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LETTERS TO THE EDITOR

Could isotretinoin be a protective agent against COVID-19?: A dermatologist perspective

Dear Editor,

Being a "trending" unique treatment for moderate-to-severe acne, isotretinoin (13-cis retinoic acid) (ISO) is currently considered by experts the first-line treatment even for mild acne, unless there is an absolute contraindication. ISO was identified, among other retinoids, to inhibit SARS-CoV-2 replication in Vero E6 cells. Shoemark et al.[1] noted that ISO may bind to the SARS-CoV-2 spike protein at SARS-CoV-2 spike fatty acid site, influencing the conformational changes required for receptor binding, stabilizing the locked ACE2 conformation of the spike protein. That reduces the opportunity for receptor-mediated cell entry via interaction with ACE2. In this way, isotretinoin may affect viral entry, particularly in the early stage of the infection process.[1] Moreover, ISO upregulates the host antiviral response, through stimulation of interferon-1 (IFN-I) secretion, potentiating immune response to it, and eventually reduces viral infectivity.[1] Spike protein interaction is limited not only to ACE2, but also to neuropilin receptors (NRPs) in cells where ACE2 expression is low. Notably, NRPs are highly expressed in human lung tissue and olfactory epithelium compared to ACE2. Interestingly, NP1 is highly expressed in keratinocytes. Thus, NRPs act as co-receptors for SARS-CoV-2 cellular entry, including keratinocytes.[2] Keratinocytes-derived vascular endothelial growth factor (VEGF) acts on both the endothelial cells of the dermis and the same keratinocytes leading to the development of cutaneous signs of COVID-19. Hence, some patients are potential to develop cutaneous manifestations of COVID-19, while others are not, based on the degree of keratinocytes' NRP expression.[2] VEGF-A is a key regulator for the differentiation of progenitor endothelial cells. ISO has shown, perhaps in a dose-dependent manner, a decreasing effect on the soluble level of its receptor (sVEGFR1). Calprotectin is a heterodimer involved in neutrophil-related inflammatory processes. Circulating calprotectin mediates the cytokine storm associated with an increased severity of COVID-19.[3] ISO may decrease high level of circulating calprotectin in patients with severe acne lesions. In a Turkish study, the authors noted that of the 302 acne patients on ISO, 33 had PCR test for SARS-CoV-2 and 2 of the 33 patients tested for SARS-CoV-2 had positive PCR. On the contrary, of the 329 patients who were on topical treatment, [4] of the 45 patients tested for SARS-CoV-2 had positive PCR. One of the two patients who had PCR positivity while on ISO was on a daily dose of 30 mg of isotretinoin for 6 months, presented with only mild fever. The other one was on a daily dose of 40 mg of ISO for 4 months, presented with mild fever and headache.[5] Donnarumma et al.[4] noted four of 34 patients on ISO reported cough and rhinorrhea; of them, only two patients reported 2-day elevation of body temperature not over 37.5. However, none had been diagnosed for COVID-19. Dryness of nasal mucosa was reported in 47% of their cohort. That may carry a concern for possible dryness of lung secretions with a subsequent increased risk of pulmonary infection secondary to mucus plugs fixed in the lungs. Intriguingly, no worsening of lung function has been reported in cystic fibrosis patients while on ISO; rather, there was an improvement in lung function with no secondary infection in one patient.[6] Following infection, SARS-CoV-2 could induce initial rapid loss of the mature lung alveolar epithelial program followed, later, by cellular toxicity and loss of alveolar facultative progenitors. Fauchère et al.[7] reported maturation of the lungs in a nonviable fetus of 22 weeks' gestational age following accidental maternal intake of 30 mg/day of ISO till delivery. The administration of ISO to the critically hospitalized COVID-19 patients may burdensome. The ISO administration via powder aerosol was demonstrated to achieve higher concentrations in the lungs than in the oral route.[8] Based on the findings of such preliminary reports, further well-designed studies to explore the benefits of ISO re-purposing in COVID-19 are warranted.

KEYWORDS

isotretinoin, COVID-19, skin

ETHICAL APPROVAL STATEMENT

Authors declare human ethics approval was not needed for this study.

AUTHOR CONTRIBUTIONS

Ayman Abdelmaksoud considered the idea of the manuscript, retrieved data from the literature, involved in the initial writing, and submitted the manuscript. Anant Patil retrieved the data from literature. Recep Dursun reviewed the initial draft. Selami Aykut Temiz searched for similar published articles and involved in English editing. Erhan Ayhan contributed to manuscript perception. Mohamad Goldust involved in the initial scientific editing. Michelangelo Vestita wrote the final draft. All the authors reviewed the manuscript and accepted its final version for submission to *Journal of Cosmetic Dermatology*.

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