September 2014 Tucson Pulmonary Journal Club: PANTHEON Study

Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P et al. for the PANTHEON study group. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomized, double-blind placebo-controlled trial. Lancet Respir Med. 2014; 2(3):187-94. [CrossRef] [PubMed]

Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity, mortality, and healthcare utilization. Oxidative stress is thought to be important in COPD pathogenesis, and thus antioxidant therapy has been of great interest, including N-Acetylcysteine (NAC). However, prior studies of NAC in COPD patients have shown varied results. The PANTHEON study was designed to examine the effects of NAC on exacerbation rate in Chinese patients with COPD using a daily dose that is twice as high as that previously studied.

PANTHEON was a randomized double-blinded placebo-controlled trial that enrolled patients aged 40-80 years with GOLD class II, III and IV COPD from 34 academic pulmonary clinics in China. Patients with asthma, oxygen dependence, or poor compliance were excluded. The primary outcome was the COPD exacerbation rate following one year of observation. Exacerbations were defined using the Anthonisen instrument which relies on daily diary reporting. Important secondary outcomes included time to first exacerbation, time to subsequent exacerbations, number of patients requiring antibiotics or steroids, and number of patients requiring hospitalization. The enrollment goal was 1250 patients which would have provided have 95% power to detect a 20% reduction in the exacerbation; however, only 1006 patients were actually randomized. Nevertheless, the study was adequately powered for the primary outcome. More than 80% of the patients were males; 46% had GOLD II severity, 53% had GOLD III severity, and 1% had GOLD IV severity. Mean FEV1 was 1.2 L. Twenty-five percent were non-smokers; 48% were using both ICS and a long-acting bronchodilator at enrollment; and 27% were taking theophylline.

As compared to placebo, twice daily treatment with 600mg of NAC led to a significant reduction in the annual COPD exacerbation rate (RR 0.78, 95% CI 0.67–0.90; p=0.001) and the rate of steroid or antibiotic-requiring exacerbations (RR 0.83 95% CI 0.69-0.99; p=0.04) but not the annual rate of hospitalizations. Interestingly, the time to first exacerbation did not differ between the groups but the time to second and third exacerbations was longer in the NAC group.

This study suggests that NAC, a relatively inexpensive compound that is available over-the-counter, may reduce exacerbation risk among patients with COPD. Given that NAC is safe and the costs would be borne entirely by the patient, it is reasonable to advise patients of this potential treatment option. Patients should be cautioned that the data supporting the benefits of NAC are not conclusive and the magnitude of benefit is likely to be modest. The major limitation includes reliance on a Chinese population of COPD patients in whom the benefits may not be generalizable to US patients. Of unknown

importance is the fact that treatment benefits were limited to self-reported outcomes rather than objective observation of hospitalizations. To the extent that the self-reported data is free of bias, the failure to detect differences in hospitalizations may not matter to patients.

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