Exploring the efficacy of the *Mycobacterium indicus pranii* (MIP) vaccine in reducing the impact of the ongoing COVID-19 pandemic

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Vaccine makers are racing to develop COVID-19 vaccines and have advanced ten candidates into clinical trials. However, vaccine development is typically a lengthy process. A number of immune response modifiers have also been explored for their efficacy in the management of COVID-19. In this short communication, we explore the possibility of using *Mycobacterium indicus pranii* (MIP) for the management of severely ill COVID-19 patients and its plausible role in the mitigation of severe disease in mildly infected patients. The MIP vaccine has a proven role in the prevention of leprosy to house-hold contacts of lepromatous leprosy, category-II tuberculosis patients, and patients with severe septicemia and low CD4 counts. It has also been used as an immune response modifier in patients with bladder carcinoma. Notably, this vaccine may be more efficacious than the BCG vaccine. The possible benefits and risks of using such an agent are described in this article. The use of such an approach could be beneficial in resource-poor countries and countries where diseases like tuberculosis and leprosy are endemic.

Keywords: COVID-19, *Mycobacterium indicus pranii* (MIP) vaccine, leprosy

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INTRODUCTION

A concerted effort to develop effective drugs and vaccines against existing and potential future coronavirus infections and other highly pathogenic virus outbreaks is necessary to minimize the overwhelming impact of such diseases on human life and worldwide healthcare systems. Given the costly and arduous process involved with vaccine development and the speed at which the pandemic is growing exponentially, we need to act fast and try to explore the already studied and developed vaccines that can be helpful in preventing or mitigating the pathological effects of the coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This predominantly respiratory disease may also feature dermatologic manifestations and its complications have been perceived as an unfolding conundrum [1]. Herein, we evaluate the plausibility of the use of a vaccine largely used by dermatologists in leprosy care in the management of COVID-19.

Immunologic basis of protection against SARS-CoV-2 infection

An effective innate immune response against a viral infection relies heavily on the interferon (IFN) type I response and its downstream cascade that culminates in controlling viral replication and inducing an effective adaptive immune response. Innate immune cells recognize pathogen-associated molecular patterns (PAMPs) by pattern recognition

receptors (PRRs) that include toll-like receptors (TLRs) and other cytosolic pathogen sensors. These PRRs set off the activation of a downstream signaling cascade that leads to the production of type I and III interferons (IFNs) and other pro-inflammatory mediators that initiate the host's innate and adaptive immune response [2]. Current evidence strongly indicates that the T-helper 1 (Th1) type response is the key for the successful control of the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV); this is also probably true for the SARS-CoV-2.

Cytokines and IFNs facilitate inflammation but are also involved in the pathophysiology of lung injury during the acute viral infection. In severe cases of COVID-19, patients have high levels of innate pro-inflammatory cytokines and type I IFNs. Similar to SARS-CoV and MERS-CoV infections, several reports show increased neutrophil and reduced lymphocyte counts in COVID-19 patients with the onset of the so-called "cytokine storm", supporting the hypothesis of the importance of the innate immune response as both a protective and destructive mechanism [3].

Two-phase immune responses induced by SARS-CoV-2 infection

Clinically, the immune responses induced by the SARS-CoV-2 infection are two-phased. During the incubation and non-severe stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages. The cytokine release syndrome (CRS) seems to affect patients with severe conditions. Since lymphocytopenia is often seen in severe COVID-19 cases, the CRS caused by SARS-CoV-2 has to be mediated by leukocytes other than T cells.

Mycobacterium indicus pranii

Mycobacterium indicus pranii (MIP), a non-pathogenic vaccine candidate, has shown strong immunomodulatory activity in patients with leprosy, tuberculosis, cancer, and genital warts, where its administration shifted the host's immune response toward the Th1-type pathway. The microorganism is also being studied in animal models to obtain an insight into the mechanisms contributing to its protective efficacy as a vaccine candidate. Studies have demonstrated the potential immunomodulatory properties of MIP, the most significant being the ability to induce a strong Th1-type response, enhance the expression of pro-inflammatory cytokines, activate APCs and lymphocytes, and elicit *Mycobacterium tuberculosis* (M. tb)-specific poly-functional T cells. All of these represent crucial components of the host's immune response during M. tb infection. Also, MIP was found to be a potent inducer of autophagy in macrophages, resulting in the enhanced clearance of M. tb from cells co-infected by MIP and M. tb [4]. The MIP vaccine is an immunotherapeutic-cum-immunoprophylactic vaccine based on an atypical, cultivable mycobacterial species, originally coded as *Mycobacterium w* (Mw). This vaccine has received Drugs Controller General of India (DCGI) approval for its use in leprosy prevention among household contacts and in combination with multi-drug therapy in leprosy patients with high bacillary index levels [5]. Apart from leprosy, it has also been found to be a useful agent in the management of tuberculosis category II [6], anogenital warts (intralesional immunotherapy) [7,8], cancer [9], and HIV/AIDS. Furthermore, the mycobacterial antigens of this vaccine attenuated the late phase response, airway hyperresponsiveness, and bronchoalveolar lavage eosinophilia in a mouse model of bronchial asthma. It can also help in the treatment of Gram-negative septicemia and obstructive lung disease [10].

Exploring the use of immunomodulators for the treatment of COVID-19

In the absence of proven antiviral agents or an effective vaccine, substances with immunomodulatory activity may be able to inhibit inflammatory and Th1 cytokines and/or yield an anti-inflammatory and/or Th2 immune response to counteract COVID-19 symptoms and severity [11]. Examples of such immunomodulators considered to be effective in COVID-19 are low dose interferon alpha, microdose DNA, low-dose thiomersal, and Bacillus Calmette-Guérin (BCG) among many others. In this viewpoint, we shall focus on the use of the MIP vaccine for COVID-19 prevention and for the management of moderate to severely affected COVID-19 patients.

The putative role of BCG in prevention/ reduction of viremia

The tuberculosis vaccine Bacillus Calmette-Guérin (BCG) has been proposed to overcome the delayed or suppressed type I IFN response during the initial infection with SARS-CoV-2 as it offers heterologous beneficial effects against non-related infections. The basis of these effects has been poorly explored in humans. In a randomized placebo-controlled human challenge study, Arts RJW *et al.* found that BCG vaccination induced the genome-wide epigenetic reprogramming of monocytes and protected against experimental infection with an attenuated yellow fever virus vaccine strain. Epigenetic reprogramming was accompanied by functional changes indicative of trained immunity. The reduction of viremia was highly correlated with the upregulation of interleukin (IL) 1β, a heterologous cytokine associated with the induction of trained immunity but not with the specific IFN-γ response. The importance of IL-1β for the induction of trained immunity was validated through genetic, epigenetic, and immunological studies [12]. This generation of Th1 (IFN-γ) and Th17 (IL-17 and IL-22) immune responses to non-mycobacterial stimulation remained strongly elevated even one year after BCG vaccination [13,14]. In any case, BCG vaccination is a good example of how an immune response modifier can also provide protection against other viral antigens.

Advantages of *Mycobacterium indicuc pranii* (MIP) over BCG

Though BCG too acts as a potential immune response modifier, it is a live vaccine with limitations such as the fact that it cannot be given to immunocompromised/immunosuppressed individuals like HIV positive patients. However, MIP which is a killed vaccine can be administered even to immunocompromised individuals and it was found to convert HIV-positive tuberculin-negative individuals to tuberculin-positive individuals. Experimental studies on the aerosol vaccine of MIP have documented it to be more effective than intradermal route and BCG [15].

Clinical trials in the pipeline

The Council of Scientific and Industrial Research in India has commenced a clinical trial for the use of Mycobacterium w (Mw) in critically ill COVID-19 patients [16]. The study is a randomized, blinded, two-arm, active comparator-controlled clinical trial for evaluating the safety and efficacy of Mw (0.3 ml suspension delivered via the intradermal route for three consecutive days) in combination with standard care as per hospital practice versus standard care alone in critically ill adult patients suffering from COVID-19. In 2017, a large scale clinical trial was conducted in three districts of Gujarat, India for the use of MIP in the prevention of leprosy. However, little is known about the results of this trial. It may be worthwhile to look back at the surviving population of this clinical trial in Gujarat, which is experiencing a large number of COVID-19 cases, to see whether the MIP-vaccinated population has any protective immunity against COVID-19; a follow-up survey can be conducted for this purpose.

Possible risks of vaccinating with MIP

As yet, knowledge regarding COVID-19 is still evolving, and we are unaware of the exact pathogenesis of the disease. Furthermore, the two-phased immune response and cytokine storm occurring in severe cases make it difficult to predict the outcome. We believe that the timing of the MIP vaccine may be very crucial in such patients because if given late when patients are severely ill, it may even accelerate the immune response and induce the cytokine storm, leading to a worse outcome. Though serious side effects of MIP are rare, severe local adverse skin reactions at the site of injection in the form of blister, abscess or ulcer formation are more likely in patients who have had a history of tuberculosis [12].

CONCLUSION

We agree that mankind is suffering from perhaps the worst pandemic it could have possibly imagined. This has put a kind of pressure on doctors, scientists, and researchers to come up with a vaccine in a short period of time, resulting in the conduction of clinical trials on almost all possible agents for the treatment of COVID-19. We may only know in hindsight whether these agents conferred benefits or caused more damage, so we need to be cautious

when opting for such an approach. The MIP vaccine, as an immune response modifier, is worth a try based on its multiple therapeutic properties proven in various conditions. However, this too may not be without risk. Lastly, dermatologists and/or leprologists experienced in using the MIP vaccine should be included in the clinical trial team for such projects.

Conflict of interest: None declared.

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