

# Systemic retinoids in the COVID-19 era – are they helpful, safe, or harmful? a comprehensive systematized review

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Nowadays, the coronavirus disease 2019 (COVID-19) pandemic has become a global health problem and, given the high mortality and transmission rate of this infection and the lack of approved or specific treatments for it so far, the exploitation of the potentials of existing drugs is of paramount importance, hence, we aimed to investigate all possible COVID-19-related mechanisms of systemic retinoids.

We systematically searched all related evidence in various data bases about the effect of retinoic acids on respiratory failure as the most important COVID-19-related complication and the other important potentials of this drug to affect COVID pathomechanism.

Considering the various behaviors and presentations of this virus in different people, paying attention to the underlying diseases, physical conditions, genetics, and medications that cause these differences may be helpful in reducing the mortality and morbidity of the disease. In the field of dermatology, retinoids are a group of drugs that have controversial evidence regarding their effects when administered to patients with COVID-19.

On one hand, these drugs offer immunomodulatory, immune-enhancing, antiviral, and antiangiogenesis activity, and can stimulate the differentiation and repair of epithelial cells. On the other hand, they can increase inflammation and cause the fragility of oral and nasal mucosae. When prescribe systemic retinoids, all of these aspects should be considered in all fields of the medicine and dermatology is not an exception.

**Keywords:** coronavirus, COVID-19, retinoids, immuno-modulatory, angiogenesis

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## INTRODUCTION

In the final months of 2019, the world entered its biggest challenge of the past few decades due to the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), which is responsible for the coronavirus disease 2019 (COVID-19). This infection spread rapidly and became pandemic in less than a few months<sup>1</sup>. Since the mortality rate and burden of this infection are increasing every

day<sup>2</sup> and considering that there is no effective and specific treatment for it so far, it is important to pay attention to lifestyle and limit the possibly harmful physical or nutritional exposures in this pandemic era. Underlying diseases and medications are major concerns and researchers across all disciplines are trying to evaluate the effect of common medications, especially immunosuppressive drugs, on COVID-19<sup>3,4</sup>.

Systemic retinoids comprise a group of drugs

that are commonly used in dermatology for various therapeutic and cosmetic purposes. Various mechanisms for the actions of these drugs have been proposed, including anti-inflammatory and immunomodulatory effects, antiviral effects, enhancement of cell proliferation and differentiation, and inhibition of angiogenesis<sup>5,6</sup>. Due to the fact that the respiratory tract represents perhaps the main route of body entrance for the SARS-Cov-2, and considering that one of the common side effects of systemic retinoids is inflammation and dryness of the mucous membranes of the lips and nose, there are many concerns and obscurities among both doctors and patients about the usage of these drugs during the COVID-19 pandemic<sup>7</sup>.

However, as mentioned, systemic retinoids also have antiviral and immunoregulatory effects that may even be beneficial to patients with COVID-19. Due to these controversies about the use of systemic retinoids during the pandemic, we decided to review the mechanisms of these drugs, particularly in studies that are related to COVID-19.

To write this review article, we searched all related evidence in various data bases about the effect of retinoic acids on the most important COVID-19 complication, i.e., respiratory failure. We also surveyed the literature to obtain data on the anti-inflammatory, immune-stimulating, and antiviral characteristics of these drugs.

**Effects on the mucosal and respiratory epithelium.** The effects of retinoids on the mucosal epithelium are debatable from two views. The first is the obvious effect of these drugs to increase the differentiation of respiratory epithelial cells, which results in a reduction in the viral shedding period of these infected cells and accelerates the repair process of epithelium damaged by the infection or inflammatory response. Furthermore, viral respiratory infections can cause metaplastic changes to the squamous cells in the respiratory epithelium in the repair process that makes them more susceptible to a secondary infection, and these changes are more common in the case of vitamin A deficiency than in normal status<sup>6</sup>. The second point is related to the influence of retinoids on mucosal epithelia as a common side effect of these drugs including the inflammation, dryness, and increased fragility of the oral and nasal mucosa. Angiotensin-converting enzyme 2 (ACE2) receptors are the key route for the

SARS-Cov-2 to enter the body, and are commonly expressed in the oral and nasal mucosa, especially in their basal layers<sup>7,8</sup>. Therefore, in the event of fragility or inflammation in the mucosa caused by the retinoids, it is assumed that the use of these drugs may facilitate the penetration of the virus into the body<sup>9</sup>.

**Immunologic effects.** The innate immune response is the first step of body defense against viral infections via the activation of NK cells. After activation, these cells increase tumor necrosis factor and interferon-gamma serum levels, leading to a high level of cell-mediated immune response. It has been shown that the number of NK cells decreases in vitamin A deficiency. Other immune functions of retinoids include the promotion of the secretory IgA response, IL2 receptor transcription, and lymphocyte development and maturation. Moreover, it has been determined that infection and inflammation alter retinoic acid metabolism, decrease hepatic synthesis of retinoic acid-binding protein (RBP), and increase renal secretion of vitamin A and RBP. All of this leads to an apparent dysfunction of vitamin A, especially in those who had been deficient in vitamin A prior to the infection; such patients may experience a more severe form of the disease than patients who have normal levels of vitamin A or take supplements during infection. In addition to its immune-enhancing effects, retinoic acid modulates the immune response and inflammation<sup>10</sup>, making it suitable for treating many inflammatory diseases, including skin diseases. In the case of COVID-19, an overactive immune response and excessive inflammatory mediators have been proposed possible factors related to disease severity and mortality. Hence, anti-inflammatory and immunomodulatory drugs may be effective for better management of these patients, especially in severe and deteriorated conditions<sup>11,12</sup>, though most of these drugs have immunosuppressive characteristics that give rise to concern about their use in the setting of an infectious disorder although it seems worth to try them. Therefore, finding an agent with both antiviral and immunoregulatory properties can be promising for such patients. In our view, retinoids have immunoregulatory, immune-enhancing, and probable antiviral effects, providing great overall value.

**Antiviral effects.** As mentioned, the way that

SARS-Cov-2 enters the body is through the ACE2 receptor. Recent studies have shown that retinoids can reduce the expression of this receptor on cells and thus reduce the risk of infection<sup>13</sup>. Isotretinoin (a retinoic acid derivative) has also been shown to inhibit the papain-like protease of SARS-Cov-2, which may result in reduced viral proliferation<sup>14</sup>. Considering their potentially beneficial mechanisms and functions, vitamin A and retinoic acid have been investigated in terms of their effects on a few cases of ARDS and many viral infections including respiratory viral infections such as measles, influenza, respiratory syncytial virus, human immunodeficiency virus, hepatitis C virus, and herpes simplex virus, with positive findings having been reported in a number of studies<sup>15-18</sup>.

**Anti-angiogenesis effect.** One of the new pathological findings in the pulmonary tissue biopsies of COVID-19 patients is vascular injury and intussusceptive angiogenesis, which can be one of the reasons for the occurrence of pulmonary edema and the decrease in therapeutic response<sup>19</sup>. According to these findings, a clinical trial study has been registered to evaluate the therapeutic effect of Bevacizumab (an anti-VEGF drug) on critical cases of COVID-19 (NCT04275414). Retinoids are one group of drugs that have been shown to have inhibitory effects on diseases with aberrant angiogenesis (e.g., tumors), meaning that they may also be effective in curtailing this part of the pathogenesis of COVID-19<sup>20</sup>.

## CONCLUSION

Given the points mentioned, it is noteworthy to evaluate the effect of retinoids, including isotretinoin, on the course of COVID-19. For this purpose, retrospective analyses of COVID-19 patients should be initiated from the point of view of retinoid use, the severity of the disease, and the rate of death and recovery. If positive results are obtained, clinical trials can subsequently be performed with more confidence in the same way that many other multipotential drugs have been proposed as adjuvant preventive or therapeutic options for COVID-19<sup>21-24</sup>.

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