Current approach to the treatment of pulmonary arterial hypertension and our experience in the Cardiology Department of Ege University Faculty of Medicine

Pulmoner arteryel hipertansiyon tedavisine güncel yaklaşım ve Ege Üniversitesi Tıp Fakültesi Kardiyoloji Kliniği'nin deneyimi

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Pulmonary arterial hypertension is a progressive disease marked by increased pulmonary artery resistance leading to right heart failure and has very high mortality. Survival rates have somewhat improved in recent years due to the development of new drugs and early diagnosis. This review aims to summarize the current therapeutic approach to pulmonary arterial hypertension and to share our experience at our center.

Key words: Hypertension, pulmonary/drug therapy; pulmonary artery.

Artmış pulmoner vasküler direnç nedeniyle sağ kalp yetersizliğine yol açan ilerleyici bir hastalık olan pulmoner arteryel hipertansiyonda mortalite yüksektir. Son yıllarda geliştirilen ilaçlar ve erken tanı sayesinde bu hastalarda hayatta kalım süresinde belirgin uzama elde edilmiştir. Bu derlemede, pulmoner arteryel hipertansiyon tedavisine güncel yaklaşım, kendi deneyimimiz de paylaşılarak aktarılmıştır.

Anahtar sözcükler: Hipertansiyon, pulmoner/ilaç tedavisi; pulmoner arter.

Pulmonary artery hypertension (PAH) is a term used to describe a group of progressive diseases which lead to right heart failure due to increased vascular resistance, despite normal pulmonary capillary wedge pressure. [1-12] It is a rarely disease with a very high mortality rate.

The mean treatment-free survival following the diagnosis of idiopathic PAH was 2.8 years.[3] This very high mortality rate is attributed to the normal course of the disease and frequent diagnosis only at the late stage.[4-6]

In this review we present current treatment approaches to PAH, our clinical experiences and comments. It is important to discuss the difference of PAH with the other types of pulmonary hypertension when discussing treatment measures. Pulmonary hypertension is divided into five groups according to similarities in the pathophysiology and treatment responses (Table 1). Pulmonary artery hypertension is the first of these five subgroups. Accordingly, PAH includes idiopathic PAH (previously termed primary) and hereditary PAH with concomitant connective tissue disease, HIV, congenital heart disease or portal hypertension-associated PAH, drug and toxin-associated PAH. PAH is defined as a mean pulmonary artery pressure (PAP) of >25 mmHg obtained at rest or of >30 mmHg on exertion, measured by cardiac catheterization and in the absence of any severe left heart disease, pulmonary disease or chronic thromboembolism. However, in order to make a diagnosis of PAH the pulmonary capillary wedge pressure should be normal (<15 mmHg).[2] At the 4th World PAH Symposium organized in Dana Point 2008, recommendations were made to define a mean PAP of 20-25 mmHg as pre-pulmonary hypertension. However, in the latest ACC/AHA pulmonary hypertension guidelines published in 2009, this recommendation did not gain approval.[12]

Pulmonary artery hypertension is a progressive clinical picture characterized by marked vasoconstriction in the pulmonary artery, vascular remodeling/reconstruction and thrombosis.[1] Physiopathologically three systems are affected; including the endothelin system, prostacyclin pathways and the nitric oxide/cGMP pathway. Great success has been achieved in the treatment of PAH through the development of new drugs (Table 2) for these three different physiopathological pathways.[5,7] Early treatment has especially been know to significantly prolong survival in patients with PAH.[5,7] Although not con-

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sidered in the same group with PAH, these new drugs have also been considered to be beneficial in the management of chronic thromboembolic pulmonary hypertension (CTEPH) cases who have not undergone endarterectomy.[8] This is due to triggering of a pathophysiologic process similar to that of chronic thromboembolism, leading to increase in PAP.[9]

Current treatment of PAH can be classified under four topics: (i) conventional, (ii) treatment oriented towards the physiopathology of the disease, (ii) treatment oriented towards the etiopathology, and (iv) other treatments. All treatment approaches are aimed at alleviating symptoms, increasing quality of life and prolonging survival.

Conventional treatment and life style changes

Theoretically, vasodilator agents are expected to be beneficial in the management of pulmonary artery hypertension, since the underlying pathologic picture involves a combination of smooth muscle cell hypertrophy and vasoconstriction.[10] As a result, calcium channel blockers (CCB) have been used for several years. However, CCB have been beneficial in only a highly selected small number of patients. In a retrospective evaluation performed by Sitbon et al.[11] on 557 patients detected with vasoreactivity, initiation of CCB provided only a 6.8% clinical improvement. These were patients in the early stage of the disease when there was possible reversion of vasoconstriction. Vasoreactivity testing should thus be performed before initiating treatment to determine whether or not the increase in pulmonary vascular resistance is permanent at the early stage of the disease; in other words, whether or not CCB would be beneficial (Table 3). The test was considered to be successful if during the test the response to short acting selective vasodilators (adenosine, nitric oxide, prostacyclin, or iloprost) was in the form of mean PAP decrease of 15-20% before a decrease in cardiac output, or at least a 10 mmHg decrease compared to the baseline value and a decrease of mean PAP below 40 mmHg as absolute value.[10,11]

Results obtained from patients who were follow-up in our center demonstrated a positive vasoreactivity testing in patients at the early stage of the disease and more beneficial response to CCBs. According to guidelines vasoreactivity testing may not be performed under conditions where chronic CCB treatment can not be implemented, such as marked left heart failure or presence of hemodynamic instability. However, under the drug refund scheme the Social Security Institution has made vasoreactivity testing compulsory for drugs presently used in Turkey.[12] The CCB, verapamil is not preferred in the treatment of PAH due to its negative inotropic effects. There not enough data concerning the use of new generation CCB in the treatment of PAH. Studies recommend starting with low doses (30 mg nifedipine SR 2x1 or 60 mg diltiazem 3x1) and to increase dosage to the patient's maximum tolerable level. The recommended highest doses are 240 mg/day for nifedipine and 900 mg/day for diltiazem (Table 3). On the other hand, beneficial results are obtained with CCB during the early stages of idiopathic PAH; however, CCB are generally not effective in the treatment of PAH associated with scleroderma and congenital heart diseases.[13]

There is a risk of pulmonary thromboembolism in patients with PAH due to in situ microscopic thrombosis observed in the physiopathology of the disease and also

Table 1. Classification of pulmonary hypertension*

1. Pulmonary artery hypertension (PAH)
   - Idiopathic PAH
   - Hereditary PAH
   - Drug and toxin-associated PAH
   - PAH associated with other diseases
     - connective tissue disease
     - HIV
     - Portal hypertension
     - Systemic-pulmonary shunt
     - Sistomiasis
     - Chronic hemolytic anemia

1. Pulmonary venooclusive disease – pulmonary capillary hemangiomatosis
2. Pulmonary hypertension (PHT) associated with left heart failure
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular heart diseases
3. Pulmonary diseases / PHT associated with hypoxia
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Other pulmonary diseases
   - Sleep apnea syndrome
   - Chronic high altitude
   - Developmental lung abnormalities
4. Chronic thromboembolic PHT
5. The other group
   - Hematologic disorders (myeloproliferative, splenectomy, etc.)
   - Systemic disorders (vasculitis, sarcoidosis, histiocytosis, neurofibromatosis)
   - Metabolic diseases (glycogen storage diseases, Gaucher's disease, thyroid disorders)
   - Congenital heart diseases (excluding shunt)
   - Others (tumor obstruction, fibrosing mediastinitis, hemodialysis, etc.)

*4th World PAH Symposium organized in Dana Point, 2008.

Table 2. Drugs and dosages used in the treatment of pulmonary artery hypertension

Calcium channel blockers (to be used only if the vasoreactivity test is positive)	
Nifedipine SR	Starting dose of 30 mg 2x1 Increased to target dose within weeks (240 mgr/day)
Diltiazem	Starting dose of 60 mg 3x1 Increased to target dose within weeks (900 mg/day)
Prostacyclin and analogs	
Epoprostenol (Flolan)	Starting dose of 1-2 ng/kg/min Increase dose of 1 ng/kg/min every 15-30 min (until side effects develop, normally 10 ng/kg/min), and later increased dosage every 3 months or according to the clinic. Ideal dosage 22-45 ng/kg/min
Iloprost (Ventavis)	2.5 Ìg/day in 6-9 times inhalations Increased to supplementary dose of 5 Ìg/day, 6-9 times if tolerable
Treprostinil (Remodulin)	Starting dose of 1.25 ng/kg/min, increases by maximum dose of 1.25 ng/kg/min every week, for 4 weeks, and later maximum weekly dose of 2.5 ng/kg/min
Beraprost	Starting dose of 20 Ìg 4x1 orally Increased to 20 Ìg/daily if tolerable
Endothelin receptor antagonists	
Bosentan (Tracleer)	Starting dose of 62.5 mg 2x1 orally Increased to supplementary dose 4 weeks later (125 mg 2x1)
Ambrisentan (Letairis)	Starting dose of 5 mg/day orally Supplementary dose of 10 mg/day if tolerable
Sitaxsentan (Thelin)	100 mg/day orally
Phosphodiesterase inhibitors	
Sildenafil (Revatio)	20 mg 3x1

to stasis associated with right heart failure. As a result, anticoagulant therapy (warfarin INR 1.5-2.5) is recommended for all patients with PAH, in the absence of any clinical contraindication. [13,14] However, the high risk of gastrointestinal hemorrhage should be taken into consideration in patients with portopulmonary hypertension and scleroderma. The practical approach in our center is to maintain INR in the range of 2.5-3.0 in patients with PAH and CTEPH; however, in patients with portopulmonary hypertension and scleroderma precaution is taken to keep INR below 2.5. On the other hand, bleeding from the pulmonary artery is one of the most common causes of mortality in patients with PAH associated with congenital heart diseases. As a result, anticoagulation in these patients should also be approached with great care.

Supplementary oxygen therapy is recommended in patients with PAH to maintain oxygen saturation >90%, since hypoxemia is a very strong pulmonary vasoconstrictor agent.[13] Patients should be evaluated especially for possible hypoxia during sleep. However, the benefit of oxygen therapy is controversial in patients with advanced Eisenmenger syndrome.

Diuretics are recommended in the presence of symptoms of right heart failure (peripheral edema, ascites, etc.).[13] Diuretics should be initiated in low doses and attempts should be made to maintain the intravascular volume within normal limits, with close monitoring of renal functions. Digoxin can also be used in the presence of treatment-resistant right heart failure or atrial fibrillation; however, there are limited study data on this subject.

Table 3. Vasoreactivity testing and drugs used during the test

Nitric oxide	10-20 ppm dose Given as an inhalation for 5 min.
Adenosine	Starting with a dose of 50 Ìg/kg/min, and increasing dosage every 2 minutes until side effects or hypotension develop or up to a dose of 200-250 Ìgr/kg/min.
Epoprostenol	Starting with an infusion dose of 1-2 ng/kg/min, and then increasing dosage of 2 ng/kg/min every 5-10 minutes until significant decrease in blood pressure, increase in heart rate, or development of side effects (nausea, vomiting).
Positive response	≥10 mmHg decrease in mean pulmonary artery pressure and a fall of below 40 mmHg level together with increased or stable cardiac output.

As part of conventional therapy in all patients diagnosed with PAH, quality of life management is also a recommended approach. As a precaution from the risk of hypoxic pulmonary vasoconstriction these patients should primarily refrain from living at high altitudes and should not go on long flights above 2000 meters. If a long journey by plane is compulsory patients should be advised to take along some oxygen support. Heavy physical activity and isometric exercises should be avoided since they can lead to syncope. However, they should be encouraged to do tolerable light aerobic exercises (walking, etc.). A diet low in sodium should be given especially to those with a risk of right heart failure. Influenza and pneumococcal vaccines should be administered against airway infections. The use of decongestants together with anorexigens should be prohibited. Birth control should be advised for young PAH patients and general anesthesia should be avoided. Psychosocial support should also be included in the patient's treatment. Psychosocial support has been defined as social support and educational programs which should be provided by specialized individuals and institutions, also including the family and friends.[12]

Drugs directed towards the physiopathology of pulmonary artery hypertension

Prostacyclin and analogs. Prostacyclin production is found to be reduced in patients with pulmonary artery hypertension.[15] Prostacyclin is a strong vasodilator and at the same time inhibits vascular proliferation and platelet aggregation. Due to these properties prostacyclin and their analogs are used in the management of PAH.

The synthetic prostacyclin, ***epoprostenol*** (Flolan, Gilead) was the first drug to be approved by the FDA and has thus been through a long experience. Comparison with conventional therapy has demonstrated that it provides significant improvement both in the functional capacity and hemodynamic parameters with a marked increase in the survival rate, in patients with advance idiopathic PAH (functional class IV or right heart failure or patients awaiting lung transplantation).[16] It has also been shown to increase the survival rate in patients with PAH associated with scleroderma, HIV and congenital heart diseases.[17] However, treatment with epoprostenol is very laborious involving continuous i.v. infusion, due to its half life (<6 min). On the other hand, due to the non stable room temperature cold conditions should be provided. The risk of sepsis and i.v. catheter infections (0.1-0.6 cases per patient years) is an important cause of mortality.[16,18] Any development of thrombus in the catheter may also be life threatening due to sudden interruption of drug infusion. The most common side effects include headache, chin pain, flushing, nausea, diarrhea, skin eruptions and muscle pain. Chronic use of this drug has been reported although it is not found in Turkey. A patient with idiopathic PAH was also monitored in our center for approximately 10 years with successful epoprostenol treatment. The patient's sociocultural and financial conditions should be good to enable continuous drug infusion under sterile conditions. Despite these difficulties in its use, it remains the most effective treatment and recommendations are made for the referral of patients with advanced PAH for epoprostenol administration at specialized PAH centers.[16,18]

Iloprost (Ventavis, Schering), is a chemically stable prostacyclin analog with a half life of 20 minutes. It has both inhalation and i.v. forms. Iloprost was first used in Germany, and was demonstrated to provide significant improvement both in the functional capacity and hemodynamic parameters, when compared to placebo in a multicenter European study.[19] Opitz et al.[20] reported an event-free survival of 53% for one year, 29% for two years and 20% for three years in idiopathic PAH patients using iloprost alone. 6-9 times inhalation is recommended during the day when the patient is awake. As in all prostacyclin analogs the most common side effects are coughing, headache, flushing, and chin pain. Its greatest advantage is its lower incidence of systemic side effects. However, its disadvantages included the need for frequent and sustained inhalation and the inability to continue treatment during sleep. Iloprost was approved by the FDA in 2004 for use in patients with PAH functional class III and IV. Iloprost was approved in October 2002 in Turkey by the Ministry of Health for the management of idiopathic PAH, PAH associated with scleroderma, PAH associated with drug use, and lastly in March 2007 for the treatment of CTEPH. However, approval for use in CTEPH patients was later revoked. On the other hand, the drug refund scheme of the Social Security Institution only allows use of iloprost for the management of Class III and IV patients. Our clinical experience has shown that good results are obtained from the use of iloprost inhaler by patients who can practice good inhalation. We prefer administering the intravenous form mostly in decompensated PAH patients who present with right heart failure. Treatment has proven successful in five of the 10 patients whom we treated with inhalation iloprost alone for the past three years. Combination with iloprost inhalation was used as a second drug in the other five patients. Three of these patients were those in functional class IV who died despite the combination therapy. All patients who died were also those who were diagnosed at the advanced stages of the disease.

Treprostinil (Remodulin, United Therapeutics) is a

prostacyclin analog with the longest half life (3-4 hours) and it is stable under room temperature. It was first administered as continuous subcutaneous infusion, with the later development of i.v. infusion, inhaler and oral forms. Although it is not still present in Turkey, application for a licence for its subcutaneous form has been made and it is expected to be in the market within two years. In a multicenter, placebo-controlled study on PAH (idiopathic or associated with connective tissue disease or congenital heart disease, n=470) patients with functional class II, III, or IV, significant improvement was reported in the effort capacity and hemodynamic parameter within 12 weeks, following the administration of continuous subcutaneous treprostinil infusion.[12] However, erythema and severe pain developed at the site of infusion in 85% of the patients independent of drug dose. Administration of topical analgesics and anti-inflammatory drugs has been reported to reduce the severity and frequency of pain to an acceptable level. In 2002 the FDA approved treprostinil as a safe and effective drug in PAH patients (functional class II-IV) who could tolerate continuous subcutaneous treprostinil infusion. Other frequently encountered side effects include headache, diarrhea, skin eruption and nausea. Long term use has been shown to improve survival in addition to improvement of effort capacity.[22] The rebound effect is said to develop immediately after interruption of infusion when i.v. treprostinil is administered, due to its longer half life compared to epoprostenol.[23] The i.v. form of treprostinil was approved by the FDA in 2004 for use in PAH patients with functional class II, III and IV; however, there is no completed long term study on the i.v. form. Studies are continuing following the observation of gram-negative infections of i.v. catheter more frequently with treprostinil, compared to epoprostenol.[24] Phase III studies on the inhaler and oral forms of treprostinil are still underway. Positive results from a just ended pilot study have been obtained especially on the inhaler form.[25]

Beraprost (Toray Industries, New York) is a prostacyclin analog with a short half life (35-40 min), administered orally. Its use has for the time being been approved only in Japan and Korea. In a 12-week placebo-controlled study conducted in Europe, a moderate (25 m) but significant improvement was reported in 13 PAH patients during a 6-minute walking distance.[26] In a 12-month randomized study conducted in the USA improvement was observed in the 6-minute walk test on the 3rd and 6th months; however, this effect was not maintained on the 9th and 12th months.[27] Long term studies are required to enable the extensive use of this drugs.

Endothelin receptor antagonists. Endothelin-1, a strong vasoconstrictor and mitogen is found to be increased in PAH and is associated with the severity of the disease.[1] As a result, endothelin receptor antagonists have been experimented in the treatment of PAH and successive results have been reported. Three endothelin receptor antagonists are currently in use for this purpose. These include bosentan, ambrisentan and sitaxsentan and are orally administered. Bosentan affects endothelin A and B, whereas ambrisentan and sitaxsentan have been shown to block only endothelin A.

Bosentan (Tracleer, Actelion) was produced as the first oral drug in this area and as a drug against epoprostenol due to its effect on endothelin receptor. In the first pivotal efficacy study, BREATHE-1, bosentan was shown to provide marked improvement in the effort capacity and functional class, and a significant decrease in the risk of clinical deterioration.[28] Long term use of bosentan has been shown to prolong survival in patients with idiopathic PAH. As a result, many guidelines have approved the first-line use of bosentan as treatment approach a in PAH patients with functional class III.[13] In the just ended EARLY study bosentan was also shown to be effective when initiated at the early stages (functional class II) in the treatment of patients with PAH.[29]

Bosentan has been in use in Turkey since 2005 for PAH patients. The ministry of Health approved its use in patients with idiopathic PAH and PAH associated with scleroderma in 2005, and patients with PAH associated with congenital heart diseases in February 2008. The starting dose of bosentan treatment is 62.5 mg 2x1 tb. It is recommended to increase the dose to 125 mg 2x1 if no side effects are observed. The main side effect is hepatic function disorder, since it is metabolized by cytochrome P450 enzyme. Increase in transaminase levels was observed in only one of the 21 patients who were treated with bosentan in our clinic; this increase was eliminated by reducing the drug dose to half. The literature study described the hepatotoxic effect as dose-dependent and reported that the rate of three-fold transaminase increase was 10-12%.[28] Monthly monitoring of transaminase levels is recommended during the treatment. Other side effects of bosentan include headache, flushing, edema of the lower extremity and anemia. Another important precaution concerning the use of bosentan is its ability to reduce the effects of oral contraceptives. This demonstrates that PAH patients who are supposed to avoid pregnancy should try other methods of contraception. On the other hand, bosentan is a teratogenic drug. It should not be used together with glyburide and cyclosporine-A due to the high risk of hepatotoxicity from its interaction with these agents. Unlike the other endothelin receptor antagonists, bosentan does not interact with warfarin. Another important side effect requiring great attention

by patients and physicians alike is edema of the lower extremity observed a few weeks after starting the drug, which easily disappears with diuretics. During the last seven years to the beginning of 2008, a total of 21 patients were treated with bosentan in our clinic. The etiologies in these patients were connective tissue disease in four patients, CTEPH in three patients, idiopathic PAH in six patients, portopulmonary hypertension in two patients, and PAH associated with congenital heart disease in six patients. Clinical improvement was reported in 17 patients during the follow-up period, whereas combination therapy was initiated in four patients following inadequate response form treatment. A total of five patients died. Three of these patients died following the lack of clinical improvement from combination therapy. The other two responded well to monotherapy, but one died from sudden death and the other from pneumonia. The common feature observed in the patients who died was the presence of functional class IV at the time of initiating treatment; in other words, treatment was initiated at a very advance stage of the disease.

Ambrisentan (Letairis, Gilead) is a selective endothelin-A receptor antagonist. The drug is not currently used in Turkey. However, it was approved by the FDA in 2007 for the improvement of effort capacity and delay of clinical deterioration in PAH patients with symptoms of functional class II or III. Its effect on the liver function is less than that of bosentan (3.1%) and no drug interactions have been reported apart from a non-significant clinical interaction with warfarin.[30] In the ARIES-1 and ARIES-2 studies ambrisentan administered for 12 weeks to approximately 400 demonstrated a positive effect which increased with dosage, when compared to placebo during the 6-minute walking distance.[31] The most serious side effects were peripheral edema, nasal congestion and sinusitis.

Sitaxsentan (Thelin, Encysive) is a selective endothelin-A receptor antagonist which has been approved for use only in Europe and Canada on patients with PAH. In the first randomized controlled trial (STRIDE-1) during the 6-minute walk test, a marked improvement was observed; however, severe increases in transaminase levels and significant interactions with warfarin (marked increases in INR) were reported in a group administered 300 mg.[32] When lower doses (50 and 100 mg) were administered in the second randomized trial, significant increases were observed in the 6-minute walking distance when compared to bosentan, especially during the 18-week administration of a dose of 100 mg (sitaxsentan 31.4 m, bosentan 29.5 m).[35] Its effect on liver function test when administered at these low doses is less frequently observed compared to bosentan; however, the difference is not statistically significant. The common side effects are headache, peripheral edema, nausea and nasal congestion.

Phosphodiesterase inhibitors. Endogenous nitric oxide provides smooth muscles relaxation and vasodilation by increasing the level of cGMP through activation of intracellular guanylate cyclase. On the other hand, phosphodiesterase eliminates this effect by breaking down cGMP.

Sildenafil (Revatio, Pfizer) is used in the management of PAH as a vasodilator through its effect of preventing the destruction of cGMP and as a result prolonging the effect of cGMP through selective inhibition of phosphodiesterase type 5. It was initially included in the treatment of PAH as a combination treatment to prolong the duration of the effect of short acting drugs such as epoprostenol and iloprost and hence reduce the cost of treatment. However, in the SUPER study monotherapy with sildenafil was reported to improve effort capacity and hemodynamic parameters in 278 patients with idiopathic PAH.[34] In a double blind placebo controlled trial, 20, 40, and 80 mg of sildenafil were administered three times a day to patients with idiopathic PAH or PAH associated with connective tissue disease or corrected congenital heart disease. Following a 12-week administration of the drug the 6-minute walking distance was prolonged 45, 46, and 50 m respectively ($p<0.001$ for all comparisons); however, and no difference was observed during the period till the time of clinical deterioration. The 51 m prolongation of the 6-minute walking distance, compared to the period before treatment was maintained during the one-year study period in patients who completed sildenafil monotherapy. Side effects of sildenafil include headache, flushing, loss of appetite, and epistaxis. In 2005 the FDA approved the use of 20 mg of sildenafil three times a day for the treatment of PAH. The Turkish Ministry of Health has just recently approved the use of sildenafil for the treatment PAH. Three patients who received sildenafil monotherapy were follow-up in our clinic. These were patients with idiopathic PAH, CTEPH and PAH associated with scleroderma all of whom remained in Class-II functional capacity with treatment.

Combination therapy. Using various drugs together in the treatment of pulmonary artery hypertension provides a means for increasing the efficacy of treatment by targeting various pathologic processes, and for reducing frequency of side effects. For example, sildenafil reduces the destruction of prostanoids prolonging their duration of action and providing a synergistic effect. However, care should be taken for possible drug interaction. For example, combination of bosentan and sildenafil increases the effect of bosentan but decreases the effect of sildenafil.[35] Combination therapy should

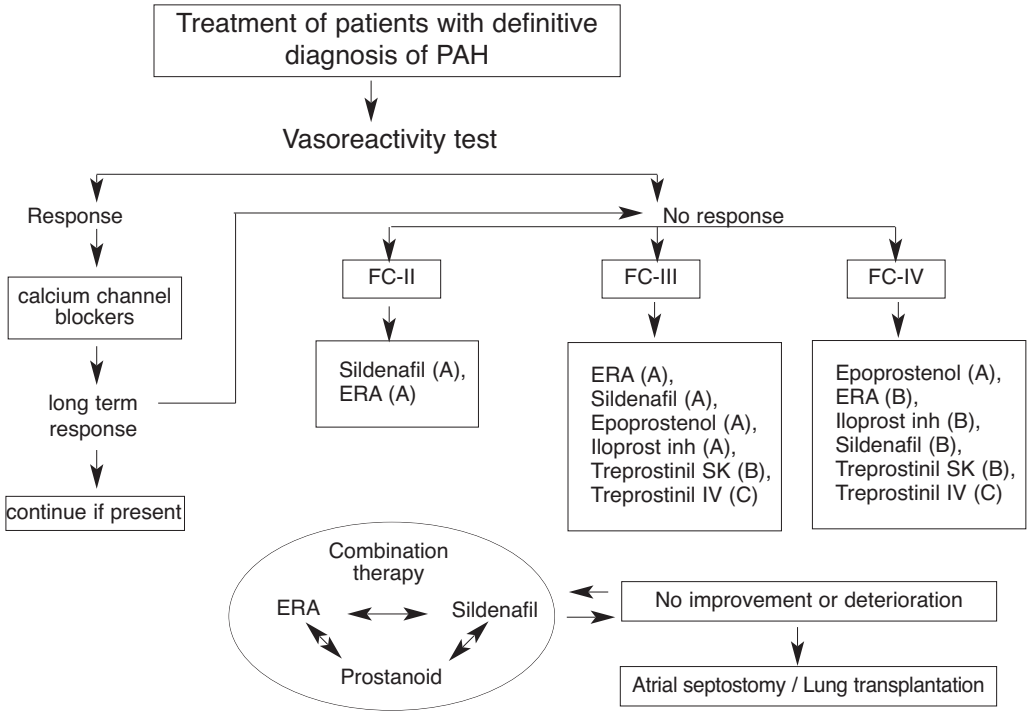

Figure 1. Treatment approach in patients with pulmonary artery hypertension (4th World Pulmonary Artery Hypertension Symposium organized in Dana Point, 2008.). A: strong recommendation; B: moderate recommendation; C: weak recommendation; FC: functional capacity; ERA: endothelin receptor antagonist; SC: subcutaneous; IV: intravenous

be considered if while on monotherapy the patients remains in NYHA functional Class III, or if the 6-minute walking distance is <205 m, or if oxygen saturation falls ≥10% during the 6-minute walk test.[36] Our clinical approach is to start with bosentan or iloprost depending on the indication and according to patient compliance, and to continue with both drugs when no positive response is obtained from monotherapy or if tachyphylaxis occurs; and then to add sildenafil as a third drug in the absence of any response. Figure 1 shows combination outline recommended by various guidelines. Several randomized controlled trials on combination therapy are still underway, which would give way to a better understanding of this subject.

Treatment directed at the disease underlying the etiology of pulmonary artery hypertension

This topic may include interventions to eliminate a shunt during treatment of scleroderma with immunosuppressive and antiproliferative drugs and in cases with congenital heart diseases in the absence of Eisenmenger syndrome.

The basic treatment of chronic thromboembolic pulmonary hypertension is surgery – endarterectomy. Endarterectomy is a life saving surgical approach with a mortality rate of about 20%. However, this rate is reduced to <5% at experienced centers. Attempts to use medical treatment as a bridge to surgery are also made in cases when endarterectomy is not implemented. Results have also been reported concerning the use of epoprostenol,[37] beraprost,[38] inhaled iloprost[39] and sildenafil[40] especially in patients with distal lesions who cannot undergo surgery. However, none of these medical treatments is superior to surgery. Finally, in the BENEFIT trial significant improvement of hemodynamic parameters was obtained in the 16-weeks treatment with bosentan of 150 CTEPH patients; however, no change in the exercise capacity was registered.[41] Medical treatment was administered in patients who were diagnosed in our clinic with CTEPH but who could not undergo endarterectomy. Successful results were obtained after administration of bosentan monotherapy in three of these patients, inhaled iloprost monotherapy in two patients, sildenafil monotherapy in one patient, and iloprost plus sildenafil combination therapy in one patient.

Other treatments

Lung transplantation should be considered in patients with continuous symptoms of functional class III or IV, those with right atrial pressure of >15 mmHg, or in patients with a cardiac index of <21/min/m2, despite treatment. Combination therapy and septostomy may be implemented in patients awaiting transplantation. A single

lung or both lungs can be used for transplantation. Early stage post operative survival in PAH patients is lower than in the other patients who undergo lung transplantation; however, their 5-10 survival rate is similar (50%).[42] On the other hand, it should also be remembered that the average waiting time for transplantation is two year even in the best transplantation centers and at least half of the patients die while still in the waiting for transplantation. It is gratifying to know that the use of prostacyclin and drugs effective for endothelin pathways has reduced the need for lung transplantation.

Developing treatment approaches. New treatment approaches targeted at some mediators which play a role in pulmonary angiogenesis are being developed. Among these are drugs effective on serotonin,[43] vasoactive intestinal polypeptide,[44] Rho-kinase inhibitors,[45] and platelet-originated growth factors.[46] Stem cell transplantation is one of the most promising methods in the treatment of PAH. After successful results from animals studies, the first study on humans was conducted on 31 PAH patients. [47] Significant hemodynamic improvements were obtained by the 12th week during the 6-minute walking distance after administering autologous endothelial progenitor cells. However, there are reservations concerning the safety of these studies which are still at their early stages.

Follow-up and prognosis in the treatment of pulmonary artery hypertension

Prognosis in patients with pulmonary artery hypertension is directly related with right heart failure. As a result clinical and laboratory markers of right heart failure are used to determine the prognosis. Methods used for this purpose include echocardiography, right heart catheterization, B-type natriuretic peptide (BNP) level, and cardiac magnetic resonance imaging. Predictors of prognosis especially during treatment include increase in right atrial pressure, low cardiac index, low mixed venous oxygen saturation, low exercise capacity, functional capacity of class III-IV despite treatment, presence of pericardial effusion and increased BNP levels.

Follow-up indicators of PAH and the frequency of implementation as recommended by the latest guidelines are summarized in Table 4. Right ventricular systolic pressure measured by the commonly used echocardiography during follow-up is not an indicator of the survival rate. However, echocardiographic findings of right atrial dilatation, deviation of the interventricular septum towards the left during diastole (empty or small left ventricle), increased Tei index, and decrease in the tricuspid annular plane systolic excursion (TAPSE) are indicators of right ventricular dysfunction or a poor prognosis.[48,49] A yearly follow-up with cardiac catheterization is indicated in most centers during the treatment PAH. During catheterization it is important to regulate the drug dose especially in patient using i.v. or subcutaneous infusion. It is not recommended to use PAP to follow-up patients treated for PAH. Most centers even discontinue therapy when PAP can not be reduced with vascular protection drugs; whereas there is no such recommendation in the guidelines. Lack of further increases in pulmonary artery pressure is also a response to treatment. The most

Table 4. Follow-up markers, frequency of evaluation and risk levels in patients with pulmonsry artery hypertension

	How often should evaluation be performed?[12]	Low risk (good prognosis)	High risk (poor prognosis)
Findings of right heart failure	Once every 3-6 months	Absent	Present
Improvement of symptoms	During every clinical visit	Slow	Fast
WHO functional class	During every clinical visit	I-II	III-IV
6-min walking distance	During every clinical visit	>400 m	<300 m
Peak VO2 in cardiopulmonary exercise test	No particular recommendation	>10.4 ml/kg/min	<10.4 ml/kg/min.
Echocardiographic findings	Once every 12 months if clinically stable, once every 6-12 months or according to the center's follow-up plan if not stable	Mild right ventricular failure	Pericardial effusion, severe right ventricular dilatation/dysfunction, right atrial dilatation
Hemodynamic evaluation (right heart catheterization)	In case of clinical abnormality or according to the center's follow-up plan	Right atrial pressure <10 mmHg; cardiac index >2.5 l/min/m^2	Right atrial pressure <20 mmHg; cardiac index >2.0 l/min/m^2
B-type natriuretic peptide	According to the center's follow-up plan	Mildly high	Severely high

important factor is to analyze clinical improvement. Investigators recommend discontinuation of treatment in the absence of an improvement also in the clinical parameters and switching to combination therapy.[13] The most commonly used follow-up parameter during clinical trials is the 6-minute walking distance. The 6-minute walk test involves walking for a period of six minutes on a relatively flat and unobstructed surface, under the supervision of a trained nurse. Pulse oxygen saturation and blood pressure are monitored during the test. Walking a distance of less than 380 meters after treatment is an indication of poor prognosis. The cardiopulmonary exercise test is also used for this purpose. However, the test is considered by guidelines to produce very low be safety results in PAH patients when not performed at experienced centers.[13] Pro-BNP is a parameter which is also directly indicative of right ventricular failure; >150 pg/ml during follow-up indicates a poor prognosis.[50]

In our clinic PAH patients are monitored by the 6-minute walking distance and pro-BNP measurement every three months. Echocardiographic evaluations of the right ventricular function of patients undergoing treatment are also performed every 3-6 months depending on the clinical condition of the patient. On the other hand, cardiac catheterization is performed on all patients primarily before treatment and also during diagnosis. Routine follow-up with cardiac catheterization is not implemented. However, catheterization is repeated in case of any abnormality in the patient's treatment response of clinical picture and if there is no reason to explain this condition, or when there is a need to add a second drugs to the treatment or when transplantation is considered.

In conclusion, prolongation of survival and improvements in the quality of life of patients with PAH has been reported during the last 10 years due to advances in treatment approaches. Despite these gratifying results there is still no definite treatment for PAH and many patients are symptomatic despite treatment. More successful results are expected in the coming years from new drugs aimed at different pathophysiologic processes. However, the most important combination in treatment is diagnosis during the early stages of the disease and early initiation of therapy. Implementation of multidisciplinary measures at experienced PAH centers is known to increase the success rate of treatment in patients with PAH.

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