AT1 Receptor Blockers (“sartans”) for Severe Acute Respiratory Syndrome (SARS)

The reason why the coronavirus kills in SARS is because of the exuberant host response, not because of tissue damage by the virus. Patients die of high fever and respiratory insufficiency. The lung interstitium is invaded by inflammatory cells, and alveoli fill with an inflammatory exudate. As a result, alveoli cease to become gas-exchanging units. Even in the absence of alveolar exudate, the distance between the alveolus containing oxygen-rich air and oxygen-transporting hemoglobin in the red cells of pulmonary capillaries widens because of the interstitial inflammation. Gas exchange becomes grossly impaired.

Similarly, coronavirus does not cause fever; the body's immune response does. Both interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) are the pyrogens causing the high fever. But these interleukins are made by the host's T cells and antigen-presenting cells (APCs), including activated macrophages.

Decreasing the host's over-exuberant immune response to the coronavirus should reduce such symptoms.

It is our belief that angiotensin II is an as yet unrecognized major stimulator of the immune response. The rate-limiting step for its synthesis is the angiotensin I-converting enzyme (ACE). ACE is present on the plasma membrane of T cells and appears on the plasma membrane of antigen presenting cells (APCs) such as monocytes and macrophages once they have become activated.

Angiotensin II does a number of things. It probably stimulates the production of interferons by CD4+ T cells (helper T cells). CD4+ cells stimulate the activity of CD8+ cells (cytotoxic T lymphocytes, or CTLs). The primary job of CTLs is to kill virally infected epithelial cells.

Interferon-γ in particular is a major cytokine released by CD4+ helper T cells (T_H1 cells) in response to viral infection, and a major activator of CD8+ CTLs. Angiotensin II, operating through angiotensin II type 1 receptors (AT1Rs) appears to enhance the production of interferon-γ. Thus, angiotensin II operates as a very early amplifier of the host defense system against viral infection.

Angiotensin II also increases vascular permeability. It causes vasoconstriction of pulmonary arterioles in areas of inflammation, thus minimizing V/Q mismatch. Angiotensin II is probably the normal mechanism for controlling V/Q matching in the lung, in fact. When the pulmonary interstitium fills with inflammatory cells, or the alveolus itself fills with an inflammatory exudate and gas exchange becomes impaired, the arteriole leading to that alveolus undergoes vasoconstriction so blood no longer goes to the non-functioning alveolus. This physiological response is referred to as matching ventilation (V) with perfusion

(Q). It likely occurs because ischemic tissue generates adenosine, which increases blood velocity, activating pulmonary endothelial ACE acting as a mechanosensor.

In the case of infection, ACE on T cells and activated macrophages (including resident alveolar macrophages) adds significantly to local angiotensin II production, further promoting vasoconstriction of the arterioles feeding the inflamed alveoli.

Two treatment possibilities appear promising. One is inhibition of ACE, but effective inhibition of tissue ACE requires a very high dose of ACE inhibitor, e.g. 2 mg/kg/d quinapril.

Another possibility is selective AT1R inhibition using an angiotensin II receptor blocker ("sartan") such as valsartan (DIOVAN), irbesartan (AVAPRO), losartan (COZAAR), candesartan (ATACAND), telmisartan (MICARDIS), or eprosartan (TEVETEN). The lowest dosage should be used, and even these tablets should be split in half to minimize the danger of excessive lowering of blood pressure in volume-depleted acutely ill patients.

For example, an 80 mg DIOVAN capsule can be split in half, and 40 mg given once a day while the patient is in bed (e.g. at bedtime, or q am if the patient is already hospitalized). Irbesartan (AVAPRO) comes in 75 mg tablets which can be further split in half, and ˜37 mg given to the patient once a day.

The evidence for this approach is circumstantial at the moment. Until we have patient outcomes data for SARS, it will remain so. However, the alternative for SARS patients is to do nothing and run a 10% risk of acute mortality. The evidence consists of the following:

- 1. CD4+ T_H1 cells produce interferon-γ in alopecia greata; this disease, in its active form, can be shut down within 36 hours of starting valsartan 40 mg po qhs (n=1). In its more chronic form, it takes more than 5 days for valsartan to have an effect (n=1).
- 2. Infection by several common viruses, including hepatitis A and B, and HIV, are associated with overactivity of ACE, specifically the ACE deletion/deletion (D/D) genotype. So is infection with tuberculosis. So is progression of HIV to AIDS. [Ref. Moskowitz D W. Is ACE a 'master' disease gene? Diabetes Technology & Therapeutics 4(5): 683-711, 2002.] It appears that activation of T cells is an important step for viral replication. Angiotensin II is also important for many of the complications of HIV, such as HIV-associated nephropathy, and Kaposi's sarcoma. The latter is a tumor of hyperproliferating macrophages. Mesangial cell hyperplasia is the pathology of HIV-associated nephropathy; mesangial cells are essentially resident macrophages within the glomerulus.
- 3. Another autoimmune disease characterized by T cell autoimmunity, psoriasis, responded dramatically to high dose quinapril (2 mg/kg/day). A 62 yr old white man was able to stop his daily dose of 75 mg methotrexate after several months on high dose quinapril for diabetes and hypertension. Only residual psoriatic disease remains at the site of formerly exuberant disease.

Use of angiotensin receptor blockers (ARBs) to treat diseases associated with excess ACE

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