Antioxidant therapy in COVID-19: The crucial role of early treatment and antioxidant typology

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TO THE EDITOR –

I read with interest the paper by de Alencar et al. dealing with possible therapeutic effects of N-acetylcysteine (NAC) in patients with severe COVID-19 [1]; intravenous NAC, a well-known hydrophilic thiol antioxidant, was clinically ineffective compared to placebo. Central problematic aspects of this study are the selection of patients and the type of antioxidant used. Regarding the patients considered, they had already a severe form of COVID-19 with evident pneumonia, a pathological condition conceivably not amenable at that stage to antioxidant treatment. Oxidative stress and lipid oxidation are involved in the pathogenesis of COVID-19-related pulmonary damage. In particular, virus-induced uncontrolled oxidant species generation in monocytes/macrophages results in formation of oxidized phospholipids (Ox-PLs) particularly from lung surfactant, which contains 80-90% phospholipids including unsaturated phosphatidylcholine as oxidizable substrate [2]. Relevantly, OxPLs can activate the macrophage Toll-like receptor 4 (TLR4) signalling cascade, leading to cytokine overproduction and acute lung injury (ALI) eventually culminating in acute respiratory distress syndrome (ARDS) [2]. Thus, a fundamental aspect of antioxidant therapy in COVID-19 is the timing of antioxidant administration, namely antioxidants should be administered early in the course of disease, ideally before pneumonia development, to prevent oxidant-induced OxPLs formation and TLR4 activation. Regarding the antioxidant used, NAC, after intravenous administration, undergoes extensive reaction with plasma and tissue proteins greatly limiting the amount of circulating free drug and its direct antioxidant effects [3]. On the other hand, NAC, in a more lipophilic liposomal formulation, is superior to conventional NAC showing better pharmacokinetic-pharmacodynamic profile [4]. Indeed, there is experimental evidence that liposomal NAC, but not conventional NAC, can afford significant protection against lipopolysaccharide-induced ALI reaching far higher lung concentrations [5]. Lipophilic antioxidants are relevant since they directly protect lung surfactant and cell membrane phospholipids against

oxidative injury. This is the case of vitamin E (V-E), namely α-tocopherol, the most important lipophilic antioxidant in the lung and an integral constituent of alveolar surfactant [6]. Notably, V-E administration can reportedly attenuate experimentally-induced ALI [7] and improve APACHE II score in ARDS patients [8]. V-E acts as an efficient radical scavenger in the lipid phase [9]; as a result, V-E is converted into a radical species, namely α-tocopheroxyl radical, which may be further oxidized into α-tocopheroxyl quinone or reduced back to V-E by reducing compounds with V-E regeneration [9]. The antioxidant ascorbic acid (AA) can reduce α-tocopheroxyl radicals to V-E undergoing oxidation to dehydroascorbic acid [9]; this latter is in turn readily reduced for example by dihydrolipoic acid (DHLA) in the couple lipoic acid/DHLA, so that the association of V-E, AA and DHLA is particularly effective against lipid oxidation [9]. α-tocopheroxyl radicals are reduced directly and efficiently to V-E also by the lipophilic antioxidant ubiquinol but not by thiols [9]. The aforementioned antioxidants may be incorportated into liposomes [4] (Figure 1), in turn prepared using also plasmalogens, ether phospholipids with antioxidant properties present in lung surfactant [10]. Inhalational administration of liposomal antioxidants expectedly maximizes pulmonary therapeutic effects as occurring with nebulized liposomal antibiotics. Early treatment of COVID-19 with this specific antioxidant therapy warrants further investigation.

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Figure 1. Schematic representation of antioxidants incorporated into phospholipid liposome. The hydrophilic antioxidants ascorbic acid, N-acetylcysteine (NAC) and reduced glutathione (GSH) are located in the central hydrophilic liposomal structure (straight arrow), while the lipophilic antioxidants, in particular vitamin E (α-tocopherol), are located within the peripheral lipophilic phospholipid compartment (rectangular arrow). LA/DHLA: lipoic acid/dihydrolipoic acid. GSH, whose biosynthesis is boosted by NAC, is a major endogenous antioxidant available in a liposomal formulation. See text for further explanations.

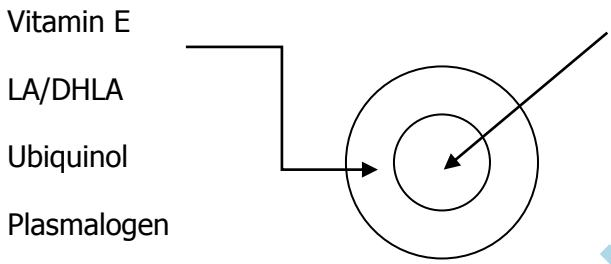

Figure 1