Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with haemoglobinopathies

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Disclosures

I have nothing to disclose with respect to this presentation
Pulmonary Hypertension

...progressive increase in the blood pressure in the pulmonary vascular bed
**Histopathology**

**Main vascular changes of PAH**
- Vasoconstriction
- SMC and endothelial-cell proliferation
- Fibrosis
- Thrombosis

1. Severe concentric laminar intimal fibrosis
2. Medial hypertrophy
3. *in situ* thrombosis of the small residual lumen
Progression of PAH

- Preclinical
- Symptomatic / stable
- Progressive / declining

Cardiac output at peak exercise
Cardiac output at rest

Pulmonary pressure

Increasing PVR

Level vs. Time
Pulmonary Hypertension

Consequence…

…right heart failure and death
Pulmonary hypertension is one of the leading causes of morbidity and mortality in adult patients with sickle cell disease and thalassemia.

The pathogenesis of pulmonary hypertension in hemolytic disorders is likely multifactorial

Machado RF, Gladwin MT. Chest. 2010 Jun;137:30S-38S.
Pumonary Hypertension and Hemolytic Anemias: links

Chronic hemolysis
Thrombophilia
Asplenia
Chronic hypoxia
Chronic liver dysfunction
Iron Overload
Impaired nitrooxide (NO) bioavailability
Chronic Anemia

Patients with chronic anemia increase their cardiac output to maintain oxygen delivery, resulting in increased cardiac dimensions and heart rate.

Anemic patients have larger hearts on CXR, echo, and MRI measurements than patients with normal hemoglobin levels, even without any other pathology.

Thus, normative data generated from non-anemic patients is inappropriate for patients with hemoglobinopathies.

The larger cardiac dimensions, stroke volumes, and heart rates carry metabolic cost; chronically anemic patients have higher resting oxygen consumption and decreased reserves.
Iron Overload

Patients with thalassemia develop iron overload through increased iron absorption and transfusional therapy. Iron is toxic to all the endocrine glands that support the heart. Insulin-resistance and frank diabetes are relatively common. Hyperglycemia and insulin resistance are powerful oxidative stressors to the heart, worsening the effects of iron overload. Iron may also poison the thyroid and parathyroid gland, impairing metabolism and calcium regulation respectively. Iron-mediated adrenal insufficiency may also manifest itself during metabolic stress. Deficiencies of growth hormone and the sex steroids impair cardiac function.
Hypersplenism is relatively common in the thalassemias and may necessitate spleen removal. Splenectomy may also be performed to lower blood transfusion requirements. However, the spleen plays a critically important role in removing hematologic debris from the cardiovascular system. Phosphoserine positive platelets, platelet fragments, and red cell fragments are powerful procoagulants. The spleen also removes brittle senescent red cells from the circulation, suppressing intravascular hemolysis. Cell-free hemoglobin is a powerful oxidant and scavenger of nitric oxide. As a result, splenectomy is a strong risk factor for intravascular thrombosis and pulmonary hypertension.
Splenectomy prevalence

In adult pts with Thalassemia Major:
530/231  44%

(Webthal 2005 report)
Tromboembolics events

3.9 % in TM
9.6 % in TI

2 % in TM
29 % in TI
Complications in Thalassemia Intermedia

• Extramedullary erythropoiesis
Right heart Catheterization

The diagnosis of PAH cannot be confirmed without right heart catheterization (gold standard)

patients with PAH should have a low or normal pulmonary capillary wedge pressure
Contemporary Reviews in Cardiovascular Medicine

Pulmonary Hypertension Associated With Hemoglobinopathies
Prevalent But Overlooked

Dimitrios Farmakis, MD, PhD; Athanasios Aessopos, MD, PhD

2012
<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Hemoglobinopathy</th>
<th>N</th>
<th>Method for PH Diagnosis</th>
<th>Echocardiographic Criterion for PH</th>
<th>Prevalence of PH, %</th>
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<tbody>
<tr>
<td>Grisaru et al³</td>
<td>1990</td>
<td>Thalassemia major</td>
<td>35</td>
<td>Echo</td>
<td>PAT/RVET</td>
<td>75</td>
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<td>Du et al⁴</td>
<td>1997</td>
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<td>Echo</td>
<td>TPG+RAP ≥30 mm Hg</td>
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<td>Derchi et al⁵</td>
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<td>Aessopos et al⁶</td>
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<td>Thalassemia major</td>
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<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
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<tr>
<td>Aessopos et al⁷</td>
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<td>Aessopos et al⁸</td>
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<td>Aessopos et al⁹</td>
<td>2001</td>
<td>Thalassemia intermedia with heart failure</td>
<td>110</td>
<td>Echo and RHC</td>
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<td>Gladwin et al¹⁰</td>
<td>2004</td>
<td>Sickle cell anemia</td>
<td>195</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>32</td>
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<td>Machado et al¹¹</td>
<td>2006</td>
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<td>226</td>
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<tr>
<td>Sachdev et al¹²</td>
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<td>Sickle cell anemia</td>
<td>235</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
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<td>De Castro et al¹³</td>
<td>2008</td>
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<td>125</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
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<td>Echo</td>
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<td></td>
<td>sickle-HbC</td>
<td>27</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
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<td>Moysakos et al¹⁵</td>
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<td>Sickle thalassemia</td>
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<td>Echo</td>
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<td>Voskaridou et al¹⁵</td>
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<td>Sickle thalassemia</td>
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<td>Echo</td>
<td>TPG+RAP ≥35 mm Hg or TRV ≥2.5 m/s</td>
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<td>Aessopos et al¹⁷</td>
<td>2009</td>
<td>Sickle thalassemia</td>
<td>115</td>
<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
<td>27</td>
</tr>
</tbody>
</table>

PH indicates pulmonary hypertension; Echo, echocardiography; PAT/RVET, pulmonary valve acceleration time to right ventricular ejection time ratio; TPG, tricuspid systolic pressure gradient; RAP, right atrial pressure; RHC, right heart catheterization; sickle-HbC, sickle cell–hemoglobin C; sickle-HbO₂Arab, sickle cell–hemoglobin O-Arab; and TRV, tricuspid regurgitation velocity.
Italian Multicenter study
(8 Italian centers taking part of the WebThal project)

Methods

This was a multicenter cross-sectional study of 1309 Italian β-thalassemia patients
mean age 36.4 ± 9.3 years; 46% men;

74.6% TD, 25.4% NTDT.

Patients with a tricuspid-valve regurgitant jet velocity ≥3.2 m/s (3.6%) on transthoracic echocardiography further underwent right heart catheterization to confirm the diagnosis of PAH
Study flow chart.

1309 underwent Doppler echocardiography [TM: 977, TI: 332]

Group A (PH unlikely)
1234 had TRV <3.0 m/s [TM: 946, TI: 288]

Group B (PH likely)
47 had TRV ≥3.2 m/s [TM: 16, TI: 31]

Group C (PH possible)
28 had TRV >3.0 and <3.2 m/s [TM: 15, TI: 13]

7 declined right heart catheterization [TM: 0, TI: 7]

7 excluded [TM: 3, TI: 4]

1 [TI] dead
3 [TM: 2, TI: 1] severe anemia
2 [TM: 1, TI: 1] chronic cardiopulmonary disease
1 [TI] erythropoietic extramedullary mass

33 underwent right heart catheterization [TM: 13, TI: 20]

PH
31 had mean PA pressure ≥25 mm Hg [TM:12, TI: 19]

PAH (Pre-capillary PH)
27 had PCWP ≤15 mm Hg [TM: 11, TI: 16]

Post-capillary PH
4 had PCWP >15 mm Hg [TM: 1, TI: 3]

No PH
2 had mean PA pressure <25 mmHg [TM: 1, TI: 1]

Prevalence and Risk Factors for Pulmonary Arterial Hypertension in a Large Group of β-Thalassemia Patients Using Right Heart Catheterization

by Giorgio Derchi, Renzo Galanello, Patrizio Bina, Maria Domenica Cappellini, Antonio Piga, Maria-Eliana Lai, Antonella Quarta, Gavino Casu, Silverio Perrotta, Valeria Pinto, Khaled M. Musallam, and Gian Luca Forni

Volume 129(3):338-345
January 21, 2014
Conclusions

—The prevalence of PAH in β-thalassemia patients as confirmed on right heart catheterization was 2.1%, with an ≈5-fold higher prevalence in NTDT than TDT.

Advanced age and splenectomy are risk factors for PAH in this patient population.
Probability of having pulmonary arterial hypertension (PAH) confirmed on right heart catheterization as a function of age in all patients as well as according to splenectomy status.

Correlation between pulmonary arterial systolic pressure (sPAP) estimated on transthoracic echocardiography and measured on right heart catheterization (r=0.472, P<0.005).

How we treat?
# Hematological General Care

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusional therapy</td>
<td>To maintain adequate Hb level and reduce hypoxic stimulus to vasoconstriction</td>
</tr>
</tbody>
</table>
| Hydroxiurea     | Increase in Hb F, MCV  
                  Improvement in the effectiveness of erythropoiesis  
                  Reduction of ineffective erythropoiesis masses  
                  Increase of NO bioavailability |
How we treat it in 2003?

Vasoactive medications

Prostacyclins

- Epoprostenol (synthetic prostacyclin (PGI2) aka Flolan®)
- Treprostinil (Remodulin®), Iloprost (Ilomedin®, Ventavis®)

Endothelin receptor antagonists

- Bosentan (Tracleer®), Sitaxsentan (Thelin®), Ambrisentan (Letairis®)
How we treat?

Phosphodiesterase type 5 inhibitors

- Sildenafil
- By decreasing cyclic Guanosine Monophosphate-specific Phosphodiesterase cGMP
- Decrease degradation & increased apoptosis of PAMSCs
- Increases RV inotropy

Not approved in 2003 for PH
2003
Multicenter Pilot Study
(spontaneous, not sponsored)

“Sildenafil in the treatment of severe Pulmonary Hypertension in patients with Hemoglobinopathies”
Study design

Inclusion criteria:
Patients suffering from severe Pulmonary Hypertension (NYHA functional class III and IV) despite treatment with oral and/or iv drugs
Mean tricuspid gradient at rest $\geq 45\text{mmHg}$ at ecodoppler
Study design

Primary end point
Change from baseline to week 12 in TG at echodoppler

Secondary
Change in NYHA functional class
2003 Pilot Study design

Outcome measures of efficacy:
Change from baseline to week 12, 24, 48 and every six months in TG at echodoppler
Change from the baseline in functional class (modified NYHA)
Safety and tolerability of long-term therapy
Titration of Sildenafil therapy in:

- 25 mg/ test dose in hospital
- 25 mg x 2 first day in hospital
- 25 mg x 3 second day in hospital
- 50 mg x 2 third day in hospital
- 50 mg + 50 mg pts was discharged from the hospital
<table>
<thead>
<tr>
<th>Pt #</th>
<th>Sex (age in years)</th>
<th>Diagnosis</th>
<th>Concomitant therapies</th>
<th>Mean Hb-pre</th>
<th>Mean ferritin</th>
<th>Units of blood/year</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Male (40)</td>
<td>Thalassemia intermedia</td>
<td>Deferoxamine s.c. 50 mg/kg/day (5 days/wk) Hydroxiurea 20 mg/kg/day Deferoxamine s.c. 50 mg/k</td>
<td>8.0 mg/dl</td>
<td>1230 ng/dl</td>
<td>32</td>
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<tr>
<td>2</td>
<td>Male (36)</td>
<td>Thalassemia intermedia</td>
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<td>10.0 mg/dl</td>
<td>2500 ng/dl</td>
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<td>3</td>
<td>Male (34)</td>
<td>Thalassemia intermedia</td>
<td>Deferoxamine s.c. 50 mg/kg/day</td>
<td>8.5 mg/dl</td>
<td>800 ng/dl</td>
<td>48</td>
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<td>4</td>
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<td>Thalassemia major</td>
<td>Deferoxamine 40 mg/kg/day</td>
<td>10.4 mg/dl</td>
<td>540 ng/dl</td>
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<td>5</td>
<td>Male (38)</td>
<td>Sickle cell anemia</td>
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<td>11.5 mg/dl</td>
<td>4500 ng/dl</td>
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<td>6</td>
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<td>7</td>
<td>Male (41)</td>
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<td>Deferoxamine s.c. 50 mg/kg/day</td>
<td>8.6 mg/dl</td>
<td>713 ng/dl</td>
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</table>
Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with hemoglobinopathies

Background and Objectives. During the last decade new approaches to the treatment of pulmonary arterial hypertension (PH) have increased symptomatic relief and prolonged survival. PH is a common sequel of the hemoglobinopathies, thalassemia and sickle cell anemia, but the use of standard oral treatment options, such as calcium channel blockers, endothelin receptor antagonists, and long-term anticoagulation therapy, is limited because of toxicity and poor effectiveness. Sildenafil citrate is a selective and potent inhibitor of cGMP-specific phosphodiesterase-5 (PDE5) which promotes selective smooth muscle relaxation in lung vasculature and has been utilized successfully in the treatment of PH. The primary objective of this study was to evaluate the efficacy of sildenafil treatment in the control of PH in patients with hemoglobinopathies.
Figure 2. Change in NYHA class (individual patient data shown)
Figure 1. Change in tricuspid gradient (individual patient data shown) at 4-12 weeks controls

Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with hemoglobinopathies.
Haematologica. 2005 Apr;90(4):452-8
Changes in Six-minute Walk Test distance (individual patient data shown) at baseline and controls
CONCLUSIONS:
These data, in a small group of patients with severe PAH, indicate that Sildenafil citrate is effective in the treatment of this disease in hemoglobinopathies that cannot be treated with alternative oral drugs and is well tolerated long-term at a daily dose of 100 mg, though studies including more patients may uncover toxicities and limitations of efficacy.

G Derchi. GL Forni et al Haematologica 2005; 90:452-458
Efficacy and safety of sildenafil for the treatment of severe pulmonary hypertension in patients with hemoglobinopathies: results from a long-term follow up

Giorgio Derchi, Manuela Balocco, Patrizio Bina, Vincenzo Caruso, Domenico G D’Ascola, Roberto Littera, Raffaella Origa, Maria D. Cappellini, Gian L. Forni

Haematologica February 2014 99: e17-e18
Throughout all assessments during long-term follow up, all patients maintained the significant decrease in TG level which was initially noted at the end of the 12 weeks of therapy.

Similarly, patients had long-term persistent improvement in NYHA class (from Class III to Class I; \( P<0.05 \)) and in 6MWT (from 199 to 582 meters; \( P<0.01 \)). Furthermore, none of the patients experienced drug-related adverse/collateral effects.

There were no significant changes in mean hemoglobin level or blood requirement during the follow-up period.
Sildenafil Therapy In Thalassemia Patients With Doppler-Defined Risk Of Pulmonary Hypertension


Haematologica September 2013 98: 1359-1367;
PDE-5 inhibitors

1. **SILDENAFIL**:
   - By decreasing cGMP degradation – decreased proliferation & increased apoptosis of PASMCs
   - Increases RV inotropy (NEJM 2009;361:1864-1871)
   - 20 mg tds is the recommended starting dose – titrated to 80mg tds as tolerated
   - Onset ~ 45-60mins
   - Approved for PAH in 2005
   - Even though used off-label for paediatric PAH, FDA in 2012 recommended against their use\(^1\).
   - Long term beneficial effects have recently been reported in the SUPER-2 study\(^2\)

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Thank you so much for the invitation