Efficacy and safety of sildenafil for the treatment of severe pulmonary hypertension in patients with hemoglobinopathies: results from a long-term follow up

We read with interest the article by Morris *et al.*[1] evaluating the role of sildenafil therapy for thalassemia patients with Doppler-defined risk for pulmonary hypertension (PH). Here we reflect on the Authors' findings and highlight our experience with sildenafil therapy in a similar patient group, although on long-term therapy. PH of varying severity is commonly observed in patients with hemoglobinopathies, including beta(β)-thalassemia and sickle cell disease.[2,3] There are currently no specific guidelines for the management of PH in patients with hemoglobinopathies. Conventional oral therapies used in the management of PH in people without hemoglobinopathies are of limited value in thalassemia patients because of toxicity and poor effectiveness. Sildenafil citrate is a selective and potent inhibitor of cGMP-specific phosphodiesterase-5 (PDE5) that promotes selective smooth muscle relaxation in lung vessels. It has so far demonstrated beneficial effects in the treatment of PH[4,5] even in patients with hemoglobinopathies, as described previously by our group,[6,7] and as recently reported by Morris and colleagues in this Journal.[1] In both trials,[1,7] results reflecting 12 weeks of sildenafil therapy were described. In our study,[7] we noted a significant improvement in the New York Heart Association (NYHA) functional classification and the 6 Minute Walking Test (6MWT) functional capacity following therapy in patients who had severe PH with high tricuspid regurgitant velocity (TRV) and low 6MWT at baseline. However, Morris *et al.*[1] only noted improvement in TRV in patients with Doppler-echocardiography defined increased risk for PH (TRV >2.5 m/s) without improvement in 6MWT. We believe the lack of improvement in 6MWT may be due to the fact that the base-line values in this group of patients were almost normal.

Here we also up-date our experience with sildenafil therapy (at 50 mg twice daily) and report findings from long-term follow up of the original 7 patients suffering from severe PH for whom we had previously reported results of short-term treatment (β-thalassemia intermedia n=4; β-thalassemia major n=2; sickle/β-thalassemia n=1).[6,7]

Included patients were required to have a base-line mean tricuspid gradient (TG) of 45 mmHg or over at rest, as determined by continuous wave echo-Doppler, as well as a modified NYHA functional classification of III or IV despite previous therapy. For each patient, the following parameters were evaluated: mean annual hemoglobin level, blood requirement, functional class (NYHA Class), exercise capacity (6MWT), and pulmonary pressure evaluated as TG. Assessments were made at the following time points: 12 weeks, 48 months, and 10 years (Table 1). The mean follow-up period was 75 months (6.25 years; range 30-120 months). During follow up, 3 patients died for causes unrelated to PH: one patient died from hepatocellular carcinoma related to hepatitis C virus infection (follow up 60 months), one patient died from gastrointestinal bleeding (follow up 84 months), and one patient with sickle cell disease died from pneumococcal sepsis (follow up 30 months). During follow up, 2 patients underwent right heart catheterization confirming their diagnosis of pulmonary arterial hypertension.

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.

These data show that a 100 mg daily dose of sildenafil citrate has long-term effectiveness for the treatment of PH in hemoglobinopathies. Moreover, the drug is well tolerated and the observed benefits it induces on hemodynamic and functional status remain consistent over the long term. Although larger studies may uncover safety concerns or limitations of efficacy, our data clearly show that therapy with sildenafil citrate in selected patients with severe PH and impaired NYHA functional class is effective for symptom relief and improving functional capacity. Such effects remain consistent for an extended duration of time and are not associated with any safety concerns or effects on transfusional balance.

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Table 1. Hemodynamic and hematologic characteristics of patients at baseline and end of follow up.

Pt	Age (years) T0	Gender (F/M)	Follow up (mo)	TG (max/mean) T0	TG (max/mean) TF	Mean Hb-pre (g/dL) T0	Mean Hb-pre (g/dL) TF	Blood units/year T0	Blood units/year TF	NYHA (class) T0	NYHA (class) TF	6MWT (m) T0	6MWT (m) TF
1	40	M	60	90/55	71/50	8	7.8	32	36	III/IV	II	55	750
2	36	M	84	105/70	70/25	10	8.2	32	34	IV	II	0	520
3	34	M	120	56/42	40/26	8.5	8.5	48	48	III	I	415	520
4	40	F	75	158/11	70/60	10.4	10.6	41	40	III	I	115	600
5	38	M	30	51/32	77/43	11.5	11	11	12	III/IV	II/III	110	450
6	44	F	78	120/87	98/55	10.3	8.4	20	24	III	I/II	300	750
7	41	M	75	68/47	80/55	8.6	9.3	30	34	III	II/III	400	490

Pt: patient; TG: tricuspid gradient expressed as mmHg; Hb: mean pre-transfusional hemoglobin level during the last year; NYHA: New York Heart Association functional class; 6MWT: Six Minute Walk Test expressed in meters; T0: data obtained at baseline; TF: data obtained at the end of follow up.

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