PAH Patient Case

Chris Schutte
PharmD Candidate 2017

HPI

SH is a 67 year old female with severe WHO Group 1 pulmonary arterial hypertension who was admitted to UKMC on 6/30/16 for initiation of Veletri (epoprostenol). Symptoms include dyspnea on exertion, fatigue, and edema.

Right heart cath results from 3/3/16:

- Right atrium 8 mm (2-6)
- Right ventricle 83/9 mmHg (15-30/2-8)
- Pulmonary artery 80/24 (15-30/8-15)
- Mean pulmonary artery pressure 48 mmHg (9-18)
- Pulmonary capillary wedge 3 mmHg (6-12)

PMH

Idiopathic pulmonary arterial hypertension
Scleroderma
Hypertension
GERD
Glaucoma
Raynaud's disease
Rosacea

Home Medications

sildenafil 20 mg 2 tabs orally 3 times a day
macitentan (Opsumit) 10 mg 1 tab orally once a day
selexipag 1600 mcg 1 tab orally 2 times a day

warfarin 2.5 mg one tab orally once a day except half tablet on Tues and Thurs
aspirin 81 mg 1 tab orally once a day
furosemide 40 mg 1 tab orally once a day
pentoxifylline 400 mg extended release 1 tab orally 2 times a day
Combigan 0.2%-0.5% ophthalmic solution 1 drop to each eye every 12 hours
loperamide 2 mg 2 tabs orally every 4 hours, as needed for diarrhea
ferrous sulfate 325 mg (65 mg elemental iron) oral delayed release tablet orally 2 times a day
Klor-Con 10 mEq extended release 1 tab orally 2 times a day
Centrum Silver 1 tab orally once a day
bilberry/evening primrose/flax 40 mg-500 mg-1000 mg 1 capsule orally once a day
turmeric curcumin complex 500 mg 1 tab orally once a day

WHO Class I Functional Classes

Class	Description	Significance
1	No limitation of activity	Doing great!
2	Slight limitation: ordinary activities cause some sx	Acceptable
3	Marked limitation: less than ordinary activity causes sx	Caution
4	Severe limitation: any activity causes sx. Overt RHF	Emergency

http://pulmonaryhypertensionrn.com/functional-classification-of-pulmonary-arterial-hypertension-pah/

Sildenafil (Revatio)

Class: Phosphodiesterase Type-5 Inhibitor

MOA: Inhibits the breakdown of NO. Increased NO relaxes smooth muscle (aka pulmonary arteries).

Literature: Studies were done in predominantly Functional Class II and III patients. Sildenafil significantly increased 6 minute walk test versus placebo at 4, 8, and 12 weeks. It was also shown effective at reducing 6 minute walk when combined with IV epoprostenol versus epoprostenol alone.

Dose: Max effective dose is 20 mg TID

Macitentan (Opsumit)

Class: Endothelin Receptor Antagonist

MOA: Prevents vasoconstriction and decreases cell proliferation

Literature: SERAPHIN study showed a reduction in the primary combined endpoint with macitentan versus placebo when added to background PAH therapy. Significance of the endpoint was driven by 6 minute walk distance, worsening of PAH symptoms, and initiation of additional PAH treatment. There was no significant difference in deaths.

Dose: 10 mg once daily

Selexipag (Uptravi)

Class: Oral selective prostacyclin receptor agonist

MOA: Binds to the prostacyclin receptor to activate cAMP and dilate pulmonary arteries

Literature: GRIPHON study showed a reduction in the primary combined endpoint with selexipag versus placebo when added to background PAH therapy. The majority of patients were functional class II and III. Significance of the endpoint was driven by reduced hospitalizations and reduced disease progression.

Starting dose: 200 mcg BID Max dose: 1600 mcg BID

IV Epoprostenol (Veletri)

Class: IV Prostanoid

MOA: Prostacyclin analogue that binds to the prostacyclin receptor to activate cAMP and dilate pulmonary arteries. Also inhibits platelet aggregation.

Literature: Besides increasing 6 minute walk distance in Functional Class III and IV patients, there are two studies that suggest mortality benefit of epoprostenol.

A small study found 8 patients out of 40 died in placebo group while 0 patients of 41 died in Veletri group.

Another study showed survival rates for patients on epoprostenol at 1, 2, and 3 years were 87.8%, 76.3%, and 62.8%, respectively. These rates are significantly greater than the historical average survival rates of 58.9%, 46.3%, and 35.4%.

IV Epoprostenol (Veletri)

Starting Dose: 2 ng/kg/min

Titrate up to max tolerated dose

Dose limiting adverse effects:

Flushing, Headache, N/V, Jaw pain, Hypotension

Needs a continuous infusion pump. Patients mix and change bags at home.

Veletri can be stored at room temperature for 48 hrs (as opposed to Flolan which needs to be stored on ice during infusion).

Other Recommended PAH Therapies

Oxygen

Diuretics

Anticoagulation with warfarin

Influenza and Pneumococcal Vaccines

Hospital Day 1

- Insert Hickman catheter
- Start Veletri at 2 ng/kg/min; Titrate to 4 ng/kg/min this evening
- D/C Uptravi
  - Give 800 mg tonight and 400 mg in the morning
- Continue Opsumit 10 mg orally daily
- Continue Sildenafil 20 mg TID
- Continue aspirin, metoprolol, coumadin, furosemide, combigan, pentoxifylline, and ferrous sulfate
- Planned lung transplant evaluation

Complication

On Hospital Day 2, SH was exceedingly short of breath. She was on 3 L of oxygen at home, but began requiring high flow oxygen. When she removed the mask to take a bite of food, she became dyspneic. O2 Sats: 85-95%.

Thoracic was consulted and found a small pneumothorax in the LUL apex from the placement of the Hickman Catheter.

Daily chest X-rays were performed showing improvement in the pneumothorax over the next 3 days. No chest tube was required.

Complication Cont.

Difficulty breathing persisted and patient continued to require high flow oxygen with BiPAP at night to keep sats >85%.

ABGs Day 5: pO2 59, pH 7.45, pCO2 25, O2 sat 90%, bicarb 17

The team thought the shortness of breath may have been a side effect of the Veletri, so dose titration was halted on hospital Day 5.

Veletri Titration Schedule

Dosing Weight - 62 kg

Day	Dose	Concentration	Rate
Day 1	2 ng/kg/min	5,000 ng/mL	1.5 mL/hr
Day 2	3 ng/kg/min	5,000 ng/mL	2.2 mL/hr
Day 3	4 ng/kg/min	10,000 ng/mL	1.5 mL/hr
	5 ng/kg/min	10,000 ng/mL	1.9 mL/hr
Day 4	6 ng/kg/min	10,000 ng/mL	2.2 mL/hr
Day 5	7 ng/kg/min	10,000 ng/mL	2.6 mL/hr
Day 6	5 ng/kg/min	10,000 ng/mL	1.9 mL/hr
Day 7	7 ng/kg/min	10,000 ng/mL	2.6 mL/hr

Hospital Day 7

- SH in worsening respiratory distress and transferred to the ICU.
- NO administered.
- Critical care team recommended avoiding intubation because of high risk of inducing right heart failure and death.
- Patient and husband requested intubation despite the risks.
- At 21:48, SH went into PEA arrest during tube placement, and husband chose to discontinue ACLS.

References

1. "Functional Classification of Pulmonary Hypertension." Pulmonary Hypertension RN. Inspire Pulmonary Media, LLC. Web. 19 July 2016. <http://pulmonaryhypertensionrn.com/functional-classification-of-pulmonary-arterial-hypertension-pah/>
2. REVATIO [package insert]. New York, NY: Pfizer Inc; 2014. Reference ID: 3471998.
3. OPSUMIT [package insert]. San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2016.
4. Pulido, Tomás; Adzerikho, Igor; Channick, Richard N; et.al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. N Engl J Med. 2013; 369:809-818. DOI: 10.1056/NEJMoa1213917. Accessed July 19, 2016.
5. UPTRAVI [package insert]. San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2015.
6. Barst, Robyn J.; Rubin, Lewis J.; Long, Walker A.; et.al. A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension. *N Engl J Med.* 1996; 334:296-301. DOI: 10.1056/NEJM199602013340504. Accessed July 20, 2016.
7. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002. 17;106(12):1477-82. PubMed PMID: 12234951. Accessed July 20, 2016