HYPOTHESIS LETTER

Does autoimmune vitiligo protect against COVID-19 disease?

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Abstract

The SARS-CoV-2 pandemic has evolved to a global health problem with a dramatic morbidity and mortality rate impacting our daily life and those of many patients. While there is evidence that some diseases are associated with an increased risk for development of a more severe course of COVID-19, little is known on protective conditions. Importantly, clearance of viral infection and protection against disease manifestation crucially depends on functional innate and adaptive immunity and the interferon signalling axis. Here, we hypothesize that patients with non-segmental vitiligo (NSV), an autoimmune skin (and mucosal) disorder, may clear SARS-CoV-2 infection more efficiently and have a lower risk of COVID-19 development. Conversely, in case of COVID-19 development, vitiligo autoimmunity may influence the cytokine storm-related disease burden. In addition, immune activation during SARS-CoV-2 infection or COVID-19 disease might increase vitiligo disease activity. Our hypothesis is based on the shift of the immune system in NSV towards adaptive type 1 (IFNγ and CD8 T cells) and innate immune responses. Identified susceptibility genes of NSV patients may further confer increased antiviral activity. To validate our hypothesis, we suggest an international consortium to perform a retrospective data registry and patient-reported study on a large number of NSV patients worldwide during the COVID-19 pandemic.

KEYWORDS
autoimmunity, coronavirus SARS-CoV-2, COVID-19, inflammation, vitiligo

1 | BACKGROUND

The ongoing pandemic of SARS-CoV-2 has evolved to a global health problem with over 3 million death and 162 million confirmed COVID-19 cases.[1] The morbidity and mortality of this infection is impacting our life. Moreover, the pandemic affects our care of dermatological patients, with economic and healthcare consequences.

Besides elderly populations, immune-compromised patients and distinct comorbidities such as obesity, respiratory or cardiovascular diseases,[2-4] our knowledge on risk and protective factors for the severity and mortality of COVID-19 is still limited. Men have a higher prevalence of the above risk factors, while women more frequently have autoimmune diseases.[5] Notably, more men than women become seriously ill—and die—from COVID-19.[4] On the other hand, the late stage of COVID-19 disease is due to an excessive inflammatory response while viral levels are decreased.

A provocative idea is that some diseases may confer protection against SARS-CoV-2 infection and, more importantly, from COVID-19 manifestation. Non-segmental vitiligo (NSV) is an autoimmune-mediated inflammatory disease.[6] It can involve the skin and mucosal epithelium. The autoimmune nature of NSV is evident from autoimmune comorbidities, especially thyroid autoimmunity. Moreover, the genetic susceptibility profile for NSV consists of genes involved in immune activation and regulation.[7] These vitiligo-associated

SNPs point to altered gene function that may predispose patients to autoimmunity but may also confer increased antiviral immunity. Interestingly, NSV has been shown to protect against melanoma and non-melanoma skin cancer.[8,9] The pathobiology of NSV involves adaptive type 1 immune responses with interferon (IFN)-γ signalling and CD8^{+} T cells but also innate immune responses.

Both innate and adaptive immune pathways are important in clearing viral infections, by early innate responses of type I IFN and IFN-γ producing NK cells, followed by adaptive immunity including IFN-γ-producing T-cell responses and antiviral antibody response.[10,11] Related corona viruses SARS-CoV and MERS-CoV are able to disrupt IFN signalling by Orf6 and Orf3b proteins, resulting in a delayed type I IFN response with loss of viral control during the early phase of infection.[12,13] In SARS-CoV-2, these proteins are truncated with a diminished anti-IFN activity. Therefore, SARS-CoV-2 is more sensitive to IFN than related coronaviruses.[14] Interestingly, type I IFN treatment has been shown to decrease infection rate and viral replication of respiratory viruses.[15] The role of IFN in protection against SARS-CoV-2 infection is apparent in seriously ill COVID-19 patients with genetic defects of the type I IFN pathway.[16] Moreover, neutralizing autoantibodies that impair type I IFN immunity were found in 10.2% of the patients with life-threatening COVID-19 pneumonia, as compared to 0.33% of the patients with asymptomatic or mild symptoms of SARS-CoV-2 infection.[17] As compared to other respiratory viruses, SARS-CoV-2 induces an aberrant, less functional antiviral transcriptional response in infected cells, characterized by low type I and III IFN levels and high expression of chemokines and IL-6, which may drive COVID-19.[18] During the late phase of COVID-19 the production of type I and III IFN remained low, accompanied by increased production of inflammatory cytokines such as IL-6, IL-8 and TNF-α.[18,19] Moreover, IL-6 plasma levels were found higher in ICU patients compared to healthy subjects. Other showed that IL-6 levels were significantly higher in patients with severe disease than in patients with mild disease, suggesting to be a predictive of mortality.[20] Further, lower systemic IFN-γ levels were associated with lung fibrosis among COVID-19 patients.[21] The relationship of autoimmunity and COVID-19 has been described by COVID-19 disease characteristics that resemble autoimmune or autoinflammatory disorders, whereas the relative risk of autoimmune patients for COVID-19 is not known.[19,22] To date, there are no data of patients with autoimmune thyroid disease, rheumatic diseases, systemic lupus or other autoimmune disorders being at higher risk of SAR-Cov-2 infection or more severe COVID-19 disease severity.[23-25] The relative susceptibility of patients with pre-existing autoimmunity to COVID-19 may be obscured by the potential benefit of immunosuppressive drugs, used in these patients, against COVID-19 disease development, or as COVID-19 treatment. In vitiligo, the absence of systemic immune suppressive treatment allows studying this relationship more specifically.

SARS-CoV infection is recognized by the immune system through viral protein that serve as a pathogen-associated molecular pattern (PAMP) by a TLR-related-TRAF3-independent mechanism.[26,27] Furthermore, the infection triggers an inflammatory response characterized by increased production of interleukin IL-6, IFN-γ and activation of NF-κB.[28] This MDA5-MAVS-NF-κB/IRF3 signalling pathway orchestrates the secretion of CXCL10 leading to CXCR3B activation and inducing apoptosis of melanocytes.[29] Moreover, vitiligo patients show an increased presence of NK and ILC1, cells that are more liable to respond to PAMPs.[30] These data suggest a SARS-CoV-2 infection could potentially induce flares of vitiligo.

2 | HYPOTHESIS

1. We hypothesize that considering the activated type I immune status of NSV and the genetic association with antiviral genes, vitiligo patients might clear a viral infection more efficiently and have a lower risk of COVID-19 development.

1a. In case of COVID-19 development, vitiligo autoimmunity may influence the cytokine-storm-related disease burden.

2. In addition, immune activation during SARS-CoV-2 infection or COVID-19 disease might increase vitiligo disease activity. Based on this hypothesis, the following three questions can be answered: *1*. What is the relation between NSV and coronavirus infection risk or COVID-19 disease development? *1a*. How does vitiligo affect the severity and mortality of COVID-19 disease? *2*. Is disease activity of vitiligo affected by COVID-19 disease?

3 | HOW TO TEST THE HYPOTHESIS

We propose an international consortium to perform a retrospective study in a large number of NSV patients worldwide during COVID-19 pandemic. To address the above questions, our concept includes a patient-reported study and a patient data registry study.

Employing a questionnaire study among NSV patients and controls (age between 16 and 55 years). Participating institutes will collect demographic patient data (age, gender, ethnicity, skin type) and data related to vitiligo disease activity, affected body surface area measured by the Self-Assessment Vitiligo Extent Score, medication (both vitiligo-related as other concurrent, including immune suppressive therapies), other autoimmune disorders, comorbidities and life style risk factors frequently found in COVID-19 patients (obesity, smoking, hypertension, diabetes, respiratory system disease and cardiovascular disease),[2,3] COVID-19 disease development according to Core Outcome Sets,[31] including respiratory symptoms, hospital admittance due to COVID-19, intensive care unit admittance due to COVID-19, vitiligo disease activity during COVID-19. The questionnaire will contain questions of validated dermatology and COVID-19 questionnaires and previously developed vitiligo patient-reported outcome measures for vitiligo extent[32] and activity.[33] To analyse the relation between vitiligo and COVID-19 disease development risk and disease severity (**questions 1 and 1a**), partners of patients or a best friend not suffering from vitiligo will be asked to fill out the same questionnaire (except for vitiligo-related questions) and thereby will serve as control group. Considering the infectiousness

of SARS-CoV-2, chances are high partners, will be infected in case one of the two has been exposed to the virus. COVID-19 disease development and disease severity in vitiligo patients will be compared to the control group. This control group presumably matches well with regard to age, sex, skin type, ethnicity, social status and risk for SARS-CoV-2 infection. The patient and control groups analysed are confined to the age group between 16 and 55 years, to minimize the effect of increased risk in elderly and decreased risk in children on the analyses of this study. Since the history of autoimmune comorbidities of both vitiligo patients and controls is also collected, we can subsequently determine the effect of other frequently found autoimmune diseases on COVID-19 disease development and severity. The effect of COVID-19 on vitiligo disease activity (**question 2**) will be analysed among vitiligo patients, in which vitiligo disease activity in vitiligo patients with COVID-19 will be compared to vitiligo patients without COVID-19. In case of increased vitiligo disease activity due to COVID-19, this will become apparent by the formation of new vitiligo lesions during the 3 months after COVID-19 disease suffering. The effect of COVID-19 on vitiligo could either be direct, due to increased immune activation, or indirect due to increased emotional stress of patients and resulting flares of increased vitiligo disease activity. To minimize the recall bias, the questionnaire will be conducted just after the summer.

In case all patient data registration is centralized in a national registry or health insurance registry, we will analyse (i) the vitiligo prevalence among patients with COVID-19 disease-related hospitalization or ICU admittance in 2020 as compared to non-COVID patient ICU data registered from 2000 until 2019 prior to the pandemic, as well as the prevalence of vitiligo in the general population, and (ii) the COVID-19 incidence among vitiligo patients as compared to the COVID-19 incidence in the general population. This more reliable analysis will strengthen the patient questionnaire study and will provide insight to what extent vitiligo is underrepresented in the COVID-19 patient population, when corrected for confounding factors (eg age, use of immune suppressive therapies). In these analyses, the gender distribution will also be analysed. Vitiligo generally occurs more equally in males and females[34,35] than most autoimmune disorders having an approximately 60/40 distribution for females/males. Based on this, these analyses will reveal whether the lower risk of COVID-19 disease development in females can be associated with vitiligo or another autoimmune disease. The relatively high prevalence (estimated 0.5%–2%) of vitiligo independent of sex or ethnicity is sufficiently comparable worldwide,[34,35] to enable combining patient data across countries.

4 | RELEVANCE AND PERSPECTIVES

Our study may add a novel twist on the pathobiological (and evolutionary) role of NSV during viral infection. Validation of our concept may disclose new mechanistic and disease-interrelating insights into the pathophysiology of the SARS-CoV-2 pandemic.

AUTHOR CONTRIBUTIONS
R. M. L., A. W., M.W.B. and N. F. P. developed the idea. R. M. L, A. W., N. F. P. and M. W. B. wrote, edited and approved the manuscript.

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