Docket #: S21-337

Vactosertib (small molecule inhibitor of the TGF-beta pathway) for the treatment of ventilator induced diaphragm dysfunction

Mechanical ventilation (MV) is a widely used treatment modality for the management of respiratory failure in intensive care units (ICU). An estimated 300,000 patients undergo MV annually in the U.S. In these patients, timely extubation promotes improved health outcomes and minimizes the risk of important complications such as pneumonia, delirium, gastrointestinal bleeding, and death. Progressive and dramatic diaphragm weakness and atrophy can result from MV, called ventilator induced diaphragm dysfunction (VIDD), beginning after as little as 2 days of MV. VIDD is characterized by the early reduction in the ability of the diaphragm to generate force in the absence of atrophy, and later development of frank diaphragm muscle fiber atrophy. It has also been established that VIDD is an important driver of failure to wean patients from MV.

Prevention of VIDD is likely to reduce ICU stay, complications, and mortality in ventilated patients. The Shrager lab has demonstrated that components of the TGF-beta pathway, specifically Smad3, are critical to the development of VIDD in rats. Use of a Smad3 inhibitor prevented VIDD in rats in a published study. The inventors hypothesized that administering Vactosertib to patients undergoing MV would disrupt diaphragm dysfunction and atrophy and thereby promote timely extubation. The novel treatment method would likely decrease ventilator days and resultant complications and deaths stemming from intubation and MV. It would have the potential to become a drug widely used in the management of ICU patients requiring MV. There are no medications currently approved for the treatment of diaphragm dysfunction or atrophy related to mechanical ventilation. While device-based approaches exist, these are cumbersome and invasive. The novel method of inhibiting Smad3 is simple enough to be used as a prophylactic.

Applications

- If approved by the FDA, this drug would ideally be given to intubated patients in the intensive care unit (ICU) to reduce ventilator days and related complications

Advantages

- There is currently no approved drug for the treatment of diaphragm atrophy related to mechanical ventilation
- Less invasive and less complex method compared to currently available methods (transvenous stimulation device)

Publications

- Tang, H., L Kennedy, C., Lee, M., Gao, Y., Xia, H., Olguin, F., ... & Shrager, J. B. (2017). "Smad3 initiates oxidative stress and proteolysis that underlies diaphragm dysfunction during mechanical ventilation." Scientific reports, 7(1), 1-14.
- Tang, H., Smith, I. J., Hussain, S. N., Goldberg, P., Lee, M., Sugiarto, S., ... & Shrager, J. B. (2014). "The JAK-STAT pathway is critical in ventilator-induced diaphragm dysfunction." Molecular Medicine, 20(1), 579-589.

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