Efficacy and Safety of Tadalafil and Sildenafil in Pulmonary Arterial Hypertension: Results of a Systematic Literature Review

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Background

- Tadalafil and sildenafil are the two main PDE5is approved in PAH that target the nitric oxide pathway, one of the pathogenetic pathways involved in the disease. According to guideline recommendations, the combination of a PDE5i with an ERA is the foundation of PAH treatment.[1]
- Despite difference in dosages and frequency of administration (given the different pharmacokinetics),[2] direct comparison studies assessing efficacy and safety of tadalafil versus sildenafil in PAH are lacking.

Methods

- MEDLINE, Embase and Cochrane Libraries were searched from inception to February 2023, supplemented by clinical trial registries/relevant congresses/SLR bibliographies' searches.
- Two reviewers performed abstract/full-text screening, with conflicts resolved by a third reviewer.
- The presented results are part of a broader SLR. This included randomized control trial (RCTs) and real-world evidence (RWE) studies involving adults with PAH treated with PDE5is, ERAs and riociguat (soluble guanylate cyclase stimulator also acting on the nitric oxide pathway as with PDE5is).
- Relevant outcomes were 6-minute walk distance (6MWD), pulmonary vascular resistance (PVR) and safety, among others.
- This qualitative synthesis focuses only on results reported in RCTs.
- The quality of all included RCTs was assessed using the quality assessment tool developed by York Centre for Reviews and Dissemination (CRD), completed by one individual and verified by a second reviewer.[3]

Results

Evidence base

- The SLR identified 200 publications reporting on 34 RCTs/37 RWE studies (**Figure 1**).
- A scope expansion identified an additional 29 publications; 4 RCTs and 4 observational studies of riociguat; none of the studies from the scope expansion were included in the analyses presented here (PRISMA diagram not shown).
- 22 RCTs were identified for this analysis where study intervention was either sildenafil or tadalafil, but only 15 RCTs used a licensed dose (sildenafil: 60 mg; tadalafil: 40 mg) and of those, 11 reported either 6MWD or PVR at a timepoint of 6, 12, 24 and/or 26 weeks. 6 RCTs investigated PDE5is as monotherapy; 3 RCTs as PDE5is+ERAs and 2 RCTs investigated both (**Table 1**).[4–14]

Study results

- **Table 1** summarizes studies with at least one arm reporting on the approved maintenance daily dose for either tadalafil (40 mg) or sildenafil (60 mg).

6MWD

- 10 RCTs reported mean change from baseline (CFB) in 6MWD for tadalafil and sildenafil monotherapies (n=5 RCTs each) and 5 RCTs reported this outcome for tadalafil and sildenafil combination therapy with ERAs, 3 for tadalafil (N=437) and 2 for sildenafil (N=67), most commonly at Week (W) 12 and W24/W26 (**Figure 2**).
- As monotherapy, at W12, CFB in 6MWD was comparable between tadalafil (n=1 RCT, N=37) and sildenafil (n=3 RCTs, N=120). At W24, improvements in 6MWD were greater for tadalafil (n=2, N=131) than sildenafil (n=1, N=17).
- In combination with ERAs, at W12 and W24/W26, tadalafil+ ambrisentan/macitentan (n=3 RCTs, N=437) resulted in greater improvements in 6MWD than sildenafil+bosentan (n=2 RCTs, N=67).

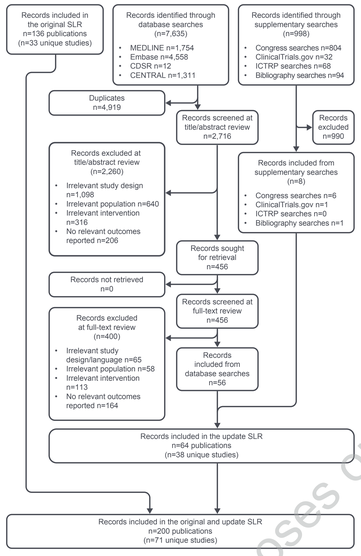
PVR

- 4 RCTs reported PVR for tadalafil and sildenafil monotherapies at W6/12/16: tadalafil (n=2, N=107) led to greater reductions in PVR than sildenafil (n=2, N=114) at W12 (**Figure 3**).
- For combination therapy, tadalafil+macitentan (n=1; N=124) led to a greater reduction in PVR at W26 than tadalafil+ambrisentan (n=1; N=60) at W16 (**Figure 3**).

Safety

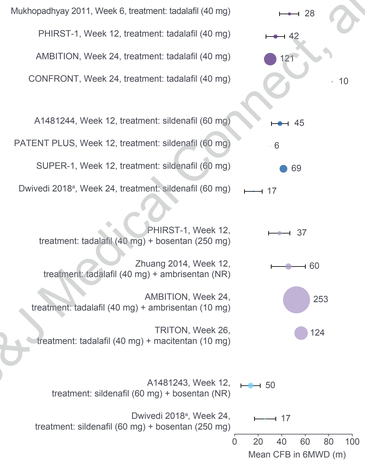
- 6 RCTs reported serious adverse events (SAEs), but due to different exposure times for which these were reported, no conclusions on comparative safety between sildenafil and tadalafil could be drawn.
- SAEs for tadalafil monotherapy (n=2) were 8.9% (W16)/10.0% (W24); SAEs for tadalafil+macitentan/ ambrisentan (n=2) were 31.5% (W26)/36.4% (W87); SAEs for sildenafil monotherapy (n=1) were 6.7% (W12), and SAEs for sildenafil+bosentan (n=1) were 18.0% (W12).

FIGURE 1: PRISMA flow diagram



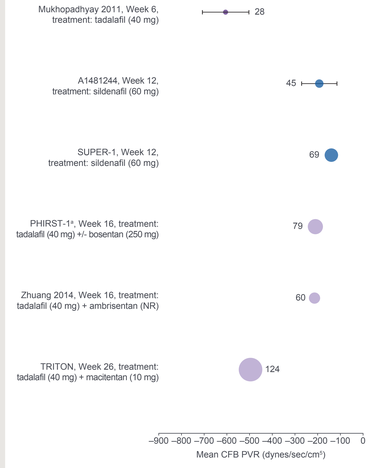
Abbreviations: CDSR: Cochrane Database of Systematic Reviews; **CENTRAL:** The Cochrane Central Register of Controlled Trials; **ICTRP:** International Clinical Trials Registry Platform; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SLR:** systematic literature review.

FIGURE 2: Mean CFB in 6MWD (m) in patients receiving tadalafil 40 mg or sildenafil 60 mg daily as a monotherapy or in combination with ERAs in PAH



Of the 15 RCTs identified, data are only presented for RCTs that report either mean CFB in 6MWD at W8, W12, W24 and W26 for tadalafil 40 mg and sildenafil 60 mg daily as a monotherapy or in combination with ERAs. For studies where multiple time points were recorded, only W12 was presented. The bubble width represents the number of patients within the study population and is scaled to 40%. The size of the study population is labelled on the bubble. The lines of the graph indicate the standard error, where reported. [a]Patient population consisted of patients with SSc-related PAH. **Abbreviations: 6MWD:** 6-minute walk distance; **CFB:** change from baseline; **ERAs:** endothelin receptor antagonists; **PAH:** pulmonary arterial hypertension; **RCT:** randomized controlled trial; **SSc:** systemic sclerosis.

FIGURE 3: Mean CFB in PVR (dynes/sec/cm^5) in patients receiving tadalafil 40 mg and sildenafil 60 mg daily as a monotherapy or in combination with ERAs in PAH



Of the 15 RCTs identified, data are only presented for RCTs that report either mean CFB in PVR at W6, W12, W16 and W26 for tadalafil 40 mg and sildenafil 60 mg (i.e., 20 mg three times daily) daily as a monotherapy or in combination with ERAs. Data are presented for the ITT population. The bubble width represents the number of patients within the study population and is scaled to 40%. The size of the study population is labelled on the bubble. The lines on the graph indicate the standard error, where reported. [a]Patient population consists of both patients who received prior bosentan and patients with no prior exposure to bosentan. **Abbreviations: CFB:** change from baseline; **ERAs:** endothelin receptor antagonists; **PVR:** pulmonary vascular resistance; **PAH:** pulmonary arterial hypertension; **RCT:** randomized controlled trial.

TABLE 1: Study characteristics of reported RCTs evaluating tadalafil and sildenafil as a monotherapy or in combination with ERAs in PAH

Study name	Setting, phase	PDE5i treatment (total daily dose)	ERA treatment (total daily dose)	N	Timepoint	Mean CFB 6MWD (SE), m	Mean CFB PVR (SE), dynes/sec/cm^5
Tadalafil							
Mukhopadhyay 2011[11]	Single center, phase II	Tadalafil (40 mg)	–	28	Week 6	+46.4 (8.44)	−605.6 (104)
PHIRST-1[9]	Multicenter, phase III	Tadalafil (40 mg)	–	37	Week 12	38 (9.18)	NR
			Bosentan (NR)	42	Week 12	34.6 (8.176)	NR
Zhuang 2014[14]	Single center, NR	Tadalafil (40 mg)	–[a]	79[a]	Week 16	*41.14 (49.39)*	−209 (−406; −13)[b]
			Ambrisentan (NR)	60	Week 12	+45.5 (14.85)	NR
					Week 16	*+54.4 (12.85)*	−214 (NR)
AMBITION[8]	Multicenter, phase III/IV	Tadalafil (40 mg)	–	121	Week 24	+30.25 (NR)	NR
			Ambrisentan (10 mg)	253		+52.5 (NR)	NR
CONFRONT[5]	Multicenter, phase IV	Tadalafil (40 mg)	–	10	Week 24	+82.63 (NR)	NR
TRITON[4]	Multicenter, phase III	Tadalafil (40 mg)	Macitentan (10 mg)	124	Week 26	+56.4 (NR)	−496 (NR)
Sildenafil							
A1481244[13]	Multicenter, phase IV	Sildenafil (60 mg)	–	45	Week 12	+38.36 (7.239)	−192 (79.44)
PATENT PLUS[10]	Multicenter, phase II	Sildenafil (60 mg)	–	6	Week 12	+30 (NR)	NR
SUPER-1[7]	Multicenter, phase III	Sildenafil (60 mg)	–	69	Week 12[c]	+41.3 (NR)	−140 (NR)
A1481243[12]	Multicenter, Phase IV	Sildenafil (60 mg)	Bosentan (NR)	50	Week 12[c]	+13.62 (8.535)	NR
Dwivedi 2018[6,d]	Single center, phase IV	Sildenafil (60 mg)	–	17	Week 24	+15.88 (7.72)	NR
			Bosentan (250 mg)			+25.88 (9.277)	NR

Of the 15 RCTs identified, data are only presented for RCTs that report either mean CFB in 6MWD at W6, W12, W16, W24 and W26; or mean CFB in PVR for tadalafil 40 mg and sildenafil 60 mg (i.e., 20 mg three times daily) daily as a monotherapy or in combination with ERAs. Data are presented for the ITT population. Values in italics not presented graphically for 6MWD as W12 values available. [a]Patient population consists of both patients who received prior bosentan and patients with no prior exposure to bosentan. [b]Mean CFB PVR (95% CI). [c]Data presented for W12 are last observation carried forward. [d]Patient population consisted of patients with SSc-related PAH. **Abbreviations: 6MWD:** 6-minute walk distance; **CFB:** change from baseline; **CI:** confidence interval; **ERA:** endothelin receptor antagonists; **ITT:** intention-to-treat; **NR:** not reported; **PAH:** pulmonary arterial hypertension; **PDE5i:** phosphodiesterase type 5 inhibitors; **PVR:** pulmonary vascular resistance; **RCTs:** randomized controlled trials; **SE:** standard error; **sec:** seconds; **SSc:** systemic sclerosis; **W:** Week.

Objective

By using a systematic literature review (SLR), to understand how the phosphodiesterase type 5 inhibitors (PDE5is), tadalafil and sildenafil, compare to each other on clinical endpoints (efficacy and safety) in pulmonary arterial hypertension (PAH) either as monotherapy or in combination with endothelin receptor antagonists (ERAs).

Conclusion

Qualitative syntheses of RCT data suggest that tadalafil monotherapy/ combination therapy with ERAs may have more favorable improvements in 6MWD and reduction in PVR in adults with PAH versus sildenafil.

Pulmonary Hyptertension

Acknowledgements

This study was funded by J&J IM. Medical writing support was provided by Ania Bobrowska, PhD, of Costello Medical, UK, and Isabella Clements, MSc, of Costello Medical, UK, design support was provided by Jon Green, of Costello Medical, US, and funded by J&J IM.

Disclosures

NR, AS: consultant, ownership or employment by J&J IM. MS: consultant, ownership or employment by J&J IM; stocks or options held in J&J. DL, GGR: consultant, ownership or employment by J&J IM. AK, AW, EB: employees of Costello Medical Consulting at the time of this research, and supported by a grant from J&J IM for this study. SS: past consultant of J&J, Bayer, United Therapeutics, Gossamer Bio, Liquidia technologies, Keros; past clinical trial support for United Therapeutics, Gossamer Bio, Liquidia technologies, Keros, J&J IM, Altavant Sciences, Novartis; past speaker bureau for J&J IM; research grant from United Therapeutics.

Presented at ATS 2024 Congress | San Diego, United States | 17–22 May, 2024

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