LETTER TO THE EDITOR

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The effect of BCG vaccine in the era of COVID-19 pandemic

Coronavirus Disease-2019 (COVID-19) has become a worldwide emergency and announced as a pandemic recently with variable incidence and mortality in different geographical areas.[1] The relationship between COVID-19 and Bacille Calmette Guérin (BCG) vaccine is still under investigation, and we aim to clarify this matter.

Bacille Calmette Guérin is a live attenuated tuberculosis vaccine. BCG vaccination of adult humans induces strained circulating monocytes having an increase in their capacity to produce proinflammatory cytokines.[2] This effect translates to non-specific protection against unrelated pathogens, an example of which is *S aureus* and *C Albicans*. Also, vaccination of BCG of healthy volunteers showed an increase in the capacity of natural killer (NK) cells to secrete proinflammatory cytokines, such as IL-1β and IL-6 after stimulation with *M tuberculosis* or unrelated pathogens (*S aureus, C Albicans*).[3] Therefore, BCG induces non-specific protection against unrelated pathogens.[4] In trained immunity, the human immune cells experience metabolic and epigenetic changes that strengthen the immune response to heterologous reinfection. Therefore, BCG vaccine may play a role in the COVID-19 pandemic.[5]

Bacille Calmette Guérin vaccine is given at birth or/and during childhood induces a long-lasting immunity not only against tuberculosis (TB), but also against other infections. It has had a successful outcome in the treatment of TB and other lung diseases as it decreases mortality by the protection against respiratory infections and neonatal sepsis. BCG causes an epigenetic modification of the monocyte immune cells, which may anticipate protection against COVID-19. Relative to countries with compulsory BCG vaccination protocol and countries without, low rates of COVID-19-related deaths are recorded in countries with BCG vaccination policy compared to other countries.[6] This may be due to the so-called herd immunity under which the virus cannot spread among people.[7]

Apart from the use of the BCG vaccine for the prophylaxis of TB and against leprosy, it has demonstrated efficacy in patients with various diseases, including viral infections, autoimmune diseases, superficial bladder cancer and oral aphthous ulcers.[8] This is explained by the immune response mediated by BCG vaccination, which shows cross-antigenicity. Therefore, a combination of oral zinc sulphate, which enhances the immune response against many diseases, and BCG vaccination will help improve the protection from various infections including COVID-19, especially in countries where the policy of universal BCG vaccination is already applied.[8]

Previous studies assumed that there is no noteworthy correlation between BCG vaccination coverage and COVID-19 case fatality rate among the countries with universal BCG vaccination policy.[9] Statistical studies showed confusion about the value of BCG vaccine in COVID-19 pandemic. One study showed that mean of cases per population ratio is statistically significantly lower in 138 BCG-vaccinated countries versus 37 BCG-non-vaccinated countries.[10] A systemic review showed that countries with no policy of BCG vaccination, such as Italy and USA, showed higher mortality associated with COVID-19 than countries with long-standing BCG vaccination policies, such as South Korea and Japan.[11] However, another recent study among those who were born in israel before and after the time of policy of BCG vaccination showed no statistically significant difference in the proportion of positive COVID-19 cases among the BCG-vaccinated group (11.7%) vs the -unvaccinated group (10.4%).[12] Another regression analysis showed no actual relationship between BCG vaccination and reduced cases of severe COVID-19.[13]

As a limitation, all previous studies are observational and no completed clinical trials up till now to confirm or exclude the hypothesis. However, there are ongoing clinical trials investigating the safety and efficacy of BCG vaccine for healthcare workers in prophylaxis against COVID-19.[11]

In conclusion, the BCG vaccine could have a protective role against COVID-19 with lower mortality rates in already infected patients. However, further clinical trials are recommended to prove that.

CONFLICT OF INTEREST
The authors state that there are no conflicts of interest.

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