REVIEW

Therapeutic approaches in adults with congenital heart disease-associated pulmonary arterial hypertension

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ABSTRACT: **Pulmonary arterial hypertension is a major contributor to reduced functional capacity in patients with congenital heart disease. Expert care is essential. Whilst careful supportive management has traditionally been the mainstay for these patients, in recent times significant improvements in exercise capacity and even survival have been observed with the use of disease-targeted therapy, including endothelin receptor antagonists, phosphodiesterase inhibitors and prostanoids. In this review we will discuss current therapeutic options and summarise the recent literature on disease-targeted therapy.**

KEYWORDS: Atrial septal defect, congenital heart disease, Eisenmenger syndrome, left-to-right shunt, pulmonary arterial hypertension, ventricular septal defect

Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) has a more favourable prognosis than idiopathic PAH (IPAH) [1]. Notwithstanding, pulmonary vascular disease is present in around a third of patients with atrial septal defect, ventricular septal defect or cyanotic CHD and is associated with significant functional impairment [2]. Patients with untreated systemic-to-pulmonary shunts, consequent PAH and right-to-left shunting (Eisenmenger physiology) are the most physically impaired of the entire CHD group [3] and have a median survival at least 20 yrs less than a healthy individual. Other studies have found a 5-yr mortality rate of >20% [4] with functional class being a major predictor of mortality [5].

Whilst a significant proportion of patients with CHD-PAH can be classified as having Eisenmenger physiology, the majority are not. Other lesions may be simply classified as moderate to large systemic-to-pulmonary shunts without cyanosis, small defects with a clinical course similar to that of IPAH and PAH after corrective surgery. For a more detailed discussion, the recently updated clinical classification formulated at the Fourth World Symposium on Pulmonary Hypertension is a useful reference [6].

Historically, patients with severe CHD-PAH have had limited treatment options available to them;

avoidance of high-risk situations such as non-cardiac surgery, palliation or heart-lung transplantation were the only alternatives. The advent of medications that act on key pathways involved in the pathogenesis of PAH has marked a new era in the management of the disease. Recently, retrospective data have suggested that disease-targeted therapy for patients with Eisenmenger syndrome improve survival, even for patients in New York Heart Association (NYHA) Class III and IV (fig. 1). DIMOPOULOS *et al.* [4] reported that out of 229 patients, 30% of whom were on therapy, 52 died over a median follow-up of 4 yrs. Of those, only two were on disease-targeted therapy even though the treatment group was more impaired at baseline.

Disease-targeted therapies may potentiate protective mechanisms or interrupt key pathogenetic pathways involved in PAH. Apart from vasoconstriction, this disease is characterised by vascular remodelling with smooth muscle hypertrophy and, frequently, thrombosis. In recent years several molecular pathways have been identified that converge to produce these vascular changes. A genetic substrate combined with injury to the pulmonary vascular bed through elevated shear stress leads to an imbalance of vasoconstrictors such as endothelin-1 and vasodilators, including prostacyclin and nitric oxide. In order to address this imbalance, targeted current therapies for
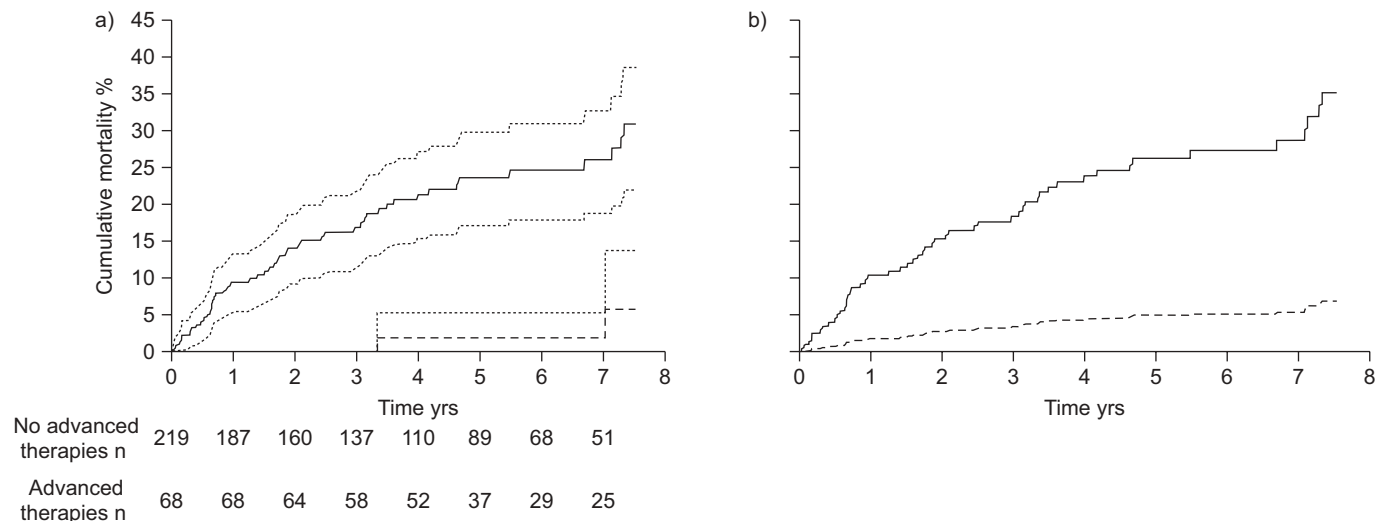
FIGURE 1. a) Unadjusted survival rate curves (with 95% CI: ·······) by treatment with pulmonary vasodilator therapy. p=0.03 with reference to the Cox model. b) Adjusted survival-rate curves based on the propensity score-adjusted Cox model of patients within the third propensity score quartile, with and without pulmonary vasodilator therapy. Quartiles of propensity score are based on the average propensity scores from the 10 imputed databases. p=0.015 with reference to the Cox model. ——: no advanced therapies; - - - -: advanced therapies. Reproduced from [4] with permission from the publisher.

PAH include endothelin receptor antagonists, prostanoids and phophodiesterase inhibitors that potentiate nitric oxide.

Most data investigating disease-targeted therapy has focused on patients with IPAH and PAH associated with connective tissue disease. Apart from substantially different survival prospects, other important differences probably exist between those subjects and patients with CHD-PAH. For example, the right ventricle may be more adaptable to high pressure load in the setting of CHD, especially if the right ventricle has not ''detrained'' postnatally; and in Eisenmenger physiology the failing right heart can ''decompress'' through the intracardiac communication with potential clinical benefit. Because of these and other differences in disease pathophysiology more research specifically examining the effectiveness of therapies in the CHD-PAH group is needed.

CONVENTIONAL THERAPY
General measures
When possible, patients with CHD-PAH should be managed at centres that specialise in the fields of both CHD and pulmonary hypertension. In general, stable patients should be reviewed at least annually. Routine assessment should include careful documentation of functional class, usually a 6-min walk test (6MWT) with monitoring of transcutaneous oxygen saturation to assess and monitor some measure of exercise capacity, electrocardiography, echocardiography to assess ventricular function and estimate pulmonary pressure, full blood count, iron studies and blood chemistry. It is important that patients are well educated about their condition, particularly the avoidance, where possible, of hazardous situations (*e.g.* pregnancy, as noted below).

Volume depletion should be avoided. Pregnancy carries a high probability of mortality (up to 40% with particular risk in the early post-partum period) and should be discouraged [7]. Patients should be advised about safe methods of contraception (barrier methods and progesterone only solutions are preferable

to oestrogen-containing contraceptives) and have regular influenza and pneumococcal vaccinations, as well as endocarditis prophylaxis when indicated. Because of the risk of sudden death, patients with CHD-PAH should be discouraged from vigorous exercise although regular light physical activity is advisable. Patients are susceptible to haemodynamic compromise with the development of tachyarrhythmias and, therefore, these should be treated swiftly. Diuretics may be useful to manage congestion although caution must be exercised to avoid dehydration resulting in dangerously low pulmonary blood flow and cardiac output, as well as increased risk of thrombosis.

Anticoagulation
Because of the increased risk of proximal pulmonary artery thromboses observed in patients with Eisenmenger syndrome [8] some experts recommend routine anticoagulation in this group, however, unlike IPAH (where there is at least historical control data to support the use of anticoagulation [9]), there is currently no evidence to support this practice in the management of CHD-PAH. Moreover, the use of anticoagulation in patients with cyanosis may actually be harmful because of coexistent disordered haemostasis and enhanced risk of uncontrolled bleeding, particularly intrapulmonary haemorrhage [10].

Erythrocytosis
The management of compensatory erythrocytosis in patients with cyanosis has been an area of controversy in recent times. Routine venesection is not recommended and may actually cause harm through iron deficiency and increased risk of stroke [11–13]. Iron deficiency also reduces the oxygen carrying capacity of blood through lowered haemoglobin concentration and this may lead to impaired exercise performance [14]. Conversely, inappropriate or extreme compensatory erythrocytosis may lead to reduced cardiac output [15, 16] and symptoms of hyperviscosity. In the presence of significant symptoms of hyperviscosity and haematocrit >65%, phlebotomy is reasonable ensuring adequate volume repletion and

adequate iron stores, and with careful monitoring of the clinical response.

Oxygen therapy

Nocturnal oxygen therapy has been shown to be of no benefit in patients with Eisenmenger syndrome [17], whilst in other patients with CHD-PAH data are lacking. However, some patients note improved symptomatology with oxygen and it is unlikely to be harmful.

Air travel

Air travel on pressurised commercial aircraft is not contra-indicated in most patients with CHD-PAH. In those with cyanosis, we perform a high-altitude simulation test (HAST) to assess the degree of desaturation that would occur during air travel. If oxygen levels become dangerously low we advise supplemental oxygen for the flight.

Vasoreactivity testing

Vasoreactivity testing during cardiac catheterisation using a non-rebreather mask with 100% oxygen, inhaled nitric oxide, intravenous adenosine or prostacyclin has been used in IPAH as a tool to guide therapy. Whilst even patients with advanced CHD-PAH may demonstrate a significant response during vasoreactivity testing [18], no such role has been described in patients with CHD-PAH to aid decision making for appropriate medical therapy. Notwithstanding, it may be an important tool to assess suitability for surgical repair. In this regard, a reduction in mean pulmonary artery pressure >10 mmHg with a mean pulmonary artery pressure ⩽40 mmHg without a drop in cardiac output is traditionally considered a positive test of vasoreactivity in patients without an important intracardiac shunt; although, levels signifying true reversibility (*i.e.* return to normal pulmonary artery pressure after operation) have not been conclusively established. In the setting of a significant left-to-right shunt, pulmonary arterial pressure will not normalise with disease-targeted therapy. LOPES *et al.* [19] and GIGLIA *et al.* [20] provide a more detailed discussion on this topic, albeit focused on the paediatric population.

Non-cardiac surgery

In patients with Eisenmenger syndrome, perioperative mortality associated with non-cardiac surgery is significant [21] and data has suggested it may account for almost a quarter of deaths in the Eisenmenger group overall [22]. Patients with less severe pulmonary hypertension are also at increased perioperative risk [23]. Surgery should only be undertaken if absolutely necessary. Procedural time should be minimised and the case should be managed by an anaesthetist experienced in the area of CHD-PAH. Perioperative care should occur in a high-dependency area with cardiac monitoring and careful volume management administered by an experienced team. In patients with right-to-left shunting, particular care should be taken to avoid paradoxical air emboli and deep venous thrombosis.

Surgical repair of cardiac defects

An important consideration in many patients with CHD-PAH is whether surgical repair is feasible. A multidisciplinary approach is essential and successful repair is dependent upon the cardiac morphology and whether pulmonary vascular disease is reversible. In general, consideration should be given to closure of a left-to-right shunt if the pulmonary-to-systemic flow ratio is >1.5 and the pulmonary artery pressure is less than two thirds of systemic pressure [24]. The decision regarding surgical feasibility is more complex in patients with higher pulmonary pressure. In brief, a positive vasoreactivity test provides potentially reassuring information about suitability for surgery. For simple lesions, acute balloon test occlusion of a defect without an increase in right ventricular filling pressures or drop in cardiac output is also a useful tool. Even mildly elevated pulmonary vascular resistance in more complex lesions with essentially single-ventricle physiology is a contraindication for conversion to a Fontan-type circulation. The literature that exists in this difficult area has been reviewed comprehensively elsewhere [19, 20]. The potential role of using disease-targeted therapy with the aim of reducing pulmonary pressure pre-operatively to improve operative suitability is an area that is still under investigation [25].

Transplantation

Heart-lung transplantation may be considered in a select group of patients with end-stage disease. Patients with Eisenmenger syndrome that undergo transplantation have a survival comparable to other patients undergoing transplant [26].

DISEASE TARGETED THERAPY

BREATHE (Bosentan Randomised trial of Endothelin Antagonist THERapy)-5 [27] was the first randomised controlled trial designed to demonstrate the benefit of disease-targeted therapy in patients with CHD-PAH (fig. 2), specifically in Eisenmenger syndrome (simple lesions, in subjects without Down syndrome). Subsequently, research in this area has expanded, although randomised controlled data is still lacking. The major trials of disease-targeted therapy in CHD-PAH are summarised in table 1.

Three major classes of drugs currently exist for the long-term management of CHD-PAH, endothelin receptor antagonists, prostanoids and phosphodiesterase inhibitors. Each class has
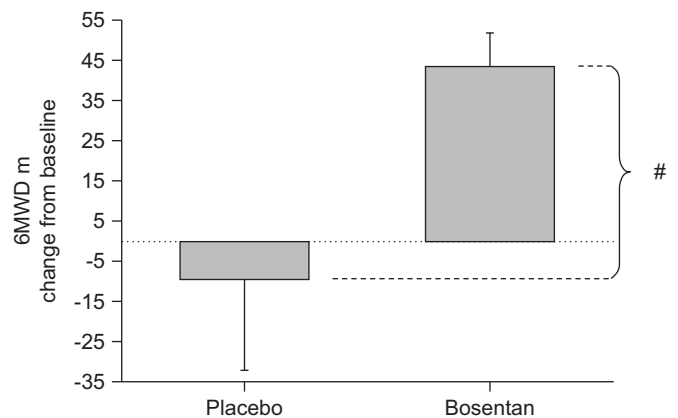
FIGURE 2. Change from baseline of 6-min walk distance (6MWD) in the placebo (n=17) and bosentan (n=37) groups in the BREATHE (Bosentan Randomised trial of Endothelin Antagonist THERapy)-5 study. #: treatment effect=53.1 m, p=0.008. Reproduced from [27] with permission from the publisher.

TABLE 1 Summary of the major trials of disease-targeted therapy in congenital heart disease (CHD)-associated pulmonary arterial hypertension

First author [Ref.]	Year	Drug	Study design	Patients n	Patients with CHD %	NYHA class	Mean age yrs	Outcome[#]	Change in 6MWT m	Follow-up period
CHRISTENSEN [28]	2004	Bosentan	Retrospective	9	100	III/IV	47	NA	Not reported	9.5 months
SCHULZE-NEICK [29]	2005	Bosentan	Open label, prospective	33	100	II-IV	43	Functional class 6MWT Haemodynamics	77	2.1 yrs
GATZOULIS [30]	2005	Bosentan	Open label, prospective	10[¶]	100	III	42	O_2 saturation 6MWT	99	3 months
GALIE [27]	2006	Bosentan	Randomised, double-blind, placebo controlled	54	100	III	37 (treatment arm)	PVR	43	16 weeks
KOTLYAR [31]	2006	Bosentan	Retrospective	23[¶]	100	II-IV	37	NA	0	15 months
BENZA [32]	2006	Bosentan	Retrospective	24	100	II-IV	50	NA	31	1 yr
SITBON [33]	2006	Bosentan	Retrospective	27	100	III/IV	35	NA	66	15 months
D'ALTO [34]	2007	Bosentan	Open label, prospective	22	100	II-IV	38	Functional class Haemodynamics 6MWT O_2 saturation	67	1 yr
APOSTOLOPOULOU [35]	2007	Bosentan	Open label, prospective	18	100	II-IV	22	O_2 saturation 6MWT Functional class Peak exercise capacity	0	2 yrs
DILLER [36]	2007	Bosentan	Retrospective	18	100	III	41	NA	124	29 months
VAN LOON [37]	2007	Bosentan	Retrospective	20	100	II-IV	39	NA	0	2.1 yrs (median)
GATZOULIS [38]	2008	Bosentan	Open label extension of BREATHE-5	37[¶]	100%	III	40	6MWT Functional class	61	40 weeks
BARST [39]	2004	Sitaxsentan 100 mg and 300 mg	Randomised, double-blind, placebo controlled	178	24	II-III	46	Peak $V'O_2$	35 (100 mg) 33 (300 mg)	12 weeks
BARST [40]	2006	Sitaxsentan 50 mg and 100 mg	Randomised, double-blind, placebo controlled	245	11	II-IV	54	6MWT	24 (50 mg) 31 (100 mg)	18 weeks
SINGH [41]	2006	Sildenafil 300 mg	Randomised, double-blind crossover, placebo controlled	10[¶]	100	II-IV	Median 15 (4–35)	6MWT	97	12 weeks
CHAU [42]	2007	Sildenafil 150 mg	Prospective open label	7[¶]	100	Mean 3.3	37	Functional class O_2 saturation Haemodynamics 6MWT	NS 28[†]	6 months
GARG [43]	2007	Sildenafil 300 mg	Prospective, open label	44	48	II/III	26	Functional class O_2 saturation Haemodynamics 6MWT	119	19 months
TAY [44]	2010	Sildenafil 60 mg·day^{-1}	Prospective open label	12	100	III	34	Quality of life O_2 saturation 6MWT	45	3 months

TABLE 1	Continued									
First author [Ref.]	Year	Drug	Study design	Patients n	Patients with CHD %	NYHA class	Mean age yrs	Outcome#	Change in 6MWT m	Follow-up period
MUKHOPADHYAY [45]	2006	Tadalafil	Observational, prospective	16¶	100	II/III	25	Functional class O₂ saturation Haemodynamics 6MWT	43	12 weeks
GALIE [46]	2009	Tadalafil	Randomised, double-blind, placebo-controlled	405	12	II-IV	53	6MWT	33	16 weeks
ROSENZWEIG [47]	1999	Epoprostenol i.v.	Retrospective	20	100	II-IV	15	NA	52	1 yr
FERNANDES [48]	2003	Epoprostenol i.v.	Retrospective	8	100	III/IV	Median 37 (15–57)	NA	299	3 months
SIMONNEAU [49]	2002	Treprostinil s.c. max dose 22.5 ng·kg⁻¹·min⁻¹	Randomised, double-blind, placebo-controlled	470	23	II-IV	44	6MWT	16	12 weeks
TAPSON [50]	2006	Treprostinil i.v. mean dose 41 ng·kg⁻¹·min⁻¹	Prospective, open label	16	13	III/IV	45	6MWT Functional class Haemodynamics	82	12 weeks
LANG [51]	2006	Treprostinil s.c. mean dose 40 ng·kg⁻¹·min⁻¹	Retrospective	99	23	II-IV	47	NA	139	26 months

Drugs were administered orally unless otherwise stated. If trials differed in drug doses, these are specified. Studies that were not entirely comprised of patients with CHD are those by BARST [39, 40], GARG [43], GALIE [46], SIMONNEAU [49], TAPSON [50] and LANG [51]; BREATHE-5: Bosentan Randomised trial of Endothelin Antagonist THErapy-5; NYHA: New York Heart Association; NA: not applicable; 6MWT: 6-min walk test; PVR: pulmonary vascular resistance; V'O₂: oxygen uptake; NS: not statistically significant. #: primary outcome only in randomised controlled trials; ¶: all Eisenmenger; †: actual class not specified.

been shown to cause significant haemodynamic and functional improvement in patients with CHD-PAH (table 1), although the strongest evidence (*i.e.* from a randomised, placebo-controlled trial) exists for bosentan as first-line therapy. Observational data suggest a survival benefit [4], although randomised controlled trials have not yet demonstrated such results.

Whilst most current guidelines recommend the commencement of therapy in class III CHD-PAH patients, the optimal time for introducing therapy is not established. Although BREATHE-5 [27] recruited patients with class III symptoms, many other studies of disease-targeted therapy have included patients with less severe disease (table 1) and shown benefit. Theoretically starting targeted therapies earlier should delay time to clinical worsening. Animal studies also suggest that these treatments may halt or even reverse pathological changes in the pulmonary vascular bed [52]. At this time this issue is unresolved.

Prostanoids
Prostacyclin is an important pulmonary vasodilator with anti-proliferative and anti-platelet activity. Expert consensus recommends intravenous prostacyclin as a first-line therapy in patients with class IV symptoms [53] because of data extrapolated from the IPAH group and other heterogeneous studies.

Whilst prostacyclin and its analogues showed early promise for the long-term management of PAH, chronic use has been limited by difficulties related to cost and means of administration. Inhaled iloprost has a short half-life and requires dosing up to nine times a day. Data in CHD is scarce but iloprost has been shown to improve 6MWT distance and reduce symptoms in patients with IPAH and other secondary forms of pulmonary hypertension [54]. Retrospective data has shown that intravenous epoprostenol improves 6MWT distance, oxygen saturation and haemodynamics in CHD-PAH [47, 48]. While not specifically studied in the CHD population, in heterogeneous groups subcutaneous treprostinil has demonstrated an improvement in 6MWT and haemodynamics along with reduced symptoms [49, 51], as has intravenous administration [50]. Major issues related to requisite parenteral administration include line infection and pain at the injection site in the case of subcutaneous infusion. Intravenous dosing may be complicated by endocarditis as well as thrombosis and, in cases of right-to-left shunt, by paradoxical emboli. Significant gastrointestinal bleeding may also occur with this class of drugs [49].

Endothelin receptor antagonists
Endothelin is a potent vasoconstrictor and mitogen. It mediates its effects through endothelin A and B receptors on vascular smooth muscle and endothelial cells, with the latter receptor also being important for the clearance of endothelin and production of nitric oxide, an important physiological vasodilator. Non-selective and selective receptor antagonists have been developed. Drugs of this class are administered orally. The major side-effect observed is hepatic dysfunction, which occurs in up to 10% of patients on bosentan and less frequently with the selective endothelin A receptor antagonists. [40, 55, 56]. Cessation of treatment because of raised transaminases is rarely necessary [27].

Bosentan is a dual endothelin receptor antagonist. It is the most well-investigated drug in CHD-PAH with robust data to support its use [27–38, 55]. The double-blinded BREATHE-5 trial [27] randomised 54 patients aged >12 yrs with Eisenmenger syndrome to either bosentan or placebo with a 16-week follow-up period. Other key inclusion criteria were World Health Organization functional class III and 6MWT distance between 150 m and 450 m with oxygen saturation between 70% and 90%. Patients were excluded if they had complex CHD or PAH related to a patent ductus arteriosus, a left ventricular ejection fraction <40% and/or significant pulmonary or hepatic dysfunction. Primary end-points were room air oxygen saturations (a safety end-point) and improvement in pulmonary vascular resistance. Secondary end-points included haemodynamic and functional improvement. The trial demonstrated a significant improvement in exercise capacity (fig. 2) and haemodynamics. Open-label, long-term follow-up at 40 weeks showed sustained efficacy [38] although some controversy remains, with other trials up to or exceeding 2 yrs of follow-up failing to find significant benefit [35, 37]. Neither of these trials were of randomised control in design.

Selective endothelin-receptor A antagonists ambrisentan and sitaxentan have a theoretical advantage over dual receptor blockade because type B receptors eliminate endothelin and increase nitric oxide. Whilst trials of the selective endothelin A receptor antagonist sitaxentan have included a small proportion of patients with CHD-PAH and shown benefit with improvement in 6MWT distance, haemodynamics, symptoms and time to clinical worsening [39, 40], data specifically addressing the CHD cohort is lacking at present.

Phosphodiesterase inhibitors

Nitric oxide is a potent vasodilator. It mediates its effects through cyclic guanylate monophosphate within vascular smooth muscle cells. Cyclic guanylate monophosphate is degraded by phosphodiesterases. It follows that inhibitors of these enzymes may mediate a vasodilatory effect on the vascular bed.

Sildenafil has been shown, in a small randomised controlled trial, to improve 6MWT distance, haemodynamics and functional status in 10 Eisenmenger patients [41] and prospective data support these findings [42–44]. A larger randomised trial of 278 patients, including 7% with Eisenmenger syndrome, showed significant benefit after 19 months [57].

Sildenafil is generally well tolerated and rarely causes significant hypotension with careful dose titration. Most common side-effects include headache, nasal congestion and flushing. Serious epistaxis is rarely an issue [57]. At present, the use of bosentan in CHD-PAH is supported by evidence from the only large randomised controlled trial in this group; therefore, sildenafil is often regarded as a second-line agent in patients that have not tolerated first-line therapy. It is sometimes used as an add-on agent in patients without a significant clinical response to bosentan, and the role for combination therapy with sildenafil in CHD-PAH has been supported, although not proven, in a recently published clinical trial in Eisenmenger patients [44].

Recently, tadanafil has emerged as a promising therapy demonstrating significant improvement in 6MWT distance,

haemodynamics and oxygen saturations in patients with CHD-PAH [45, 46].

Combination therapy

Randomised data designed to examine the benefit of combination therapy in CHD-PAH is scarce; however it is reasonable in patients that continue to deteriorate on a single first-line agent to cautiously introduce a second disease-targeted therapy such as sildenafil. A recent randomised, placebo-controlled trial examined whether the addition of sildenafil to bosentan was beneficial in patients with Eisenmenger syndrome. Although additional improvement in 6MWT walk distance was not observed there was a significant increase in oxygen saturations [58]. In a study of 267 patients with PAH that included a small number of patients with CHD (the exact number was not specified), SIMONNEAU et al. [59] demonstrated that the addition of sildenafil to long-term epoprostenol was safe and led to an improvement in 6MWT distance, haemodynamics and delayed clinical worsening. Sildenafil added to bosentan has been shown to improve functional status and 6MWT in patients with IPAH [60], as has sildenafil as an adjunct to inhaled iloprost in this patient group [61].

FUTURE DIRECTIONS

The cascade of events that leads to pulmonary vascular disease is highly complex. Increasingly it is postulated that a vulnerable genotype may be an important precursor in disease development. Perhaps the most well-recognised of these is bone morphogenic protein receptor type-2, although this has only been found in 6% of patients with CHD-PAH [62]. Understanding the genetic make-up of individuals may facilitate the development of therapy to target specific gene mutations. Similarly current therapies may be better utilised in patients with a known genetic defect.

As the complex interaction between protective and destructive substances is being unravelled an increasing array of potential targets for therapy arises. Rho-kinase inhibitors are one such class of drugs that have delayed the progression of PAH in animal models and positively affect haemodynamics in humans with PAH [63, 64]. The role of angiogenesis in the pathogenesis of PAH is currently being debated in the literature. Stem cell research holds promise. In rats, the development of monocrotaline induced PAH can be attenuated with the administration of endothelial progenitor cells [65]. A recent comprehensive review has summarised current knowledge in the area [66].

CONCLUSIONS

CHD-PAH is a significant problem leading to increased morbidity and mortality for patients born with congenital heart defects. It should now be considered a medically treatable disease. Uncertainties remain including the role for combination disease-targeted therapy and whether early PAH diagnosis and treatment is of major benefit for these patients.

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