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A REVIEW ARTICLE ON PULMONARY ARTERIAL HYPERTENSION AND EFFECT OF TREATMENT

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ABSTRACT

Endothelial dysfunction and vascular remodelling block tiny pulmonary arteries, resulting in increased pulmonary vascular resistance and pulmonary pressures. This results in a reduction in cardiac output, right heart failure and death. We want to give an explanation in terms of categorization, diagnosis, patho physiology, treatment prognostic variables in this study, which aims to answer some essential concerns often posed by patients diagnosed with pulmonary arterial hypertension. Endothelin-1, reactive oxygen species and endothelial and smooth muscle proliferation are all discussed as key molecular mechanisms in the patho physiology of pulmonary arterial hypertension[1].

KEYWORDS

Pulmonary arterial hypertension, Classification of PAH, Patho physiology and Novel treatment options targeting specific pathways in PAH.

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INTRODUCTON

Pulmonary arterial hypertension (PAH) results in right ventricular failure due to excessive pulmonary arterial pressures[1]. Medial hypertrophy, intimae thickening, adventitial thickening and complicated lesions are the most common histopathological characteristics of pulmonary arteriopathy. The cross sectional area of the media of pre and intra-laminar pulmonary arteries increases with medial hypertrophy. It is caused by smooth muscle fibre hypertrophy and hyperplasia, as well as an increase in connective tissue matrix and fibrin in the media of muscular arteries. Defination: Right-heart catheterization (RHC) demonstrating pre capillary pulmonary hypertension with a mean pulmonary

artery pressure (mPAP) of >25mm Hg and a normal pulmonary artery wedge pressure defines pulmonary arterial hypertension (PAH) (PCWP)[2]. PAH was originally documented in 1891 by German doctor E. Romberg, described a patient with pulmonary artery thickening at autopsy but no heart or lung disease that might have caused the condition. In 1951, Dr. D. T. Dresdale documented three cases in the United States and the illness was dubbed primary pulmonary hypertension for the first time[3]. PAH is a rare, progressive disease characterised by high blood pressure (hypertension) in the lungs' arteries (pulmonary artery) for no apparent reason. Blood is transported from the heart to the lungs via the pulmonary arteries. Pulmonary arterial hypertension (PAH) is a serious and progressive disease characterised by a pathological increase in the resistance of the pulmonary circulation. High pulmonary vascular resistance causes right ventricular dysfunction, severe disability and early death (PVR)[4]. PAH is caused by pulmonary vascular injury, which can occur on its own or as a result of other illnesses or exposures. It's most likely the result of a combination of genetic susceptibilities and environmental or disease-related triggering events. Treatment options have improved over the previous decade and there is now six FDA-approved medications available[5].

Figure gives the information about classification of pathology[6].

PATHO PHYSIOLOGY

Pathological alterations have recently received a lot of attention (Humber *et al*, 2019)[7]. Over the last several decades, the basic idea that pulmonary vascular remodelling is influenced by a variety of genetic, epigenetic, and environmental factors has evolved into a more nuanced picture in which pulmonary vascular remodelling is influenced by a variety of genetic, epigenetic and environmental variables has evolved into a more nuanced picture in which pulmonary vascular remodelling is influenced by a variety of genetic, epigenetic and environmental variables (Humber *et al*, 2019)[7]. PAH resembles cancer in many respects and might be regarded as a pseudo-malignant disease (apoptotic resistance, altered metabolism, and over expression of growth factor receptors; Boucher at, Vitry *et al*, 2017)[8]. Medial hypertrophy/hyperplasia, intimae and adventitial fibrosis, (in situ) thrombotic lesions and plexiform lesions, as well as per vascular infiltration of inflammatory cells, define the pulmonary vasculature remodelling that underpins PAH (B- and T-lymphocytes, mast cells, dendrite cells, macrophages, etc.; Hubert *et al*, 2019)[7].

Mostly affect distal muscular-type pulmonary arterial vessels and tiny pre-capillary arterioles (diameters of 70-500m and 20-70m in humans, respectively), although it can also affect post capillary veins and bronchial arteries to various degrees. Despite the fact that the processes underlying the latter are unknown, bronchial arteriole-venous shunting may be involved (Humber *et al*, 2019)[7]. These factors will raise pulmonary vascular tone and promote remodelling, making those good pharmacological targets. Other mediators, including as pro-inflammatory cytokines (interleukin-1 and -6, tumour necrosis factor a), chemokines, serotonin, angiopoietins, bone morphogenetic proteins (BMPs), growth factors and immune system members, are considered to have a role in PAH patients in subsets. Autoimmunity and extracellular matrix proteolysis are also thought to have a role in disease pathobiology. The significance of the TGFb super family in pulmonary vascular remodelling has been highlighted by cases of heritable PAH caused by gremlin mutations in BMPR2, ACVRL1, and Enderlin. The products of these genes are involved in the control of pulmonary artery endothelial and smooth muscle cell development, differentiation and death. Idiopathic and heritable PAH afflict twice as many women as men, suggesting that other variables, including as sexual hormones and pregnancy, may play a part in the pathobiological processes that lead to PAH[8].

DIAGNOSIS

This is an illustration of a clinical scenario. Hypotension dyspnoea is the most common symptom of PAH and it can last for months or even

years. Women are more likely than males to be afflicted and persons of all ages can be impacted. Exceptional chest discomfort, syncope and oedema of the lower limbs are symptoms indicating more severe pulmonary hypertension with a weaker right heart. The typical age of diagnosis has been reported to be between 36 and 50 years old, with more recent studies and individuals with concomitant PAH (especially scleroderma) reporting greater mean ages at diagnosis. Because of the lack of precise findings on physical examination and the nonspecific symptoms that most patients describe, diagnosis is usually delayed. This is a diagnostic assessment. A thorough assessment is required to identify the diagnosis and cause of PAH, which includes pulmonary function tests, connective tissue disease serology, echocardiography and cardiac catheterization. Confirming the diagnosis, identifying the clinical class of PH and the type of PAH, and measuring functional and hemodynamic impairment are all part of the PH diagnostic process. For practical reasons, following a four-step sequential method can be useful[9].

Clinical suspicion of pulmonary hypertension

Any episode of breathlessness that is not accompanied by overt symptoms of a particular heart or lung disease, or in patients with underlying lung or heart disease when there is increasing dyspnoea that is not explained by the underlying disease, should raise clinical suspicion of PH. PH symptoms include fatigue, weakness, angina, syncope and abdominal distension. Finally, when abnormal electrocardiographic, chest radiography, or echocardiography results are detected during procedures performed for other clinical reasons, PH may be evaluated.

Detection of pulmonary hypertension

The following poses use to determine pulmonary hypertension.

- ECG
- Chest radiograph
- Tran thoracic Doppler-echocardiography.

Pulmonary hypertension clinical class identification

- Pulmonary function test and arterial blood gases.
- Ventilation and perfusion lung scan.
- High resolution CT of lung
- Contrast enhance spiral CT of lung, pulmonary angiography and magnetic resonance imagine.

Pulmonary arterial hypertension evaluation (type, Functional capacity, hemodynamic)

- Blood tests and immunology.
- Abdominal ultrasounds scan.
- Exercise capacity.
- Hemodynamic and lungs biopsy[10]

THERAPY

The treatment of PAH has historically been characterised by a lack of alternatives and a high level of difficulty. We've just seen a significant shift from decades of sluggish development to a record number of randomised controlled trials (RCTs) completed in the last few years. However, we have inherited a variety of therapies that are widely thought to be effective (e.g., oral anticoagulants, oxygen and CCBs), despite the fact that they are not supported by RCTs and are not explicitly authorised by regulatory agencies for the specific PAH indication[11].

Pulmonary arterial hypertension (PAH) is a rare disease which the Patient may

Face vascular failure. Due to which it lead to cardiac failure and thrombosis this can be treated with high dose of calcium agonists, anticoagulant agents and oxygen.

Diuretics and supplementary oxygen are given to reduce symptoms such as dyspnoea and peripheral oedema commonly used medicament is tracleer i.e. it contain Bosentan. Treated by blocking the action of endothelia molecules it reduce elevated blood pressure. It is also known as endothelia receptor antagonists (ERAs)[12].

PHARMACOLOGICAL TREATMENT

Oral anticoagulant treatment

The use of oral anticoagulants in PAH patients is justified by the presence of traditional venous thromboembolic risk factors such as heart failure and a sedentary lifestyle, as well as the demonstration of thrombophylic predisposition and thrombotic changes in the pulmonary microcirculation and elastic pulmonary arteries. The evidence for the beneficial benefits of oral anticoagulant therapy in patients with IPAH or PAH-related anorexigens is based on a retrospective review of single-centre research. Oral anticoagulants were given to 51-86 percent of patients in recent RCTs. Surprisingly; the studies with the highest incidence of oral anticoagulant therapy comprised more IPAH patients in NYHA classes III and IV, whereas the trials with just scleroderma patients had the lowest rate. It is important to note that there is no indication of a difference in the efficacy of oral anticoagulant treatment based on functional class or other severity parameters.

Diuretics

Fluid retention occurs in patients with decompensate right heart failure, resulting in increased central venous pressure, abdominal organ congestion, peripheral edoema and in severe cases, asides. Even if no specific RCTs have been done, appropriate diuretic therapy in the event of right heart failure provides for obvious symptomatic and clinical benefits in patients with PAH. However, due to a paucity of studies with specific diuretic classes in PAH and individual heterogeneity in responses, the kind and amount of medication to be administered in individual patients is left to the physician's discretion. Patients on diuretic treatment should have their serum electrolytes and renal function indicators regularly monitored.

Oxygen

At rest, most individuals with PAH (excluding those with congenital heart disease) have relatively modest levels of arterial hypoxemia. Poor mixed venous oxygen saturation due to low cardiac output and very marginally changed ventilation perfusion matching are the path physiological reasons in this instance. A subsequent opening of a patent foramen ovale can be observed in certain individuals with severe hypoxia. Hypoxemia is linked to the reversal of left-to-right shunting and is resistant to increased inspired oxygen in patients with PAH associated with congenital heart defects.

Digitalis and dobutamine

Isotropic drugs have been investigated for the treatment of right heart failure since a decrease in myocardial contractility appears to be one of the major events in the development of the disease. In IPAH, short-term IV dioxin treatment results in a moderate increase in cardiac output and a significant decrease in neither circulating nor epinephrine levels[13].

ENDOTHELIN-1 RECEPTOR ANTAGONISTS

Endothelin-1 (ET-1) is a peptide that is generated predominantly by vascular endothelial cells and is a potent vasoconstrictor and smooth muscle mutagen. ET-1 interacts to two receptor types: ET A and ET B.

ET-receptors are present in smooth muscle cells, but they are also found in endothelial cells and smooth muscle cells. ET-1's vasoconstrictive and mutagenic actions are mediated via the activation of ET A and ET -receptors on smooth muscle cells. Endothelial ET B-receptor stimulation promotes ET-1 clearance, No activation and prostacyclin release[14].

BOSENTAN

- Bosentan is a dual endothelia receptor antagonist marketed under trade name trancler.
- Bosentan is the one of the drug used for the treatment of pulmonary arterial hypertension.
- Bosentan monohydrate (pictured below) is a fine white to yellowish powder with a solubility of 1mg/100ml in water. It is not hygroscopic and is archival.

PHARMCODYNAMICS

Endothelia receptor antagonists, such as Bosentan, are a kind of medication (ERAs). Endothelia, a strong blood vessel constrictor, are found at high quantities in the plasma and lung tissue of PAH

patients. Bosentan prevents endothelia from attaching to its receptors, neutralising endothelia's harmful effects.

MECHANISM OF ACTION

Bosentan will bind to the neurohormone release receptor such as ET_a and ET_b. These are will reduce the release of hormone by which functioning of elevated in plasma and lung tissue of patients. So it reduce the pulmonary arterial hypertension and it get eliminated by metabolism of liver by cytochrome P- 450 enzyme. In normal adult it get eliminated by body in 5 hour. Albumin contributes more than 98 percent of the plasma protein.

Metabolism

It mainly metabolized in the liver by the cytochrome p-450 enzyme CYO2C9 and CYP3AL. Due to which only 10 to 20% activity is seen in parent compound. Following liver metabolism, binary excretion occurs.

Toxicity

It can be administered up to 2400mg in normal volunteers or up to 2000mg/day for two month in patients, without any major clinical consequences.

Drug Interaction

In the cyclosporine a interaction study 500 to 1000mg of BOSENTAN given result in headache, nausea and vomiting but not serious adverse effect. Over dose may cause pronounced hypertension requiring active cardio vascular support[15].

QUALITY

The suggested product is a dispersible tablet for children that come in blister packs with 14 tablets per blister strip and 56 tablets each carton. Acceptable specifications for appearance, colour, average mass (of 10 tablets), friability, uniformity of dosage unit by content uniformity, assay, degradation products, disintegration, fineness of dispersion and microbiological contamination are used to ensure product quality. The suggested time limitations for release and expiration have been approved. The analytical procedures for analysing the product were well-described and confirmed. The taste of the tablet's flavouring ingredient is acceptable.

NON-CLINICAL

The findings of the toxicity studies warrant the use of Bosentan in children, according to the nonclinical assessor. A dosage range finding research, toxicity study and fertility evaluation in neonatal/juvenile Han Westar rats was used to determine the safety of Bosentan in the juvenile population. In terms of growth, development, cognition, sensory and reproductive function, there are no serious concerns about juvenile toxicity. While no testicular findings have been reported in adult rats treated with Bosentan, testicular findings have been reported in adult rats treated with other endothelia receptor antagonists such as macitentan and [information redacted] and decreased sperm concentrations have been observed clinically with BOSENTAN, necessitating the inclusion of appropriate warnings in the PI and RMP[16].

PHARMACOLOGY

Peak plasma concentration is reached 3.7 1.7 hours after a single oral dosage in healthy individuals, with a half-life of 5.6 1.6 hours. In PAH patients, clearance is 3.8 L/hour compared to 8.8 L/hour in healthy people. Bosentan is strongly plasma protein bound (> 98%). Oral Bosentan has a 41 percent absolute bioavailability. Food administration had little effect on the amount of absorption, although it did enhance Cmax by 20%. Bosentan is metabolised by CYP2C9 and CYP3A4 in the liver and it also stimulates both of these enzymes. Bosentan plasma concentrations are 50 to 65 percent higher after several doses than they are after a single dosage.

TOXICITY

Bosentan has been administered as a single dosage of up to 2400mg in healthy volunteers, or as a daily dose of up to 2000mg for two months in patients, with no serious side effects. Headaches of mild to moderate severity were the most prevalent adverse effect. In the cyclosporine a interaction study, trough plasma concentrations of bosentan increased 30-fold when dosages of 500 and 1000mg bid. Of bosentan were administered concurrently with cyclosporine A, causing severe headache, nausea and vomiting but no major side effects. There were

minor drops in blood pressure and increases in heart rate.

Sitaxsentan - In one RCT, 178 patients with NYHA class II, III and IV PAH were given Sitaxsentan, a selective orally active ET-receptor antagonist.

Ambrisentan - A selective orally active ET-receptor antagonist, Ambrisentan, has been tested in 64 PAH patients in a pilot blinded dose-comparison trial. Preliminary findings demonstrate benefits in exercise capacity and hemodynamic that is consistent with those seen with the other ERAs. A 150-word essay Ambrisentan is now undergoing two RCTs to better investigate its efficacy and side effect profile, as well as get regulatory approval. Because Ambrisentan is presently exclusively available for patients engaged in RCTs, no recommendation rating is offered[17].

NOVEL TREATMENT OPTIONS TARGETING SPECIFIC PATHWAYS IN PAH

Novel medication preclinical and clinical research is now focused on PAH, which has typical pulmonary vascular remodelling features. This study focuses on innovative concepts that have been validated in preclinical models and then used in clinical studies. There are also some brand-new researches on preclinical methods discussed. Preclinical models have been effectively utilised to assess therapy alternatives in PAH, despite the fact that they only partially represent PAH characteristics. Several additional models with knockdown of key pathways have been reported, but none of them is capable of reproducing all of PAH's histopathological abnormalities.

Circulating hormones

- Sex hormones
- Dehydroepiandrosterone
- Renin-angiotensin-aldosterone system
- Atria natriuretic peptide
- Neurohormone regulation
- Other hormones

GPCR Pathway

- Rho-associated protein kinas
- Apelin
- Novel preclinical targets

Ion channels

Mitochondrial and metabolic adaptation

- Cellular metabolic alterations-The Warburg effect.
- Systemic metabolic alterations.

Epigenetic alterations and interaction with metabolic pathways

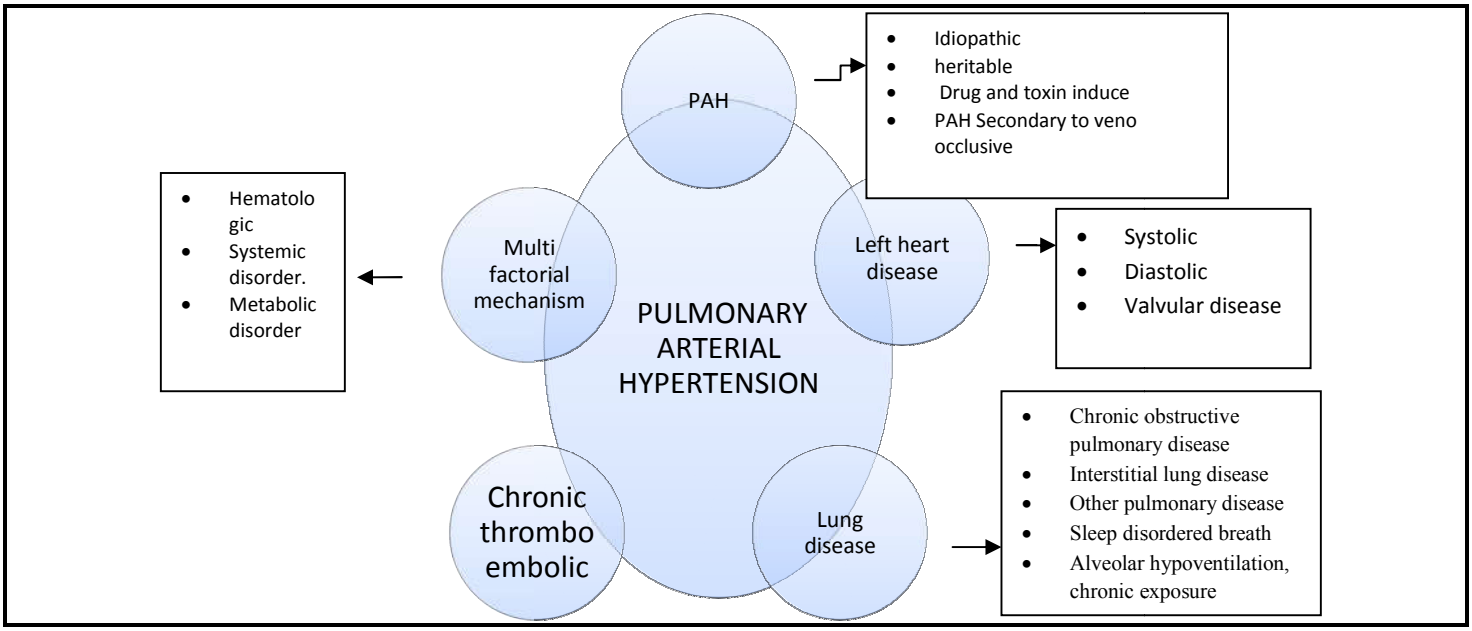
Oxidative stress-related pathways

Inflammatory mediators[18].

GENERAL MEDICATION DOSE

S.No	Drugs	Dosage form	Maximum dose	Interval
1	Bosentan(tracleer)	Tablet, Film coated.	62mg by oral twice daily	Increase to 125mg bid after 4 week
2	Ambrisentan (Letairis)	Tablet	5mg daily	Gradually increase to 10mg.
3	Sitaxsentan (Thelin)	Tablet	100mg	Maximum is 100mg
4	Sildenafil (Revatio)	Tablet	20mg	Oral route 3 times daily
5	Beraprost	Tablet	20g	Oral route 4 times a day
6	Iloprost (Ventavis)	Inhaled	2.5g	6 to 9 times daily
7	Epoprostenol (Flolan)	Initiate	2mg/kg/min	Tolerated increase to 5g
8	Treprostinil (Remodulin)	Initiate	1.25mg/kg/min	Weekly for 4 weeks. than 2.5mg/kg/min weekly.1

CLASSIFICATION OF PAH



CONCLUSION

Over the last several decades, the number of treatment options for pulmonary arterial hypertension (PAH) has grown. The introduction of pharmaceutical treatments that target the prostacyclin, endothelia and NO pathways has improved results substantially. However, PAH remains a life-limiting condition for the great majority of sufferers, with little hope of a cure. Pulmonary vascular remodelling is a feature of PAH. Bosentan agonist is a good therapy but when it is consume in form of tablet bioavailability is not fully obtain because of first pass metabolism targeting the fundamental mechanisms of abnormal proliferation, migration and death is the focus of current research. Despite preclinical progress, a variety of new methods targeting cellular GPCRs, ion channels, metabolism, epigenetic, growth factor receptors, transcription factors and inflammation have yet to be developed.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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