Bacillus Calmette–Guérin Vaccine against Mycobacterium leprae Infections

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Bacillus Calmette–Guérin (BCG) is a vaccine made from attenuated strains of *M. bovis*, a close relative of *M. tuberculosis*, and is routinely used in countries where tuberculosis (TB) is hyper-endemic. *Mycobacterium leprae* is a non-motile, acid-fast bacillus from the mycobacterium family. *M. leprae* is a non-culturable, obligate intracellular pathogen that causes a chronic granulomatous infection characterized predominantly by peripheral nerve damage and prominent skin lesions known as Leprosy or Hansen's disease.

non-tuberculous mycobacteria BCG M. leprae

1. Introduction

The species of bacteria in the genus mycobacterium are known to cause a variety of infections in humans. Due to the interplay of the host defense and the infectious agent, these infections are classified as *M. tuberculosis* complex (MTC) or non-tuberculous mycobacteria (NTM).

Non-tuberculous mycobacteria include all the species of mycobacterium other than the ones that cause TB or leprosy [1]. *Mycobacterium leprae,* a non-motile, acid-fast bacillus from the mycobacterium family, is a non-culturable, obligate intracellular pathogen that causes leprosy, a chronic granulomatous infection characterized predominantly by peripheral nerve damage and prominent skin lesions.

According to Runyon classification, NTM are further classified according to their growth rates as slow growing mycobacteria, SGM (types I, II, III), which take more than 7 days, and rapid growing mycobacteria, RGM (type IV), which takes less than 7 days. Within SGM, each type is defined by its ability to produce pigment. Type I can only produce a yellow pigment in the presence of sunlight, i.e., photochromogen, type II can produce pigments irrespective of the presence of light, i.e., scotochromogen, and type III produce very little or no pigmentation, i.e., achromogen. Type IV or RGM is not associated with the characteristic of pigmentation [2][3].

The infections caused by these NTM can be from about 200 different species and are predominantly found in the environment and animals [4]. Although the incidence of TB has declined, an inverse relationship has been observed between TB and NTM infections, with the rates of NTM infections showing a simultaneous and significant increase worldwide within the past 70 years [5].

As a result of the control programs implemented by Western countries such as the USA and Canada, infections due to the MTC are significantly less than those caused by NTM [6]. Due to the prevalence of NTM existing in the environment, the infecting agent has the ability to spread much easier when compared to infections causing TB and leprosy, which involve more human contact [7]. As a result, it makes these NTM highly opportunistic, which increases their chance of infecting the immunocompromised including individuals with HIV, genetic immunodeficiencies, or acquired decrease in their immune system [3][8].

As opposed to MTC that cause TB and leprosy, NTM have been shown to be less virulent [9], although *M. abscessus* is known to be one of the most drug-resistant of all mycobacteria. *M. avium-intracellular* complex are common NTM that can cause active pulmonary and extra pulmonary disease. Other NTM that are commonly associated with skin infections are *M. ulcerans* and *M. abscessus*.

Bacillus Calmette–Guérin (BCG) is a vaccine made from attenuated strains of *M. bovis*, a close relative of *M. tuberculosis,* and is routinely used in countries where TB is hyper-endemic. While it is hitherto not used in the Western countries owing to the lower incidence of TB, and the varying effectiveness of the vaccine against TB, it might be of use in preventing NTM infections. It is the most widely administered vaccine and usually a part of the routine newborn immunization schedule. BCG vaccine also offers partial protection against non-tuberculous mycobacterial infections like leprosy and Buruli ulcer [10]. Calmette and Guérin began their research in 1900 for an antituberculosis vaccine. After more than a decade of attempts to develop a vaccine for TB, they found success in using an attenuated *M. bovis* strain. In 1919 they attempted a vaccination trial using guinea pigs, rabbits, cattle, and horses. They were successful in preventing the vaccine subjects from contracting progressive TB [11]. Thus, in 1921 they decided it was time for trials involving human subjects for the vaccine. The vaccine was given via oral route to infants at the Charité Hospital in Paris, and later it was concluded that there was a decrease in TB mortality among the infants that were given the BCG vaccine. As a result, BCG vaccination spread to various countries [10][11]. A probable protective effect of BCG vaccine against NTM infections could be drawn from a nationwide surveillance study conducted in Sweden after it discontinued general BCG vaccination of newborns in 1975. Annual incidence rate of NTM infections per 100,000 children less than 5 years of age increased from 0.06 between 1969 and 1974 to 5.7 during 1981–1985. The cumulative incidence rate of NTM infection per 100,000 children less than 5 years of age between 1975 and 1985 was estimated to be 26.8 among non-BCG vaccinated children, and 4.6 among BCG vaccinated [12]. Mycobacterial cervical adenitis, caused by a NTM infection, was an uncommon disease in Finland from 1977–1986, where neonatal BCG vaccination was in practice, with an incidence rate of 0.3 per 100,000 children. Contrast that with that in Sweden, where the BCG vaccination had been discontinued, and where the incidence was 30 times higher [13].

2. *Mycobacterium leprae*

Mycobacterium leprae is a non-motile, acid-fast bacillus from the mycobacterium family [14]. *M. leprae* is a non-culturable, obligate intracellular pathogen that causes a chronic granulomatous infection characterized predominantly by peripheral nerve damage and prominent skin lesions known as Leprosy or Hansen's disease [15]. Endemic mostly to tropical underdeveloped and developing countries, most commonly Brazil and India, *M. leprae*

is transmitted mainly by entry through the nasal mucosa into the upper airway, which constitutes one of the most important entry routes [16][17][18][19]. *M. leprae* is found within environmental soil and water and is zoonotic with a natural host most commonly being the nine-banded armadillo [17]. *M. leprae* has a slow doubling time of 12 days, and thus in its early stages of infection is not highly contagious. Clinical diagnosis of leprosy is based on the manifestation of skin lesions with associated sensory loss and can be made primarily through skin biopsy, but also it includes serological and polymerase chain reaction tests [20][21]. In its early or indeterminate stages, leprosy is characterized by poorly demarcated borders and hypopigmented macules. Furthermore, in its determinate stages, leprosy presents with various histopathological manifestations that are dependent upon cellular responses towards the pathogen. Based on the Ridley–Jopling system, leprosy has been classified into the following categories based on the Ridley–Jopling classification: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), lepromatous (LL), and indeterminate (I). Individuals who are immunocompetent present with the tuberculoid form, also known as paucibacillary leprosy; individuals who are immunocompromised present with the lepromatous form, also known as multibacillary leprosy [14][20][22][23]. Additionally, lepromatous leprosy patients are also at risk of developing type 1 (T1R) and type II reactions (T2R). T1Rs or reversal reactions (RR) are inflammatory exacerbations of the skin lesions and nerve trunks, resulting in sensory and motor alterations. T2Rs are characterized as acute with systemic involvement, also known as erythema nodosum leprosum (ENL). Leprosy is an important global health concern [24]. Contrary to popular folklore, leprosy is not highly contagious, and effective treatment is available.

2.1. Pathogenesis and Etiology

Infection of peripheral nerves by *M. leprae* is a hallmark of leprous neuropathy, causing sensory, motor, and autonomic disability, thus making it one of the most common causes of peripheral neuropathy worldwide [25][26]. Although *M. leprae* has a strong predilection for Schwann cells of peripheral nerves, it also infects histiocytes and keratinocytes [15]. Normally, upon pathogenic infection, antigen-presenting host dendritic cells (DC) phagocytose the pathogen and present its antigen on major histocompatibility (MHC) complexes class I and class II to T cells, which then trigger cell-mediated immune responses towards the pathogen. Although individuals affected with paucibacillary leprosy present with skin and nerve lesions, T cells in these individuals act to localize bacterial spread, thereby limiting dissemination of the disease. However, in those affected with multibacillary leprosy, cell-mediated responses are not elicited sufficiently, leading to more severe manifestations of leprosy [27]. Furthermore, in vitro analysis of *M. leprae* in the presence of human peripheral blood cells shows that antigen presentation via MHC I and II was downregulated, with greater downregulation associated with a greater inoculated dose of *M. leprae.* As a result, *M. leprae*-infected DCs and macrophages are not able to strongly stimulate CD4+ and CD8+ T cells, thus compromising host defenses against *M. leprae,* which are primarily mediated by interferon gamma (IFN-γ) secreted by cytotoxic T cells [28][29]. In addition, *M. leprae* has been shown to elicit decreased production of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and unremarkable levels of IL-8, IL-10, and IL-12p40 [30].

2.2. Vaccination

There is currently no vaccine, specific against *M. leprae*, which provides complete protection towards leprosy; however, administration of the BCG has been shown to provide some protective effects among those susceptible to infection by *M. leprae.* Although the BCG vaccine was originally intended for use against *M. tuberculosis***,** the proposed mechanism for the protective properties of BCG against *M. leprae* involve cross-reactivity B cells and T cells against mycobacterial antigens that are shared between different mycobacterial species [31]. In a randomized controlled trial conducted by Lwin et al. in Myanmar in 1985, 13,066 children aged 0–14, including 1531 children who were household contacts of leprosy patients, were inoculated with the BCG vaccine and shown to have an overall protective effect of 20.4% against *M. leprae* [32]. Fortunately, recent development of the *Mycobacterial indicus pranii* (MIP) vaccine derived from the non-pathogenic MIP has shown to improve treatment outcomes in patients affected with multidrug-resistant leprosy. MIP vaccine is an inactivated, non-tuberculous mycobacterial vaccine used for multibacillary leprosy patients as an adjunct immunotherapeutic agent by reducing the bacterial load and by reducing the duration of multidrug therapy in such patients by modulating the immune response towards the Th1 subtype [33][34]. In a study using guinea pig models, it was found that when the MIP vaccine was given as a booster in conjunction with the BCG vaccine, pro-inflammatory cytokines such as IL-12, IFN-γ, IL-2, IL-17, and TNF-α were increased in the infected lungs of these guinea pigs, relative to guinea pigs that were inoculated with only the BCG vaccine [35]. In addition to the MIP vaccine, the LepVax subunit vaccine based on an *M. leprae* recombinant polyprotein, which has been newly developed in the United States, has showed positive immunotherapeutic response by decreasing the neuropathic effects of *M. leprae* infection; however, testing of this vaccine in humans is currently ongoing [32].

2.3. Treatment and Current Research

Based on WHO guidelines, current treatment of leprosy in adults involves multidrug therapy of antibiotics. Treatment of single paucibacillary skin lesions includes a single dose of rifampicin, ofloxacin, and minocycline. Treatment of multiple paucibacillary skin lesions includes rifampicin and dapsone for six months. Treatment for multibacillary leprosy includes rifampicin, dapsone, and clofazimine for 12 months [21]. Neuritis caused by *M. leprae* must be treated aggressively to prevent or minimize nerve injury and thus prevent deformity and disability. Corticosteroids are the primary treatments suggested for neuritis and subclinical neuropathy in leprosy [36]. Use of corticosteroids and polychemotherapy to suppress the immune response are the most efficient treatment option for reversal reactions of leprosy [24]. Since *M. leprae* infects macrophages, it leads to the suppression of the vitamin D antimicrobial pathway, thus preventing the production of antimicrobial peptides, which are essential for the suppression of mycobacterial infections. As a result, supplementation of vitamin D activates the vitamin D receptor (VPR) on T cells, eliciting transformation of T cells from immature to mature. This initiates activation of the vitamin D antimicrobial pathway, which leads to the production of antimicrobial peptides, particularly cationic cathelicidins [21][29][37][38]. Another supplemental component that may aid in host defense is the use of glutathione. Glutathione is the most important endogenous tripeptide antioxidant synthesized in cells, which can exist in a reduced (GSH) or oxidized (GSSG) form. In its reduced form, GSH contains a sulfhydryl group that is involved in a plethora of reduction reactions, with its primary role being to reduce reactive oxygen species (ROS), such as peroxide and hydroxide radicals [39]. Normally, ROS produced from phagocytic cells upon pathogenic infection help damage pathogenic cells to limit the spread of infection. GSH as a reducing agent acts to reduce ROS to prevent excessive

damage of host cells, thus maintaining physiological balance of ROS within the body [40]. In leprosy patients with poor immune status, severe oxidative stress has been reported because of the influence *M. leprae* has on significantly decreasing GSH levels in the body, resulting in elevated levels of ROS that will damage cellular proteins, lipids, and nucleic acids, which would ultimately lead to the progression or onset of other diseases [41][42]. To combat the rise of ROS in leprosy patients and potentially decrease the severity of disease, supplementation of GSH with N-acetylcysteine, to provide reducing equivalence, can be further researched. Furthermore, vaccination with BCG is partially protective against *M. leprae*.

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