Cochrane study poorly designed, ignores wealth of data, does disservice to rare disease patients, says Alpha-1 Foundation

MIAMI, FL – The Alpha-1 Foundation today challenged a newly published review which questions the value of augmentation therapy for Alpha-1 Antitrypsin Deficiency (Alpha-1).

The article, “Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease” by Peter C. Gøtzsche and Helle Krogh Johansen, was published this week by the Cochrane Library.

“The Cochrane Library has been respected in the scientific community for carefully performed reviews based on solid evidence,” said Foundation President and CEO John Walsh. “But this report is so flawed in its methodology that it may threaten the reputation of the Cochrane Library. The report does a disservice to rare disease patients everywhere. We hope that therapies for other rare conditions won’t become victims of the same poorly designed analysis.”

The Gøtzsche report, preceded by a press release that created a stir in the Alpha-1 and plasma therapy communities, concluded that augmentation therapy “cannot be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment.”

Robert Stockley, MD, Director of Research and Development at Queen Elizabeth Hospital, Birmingham, UK, had this critique:

“This conclusion was based on retrospective analysis of published data from only two small pilot placebo-controlled studies that were not powered to evaluate the effectiveness of augmentation therapy. This flies in the face of carefully crafted guidelines from the American Thoracic Society, the European Respiratory Society, the American College of Chest Physicians, and the American Association for Respiratory Care – all prestigious organizations that recommend augmentation therapy for the treatment of patients with lung disease due to Alpha-1. The guidelines are based on the totality of the evidence,
scientific understanding of the disease, correcting the biochemical defect, and a wealth of observational studies.”

Danish researcher Asger Dirksen, MD, originally listed as a co-author of the Gøtzsche review, had his name removed before publication.

Dirksen, who was the lead author of both augmentation studies cited by Gøtzsche, said today:

“After seeing the first draft I realized that our points of view were so far apart that collaboration with Peter Gøtzsche and his wife (Helle Krogh Johansen) would not be possible.”

Augmentation therapy is the only available specific treatment for the lung disease associated with Alpha-1, a rare genetic condition. The therapy supplements the missing protein, alpha-1 antitrypsin, in the blood of individuals with Alpha-1, using alpha-1 antitrypsin protein purified from the plasma of healthy donors. Originally developed by National Institutes of Health researchers in the early 1980s, augmentation therapy has been approved by the US Food and Drug Administration (FDA) for more than 20 years.

The Gøtzsche publication relies on combining the results of these two small randomized, placebo-controlled trials (each enrolling less than 100 study subjects), and is not based on the raw data from these studies. The review neglects the fact that the two studies had a significant number of individuals who enrolled in both studies and hence should not be included twice in combined analysis as this biases the data, said the Foundation statement.

“The article also discards an important endpoint of both studies, the evaluation of loss of lung tissue as judged by CT scans, as being of no clinical interest. In fact, CT scans are the most direct method for evaluating the extent and progression of emphysema – the primary lung disease suffered by those with Alpha-1 – and now accepted as the best predictor of mortality in this disease,” said Robert A. Sandhaus, MD, PhD, Foundation Clinical Director. “In fact, the meta-analysis by Gøtzsche did show a benefit of augmentation therapy in reducing the loss of lung tissue as measured by chest CT.”

Sandhaus said the review also “overlooks the effect of study dropouts related to worsening lung function in the placebo groups, which unbalances the differences in treatment groups. Finally, while arguing that augmentation therapy is too costly, the authors ignore the several publications that have actually studied the cost effectiveness of augmentation therapy.”

Added Sandhaus: “In selecting only these two small studies on which to base their sweeping recommendation, Gøtzsche and his co-author have ignored the wealth of other data in the medical literature regarding the effectiveness of augmentation therapy in Alpha-1.” Several large observational studies have concluded that augmentation therapy
slows the progression of lung disease and the largest of these studies, including over 1,100 individuals with Alpha-1, has also shown longer survival among those on augmentation therapy, Sandhaus said.

“While large randomized, controlled, blinded studies remain the gold standard in the evaluation of therapeutics, performing such studies in a population of patients with a rare genetic condition presents almost insurmountable obstacles,” said Sandhaus. “In these situations, scientists, clinicians, and patients must rely on the best evidence available, and the preponderance of scientific data support the use of augmentation therapy in Alpha-1 as recommended by experts representing the leading respiratory societies in both the USA and Europe.”

The Foundation statement said that virtually everyone in the Alpha-1 community agrees that additional studies are needed to help evaluate the effectiveness of augmentation therapy, but Gøtzsche and his co-author end their article with the conclusion that “further studies with surrogate markers cannot be recommended, if the aim is to elucidate whether or not augmentation therapy with alpha-1 antitrypsin has a relevant clinical effect.”

The Foundation’s Medical and Scientific Advisory Committee notes that not every patient with Alpha-1 requires this therapy, and along with several recognized experts in the international scientific community, both in the USA and Europe, is currently preparing a formal response to the Gøtzsche article.

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**About the Alpha-1 Foundation:**
The mission of the Alpha-1 Foundation is to provide the leadership and resources that will result in increased research, improved health, worldwide detection, and a cure for Alpha-1 Antitrypsin Deficiency. For more information, visit [www.alpha-1foundation.org](http://www.alpha-1foundation.org).