

Acetylcysteine as Adjuvant Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Antibody

To the Editor:

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, including Wegener's granulomatosis (WG) and microscopic polyangiitis, is a multisystem autoimmune disorder characterized by vasculitis predominantly affecting microscopic vessels and circulating autoantibodies to neutrophil cytoplasmic antigens. Treatment of this vasculitis has 2 main components, induction of remission and maintenance immunosuppressive therapy to prevent relapse. Recently, new treatments have been used, such as rituximab^{1,2,3}, although the combination of cyclophosphamide and glucocorticoids is the preferred regimen as initial immunosuppressive therapy. Once remission is induced with cyclophosphamide, patients are switched to maintenance treatment with less toxic immunosuppressive drugs, usually methotrexate or azathioprine.

The IFIGENIA trial (Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual study) was published in 2005⁴, describing the effectiveness over 1 year of high-dose oral acetylcysteine (600 mg three times daily) added to standard therapy with prednisone plus azathioprine in patients with idiopathic pulmonary fibrosis. This study demonstrated that therapy with high-dose acetylcysteine given for 1 year, added to prednisone and azathioprine, significantly ameliorated disease progression in terms of vital capacity and diffusing capacity.

The dose of azathioprine in the IFIGENIA trial was similar to doses used in patients with ANCA-associated vasculitis. A notable result of the trial was that toxicity for bone marrow cells was significantly less frequent with acetylcysteine than with placebo. This lower toxicity appeared to be due to the augmentation of glutathione biosynthesis induced by acetylcysteine. One function of glutathione is to detoxify a wide variety of reactive oxygen species (ROS) that are generated within and outside of cells; tissues that are depleted of glutathione are more susceptible to injury⁵.

At present, we are evaluating a 48-year-old man with a relapse of WG, with involvement of the upper respiratory tract and lung (cavitated masses). We conducted a Medline search on the use of acetylcysteine in patients with WG, with no results. Two studies on the usefulness of acetylcysteine in an experimental model of vasculitis showed different results^{6,7}. These studies were performed in a model of mercuric chloride-induced vasculitis in Brown Norway rats, which has significant limitations as an animal model for human ANCA-associated vasculitis⁸. Thus, it is difficult to extrapolate the results of these experiments in animal models to humans. In another study⁹, it was observed that antimyeloperoxidase antibodies in patients with microscopic polyangiitis triggered myeloperoxidase activation *in vitro* and generated a ROS that was highly harmful to endothelial cells. In that study, N-acetylcysteine significantly reduced the activation of myeloperoxidase and improved the survival of endothelial cells exposed to

the byproducts of myeloperoxidase activation. Considering the results of that study⁹ and the IFIGENIA trial⁴, we believe it would be of interest to study whether acetylcysteine may be useful as adjuvant therapy for patients with ANCA-associated vasculitis who are treated with azathioprine. Similarly, if levels of glutathione were decreased in patients with limited forms of WG with pulmonary involvement, it would be interesting to determine whether high-dose acetylcysteine as adjuvant therapy might help prevent relapses in patients with WG in remission.

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