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Review article

Bacille Calmette-Guérin: An ophthalmic perspective

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ARTICLE INFO

Article history:
Received 30 June 2020
Revised 27 July 2021
Accepted 27 July 2021
Available online 31 July 2021

Keywords:
Autoimmunity
Adverse drug events
Angiotensin converting enzyme
Bacille Calmette-Guérin
COVID-19
Endophthalmitis
Heterologous immunity
trained immunity
SARS CoV-2
Uveitis

ABSTRACT

Vaccines such as bacille Calmette-Guérin (BCG) are known for their heterologous effects mediated through a number of mechanisms, including trained immunity constituted by monocyte-macrophage based innate immunity. Other events such as direct hematogenous spread and induction of autoimmunity are also described. There has been a resurgent interest in harnessing some of the benefits of trained immunity in the management of COVID-19, even as several specific vaccines have been approved. We summarize the current knowledge of ocular effects of BCG. Potential effect of granulomatous inflammation on angiotensin converting enzyme activity and accentuation of cytokine storm that may result in undesirable ocular and systemic effects are also discussed.

Abbreviations: ACE2, Angiotensin converting enzyme; ADEM, Acute disseminated encephalomyelitis; APC, Antigen presenting cells; BCG, Bacille Calmette-Guérin; Covid-19, Corona virus disease 2019; CFA, Complete Freund's Adjuvant; CRALBP, Cellular retinal-binding protein; ED, Eales' disease; EPI, Expanded Programme of Immunization; FAP, Fibronectin attachment protein; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HLA, Human leucocyte antigens; IBCG, Intravesical BCG; IFN-γ, Interferon $-\gamma$; IGRA, Interferon gamma release assay; IL-2, Interleukin-2; Il-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-9, Interleukin-9; IL-10, Interleukin-10; IL-13, Interleukin-13; IRBP, Interphotoreceptor Retinoid Binding Protein; IRIS, Immune reconstitution inflammatory Syndrome; IRU, Immune recovery uveitis; LPS, Lipopolysachharide; LT-α, Lymphotoxin-α; MHC, Major histocompatibility antigen; NMIBC, Non-muscle invasive bladder cancer; PPD, Purified protein derivative; Retinal-S Ag, Retinal soluble antigen; SARS CoV-2, Severe acute Respiratory Syndrome Corona Virus -2; TNF-α, Tumor necrosis factor alpha; VKH disease, Vogt-Koyanagi-Harada's disease.

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https://doi.org/10.1016/j.survophthal.2021.07.005

1. Introduction

In many parts of the world, tuberculosis (TB) causes significant mortality and morbidity, including deleterious effects to the eye. In areas that have a high prevalence of TB, bacille Calmette-Guérin (BCG) can reduce the incidence of TB. BCG is a live attenuated vaccine derived from *Mycobacterium bovis* that was developed over a period of 13 years by French bacteriologists Albert Calmette and Camille Guérin[81] . After an initial setback while trying to produce a homogeneous suspension of bacilli on a glycerin and potato medium and subsequent interruption of a trial on cattle with the outbreak of World War I, they succeeded in attenuating the bacilli by adding ox bile[20]. The attenuated vaccine was initially termed bacille bilie Calmette-Guérin; over the years "bilie" was dropped, and BCG was agreed on. Oral administration was chosen for human trials since Calmette considered the gastrointestinal tract to be the usual route of natural infection by the tubercle bacillus[81]. Calmette and Guérin were subjected to much criticism in 1930 following the Lübeck disaster during which 72 babies died out of the 251 vaccinated; however, during this trial in 1931, negligent contamination of the vaccine by virulent bacilli in the Lübeck laboratories was proven as the cause, and the vaccine was exonerated[81]. The emergence of tuberculosis following World Word II led to numerous studies proving the usefulness and efficacy of BCG vaccine. Despite its widespread use, BCG has been associated with heterologous effects[59,144]. Lamm and coworkers reviewed over 1000 publications between 1921 and 1982 that reported 10,000 complications of BCG vaccination[65]. The incidence of ocular side effects is not known as the bulk of information is based on case reports.

Much of our understanding of these adverse effects of BCG comes from its intravesical use (Intravesical BCG, IBCG) in cancer immunotherapy, during which multiple cycles of BCG vaccine are administered. Additionally, BCG is used as an immunomodulator in the treatment of melanoma. Applications in conjunctival malignancies have also been explored.

In contrast, the potential beneficial impact of BCG vaccine to reduce all cause mortality has been significant[6,45,51,54,116155]. A decrease in mortality from infectious agents other than tuberculosis such as bacteria (*Staphylococcus aureus*), fungi (*Candida albicans*), and viruses (yellow fever viruses) had prompted researchers to explore the immunologic basis of these effects[62,63]. A resurgent interest in harnessing the beneficial effects of BCG vaccine is also based on the epidemiological patterns of corona virus disease (COVID-19) and different national BCG vaccination policies[156], though a maladjusted immune system could also result in immunopathology[70]. The above scenario in the current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, prompted us to review the ophthalmic adverse effects of BCG including both infectious and immune-mediated mechanisms. Meanwhile, six vaccines are approved by the WHO for emergency use against COVID-19. These are produced by Pfizer BioNTech, Moderna, Janssen, AstraZeneca/Oxford, Sinopharm, and Sinovac. The first three of these are also approved by the USFDA[158,157].

2. Immune system and mycobacteria

Innate immunity, constituted by the monocyte-macrophage system, provides the primary response to mycobacterial infection and results in wider nonspecific "trained immunity"[6,63,67,98]. The evidence for aforementioned trained immunity originates from studies that demonstrated production of higher quantities of cytokines, such as IL-1β, IL-6, IFN-γ and TNF, in response to various infections[6,62–64]. Heterologous immunity needs a few weeks to develop; instead, an epigenetic reprogramming of immune cells that involves methylation of histones has been proposed[62]. These effects remain active even after a year post vaccination. Equally important in the pathogenesis of tubercular diseases are the evasive strategies developed by the mycobacteria[27,124]

2.1. *The Th1 and Th2 responses*

Ever since Mossmann and coworkers described the differentiation pathways of $CD4^+$ naïve Th0 cells into two different effector cell lines,Th1 and Th2 cells, our understanding of the response of the immune system to different immunologic challenges has evolved significantly[58,93,128]. By default, the phagocytosable microbes including mycobacteria lead to a Th1 response, initiated by the release of IL-2. Subsequently, mature Th1 cells secrete IFN-γ, and LT-α (Fig 1). As the mycobacteria are destroyed, there is a gradual switch to Th2 response through multiple cell divisions[58]. Apart from stimulating phagocytosis, IFN-γ induces the oxidative burst, intracellular killing of microbes, and expression of class I and class II major histocompatibility complex (MHC) molecules on a variety of cells, such as endothelial cells, keratinocytes, and fibroblasts. They also stimulate adhesion molecule expression on endothelial cells[38,58,78,98,133].

In contrast, Th2 response is the default response to large non-phagocytosable, extracellular pathogens such as helminthes (Fig 1). Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13. There is a considerable overlap in the pattern of cytokines secreted by Th1 and Th2 cells especially IL-10 and IL-13. Because of this overlap, the two responses are conventionally described by their ability to secrete either IFN-γ or IL-4. The culmination of Th2 response is B cell proliferation, antibody production, and eventual switch from IgG to IgE antibodies. IgE titers reflect an indirect measure of Th2 activity implicated in allergic and atopic reactions. Interestingly, Th1 and Th2 cells cross-regulate one another and can be influenced by pharmacological interventions or vary during the phases of evolution of an infectious disease[75,78,131]. In the case of leprosy, the paucibacillary tuberculoid leprosy is a manifestation of an aggressive Th1 response, while the lepromatous end of leprosy is dominated by a Th2 response[141,142]. A similar dichotomy is evident in immune responses against *Mycobacterium tuberculosis*[82,83]. Therefore, patients with active tuberculosis have a poor cell-mediated response, delayed hypersensitivity reaction, and a decreased cell proliferation and IFN-γ production in response to tuberculin or purified protein derivative (PPD); rather these patients exhibited higher IL-4[82]. An effective Th1 response is clinically evident in Type IV or

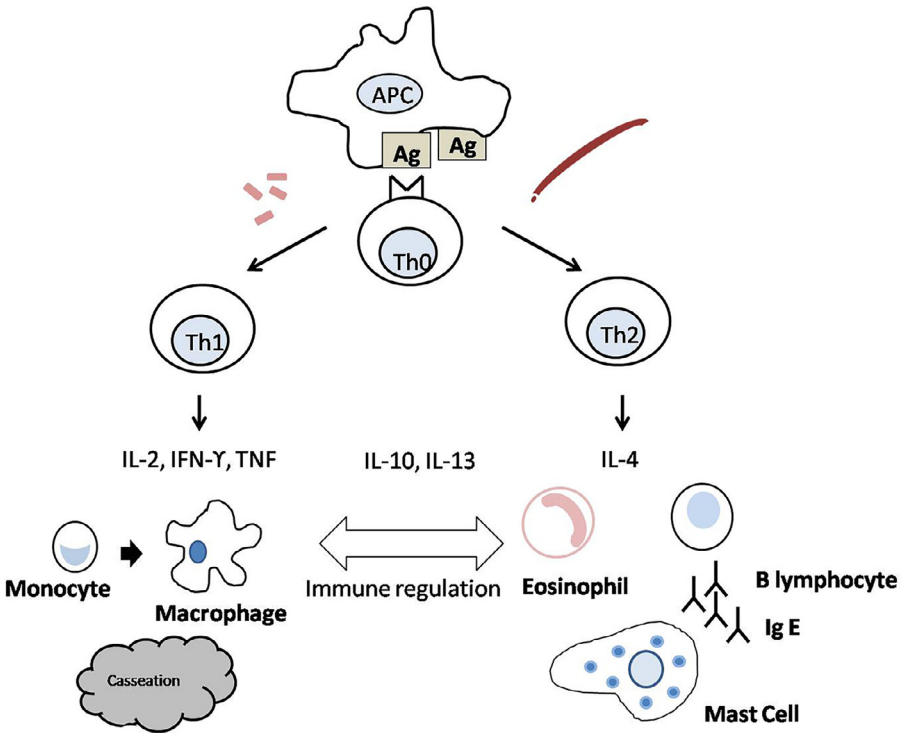

Figure 1 – APC: Antigen presenting cell that presents an antigen Ag to Th0 - a naïve T lymphocyte. Th0 either progresses to a Th1 pathway following an exposure to phagocytosable material such as mycobacteria or Th2 pathway, if a non phagocytosable material such as a parasite is encountered. Subsequent chain of events, the cytokine profile, the activation of monocyte-macrophage system, B lymphocyte or mast cell is illustrated.

delayed hypersensitivity, while Th2 response is seen in Immediate or Type I hypersensitivity.

2.2. *Immune response to BCG*

Over a century, the BCG vaccine has been administered to more than three billion children in the Expanded Programme on Immunization (EPI) across all regions[152]. Globally single-dose BCG vaccine is administered to approximately 100 million newborns each year[159]. A British study reported 50% protection that lasted 20 years[86]. Although BCG has contributed to reducing both the infant tuberculosis-related mortality, as well as general childhood mortality, its efficacy among adults in preventing TB varies between 0-80%,[3] and there is no good evidence that it lasts more than 10 years post vaccination.[129]An exception is the native Alaskan Indian community where it lasts for over 50 years[5]. Conversely, complete lack of protection has also been cited in an endemic zone in India[7,90]. Substrain variability, host genetics, nutritional status, and presence of helminthes co-infections have been considered as explanations of differential efficacy[91,90,92,103,106]. Additionally, suppression of T lymphocytes by TGF-β and IL-10 produced by regulatory T cells (Tregs) in response to environmental mycobacteria has been suggested. Environmental mycobacteria can have a masking or blocking effect. Palmer and colleagues suggested that exposure to various environmental mycobacteria could itself provide some protection against tuberculosis and affect the immune system in various ways, thus masking the effect of BCG[106]. In contrast, the blocking effect implies that the prevailing cell-mediated immunity to environmental mycobacteria eliminates the attenuated bacilli following BCG inoculation[109]. Further, neonates' immature immune system readily switches from the naïve Th0 status to Th1 or Th2 unlike adults who have an established Th1/Th2 profile[110].

Of the 21 substrains developed from the initial strain, the Denmark/Copenhagen strain 1331, Russian/Moscow, Japanese/Tokyo 172 BCG, Pasteur 1173 P2 and the Moreau RDJ strains account for more than 90% of BCG vaccines administered globally[30,159]. The Pasteur 1173 P2 and Danish 1331 strains appear to induce more adverse events[160].

2.3. *Implications of antimycobacterial immunity*

The above understanding of antimycobacterial immunity is clinically relevant. Ocular tuberculosis does not have a diagnostic gold standard, and many cases continue to be presumptive. Differentiating TB from sarcoid anergy remains challenging. Further, the pattern of tubercular ocular inflammation may be different in immune-compromised or immune-suppressed patients. Because of its slow growth rate, culture takes up to ten days, causing delay in the institution of antitubercular therapy. While polymerase chain reaction and interferon-gamma release assays (IGRA) are available, health care systems in low to moderate income countries continue to rely on the PPD-based Mantoux test. Unlike IGRA, the Mantoux test can potentially reboost delayed hypersensitivity or alter the immunologic milieu[18].The subsequent im-

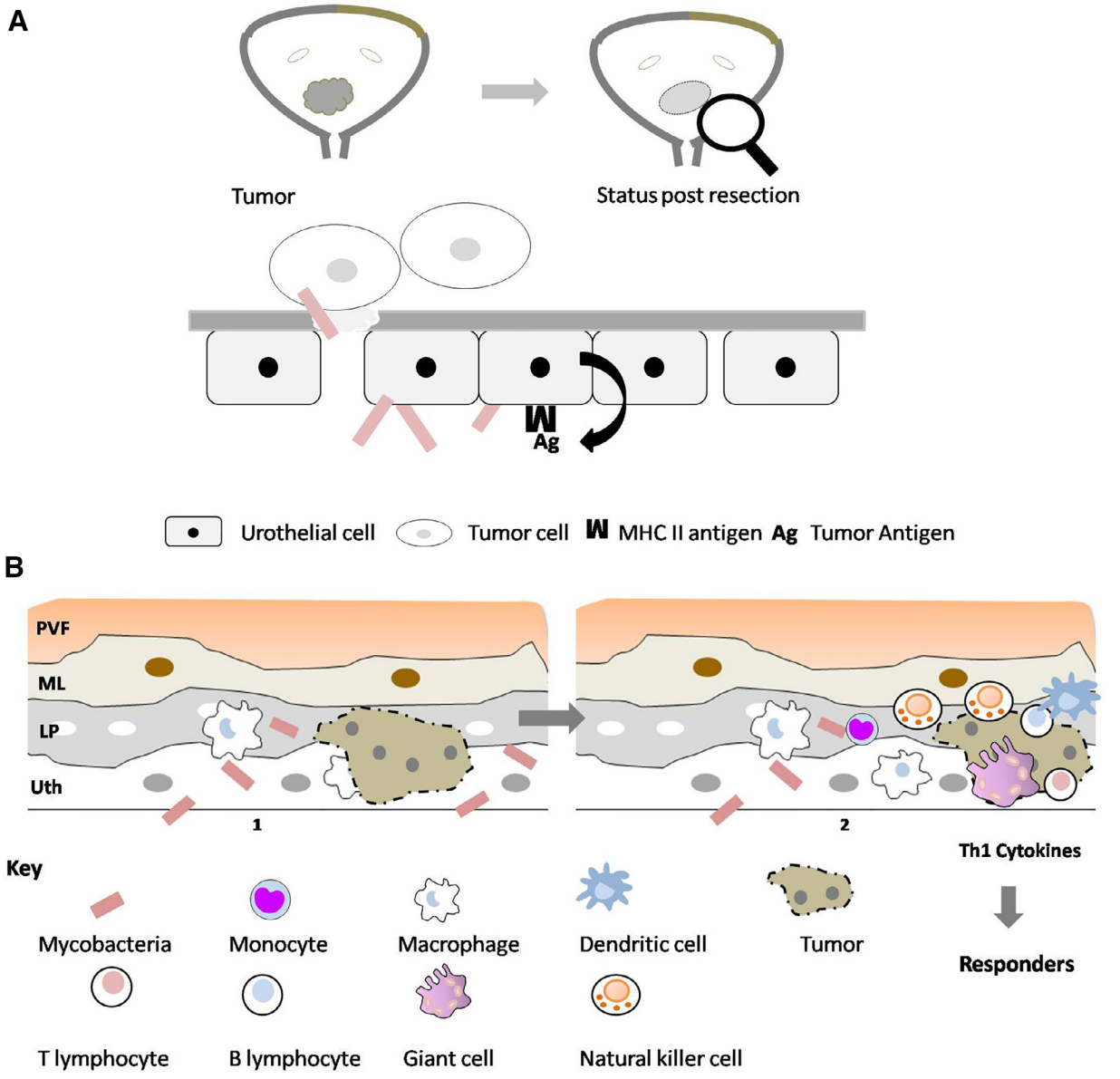

Figure 2 – (A): BCG Immunotherapy: Alterations in the basement membrane provide better access of mycobacteria to tumor cells, while attachment to the urothelial cells induces expression of MHC class II antigen enabling them to function as antigen presenting cells. (B): Monocyte-macrophage system along with other cells drives the immune response to Th1 type; non-responders display Th2 type cytokine profile. (Uth: Urothelium, LP: lamina propria, ML: muscular layer, PVF: perivesicular fat)

pact on ocular inflammation has not been overtly studied, except for isolated case reports[18,33]. Further, BCG vaccination too can lead to a positive Mantoux test. Many instances of paradoxical worsening of ocular inflammation with antitubercular drugs are reported[21,66]. The increased availability of tubercular antigens from hasty killing of mycobacteria or improved immune status leads to phenomenon such as immune reconstitution inflammatory syndrome (IRIS), also called immune recovery uveitis (IRU), following highly active antiretroviral therapy[12,5066]. Conversely, a primary immune mediated ocular inflammation sometimes progresses to an infectious entity[85]. Similar phenomena are observed in the reversal patterns of leprosy and in Jarisch-Herxheimer reaction of syphilis[19,140,141]. Thus, the role of aggravated Th1 response is not ruled out on re-challenge with PPD.

2.4. *BCG vaccination in Covid-19*

A large study from Brazil did not find any statistically significant difference in the rate of adverse events with revaccination as compared to primary vaccination[35]. Similarly, studies from Malawi and Brazil found no evidence of enhanced protection against TB through revaccination[8,60]. At the time of writing, there are twenty trials studying the protective effects of BCG vaccination, of which 11 involve healthcare workers[161]. World Health Organization's Strategic Advisory Group of Ex-

perts on Immunization (SAGE) does not currently approve BCG for such protection; nevertheless, the outcome of above studies will be pertinent with regards to future pandemics.

3. BCG immunotherapy

William Coley, considered as the father of modern cancer immunotherapy, described the potential role of microorganisms in immunotherapy after witnessing regression of sarcoma in patients with erysipelas caused by *Streptococcus pyogenes*[28]. An autopsy study reported a lower incidence of malignancies among those who had BCG vaccination[88]. Alvaro Morales described the use of BCG in cancer immunotherapy in 1976[92]; however, its mechanism unfolded slowly[87]. The use of BCG therapy to reduce tumor burden following its resection depends on the ability to get live bacteria proximal to the malignancy and a deranged glycosaminoglycan layer allowing for better immunologic access to the tumor[112].Additionally, antigen 85 and fibronectin attachment protein (FAP) expressed by BCG facilitate specific receptor-ligand-mediated attachment to the urothelium. Once attached, the BCG induces expression of the MHC class II molecules on urothelial cells enabling them to function as antigen-presenting cells (APC)[107]. Moreover, there is robust production of cytokines such as IL-6, IL-8, GM-CSF and TNF-α[135]. These events lead to the formation of epithelioid and giant cell granulomas that contain macrophages, dendritic cells, lymphocytes, neutrophils, and fibroblasts (Fig 2 A & B)[111].

All high-grade and some low-grade non-muscle invasive bladder cancers (NMIBC), including carcinoma *in situ* are candidates for IBCG therapy; however, a recent review suggests that only 50% of high-risk patients actually receive it, and primarily because of adverse events, only 16%-29% complete the 3 year course of immunotherapy[79]. In another series of 1316 patients on IBCG, 69.5% reported complications that ranged from irritative cystitis to severe systemic sepsis. Of these 62.8% had local and 30.6% had systemic complications[17]. As some patients are non-responders to BCG immunotherapy, and because there is some risk associated with the dissemination of an attenuated bacteria, mycobacterial cell wall extract and mycobacterial cell wall nucleic acid complex have also been explored[71,105]. Although detailed immunological studies were not carried out, this approach rendered 26.5% of patients with carcinoma *in situ* and 61.2% of patients with papillary tumors disease-free for at least 1 year with an intact bladder[71].

Interestingly, cell wall components form part of complete Freund adjuvant (CFA), which contains inactivated and dried mycobacteria and is used along with emulsified uveitogenic antigens to induce experimental autoimmune uveitis and sympathetic ophthalmia[22,114]; however, nonspecific immune stimulation with BCG had no protective effect against infectious keratitis[67,94,127].

4. BCG and ocular cancer immunotherapy

Rutgard and coworkers demonstrated subconjunctival administration of BCG organisms in New Zealand albino rabbits without producing toxic effects locally or within the eye[119]. This was the foundation of BCG immunotherapy in ocular experimental tumors[119]. Other investigators observed reduced recurrence of bovine ocular squamous cell carcinoma by repeated intralesional injections of live BCG or BCG cell wall components compared to a previous study by the same group where single injections were used[120]. Both studies showed that the delayed hypersensitivity to PPD persisted longer in animals that showed tumor regression.

5. BCG and experimental uveitis

Larson and coworkers had previously demonstrated BCG's role in protection against *Herpes virus hominis* type 2 administered by vaginal instillation, intracorneal injection, and scarification of the cornea in Dutch-belted and New Zealand rabbits[67]. Following this, Tabbara and coworkers tested BCG's potential to provide nonspecific resistance to microbial ocular infections (Fig. 3).One group of rabbits was immunized by intravenous administration of BCG, the second group received a unilateral retrobulbar injection of BCG, and the third group, which served as a control, received a unilateral retrobulbar normal saline injection[130]. Subsequently, experimental toxoplasmic retinochoroiditis was induced by injecting *Toxoplasma* organisms in the suprachoroidal space. Although *Toxoplasma* was isolated from chorioretinal tissues in all three groups, the onset of the ocular inflammation varied, and the severity, reduced in the TB groups. Intravenous administration had greater protection compared to the retrobulbar group. *Toxoplasma* antibodies were detected in only one animal; however, this may be because the innate immune system likely eliminated the organisms. Both mycobacteria and *Toxoplasma* are intracellular pathogens and evoke a Th1 type immune response[74].

Castro and coworkers designed a novel rabbit model of ocular inflammation to test the anti-inflammatory potential of thalidomide[23]. After two subcutaneous injections of BCG to prime the immune system, they injected BCG intravitreally to induce panuveitis. They demonstrated a rise in the inflammatory proteins N-acetyl-b-glucosaminidase and myeloperoxidase in ocular tissues, which dwindled following a single intravitreal injection of thalidomide. The authors also confirmed the response with electrophysiology and histopathology.

6. Ocular immunology and retinal autoimmunity

Some of the critical events in the development of autoimmune uveal and retinal disorders are a non-constitutional expression of MHC II antigens, molecular mimicry involving a native antigen such as retinal soluble antigen (Retinal-S Ag), interphotoreceptor retinoid binding receptor (IRBP), and generation of a vast array of autoreactive lymphocytes through polyclonal activation. Cell wall components such as lipopolysaccharides (LPS) are involved in this. Non-constitutional expression of MHC II antigens by retinal resident cells enables them to function similarly to infiltrating hemopoietic cells. The retinal pigment epithelium, vascular endothelium, and other cells

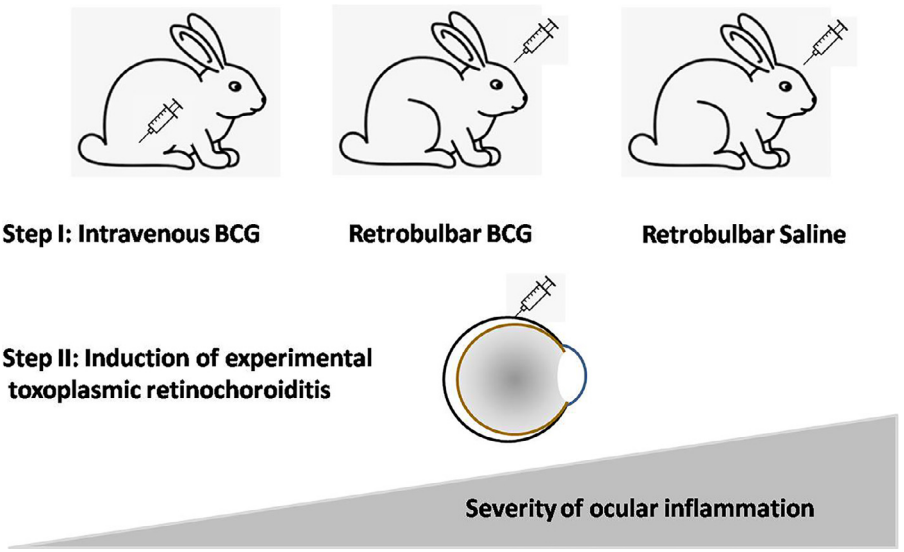

Figure 3 – Immuno-modulation of experimental toxoplasmic retinochoroiditis by BCG

in the neurosensory retina can serve as APCs[75,78]. In a case of uveitis related to BCG, Garip and coworkers demonstrated proliferation as well as secretion of proinflammatory cytokines in response to PPD, retinal-S Ag, IRBP, IRBP-peptide and cellular retinal-binding protein (CRALBP)[42]. Significant amino acid sequence homology was found between proteins from *M. tuberculosis*, BCG, and retinal antigens, suggesting molecular mimicry as a potential cause of uveitis in this patient.

Further evidence of autoimmunity induced by BCG comes from studies on cases of reactive arthritis[10]. It is an immune-mediated syndrome triggered by autoreactive T lymphocytes induced by bacterial fragments such as LPS and nucleic acids. The prevalence of HLA-B27 in reactive arthritis varied between 30% and 50%[10,154]. Cross-reactivity between mycobacterial antigens, particularly the 65-kD heat-shock protein, and HLA-B27 tissue antigen had also been discussed[139]. Of four cases in the English literature, three developed reactive arthritis after the fourth cycle of BCG, and the other after the fifth cycle[50,53,107,121]. This probably underlines a prerequisite of recurring booster effect. One of these cases tested positive for both HLA-B27 and HLA-DR4[53]. HLA-DR4 is associated with high responsiveness to mycobacterial antigens[102]. Idiopathic retinal vasculitis is another entity often thought to have tubercular association that is associated with HLA-B51, HLA-DR1 and HLA-DR4[14]. Nevertheless, many uveitic entities associated with tuberculosis are noninfectious and driven by consequential autoimmune mechanisms[36].

7. Clinical spectrum of ocular inflammation associated with BCG

The spectrum of ocular inflammation associated with BCG includes both infectious and immune-mediated diseases[79]. Based on the Naranjo scoring system, these associations are classified as definite[80,96,97].

Table 1 – Miettinen's observations on Ocular inflammation associated with BCG.

Phlyctenular conjunctivitis	62
Scleritis	1
Sclerokeratitis	7
Retinal periphlebitis	2
Iridocyclitis	42
Choroiditis	11
Uveitis	16
Keratitis	8

7.1. *Historic accounts of BCG associated eye disorders*

Many historic accounts appeared in the literature shortly after the introduction of BCG vaccination[4,39,56,76,89,132]. Although many features of these illnesses resembled the current description of conditions associated with ocular tuberculosis[47], the limitation of these studies was poor feasibility of appropriate work up or availability of vitreous samples in the "pre-vitrectomy era". Miettinen described 149 patients with ocular inflammation post BCG vaccination between 1942 and 1956[89]. He classified 73 events (49%) as tubercular in origin while the rest 76 events (51%) were presumed tubercular associations. His astute observations included both infectious and noninfectious conditions (Table 1). As the prevalence of tuberculosis in Europe was presumably higher, some of these cases could be caused by infection with *M. tuberculosis* itself rather than dissemination of *M. bovis* through vaccination[133]. Some of these events described by Miettinen developed fairly quickly after vaccination, with the earliest reported case one day after vaccination[88]. His contemporary Damato reported 11 cases in Malta in children between 4 to 8 years of age within 2 to 6 weeks post vaccination[32]. He mentioned two other cases and concluded that the sudden surge in the incidence of this otherwise rare entity implied the induction of a clinically use-

ful immunity by BCG. Children in this cohort had tested negative to PPD before vaccination, giving further credence to Miettinen's putative association.

In recent years with the use of IBCG, new associations were described: Liu and coworkers mentioned only 15 cases of ocular inflammation following IBCG[79]. Buchs, on the other hand published a much higher proportion of ocular inflammation, with as many as 25% of cases[16].

7.2. *Conjunctivitis*

Tinazzi and coworkers conducted a systematic review of reactive arthritis following IBCG instillation and reported that 24% of cases developed ocular involvement, excluding 2% who had Sjögren syndrome[132]. Ng and coworkers described a case of urethral discharge, bilateral conjunctivitis, and low back pain after the fourth cycle of BCG immunotherapy[99]. Apart from conjunctivitis associated with reactive arthritis[49], a case of follicular conjunctivitis 24 hours following accidental spillage of BCG vaccine on a healthcare worker is reported[113]. During attempted intradermal injection of BCG vaccine into a struggling neonate's upper arm, the syringe slipped out of the infant's skin discharging its contents into the injector's eye. In view of previous BCG vaccination, the response was considered as a manifestation of delayed hypersensitivity. The doctor was treated with topical steroids along with a one-month course of oral isoniazid. Similarly, a case of BCG reactivation with concurrent mucocutaneous involvement including conjunctivitis was described in an infant two months following BCG vaccination, and this was in association with Kawasaki disease[40].

7.3. *Corneal involvement*

Chakraborty and coworkers reported a case of bilateral symmetrical corneal ulceration with mucopurulent conjunctivitis and dry eye following the fourth dose of IBCG[24]. The case went on to have a bilateral descemetocele and ocular perforation. They did not isolate acid-fast bacilli on culture and considered it as an immune-mediated response. There are no reports of molecular mimicry or sequence homology between tubercular and corneal antigens.

7.4. *Endophthalmitis*

In a study of 256 subjects treated with IBCG, 4.3% had disseminated systemic infection[110], and localized ocular involvement was seen in 9% subjects. Culture-positive *M. bovis* endophthalmitis has been reported in eight eyes of five cases, which confirmed a direct vitreous invasion after hematogenous dissemination of the microorganism[43,48,55,68,79,138]. The first case, reported by Lester and coworkers, was a 66-year-old patient with bilateral endophthalmitis with a proven reduction in the size of retinal lesions with antitubercular therapy before the patient's death[68]. Bilateral retinal vasculitis and infiltrative retinitis were seen in one case[48]. The third case reported by Gerbrandy had a severe vitritis complicated by serous detachment and multiple choroidal granulomatous lesions[43]. Vadboncoeur and coworkers described another unilateral case with significant vitritis and vitreous condensation as well as a fluffy granulomatous retinal mass[138]. In this case, the real-time polymerase chain reaction for mycobacteria was positive. No acid-fast bacilli were seen initially, but culture performed during a second vitrectomy for complicated vitreous hemorrhage came back positive. This patient had received IBCG three years before ocular presentation. The most recent case described by Huggins and coworkers had bilateral endophthalmitis, where the right eye had dense vitreous haze, and the left eye demonstrated multifocal, yellow, round subretinal pigment epithelial lesions in the macula and inferotemporal retina (Fig. 4)[55]. This case was initially diagnosed as intermediate uveitis and treated with sub-tenon triamcinolone elsewhere before endogenous endophthalmitis was suspected owing to the presence of an indwelling catheter. It was only after the second diagnostic pars plana vitrectomy that acid-fast bacilli were seen on histopathology. The interval between the previous IBCG and endophthalmitis was four months. These cases highlight the inherent difficulties in establishing the diagnosis and the often poor outcome despite adequate antimycobacterial therapy. Thus, a high index of suspicion is advised in patients with a history of IBCG. Mycobacterial cultures take time, and molecular diagnostic techniques are crucial. Some other cases that initially appeared ambiguous may likely have been infectious, especially as vitreous haze (45.4%) and choroidal involvement (64.4%) are significant features of ocular tuberculosis[1]. A favorable response to antitubercular drugs without steroids reclassified some of these as infectious[46].

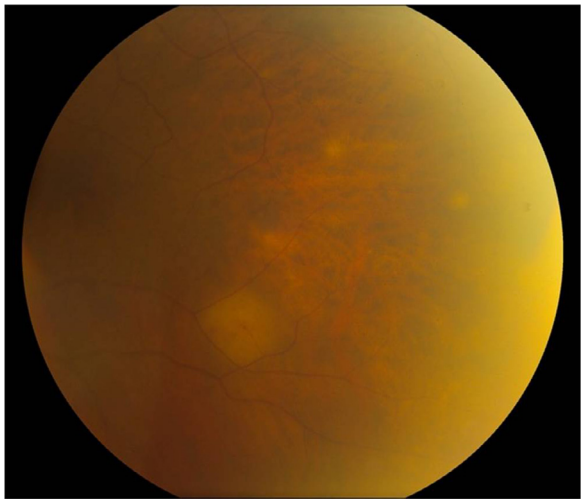

Figure 4 – Multifocal, yellow, round sub retinal pigment epithelial lesions following IBCG (Color version of figure is available online)

7.5. *Uveitis*

Benage and coworkers identified 21 cases of BCG associated uveitis between 1984 to 2014 from the National Registry of Drug-Induced Ocular Side Effects, the World Health Organization Monitoring Centre (Uppsala, Sweden), and the FDA spontaneous reporting system[9]. Most cases of iridocyclitis are associated with reactive arthritis[16,25,26,108,136,145]. Wertheim was the first to describe a bilateral isolated anterior uveitis in a

HLA-B27 negative patient after IBCG[145]. Another similar HLA-B27 negative case with bilateral iritis following immunotherapy had positive anti-nuclear antibodies possibly suggestive of a polyclonal activation[109]. Uppal reported rebound inflammation following the withdrawal of steroids in panuveitis induced by BCG[136]. Occasionally, severe iritis has preceded reactive arthritis[18]. A young girl with a serous retinal detachment in one eye and choroiditis in the other eye probably reflected a similar pathogenesis[25].

Dogan described two cases of Vogt-Koyanagi-Harada (VKH) disease following four cycles of IBCG[33]. One of these had a previous history of tuberculosis and had received antitubercular drugs for nine months. Sequential rechallenge likely led to accentuated immune response. Dogan considered immune dysregulation and subsequent immunological reaction as the underlying mechanism.

Uveitis with vitiligo has also been reported following BCG and tumor infiltrating lymphocyte immuno-therapies for malignant melanoma, with an implicit role of autoimmunity targeted against melanocytes[34,37,149]. A proinflammatory surge was noted in the aqueous humor[34]. Gao and coworkers described a case presenting with choroiditis and granulomatous hepatitis subsequently complicated by upper gastrointestinal hemorrhage secondary to aortoduodenal fistula. Pathology specimen resected at the time of surgery led to the identification of non-caseating granulomas in the tissue, indicating mycobacterial infiltration[41]. A presentation similar to cancer associated retinopathy without autoantibodies to recoverin has also been described[123].

7.6. *Vasculitis*

Vasculitis represents an area with a considerable infectious-autoimmunity overlap. Both infections and vaccinations have been incriminated[112]. The endophthalmitis case described by Han exhibited retinal vasculitis, signifying an immune-mediated response to a pathogen[48]. In a large multinational cohort of ocular tuberculosis, Agrawal et al reported retinal vasculitis in 42.8% cases[1].

From a current perspective, both mycobacteria and SARS-CoV-2 infections are associated with vasculitis. COVID-19 is characterized by Kawasaki-like disease, a condition with systemic vasculitis[118,134,140]. Interestingly, reactivation and erythema at the BCG inoculation site have been reported in up to 50% of children with Kawasaki disease, predominantly in males preponderance[1,134]; Cross-reactivity between mycobacterial heat-shock protein 65-kD (HSP65) and the human homolog is reported as a possible cause of this reactivation[148]. An alternative explanation was a possible reactivation and multiplication of mycobacteria at the inoculation site in an immunocompromised state induced by a viral illness[95].

Idiopathic retinal vasculitis or Eales disease (ED) is long thought to be associated with tuberculosis. Although no difference was found in the humoral and cell mediated immune response to mycobacterial A60 antigen, ED has a shared human leucocyte antigen predisposition (HLAB51, DR4) similar to Behçet disease and VKH disease[13,14]. Natural course of this entity can change over time as a previously immunocompetent tuberculin negative ED subject with occlusive vasculitis developed tuberculoma six years after initial presentation[84].

7.7. *Optic neuritis*

Yen and coworkers described the first case of a 12-year-old girl who developed reversible bilateral optic neuritis five days after BCG vaccination[147]. Hegde and coworkers reported a case of simultaneous uveitis and optic neuritis[50]. The ocular inflammation in this 14-year-old previously PPD-negative girl was probably cell mediated as she had a personal and family history of immunoglobulin (IgA and IgM) deficiency. A wider ramification of autoimmunity was implicit in a case of bilateral panuveitis with optic neuritis, where an 8-month-old girl with left axillary lymphadenitis and rashes subsequently developed acute disseminated encephalomyelitis (ADEM) with cerebral demyelination and optic neuritis after receiving BCG in her left deltoid[2]. ADEM is an immune-mediated inflammatory demyelinating disorder postulated to occur from a cross-reaction between the triggering infectious agents and the neural tissue[104]. Left axillary lymph node excision biopsy revealed *Mycobacterium tuberculosis* complex. She was treated as post-infectious cerebral demyelination with intravenous antibiotics, methylprednisolone, and immunoglobulin and showed significant recovery after 2 weeks. An acute, severe, and irreversible response to BCG was reported in a child with multiple sclerosis who developed optic neuritis within half an hour of administration of Mantoux test[77].

Zaki and coworkers described a 5-year-old boy who developed bilateral reversible optic neuritis following administration of antitubercular drugs despite being off ethambutol[150] The authors considered this to be an immunologically mediated response. Of importance, there is a distinct possibility of re-exposure to mycobacterial antigens in this case. Optic neuritis has also been reported in conjunction with anti-TNFα therapy, including with monoclonal antibodies[61,72,100,125]. Interestingly, other workers found that BCG vaccination was beneficial in clinically isolated syndromes related to multiple sclerosis in a randomized control trial[29,117]. Collectively, these reports suggest that multiple factors, including exposure to antigens, molecular mimicry and interplay of cytokines are involved in the induction of optic neuritis. The aggravation with a simple Mantoux test indicates that it may be prudent to use an *in vitro* test such as IGRA rather than the *in vivo* tests aimed at quantifying the cell-mediated immunity or delayed hypersensitivity.

7.8. *Orbital inflammation*

Only one case of orbital inflammation following IBCG has been reported in a patient presenting with bilateral chemosis, proptosis and thickened extraocular muscles along with reactive arthritis[131]. Thyroid autoantibody profile of this patient was normal. All inflammatory features abated in response to oral steroids.

8. Angiotensin converting enzyme, Granulomatous inflammation and Covid-19

Th1 response mediated through pro-inflammatory cytokines such as IL-2, IFN-γ results in granulomatous inflammation[57].

BCG induces an increase in the level of angiotensin-converting enzyme (ACE) levels[73].

BCG-induced animal models of chronic granulomatous pulmonary inflammation also show enhanced ACE-like activity that determines the intensity of inflammation[122]. Thus, ACE is a molecular marker of BCG-induced granulomatous inflammation in the lung. It is involved in both the innate and adaptive immunity. Over-expression of ACE on neutrophils and macrophages facilitates enhanced immune responses. Similarly, by virtue of its peptidase activity, it is involved in the molecular trimming and display of MHC class I and class II antigens on APCs. As the cells change their ACE production, the peptides they display also change though this may not necessarily result in enhanced immunogenicity[11].

ACE2 is a transmembrane peptidase[146]. Metalloproteinases cleave this "full length ACE2," and the soluble version is released in the extracellular environment as circulating ACE2. The cellular ACE2 molecule itself acts as the functional receptor for the spike glycoprotein of the human coronavirus HCoV-NL63, SARS-CoV and SARS-CoV-2, while the "abridged version" is part of the protective and counter-regulatory mechanisms[146]. It reduces inflammatory cytokines, protects the cardiovascular system and kidneys, regulates immune responses, and overall protects lungs from SARS-CoV2 infection.

A crucial aspect of the severe COVID-19 disease is the induction of a 'cytokine storm', an umbrella term characterized by higher-than-normal production of pro-inflammatory cytokines[151]. Wider expression of cellular ACE2 enhances viral entry, but eventually leads to cellular destruction, thus cutting off the supply of free ACE2. ACE2 is then unavailable to play its intended physiological roles that would prevent a cytokine storm and inflammatory damage to multiple organs.

Meanwhile, apart from epidemiological studies, some immunological evidence has accrued that supports the BCG's utility in protection against acute respiratory tract infections in the elderly. This effect seems to emanate from enhanced IFN-γ and IL-10[144].

While trained immunity induced by BCG has a protective effect on other viral infections, there is a caveat: ACE2 is the molecular docking port for SARS CoV-2 virus entry. Its expression has been demonstrated in alveolar macrophages[150]. Th1 cytokines were significantly elevated in severe cases of COVID-19; GM-CSF and IL-6 induce further monocyte migration and mediate infiltration of inflammatory macrophages and dendritic cells aggravating lung injuries, an effect that can aggravate if the free ACE2 levels were modulated[146,150]; IL-6 is a biomarker of progression and severity of COVID-19[135].

Additionally, the ACE2 is expressed in the heart, kidney, blood vessels, and alveolar epithelium, the other potential targets of the virus[153]. It is also upregulated in the lower airway epithelium of smokers and chronic obstructive pulmonary disease[69]. Wang and coworkers have shown a 5.9-fold increase in the adverse effects of COVID-19 and 63% higher mortality in this group of patients[143]. ACE2 activity is more pronounced in these two groups though the exact risk of developing a cytokine storm is unknown[52,126]. These diseases and tuberculosis are essentially driven by the monocyte-macrophage system that has a preponderant role in the immunopathology associated with severe outcome in SARS-CoV-2 infection[44]. Cytokine storm is an excessive and uncontrolled release of pro-inflammatory cytokines that leads to a drop in lymphocytes counts, including $CD8^+$ T cells and natural killer cells [153]. It is unclear what the effect of up-regulating the expression of ACE2 on immune cells would be. It is also unknown if an upsurge in proinflammatory cytokines aggravate an existing cytokine storm.

Another concern is about the potential risk related to medications that act on the renin-angiotensin-aldosterone system, of which ACE is an essential component in patients exposed to Covid-19[31,85,115]. Current evidence suggests that the immune response to BCG varies across populations. Thus, the cytokine response following BCG vaccination is different in Malawian and British infants[64]. Recently, Boer and coworkers have shown that BCG induces a divergent immune response in naïve adults that could be either $CD4^+$, $CD8^{+\ T}$ cells mediated pro-inflammatory (IL-2, IFN-γ and TNF-α) or $CD8^+$ regulatory T cells mediated "virtually absent cytokine" response[15]. Definitive answers to the above complex questions would finally emerge once the outcome of the ongoing trials is known[161159].

Interestingly, sequence homology between several SARS-CoV-2 and BCG epitopes including the envelope protein and the receptor-binding domain of the spike glycoprotein provides an additional mechanistic basis for the potential cross-reactive adaptive immunity[101,137].

9. Conclusion

Eyes exhibit a wide range of effects of BCG vaccination that range from innocuous follicular conjunctivitis to bilateral endophthalmitis and optic neuritis. These effects are more commonly seen with IBCG compared to routine immunization, likely due to the more frequent and higher doses involved. While harnessing the potential benefits of trained immunity is tempting, the heterologous ill effects must be kept in mind. With diverse immune responses elicited by BCG, different populations may exhibit different levels of protection or adverse events. Given that the BCG-driven granulomatous response can potentially up-regulate the ACE2 activity, it is a theoretical concern that these patients may be at higher risk for severe COVID-19 infections and resultant cytokine storm. As we await the outcome of ongoing randomized control trials, the medical community needs to be aware of ophthalmic and other effects of BCG. Although many vaccines have been approved for emergency use for COVID-19, the current impetus on trained immunity research may provide a bridging tool in mitigating future zoonotic diseases.

10. Method of literature search

A comprehensive search of ophthalmology literature that included case reports was carried out from 1940 to 2020 through the PubMed database Search terms included adverse drug events, angiotensin converting enzyme, autoimmunity, Bacille Calmette-Guérin cancer Immunotherapy, conjunctivitis,choroiditis, Covid-19, Eales' disease, granulomatous inflammation, idiopathic vasculitis human leucocyte

antigens, immune responses, major histocompatibility antigens molecular mimicry, mycobacterium tuberculosis, ocular immunotherapy, optic neuritis, orbital inflammation, purified protein derivative, SARS CoV-2, endophthalmitis, panuveitis, retinal autoimmunity, reactive arthritis, Th1 and Th2 immune response, trained immunity, tuberculin test, uveitisand vasculitis. These terms were searched independently or along with Bacille Calmette-Guérin / intravesical Bacille Calmette-Guérin. Targeted searches were also performed for selected articles in the references of the articles found on aforementioned search terms. Non-English literature with English abstracts was included. Only selected article published before 1990 were used for historical purpose.

Declaration of interest

MJ, JV and JB report no proprietary or commercial interest in any product mentioned or concepts discussed in this article. Dr. SJG is a consultant for Bausch and Lomb, Johnson and Johnson, Deciphera and has his research supported by Apellis, Genentech and Regeneron.

Funding

None

Disclosures

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