Pentoxifylline for slow to resolve hepatopulmonary syndrome post liver transplantation : Helpful or Unnecessary ?

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To the Editor,

Hepatopulmonary syndrome (HPS), characterized by hypoxia due to intrapulmonary vasodilation and shunting usually in the setting of cirrhotic portal hypertension, affects at least 20% of cirrhotic patients (3). While liver transplantation (LT) is the only effective treatment for HPS, depending on the severity, recipients may experience protracted hypoxia post-LT (1). Hypoxia following LT imposes risks to the recipient such as graft ischemia. Although patients with HPS receive priority for LT, these patients have inferior outcomes, with 1 year recipient survival rates approximating just 70% as compared to 90% in age-matched controls (1,2). Furthermore, patients transplanted with HPS may suffer psychological hardship in the postoperative setting with residual HPS, and there are no reliable means to predict the duration of the resolution after transplant. Nitric oxide and tumor necrosis alpha (TNF-alpha) are potent vasodilators implicated in the pathogenesis of HPS (4,5). The degree of severity of HPS is determined by the recipient's P02 on a room air arterial blood gas ; patients with P02 < 60 mm Hg have severe HPS and the worst survival. Following LT, subjects with advanced HPS may require prolongation of invasive or non-invasive ventilation. There is limited data on the epidemiology and natural history of severe HPS post-LT. The mean duration of residual HPS in subjects transplanted with severe HPS that required pre-operative non-invasive ventilation was 40 days in a report of 5 subjects (6).

In addition to oxygen therapy, several medical therapies have been assessed for HPS, and a summation of their evidence for safety and efficacy are well described in the literature. It should be noted that these agents have been studied in the pre-LT setting only. Therapies such as almitrine, indomethacin and plasma exchange have failed to show benefit in small trials, but both garlic powder (allium sativum) and aspirin are associated with mild improvements. The proposed mechanisms of actions of these latter agents are a reduction in pulmonary vasodilation due to decreased nitric oxide production.

Given the role of TNF-alpha in the pathogenesis of HPS it is not surprising that there is data – albeit limited – to support pentoxifylline, a TNF-alpha inhibitor, as a novel treatment for HPS. Gupta *et al*. reported on a pilot study of 9 patients with HPS who received pentoxifylline 400 mg PO TID for 12 weeks (7). 8 subjects (88.9%) had complete response to therapy (defined as an increase in PaO2 of > 10 mm Hg from baseline level or PaO2 ≥ 80 mm Hg) (7). Adverse events (non-severe) were frequent, with gastrointestinal side effects in 5 subjects (55.6%) (7). In another study by Tenikella *et al*., pentoxifylline was ineffective in HPS (8). However, therapy in this study was for a shorter duration (6 weeks) and only 1 of 9 subjects (11.1%) tolerated the target dose of pentoxifylline.

We herein report on 2 patients (subjects A and B) with residual HPS post-LT. Subject A, a 27 year old man with advanced primary sclerosing cholangitis, was hospitalized for severe HPS and encephalopathy, and subsequently underwent an uneventful deceased donor LT. Postoperatively, he continued to be symptomatic from HPS and required oxygen supplementation. After 2 weeks, he was started on pentoxifylline, and therapy was discontinued 3 months later when his oxygenation normalized.

Subject B was a 59 years old man with alcoholic cirrhosis and resultant ascites and HPS. He was treated with oral diuretics and oxygen, and after 5.5 months on the waitlist, he had an uncomplicated transplant. His postoperative hospitalization was prolonged due to his underlying HPS necessitating high flow oxygen. He was started on pentoxifyllin, and 51 days later, his oxygenation parameters normalized.

In both subject A and B, neither of whom experienced side effects, oxygenation did not begin to improve until 10 and 15 days following initiation of pentoxiphylline, respectively, and pentoxiphylline was thus deemed efficacious.

LT is the only proven curative therapy for HPS. Given the absence of controlled trials showing the efficacy of pentoxyphylline on accelerating HPS recovery after LT, it is unclear if pentoxifylline has any role. However, based on the limited observational data in LT recipients, it appears that this agent is safe. Physiologic studies and clinical trials are needed to confirm if pentoxyphylline

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accelerates resolution of severe HPS after LT, and until such trials are conducted, the use of pentoxifylline for this indication remains experimental.

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