Trials in Vaccinology 3 (2014) 143–149

Contents lists available at ScienceDirect

Trials in Vaccinology

journal homepage: www.elsevier.com/locate/trivac

Review Article

Non-specific immunity of BCG vaccine: A perspective of BCG immunotherapy

Najeeha Talat Iqbal [a,*], Rabia Hussain [b]

[a] Department of Paediatrics and Child Health and Biological & Biomedical Sciences, Aga Khan University, P.O Box 3500, Stadium road, Karachi, Pakistan
[b] Department of Pathology and Microbiology, Aga Khan University, P.O Box 3500, Stadium road, Karachi, Pakistan

ARTICLE INFO

Article history:
Received 13 February 2014
Revised 19 August 2014
Accepted 29 August 2014

Keywords:
BCG vaccine
Immunotherapy
Cancer

ABSTRACT

BCG is a widely used vaccine worldwide for neonates including Pakistan. BCG has more than 90% coverage through the EPI program which was introduced in 1965 in Pakistan. BCG has limited efficacy against the transmissible form of pulmonary tuberculosis in high TB endemic countries. However, BCG vaccination continues in these countries because BCG confers protection against the disseminated form of TB in children. BCG has also shown some protection against leprosy and certain forms of cancers. One reason for such nonspecific protection may be that BCG activates APCs via PAMPS that interacts with TLRs (2, 4 & 8), which initiate the inflammatory cascade thereby recruiting inflammatory cells to the site of infection and providing maturation signals for neutrophils, macrophages and dendritic cells. Such activation may be crucial for restricting the infection at the initial site. Furthermore, activation of the pro-inflammatory cascade also results in expression of adhesion molecules, co-stimulatory molecules as well as MHC class II molecule. MHC class II molecules engage CD4+ cells via the TCR receptor while the adhesion and costimulatory molecules bind to their respective receptors on CD4+ T cells for additional high affinity binding for T cell activation. Although activation of the innate arm may not provide subsequent memory, activation of T cells may introduce a certain level of memory response and therefore, may form a rational basis for BCG immunotherapy. This review, therefore, focuses on the immune activation related to both the innate and adaptive arm of the immune response that has been reported and further explores the utility of BCG immunotherapy related to non TB conditions.

Contents

* Corresponding author. Address: Department of Paediatrics and Biological & Biomedical Sciences, P.O Box 3500, Aga Khan University, Stadium Road, Karachi 74800, Pakistan. Tel.: +92 21 34864544.
E-mail addresses: najeeha.iqbal@aku.edu (N. Talat Iqbal), professorrabiahussain@gmail.com (R. Hussain).

http://dx.doi.org/10.1016/j.trivac.2014.08.002
1879-4378/

1. History of BCG vaccine

BCG is an attenuated strain isolated from *Mycobacterium bovis*, and was first identified by a French scientist Albert Calmette Guerin. BCG was first used in 1921 as a vaccine in humans. It is a widely used vaccine to protect against tuberculosis and leprosy [1,2]. The serial passage of virulent strain of bovine tuberculosis on glycerine bile potato media reduces its virulence while retaining its antigenic properties. The efficacy of BCG against pulmonary tuberculosis is still controversial in several parts of the world with the highest burden of TB [2,3]. The duration of immunity is somewhere between 15 and 60 years post immunization in different trials [4,1]. The variable efficacy of vaccine in different trials has been attributed to variation in different BCG strains, genetic differences in different population [5], prior exposure to non tuberculous mycobacteria [6], and recurrent parasitic infection [7]. However, the reasons for variable protective immunity still remain unclear. To address these issues, a large scale trial was initiated in Chingleput area of South India in 1968 (15 year follow-up was completed in 1987) with the assistance of Indian Council of Medical Research. These results revealed no convincing protection against pulmonary tuberculosis. Irrespective of the finding of the Chingleput trial, BCG vaccination was incorporated in EPI program in 1974 and continued as part of routine vaccination at birth.

Efficacy of BCG in protection against adult tuberculosis is both debatable and controversial. A wide range of efficacy (0–80%) has been reported in case control [8] and cohort studies [2] as well as in clinical trials [9–11]. The reasons for these variable results are not clear; however there is consensus that these are true biological effects and not just due to sampling errors [3]. However, BCG does provide some extent of protection against TB meningitis and miliary disease. This is evidenced in Chingleput trial (initiated in 1968) where no case of TB meningitis or miliary TB was reported for over a 14 year period. The protective effect in randomized controlled trials was 86% (95% CI: 65–95) and in case-control studies was 75% (95% CI: 61–84). The reason of homogenous response is partly due to younger subjects who were less likely to be exposed to atypical mycobacteria. Exposure to atypical mycobacteria presumably obviates protective effect [12]. The role of BCG in infectious diseases was studied thoroughly in both TB and leprosy before observation of its non-specific effects in some cancers. Though BCG was recognized as a vaccine for tuberculosis, widespread BCG coverage has significantly declined the cases of leprosy. It was also evident that BCG vaccinated population in high TB endemic setting had significant impact in declination of leprosy cases [2,13,14]. The efficacy against leprosy ranges between 20 and 80% in controlled trials and observational studies [2,15]. BCG was equally effective against lepromatous as well as a tuberculoid form of leprosy. Given the efficacy of BCG against leprosy, countries like Brazil, Cuba and Venezuela recommended the use of BCG for leprosy contacts. A meta-analysis of 26 studies, that included 7 clinical trials and 19 observational studies (cohort and case control) showed an overall average protection of 26% (96% CI: 14–37%) against leprosy [16]. In observational studies, the protective effect was 61% (95% CI: 51–70%) with significant heterogeneity ($P < 0.00001$). The reason for heterogeneity between studies could be explained by different population, method of exposure and outcome assessment.

2. Rationale of BCG use as adjuvants

The first observation for the use of BCG in enhancement of immune response was evidenced by use of mycobacteria in preparation of Freund's adjuvant in the late 1950s [17]. Complete Freund's adjuvant (CFA) contains heat killed mycobacteria or BCG and trehalose 6,6' dimycolate (TDM) that activates some innate receptors including TLR2, 4 and 9. CFA stimulates a delayed type hypersensitivity reaction at the site which is skewed towards Th1 immunity. In contrast, incomplete Freund's adjuvant (IFA) which lacks mycobacterial component induces Th2 or antibody mediated immunity [18,19]. This is the first observation regarding use of BCG for activation of immune system. The findings of CFA induced arthritis and autoimmune reaction in experimental animals also provide us a rationale of BCG therapy in non-communicable diseases [20,21] . Historically, it was also shown that parasitic, viral and bacterial infection resulted in regression of tumors [22]. The hypothesis of concomitant or cross over immunity due to the presence of cross reactive antigen (parasite's egg) also provides an indirect evidence of protection against reinfection in intermediate host [23,24]. It is a well established fact that parasitic infection induced Th2 immunity [25] and therefore, a switch from Th1 to Th2 immunity is thought to be involved in tumor regression [26,27]. This host parasite relationship was first brought into concept of tumor immunology by Dr. William Coley in 1898. Coley administered his vaccine directly into tumor and observed tumor regression. Coley's toxin or vaccine comprised of a mixture of killed bacteria, (Serratia marcescens and S. pyogenes), which was effective against inoperable sarcomas. In case of Coley's vaccine, an infection precedes spontaneous regression of tumor, supports the idea of non-specific innate immunity in regression rather than adaptive immune response. This idea was further translated into BCG adjuvant therapy in melanoma and bladder cancers. The immune mechanism related to BCG is largely unknown. In this review, we try to shed some light on non-specific immunity conferred by BCG in melanoma and bladder cancers.

2.1 BCG immunotherapy in melanoma cancer

Cutaneous melanoma is the most common skin cancer in United States with annual adjusted incidence of 22/100,000 population in men and 14/100,000 population in women of all races [28]. The incidence is lower in black and Asian Pacific Islander (API) compared to whites with predominance of males affected by this disease [29]. Approximately 15% of primary melanomas develop into distant metastases; the five year survival rate for metastatic melanoma is still less than 5% despite of advancement in treatment and diagnosis. Melanoma is one of the cancers that show regression spontaneously or due to intervention with adjuvant immunotherapy presumably because of infiltration of immune cells at the tumor site [30,31]. The adjuvant immune therapy with BCG has also shown promising results for patients after surgical resection in advanced malignant melanoma [31].

Prior vaccination with BCG or vaccinia in childhood had significant effect in case reduction compared to the non-vaccinated group. A multicenter case control trail of Febrile infection and melanoma (FEBIM), evaluated risk of melanoma and vaccination status in child hood for either BCG or vaccinia or both in six European countries and Israel. This study also addressed the effect of severe infection and risk of melanoma compared to subjects either vaccinated with BCG or vaccinia. The odds ratio for individuals not vaccinated for any of the vaccine were compared to BCG [OR 0.23;(95% CI: 0.05–0.91)] and vaccinia [OR 0.33;(CI:0.10–1.06)] in persons below 50 years of age, signifies the effect of severe infection on reducing risk of melanoma [32]. Prior immunization with BCG or vaccinia vaccine was further evaluated on survival of melanoma patients during a five year follow up. A hazard ratio of 0.69 (95% CI: 0.49–0.98) with BCG compared to 0.52 (95% CI: 0.34–0.79) with vaccinia vaccine for development of melanoma suggests an immune surveillance mechanism of BCG for melanoma skin cancer [33]. Human endogenous retroviral genes (HERV–K) encoded envelop protein is expressed in many cases of melanoma [34] which cause malignant transformation by altering intracellular redox potential [35]. The immune surveillance mechanism of BCG, vaccinia or contact with other infectious agents was described by the presence of