonary hypertension, based on the cause and symptoms of the disease.

Group 1 - Also called pulmonary arterial hypertension (PAH), is caused by a narrowing of the arteries. There are multiple sub-types: idiopathic (no known cause); inherited; due to drugs or toxins; and related to other conditions (such as HIV or congenital heart disease).

Group 2 - It includes PH caused by left heart disease. This is the most common type.

Group 3 - It is pulmonary hypertension due to lung diseases such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and sleep apnea.

Group 4 –It is the PH caused by chronic blood clots in the lungs, also known as chronic thromboembolic pulmonary hypertension (CTEPH).

Group 5 – It is the PH with an unclear cause occurring alongside other diseases. This can include blood disorders, metabolic disorders, sarcoidosis, or tumors[11-12].

DEFINITION OF PULMONARY ARTERIAL HYPERTENSION: Pulmonary arterial hypertension is defined as a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise, with mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mm Hg[13]. Pulmonary arterial hypertension (PAH) is a progressive disease caused by narrowing and tightening (constriction) of the pulmonary arteries, which connect the right side of the heart to the lungs. As PAH develops, blood flow through the pulmonary arteries is restricted and the right side of the heart becomes enlarged due to the increased strain of pumping blood through the lungs. It is this strain on the heart and the decrease in blood to the left heart and systemic circulation through the lungs that leads to the common symptoms of PAH, such as breathlessness, fatigue, weakness, angina, syncope, and abdominal distension.

CAUSES OF PULMONARY ARTERIAL HYPERTENSION

One of the more common forms of PAH is neither idiopathic PAH (IPAH), which is a sporadic disease in which there is neither a family history of PAH nor an identified risk factor. Heritable PAH (HPAH) accounts for at least 6% of cases of PAH 5 and mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in the majority of cases. PAH can also be caused by the use of certain anorexigenic agents, such as fenfluramine[7]. However, the incidence of drug-induced PAH related to fenfluramine is decreasing as this agent is no longer available. PAH can also be associated with a number of other conditions (associated PAH, APAH), which together account for most other cases. These conditions include connective tissue disease; HIV infection; portal hypertension; congenital heart disease; schistosomiasis and sickle cell disease.

IMPACT OF PULMONARY ARTERIAL HYPERTENSION ON PATIENTS

Changes to the pulmonary vasculature leading to the typical symptoms of PAH, which include: breathlessness (dyspnea), particularly during physical activity; fatigue; dizziness; syncope, also on physical activity; peripheral edema and chest pain, again particularly during physical activity[14-18]. These symptoms can severely impact a patient's ability to carry out normal daily activities. As the disease progresses, some patients may experience constant dyspnea and fatigue so that even simple tasks, such as getting dressed and walking short distances, become difficult. Many caregivers (84.2%) reported a reduction in intimacy and decreased sexual relations since their spouse became ill that declined further as PAH progressed. The physical impact of PAH is the decline inability to work, exercise and travel, loss of intimacy and lack of interest in sex, which grew worse as FC declined.

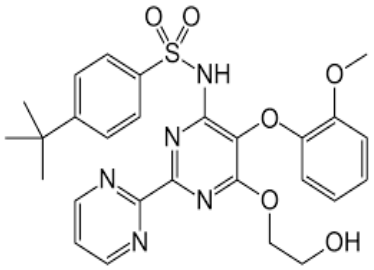
BOSENTAN IN THE PULMONARY ARTERIAL HYPERTENSION TREATMENT

In the US, bosentan has been approved since November 2001 for the treatment of PAH in patients in November 2001 for the treatment of PAH in patients exercise ability and decrease worsening. The drug was approved in Europe in May 2002 for the treatment of PAH to improve the grade III WHO functional class. PAH is a progressively deteriorating syndrome characterised by an increase in pulmonary vascular resistance resulting from a progressive thickening of arterial vessel walls. Orally active preparation of treprostinil was approved by the Food and Drug Administration (FDA) in December 2013 and selexipag, an oral prostacyclin receptor agonist, received FDA approval in 2015. In 2014, CHEST published the most recent guideline and expert panel report regarding pharmacotherapy for PAH based on the evidence available before November 2013.

DRUG PROFILE OF BOSENTAN

IUPAC Name: Bosentan is a 4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl] benzene-1-sulfonamide.

Structure –



Molecular Formulae: $C_{27}H_{29}N_5O_6S$

Molecular weight: 551.6

Mechanism of Action: Pulmonary arterial hypertension (PAH) is mainly developed according to three factors: pulmonary vasoconstriction, vascular remodelling caused by vascular smooth muscle proliferation, and inflammation. Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. It displays a slightly higher affinity towards ET_A receptors than ET_B receptors. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Pulmonary arterial hypertension (PAH) is mainly developed according to three factors: pulmonary vasoconstriction, vascular re-modelling caused by

vascular smooth muscle proliferation, and inflammation.

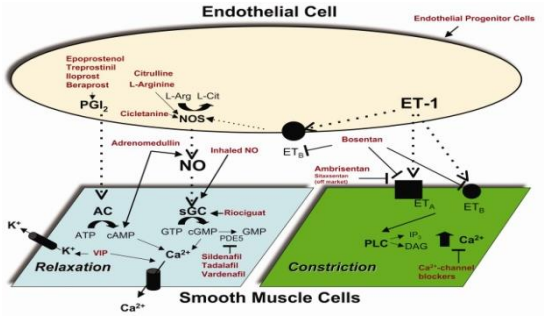


Figure1: Representation of MOA of Bosentan

MEDICAL USES: Bosentan is indicated mainly for the treatment of pulmonary hypertension. In 2007, Bosentan was also approved in the European Union for reducing the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. In the United States, Bosentan is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II-IV symptoms, to improve exercise capacity and decrease the rate of clinical worsening.

PHARMACOKINETICS

Absorption - The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes. The volume of distribution is about 18 L.

Metabolism - Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A and possibly also of CYP2C19. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50-65% of those seen after single-dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3-5 days.

Elimination - Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine. Total clearance after a single intravenous dose is about 4 L/h in patients with PAH.

ADVERSE EFFECTS: Very common adverse effects (occurring in more than 10% of people) may include: Headache, Nausea, Vomiting, Fever, Unusual tiredness, Stomach area (abdominal) pain, Elevated Transaminases, and Edema

I. Common adverse effects (between 1% and 10% of people) may include

Reduced haemoglobin, Yellowing of the skin or the whites of your eyes (Jaundice), Hypersensitivity reactions, Skin Inflammation, Itchiness, Rashes, Red skin, Flushing, Fainting, Heart Palpitations, Low Blood Pressure, Nasal Congestion, Gastro-Esophageal Reflux disease, and Diarrhoea.

II. Bosentan cause serious adverse effects which are as follows

- *Serious birth defects:* When bosentan is used in pregnancy then cause serious birth defects.
- *Fluid retention and swelling of ankles and legs:* Bosentan (Tracleer) can cause in the body to hold too much water, and may get swelling of ankles and legs.
- *Lower Sperm Count*
- *Low red blood cell levels (anaemia).*

DRUG INTERACTIONS: Bosentan induces members of the cytochrome P450 family. Concomitant administration of bosentan and inhibitors of CYP3A4 can increase the peak plasma concentration of bosentan by more than 2-fold.

WHY BOSENTAN IS SELECTED AS FIRST LINE THERAPY OF PAH?

- It efficiently improves exercise tolerance and the patient's quality of life.
- There is an improved survival rate in PAH patients on long term treatment.
- Also the progression of PAH is stopped effectively by the use of Bosentan.
- It improves functional class (QoL) on long term use.

BOSENTAN IN COMBINATION THERAPY

As pulmonary arterial hypertension (PAH) is a disease with varying patho-etiology attempting to arrest its natural progression with a single type of pharmacological molecule might, sometimes, simply not be enough. The bosentan has resulted in significant improvements in exercise capacity, cardiopulmonary hemodynamics and survival.

DRUG	INTERACTION
Acebutolol	The therapeutic efficacy of Bosentan can be increased when used in combination with Acebutolol.
Balsalazide	The therapeutic efficacy of Bosentan can be decreased when used in combination with Balsalazide
Dapsone	The metabolism of Dapsone can be increased when combined with Bosentan.
1-benzylimidazole	1-benzylimidazole may decrease the antihypertensive activities of Bosentan.
4-hydroxycoumarin	The metabolism of 4-hydroxycoumarin can be increased when combined with Bosentan.
Aceclofenac	The therapeutic efficacy of Bosentan can be decreased when used in combination with Aceclofenac.
Aliskiren	Bosentan may increase the hypotensive activities of Aliskiren.
Albendazole	The metabolism of Albendazole can be increased when combined with Bosentan.
Valproic acid	The metabolism of Valproic acid can be decreased when combined with Bosentan.
Troglitazone	The risk or severity of liver damage can be increased when Troglitazone is combined with Bosentan.
Tetraethylammonium	The risk or severity of adverse effects can be increased when Bosentan is combined with Tetraethylammonium.
Rivaroxaban	The metabolism of Rivaroxaban can be increased when combined with Bosentan.

Table1: Bosentan Interaction with other drugs

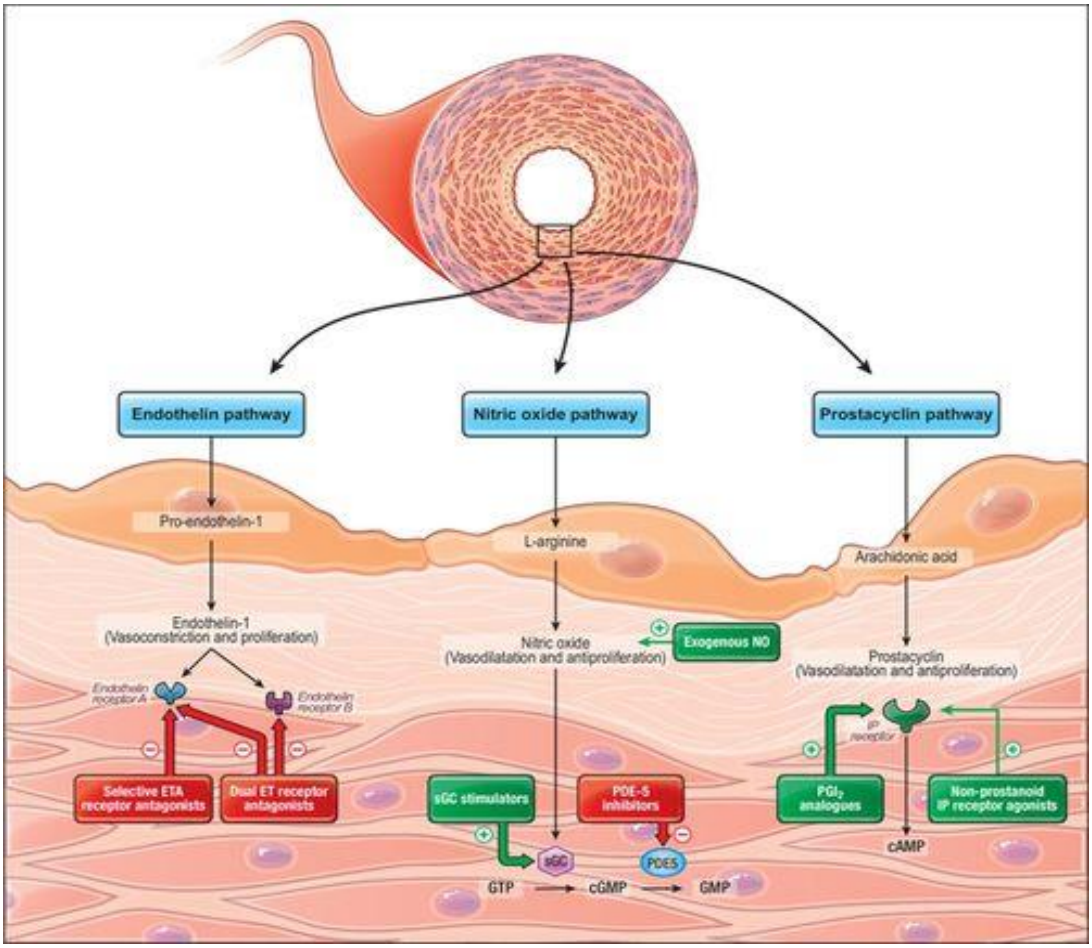


Figure 2: Representation of different therapeutic pathways in the treatment of PAH

However, responses are variable and in many patients, the disease progresses despite therapy. As a result, an increasing number of patients are being considered for combination therapy. . Pharmacological therapy would represent a use: Calcium Channel Blockers, Prostacyclin Analogues, Endothelin Receptor Antagonists and Phosphodiesterase-5 Inhibitors[12]. Current therapies in the treatment of PAH act on the three intracellular pathways, endothelin, nitric oxide and prostacyclin, known to be abnormal in PAH[18-24].

Endothelin Pathwa:ET-1, released predominantly from endothelial cells, is one of the most potent vasoconstrictors known in biology and exerts its effects on 2 distinct receptor subtypes, ETA and ETB receptors. ETA receptor is localized to PASMC, whereas the ETB receptor is found predominantly on the endothelium but is also present on PASMC. Smooth muscle constriction and proliferation are mediated by both ETA and ETB receptor isoforms, but the ETB receptor is involved in the local clearance of ET-1 and can induce vasodilatation via the release of NO and PGI2 from endothelial cells. In addition to promoting pulmonary artery endothelial cells and PASMC proliferation, ET-1 also induces fibroblast activation, contraction, and synthesis of the extracellular matrix.

Bosentan - Bosentan is a non-selective dual ET-1 receptor antagonist and was the first oral agent approved for the treatment of PAH. Bosentan was associated with a gain of 44 m in 6MWD and improvement in FC status at 16 weeks. Bosentan has also been studied specifically in congenital heart disease PAH and improved both exercise capacity and haemodynamics. Liver transaminase elevation is a common side effect. Thus, monthly monitoring of liver function tests is mandatory during bosentan therapy, but the hepatic injury is fully reversible on drug cessation. Patients receiving bosentan also had improvement in the time to clinical worsening (defined as death, lung transplantation, hospitalization for pulmonary hypertension, a lack of clinical improvement or worsening leading to discontinuation of treatment, a need for epoprostenol therapy, or atrial septostomy). No dose -response effect with respect to efficacy could be ascertained.

Nitric Oxide-cGMP Pathway: A key feature of endothelial dysfunction has reduced NO production and bioavailability in endothelial cells. NO is produced from l-arginine via the enzymatic action of nitric oxide synthase (NOS) and activates soluble guanylate cyclase (sGC), which then catalyzes the formation of the second messenger cyclic guanine monophosphate (cGMP), resulting in smooth muscle relaxation. NO is also an inhibitor of smooth muscle proliferation and platelet activation. This pathway can be manipulated via direct administration of NO, inhibition of phosphodiesterase-5 (PDE-5) (the enzyme responsible for cGMP degradation) or stimulation of sGC.

Sildenafil: Sildenafil was the first PDE-5 inhibitor approved for the treatment of PAH. The intracellular degradation of cGMP is regulated by PDEs, and PDE-5 plays a key role in the regulation of smooth muscle tone in the pulmonary vascular bed and the corpus cavernosum. Sildenafil and tadalafil are reversible competitive inhibitors of the catalytic domain of PDE-5 involved in the hydrolysis of cGMP. Sildenafil was the first PDE-5 inhibitor approved for the treatment of PAH and its efficacy was demonstrated in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER1) RCT that enrolled 278 patients[15].

Prostacyclin Pathway

Endogenous PGI2 is produced mainly by endothelial cells from arachidonic acid via prostacyclin synthase and preferentially binds to prostaglandin I (IP) receptors with downstream effect enable administration via the IV, subcutaneous (SC), inhaled, and oral routes. Continuous SC treprostinil avoids the practical difficulties and complications associated with indwelling central venous catheters.

Epoprostenol - (Intravenous) Epoprostenol is still considered the gold standard therapy in severe PAH and has reduced the need for lung transplantation in patients with advanced disease. However, the administration of IV Epoprostenol is complex, and it must be given as a continuous infusion via an indwelling catheter with its associated potential complications. Patients and caregivers require counselling on catheter care and the prevention of catheter-related infections. Furthermore, abrupt interruption of therapy may result in potentially life-threatening rebound PH.

OVERDOSE OF BOSENTAN: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2

months in patients, without any major clinical consequences. The most common side effect was the headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed. On theoretical grounds, massive over dosage may result in pronounced hypotension requiring active cardiovascular support[25].

CONCLUSION

In conclusion, the present study suggests that the treatment of first-line bosentan therapy, followed by the addition of other pulmonary arterial hypertension therapies if needed, improves survival in patients with advanced primary pulmonary hypertension. Given the ease of administration and favourable side-effect profile, the strategy of treatment with first-line bosentan should be considered for the World Health Organization functional class III primary pulmonary hypertension patients. A study has reported significant improvement in Quality of Life measures after 3 months of bosentan therapy, compared with baseline measures. Benefits were seen across all physical and emotional domains and were maintained over time. The dual endothelin receptor antagonist bosentan given at a dose (in adults) of 62.5 mg twice daily for four weeks followed by 125 mg twice daily is a safe and efficacious therapy in PAH. The use of bosentan as part of a comprehensive management plan has resulted in improvements in exercise capacity, functional class, quality of life and survival. Patients require regular monthly monitoring of liver function tests. Bosentan has been extensively used as mono-therapy in PAH especially in patients with idiopathic PAH and scleroderma associated PAH but also appears to be efficacious in other forms of pulmonary hypertension including other connective tissue disease-associated PAH. So Bosentan could be an attractive target for the generic industries. However, none of the approved therapies have shown the ability to cure the disease. New research should be performed to develop promising new therapies. The surge of novel potential options has created new challenges in clinical care and future drug development programs.

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