EDITORIAL

Dexamethasone for COVID-19? Not so fast

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Recent announcements indicated, without sharing any distinct published set of results, that the corticosteroid dexamethasone may reduce mortality of severe COVID-19 patients only. The recent Coronavirus [severe acute respiratory syndrome (SARS)-CoV-2]-associated multiorgan disease, called COVID-19, has high morbidity and mortality due to autoimmune destruction of the lungs stemming from the release of a storm of pro-inflammatory cytokines. Defense against this Coronavirus requires activated T cells and specific antibodies. Instead, cytokines are responsible for the serious sequelae of COVID-19 that damage the lungs. Dexamethasone is a synthetic corticosteroid approved by the FDA in 1958 as a broad-spectrum immunosuppressor and it is about 30 times as active and with longer duration of action (2-3 days) than cortisone. Dexamethasone would limit the production of and damaging effect of the cytokines, but will also inhibit the protective function of T cells and block B cells from making antibodies, potentially leading to increased plasma viral load that will persist after a patient survives SARS. Moreover, dexamethasone would block macrophages from clearing secondary, nosocomial, infections. Hence, dexamethasone may be useful for the short-term in severe, intubated, COVID-19 patients, but could be dangerous during recovery since the virus will not only persist, but the body will be prevented from generating protective antibodies. Instead, a pulse of intravenous dexamethasone may be followed by administration of nebulized triamcinolone (6 times as active as cortisone) to concentrate in the lungs only. These corticosteroids could be given together with the natural flavonoid luteolin because of its antiviral and anti-inflammatory properties, especially its ability to inhibit mast cells, which are the main source of cytokines in the lungs. In the end, we should remember that "The good physician treats the disease; the great physician treats the patient who has the disease" [Sir William Osler's (1849-1919)].

Recent announcements indicated, without sharing any distinct published set of results, that use of the corticosteroid dexamethasone in a large trial in the UK apparently reduced mortality of only severe, intubated, COVID-19 patients by about 30% (1). It is obviously important to await the publication of the complete set of results, as well as the subsequent course of the patients enrolled.

The recent Coronavirus [severe acute respiratory syndrome (SARS)-CoV-2]-associated multiorgan disease, called COVID-19 (2), has high morbidity and mortality due to autoimmune destruction of the

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lungs stemming from the release of a storm of pro-inflammatory cytokines (3). Defense against this Coronavirus requires activated T cells and specific antibodies (4, 5). Instead, cytokines are responsible for the serious sequelae of COVID-19 that damage the lungs (6).

Dexamethasone is a synthetic corticosteroid approved by the FDA in 1958 as a broad-spectrum immunosuppressor and it is about 30 times as active and with longer duration of action (2-3 days) than cortisone (7). Dexamethasone would limit the production and damaging effect of the cytokines (8), but will also inhibit the protective function of T cells and reduce the ability of B cells to synthesize antibodies (7). Moreover, dexamethasone would block macrophages and NK cells from clearing secondary, nosocomial, pathogens (9).

Clinical evidence does not support the use of corticosteroids in COVID-19 (10). Even worse, the use of corticosteroids has been associated with increased plasma viral load that will persist after a patient survives SARS (11). Hence, dexamethasone may be useful for the short-term in severe, intubated, COVID-19 patients, but could be outright dangerous during recovery since the virus will not only persist, but host defense mechanisms will be curtailed.

A safer approach would be to administer a pulse of intravenous dexamethasone, followed by nebulized triamcinolone (6 times as active as cortisone) to concentrate in the lungs. Once patients leave the hospital, they could be given anti-cytokines (12), such as the anti-IL-6 biologic tocilizumab (13), or inhibitors of other IL-1 family members (14).

A key source of pro-inflammatory cytokines are the mast cells (15) that release large amounts of IL-1β (16), IL-6 (17), and TNF (18). In this context, it would be important to inhibit mast cells in COVID-19 (19), with the natural flavonoid luteolin, which is safer than corticosteroids (20). Luteolin is a potent inhibitor of mast cells (21, 22), but also has anti-inflammatory (22, 23) and antiviral (19) properties.

Covid-19 is a multiorgan disease that requires not only addressing the causative agent, (SARS)-CoV-2, but care of the whole patient. As such, we should remember Sir William Osler's (1849-1919) statement that "The good physician treats the disease; the great physician treats the patient who has the disease" (24).

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