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Candidate immunomodulators for COVID-19: Heat-killed *Mycobacterium w* and BCG vaccine

To the Editor

Coronavirus disease 2019 (COVID-19) has emerged as a pandemic and has killed millions across the globe [1, 2]. This pandemic is associated with relatively higher mortality than other previously known respiratory viral infections. The virus is predominantly transmitted by respiratory droplets and incites a systemic disease. There is also evidence of environmental factors affecting disease transmission [3]. Currently, effective vaccines are being developed for the prevention of the disease. However, the treatment options are limited as most agents targeting the virus or immune system have demonstrated limited ability except for systemic corticosteroids [4, 5].

One feature associated with severe COVID-19 is the cytokine storm wherein there are very high levels of pro-inflammatory as well as anti-inflammatory cytokines [6]. A significant proportion of the individuals dying due to COVID-19 have cytokine storm, and high cytokine levels tend to persist even after the individuals start showing signs of recovery from the acute illness. Cytokines levels are also higher among individuals admitted to ICU who die due to COVID-19 as compared to those who survive the illness. Cytokine levels seem to play a significant role in morbidity and mortality in patients with COVID-19. This clinical situation is similar to what is seen in patients with gram-negative sepsis. Also, it is well known that an individual's immune response to the virus is responsible for clearance as well as is associated with the severity of illness. The innate immune response is the initial and prompt body mechanism for resistance against pathogenic organisms. This is done by recognition of pathogen-associated molecular patterns (PAMP) of an infectious agent by pathogen recognizing receptors (PRR) like toll-like receptors (TLR). This immune response is the first protection against infection and is considered relevant to COVID-19 as well. This has led to scientific thinking towards the use of immunomodulators in patients with COVID-19. One of such immunomodulatory therapy is heat-killed *Mycobacterium w* (Mw).

Mycobacterium w is a nonpathogenic, rapidly growing atypical mycobacterium and has been renamed as *Mycobacterium indicus pranii*. This species shares T and B cell determinants with *Mycobacterium leprae* as well as *Mycobacterium tuberculosis*. Heat-inactivated Mw has been used in various conditions as immunomodulators as it evokes antigen-specific cell-mediated immunity and augments Th1 type of cross-reactive response. Immune response to a pathogen can be of Th1 or Th2 type. Th1 immune response is associated with clearance of infection while Th2 type of response is associated with persistence and allergy response.

Following the administration through intradermal route, Mw induces a potent Th1 response.

This vaccine was initially developed for leprosy [7]. However, due to its immune-boosting effects, it has been used to prevent tuberculosis and treat sepsis. The intralesional vaccine is also being tried for the use in cutaneous warts [8]. Mw reduces overexpressed pro-inflammatory as well as anti-inflammatory cytokines. It also reduced mortality in established sepsis-induced by *E.coli* when added to standard therapy (antibiotics plus glucocorticoids). In a randomized

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controlled study among fifty patients with sepsis, administration of 0.3 ml of Mw per day for three days (as compared to placebo) resulted in a statistically significant and clinically relevant faster recovery (ventilator days 6 *vs* 9, p = 0.025; length of ICU stay 7 *vs* 12 days, p = 0.006; and length of hospital stay 10 *vs* 16 days, p = 0.007). However, there was no difference in mortality between the two groups [9]. It is thought to work by overcoming the immune paralysis in severe sepsis. There are few initial reports of its safety in patients with COVID-19 [10]. However, there are ongoing trials regarding its efficacy and safety in COVID-19 patients with varying severity levels (CTRI/2020/05/025271, CTRI/2020/04/024846). Mw has undergone thorough preclinical and clinical studies and is now approved as an adjunct therapy for the management of gram-negative sepsis in India. Its role in COVID-19 prevention and treatment is being studied, and it may emerge as a potential treatment option for the same (CTRI/2020/05/025277).

BCG vaccine, which has been used for prevention of tuberculosis, is another immunomodulator that is being tried to prevent COVID-19 (NCT04534803). There are multiple publications regarding the community BCG vaccination conferring protection from COVID-19 [11]. Both BCG and *Mw* differ in their immune response generation by TLR agonism and ligand presentation. The concept of using these agents to modulate the innate immune response to confer protection and hasten recovery from various pathogens, including SARS-CoV-2, seems reasonable. However, the results of the ongoing trials will provide the evidence for any such use.

Conflict of interest

None declared.

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