2020

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Received: 13 May 2020 | Accepted: 19 May 2020

DOI: 10.1111/1440-1681.13354

CEPP Clinical and Experimental Pharmacology and Physiology WILEY

LETTER TO EDITOR

A role for retinoids in the treatment of COVID-19?

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Abstract

The 2020 global outbreak of the novel coronavirus (SARS-CoV-2 or COVID-19) is a serious threat to international health, and thus, there is an urgent need for discovery of novel therapies or use of repurposed drugs that can make a significant impact on slowing the spread of the virus. Type 1 interferons (IFN-I) are a family cytokines of the early innate immune response to viruses that are being tested against SARS-CoV-2. However, coronaviruses similar to SARS-CoV-2 can suppress host IFN-I antiviral responses. Retinoids are a family molecules related to vitamin A that possess robust immune-modulating properties, including the ability to increase and potentiate the actions of IFN-I. Therefore, adjuvants such as retinoids, capable of increasing IFN-I-mediated antiviral responses, should be tested in combinations of IFN-I and antiviral drugs in pre-clinical studies of SARS-CoV-2.

KEYWORDS

COVID-19, IFN-I, interferons, retinoids, RIG-I, SARS-CoV-2, vitamin A

1 | CLINICAL TRIALS OF TYPE I INTERFERONS (IFN-I) AGAINST SARS-COV-2

SARS-CoV-2 is a novel single-stranded RNA (ssRNA) coronavirus that emerged in China in December of 2019 that has infected more than 6 million people worldwide and is responsible for over 350, 000 deaths as of May of 2020. In the absence of a vaccine or effective treatment, numerous novel or repurposed antiviral drugs and therapies are being considered,[1,2] including type 1 interferons (IFN-I).[2] IFN-I is a family of cytokines with potent antiviral properties that mediate the early innate immune response to viral infections.[3] IFN-I is comprised of α and β subtypes (IFNα, IFNβ),[3] which are secreted by a number of cell types, including pulmonary epithelial cells, macrophages, but most notably plasmacytoid dendritic cells (pDC).[4] IFN-I mediates cellular immune actions through activation of membrane interferon-α/β receptor (IFNAR) and the downstream regulation and expression of IFN-stimulated genes (ISGs), which act to inhibit of viral replication and stimulate adaptive immune responses.[4]

There are currently a number of clinical trials being conducted to examine the combinations of IFNα with antiviral drugs lopinavir/ritonavir (ChiCTR2000029387), favipiravir (ChiCTR2000029600), and lopinavir/ritonavir + glucocorticoids (ChiCTR2000029386), or IFNβ in combination with lopinavir/ritonavir and ribavirin for treatment of SARS-CoV-2 (NCT04276688).[5] Use of IFNα treatment is part of the latest edition of the standards of clinical care and treatment of patients with SARS-CoV-2 published by the National Health Commission (NHC) of the People's Republic of China. The protocol is 5 million U of IFN-α by vapour inhalation in combination with ribavirin twice per day.[1]

2 | CORONAVIRUS EVASION OF IFN-I ANTIVIRAL RESPONSES

To date, no studies that have examined if IFN-I can inhibit SARS-CoV-2 in cells or animal models; however, there is a large body data that IFN-I is effective in inhibiting two closely related coronaviruses, SARS-CoV and MERS-CoV in vitro, either alone or in combination with antiviral drugs.[6] Results of the clinical efficacy of IFN-I against SARS-CoV and MERS-CoV in human studies, however, are mixed and overall IFN-I treatments typically fail to significantly mitigate these coronavirus infections in humans.[6] It is unclear why there is a lack of consistent clinical efficacy of

IFN-I in human trials given the known antiviral properties of IFN-I. Evidence suggests that the timing of IFN-I administration and the presence and severity of comorbidities in patients infected with coronaviruses are some of the determinants of clinical response to IFN-I treatments.[7,8]

There is also a convincing body of evidence demonstrating that SARS-CoV and MERS-CoV, like many viruses, can disrupt the IFN-I signalling in host cells.[9-12] For example, SARS-CoV can suppress host IFN-I responses by inhibiting interferon regulatory factor 3 (IRF-3), a key transcription factor required for IFN-I promoter activation, and retinoic acid-induced gene I (RIG-I).[10,11] RIG-I is a pattern recognition receptor responsible for sensing RNA viruses and plays a key role in inducing IFN-I and the early innate antiviral immune responses.[13] Activated RIG-I signals through IRF-3 and NF-κB, which increase the mRNA expression of numerous antiviral genes including IFN-I and type III interferons.[13] MERS-CoV can also antagonize RIG-I[13] and IFN-I antiviral responses through ORF4b-encoded accessory proteins.[12] It is therefore reasonable to predict that, as part of its immune-evasive programme, SARS-CoV-2 would act to disrupt IFN-I-mediated antiviral responses in a similar fashion. These data suggest that adjuvants capable of stimulating and enhancing the antiviral effects of IFN-I should be given serious consideration when developing anti-SARS-CoV-2 pharmacological and treatment protocols.

3 | RETINOIDS AS IMMUNOMODULATORS AND POTENTIAL ADJUVANTS WITH IFN-I PROTOCOLS FOR SARS-COV-2

Retinoids are a family of molecules that possess qualitative activity relative to all-trans retinol (vitamin A) that includes retinyl-esters, all-trans retinal and all-trans-retinoic acid (RA).[14] RA is the biologically active retinoid metabolite that, acting through its cognate receptors RA receptors (RAR α, β and γ), regulates the expression of genes involved numerous biological pathways including both adaptive and innate immune responses [reviewed in [15]]. Retinoids act as effectors of the T-cell-mediated adaptive immunity and innate immune responses through stimulation of NK cells, antigen-presenting dendritic cells (DCs) and innate lymphoid cells (ILCs).[15,16] The rationale for testing the combination of retinoids and IFN-I is strong and based on a large body of pre-clinical and clinical data showing that retinoids stimulate secretion and potentiate the effects of IFN-I.[17,18] Retinoids can directly stimulate the mRNA expression of ISGs, including RIG-I, and IFN regulatory factor 1 (IRF-1).[16,17,19-21] The IFN-I-potentiating effects of retinoids have been documented in cell and animal models of cancer, in human cancer clinical trials[17,19] and in treatment of multiple sclerosis (MS).[22] Qu et al[22] reported that RA-treated peripheral blood mononuclear cells from patients with MS increased IFN-β response and restored CD8+ T-suppressor cell functions. Similarly, in phase 1 clinical trials in patients with MS, it was reported that treatments with the synthetic retinoid Etretinate enhanced the effect of IFN-β on T-cell function and restoration of T suppressors.[23]

A key mechanism through which retinoids enhance IFN-I is with activation of RIG-I. As the name indicates, RIG-I is stimulated by RA, and numerous lines of evidence support that IFN-I enhancing and antiviral effect of retinoids occurs through direct stimulation of RIG-I mRNA and functions.[24-26] Soye et al[24] demonstrated that RA inhibition of measles virus (MeV) replication in U9370 and Huh-7-infected cells occurs through IFN-I-mediated pathways driven by RA:RARα promoter activation of the RIG-I gene and its downstream effectors. Similarly, Chen et al reported that the antiviral effects of RA against enterovirus 71 are mediated through IFN-α and RIG-I.[25] Natural and synthetic retinoids also have direct inhibitory effects on replication of a number of viruses, including hepatitis B virus (HBV), cytomegalovirus, influenza, MeV, and norovirus.[27-30] There is also evidence that activation of retinoid signalling can potently inhibit coronaviruses.[31] Through a library screen, Yuan et al demonstrated that Am580, a specific agonist for RARα, is a potent inhibitor of SARS-CoV and MERS-CoV viruses through disruption of SREBP-mediated lipogenic pathways.[31]

Given that the coronaviruses SARS-CoV and MERS-CoV can inhibit IFN-I mediated antiviral responses and possibly hinder treatments,[9-12] the data supporting that retinoids can potentiate host IFN-I signalling, and their well-documented safety profiles after almost 60 years of clinical use[14] warrant the pre-clinical testing of combinations of IFN-I and retinoids in cell and animal models of SARS-CoV-2.

ACKNOWLEDGEMENTS

Many thanks to Dr. Lorraine Gudas for her invaluable scientific input on this topic.

CONFLICT OF INTEREST

SET has no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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How to cite this article: Trasino SE. A role for retinoids in the treatment of COVID-19? *Clin Exp Pharmacol Physiol*. 2020;00:1–3. https://doi.org/10.1111/1440-1681.13354