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Perspective

The Potential Role of Isotretinoin (13-Cis-Retinoic Acid) in the Medical Therapy of COVID-19

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ABOUT THE STUDY

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, has infected over 100 million people and killed over 2.4 million people worldwide, and it is still spreading. Given the urgency of the COVID-19 pandemic, the clinical investigation of approved drugs is a promising alternative to find a timely effective treatment.

Isotretinoin can be used in the treatment of SARS-CoV-2 according to the findings of previous studies and researches. Isotretinoin could strongly inhibit both inflammation and viral entry in severe acute respiratory syndrome coronavirus 2 infection *via* decreasing the overproduction of early response proinflammatory cytokines. It could also block the entry of COVID-19 by inhibiting androgenic factors that may induce serine 2 Transmembrane Protease (TMPRSS2) expressions.

Moreover, isotretinoin is a potential repressor and inhibitor of Papain-Like protease (PLpro), which is a lethal protein, expressed by COVID-19 genes and is an enzyme of deubiquitination which facilitates virus replication in patients with COVID-19. Furthermore, the genome of middle east respiratory syndrome coronavirus is recognized by Melanoma Differentiation-Associated protein-5 (MDA5) and endosomal Toll-Like Receptor 3 (TLR3) as pathogen-associated molecular patterns. This recognition may results in the formation of type-1 Interferon (IFN1). As an evasion mechanism, virus synthesizes proteins that interfere with IFN induction pathway. 13-cis retinoic acid was found to induce significant upregulation of Toll-Like Receptor 3 (TLR3), Mitochondrial Antiviral-Signaling protein (MAVS) and IFN regulatory factor 1 expression an immune boosting action that may result in an immune response to dsRNA intermediate leading to the production of type I IFNs which is important to enhance the release of antiviral proteins for the protection of uninfected cells. According to our recent findings COVID-19 was found to bind to STRA6 receptor of retinol. Consequently COVID-19 may lead to retinoic acid deficiency and immunosuppression which commonly showed in COVID-19 patients.

This showed a marked reduction in the cholesterol levels of COVID-19 infected patients compared with healthy controls. Also, during the early stages of infection, it was found that cholesterol levels decline rapidly and increase as the patient starts to recover. Therefore, indicating that cholesterol may play an important role in defending the body against such infections. Stemming from previous studies, there is a strong relation between immune response and cholesterol levels. The immune response is compromised and antiviral immune cells are reduced and suppressed when cholesterol levels are inhibited in the case of viral infection such as COVID-2019 infection. Intracellular cholesterol level is regulated by two competing pathways, cholesterol uptake and efflux, and ATP-Binding Cassette Transporter (ABCT) plays a major role in the cholesterol efflux pathway.

Retinoic acid induces macrophage cholesterol efflux and inhibits atherosclerotic plaque formation in apoE-deficient mice. In addition Retinoic acid induces homing of protective T and B cells to the gut after subcutaneous immunization in mice. Moreover, the high neutrophil to lymphocyte ratio observed in critically ill patients infected with COVID-19 is associated with excessive levels of Reactive Oxygen Species (ROS), which promote a cascade of biological events that drive pathological host responses. Isotretinoin produces significant inhibition of neutrophil chemotaxis and monocyte in *vivo* in patients with cystic acne. In addition, 13-cisretinoic acid has more therapeutic features which may make it promising treatment against COVID-19.

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