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ISOTRETINOIN: A POTENTIAL TREATMENT FOR COVID-19

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ABSTRACT

The emergence of coronavirus disease-2019 (COVID-19) pandemic and its catastrophic consequences resulted in extreme demand for treatment. Nevertheless, it requires a relatively long time to approve new drugs to be used on humans. Therefore, researchers are reconsidering widely available and already approved drugs to be used in the treatment of COVID-19. This review illustrates the promising effect of isotretinoin in the treatment of SARS-CoV-2 owing to its ability to reduce Angiotensin Converting Enzyme (ACE2) receptor expression and its impact on immunity, androgen receptors, and respiratory diseases.

INTRODUCTION

Tretinoin, also known as All-Trans Retinoic Acid (ATRA), was patented in 1957 and approved for medical use in 1962.[1] It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.[2] Its Isomer isotretinoin was patented in 1969 and approved for medical use in 1982.[1] Its mainly used for severe cystic acne or acne that has not responded to other treatments.[3]

MATERIALS AND METHODS

Isotretinoin could be a potent intervention arm in the treatment of coronavirus disease-2019 (COVID-19) owing to its actions on many arms, which are believed to counter the effects of the virus. These arms are as follows:

- ACE2 Downregulation
- Papain-like proteinase (PLpro)
- Immunity Modulation and Cytokine Release Syndrome
- Metabolism into Retinoic Acid and its benefits
- Androgen Receptors and TMPRSS2 expression
- Treatment of Emphysema and Alveolar induction

RESULTS

1. ACE2 Receptors, SARS-CoV-2, and Isotretinoin

In January 2020, during the early stages of the outbreak, scientists published that the virus utilized Angiotensin Converting Enzyme (ACE2) receptor on cells for entry.[4] ACE2 is an essential host cellular protein required for the virus entry, and its expression has been significantly found in a multitude of body tissues, including alveolar epithelial type II cells in the lungs, oral mucosa, intestine, heart, kidney, endothelium, and skin. ACE2-expressing cells can act as home cells and are especially prone to SARS-CoV-2 infection. A study reviewing the effects of 672 clinically approved drugs in CMAP, found that isotretinoin was the strongest down-regulator of ACE2 expression in cells.[5]

2. Papain-like proteinase (PLpro), SARS-CoV-2, and isotretinoin

PLpro is responsible for the cleavages of N-terminus of the replicase poly-protein to release Nsp1, Nsp2, and Nsp3, which is essential for correcting virus replication.[6] PLpro was also confirmed to be significant to antagonize the host's innate immunity. As a crucial enzyme in the process of coronavirus replication and host infection, PLpro has been a favorite target for coronavirus inhibitors. Yet, the FDA has approved no inhibitor for medical use. A computational analysis of therapeutic targets found isotretinoin to be a potential inhibitor.[7]

3. Immunity Modulation and Cytokine Release Syndrome, SARS-CoV-2, and Isotretinoin

Recent studies revealed that COVID-19 fatal complications also include Cytokine Release Syndrome (Cytokine Storm).[8] Isotretinoin (13cRA) exerts a suppressive activity on T cell-mediated immunity, which is intensive enough to suppress an ongoing immune response. This effect can be achieved at nontoxic concentrations that may also be attained in human therapy.[9] Therefore, isotretinoin may mitigate the severity of the complication.

4. Isotretinoin metabolism into Retinoic Acid and its benefits

As documented by the FDA, Isotretinoin's metabolites include All-Trans Retinoic Acid (ATRA). RA is vital in the activation of dendritic cells, and inhibition of spontaneously activated human T lymphocytes in vitro. 13-cis RA also activates Th2 cytokine production, enhancing circulating dendritic cell numbers. This may counter the reduced lymphocytic count demonstrated in COVID-19 patients. COVID-19 has been documented by autopsies to cause DIC.[10] Retinoic acid is known to possess in vivo anti-inflammatory, antiplatelet and fibrinolytic activities.[11]

5. Androgen Receptors, DHT and TMPRSS2 expression

It has been documented across the world and especially in China and Italy, that the disease is more severe in adults more than children, and in males more than females.[12] Moreover, it was found that ACE2 expression in younger rat lungs is increased. Therefore, this may explain the reduced infections in children.[13] Also, the TMPRSS2 gene was found to be part of the priming process of SARS-CoV-2's spike protein.[14] Additionally, TMPRSS2 is sensitive to Dihydrotestosterone (DHT), and its expression is increased in a dosage-dependent manner. Isotretinoin was found to inhibit the production of DHT, thus resulting in an inhibition of androgen receptor stimulation, a lower expression of TMPRSS2.[15,16] and, hopefully, reduced viral infection.

6. Treatment of Emphysema and Alveolar induction

A study on rats found that ATRA can reduce the harmful effects of emphysema in mice, and is feasible for further research in humans.[17] An individual case found improved Alveolar septation in 2009.[18] Furthermore, isotretinoin has not shown any harmful effects, and it has been recommended to continue prescribing the drug for both dermatological and cancer patients.[19]

DISCUSSION

Isotretinoin is proved to be the strongest down-regulator of ACE2 receptors expression, the target receptor for COVID-19. Moreover, isotretinoin was found to be a potential inhibitor of Papain-Like proteinase, an indispensable enzyme in the process of coronavirus replication and host infection. Additionally, it has exerted a suppressive effect on ongoing immune response, which may lead to less severe complications of COVID-19. Also, retinoic acid, an isotretinoin metabolite, may counteract DIC and reduced lymphocytic count in COVID-19 patients. Furthermore, isotretinoin has diminished the expression of TMPRSS2, which was found to be part of the priming process of SARS-CoV-2's spike proteins. Therefore, along with the wide availability and absence of evidence of harmful effects towards COVID-19 patients, isotretinoin may be a promising agent against COVID-19 and is urgently recommended for further study and evaluation.

Conflict of interest: The authors state that there are no conflicts of interest.

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