Response to "Efficacy and safety of sildenafil for the treatment of severe pulmonary hypertension in patients with hemoglobinopathies: results from a long-term follow up " Haematologica 2014;99(2):e17-18.

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We read with interest the response by Derchi *et al.*[1] to our recent publication[2] evaluating the role of sildenafil therapy in thalassemia patients with Doppler-defined risk for pulmonary hypertension (PH). The use of sildenafil in the treatment of PH related to hemoglobinopathies remains controversial[3] and, in thalassemia, the experience is limited to small case series.[4,5] The data presented in this letter represent the first long-term assessment of sildenafil use in thalassemia and suggests that in selected thalassemia patients this improves functional capacity and, potentially, hemodynamics. We express caution on utilizing echocardiography alone in defining a hemodynamic benefit, a limitation in our recent trial as well,[2] but find the six minute walk test (6MWT) and survival data in the Derchi cohort encouraging and supporting the concept that this is a true phenomenon.

Derchi and colleagues reflect on the current lack of guidelines for treatment of hemoglobinopathy-related PH. While we are happy to report that Clinical Guidelines for the Diagnosis and Treatment of PH in Sickle Cell Disease (SCD), sponsored by the American Thoracic Society, are due to be published in late 2014,[7] we are not convinced that these will be applicable to thalassemia, as there are apparent differences in the PH observed in each despite the many similarities.[8-10] Importantly, both thalassemia and SCD are characterized by increased hemolysis with resultant effects on nitric oxide and arginine bioavailability.[11-13] PH in thalassemia appears to be more reliably associated with prior splenectomy, supporting a substantial role for a hypercoagulable state in the pathogenesis.[9,14,15] The recent implication of elevated circulating platelet and erythrocyte microparticles in thalassemia patients associated with markers of hemolysis as well as vascular dysfunction, PH risk, and prior splenectomy,[16] reveal an overlap in these potential mechanisms that requires further study.

Although patients with PH of SCD experienced an increase in vasoocclusive pain events with sildenafil use, this is an adverse effect not expected in thalassemia.[3] Despite the disappointing results of this clinical trial, anecdotal experience confirms that SCD patients with pulmonary arterial hypertension (PAH) diagnosed by right heart catheterization actually receive clinical benefits from this medication.

Patients with thalassemia often have pulmonary venous hypertension due to elevated left-sided pressures and iron deposition in the myocardium. Even so, recent right heart catheterization data suggest that PAH occurs in 2.1% of thalassemia major patients and can be present in approximately 4% of those with thalassemia intermedia.[14] Although this study likely underestimates the true prevalence of PAH in thalassemia given the high cut off for tricuspid regurgitant jet velocity of over 3.2 m/s used for screening, it suggests a potential role for pulmonary vasodilator therapy in selected patients. While the data presented in the current sildenafil study are promising, we would favor the use of pulmonary vasodilators in thalassemia patients only in those who have had PAH confirmed by right heart catheterization. Ideally, we believe that a randomized clinical trial in this population should be undertaken.

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