Why AT1R blockade makes sense for SARS

Sixty percent of the genomic sequence of the SARS coronavirus differs from the only two known strains of human coronavirus[1,2]. Human coronaviruses produce a mild "cold," but SARS often produces acute respiratory distress syndrome (ARDS).

The novelty of coronavirus antigens apparently provokes an exaggerated immune response in the host, which explains why steroids, which depress the immune response, are of greater clinical utility in this disease than antiviral therapy[3]. Cytokines, especially TNF-alpha, are responsible for the early flu-like symptoms of fever, headache, myalgia seen in SARS. The high degree of fever suggests that TNF-alpha release is unusually strong. Indeed, the host's exuberant immune response to novel antigen(s) likely explains why SARS resembles the 1918 influenza pandemic in its disease severity[4].

TNF-alpha is released by virally infected macrophages[4,5]. Macrophages express angiotensin I-converting enzyme (ACE) on their plasma membrane when they become activated, and ACE is the rate-limiting step for angiotensin II production[6-8]. TNF-alpha synthesis and secretion is enhanced by angiotensin II in renal macrophages, although the effect of angiotensin II on alveolar macrophages has not yet been studied[9].

Virally infected alveolar type II pneumocytes and macrophages recruit additional monocytes, in part through synthesis and secretion of monocyte migration inhibitory factor (MMIF). The synthesis and release of MMIF is stimulated by angiotensin II, at least in renal tubular epithelial cells[10].

Apoptosis of alveolar macrophages after viral infection amplifies the immune response and lung damage[11]. Alveolar apoptosis may be stimulated by angiotensin II, as in apoptosis of pulmonary epithelial cells (see below).

A major problem of SARS is that, after about a week of infection, virally infected type II pneumocytes lift off from the alveolar basement membrane leaving hyaline membranes behind, similar to the behavior of Vero cells (African green monkey kidney cells) in culture[2]. This process clearly involves apoptosis of the sheet of epithelial cells[1,2]. Type II pneumocyte apoptosis is stimulated by angiotensin II, probably acting through type 1 receptors (AT1R's)[12,13]. Pulmonary epithelial cell apoptosis is a common feature of the acute respiratory distress syndrome (ARDS).

Several viral diseases, including HIV, hepatitis A and B are more frequent in patients with the ACE deletion/deletion genotype (ACE D/D genotype), which is associated with overactivity of ACE[7].

On pathology, SARS lung can look like organizing bronchiolitis obliterans or diffuse alveolar damage[1,2]. The latter is typical of acute respiratory distress syndrome (ARDS). In a mouse model, a ten-fold higher dose of virus was sufficient to convert bronchiolitis obliterans into ARDS[14]. Inhibition of angiotensin II should therefore be effective in the treatment of ARDS[15], and SARS in particular.

However, SARS patients cannot tolerate ACE inhibition, since their blood pressure is already low because of volume depletion. A small dose of an AT1R antagonist (angiotensin II receptor blocker, or "ARB") can inhibit T cell production of IFN-gamma and stop hair loss within 36 hours in active alopecia areata in a 14 year old girl, with only minimal lowering of blood pressure (Moskowitz DW,

unpublished case report). Apart from lowering blood pressure, ARBs have no known side effects.

A similarly small dose of an ARB should be useful for treatment of patients with established SARS, as well as prophylaxis in uninfected patients. If the above line of reasoning is correct, even a small dose of an ARB should convert infection with the SARS coronavirus into a mild disease which more closely resembles infection with one of the two known human strains of coronavirus than ARDS[16].

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