Bacillus Calmette-Guerin: Established and emerging roles for an old friend

Fotios Sampsonas

Respiratory Medicine Department,
University Hospital of Patras, Greece

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Correspondence to:
Fotios Sampsonas,
Consultant Respiratory Medicine,
University Hospital of Patras,
26504, Rion, Patras, Greece
Tel: +306977713684
Fax: +302610999523
Email: fsampsonas@gmail.com

Bacillus Calmette-Guerin (BCG) has been used from the 1920s[1] as a stimulant of the Th1 immune response in order to slow down tuberculosis (TB) dissemination[2]. Globally, almost 2 billion people are estimated to be infected and 10 million people have develop active disease every year. BCG vaccination is still one of the cornerstones for the prevention of the disease. It remains even today one of the most used vaccines globally[3]. In the region of eastern Mediterranean 87% of countries do have an active BCG vaccination plan in place, but inconsistency issues and high left out/dropout rates are still encountered[3].

Three different BCG strains are globally most often used: the Moscow-368, Tokyo 172-1 and Sofia SL222 variants[2]. Vaccines contain dead and living bacilli as per WHO guidelines in terms of safety, quality and efficacy[1,2]. In previous decades many concerns have risen for its safety and efficacy with regards to pulmonary and extrapulmonary TB prophylaxis. All these have been grossly addressed by randomized control trials (RCTs) that showed significant protection rates of BCG vaccination of neonates, especially against meningeal and miliary TB. These protective properties of the vaccine were questionable, especially when performed at school-age children that have not been screened prior of the vaccination with a standard Tuberculin Skin Test (TST)[4-6].

Following the initial perception that BCG vaccination protects against severe disease only, a recent meta-analysis revealed that BCG might as well have a role in protecting against primary infection from TB[7], leprosy[8] and non-tuberculous mycobacteria (NTM)[9]. On top of that, multiple immunomodulatory effects of BCG have been described over the last 3 decades, highlighting an additional role of BCG in reducing all-cause mortality especially in infancy and childhood. It has been documented that children have a relative risk of 0.70 for all-cause mortality when vaccinated[10].

BCG vaccination's beneficial effect is larger than somebody would expect from their direct effect on the disease that are directed against to. Interestingly, BCG vaccination is in vitro grossly protective against extensive lung injury from many pathogens that can reach alveolar space, like Influenza. This could occur by augmenting successful efferocytosis and preventing diffuse lung damage from Influenza A virus[11]. In other words, BCG vaccination seems to orchestrate the successful lung inflammatory homeostasis, promotes and maintains a balanced lung inflammation with minimal side

damage to the lung parenchyma per se, diminishing at the same time the subsequent development of fibrotic scaring[11]. BCG vaccination has also been associated with reduced infection rates from yellow fever, fungi like *Candida spp, Plasmodium* malariae and others[12-14].

Of note, a recent a 60-year retrospective study revealed that BCG vaccinated children of Indian American and Alaska native origin had a lower lung cancer development rates in adulthood, after adjusted for significant epidemiological variables like sex, smoking habit and age[15]. Authors highlighted the fact that BCG protective effect against lung cancer was not related to its protective properties against tuberculosis per se, but seemed to be related to a direct immunomodulatory activity. This activity is of no surprise, since BCG is one of the mainstream immunotherapy treatments for non-invasive bladder cancer[16] or even for stage III non operable in-transit melanoma as direct intralesional infusion[17]. In vitro incubation of various cancerous and non-cancerous cell lines with BCG seems to stimulate and regulate the release of numerous pro-inflammatory cytokines such us TNF-α, IL-1β, IL-6 among others. Previous reports for associations of BCG with lymphomas have been addressed and rejected by a recent metanalysis[18]. A BCG vaccination in early life could also shift the immune response towards Th1-type of inflammation that eventually would also be transiently protective against asthma[19].

In view of the above mentioned immunomodulatory and broad-spectrum, lung protective, properties of BCG vaccination, recent studies report that widespread BCG vaccination may facilitate in flattening the curve of the increase of new COVID-19 cases[20]. BCG vaccination could be more effective against the COVID-19 infection if multiple doses are being administered[21].

In conclusion, BCG vaccination might offer a widespread protection not only against TB, but also against other pathogens that affect respiratory tract and parenchyma, like severe respiratory syndrome related to COVID-19. BCG is also widely used against melanoma and bladder cancer and might have a favorable role in other chronic inflammatory disorders.

CONFLICTS OF INTEREST

No conflicts of interest to declare.

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