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THE CURRENT TREATMENTS OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary hypertension is a debilitating chronic disease. In the last 20 years, there has been impressive progress in the treatment strategy of pulmonary arterial hypertension. This led to a significant increase in the awareness and improvement in the clinical outcome, though there was no substantial improvement in the rate of mortality. This review summarizes the current state of the art of the treat-ment of pulmonary arterial hypertension, including the three main categories of pulmonary hypertension specific medication which were introduced in the last 20 years. Mainly drugs that restore prostaglandins function of the endothelial cells, drugs that restore Cyclic GMP in the endothelial cells and various forms of medication that inhibit Endothelin receptors. The current strategy to treat patients with pulmonary arterial hypertension is to initiate drug therapy as early as possible and to adopt combinational therapy using two or more classes of drugs simultaneously. There are current efforts to introduce future medica-tion that can be more specific to a phenotype of pulmonary hypertension.

Key words: hypertension, arterial, physical activity.

Introduction

The normal mean pulmonary arterial pressure (mPAP) at rest is 14 ± 3 mm Hg. When this pressure increases significantly, it will cause a debilitating chronic disease known as pulmonary hypertension. It is customarily defined as an increase in mean pulmonary arterial pressure of ≥ 25 mmHg (and pulmonary vascular resistance (PVR) ≥ 3 Wood Unit) but with normal pulmonary capillary wedge pressure of ≤ 5 mm Hg when measured during the right heart catheterization [1]. However, in 2018, the 6th World Symposium on Pulmonary Hypertension in Nice, France suggested that the condition should be redefined and proposed revising the haemodynamic definition by lowering the threshold from ≥ 25 mmHg to >20 mmHg [2]. This is still debatable as no clinical data available and that the new definition may lead to overdiagnosis and overtreatment pulmonary hypersion. The general trends to recommend adopting this new definition [3]. The definition also considered mPAP during exercise (>30 mmHg) (4,5), but once again during the 6th World Symposium on Pulmonary Hypertension this notion has been challenged and the subject needs further evaluation [2].

Pulmonary hypertension should be considered as a syndrome because of many local and systemic diseases. It was classified from the early days of the World

Symposium on Pulmonary Hypertension into five groups depending on the clinical presentation, pathological findings and haemodynamic character-ristics. These groups are continuously changing by the World Symposium on Pulmonary Hypertension as per the emerging data [1]. Table 1 summarises the up-to-date classification as per the latest 6th World Symposium on Pulmonary Hypertension in Nice, France [2]. In this review we are focusing on group I, that is pulmonary arterial hypertension.

Furthermore, pulmonary hypertension is scored based on the severity of specific symptoms into four different World Health Organisation (WHO) functional classes [6] [7]:

WHO functional class I: Patients with pulmonary hypertension, but without resulting limitation of physical activity.

WHO functional class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity, being comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue.

WHO functional class IlI: Patients with pulmonary hypertension resulting in marked limitation of physical activity.

WHO functional class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms.

This system helps clinicians to guide their decisions regarding appropriate treatment and

accurate assessment of prognosis. The functional status, the levels of PVR and mPAP ultimately determine the outcome and treatment of patients with pulmonary arterial hypertension.

In the last 20 years there has been progress in the management of pulmonary hypertension with the introduction of many modalities of treatments including drugs, and interventions. However, despite this progress we still have no cure for pulmonary hypertension, other than lung transplantation, and more works are needed.

Pathology

The main pathology of pulmonary hypertension **is** the proliferation and remodelling of small pulmonary arteries of 500 µm down to 20 µm. It is often associated (*in situ*) with thrombotic lesions and with different perivascular types of inflammatory cells. These will cause stiffening of large elastic arteries, mainly lobar and segmental pulmonary

arteries. Although these pathological changes are common in most types of pulmonary hypertension, the causes and molecular changes and types of changes in the pathology can vary according the aetiology.

The remodelling causes construction and lose of vascular reactively which results in the rise in pulmonary arterial pressure and an increase in PVR, remodelling, and altered pulmonary vascular hemodynamic [8– 10].

Natural history of pulmonary hypertension

Pulmonary Hypertension is a progressive condition that eventually increases the burdens on the right ventricle leadings to hypertrophy and failure. It does not determine symptoms in the early and intermediate stages if not diagnosed early. If left untreated, patient condition can deteriorate rapidly, leading to signs of right ventricular failure [11– 13]; see **Figure 1**.
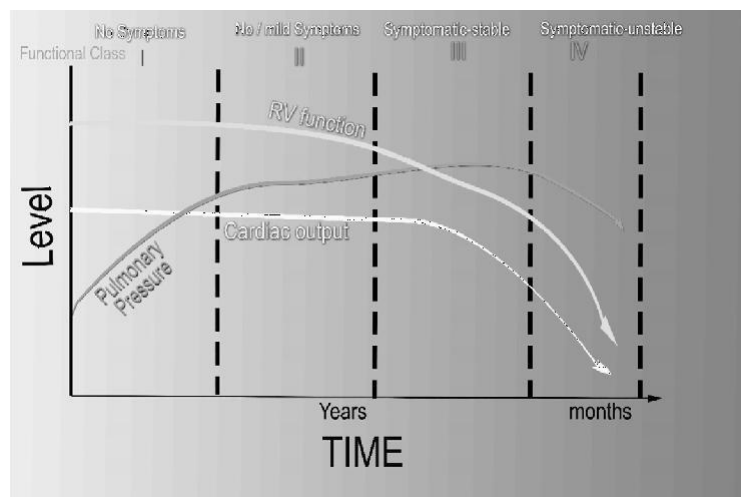

Figure 1 – schematic representation of the natural history of pulmonary hypertension

Management approach

Pulmonary arterial hypertension remains a challenging disease. In most patients a meticulous approach is necessary to arrive at the correct diagnosis, i.e. excluding PH due to left heart disease, PH due to lung disease, PH due to chronic thromboembolic disease. Clinical diagnoses started with a routine investigation like history and highly suspicious of pulmonary hypertension, as the symptoms are often nonspecific. Clinical examination involves signs of right heart failure, the accentuated pulmonary component of the second heart sound and a pansystolic murmur of

tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Chest Radiography, Electrocardiography, Echocardiography and Pulmonary Function Tests are the minimum early diagnostic work up. Routine clinical examination like a blood test pulse oximetry, assessment of arterial gases and measurement of brain natriuretic peptide (BNP) levels. BNP levels are often elevated in patients with pulmonary hypertension, loosely correlate with the severity of right ventricular hypertrophy and failure, allows an assessment of prognosis and thus predictive of clinical outcomes. Finally, If pulmonary hypertension is suspected then

right heart catheterisation is essential to confirm and grade the severity of the hemodynamic derangement, with appropriate and accurate measurement of all elements of pulmonary pressure and wedge pressure; and assessment of vasoreactivity testing. genetic assessment to rule out any family history is also essential.

It's vital to assess the functional capacity of the patient who is diagnosed with pulmonary arterial hypertension to help with further follow up and part of the routine assessment of the medications, the most common, easy to perform and inexpensive is the 6-minute walking test (6MWT). This is a submaximal exercise testing. The 6MWT must always be interpreted with the clinical context. The absolute values, but not changes in 6MWD, provide some prognostic information, further detail of the 6MWT is beyond the scope of the article, but can be found more in these references [14–17].

Although cardiopulmonary exercise testing as a maximal exercise test and provides important information on exercise capacity, this test is not commonly used because of expenses and a need of standardisation and expertise [18]. Recently, some cents started to use cardiovascular diagnostic technique like CMR and PET scanning, especially for the assessment of and measurements of right ventricular function and structure.

Current guidelines provide a detailed diagnostic algorithm and risk stratification for the diagnosis and a long-term management of patients with pulmonary hypertension, which can be consulted in these resources [5,19,20].

Finally, the management of patients with pulmonary hypertension, including confirmation of the diagnosis, start of management and long term follow up should always be done in a well-trained, specialised and designated centres. Many countries have already established such centres.

Treatment of pulmonary arterial hypertension The therapy for pulmonary arterial hypertension has evolved in the past two decades and is characterised by a complex strategy that includes the initial evaluation of severity and the subsequent outcomes, rather than just drug prescriptions. There are general management issues like lifestyle, pregnancy, birth control and post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to treatments, genetic counselling and travels. Supportive therapy should also be considered like the use of anticoagulants, diuretics, oxygen, digoxin [5]. Anticoagulants might be

warranted because of a high prevalence of vascular thrombotic lesions in patients with pulmonary arterial hypertension and as an adjunct treatment to prevent risk of catheter-associated thrombosis during treatment of specific intravenous treatment with Epoprostenol [21].

Decompensated right heart failure leads to fluid retention, therefore some centres may prescribe diuretics and even digoxin and other cardiovascular drugs. This is an empirical approach as there is yet no evidence-based data of their clinical benefit [22].

There are no sufficient data to support the clinical benefit of long-term oxygen administration in patients with pulmonary arterial hypertension, except in a certain condition where occasional use of oxygen may be clinically warranted [23].

Currently approved drugs Calcium channel blockers

Calcium channel blockers were the first drugs introduced to treat pulmonary hypertension [24,25], with a high dose of nifedipine, diltiazem or amlodipine. The current recommendation is that only patients who show a significant vasoreactivity testing can be prescribed calcium channel blockers. These are the only specific patients with pulmonary hypertension who may benefit. Therefore, this class of drugs should not be considered as the first-line therapy [5,25,26].

Restoring prostaglandins of the endothelial cells

Prostacyclin is a potent pulmonary and systemic vasodilator and an inhibitor of platelet aggregation. It is well known that endothelial cells of blood vessels in pulmonary hypertension produced less endogenous prostacyclin [27,28]. This led to the suggestion that prostacyclin administration will be beneficial as it may compensate for that decrease. During the 1990s a synthetic prostaglandin I2 (PGI2) were suggested for the treatment of pulmonary arterial hypertension and was supported by three unblinded clinical trials that showed an improvement of symptoms, exercise capacity, haemodynamic and a reduction of mortality [29–31].

The first commercially available compound was an intravenous formulation of Epoprostenol (known commercially as Flolan® (GlaxoSmithKline) or Veletri® (Actelion). Generic formulation is also available now. These formulations came in different size and packaging. Epoprostenol has a very short half-life of 2–3 min. This compound needs special diluent. Therefore the administration will be by continuous IV infusion through a central venous

catheter using an ambulatory infusion pump. The drug needs to be continuously infused for 24 hours. A special care for preparation and to prevent the risks of infection and thrombosis, blocking of the catheter and the adequate functionality of the pump. Abrupt interruption of the Epoprostenol infusion should be avoided, because in some patients this may lead to a pulmonary hypertension rebound with symptomatic deterioration and even death. Thus, the administration of this medication needs a special trained enters and adequate patient training. The started dose of 2–4 ng/kg/min, which can be increased gradually. The average dose used is 20 and 40 ng/kg/min. The main adverse effects are related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis.

Treprostinil is another prostaglandin analogue, with enough chemical stability to be administered at ambient temperature. Either intravenously or subcutaneously, making it relatively easier to administer [32–35]. The optimal dose varies between 20 to 80 ng/kg/min. The common adverse effects when admitted subcutaneously are infusion site pain and bleeding. Inhaled and oral form of this medication are also available in some countries [36,37].

Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral or aerosol administration. The inhaled formulation (brand name Ventavis®) is the most common formulation used today [38,39]. It needs a daily repetitive dosing (six to nine times of 2.5–5 μg per inhalation, median 30 μg daily) [40,41].

Oral prostaglandin analogues are also available. Beraprost was launched in Japan and Korea, but due to long term inefficiency it is now unavailable [42–44].

Selexipag is a new oral formulation with a selective prostacyclin IP receptor agonist, but structurally unique from prostacyclin [45,46]. It has recently been approved with the brand name of (Uptravi®). GRIPHON study [47,48], which is one of the largest clinical trials in pulmonary arterial hypertension (enrolled 1,156 patients) showed a 40% risk reduction in the composite endpoint of death or a complication related to pulmonary hypertension in both naïve patients (patients who were not yet on any treatment for pulmonary hypertension) and those on the background medical therapy. The initial dose of 200 μg twice daily, and can be escalated to the highest tolerated dose of 1600 μg twice daily. Thai main side effects are like other prostacyclin therapy, mainly headache, diarrhoea as well as muscle and joint pain.

Restoring Cyclic GMP in the endothelial cells

It was noticed the reduction in the expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension [49], consequently reducing the level of cyclic guanosine monophosphate (cGMP). cGMP regulates many cellular functions, ranging from contractility to growth [50,51]. Therefore, enhancing the level of cGMP can be beneficial to ease the increase in pulmonary pressure.

There are many ways to increase the cGMP level. The first is inhibition of the enzyme that inactivates and degrades cGMP; mainly Phosphodiesterase 5 (PDE5). Many drugs (now called PDE5 inhibitors) were introduced; the most common are sildenafil, vardenafil, and tadalafil. PDE5 inhibitors have become the leading oral therapy for pulmonary hypertension worldwide, especially in the developping world, mainly due to the availability at a reasonable price compared to other classes of pulmonary hypertension-specific drugs. However, PDE5 inhibitors are not universal and its effects depend on the aetiology. They are most effective in idiopathic and primary pulmonary hypertension. PDE5 inhibitors are less effective in other forms, such as for patients with pulmonary arterial hypertension due to sickle cell anaemia.

Sildenafil is an orally active, potent and selective PDE5 inhibitor [52]. It is approved for the treatment, patients with pulmonary arterial hypertension in WHO functional class II–III in Europe and WHO functional class II–IV in the USA as per the SUPER-1 and SUPER-2 clinical trials [53,54]. The recommended dose is 20 mg three times a day. The main side effects related to vasodilation (headache, flushing, epistaxis and hypotension).

Tadalafil is another oral PDE5 inhibitor like sildenafil, but with a longer half-life, thus a once-daily dosing (of 2.5, 10, 20 or 40 mg). It is approved in the USA, Europe and several other countries for the treatment of patients with pulmonary arterial hypertension with WHO functional class II–III based on the results of PHIRST-1 and PHIRST-2 clinical trials [55–57]. The side-effect profile is like that of sildenafil.

Vardenafil another oral PDE5 inhibitor given twice-daily (5 mg). It showed favourable results on exercise capacity, haemodynamic and time to clinical worsening [58,59]. The side-effect profile like that of other PDE5 inhibitors.

Another modality to increase cGMP level is by stimulating the enzyme that helps in producing it, mainly soluble guanylyl cycles (sGC). The main example of this class of drugs (called sGC

stimulator) is Riociguat. This drug was found efficacious in improving exercise capacity, haemodynamic, WHO-functional class and time to clinical worsening [60–62]. The recommended dose is up to 2.5 Mg three times a day. The most common serious adverse events are syncope bleeding, hypotension, and headache. Riociguat is the only pharmacotherapy to be approved for the treatment of two pulmonary hypertension indications, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (CTEPH) (61). Combination of sildenafil with Riociguat can cause severe hypotension; thus, it is recommended not to combine these two drugs.

The third method to enhance cGMP is by introducing Nitric Oxide gas (NO). It is an endogenous gas produced by vascular endothelial cells enzyme NO synthase. This raises the concentration level of intracellular cGMP enhancing the vasodilatory and antiproliferative activities. Nitric oxide has been used as a therapeutic option of pulmonary hypertension since 1990s [63,64], especially in paediatric age group, intensive care or post-operative period. The administration can be via face mask or nasal prong connected to a cylinder (can be a mobile cylinder) or via a centralised system in some hospitals.

Inhibiting Endothelin receptors

Endothelins (ET) are endogenous peptides. It is produced primarily in the endothelium and are very potent vasoconstrictors when binds with either ET-A and ET- B receptors [65,66]. Various studies support a prominent role for the endothelin system in the pathogenesis of pulmonary arterial hypertension [67]. Thus, inhibition of these receptors can alleviate pulmonary hypertension symptoms. Many drugs (commonly referred as an Endothelin Receptor antagonist (ERA) were approved for the management of pulmonary arterial hypertension.

The first drug introduced in this class was Bosentan [68]. It is an oral active dual endothelin receptor (ET-A and ET-B) antagonist. Various clinical trials (BREATHE- 1BREATHE-2, BREATHE-5, EARLY, and COMPASS 2) showed improvement in exercise capacity, WHO functional classes and haemodynamic [69]. It is approved in 2001 in the USA but now available in many parts of the world. It is an oral medication with the initial dose of 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily. The main side effects are anaemic; diarrhoea; gastrointestinal disturbances, flushing; and headache. It is important to note that this drug

may cause hepatic disorders. Thus, liver function testing should be performed monthly in patients receiving Bosentan.

The second drug introduced in this class was Ambrisentan, which preferentially binds with endothelin receptor type A [70]. Ambrisentan has been evaluated in two clinical trials that have demonstrated efficacy on symptoms, exercise capacity, haemodynamic and time to clinical worsening in patients with pulmonary arterial hypertension [71,72]. It is given once daily (5 mg), but can be increased to 10 mg once daily. The side effects are mainly peripheral oedema, abdominal pain; anaemia; gastrointestinal disturbances, bleeding, headaches and hypersensitivity. The incidence of abnormal liver function tests ranges from 0.8 to 3%, but monthly liver function assessment is not recommended in some countries.

The most recently introduced drugs of in this category are the dual ERA, Macitentan [73,74]. The Clinical trials showed a significant reduction in the composite endpoint of morbidity and mortality and increased of the exercise capacity among patients with pulmonary arterial hypertension [75,76]. These benefits were shown in patients who had not received treatment previously and for those receiving additional therapy for pulmonary arterial hypertension. The current recommended dose is 10 mg daily. Its main side effects are anaemia; headache; increased risk of infection; nasal congestion, but liver toxicity was not a significant finding.

Current strategy for the treatment of pulmonary arterial hypertension

The current strategy to treat patients with pulmonary arterial hypertension is to initiate the drug therapy as early as possible and to adopt combinational therapy using two or more classes of drugs simultaneously [77–82]. Combination therapy reduces the risk of clinical worsening, increases the 6MWD,reduces further the mean PAP and PVR, but the reduction in all-cause mortality was not statistically significant [82] if applied early in naïve patients [20]. The combination therapy may be applied initially (i.e. upfront) or sequentially. There is no clinical study to compare the best combination, as this depend on the aetiology and the stage of the disease, as well as the tolerance to any medication. It is an empirical decision of the treating physicians.

The early initiation of the medication or upfront combination therapy has been recommended by many trails (54,77,81,83), however this strategy still need further evaluation [20].

Future potential drugs for the treatment of pulmonary arterial hypertension

Despite recent advances in pulmonary arterial hypertension treatment, this condition is still characterised by an extremely poor prognosis. The currently used drugs described above did not show a significant improvement of mortality, though there were improvement of quality of life and symptoms.

Therefore, a move to more drugs effect on the core pathogenesis of pulmonary hypertension. There now current efforts to test drugs that affect genetically determined mechanisms or epigenetic modification of pulmonary arterial hypertension. Also, drugs that antagonise various growth factors, repair the DNA damage, modulation of metabolism, oxidative and hypoxic stress or influencing the Inflammation and immune reaction. The subject is beyond the scope of this article, but more can be found in these reviews [84–86] .

Other non-pharmacological treatment tools

Clinicians always face with patients who are not adequately managed with the current medical therapy. Therefore, many modalities and intervenetion were adopted or used with various degrees of potential success [84].

Balloon atrial septostomy [85] is a procedure where a small hole is made in the wall between the left and right atria of the heart using a cardiac catheter to reduces the pressure in the right side of the heart, thus decompress the right heart chambers and increase left ventricular preload and cardiac output [86].

In severe cases of non-responded patients lung or a heart-lung transplantation is recommended. The overall 5-year survival following transplantation for pulmonary arterial hypertension in experienced centres was considered to be 45–50%, with evidence of continued good quality of life [87,88].

There is however now potential intervention which is still in early trials like pulmonary artery denervation [89] or stem cell therapy [90,91].

Table 1 – Updated clinical classification of pulmonary hypertension (2)

Group 1 Pulmonary Arterial Hypertension

1.1 Idiopathic Pulmonary arterial hypertension

1.2 Heritable Pulmonary arterial hypertension

1.3 Drug- and toxin-induced Pulmonary arterial hypertension

1.4 PAH associated with:

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart disease

1.4.5 Schistosomiasis

1.5 Pulmonary arterial hypertension long-term responders to calcium channel blockers

1.6 Pulmonary arterial hypertension with overt features of venous/capillaries (PVOD/PCH) involvement

1.7 Persistent Pulmonary hypertension of the new-born syndrome

Group 2 Pulmonary hypertension due to left heart disease

2.1 Pulmonary hypertension due to heart failure with preserved left ventricular Ejection fraction

2.2 Pulmonary hypertension due to heart failure with reduced left ventricular Ejection fraction

2.3 Valvular heart disease

2.4 Congenital/acquired cardiovascular conditions leading to post-capillary Pulmonary hypertension

Group 3 Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Obstructive lung disease

3.2 Restrictive lung disease

3.3 Other lung disease with mixed restrictive/obstructive pattern

3.4 Hypoxia without lung disease

3.5 Developmental lung disorders

Group 4 Pulmonary hypertension due to pulmonary artery obstructions

4.1 Chronic thromboembolic Pulmonary hypertension

4.2 Other pulmonary artery obstructions

Group 5 Pulmonary hypertension with unclear and/or multifactorial mechanisms

1.1 Haematological disorders

1.2 Systemic and metabolic disorders

1.3 Others

1.4 Complex congenital heart disease

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