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Dual therapy in IPAH and SSc-PAH. A qualitative systematic review

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Review

Summary
Background: Use of endothelin receptor antagonists (ERA), phosphodiesterase type-5 (PDE-5) inhibitors and prostaglandin analogues has resulted in improved outcomes in idiopathic pulmonary arterial hypertension (IPAH) and systemic sclerosis-associated PAH (SSc-PAH) patients. However, patients often deteriorate on monotherapy. The objective of this study is to evaluate the effect of dual therapy on outcomes in IPAH and SSc-PAH.
Methods: A systematic review of MEDLINE (1950–2011), EMBASE (1980–2011) and CINAHL (inception-2011) was conducted to identify studies that evaluated the effect of any dual combination of ERA, PDE-5 inhibitors or prostaglandin analogues on 6-min walk distance (6MWD), functional class (FC), haemodynamics, quality-of-life (QoL) or time-to-clinical-worsening in IPAH or SSc-PAH. A standardized form was used to abstract design, sample size, aetiology, outcome and treatment effect.
Results: Twenty-six observational studies and 6 randomized trials were identified. Using combination PDE-5 inhibitor and prostaglandin analogues, 6/7 studies reported improvement in 6MWD, 6/8 studies reported improvement in FC, 6/6 studies reported improvement in haemodynamics and 1 trial demonstrated improvement in QoL and time-to-clinical-worsening. Using combination ERA and prostaglandin analogues, 4/6 studies and 1 trial reported improvement in 6MWD, 3/3 studies and 1 trial reported improvement in FC, 4/5 studies and 1 trial reported improvement in PAP. Using combination ERA and PDE-5 inhibitor, 4/7 studies reported an improvement in 6MWD, and 2/6 report improvement in FC.

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Conclusion: The evidence suggests a beneficial effect of dual therapy in IPAH and SSc-PAH, particularly those who are deteriorating on monotherapy. Research should focus on subsets of patients to identify the optimal timing and combination of dual therapy.

Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by elevated right heart pressure, which can lead to progressive heart failure, difficulty breathing, decreased exercise capacity, decreased quality of life, and untimely death. Using historic data of untreated patients, Idiopathic-PAH (IPAH) has a median survival of 2.8 years,[1] and systemic sclerosis (scleroderma)-associated PAH (SSc-PAH) has a median survival of 1 year,[2] making their prognosis comparable to many cancers. Conventional treatments for PAH include the use of anticoagulants, oxygen, diuretics, and digoxin.[3] Calcium channel blockers are only effective in about 7% of patients with IPAH and even less effective in other forms of PAH.[4]

The management of PAH has evolved over the last two decades with the introduction of agents that target different mechanisms in the pathogenic process.[3] Prostaglandin analogues (epoprostenol, treprostinil, iloprost, beraprost) replace endogenous prostacyclin that is underproduced in PAH. They promote vasodilation and inhibit vascular proliferation and platelet aggregation.[5] Endothelin receptor antagonists (ERA)(bosentan, ambrisentan, sitaxsentan) block the action of endothelin-1, a potent vasoconstrictor that also promotes vascular smooth muscle cell proliferation.[6] Phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil) increase the effect of nitric oxide (NO) by inhibiting the breakdown of NO second messenger, cyclic guanosine monophosphate. This results in pulmonary vasodilation and inhibition of smooth muscle cell proliferation.[7] The introduction of ERA,[8–10] PDE-5 inhibitors[11] and prostaglandin analogues[12–18] in the management of PAH have demonstrated improvements in dyspnoea scores, subjective and objective measures of function (6 min walk test distance (6MWD), functional class), haemodynamics and quality of life. However, these benefits are not sustained.[19] After achieving initial improvement, patients often decline in all measures and still succumb to a premature death.[20] The optimal management of patients deteriorating on monotherapy in not known.[19] Additionally, significant side effects and difficult drug administration are associated with many of these medications.[21] For these reasons, many believe that dual combination therapy using drugs with different mechanisms of action that may have additive or synergistic effects is the next therapeutic option.

Animal and acute haemodynamic study data suggest that dual therapy with different combinations of these agents may lead to improved outcomes. Combination beraprost and sildenafil result in improved pulmonary haemodynamics compared with each drug alone in a monocrotaline-induced rat model.[22] In a study of 8 IPAH patients receiving epoprostenol, the addition of sildenafil results in an additional 10% reduction in mean pulmonary artery pressure (mPAP), 8% increase in cardiac output, and 24% reduction in pulmonary vascular resistance (PVR).[23] Combination beraprost and sildenafil result in acute improvements in mean PAP and PVR compared to beraprost monotherapy.[24] In 5 IPAH patients, the addition of iloprost to sildenafil results in greater reduction in mPAP than monotherapy.[25]

Given these observations, we undertook a systematic review of the literature to evaluate the evidence regarding the effect of dual therapy on outcomes in IPAH and SSc-PAH. Specifically we evaluated the effect of any dual combination of ERA, PDE-5 inhibitor or prostaglandin analogues on clinically relevant outcomes (6MWD, functional class, haemodynamics, quality of life and time to clinical worsening) in adult patients with IPAH or SSc-PAH.

Methods

Search strategy

MEDLINE (1950—April 2011), EMBASE (1980—April 2011) and CINAHL (inception to week 9 2011) were searched using the following keywords with mapping to subject heading: (pulmonary hypertension or pulmonary heart disease) and (prostacyclin or epoprostenol or treprostinil or iloprost or beraprost or prostaglandin or prostanoid or cycloprostin or Pgi2 or Pgx or U 53,217 or ciloprost or Ilomedin or Sh 401or cotherix or Dolner or Procylin or Trk 100) or (endothelin receptor or endothelin receptor antagonist or bosentan or Tracleer or Ro 47 0203 or sitaxsentan or sitaxsentan or Tbc 11,251 or thelin or ambrisentan or Bsf 208,075 or letairis or volibris or lu 208,075 or tbc 11,251 or darusentan or Hmr 4005 or Lu 127,043 or Lu 135,252 or uniprost or remodulin or U62840 or Ut15 or 15AU81) or (phophodiesterase inhibitors or antiphosphodiesterase or phosphodiesterase antagonist or sildenafil citrate or sildenafil nitrate or Patrex or tadalafil or Uk 92,480 or Viagra or alfin or Andros or helping or sidegra). Drug name synonyms were identified using the National Institutes of Health database ChemIDplus. The search was limited to humans and adults, but without language restriction. Titles and abstracts were screened by three independent reviewers (SKB, SRJ, JTG) to identify studies for full review. Reviewers were blinded to the names of authors, institutions and journals. The bibliographies of included studies and review articles were also searched for relevant publications.

Inclusion and exclusion criteria

Eligible studies must 1) report original data, 2) include human subjects, 3) include adult patients >16 years of age, 4) include patients with IPAH or SSc-PAH, 5) evaluate the

use of any dual combination of prostaglandin analogues (epoprostenol, treprostinil, iloprost, beraprost), ERA (bosentan, sitaxsentan, ambrisentan), and PDE-5 inhibitors (sildenafil, tadalafil), and 6) report 6MWD, functional class (New York Heart Association (NYHA), World Health Organization (WHO)), haemodynamic parameters (PAP, PVR), quality of life (using any measure of health related quality of life) or time to clinical worsening as an outcome. Patients could use other conventional PAH medications including calcium channel blockers and anticoagulation. Studies were ineligible if they were 1) a review article, 2) non-human study, 3) included paediatric patients, 4) included patients with other causes of PAH (e.g. HIV, congenital cardiac disease etc), 5) reported only monotherapy or dual therapy with medications other that ERA, PDE-5 inhibitors or prostaglandin analogues as the intervention, or 6) only reported acute haemodynamic changes as the outcome.

Data abstraction

Data from the full text of the identified studies were independently abstracted by 2 reviewers on a standardized abstraction form. Discrepancies were resolved through consensus or by recourse to a third investigator. The following information was abstracted for each article, 1) study design (randomized trial or observational study (cohort study, case series or case report), 2) sample size, 3) aetiology (IPAH or SSc-PAH), 4) intervention, 5) outcome measure, 6) treatment effect and measure of association. The source article was used to resolve discrepancies.

Trial quality

The quality of randomized trials was evaluated using the validated Jadad quality assessment index.[26] The quality score ranges from 0 to 5, with score less than 3 indicating poor quality. Quality assessment was conducted by 2 independent assessors (JTG, SRJ), and disagreement was resolved through consensus.

Results

Search results

Systematic review of the literature identified 1143 potentially relevant citations. Review of titles and abstracts excluded 1084 citations, leaving 59 articles for review. After review of the full article, 27 were excluded. Studies were excluded if they did not evaluate the patient groups of interest, did not report the interventions of interest, did not report the outcome of interest, did not report specific outcome data for the subjects or interventions of interest or did not report original data. One study reported was excluded as it reported patients on different combinations of PH therapy as one group.[27] Thirty-two studies were identified for inclusion in this study. Fig. 1.

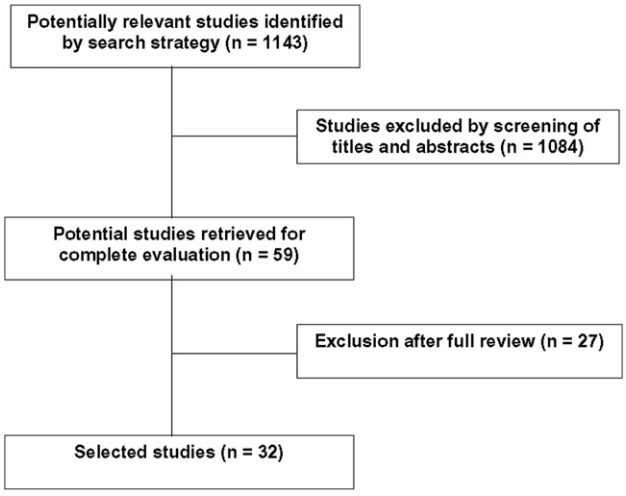

Figure 1 Flow diagram of systematic review.

Studies

Of the 32 articles, 26 articles were observational studies and 6 were randomized controlled trials. Studies of dual therapy combinations included PDE-5 inhibitors with prostaglandin analogues ($n = 13$ studies),[28–38] ERA with prostaglandin analogues ($n = 11$ studies),[38–48] and ERA with PDE-5 inhibitors ($n = 10$)[49–57] noting 2 studies reported 2 combinations[21,38]). Summaries of the studies are reported in Tables 1–3.

Combination PDE-5 inhibitor and prostaglandin analogues

Seven of the 11 observational studies reported 6MWD as an outcome, 6 of which reported a beneficial treatment effect of dual therapy.[32–36] Functional class was reported as an outcome in 8 observational studies. Six studies reported a beneficial effect[20,28,31–33,55] and 1 study demonstrated a trend towards improved functional class.[30] Six studies reported haemodynamics (PAP and/or PVR) as outcomes, all of which demonstrated a beneficial effect with dual therapy.[20,28,29,31,33,36] None of the studies reported quality of life as an outcome. Both randomized trials demonstrated improvement in 6MWD,[37,38] and one trial demonstrated improvement in quality of life and time-to-clinical worsening.[37]

Combination ERA and prostaglandin analogues

Four of the 6 observational studies reporting 6MWD as an outcome describe a beneficial effect with dual therapy.[39,41,42,44] Of the 4 randomized trials reporting 6MWD, 1 reported improvement[38] and 1 reported a trend towards benefit[47] with combination therapy. All 3 observational studies[35,39,41,42] and 1 clinical trial[47] demonstrated a beneficial effect of dual therapy on functional class. Four of 5 observational studies[40,41,43,44] and 1 randomized trial demonstrated a beneficial effect of dual therapy on PAP.[47] One trial demonstrated a beneficial effect of combination therapy on time to clinical worsening.[47]

Table 1 Summary of combination PDE-5 inhibitor and prostaglandin analogue studies.

Reference	Combination	Patients	Outcome measure	Evidence of benefit
Observational studies				
Ghofrani 2003	Iloprost + Sildenafil	9 IPAH 5 SSc-PAH	6MWD at 12 weeks: baseline 217 ± 31 m, 12-week 346 ± 26 m, 86 m (95% CI 30, 144 m) change, $p = 0.002$	Yes
			mPAP at 12 weeks:58.6 ± 2.1 mmHg, 12-week 58.6 ± 2.6 mmHg	No
			Functional class: Class IV 10/14 to 1/14	Yes
			PVR: 2494 ± 256 to 1950 ± 128 dyn s cm^{-5} $m^{2,}$ $p = 0.04$	Yes
Bhatia 2003	Epoprostenol + Sildenafil	5 IPAH	6MWD[a]: baseline 444.7 ± 111.5 m to 451 ± 114.7, $p = 0.8$	No
			Functional class 3[a]: 5 patients to 2 patients	No
Kataoka 2004	Epoprostenol + Sildenafil	1 IPAH	mPAP at 12 weekes: baseline 62 mmHg, follow-up 45 mmHg	Yes
Kataoka 2005	Epoprostenol + Sildenafil	20 IPAH	Functional class at 12 weeks: stabilization/improvement in 5 patients not responsive to epoprostenol	Yes
			mPAP at 12 weeks: 65 ± 15 to 50 ± 13 mmHg, $p < 0.0001$	Yes
			PVR at 12 weeks: 28 ± 12 to 15 ± 8 Wood units, $p < 0.0001$	
Gomberg-Maitland 2005	Treprostinil + Sildenafil	9 IPAH	Functional class: 3 improved, remainder stabilized	Trend
Miwa 2007	Beraprost + Sildenafil	1 SSc-PAH	mPAP at 4 weeks: baseline 35 mmHg, 31% reduction at 4 weeks	Yes
			PVR at 4 weeks: baseline 748 dyn s cm^{-5} m^2, 31% reduction at 4 weeks	
			3MWD at 4 weeks: 15% improvement	Yes
			Functional class at 4 weeks: III to II	Yes
Bendayan 2008	Treprostinil + Tadalafil	1 SSc-PAH	6MWD at 12 weeks: 155 m to 195 m	Yes
			Functional class 12 weeks: class IV to III	Yes
Onen 2006	Iloprost + Sildenafil	1 IPAH	6MWD: 440 m−580 m	Yes
			sPAP: 100 to 80 mmHg	Yes
			Functional class: III to I	Yes
Chua 2005	Treprostinil + Sildenafil	1 IPAH	6MWD at 3 months: improved to 480 m.	Yes
Stiebellehner 2003	Epoprostenol + Sildenafil	2 IPAH	6MWD at 5 months: 428 m−498 m	Yes
			mPAP 60 to 42 mmHg	Yes
Ruiz 2006	Epoprostenol/Treprostinil/ Iloprost + Sildenafil	13 IPAH	6MWD at 1 year: 350 ± 121 to 429 ± 86 m, $p = 0.002$	Yes
			Functional class at 1 year: 3 ± 0.47 to 2.1 ± 0.8, $p = 0.001$	Yes
Randomized trial				
Simonneau 2008 PACES Trial	Epoprostenol + Sildenafil versus Epoprostenol	212 IPAH 31SSc-PAH	6MWD at 4 months: adjusted treatment difference 28.8 m (95%CI 13.9, 43.8 m, $p < 0.001$)	Yes
			Time to clinical worsening: better in dual therapy group $p = 0.002$, stratified log rank test)	Yes
			mPAP at 4 months: mean change −2.8 mmHg versus −1.1 mmHg, (adjusted treatment difference −3.8 mmHg, 95% CI -5.6, −2.1 mmHg)	Yes
			SF-36 at 4 months: dual therapy had improvements in physical functioning $p = 0.003$, general health $p < 0.001$, vitality $p < 0.001$, social functioning $p = 0.049$ and mental health $p = 0.001$	Yes
McLaughlin 2010 TRIUMPH -1	Bosentan/Sildenafil + Treprostinil/placebo	235 PAH	6MWD at 12 weeks: The Hodges-Lehmann (HL) between treatment median difference in change from baseline in peak 6MWD was 20 m ($p = 0.0004$)	Yes
			Sildenafil group: 6MWD at 12 weeks: HL between treatment median difference in change from baseline in peak 6MWD was 9 m (p = not significant))	No

IPAH Idiopathic pulmonary arterial hypertension, SSc-PAH Systemic sclerosis associated pulmonary arterial hypertension, 6MWD 6 min walk test distance, PVR Pulmonary vascular resistance, mPAP mean pulmonary artery pressure, sPAP systolic pulmonary artery pressure.

[a] Follow-up 117 ± 69 days.

Table 2 Summary of combination prostaglandin analogue and ERA studies.

Reference	Combination	Patients	Outcome measure	Evidence of benefit
Observational studies				
Hoeper 2003	Iloprost/Beraprost + Bosentan	21 IPAH	6MWD at 12 weeks: baseline 346 ± 106 m, 12-week 404 ± 101 m, 58 ± 43 m change, $p < 0.0001$	Yes
			Functional class at 3 months: 17/21 to 13/21, 71% patients had improvement of 1 class	Yes
Akagi 2008	Epoprostenol + Bosentan	8 IPAH	sPAP: 80.1 ± 19.3 to 66.8 ± 16.5 mmHg, $p < 0.05$	Yes
			PVR: 9.7 ± 3.1 to 8.1 ± 3.2 Wood units, $p < 0.05$	
Channick 2006	Bosentan + Treprostinil	6 IPAH 3 SSc-PAH	6MWD at 12 weeks: Baseline 339 ± 86 m, 12 week 406 ± 121 m, 67 m change, $p = 0.01$	Yes
			mPAP at 12 weeks: 49 ± 10 to 44 ± 12 mmHg, −10% change, $p = 0.04$	Yes
			PVR at 12 weeks: 9.3 ± 4.9 to 6.9 ± 3.5 Wood units, −26% change, $p = 0.05$	No
			Functional class: 9/11 patients improve from class III to II	Yes
Benza 2008	Treprostinil + Bosentan	19 PAH	mPAP 55.7 ± 15.1 to 47.2 ± 11.6 mmHg, $p = 0.001$	Yes
			6MWD 332.8 ± 79.6 to 374.2 ± 110.3 m, $p = 0.07$	No
Jacobs 2009	Bosentan + Treprostinil or Epoprostenol	6 IPAH	6MWD at 4 months: 409 ± 48 to 447 ± 48 m, mean improvement 86 m, $p < 0.01$	Yes
			Functional class improved $p = 0.002$	Yes
Provencher 2006	Bosentan + Epoprostenol or Iloprost	34	6MWD at 3 months: 310 ± 108 to 347 ± 117 m, $p = 0.031$	Yes
			mPAP at 3 months: 60 ± 12 to 56 ± 11 mmHg, $p = 0.014$	Yes
Launay 2010	Bosentan + Epoprostenol or Iloprost	14 SSc-PAH	6MWD at 4 months: 223 ± 111 m, follow-up 191 ± 174 m, $p = 0.85$	No
			mPAP at 4 months: 55 ± 7 mmHg, follow-up 49 ± 7 mmHg, $p = 0.22$	No
			PVR at 4 months: 12.9 ± 3.5 mmHg/L/min, follow-up 10.9 ± 3.8 mmHg/L/min, $p = 0.17$	No
Randomized trials				
Humbert 2004 BREATHE-2	Epoprostenol + Bosentan versus Epoprostenol	27 IPAH 5 SSc-PAH	6MWD at 4 months: median change 68 m versus 74 m	No
			mPAP at 4 months: % change −2.2 ± 3.6 versus −9.0 ± 6.0, $p = 0.3$	No
			PVR at 4 months: % change −25.7 ± 7.2 versus −35.2 ± 5.4, $p = 0.3$	
			Functional class at 4 months: improvement in 13 patients (59%) versus 5 patients (45%)	No
McLaughlin 2006 STEP trial	Bosentan + Iloprost versus Bosentan	26 IPAH 29 APAH	6MWD at 3 months: 30 m ($p = 0.001$) in dual therapy, 4 m ($p = 0.69$) in monotherapy, between group difference 26 m ($p = 0.69$)	Trend
			Functional class at 3 months improvement in 11/32 (34%) versus 2/33 (6%), $p = 0.022$	Yes
			mPAP: change at 3 months −6 mmHg versus +2 mmHg, $p < 0.001$	Yes
			Time to clinical worsening: Better in dual therapy compared to monotherapy group $p = 0.02$ log rank test	Yes
Hoeper 2006 COMBI trial	Bosentan versus Bosentan + Iloprost	40 IPAH	6MWD at 3 months: monotherapy 296 m ± 79 m to 297 ± 94 m, (mean change 1 ± 27 m, $p = 0.84$); dual therapy 317 ± 74 m to 309 ± 124 m, (mean change −9 m ± 100 m, $p = 0.65$)	No
			Functional class at 3 months: 0.1 ± 0.3 versus −0.1 ± 0.2, $p = 0.64$	No
			EuroQol at 3 months: −3±11 versus 7 ± 19, $p = 0.14$	No
McLaughlin 2010 TRIUMPH-1	Bosentan/Sildenafil + Treprostinil/placebo	235 PAH	6MWD at 12 weeks: The Hodges-Lehmann (HL) between treatment median difference in change from baseline in peak 6MWD was 20 m ($p = 0.0004$)	Yes
			Bosentan group: 6MWD at 12 weeks: HL between treatment median difference in change from baseline in peak 6MWD was 25 m (95% CI 10.2, 40.0) ($p = 0.0002$)	Yes

IPAH Idiopathic pulmonary arterial hypertension, SSc-PAH Systemic sclerosis associated pulmonary arterial hypertension, 6MWD 6 min walk test distance, PVR Pulmonary vascular resistance, mPAP mean pulmonary artery pressure, sPAP systolic pulmonary artery pressure, EuroQol European Quality of Life Instrument, SF-36 The Short Form[36] Health Survey.

Table 3 Summary of ERA and PDE-5 inhibitor studies.

Reference	Combination	Patients	Outcome measure	Evidence of benefit
Observational studies				
Bhatia 2003	Bosentan + Sildenafil	3 IPAH	6MWD[a]: baseline 444.7 ± 111.5 m to 451 ± 114.7, $p = 0.8$	No
			Functional class 3[a]: 5 patients to 2 patients	No
Minai 2006	Bosentan + Sildenafil	3 IPAH	6MWD at 3 months: 1160 m, 1468 and 0 m to 1275 m, 1600 m and 645 m	Yes
			Functional class at 3 months: all 3 patients improved 1 class	Yes
Mathai 2007	Bosentan + Sildenafil	13 IPAH 12 SSc-PAH	Functional class: 5/13 IPAH and 2/12 patients improved	Trend
			6MWD: IPAH 294 ± 104 m to 340 ± 141 m, change 47 ± 77 m, $p = 0.05$	Trend
			SSc—PAH: No difference	
Hoeper 2004	Bosentan + add-on Sildenafil	9 IPAH	6MWD at 3 months: 227 ± 80 m to 392 ± 61 m, $p = 0.007$	Yes
Porhownik 2008	Bosentan + add-on Sildenafil	8 IPAH 2 CTD-PAH	6MWD at 6 months: baseline 339 m ± 107 to 401 ± 120, mean change 62.8 m, $p < 0.02$	Yes
			Functional class at 6 months: 2.2 ± 0.63 to 2.2 ± 0.63	No
Morice 2005	Bosentan + Sildenafil	1 IPAH	sPAP 130 to 50 mmHg	Yes
Preston 2005	Bosentan + Sildenafil	1 IPAH 1 CTD-PAH	Functional class: IPAH patient stabilization at class III; CTD-PAH improvement from class IV to III	Yes
Sitbon 2010	Bosentan + add-on Sildenafil	1 IPAH	6MWD at 4 months: 519 m—441 m,	No
			Functional class at 4 months: baseline class III, follow-up class III	No
Faruqi 2010	Sitaxentan + Tadalafil	3 IPAH	6MWD at 6 months: baseline 350 m, 270 m, 611 m; follow-up 370, 300, 553	Yes
Randomized trials				
Galie 2010 PHIRST trial	Bosentan + add-on Tadalafil	216 PAH	6MWD at 4 months: placebo adjusted change 23 m 95% CI -2, 48 m, $p = 0.09$	Trend
			Functional class at 4 months: 9.5% improved and 9.5% worsened in the tadalafil 40 mg group; 24.4% improved and 11.1% worsened in the placebo group, $p > 0.05$.	No
Barst 2011 PHIRST trial			Time to clinical worsening 2 patients (5%) had worsening with add-on tadalafil versus 5 (11%) for add-on placebo HR 1.9, 95% CI 0.4, 10.2.	

IPAH Idiopathic pulmonary arterial hypertension, SSc-PAH Systemic sclerosis associated pulmonary arterial hypertension, 6MWD 6 min walk test distance, PVR Pulmonary vascular resistance, mPAP mean pulmonary artery pressure, sPAP systolic pulmonary artery pressure.

[a] Follow-up 117 ± 69 days.

Combination ERA and PDE-5

Of the 7 observational studies that reported 6MWD as an outcome, 4 studies[50,52,53,57] reported a treatment benefit and 1 study[51] reported a trend towards a beneficial effect of dual therapy. Of the 6 studies that reported functional class, 2 studies[50,55] reported a benefit and 1 study[51] report a trend towards improvement in functional class with dual therapy. One case report described improvement in PAP with dual therapy.[54] No studies reported quality of life.

Randomized trial quality

The randomized trials had quality scores of 4(46), 2(52), 4(38), 5(47), 5(49) and 5(37) indicating largely good quality studies. Decreased quality scores resulted from lack of blinding,[52] inadequate description of randomization[38,52] or inadequate reporting of withdrawals and dropouts.[46]

Discussion

Use of dual combination therapy in the management of PAH is increasingly common. Data from the registry to evaluate early and long-term PAH disease management (REVEAL registry) indicates that more than 1000 patients in the United States were treated with two or more PAH specific therapies.[58] Yet medication payers (governmental programs and insurance carriers) are reluctant to cover dual combination therapy due the perceived lack of evidence. This systematic review synthesizes the current literature evaluating the effect of dual therapy with any combination of ERA, PDE-5 inhibitors or prostaglandin analogues on clinically relevant outcomes in IPAH and SSc-PAH patients. Our overview of these study findings, provides some insight that may inform current clinical practice and future research directions. The overall weight of the literature supports a beneficial treatment effect of dual therapy compared to monotherapy on multiple outcome measures. This finding has face validity as combination therapy is the standard of care for patients with other sub-optimally managed chronic diseases including cancer, rheumatoid arthritis and left ventricular heart disease.[59] The finding that a combination of two medications may be superior to monotherapy also has biological plausibility as combinations target different pathways in the pathogenesis of pulmonary hypertension.[60]

The direction and magnitude of the treatment effect on each outcome is generally consistent across the observational studies. However there is discordance between some observational studies and randomized trials. This discrepancy may be related to variations in the study designs, particularly administration of dual therapy and patient selection. Studies varied in the administration of dual therapy (simultaneous versus sequential), and the order of administration (prostaglandin analogues before or after ERA/PDE-5 inhibitor therapy). The observational studies may also suffer from small patient numbers, reporting bias and/or overestimation of treatment effect. The differences in effect between randomized trials and case series could relate to the observed differences between incident and prevalent cases of PAH and survival. Randomized trials generally enrol stable patients (prevalent cases) while case series may be evaluating non-stable (excluded from randomized trials) patients.[61] These variations may have influenced the observed outcomes.

Of the studies that administered dual therapy sequentially, there was variability in how patients were selected to receive the second agent. In studies where *stable* patients were selected/randomized to a second agent or placebo,[30,40,46,48] patients were less likely to derive a beneficial effect on outcome. Other studies identified specific subsets of patients to receive the second agent. Using a 'step-wise approach',[39,59,62] studies selected patients who *failed to reach pre-defined clinical endpoints* (e.g. using poor prognostic markers[15]: 6MWD $<$ 380 m and WHO functional class III or IV). This was done with the rationale that patients whose condition has stabilized on monotherapy may derive further improvements or to suppress side effects resulting from higher doses.[40] Using a 'rescue approach,' other studies used pre-defined criteria to select patients who were *deteriorating on monotherapy*.[28,35,36,42,51,54] This is based on the rationale that patients who are failing may be rescued by add-on therapy.[20] A few studies used a combined approach by including both types of criteria (e.g. 6MWD $<$ 380 m or a drop of 50 m on 6MWD).[52,53] The weight of evidence in this review indicates that patients who have add-on therapy in the face of deterioration on monotherapy derive greater benefits. This finding is plausible as these patients are the ones who have the most to gain.

There is insufficient data to determine the optimal dual combination. There are specific indications for which dual oral therapy is best suited. First, dual therapy may be a viable alternative for patients unsuitable for epoprostenol. Many patients are not able to use the infusion pump.[42] For other patients, the side effects are intolerable. Epoprostenol is associated with jaw and leg pain, diarrhoea, flushing, systemic hypotension, catheter infection or sepsis.[21] Dual oral therapy is also less costly than parenteral therapy.[52] The combination of two oral agents is appealing due to the ease of administration, cost and tolerability.[51]

Dual therapy may also provide a bridge to transplantation. Given the effects of transplantation on a patients' quality of life,[63] and complications limiting survival after transplantation, any therapy that can successfully temporize or reduce the need for transplantation is desirable.[64] In patients who remain on the transplant list, combination therapy may increase their chances of survival to transplantation.

Third, dual oral therapy may facilitate weaning off invasive continuous intravenous therapy. Combination bosentan and sildenafil is associated with a higher likelihood of successful transition from epoprostenol than monotherapy.[65] This strategy has also been shown to be less expensive.[66] Thus, the aims of dual oral therapy are to prevent patients from receiving invasive continuous prostaglandin analogues, wean off prostaglandin analogues or delay lung transplantation.

When considering use of dual therapy, issues of safety (drug—drug interactions, side effects associated with combination dual therapy), dosing and medication cost should be considered. The incidence of elevated transaminases is not significantly different in patients taking sildenafil and bosentan compared to bosentan

monotherapy.[64] Bosentan decreases the plasma concentration of sildenafil.[67] Sildenafil peak plasma level is reduced to a third in the presence of chronic bosentan treatment. An increase in sildenafil dose may be required in patients using bosentan.[67] In another study in healthy volunteers, sildenafil increased bosentan plasma levels by 50%.[64] These issues should be explored further. Plasma tadalafil concentrations decrease by 40% in healthy volunteers taking concomitant bosentan, however this is not considered a clinically meaningful change.[68,69] The PHIRST trial found no difference in adverse events in the combination bosentan-tadalafil group compared to the bosentan-placebo group.[69]

There were limitations to this study. Our review identified a large number of observational studies. These observational studies have small numbers of patients, are uncontrolled and not blinded to intervention or outcome. They often suffer from confounding by indication (selection bias) as treatment is given at the discretion of the treating physician. Despite their limitations however, these studies should not be discounted. In the setting of an uncommon disease and few randomized trials, they provide valuable information about practice in the real world. Through this review we have compiled all the observational studies so that the observed treatment effects can be evaluated together. In general, the direction and the magnitude of the observed treatment effects are consistent, and indicate that a signal of effectiveness is present. Due to the heterogeneity of patient groups, follow-up time, variations in outcome measurement and variations in the dual combinations, a meta-analysis of all the studies was not appropriate.[70] Others have published reviews (review,[71] systematic review,[72] guidelines,[73] expert consensus document,[74] evidence-based update[3]) relating to combination therapy in PAH. Another consideration is that our search was limited to the adult population. As such, our results may not be generalizable to the paediatric population.

The strength of this systematic review is that it reports a greater breadth of evidence (that was excluded by the others) to support our recommendations. This systematic review supplements the work already done in this area, and independently validates their findings. Our findings and recommendations are consistent with those of the evidence-based treatment algorithm from the 4th World Pulmonary Hypertension Symposium,[3] the Canadian Agency for Drugs and Technologies in Health,[72] the American College of Cardiology Foundation and American Heart Association Expert Consensus Document on Pulmonary Hypertension,[74] and treatment guidelines of the European Society of Cardiology and the European Respiratory Society.[73]

Conclusion

The results of this systematic review suggests that dual combination therapy improves multiple clinically relevant outcomes in IPAH and SSc-PAH patients, particularly those who fail to meet pre-defined clinical end-points or are deteriorating on monotherapy. Further research is needed to identify the optimal dual combination, timing of initiation, and criteria for patient selection. Until evidence is available, we support the recommendation that dual combinations should be initiated by experts in the field who have substantial experience in dealing with PAH patients, and have access to the resources of a pulmonary hypertension center of excellence.[50,73,75] The decision for appropriate dual combination should be made on an individual basis.[73] Ideally, patients should participate in clinical trials so that the optimal treatment strategy can be identified.[73]

Conflict of interest statement

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