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Consequences of Abrupt Cessation of Alpha$_1$-Antitrypsin Replacement Therapy

TO THE EDITOR: Genetic deficiency of alpha$_1$-antitrypsin (AAT), a serine protease inhibitor[1] and potent antiinflammatory and immunomodulatory protein,[2] is an inherited cause of emphysema. In February 2017, Irish health care policymakers opted against reimbursement for intravenous augmentation therapy with plasma-purified AAT for people with AAT deficiency–associated emphysema, the only approved disease-specific treatment available for the condition,[3] citing a lack of evidence of clinical benefit. A cohort of patients with AAT deficiency who had participated in the RAPID and RAPID-OLE trials of AAT replacement[4,5] continued to receive treatment with Respreeza (CSL Behring) as part of an extension agreement brokered by physicians with the manufacturer.

After the February 2017 decision, the manufacturer and Irish health care authorities entered negotiations aimed at securing public funding for treatment of these patients, but the talks concluded in September 2017 without resolution. As a result, 19 patients with severe AAT deficiency had their therapy discontinued immediately in late September.

We conducted a study involving these 19 patients, a natural experiment that would not have been ethically possible to perform under usual circumstances. At the time of withdrawal, patients had been receiving intravenous AAT administered at a dose of 60 mg per kilogram of body weight per week for a mean (±SD) of 9.2±1.2 years and had severe emphysema, with a mean forced expiratory volume in 1 second of 40.6±11.7% of the predicted value and a mean diffusing capacity for carbon monoxide of 44.5±17.6% of the predicted value. None were active smokers or vapers, and four had never smoked. Baseline characteristics of the patients are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

By mid-December 2017, after a mean withdrawal period of 77±2 days, 2 of the 19 patients had died from respiratory failure during an exacerbation. The mean (±SE) number of exacerbations per patient during the withdrawal period was significantly higher than during the corresponding period the previous year (1.5±0.2 per patient vs. 0.5±0.1 per patient; $P=0.002$) (Fig. 1A and 1B), as were hospitalizations (Fig. 1C). These clinical events were matched by decreased antielastase capacity (Fig. 1D) and increased circulating levels of C-reactive protein, lactate, and multiple inflammatory biomarkers, including interleukin-1β, interleukin-6, interleukin-8, and soluble tumor necrosis factor receptor 1 (Table S2 and Fig. S3 in the Supplementary Appendix).

The outcomes of our study were presented to governmental health care policymakers by Alpha-1 Foundation Ireland (founded by one of the authors). Subsequent to this, the government agreed to reenter mediation with the manufacturer, and an agreement was reached to reinstitute the therapy on a cost-sharing basis.

Our data have implications for future studies involving patients with AAT deficiency — in particular, studies seeking to use a drug washout period for patients currently receiving augmentation therapy. Abrupt cessation of a long-term biologic therapy in compromised persons was associated with poor health outcomes. This lesson should not be lost on researchers or policymakers.

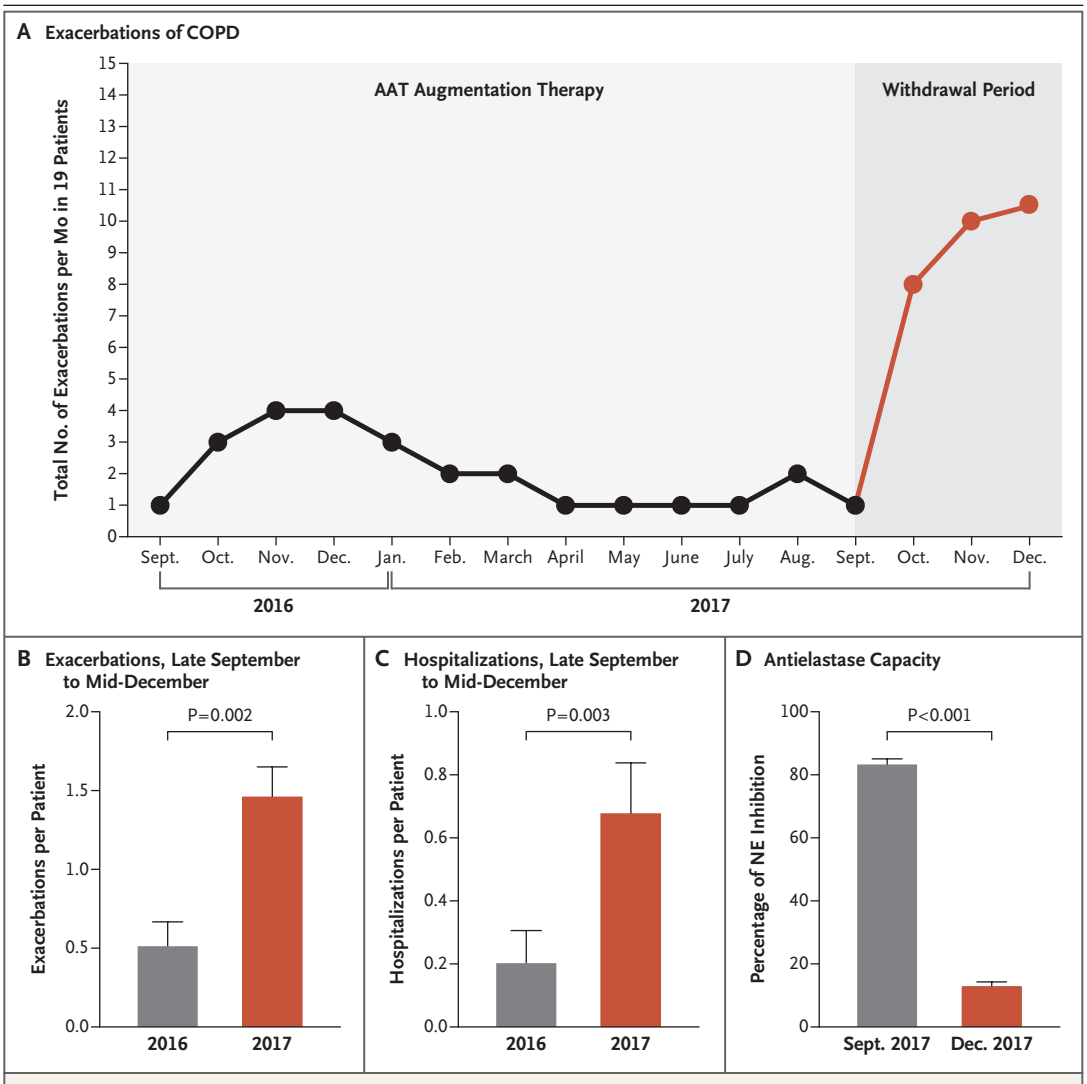

Figure 1. Withdrawal of Alpha$_1$-Antitrypsin (AAT) Augmentation Therapy and Pulmonary Exacerbations and Hospitalizations.

Panel A shows the total number of pulmonary exacerbations per month in the 19 patients in Ireland receiving AAT augmentation therapy for AAT deficiency–associated emphysema during the year before the study (black line) and during the withdrawal period (red line). An event-based definition of exacerbations of chronic obstructive pulmonary disease (COPD) was used. Panel B compares the number of exacerbations per patient during the 2017 withdrawal period with the corresponding period (late September to mid-December) in 2016. All the patients had been vaccinated against influenza and pneumococcus, none were smokers or vapers while receiving therapy or after withdrawal, and none tested positive for influenza during an exacerbation. Withdrawal of therapy was associated with an increased mean (±SE) number of exacerbations per patient (1.5±0.2 vs. 0.5±0.1, P=0.002). This was matched by an increase in the mean number of hospitalizations in the same patients (0.7±0.1 vs. 0.2±0.1, P=0.003) (Panel C). In keeping with a concomitant decrease in circulating AAT levels, a significant decrease in plasma antielastase capacity was observed in response to withdrawal of therapy, with a steep decrease in the mean percentage of inhibition against 1 μM of active neutrophil elastase (NE) between late September 2017 (during receipt of therapy) and mid-December 2017 (after withdrawal of therapy) (P<0.001) (Panel D). T bars indicate standard errors.

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LDL Cholesterol Targets after Ischemic Stroke

TO THE EDITOR: The Treat Stroke to Target trial (Jan. 2 issue),[1] which was conducted in France and South Korea, showed that patients with low-density lipoprotein (LDL) cholesterol levels of less than 70 mg per deciliter had fewer cardiovascular events than those with LDL cholesterol levels of 90 to 110 mg per deciliter after a stroke. However, the incidence of cardiovascular events among Korean patients was similar in the two groups (hazard ratio, 1.11; 95% confidence interval, 0.57 to 2.15).

A U-shaped relationship between cholesterol levels and the incidences of cardiovascular events and death from cardiovascular causes has been reported for Korean patients.[2,3] For example, a study involving 503,340 Korean adults showed that low cholesterol levels were associated with a higher incidence of cardiovascular disease or events and with higher cardiovascular mortality.[2] Another study also showed that low cholesterol levels were associated with higher cardiovascular mortality among Korean patients.[3] If there had been more Korean patients in the Treat Stroke to Target trial, is it possible that the conclusions might have been different?

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THE AUTHORS REPLY: Paraskevas suggests, on the basis of observational data, that low LDL cholesterol levels may be harmful in Asian patients. Similar observations have been shown to be confounded by factors associated with low cholesterol levels, including frailty markers, cardiac insufficiency, and cancer and its treatment. Overall, evidence from epidemiologic studies and randomized trials has shown that low LDL cholesterol levels are associated with a lower incidence of cardiovascular disease, with no heterogeneity according to ethnic group.[1,2] In our trial, which enrolled patients with atherosclerosis who had had a stroke, there was no treatment-by-country interaction and no evidence that a target LDL cholesterol level of less than 70 mg per deciliter was harmful in Korean patients.

Although our trial was not powered to detect an effect across geographic regions, there were no substantial differences in baseline characteristics between French and Korean patients. The median follow-up period, however, was 5.3 years among French patients, as compared with 2.0 years among Korean patients. Because the duration of exposure to statin treatment drives the incidence of cardiovascular events,[1] we are continuing follow-up of the 712 Korean patients for