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DERMATOLOGIC THERAPY WILEY

LETTER

Could patients taking isotretinoin therapy be immune against SARS-CoV-2?

Dear Editor,

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still expanding. Angiotensin-converting enzyme 2 (ACE2) is the key host cellular protein required for SARS-CoV-2 entry. Its expression has been demonstrated in many tissues including alveolar epithelial type II cells in lungs, oral mucosa and intestine, heart, kidney, and endothelium.[1] In the skin, ACE2 immunoreactivity was detected in basal cell layer of epidermis and hair follicles, eccrine glands, blood vessels and capillaries, sebaceous glands, and its surrounding smooth muscle cells.[1] ACE2-expressing cells can act as home cells and are prone to SARS-CoV-2 infection as ACE2 receptor facilitates cellular viral entry and replication.[1] Fang et al have suggested that patients with hypertension and diabetes mellitus may be at higher risk of COVID-19 infection, as these patients are often treated with angiotensin II type-I receptor blockers, which have been previously suggested to increase ACE2 expression.[2] This was recently supported by Sinha et al "preprint" who analyzed a publicly available Connectivity Map (CMAP) data set of pre-/posttranscriptomic profiles for drug treatment in cell lines for over 20 000 small molecules to investigate the effect of different drugs including antihypertensives on modulating ACE2 expression. They demonstrated that isotretinoin, which is a retinoic acid derivative used in treatment of acne vulgaris, was the strongest downregulator of ACE2 receptors, so it may prevent the cellular entry of SARS-CoV-2.[1] It was observed that elderly patients who mostly suffered from hypertension and diabetes mellitus were the most commonly infected with SARS-CoV-2, and this age group neither suffered from acne vulgaris, which is a disease of teenagers and young adults, nor had a history of isotretinoin intake before getting infected. This may be one of the explanations that can be added to Fang et al's[2] findings to explain the reason of this age variability. Moreover, Wu et al demonstrated that isotretinoin is a potential inhibitor of papain-like protease (PLpro), which is a protein encoded by SARS-CoV-2 genes,[3] and is a deubiquitinating enzyme, which modulates the host cell ubiquitination machinery to the advantage of the virus,[4] so it is considered one of the important proteins that should be targeted in COVID-19 treatment.[3] In addition, isotretinoin was reported to increase CD4 counts and markedly decrease viremia in HIV-positive patients suffering from acne vulgaris.[5] Moreover, it was demonstrated that isotretinoin may increase immune mechanisms and alter chemotaxis of monocytes to reduce inflammatin,[6] this may suggest an immunomodulatory action by isotretinoin. From this point, could patients taking isotretinoin be at lower risk of acquiring SARS-CoV-2? We are in need for further studies to prove that in vitro and in vivo.

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