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LETTER TO THE EDITOR

A Radiation Mitigator as a Potential Treatment for COVID-19

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In 2010 Jia *et al* published an article (1) in *Radiation Research* describing the results of experimentation in mice using the antioxidant N-acetyl-cysteine (NAC) as a mitigant for lethal acute radiation effects localized to the gut. Briefly, about 62% of mice were rescued from the lethal effects of 20 Gy of ionizing radiation, localized to the abdomen, by the administration of NAC up to four hours postirradiation. At the time we posited that this protective effect came about by tamping down the deleterious effects of high concentrations of reactive oxygen species (ROS) both locally and in the unexposed bone marrow. We concluded that the destructive effects seen in the guts of non-survivors that were mitigated in survivors, had to be coming about by modulating abscopal effects of the marrow-gut interaction.

This situation sounded much like what is posited to be underlying some of the morbidity and mortality of infections of the SARS-Cov-2 virus in the pandemic (COVID-19) currently ravaging the world. We hypothesize that excessive marrow-alveolar abscopal interactions are involved in COVID-19 and propose that treating SARS-Cov-2 virus positive patients with (COVID-19) symptoms (fever and cough) with NAC as a single agent should be investigated. A clinical trial is not only necessary to determine the NAC's efficacy but also critical prior to publicly making such a recommendation since NAC is inexpensive and widely available to the general public without a physician's prescription. There are some preliminary clinical data supporting the use of antioxidants in the management of acute respiratory distress syndrome (ARDS) (2, 3). Although difficult to directly compare, the results with NAC (2) appeared to be at least isoeffective and perhaps slightly superior to those with ascorbic acid (Vitamin-C) (3) which is consistent with the fact that NAC is generally a more potent antioxidant when ROS are the responsible intermediates. Part of our rationale for using NAC to block abscopal effects was also based on an earlier study where we found that NAC was able to blunt or eliminate the adhesion molecule induction associated with arsenic trioxide vascular damage (4). Therefore, there appears to be good rationale for a similar effect in the acute inflammation and subsequent impaired oxygen transport in COVID-patients. Notably, there are four clinical trials for COVID therapy in progress containing

ascorbate (5). We propose that since NAC already has FDA approval for clinical indications such as liver toxicity from acetaminophen (6), and may be even more potent it should also be investigated. Importantly, these liver studies have not shown significant adverse reactions at doses of about 350 mg/kg/day, similar to what we used in the murine experiments (1, 4). However, we must caution that what we are proposing is the use of NAC as a potential treatment for COVID-19 not for use of NAC as a prophylaxis since there is no sound scientific argument for using NAC in that manner and no known mechanism whereby NAC would interfere with viral endocytosis or binding to the ACE-2 receptor. What we propose is if NAC is used to treat COVID-19 it would tamp down the ROS driven cytokine storms responsible for the excessively overactive immune response to the viral infection in some patients and, hopefully, diminish mortality and the need for mechanical ventilation.

Based on our experience with mice and the available clinical evidence [e.g., (1, 2, 6)] we propose that in a clinical trial NAC could be administered orally or within medical facilities intravenously if higher dose regimens are considered [e.g. (6)].

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