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Short Communication

Mw: A Potential Non-Specific Vaccine as First Response to Future Viral Pandemics before Specific Vaccines are Available - Some Lessons from COVID-19 Pandemic

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A B S T R A C T

In absence of an effective drug or vaccine in the initial phase of COVID-19 pandemic, authors started searching the literature to repurpose existing drugs/vaccines. Mw vaccine, a heat-killed Mycobacterium W, is routinely used by clinicians to boost the immune response of leprosy patients in India as an innate immune response immunomodulator. After detailed deliberations, on September 2020, the corresponding author submitted an emergency protocol to use Mw as a booster of Innate Immunity of doctors and HCWs looking after COVID-19 Positive patients in Himachal Pradesh, India. Later Mw was arranged and 21 persons were immunised with two site intradermal 0.1 mL doses of Mw vaccine in September 2020. Later two booster doses were given one each (0.1 mL) at 3 months' interval. Regular RT-PCR was done and two persons who received vaccine were found to be positive for COVID-19. One person with diabetic status was found to have symptoms of sore throat, fatigue and high fever that responded in home isolation, without oxygen requirement and the other person was positive but asymptomatic. Subsequent studies proved that the prophylactic effect of Mw manifests quickly following the first administration of Mw, widening of the gap between two arms over time, reflecting ongoing immune remodelling. With the current COVID-19 vaccination schedule across the world and the emergence of breakthrough infection, Mw should be useful in the current pandemic too and must be tried. In future viral pandemic, we should think of using Mw as the first response non-specific vaccine till a specific vaccine is available, as Mw does not require antigen-specific changes and can be used immediately as universal vaccine. Mw stimulates innate response against viral mutation and variants as well.

Keywords: COVID-19, Mw Vaccine, Innate Immunity, Pandemic, Breakthrough Infection



Introduction

COVID-19 pandemic has done irreparable devastation to lives and livelihood of millions across the world. Globally, as of 4:51pm CET, 13 December 2021, there have been 269,468,311 confirmed cases of COVID-19, including 5,304,248 deaths, reported to WHO.¹ In view of ongoing COVID-19 pandemic, on the evening of March 24th, 2020, the Government of India declared full lockdown and all human movements were restrained except that of essential services like health care and frontline workers. Health care workers were deputed to manage COVID Care Centers and special designated hospitals for COVID-19 patients. All people were taking drugs/ herbal preparations/foods to boost their immunity to counter the virus as no drug or specific vaccine was available at that time.

Methods

Authors started searching the literature to repurpose existing drugs/ vaccines so that the immunity of health care workers and doctors deputed to COVID-19 duty could be boosted as no drug or vaccine was available against novel SARS-CoV-2. Mw vaccine, a heat-killed Mycobacterium W, a TLR2 agonist, is routinely used by clinicians to boost the immune response of leprosy patients in India as innate immune response immunomodulatory.² After detailed deliberations, on September 2020, the corresponding author submitted an emergency protocol to use Mw as a booster of Innate Immunity of doctors and HCWs looking after COVID-19 positive patients in Himachal Pradesh, India.³ Later Mw was arranged from the manufacturing company Batch No. GO20006, Manufacturing date 8-2020 and Expiry date as 07-2023. A total of 21 persons were immunised with two site intradermal 0.1 mL doses of Mw vaccine in September 2020. Later two booster doses were given one each (0.1 mL) at 3 months' interval. All vaccine recipients were also given Vitamin D prophylaxis as Vitamin D is essential for effective

immune response.⁴ At the same time in a case-control study done in Delhi, the efficacy of Mw to limit COVID-19 infection was shown and later proved in another large cohort study done at Ahmedabad in more than 2000 employees of Cadila Pharmaceuticals Limited. All these studies with Mw vaccine were done in 2020 while the world was still looking for COVID specific vaccines and helped save many lives from hospitalization or death.

Results

Out of 21 persons we vaccinated with Mw on September 2020, none needed hospitalisation or died despite two COVID-19 waves were over. The age of those immunized in our study was between 20 years to more than 80 years and majority were having one or other co-morbidities like hypertension, diabetes or inflammatory bowel disease (Chronic Colitis). Regular RT-PCR was done and two were found to be positive for COVID-19 with an infectivity rate of 9.5% and zero mortality rate.

Table I. Differences between BCG and Mw

BCG	Mw
Live attenuated pathogenic organism	Heat killed and non-pathogenic organism
Generates mixed Th 1 and Th2 response	Generates only Th1 response
May not reduce/ eliminate established infection on its own or when used along with anti-infective agents	Reduces/ eliminates established infection on its own or when used along with anti-infective agents
Contraindicated in immunocompromised subjects	Safe in immunocompromised subjects

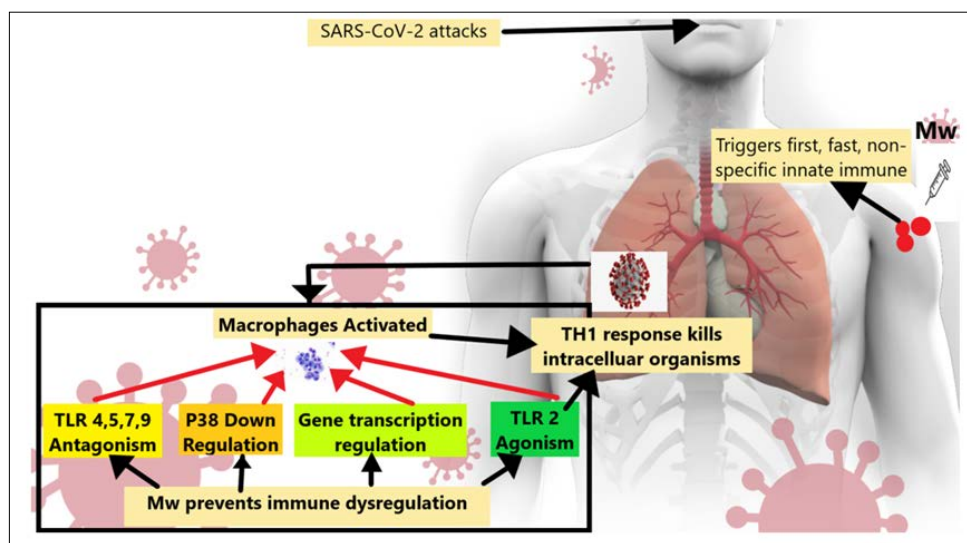


Figure 1. Mw Use in COVID-19 Patients

One person with diabetic status was found to have symptoms of sore throat, fatigue and high fever that resolved in home isolation, without oxygen requirement and the other person was positive but asymptomatic. Seven of them, including one 80 years old lady with multiple comorbidities, have still not taken any COVID-19 vaccine and are free of any COVID-19 infection despite a new variant, Omicron, in circulation.

Discussion

Innate immunity⁵ plays a vital role in fighting nonspecific pathogens, especially viruses as RIG-I-like receptors⁶ (retinoic acid-inducible gene I) detect RNA molecules that are absent from the uninfected host. DNA receptors alert the cell to the abnormal presence of that nucleic acid in the cytosol. Signalling by RNA and DNA receptors results in the induction of restriction factors that prevent virus replication and establish cell-intrinsic antiviral immunity.⁷ Innate immune response is a conserved mechanism, which promptly resists infections by recognising the conserved pathogen-associated molecular patterns (PAMP) of an infectious agent by pathogen recognizing receptors (PRR) like toll-like receptors (TLR). It is relevant in infections by novel pathogens like SARS-CoV-2.⁸ Other study findings suggest that interleukin-4 (IL-4) and interferons (IFN- γ) inhibit SARS-CoV replication partly through downregulation of ACE2.⁹ Mw action is through conserve pattern which does not change with mutation/ variations. These are species-specific and mutant variants will not change the conserve pattern, while the antigen pattern changes with mutation leading to a change in efficacy of the vaccine. While all our 21 vaccine recipients were in good health and without any side effects except local induration/ ulceration, many studies started showing evidence of Mw protection from COVID-19 as high as 93.33% which is higher than specific COVID-19 vaccines.¹⁰ Soon employees of Cadila Pharmaceuticals Limited, manufacturer of Mw, started getting infected and after deliberations, it was decided to use Mw vaccine and it was given to 2563 employees who agreed for Mw injection and the protective efficacy seen in the Mw-treated group was 70.3% for COVID-19.¹¹ The incidence of symptomatic COVID-19 over time suggests that the prophylactic effect of Mw manifests quickly following the first administration of Mw, with widening of the gap between two arms over time, reflecting ongoing immune remodelling. We decided to use Mw as a potential protective vaccine against COVID-19 because of its similarity to BCG. BCG vaccination may provide specific protection against SARS-CoV-2¹² and since BCG vaccine has also been proved to have nonspecific effects in modulating innate immune response and induce fast viral clearances in yellow fever about one month after inoculation,¹³ Mw having antigenic similarity to BCG is supposed to have a similar response. Other studies report COVID-19-attributable mortality among BCG-using countries was 5.8 times lower [95% CI

1.8-19.0] than in non-BCG-using countries¹⁴ and protective role of Environmental Mycobacteria.¹⁵ Studies reported that BCG vaccine ameliorated the severity of positive-sense RNA viruses, such as mengovirus and yellow fever virus.¹³ The current COVID-19 pandemic is caused by the positive-sense RNA virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological studies reported decreased mortality rate of BCG vaccinated individuals who were infected with SARS-CoV-2¹⁶ and authors of this paper in The Lancet have recommended Considering BCG vaccination to reduce the impact of COVID-19 till a specific vaccine is developed. A recent study in Virology concludes that vaccinated BCG patients may thus experience enhanced immune responses against SARS-CoV-2, especially in the old aged patient segment, albeit not ensuring decreased infectivity of SARS-CoV-2.¹⁷ Therefore, instead of BCG we have advocated the use of Mw vaccine, Mw was used because of its antigenic similarity with BCG but being made from heat-killed bacillus and also Mw reduces/ eliminates established infection on its own or when used along with anti-infective agents¹⁸ which is not established with BCG. The value addition of Mw over BCG is described in Table 1 and its use in COVID-19 is graphically explained in Figure 1. We recommend a larger cohort trial of Mw in countries where COVID-19 vaccine is in short supply or not available.

Conclusion

We lost many lives of doctors and HCWs during the COVID-19 pandemic. We could have saved many of these precious lives if we had used Mw till the specific vaccines against COVID-19 were made available as is evident from a few studies referred to above. In future viral pandemics, we should think of using Mw as the first response non-specific vaccine till a specific vaccine is available, as Mw does not require antigen-specific changes and can be used immediately. Unlike current specific vaccines which are not so potent against viral mutations and variants, Mw stimulates innate response against viral mutation and variants as well and may work well in new emerging variants of COVID-19.

Funding

None except 50 vials of Mw were shipped to OB and 25 to JK to inoculate doctors, friends and family members when no specific vaccine against COVID-19 was available.

Conflict of Interest

None though AA is an employee of Cadila Pharmaceuticals Limited, Producer of Mw.

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