Update Pharmacology and Therapy In Pulmonary Arterial Hypertension

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Abstract
Pulmonary arterial hypertension (PAH) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, which eventually leads to right ventricular failure and death. At present there is no cure for pulmonary arterial hypertension (PAH); however over the past decade targeted pharmaceutical options have become available for the treatment of PAH. Prior to evaluation for therapeutic options a definitive diagnosis of pulmonary arterial hypertension must be made via comprehensive physical exam and definitive diagnostic testing. Screening test of choice remains echocardiography and gold standard for definitive diagnosis is right heart catheterization. Once the establishment of a diagnosis of PAH is made therapeutic options may be a possibility based on a diagnostic algorithm and disease severity of the PAH patient. There are different classes of medications available with different mechanisms of actions which have a vasodilatory effect and improve exercise tolerance, quality of life as well as survival

Keyword: *pharmacology, Pulmonary arterial hypertension*

I. INTRODUCTION

Pulmonary hypertension (PH) defines a group of clinical conditions presenting with abnormal elevation in the pulmonary circulation pressure (Galie *et al*., 2015). The normal mean pulmonary artery pressure (mPAP) at rest is 14±3.3 mmHg, and the upper limit of normal is 20.6 mm Hg. PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC) (Galie *et al*., 2015). Available data have shown that the normal mPAP at rest is 14±3 mmHg with an upper limit of normal of approximately 20 mmHg (Galie *et al*., 2015; Vallarie *el al.*, 2015). The clinical significance of a mPAP between 21 and 24 mmHg is unclear. Patients presenting with a pulmonary artery pressure (PAP) in this range should be carefully followed when they are at risk for developing PAH [e.g. patients with connective tissue disease (CTD) or family members of patients with heritable PAH (HPAH) (Galie *et al*., 2015).

A. Anatomy, Heart Physiology, and Blood Circulation System

The lungs are one of the organs intertwined with heart in blood circulation. The systemic and pulmonary circulation is depicted by the color change from blue to red. Blood becomes full of oxygen (red), flowing through the lungs then losing several oxygen (red to blue) flowing through other organs and tissues. Deoxygenated blood is indicated in blue. In turn, each of these hearts pulsates (Toshner, Tajsic,Morrell, 2010).. The heart has two chambers accompanied with pumps composed of atria and ventricles. Atrium is a weak primary ventricle pump helping move blood to ventricles that supply the blood with the pumping force driving blood either through the pulmonary circulation by the right ventricle or through the peripheral circulation by the left ventricle. Special mechanisms in the heart cause continuous heart contractions called the heart rhythmicity. Action potential transmissions across the heart muscles create rhythmic heartbeats (Hall, 2011; Widmaier et al 2014).

B. Etiology

Pulmonary hypertension (PH) is a disease characterized by elevated blood pressure in the blood vessels of pulmonary artery causing shortness of breath, dizziness, and fainting during activities when the pulmonary arterial pressure is >22 mmHg (Kasper, Hauser, Jameson, Fauci, Longo, and Loscalzo, 2015; Chakinala and Anderson, 2017). Based on the etiology, PH is classified into five groups known as the Dana Point Clinical Classification of Pulmonary Hypertension (Bacon and Madden, 2015; Galie *et al*., 2015; Papadakis, McPhee, and Rabow, 2016; Rubin and Hopkins, 2016; Chakinala and Anderson, 2017):

Table. 1 Current classification of pulmonary hypertension (Chakinala and Anderson, 2017)

Group	Definition
Group 1	Idiopathic PAH, histopathologically characterized by angioproliferative lesions of flexiforms of endothelial cells, muscularis of precapillary arterioles, proliferations of intima cells, and thickening of media tunica causing proliferations of vascular smooth muscle cells. It increases blood pressures in the small arterial branches as well as vascular resistances of pulmonary bloodstream.

Group 2	PH due to left heart diseases, triggered by disorders in the left ventricle of the heart due to heart valve disorders as regurgitation (backflow) and mitral valve stenosis (narrowing). It manifests pulmonary edema (fluid accumulation in the lungs).
Group 3	PH due to chronic lung diseases and/or hypoxemia
Group 4	Chronic thromboembolic pulmonary hypertension
Group 5	PH associated with hematological disorders, systemic diseases besides connective tissue disorders, metabolic or other disorders, or unclear multifactorial mechanisms.

Group 1 (Pulmonary arterial hypertension, PAH) can be idiopathic (IPAH) or heritable or can be associated with other conditions, including connective tissue disease (most commonly systemic sclerosis), congenital heart disease, HIV, and portal hypertension. It can also be associated with various drugs, including amphetamines and interferon.

- *Idiopathic and heritable PAH.* Although idiopathic pulmonary arterial hypertension (IPAH) might represent the most studied form of PAH, it corresponds to a rare presentation in which no family history of PAH or associated risk factor is present. Therefore, IPAH is only diagnosed after extensive investigation ruling out alternative diagnoses. Heritable forms of PAH include those with identified gene mutations and familial cases with or without mutations. Up to 80% of familial cases of PAH have been linked to germline mutations in the gene coding for the bone morphogenetic protein receptor type II (BMPR2), a member of the transforming growth factor (TGF)-b signaling family. BMPR2 mutations have also been detected in around 20% of apparently idiopathic cases without a family history of PAH (Simmonneu *et al.*, 2013; Vallarie *el al.*, 2015).

- *Drug- and toxin-induced PAH.* A significant number of substances have been described as potentially associated with the development of PAH. Aminorex and fenfluramine derivatives are clear examples where a robust association between drug exposure and PAH has been demonstrated through the analysis of outbreaks of PAH in the 1960s and 1990s. More recently, benfluorex, a benzoate ester that shares structural and pharmacologic characteristics with dexfenfluramine and fenfluramine, has also been associated with the development of PAH. Among other classes of drugs that may be linked to the development of PAH, dasatinib, a tyrosine kinase inhibitor, gained particular attention after a case series of drug-induced PAH was reported in chronic myelogenous leukemia patients. Type I interferons have also been linked to an increased risk of developing PAH (Savale *et al.*, 2012; Vallarie *el al.*, 2015).

- *PAH associated with connective tissue diseases.* One of the most important forms of PAH is connective tissue disease (CTD)-associated PAH. CTD-associated PAH accounts for 15% to 25% of all PAH cases in worldwide registries, with systemic sclerosis and systemic lupus erythematosus as the leading causes. These patients have a particularly poor prognosis, with an estimated 30% 1-year mortality, compared to 15% in IPAH. It was recently suggested that implementation of a systematic screening program to allow earlier diagnosis and intervention might result in better long-term outcomes for this subgroup of PAH patients. Cases of reversible PAH have been reported in PAH patients with systemic lupus erythematosus and mixed CTD (Vallarie *el al.*, 2015)

- *PAH associated with human immunodefic iency virus*. Patients with human immunodeficiency virus (HIV) are at increased risk of developing PAH. The prevalence of PAH in this group is estimated to be 0.5%, with clinical and hemodynamic presentation very similar to IPAH. Prognosis of HIVassociated PAH has improved in recent years; in the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry, the survival of HIV-associated PAH was 93% at 1 year and 75% at 3 years. Cases of reversible PAH have been reported in HIV patients treated with PAH drugs and highly-active antiretroviral drugs (Vallarie *el al.*, 2015)

- *PAH associated with portal hypertension.* About 6% of patients with portal hypertension develop PAH, independent of the severity of the liver disease, although the long-term prognosis of these patients is related to the severity of both the liver and pulmonary vascular disease. Portopulmonary hypertension represents an important problem for liver transplantation programs because its presence is related to increased mortality during and after the procedure, particularly if the mPAP is >35 mm Hg. The prognosis in portopulmonary hypertension is worse than in IPAH; recently reported data suggest a 3-year survival of 40% (Vallarie *el al.*, 2015).

Group 2 (PH secondary to left heart disease, PH-LHD) is predominantly caused by passive transmission of elevated left atrial pressure(pulmonary arterial wedge pressure>15mm Hg) to the pulmonary circulation and can

be caused by left ventricular dysfunction (systolic or diastolic) or valvular disease. Nevertheless, in a subgroup of patients, a pre-capillary component might also be present, characterizing a mixed hemodynamic pattern (combined pre- and post-capillary PH). Further studies are necessary to assess the potential benefits and risks of PAHspecific therapy in this group (Chakinala and Anderson, 2017).

Group 3 (PH secondary to respiratory disease, PH-Lung) is common in the presence of severe respiratory disease but is generally relatively mild, where it is often termed cor pulmonale. This group comprises patients with parenchymal lung diseases or other causes of hypoxia (e.g., obstructive sleep apnea) in whom the presence of PH is considered directly related to these underlying diseases. Thus, all forms of ventilatory disturbances are considered: obstructive, restrictive, and the combination of both patterns. In particular, the presence of a mixed pattern (obstructive and restrictive), as in the coexistence of pulmonary fibrosis and emphysema, results in an increased prevalence of PH. Thus far, no significant benefit from the use of targeted PAH therapies has been demonstrated in this group (Vallarie *el al.*, 2015).

Group 4 (chronic thromboembolic PH, CTEPH) is caused by obstruction and narrowing of the pulmonary arterial bed by chronic, organized thromboembolic disease. Up to 4% of all patients with acute pulmonary embolism may ultimately develop chronic thromboembolic pulmonary hypertension (CTEPH), which is considered a curable form of PH when performing a pulmonary endarterectomy is possible. Operability depends on several factors, including the pattern of vascular obstruction, hemodynamic severity, and experience of the referral center, among others. More recently, PAH-specific medical therapy and balloon pulmonary angioplasty have been used (Vallarie *el al.*, 2015).

Group 5 (miscellaneous) consists of associated conditions that may have multiple or uncertain mechanisms of disease and includes sarcoidosis and myeloproliferative disease. Idiopathic PAH (IPAH) is a rare condition in the general population. Intensivists will therefore rarely manage patients with pre-existing precapillary pulmonary hypertension (i.e. PAH and CTEPH) but will more commonly manage patients with other forms of pre-existing PH. Patients with acute cardiorespiratory failure may also develop acute RV impairment and PH. In this article, we will focus mainly on patients with PAH and CTEPH who require critical care involvement. Before the availability of specific therapies, IPAH was associated with a median survival of 2.8 years. Outcomes have improved with a 5-yr survival of 75–80% in IPAH patients<50 year old (similar to the age of patients seen in historical registry data). Patients with Eisenmenger syndrome tend to have a well-conditioned hypertrophied RV and so have superior survival to other forms of PAH (Hurdman et al, 2012; Ling et al, 2012; Chakinala and Anderson, 2017).

C. Classification of functional status of patients with PAH

Here is WHO pulmonary hypertension functional classifications modified from the New York Heart Association (NYHA) functional classification/WHO Functional Classification (Rich *et al*., 2009):

Table 2 World Health Organization classification of functional status of patients with pulmonary hypertension (Rich *et al*., 2009)

Class	Clinical Description
I	HAP patients without any indication of limitation on physical activities/the physical activities do not cause dispneu, chest pain, or fatigueness.
II	HAP patients with indications of limitation on physical activities. They feel more comfortable while resting. However, physical activities do not cause them to have dispneu,fatigueness, and chest pain.
III	HAP patients with indications of limitation on physical activities. They feel more comfortable while resting than while conducting activities, causing them to have dispneu, fatigueness, chest pain, or even syncope.
IV	Patients with pulmonary hypertension indicating physical symptoms during doing activities. Patients can show symptoms of right heart failure. Meanwhile, dispneu and/or fatigueness is visible while resting. Any uncomfortable feeling increases during activities.

WHO recommend an active lifestyle that promotes general cardiovascular health, PAH patients should be counselled against activities that abruptly increase the work of the heart during exertion. Patients with mild PAH may have only minimal symptoms with exertion, whilst those with more advanced disease may experience dyspnoea at rest, exertional lightheadedness, syncope or chest pain, which are indicative of impaired right ventricular performance. Functional class is an important prognostic marker and has been used as an endpoint in PAH clinical trials.

D. Pathophysiology of PAH

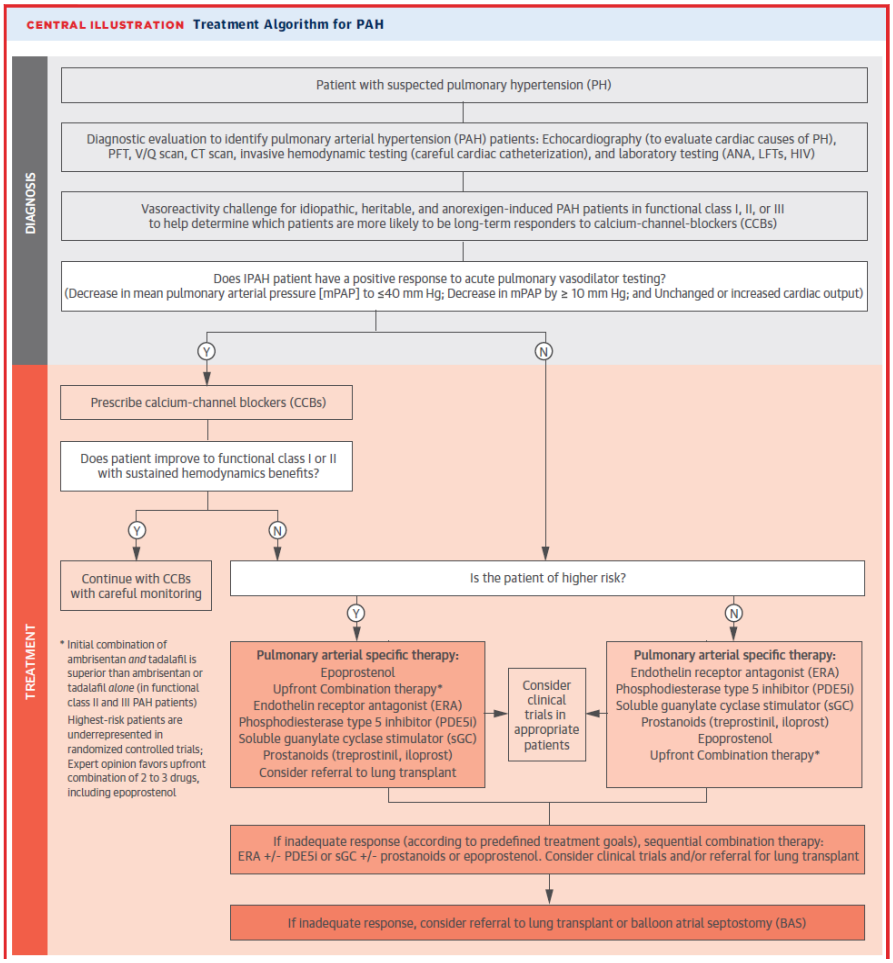
A. Pulmonary vasoconstriction has long been regarded as an early event, and excessive pulmonary vasoconstriction has been related to abnormal function or expression of potassium-channels and to endothelial dysfunction characterized by reduced production of vasodilators (nitric oxide and prostacyclin), along with overproduction of vasoconstrictors (endothelin-1). Recently, a novel channelopathy due to KCNK3 mutation has been identified in heritable cases of pulmonary arterial hypertension (PAH), which may also favor vasoconstriction (Galie, Palazzini, and Manes; 2010; Vallarie *el al.,* 2015)

B. Pulmonary vascular remodeling and inflammation: proinflammatory cytokines (interleukin-1 and -6, tumor necrosis factor a), chemokines, serotonin, angiopoietins, bone morphogenetic proteins (BMPs), growth factors, and members of the transforming growth factor (TGF)b superfamily, but also proteolysis of the extracellular matrix and autoimmunity, are key triggers in smooth muscle cells, endothelial cells, fibroblasts and pericytes proliferation and migration. Proteolysis of the extracellular matrix and autoimmunity (as evidenced here by perivascular lymphoid neogenesis) are also likely to initiate or perpetuate arterial remodeling (Galie, Palazzini, and Manes; 2010; Vallarie *el al.,* 2015)

C. Endothelial dysfunction, proliferation, and resistance to apoptosis, triggered by aberrant production of angiogenic growth factors (FGF2, PDGF, VEGF), and genetic abnormalities in TGF-b signaling (BMPR2, ACVRL1/ALK1, endoglin, SMADs), and in endothelial scaffolding protein (Caveolin-1), may favor aberrant angiogenesis (and subsequent increased vascular resistance) in PAH that is best exemplified by plexiform lesions (Galie, Palazzini, and Manes; 2010; Vallarie *el al.,* 2015)

D. Thrombotic arteriopathy, a highly prevalent pathological pattern of PAH, is an important pathophysiological feature of the disorder. Indeed, endothelial dysfunction leads to local thrombosis in PAH (Galie, Palazzini, and Manes; 2010; Vallarie *el al.,* 2015)

.**Management of PAH** (Vallarie *el al.,* 2015)



ANA = antinuclear antibody; BAS = balloon atrial septostomy; CCB = calcium-channel blockers; CT = computed tomography; ERA = endothelin receptor antagonist; HIV = human immunodeficiency virus; IPAH = idiopathic pulmonary hypertension; LFT = liver function test; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitor; PFT = pulmonary function tests; PH= pulmonary hypertension; sGC = soluble guanylate cyclase stimulator; V/Q = ventilation perfusion scan.

Fig. 1 Management of Pulmonary Arterial Hypertension (Vallarie *el al.*, 2015)

The most common treatment strategy currently employed is goal-oriented sequential Combination therapy. Although the primarily observational studies described previously do not allow for definitive conclusions, reasonable goals of therapy include:

- ✓ Modified NYHA functional class (World Health Organization functional class): I or II
- ✓ Echocardiography/CMR: normal or near-normal RV size and function
- ✓ Hemodynamics: normal indexes of RV function (right atrial pressure <8 mm Hg and cardiac index >2.5 to 3.0 l/min/m2)
- ✓ 6-minute walk distance (6MWD) >380 to 440 m
- ✓ Cardiopulmonary exercise testing: peak oxygen uptake >15 ml/min/kg and ventilatory equivalents for CO2 <45 l/min
- ✓ BNP level: "normal" (determined by local laboratory cutoff values)

Over the years, many treatment approaches have been published, including those put forth at the 5th World Symposium on PH and by the American College of Chest Physicians

Table 3 World Health Organization , Management of PAH (Hopkins, 2016)

WHO Class	Therapy		Information
I, II, III, IV	Supportive	Diuretics	Treating fluid resistance due to PH as diuresis will reduce the lung congestion, the heart, and periphery edema.
		Oxygen	Meeting oxygen demands, especially for Group 3.

		Anticoagulant	The group 4 PH (i.e. chronic thromboembolic pulmonary hypertension/CTEPH).
		Others, non-pharmacology	Performing sports in accordance with abilities.
	CCB		Patients with positive vasoreactive result tests.
II	Ambrisentan plus tadalafil		Alternatives: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, or riociguat → single therapy.
III	Ambrisentan plus tadalafil		Alternatives: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, or riociguat → single or combined therapy. In acute/progressive cases: epoprostenol IV, inhaled ilopros, treprostinil IV, SC, or INH.
IV	Epoprostenol IV		Alternative: treprostinil IV. If there is no improvement/declining: being given double or triple therapies. If there is no improvement, atrial septostomy or lung transplantation is performed.

Table 4 FDA-approved therapies of PAH based on the working mechanisms are (Kholdani, Fares, and Trow; 2014).

Category	Names of Drug	Working Mechanism
CCB (Calcium Chanel Blockers)	Oral Dihidropiridin or diltiazem	Inhibiting the entry of trans-membrane of extracellular calcium ions across myocardium cells and smooth muscle cells of blood vessels without changing the concentration of calcium serum thereby inhibiting the contractions of heart and smooth muscles of blood vessels resulting in coronary and systemic artery dilatation.
Prostanoids	Epoprostenol IV, inhalated iloprost, treprostinil IV, SC, INH, or oral	Prostacyclin (PGI2) activates the cyclic adenosine monophosphate (cAMP) mediating vasodilatation. PGI2 has antripreliferative effects on smooth muscles of blood vessels and inhibits platelet aggregation as well.
Phosphodiesterase type-5 Inhibitors (PDE-I)	Oral Sildenafil Oral tadalafil	Nitric oxides from endothelial cells activate guanylyl cyclase, resulting in cGMP (PDE5 enzymes metabolize cGMP) in smooth muscle cells of blood vessels and thrombocytes. cGMP is the second agent inducing vasodilatation through relaxations of smooth muscle cell arteries and inhibiting thrombocyte activations.
Soluble guanylyl cyclase stimulator	Oral riociguat	Stimulating guanyl cyclase to generate cGMP resulting in vasodilatation.
Endothelin receptor antagonists (ERAs)	Oral bosentan, oral ambrisentan, oral macitentan	ERA blocks the ET-1 binding, either the endothelin A (ET-A) and/or B (ET-B) receptors. The ET-A receptors are found in pulmonary arteries of smooth muscle cells mediating vasoconstriction.

Table 5 Comparative features for FDA-approved ERAs (Kholdani, Fares, and Trow; 2014).

Comparators	Bosentan	Ambrisentan	Macitentan
Date of FDA approval	2001	2007	2013
Selectivity	Nonselective	Selective	Nonselective
K_b ratio*	0.7	1.0	6.3
Half-life	5 hours	15 hours	16 hours
Dosing	62.5 mg BID or 125 mg BID	5 mg QD or 10 mg QD	10 mg QD
Study outcomes	Primary outcome:	Primary outcome:	Composite primary end point:
	6MW distance	6MW distance	Death

	Secondary outcome:	Secondary outcome:	Lung transplantation
	WHO class	WHO class	Atrial septostomy
	Borg dyspnea index	Borg dyspnea index	Parenteral prostanoid initiation
	Time to clinical worsening	Time to clinical worsening	Worsening of PAH
		Plasma B-type natriuretic peptide	Secondary end points:
			6MW distance
			WHO class
			Hemodynamic end points:
			PVR reduction
			Cardiac index increase

Abbreviations: FDA, US Food and Drug Administration; ERA, endothelin-receptor antagonist; BID, bis in die (twice daily); QD, quaque die (every day); 6MW, 6-minute walk; WHO, World Health Organization; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance.

Macitentan is a dual ET-receptor antagonist (ERA) developed in the setting of extensive efforts to maximize blockade of the ET axis while generating compounds with improved adverse-effect profiles when compared to prior compounds in the class. Unlike bosentan and sitaxsentan, macitentan is not characterized by a sulfonamide structure, but belongs to the sulfamide class of compounds (Dingemanse,*et el*., 2014; Keating, 2016). The presence of a bromine atom in the parent compound of macitentan allowed for straightforward determination of its metabolites (Sidharta ., 2011). Macitentan is metabolized via oxidative depropylation into ACT-132577 and via oxidative cleavage into ACT-373898 (Bruderer *et al*., 2012). Of the two aforementioned metabolites, only the former, ACT-132577, has been shown to be metabolically active, and like its parent compound, also demonstrates dual-receptor antagonist properties, albeit with less potency (Dingemanse,*et el*., 2014).

At a cellular level, macitentan demonstrates slower dissociation kinetics compared to all other available ERAs, in addition to insurmountable antagonism in functional pulmonary artery smooth-muscle assays (Monaco, Davila, 2016). It has been demonstrated that macitentan's functional inhibition constant (K_B) ratio of 6.3 is higher than that of both bosentan and ambrisentan (0.7 and 1.0, respectively), indicating significantly more potent antagonism. Both macitentan and its metabolites are highly bound to plasma proteins (>99%), and are primarily excreted via the hepatic and renal systems (combined hepatic and renal excretion of 49.7%±3.9%), with fecal elimination representing 23.9%±4.8% of total excretion. Pharmacokinetic evaluation of the 10 mg dose of macitentan has been shown to be safely tolerated in cirrhosis patients with Child–Pugh classes A, B, and C, with the expected caveat, given its metabolism, of decreased exposure to ACT-132577 in patients with hepatic impairment. Severe renal impairment, defined as a creatinine clearance of 15–29 mL/min, did not have any bearing on the safety profile of macitentan either (Sidharta, 2013; Dhillon, 2014.).

Evaluation of macitentan's pharmacokinetics has been extensively studied with single doses ranging from 0.2 mg to 600 mg tested in healthy subjects. Macitentan is absorbed slowly, with a time to reach maximal concentration ranging from 8 hours to 30 hours. Reliable assessment of terminal half-life has been achieved with the higher non-US Food and Drug Administration (FDA)-approved doses, and is approximately 16 hours. The half-life of its main metabolites ranges from 40.2 hours to 65.6 hours. The plasma concentration of ET-1 demonstrated a dose-

dependent rise, but was only noted to be statistically significant with doses of 25 mg and higher, which are higher than any dose used in trials evaluating macitentan's clinical efficacy (Sidharta, 2013).

Macitentan has demonstrated a favorable profile of drug interactions. With respect to combination therapy, a recent study of 12 healthy subjects demonstrated that the pharmacokinetics of macitentan were unaffected by concomitant sildenafil use, although there was a slight decrease in the concentration of ACT-132577. Cyclosporine, considered a weaker inhibitor of CYP3A4 than ketoconazole, has also been coadministered with macitentan with no clinically significant changes in the pharmacokinetic profile of the drugs. Rifampin, which is an inducer of CYP3A4, has also been coadministered with macitentan with preserved steady-state exposure to ACT-132577; however, this coadministration resulted in a nearly fourfold reduction in levels of macitentan. As such, the manufacturers advise against coadministration with strong CYP3A4 inducers, such as rifampin. In a randomized, open-label, crossover study assessing the effects of multiple doses of macitentan on the pharmacokinetics and pharmacodynamics of a single 25 mg dose of warfarin, there was no change in either the INR or factor VII activity when compared to controls. As with other ERAs, macitentan has the potential for teratogenicity, and it is therefore contraindicated in pregnancy. The manufacturers advise the use of two forms of birth control, one of which should be a barrier method, for women with PAH taking macitentan. It has not been studied in patients with pediatric pulmonary hypertension and is not approved for use in this population (Kholdani, Fares, and Trow; 2014)

.**Table 6** Adverse-effect profile for FDA-approved ERAs (Kholdani, Fares, and Trow; 2014)

Adverse effects	Bosentan	Ambrisentan	Macitentan
Aminotransferase elevations	>10% of cases	<3% of cases	<3% of cases (subject of ongoing Phase IV evaluation)
Peripheral edema	3%–10% of cases	>10% of cases	<3% of cases
Anemia	3%–10% of cases	3%–10% of cases	3%–10% of cases

The clinical trial evaluating the efficacy of bosentan in PAH, was marred by the presence of a significant amount of hepatotoxicity, with several patients developing an asymptomatic rise in serum aminotransferases that resolved with the cessation of the therapy. While rises in serum aminotransferases signal the presence of potential hepatotoxicity, they provide no insight into the mechanism. Administration of bosentan along with its three known metabolites results in inhibition of adenosine triphosphate-dependent taurocholate transport based on data from uptake experiments performed on rat liver canalicular plasma-membrane vesicles and BSEP-expressing cells. The conclusion based on these data is that the hepatotoxic profile of bosentan and its metabolites results from inhibition of the canalicular BSEP. Whereas intravenous administration of bosentan resulted in an increase in plasma bile salts in rats, this effect was not demonstrated in the case of macitentan. Peripheral edema is also a notable side effect of the ERA class, and the mechanism is also unknown. The observation that peripheral edema is less common in patients treated with dual-receptor antagonists, such as bosentan, as opposed to ETR_A-specific medications, such as ambrisentan, supports the hypothesis that the effect is mediated through circulating ET-1 and its activation of the ETR_B (Kholdani, Fares, and Trow; 2014)

II. CONCLUSION

PAH (Pulmonary Arterial Hypertension) elevation in pulmonary artery pressures is > 22 mmHg. Clinical manifestations are unspecified, characterized by the heart inabilities during activities. The symptoms are shortness of breath, lethargy, and feeling fatigue easily. The symptoms increase when the right ventricular hypertrophy occurs then the ventricle fails to expand. Treatments for PAH have not been found yet. PAH therapies are commonly symptomatic to relieve the symptoms. Macitentan is the latest ERA with highly efficacious and enduring binding properties to both ETR_A and ETR_B. In part due to the properties of its sole active metabolite, it is available for once-daily use. Extensive Phase I data have demonstrated a favorable drug–drug interaction profile, with no dosage adjustments necessary in the face of chronic hepatic or renal impairment. Unlike some prior ERAs, it has demonstrated no increased risk for hepatotoxicity, with its only notable significant adverse event being anemia. The first long-term trial designed to evaluate a PAH-specific medicine's effect on morbidity

and mortality demonstrated both favorable hemodynamic effects and significant reduction in morbidity in both treatment-naïve patients with PAH and those already on background therapies.

References

Bruderer S, Hopfgartner G, Seiberling M, et al. (2012) Absorption, distribution, metabolism, and excretion of macitentan, a dual endothelin receptor antagonist, in humans. Xenobiotica.;42(9):901–910. \

Bacon, J., & Madden, B. (2015). The Pathophysiology, Presentation, and Diagnostic Investigation of Pulmonary Hypertension. In M. Brendan, *Treatment of Pulmonary Hypertension* (pp.1-36). London: Springer International Publishing Switzerland.

Chakinala, M. M., & Anderson, A. (2017). Pulmonary Hypertention. In A. Shifren, D. E. Byers, & C. A. Witt, *Pulmonary Medicine Subspecialty Consult*. Philadelphia: Departement of Medicine, Washington University School of Medicine, pp. 205-217.

Dingemanse J, Sidharta PN, Maddrey WC, Rubin LJ, Mickail H (2014). Efficacy, safety and clinical pharmacology of macitentan in comparison to other endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. *Expert Opin Drug Saf.*;13(3) pp.391–405

Dhillon, S. (2014). Macitentan: A Review of Its Use in Patients with Pulmonary Arterial Hypertension. *Adis Drug Evaluation, Springer International Publishing Switzerland*, pp. 1495-1507.

Galie N, Humbert M, Vachiery JL et al. (2015) ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 46 pp. 903–75

Galie, N., Palazzini, M., & Manes, A. (2010). Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *European Heart Journal* , 2080-2086.

Hall, J. E. (2011). *Guyton and Hall Textbook of Medical Physiology TwelfTh edition.* Philadelphia: Saunders Elsevier.

Hopkins, W. (2016). Treatment of pulmonary hypertension in adults. *UptoDate*,pp 1-41.

Hurdman J, Condliffe R, Elliot CA et al (2012) ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J 39: pp. 945–55

Kasper, d. L., Hauser, s. L., Jameson, J. L., fauci, A. s., Longo, d. L., & Loscalzo, J. (2015). *Harrison's Internal Medicine 19th Edition.* New York Chicago San Francisco Athens London Madrid Mexico City: McGraw-Hill Education.

Keating, G. M. (2016). Macitentan: A Review in Pulmonary Arterial Hypertension. *Adis Drug Evaluation, Springer International Publishing Switzerland*.

Kholdani, C. A., Fares, W. H., & Trow, T. K. (2014). Macitentan for the Treatment of Pulmonary Arterial Hypertension. *Vascular Health and Risk Management, Dovepress*, 665-673.

Ling Y, Johnson MK, Kiely DG et al. (2012) Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 186:pp. 790–6

Monaco, T. J., & Davila, C. D. (2016). Safety, Efficacy, and Clinical Utility of Macitentan in the Treatment of Pulmonary Arterial Hypertension. *Drug Design, Development and Terapy*, pp.1675-1682.

Papadakis, M. A., McPhee, S. J., & Rabow, M. W. (2016). *Current Medical Diagnosis & Treatment Fifty-fifth Edition.* New York: McGraw-Hill Education.

Rich S.(2009) Primary pulmonary hypertension: executive summary. Evian, France: *World Health Organization*.

Rubin, L. J., & Hopkins, W. (2016). Clinical Features and Diagnosis of Pulmonary Hypertension in Adults. *UptoDate.com*.

Savale L, Chaumais MC, Cottin V, et al.(2012) Pulmonary hypertension associated with benfluorex exposure. *Eur Respir J* 40:pp1164–72.

Sidharta PN, van Giersbergen PL, Halabi A, Dingemanse J.(2011) Macitentan: entry-into-humans study with a new endothelin receptor antagonist. *Eur J Clin Pharmacol*. 67(10):pp. 977–984.

Sidharta PN, van Giersbergen PL (2013), Dingemanse J. Safety, tolerability, pharmacokinetics, and pharmacodynamics of macitentan, an endothelin receptor antagonist, in an ascending multiple-dose study in healthy subjects. *J Clin Pharmacol*.;53(11):pp1131–1138

Toshner, M., Tajsic, T., & Morrell, N. W. (2010). Pulmonary Hypertension: Advances in Pathogenesis and Treatment. *British Medical Bulletin*, 21-32.

Widmaier, E. P., Hershel, R., & Strang, K. T. (2014). *Vander's Human Physiology: The Mechanisms of Body Function, Thirteenth Edition.* New York: McGraw-Hill.

Vallerie V. McLaughlin, Sanjiv et al. (2015) Management of Pulmonary Arterial Hypertension, *Journal of The american College of Cardiology* vol. 65, no. 18, p. 1976-1998