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REVIEW/DERLEME

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Can BCG Vaccine Be a Potential Tool for COVID-19?

BCG Aşısı, COVID-19 için Potansiyel Bir Araç Olabilir mi?

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ABSTRACT

SARS-CoV-2 has affected essentially all countries worldwide and caused millions of people to become infected and die. Therefore, it is extremely valuable to investigate new approaches to stop the most scarring ongoing pandemic. BCG vaccine has been proposed that it could reduce the rate of new COVID cases and limit the severity of infection since TB and COVID-19 have similar dominant effects, such as cytokine storm and improper immune response. This review aimed to focus on the latest literature data on trained immunity as well as the possible cross protection effect of BCG vaccine against COVID-19. The first immune response to BCG vaccines has started with the stimulation of adaptive immune response and establishment of the immunological memory of antigen-specific T and B cells to target infectious agents. In the past years, innate immune response was thought to be not having the talent to adapt and "learn" from previous exposure to a pathogen. Trained immunity is conceivable as 'de facto' innate immune system memory. Some researches argue that there is a strong relationship between BCG immunization and COVID-19 although some are against this argument. Based on the data obtained from different research studies and ongoing clinical trials, there is still no evidence that BCG vaccine is effective against COVID-19. Besides assumptions, knowns and unknowns, the clinical efficiency of BCG vaccine against SARS-CoV-2 should be validated by accurate scientific clinical reports in different age groups to understand the potential benefits of BCG vaccine to limit COVID-19 incidence and mortality.

Key Words: *COVID-19; SARS-CoV-2; Tuberculosis; BCG vaccine*

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ÖZ

BCG Aşısı, COVID-19 için Potansiyel Bir Araç Olabilir mi?

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SARS-CoV-2 dünya genelinde birçok ülkeyi etkilemiş, milyonlarca kişinin infekte olmasına ve hayatını kaybetmesine neden olmuştur. Bu nedenle, devam eden COVID-19 pandemisini sonlandırmak için yeni yaklaşımların araştırılması önemlidir. Tüberküloz ve COVID-19'un sitokin fırtınası ve bağışıklık tepkisi gibi benzer etkiye sahip olması nedeniyle, BCG aşısının yeni COVID-19 vakalarının oranını azaltabileceği ve infeksiyonun şiddetini sınırlayabileceği düşünülmektedir. Bu derleme, BCG aşısının COVID-19'a karşı olası çapraz koruma etkisinin yanı sıra edinilmiş bağışıklık hakkındaki en son literatür verilerini sunmayı amaçlamıştır. BCG aşılarına karşı ilk bağışıklık tepkisi, adaptif bağışıklık tepkisinin uyarılması ve hedef infeksiyon ajanlarını amaçlamak için antijene özgü T ve B hücrelerinin immünolojik hafızasının oluşmasıyla başladı. Geçmiş yıllarda, doğuştan gelen bağışıklık tepkisinin, bir patojene önceki maruziyetten adapte olma ve "öğrenme" yeteneğine sahip olmadığı düşünülüyordu. Edinilmiş bağışıklık, doğuştan gelen bağışıklık sistemi belleği olarak düşünülebilir. Bazı araştırmalar, BCG bağışıklaması ile COVID-19 arasında güçlü bir ilişki olduğunu iddia etse de, bazıları bu görüşe karşı çıkıyor. Farklı araştırma çalışmalarından ve devam eden klinik çalışmalardan elde edilen verilere dayanarak, BCG aşısının COVID-19'a karşı etkili olduğuna dair hala bir kanıt yoktur. Varsayımların, bilinenlerin ve bilinmeyenlerin yanı sıra, BCG aşısının COVID-19 insidansını ve mortalitesini sınırlamak için potansiyel faydalarını anlamak için BCG aşısının SARS-CoV-2'ye karşı klinik etkinliği, farklı yaş gruplarında doğru bilimsel klinik raporlarla doğrulanmalıdır.

Anahtar Kelimeler: *COVID-19; SARS-CoV-2; Tüberküloz; BCG aşısı*

INTRODUCTION

Depending on the rapid spread of new Coronavirus disease-2019 (COVID-19) and high mortality incidence in elderly people, in immunocompromised patients and/or in individuals with comorbidities, and in addition, in countries with large populations, lack of access to available vaccines, alternative therapeutics or vaccines are being investigated[1,2]. As the COVID-19 pandemic continues to be devastating, countries are maintaining lockdowns, physical distances, quarantine and travel restrictions to control further spread[2]. However, the world economy has been significantly affected by the lockdown of many businesses and travel restrictions[3]. Therefore, it is extremely valuable to investigate new approaches to manage the ongoing pandemic. Clinical studies have been performed to demonstrate the role of the Bacillus Calmette-Guérin (BCG) vaccine in limiting or reducing the severity of COVID-19, as new research studies have shown that the BCG vaccine has a potential cross protective effect on many different respiratory infections including influenza as well as *Mycobacterium tuberculosis* infection[4-12]. Therefore, it is also thought that the tuberculosis vaccine could contribute to protecting and limiting COVID-19[13].

BCG vaccine has been used for 80 years. The vaccine, which provides immunity against tuberculosis disease (TB) for up to 20 years, is one of the most extensively used vaccine worldwide[14]. Approximately 80% of children in countries around the world, where a national childhood vaccination program exists, are being vaccinated with BCG[15], which leads to the prevention of pulmonary TB infections as well as reduces not only the rate of progression to meningeal TB but also TB associated deaths by around 85% and 66%, respectively[11]. Although the preventative effect of BCG has been clarified in childhood, its effect in the adult population is still uncertain[16]. In a recent randomized clinical trial against BCG vaccination in the elder population, Evangelos J et al. have reported that initial infection due to BCG occurred late and new infections occurred at a lower rate. The study has revealed that significant protection against viral respiratory infections was observed

and cytokine production in monocytes was determined[17].

In 2019, TB was reported in the largest number of new cases in South East Asian, followed by the African and Western Pacific regions with 44%, 25% and 18%, respectively. Two-thirds (87%) of new tuberculosis cases were determined in countries such as Bangladesh, China, Indonesia, India, Nigeria, Philippines, Pakistan and South Africa in the same year[18]. According to BCG World Atlas database on BCG vaccination from more than 200 countries, currently, BCG vaccine is mandatorily provided for all in countries including Argentina, Brazil, China, Japan, Jordan, Russia, Mexico, Poland, Singapore, Central and South Africa, Taiwan, Thailand, Poland, Pakistan, Hong Kong, India, Iraq and Türkiye. Although Germany, Ireland, Denmark, Austria, Slovakia and Syria stopped providing BCG vaccination to children, it is reported that in the United States of America (USA), United Kingdom, Italy, Netherlands, Spain, Australia, Canada, France, Finland, Cyprus, Israel, New Zealand, BCG vaccine is available only for private groups involving individuals at high risk[11,19,20].

This review focused on trained immunity and its contribution to resist infectious diseases, as well as presenting different arguments on the possible cross-protection of BCG vaccination against the spread and severity of COVID-19. Studies published recently in the literature have been extensively evaluated to find any existing association between the tuberculosis vaccine and COVID-19. Studies evaluating the rate of infected cases with SARS-CoV-2 and the mortality rates associated with COVID-19 in countries where universal BCG vaccination policies are implemented or not are included in this review.

Immune Response to BCG Vaccine

TB is an airborne acquired bacterial disease caused by inhalation of tiny droplets during sneezing and/or coughing of individuals infected with *Mycobacterium tuberculosis* (*M. tuberculosis).* It generally attacks the lungs and other parts of the body, as well. Therefore, we categorized TB infections as two groups: (i) latent TB infection (LTB) and (ii) patients sufferring from an active TB disease[21].

BCG vaccine developed against tuberculosis disease from a virulent strain of *Mycobacterium bovis* (*M. bovis*) at the Institute Pasteur in Paris was a live attenuated vaccine. Clinical experiments on tuberculosis vaccine were proposed first in the United Kingdom and the USA in the 1950s, and later, many countries started BCG vaccination policies[22]. The first immune response to BCG vaccines started with the stimulation of adaptive immune response and establishment of immunological memory of antigen-specific T and B cells to target infectious agents[23].

Immunologists have reported (i) two major immunological mechanisms, first as heterologous immunity, in which CD4 and CD8 memory cells can be induced in antigen-independent ways for the condition with cytokines activated by secondary infections, and second as histone modifications and epigenetic reprogramming of human monocyte (trained immunity) by vaccination of BCG[24]. According to trained immunity stimulated by BCG vaccination, increase in proinflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 provides significant protection against different viral infections[25].

Innate immune system, which is the first defense mechanism against pathogens, invades the human body. Immune cells uniformly guard different organs, such as the gastrointestinal tract, airways, and the lungs. In the past, innate immune response was thought to be not having the talent to adapt and "learn" from early exposure to microorganisms. However, some studies indicated that "training" of the innate immune system is an age-old response observed in humans[26]. This situation happened by some epigenetics and metabolic reprogramming of the immune cells like the natural killer, neutrophils macrophages, and other white blood cells[25].

Tuberculosis vaccine is thought to allow us to provide a non-specific immune response against other infectious diseases other than

Tuberculosis[27]. The question is 'how is this possible?' The answer might be based on 'trained immunity'. Trained immunity is that elevated non-specific immunological response to different microorganisms is arbitrated by the stimulation of innate immune cells which are white blood cells such as monocytes, macrophages, naturel killer cells (NK) or large granular lymphocytes (LGL) and independent of T and B cell responses that stimulate innate response. Trained immunity is also conceivable as '*de facto'* innate immune system memory[28].

BCG vaccine programs in children reduce the death rate and prolong a revised innate immune response in contrast to various microorganisms like *Staphylococcus aureus* and *Candida albicans* by 'trained immunity'[29,30,31]. Also, consecutive BCG vaccination is related with increased TNF-α, IL-1β and IL-6 which provide an important defense in contrast to viral infections with trained immunity[25].

While some researchers support that BCG vaccination may be beneficial against respiratory infections[32], some authors think otherwise[33]. Leentjens J et al. have studied the BCG vaccine for healthy volunteers before administration of the seasonal influenza vaccine, and they have reported increase in the onset of functional antibody responses, unlike the H1N1 pandemic in 2009[34]. Additionally, some studies have shown that exposure to infectious respiratory infections such as influenza A virus, respiratory synthesis virus (RSV) and herpes simplex virus type 2 (HSV-2) decreased with the BCG vaccine[35-37]. In South Africa and Guinea-Bissau where BCG vaccination is done, up to 70% decrease has been observed in the prevalence of respiratory tract infections, especially RSV[38]. Additionally, the same study has reported that BCG vaccine has an ability to provide protection against influenza (flu) virus and herpes simplex virus[38]. As a result of the studies, immunogenicity and productivity of the BCG vaccine have been widely confirmed. Moreover, cost effectiveness and easy access to BCG vaccine could make it an important key in inducing disease-trained immunity.

Similarities Between BCG and COVID-19

TB and the new Coronavirus disease have similar dominant effects like cytokine storm and the improper response of the immune system[39]. In reality, BCG provides safety and overcast of the asperity of the COVID-19 infection by the way of mediating innate immunity by enhancing macrophage activity and CD4+ T cells[40]. During the pandemic, BCG vaccine might have a significant role in activating innate immune response such as cytokine secretion in peripheral blood lymphocytes. This effect may cause excessive proliferation of CD4+ and CD8+ T cells, excessive secretion of Th1 cytokines and low secretion of Th2 cytokines[40]. Some studies have reported that BCG vaccine could reduce the progression of COVID-19 infection using trained immunity by the advance of genetic regions encoding for pro-inflammatory cytokines. For example, IL-1B which has an important regulatory role in decreasing respiratory infections and sepsis includes antiviral immunity[41]. The collaboration of innate and adaptive immune system plays an important role in the defense against viral infections. BCG vaccine may also trigger cross-reactive T cells against new Coronavirus as another immune mechanism. It is also known that BCG and SARS-CoV-2 have similar 9 amino acid sequences that can bind to common HLA class I molecules with moderate to high binding affinity[42].

Sarinho E et al. have stated that the BCG attributed immunity paradigm based on the model-based design of experiments and cohort studies includes low number of patients, which have also been determined by some epidemiological studies where possible interfering factors have not been included. It is said that this hypothesis needs to be confirmed by clinical and epidemiological studies which will be performed in real-life[28].

Comparison of the Studies on BCG and COVID-19

In particular, to understand the protection potential of BCG vaccine in the control of COVID-19 pandemic, the counts of confirmed

Coronavirus cases per country and recorded deaths from COVID-19 are evaluated using statistical data from the BCG World Atlas and World meter in research studies. Clinical trials are still in progress and no conclusive evidence that it protects people against COVID-19 is still present. Recent studies have found that nations with mandatory BCG vaccination policies have fewer cases and deaths from the Coronavirus compared to countries without those policies[43-46]. In a study by Iwasaki and Grubaugh, although Japan did not implement extensive testing, contact tracking, or strict quarantine measures, slow increase in the rate of infected cases and a death rate with 1/10 of the world average have been reported[47].

In another research, Sing and Gandharva[48] have investigated more than 80 countries including Canada, Italy and the United States, and they have observed that the number of COVID-19 cases (1043.9 versus 172.4) and related deaths (48.9 versus 4.3) per million population are significantly higher in nations where childhood BCG vaccination program is not provided comparing to those that are still using it. As the impact of the disease differs from country to country according to their incomes, different income levels have also been investigated to show any association between tuberculosis vaccine and COVID-19 related death rates. In that study, Miller et al.[44] have demonstrated that countries with no universal vaccination programs such as Italy, Netherlands and USA have been more severely affected than countries using the vaccine and BCG vaccine could be a usable tool in combating the COVID-19 pandemic as it is associated with limiting COVID cases and resisting deaths[45]. In North America, BCG vaccination began in 1950s[19] and at present, it is administered only for special groups. As of 26 April 2021, the number of confirmed COVID-19 cases is more that 140 million globally and the number of confirmed cases being reported in America has reached to 61 million with 572.000 deaths[1]. A question may come to mind. Similar to the USA, other developed countries such as the United Kingdom, Spain, Italy, and Germany have also been affected critically during the COVID-19 pandemic with the number of cases reaching 3 to 5 million[1]. If the BCG vaccine had been used in these countries, would it have prevented COVID-19 burden and reduced related deaths?

On the contrary, in a recently published systematic review, Ricco et al.[49] have also presented no correlation between BCG vaccination and SARS-CoV-2 infection occurrence. Recently published studies have also revealed that BCG vaccination has no contribution in deaths associated with COVID-19 as they could not find any statistical differences that exist in mortality rates between countries with a current national BCG vaccination policy and countries with past national BCG vaccination and countries where BCG vaccine has never been administered[50]. Aksu et al.[51] have investigated COVID-19 acquired pneumonia clinical progression in a country with routine BCG vaccination, and this retrospective cross-sectional study has revealed that although age and low income are important factors, no statistical significant relationship has been found between disease severity and BCG vaccination in COVID-19 pneumonia[50,51].

Moreover, COVID-19 generally causes infection in the adult and older aged population. Previous studies have shown that populations vaccinated during childhood have higher vaccine efficacy rates compared to populations vaccinated at older ages[52,53]. While the protective efficacy rate is 17% in persons vaccinated in childhood, protection has not been found in those vaccinated in adulthood[54]. Similarly, a study in Japan shows that routine infant BCG vaccine policy in the younger population has a significant impact on limiting the local spread of local COVID-19[55].

In another recent study conducted in Taiwan, Su et al.[56] have shown that BCG vaccination did not alter the mortality rate of COVID-19 in the young population. The null effect of BCG vaccination has been contributed to the literature by Hamiel et al.[57] as they have observed no statistically significant difference in the proportion of positive test results in the BCG-vaccinated group [361 (11.7%)] vs the unvaccinated group

[299 (10.4%); difference, 1.3%; 95% CI, -0.3% to 2.9%; p= .09) or in positivity rates per 100.000 (121 in vaccinated group vs 100 in unvaccinated group; difference, 21 per 100.000; 95% CI, -10 to 50 per 100.000; p= .15)[57].

Further, we still need to find answers to some of the questions about: (i) The duration of this BCG-triggered heterologous immunity after BCG vaccination (ii), The best time to administer BCG vaccination[58]. In addition, more research is needed to clarify the mechanisms between BCG-induced trained immunity and COVID-19 and to reveal the relationship between them.

CONCLUSION

In conclusion, based on the data obtained from different research studies and ongoing clinical trials, the efficacy of the tuberculosis vaccine against COVID-19 has not been proven. Besides assumptions, knowns and/or unknowns, the clinical efficiency of tuberculosis vaccine against SARS-CoV-2 should be validated by accurate scientific clinical reports in different age groups to understand the potential benefits of BCG vaccine for COVID-19.

CONFLICT of INTEREST

The authors do not have any conflict of interest(s) to declare.

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