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TNF- α inhibition for potential therapeutic modulation of SARS coronavirus infection

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RESEARCH LETTER

TNF- α inhibition for potential therapeutic modulation of SARS coronavirus infection

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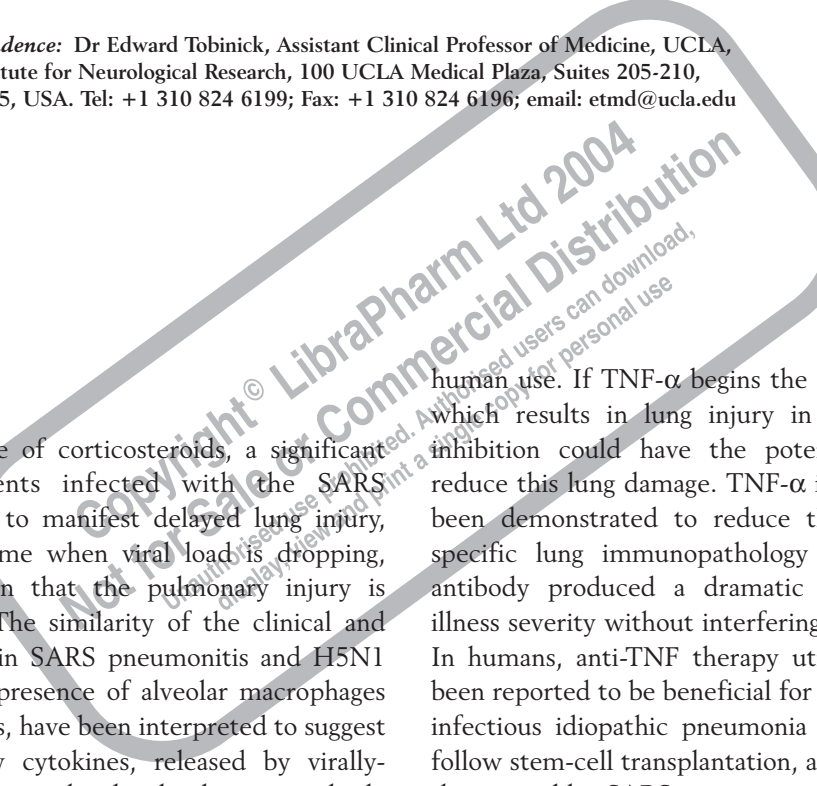
Dear Sir,

Despite the early use of corticosteroids, a significant percentage of patients infected with the SARS coronavirus continue to manifest delayed lung injury, which occurs at a time when viral load is dropping, supporting the notion that the pulmonary injury is immune in nature¹. The similarity of the clinical and pathological changes in SARS pneumonitis and H5N1 pneumonia, and the presence of alveolar macrophages and hemophagocytosis, have been interpreted to suggest that proinflammatory cytokines, released by virally-stimulated macrophages in the alveoli, play a central role in the pathogenesis of SARS². H5N1 viruses had previously been shown to be potent inducers of a specific pro-inflammatory cytokine, TNF- α , in macrophages *in vitro*³. H5N1 virus infection was found to lead to highly excessive TNF- α secretion by macrophages, quantitatively similar to that seen after stimulation with lipopolysaccharide³. Increased stimulated TNF- α secretion with increasing age was suggested as a possible explanation for the age-related severity of illness observed in individuals with H5N1 disease³. Similar age-related disease severity has been observed in SARS⁴.

Identification of the potential involvement of TNF- α may have important therapeutic implications for SARS because specific inhibitors of TNF- α are available for

human use. If TNF- α begins the inflammatory cascade which results in lung injury in SARS, then TNF- α inhibition could have the potential to dramatically reduce this lung damage. TNF- α inhibition has, in fact, been demonstrated to reduce the severity of virus-specific lung immunopathology in mice⁵. Anti-TNF antibody produced a dramatic reduction of overall illness severity without interfering with viral clearance⁵. In humans, anti-TNF therapy utilizing etanercept has been reported to be beneficial for treatment of the non-infectious idiopathic pneumonia syndrome which can follow stem-cell transplantation, a pulmonary syndrome that resembles SARS pneumonia in some respects⁶.

The use of biologic anti-TNF therapy for SARS coronavirus infection could provide a more specific and potentially more effective method of interrupting the inflammatory cascade than the use of corticosteroids, but this remains a hypothesis for the present. Despite the known potential of these agents to increase mortality in bacterial sepsis, it could be argued that to reduce coronavirus-initiated immune lung injury they might be safer than the use of pulse methyl-prednisolone. Among the three approved anti-TNF biologics – adalimumab, etanercept, and infliximab – the use of etanercept would perhaps be the agent of first choice, due to its long record of safety, short half-life, and reduced immunogenicity. In view of the possible need for rapid and potent TNF-inhibition, an increased



dose of etanercept and intravenous use might be considered.

Studies utilizing TNF- α inhibitors for coronavirus infection, *in vitro* and in animals, would be prudent prior to anti-TNF treatment of patients with SARS. If the SARS coronavirus does indeed lead to massive release of TNF- α from alveolar macrophages, then early inhibition of TNF- α , utilizing one of the FDA-approved biologic TNF- α inhibitors, might be able to prevent TNF- α mediated immune activation and therefore reduce pulmonary injury in these patients. Similarly, this approach could be of potential importance for the prevention of immune-mediated pulmonary injury with certain strains of influenza. *In vitro* and animal testing could provide important information regarding the potential efficacy of this therapeutic approach prior to a resurgence of a potent strain of either one of these viral pathogens. If TNF- α inhibition were shown to effectively reduce lung pathology following SARS coronavirus or influenza infection, then study of prophylactic use, prior to infection, in high-risk populations might also be indicated. Lastly, a note of caution is advised because anti-TNF treatment, while potentially beneficial for reducing immune-mediated pulmonary injury, might also inhibit innate anti-viral defense mechanisms. Therefore the timing of anti-TNF intervention may be important, and the concurrent use of specific anti-viral therapy, if available, is advised.

Acknowledgment: The author has an issued patent (U.S. patent 6,419,934 B1, filed 5 September 2000) which has claims covering the treatment of influenza with TNF inhibitors; he has also filed a patent application covering the use of TNF inhibitors for the treatment of SARS.

Summary: Clinical and experimental evidence implicate TNF as a possible mediator of the severe immune-based pulmonary injury which can follow infection with H5N1 influenza and SARS coronavirus. Compared with the use of corticosteroids, the use of biologic TNF inhibitors, including etanercept, has the potential to be a more specific and more effective method of ameliorating the severe alveolar damage which can occur following infection with these agents. Further study is indicated.

Key words: Coronavirus – Etanercept – H5N1 – SARS – TNF

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