This is a pre print version of the following article:

BCG and Autoimmunity / Bernini, L., Manzini, C.U., Ferri, C. - In: Vaccines and Autoimmunity / Yehuda Shoenfeld, Nancy Agmon-Levin, Lucija Tomljenovic ; [a cura di] Shoenfeld, Y.; Agmon-Levin, N.; Tomljenovic, L.. - Hoboken, NJ : John Wiley & Sons, 2015. - ISBN 9781118663431. - pp. 197-206 [10.1002/9781118663721.ch21]

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13/11/2026 14:25

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Textbook: Vaccine and Autoimmunity

Chapter: BCG and Autoimmunity

Luigi Bernini[1], Carlo Umberto Manzini[1], Clodoveo Ferri[1]

[1]Rheumatology Unit, Department of Internal Medicine, University of Modena and Reggio Emilia, Medical School, Modena, Italy

Corresponding author: Clodoveo Ferri, MD, Rheumatology Unit, University of di Modena e Reggio Emilia, Policlinico di Modena, Via del Pozzo, 71, 41121, Modena, Italy. Tel.: +39 059 4222279/4225663; fax: +39 059 4224178. E-mail address: clferri@unimore.it

1. Introduction

The Bacillus Calmette-Guerin (BCG) is a live, attenuated vaccine from *Mycobacterium bovis* obtained by Albert Calmette and Camille Guerin through 230 in vitro passages between 1908 and 1921 when it was for the first time used in Paris. Since then BCG is distributed all over the word as preventive tool against tuberculosis (TB), although its use has changed over time owing to the different epidemiological conditions and despite the debate about its preventive effect reaching only 51% of risk reduction. Indeed, the BCG vaccination shows a positive protection on extrapulmonary TB and mortality in children but has a variable and only partial prevention against pulmonary disease in adults [1,2]. Alongside this current main use, other non-specific immunological effects of BCG have become evident over the years allowing its application in clinical management of several diseases (Fig.1). Since 1976, intravesical instillation of BCG represents the immunotherapy of bladder cancer [3] and to date it is an integral and approved part of the management of non-muscle invasive bladder cancer. Other neoplasms as colorectal cancer, lung cancer and melanoma, have been, especially in the past, the targets of BCG immunotherapy. Because of their immunologic background, a variety of diseases (asthma, diabetes type 1, multiple sclerosis, leprosy) have been evaluated for treatment with BCG [4].

2. Immune mechanisms of BCG

Although not fully clarified, the protective effect of BCG is warranted by a robust response of cellular immunity that occurs with the involvement of CD4+ T cells along with the Th-1 cytokines IFNγ, TNFα, and IL17 (Fig. 2). Subsequently, CD8+ T cells are also involved in the immunization process while IL-2 has a relevant role for central memory T cell responses [5].
Similar mechanisms, even though with different biologic meanings, are evoked when antitumor immunity induced by BCG is required [6]. In this context, the local treatment of bladder cancer with BCG

instillations represents an interesting model, although not yet fully understood. Indeed, when the BCG is instilled in the bladder binds to fibronectin present at the endoluminal layer and forms fibronectin-BCG complexes embedded in both normal and tumor cells. The BCG antigens, expressed at the surface of urothelial, neoplastic and antigen-presenting cells, trigger an early, large, influx of neutrophils (75%) and macrophages then inducing a Th1 response by CD4+ T cells with production of IFNγ, TNFβ, IL-2, and IL-12. Such a Th1 response finally activates the NK cells cytotoxic T lymphocytes (CTLs) that destroy the neoplastic cells. Moreover, a Th2 cytokine profile (IL-4, IL-5, IL-6, and IL-10) is produced but Th1 response seems to exert a more favorable antitumor action. Specific effects of some interleukins are the following: IL2 has a stimulatory effect on CTLs, IL18 activates CTLs and NK cells, and IL8, produced by activated macrophages, has a recruiting effect on PMN granulocytes. These latter provide the TNF-related apoptosis-inducing ligand (TRAIL) secretion, a member of TNF family that induces apoptosis in neoplastic but not in normal cells. To achieve an effective antitumor response a functional host immune system is a necessary prerequisite [7-9]; however, a limited number of cancer cells, a juxtaposition of BCG and tumor cells, and appropriate dose of BCG are also essential factors, all fulfilled in bladder cancer, for a effective action of immunotherapy [10].

The reactive arthritis (ReA) is an aseptic synovitis triggered by several pathogens either of the genitourinary or gastrointestinal tract and, among these, intravesical BCG should be included as recently reviewed [11]. Indeed, ReA may share many immunological mechanisms involved in intravesical BCG therapy. As first step, a CD4 T-cell response occurs at the site of inflammation, stimulated and maintained by bacterial components with the subsequent participation of CD8 T cells. However, the Th1 cytokine response (IFNγ, IL-2, IL-12) is unable to remove the triggering bacterial agent so a prevalence of Th2 response (IL-4 and IL10) is produced, keeping alive the bacteria in the joints. It is conceivable that

HLA-B27, often present in patients with ReA, may act as restriction molecule for antigenic bacterial peptides, presented to and cross recognized by cytotoxic CD8+ T lymphocytes, allowing the persistence of the inflammatory process even after the elimination of the bacteria [12]. The so-called molecular mimicry is the mechanism usually invoked to explain the autoimmune effects of infectious microorganisms; in the case of intravesical BCG, the shared homology between mycobacterial heat-shock protein HSP65 and cartilage proteoglycan link protein might be determining. Thus, the bacteria or bacterial antigens spreading from the bladder to the circulation may produce a systemic immune-mediated response having the joints as target, especially in the presence of genetic predisposition (positive HLA-B27 antigen) [13].

(Fig. 1. Here)

3. Clinical applications of BCG

3.1 Tuberculosis

The specific, preventive anti-TB use, above mentioned, has revealed interesting non-specific effects of BCG vaccination because of its immunogenic action. One of these concomitant effects of BCG is a significant reduction in infant and child mortality attributable to causes other than TB. Since 1940 until the last ten years, several observations have focused on this effect in high-mortality countries; similarly, BCG immunization at birth reduce the death from respiratory infections and sepsis. Possibly, BCG immunization at birth favorably influences the antibody response to routine immunizations administered later in infancy (vaccinations against pneumococcal, *Haemophilus influenzae* type B, tetanus toxoid, and hepatitis B surface antigen)[4].

3.2 Leprosy

Leprosy is caused by infection with *Mycobacterium leprae* and the most common preventive strategy relies on BCG vaccination that was, at the beginning, widely used both for TB and leprosy [14].

This latter shares the same protective immune mechanism with TB with increased production of Th-1 cytokines, i.e. IFNγ, TNFα, and IL17. The protective impact of BCG on leprosy is variable ranging from an overall protection of 41% to 76% for multibacillary and 62% for paucibacillary forms, and with 41% for experimental trial, 60% for observational studies, 53% for general population, and 68% for contact subjects. Despite this variability there is clear-cut evidence that BCG may exert a preventive effect against leprosy, mostly in population at higher risk as household contacts; although this effect declines with time, it persists over 30 years or more. Early diagnosis and multidrug therapy are the key-points of leprosy control, but BCG vaccine retains its important preventive role [15].

Besides its definite role in the prevention of TB and leprosy, BCG vaccination has been employed in other clinical conditions given the above mentioned non-specific effects.

3.3 Asthma and other hypersensitivity diseases

The BCG has a stimulatory effect on Th1 cytokines while inhibits the Th2 immunologic response and consequently it counteracts the risk of Th2-dependent atopic diseases [16]. Based on this hypothesis an epidemiological association between BCG vaccination in early life, asthma and other atopic conditions has been evaluated with conflicting results. Some recent meta-analyses failed to prove a significant protective effect of BCG against allergy in general, atopic dermatitis or eczema, allergic rhinoconjunctivitis, urticaria, and food allergy, while it might provide some benefits against asthma [17,18]. However, other studies did not confirm the suggested protective role of BCG vaccination on asthma and/or other allergic conditions [19].

3.4 Type 1 diabetes

Type 1 diabetes results in part from impaired activation of transcription factor NF-*k*B in a subpopulation of activated T-cells, which become more sensitive to TNFα-induced apoptosis. The

cytokine TNFα selectively kills autoreactive T-cells, namely the only disease-causing cells, allowing pancreas regeneration. The ability of BCG to stimulate the production of TNFα, with similar results to those obtained with TNFα administration, has supported its use as possible treatment of diabetes type 1 [20].
In the past immunotherapy with single, low dose of BCG in patients with late-stage pre-diabetes was proved to induce a clinical remission in some patients [21], but these results were not confirmed in newly diagnosed diabetic children evaluated for 18 [22] and 24 months after vaccination [23]. However, in a recent controlled trial two low-dose BCG vaccinations in patients with long-term type 1 diabetes resulted in a rapid release of dead insulin-autoreactive T cells, as consequence of TNFα activity, and in a significant increase in C-peptide secretion, as expression of a restored beta-cell function. Interestingly, similar results were documented in a placebo patient with unexpected EBV infection, a well-known trigger of innate immunity by inducing a host TNFα response [24].

3.5 Multiple sclerosis

Multiple sclerosis (MS) is a neurological autoimmune disorder whose specific mechanisms remain to be fully elucidated [25]. The rationale for the use of BCG in MS rests on the documented suppression of autoimmune responses in experimental autoimmune encephalomyelitis, an animal model of human MS [26]. Among the complex immune-mediated processes responsible for MS a conflicting meaning seems to concern clinical results of anti-TNFα treatments as well as the biology of TNFα. This cytokine is abnormally increased in the cerebrospinal fluid and in active lesions of patients with MS, but TNFα-agonists may worse MS and induce demyelinating syndromes in other autoimmune diseases. This apparent paradoxical effect may be explained by the presence of a single nucleotide polymorphism (rs1800693) in the TNFRSF1A gene, which encodes tumor necrosis factor receptor 1 (TNFR1), associated with MS, but not with other autoimmune diseases. The MS risk

allele directs expression of a new, soluble form of TNFR1, a MS-associated TNFR1 variant,that can block TNF mimicking the effect of TNFα-antagonists in rheumatoid arthritis, psoriasis, and Crohn's disease [27].
A trial with BCG vaccine in MS has shown evidence of reduced disease activity in a period of 6 months in 14 patients with relapsing-remitting MS [28]. There was a consistent and significant reduction (57%) in the mean number of active MRI lesions from the run-in period to the post- BCG period without serious side effects.

3.6 Cancer

The observation that patients with TB were less frequently affected by cancer led to evaluate the effect of live, attenuated BCG as adjuvant immunotherapy (mostly with autologous tumor cells) for a variety of neoplasms as colorectal cancer, lung cancer, melanoma, and renal cell carcinoma. The underlying hypothesis is that increasing the immunogenicity of tumor cells with adjuvants will enhance immune responses to the endogenous tumor antigens. The prerequisite for a positive outcome was a limited tumor expansion. However, because of the lack of documented efficacy in several studies such an use was gradually abandoned also for the more concrete prospective of novel and specific vaccines. Indeed, the molecular definition of cancer-associated antigens introduced the possibility of specific vaccines and a new era in genetically engineered whole-cell vaccination has involved the modification of tumor cells through transfer of genes encoding cell membrane immunostimulatory molecules or cytokines.

To date BCG is the most common intravesical therapy for treating non-muscle-invasive urothelial carcinoma and it is able to reduce the recurrence rate and the risk of progression to muscle-invasive disease in patients with carcinoma in situ (gold standard therapy), as well as superficial bladder tumors [8]. The immunologic mechanisms of BCG therapy have been already referred;

it is interesting to note that the local immunogenic action of intravesical BCG is much more powerful if compared with systemic effect of intradermal route in other malignancies. Intravesical BCG is commonly administered once weekly for 6 weeks as induction following transurethral resection of the bladder tumor. The optimal maintenance schedules are to be determined but mostly include three weekly instillations at 3 month intervals for 3 years although reduced doses and duration has been recently proposed [29].

4. Autoimmune phenomena from BCG

As with any vaccine, BCG also can be described as a "double-acting tool" because its own immunogenicity produces on one side a preventive effect in a variety of diseases and on the other side it may trigger a number of autoimmune phenomena.
Although several immune-mediated adverse events triggered by the BCG vaccination have been reported thus far, a clear causal link has not been demonstrated. Furthermore some cases might be correlated to other environmental factors or represent normal responses to foreign proteins. Conceptually, an immune-mediated response against self could results from host response to any component of the vaccine [30]. In presence of genetic and environmental factors the host immune response may be triggered by various mechanisms mainly through non-specific B-lymphocyte stimulation with polyclonal B-cell expansion, idiotypic cross-reaction, and molecular mimicry (Fig. 2).
BCG vaccination for TB is a safe and well-tolerated with very low rate of side effects, ranging from local reactions to disseminated BCG disease, with various degree of severity, and mostly of infectious nature. To a large extent the more serious complications occur in immunocompromised subjects, as in HIV-infected infants. Equally rare, although speculatively more intriguing, are the post-vaccine autoimmune phenomena that, however, have different clinical significance according to the

route of administration (systemic-intradermal or local-intravesical).

(Fig. 2. Here)

4.1 Intradermal BCG

4.1.1 Arthritis

Arthritis following cancer immunotherapy has been described in 10 of 159 patients treated for various types of malignancy. The main clinical pattern was a bilateral and symmetric polyarthritis, which was predominantly confined to small joints of the hands, preceded by morning stiffness, and associated with elevated inflammatory markers; it occurred within 1 to 5 months from first BCG injection and it was exacerbated by subsequent BCG injection. The arthritis partially recovered in 1-3 months with non-steroid anti-inflammatory drugs treatment. Synovial fluid analysis and biopsy, when done, were negative for acid-fast bacilli and indicative of nonspecific chronic inflammation [31]. An acute inflammatory polyarthritis with skin maculopapular rash was reported in an healthy woman following intradermal BCG. The culture of synovial fluid was repeatedly negative; after failure of antibiotic multi-therapy the clinical symptoms promptly and fully subsided with corticosteroid treatment [32]

4.1.2 Dermatomyositis

This autoimmune condition is rarely reported as a consequence of BCG vaccination. Two cases (one after re-vaccination) have been diagnosed by skin and muscle biopsy [33]. Generally, a substantial increase in the incidence of dermatomyositis or polymyositis after any kind of vaccine has not been reported.

4.1.3 Takayasu’s arteritis (TA)

Based on historical, epidemiological and immunologic background a link between Takayasu’s arteritis and TB/BCG has been proposed in

the past [34]. Indeed, both diseases present a granulomatous histological feature; patients with TA produce both humoral and cell-mediated responses against antigens of *M. tuberculosis* and have an higher reactivity of peripheral lymphocytes to HSP 65 kDa heat-shock protein that is remarkably induced in the media and the vasa vasorum of TA biopsies. However, this intriguing linkage has been poorly studied and, at present, not confirmed [35].

4.1.4 Kawasaki's disease (KD)

A reaction at the BCG inoculation site (erythema, induration or crust formation) is common, especially in Japan, and it is present in about 30–50% of KD patients. Although this sign is more frequent than cervical lymphadenopathy in children with complete KD aged 3–20 months, it is not included among diagnostic criteria. The skin reaction appears early (24–48 hours) after febrile onset and is replaced by a crust immediately after the fever subsides. It is considered an important toll for early diagnosis in febrile children, especially in those younger than 2 years. It has been hypothesized that cross-reactivity may occur between specific epitopes of mycobacterial 65-kDa heat-shock protein and the human homologue, heat-shock protein 65 [36].

4.1.5 Miscellaneous adverse events

Several pathological conditions are associated with BCG vaccination, usually as anecdotal reports. Immediate hypersensitivity reactions are associated with sensitization to dextran; moreover, delayed reactions as maculopapular exanthems, erythema nodosum, urticarial vasculitis, and neutrophilic dermatoses (Sweet's syndrome and pyoderma gangrenosum) rarely occur [37]. Cutaneous sarcoidosis [38], psoriasis skin lesions [39], guttate psoriasis-like lesions [40], and an extensive ulcerating vasculitis, defined as granulomatous-type one (type IV hypersensitivity reaction) [41] have been reported after BCG vaccination. A special mention must be reserved to the relationship of BCG with MS, a disease in which the specific

immunization might be protective (see above) or inductive. In our knowledge, a causal link between BCG vaccination and MS is referred in only one case [42], while reports of MS following vaccine against hepatitis B virus are much more frequent [43]. Moreover, no significantly increased risk of developing MS after vaccination for BCG was found in a recent review [44]. In the past, cases of polyneuropathy after BCG vaccination or re-vaccination have been occasionally reported [45,46].

4.2 Intravesical BCG

Side effects from intravesical BCG are rare since they are documented in less than 5% of cases and generally classified as local and systemic, both infective, or secondary to hypersensitivity response. Because they mainly occur after systemic absorption of the vaccine a correct administration is mandatory following the absolute contraindications [47]. The analysis of the septic adverse events, either local or systemic, is not the purpose of this survey, which is focused on the autoimmune reactions induced by BCG; therefore, objective limitations are encountered to correctly review the literature, especially when the data are from urologic source. For instance, often articular symptoms are simply referred as “arthralgia” or “arthritis” without any detail and are associated to an unspecified “skin rash” and defined as “possible allergic reactions”. Similarly, side effects as granulomatous pneumonia or hepatitis are reported without sufficient data to support the possible link with intravesical BCG and the autoimmune mechanism. In such cases it may be really difficult to clearly establish whether they represent an infectious complication or a hypersensitivity reaction to BCG. Indeed, histological and cultural findings from affected organs are often unable to demonstrate the presence of acid-fast bacilli. In this contest, however, some interesting data arise to our attention.

4.2.1 Arthritis and other rheumatic diseases

An inflammatory involvement of joints is a well-known side effect of intravesical BCG, reported with a variable frequency, ranging from 0.5% to 28.1% according to various series [11]. Its clinical pattern is a polyarthritis comparable to arthritis triggered by other agents and generally characterized by typical clinical features of classical reactive arthritis (ReA). Also intravesical BCG-related ReA is characterized by the evidence of preceding infection with a known trigger bacterium of manifest source site, the articular inflammation is aseptic, and it invariably shows latency from the antigen exposure. By far, alone or in association, the large joints of lower limbs are the most involved and the asymmetry is the prevalent pattern. Inflammatory low back pain, albeit non-frequently, is also reported. As part of the musculoskeletal complaints, enthesitis, tendinitis, bursitis and dactylitis are typically present even though never as unique reactive feature. Fever is the most common associated symptom followed by typical hypersensitivity symptoms such as conjunctivitis, urethritis, uveitis, balanitis, and ketatoderma. A definite genetic link is documented by HLA B27 carriers in about half cases, supporting the concept that, when MHC class I associations occur, the failure of immunological tolerance in combination with environmental factors, such as a microbial agent in the bladder, can lead to immune-mediated inflammatory reaction in the joints. NSAIDs and/or corticosteroids are the mainstay of pharmacologic treatment, that is largely effective, and arthritis usually has a benign course with poor tendency to chronicity [11]. It is worth noting the comparison with polyarthritis secondary to immunotherapy with intradermal BCG (31,32) reported only in few cases; their different articular phenotypes might be correlated to the distinct routes of administration with quite different immunogenic action.

Other anecdotal autoimmune rheumatic diseases following intravesical BCG have been reported. In particular, Sjögren's-like syndrome, confirmed by salivary gland scintigraphy and biopsy of the submandibular gland showing a lymphoplasmacytoid sialoadenitis

without granuloma [48], polymyalgia rheumatica with temporal artheritis [49], remitting seronegative symmetrical synovitis pitting oedema [50], and cryoglobulinemic vasculitis [51].

4.2.2 Organ-specific hypersensitivity reactions

Provided that the lack of any microbiological evidence of BCG dissemination does not exclude an infection with *M. tuberculosis* or mycobacteria other than *M. bovis*, several reports of non-infective organ involvement may indicate an underlying hypersensitivity mechanism. Similar cases were also referred from intradermal BCG immunotherapy for neoplasms other than bladder cancer since viable mycobacteria had not been detected in the lesions. Pneumonitis/hepatitis were reported with a prevalence of 0.7% in a series of 2,602 patients treated intravesical BCG for superficial bladder cancer but were ascribed to systemic BCG infection [52]. Although it is debated whether these events are really due to a sterile hypersensitivity reaction, the lacking evidence of infection by acid-fast bacilli and the prompt response to steroid treatment (alone or added to anti-tubercular drugs), support this hypothesis. Pneumonitis is generally described as interstitial and bilateral with a radiological appearance of ground glass opacites and multiple pulmonary nodules, expression of non-caseating sterile granulomas [53-57]. Moreover, granulomatous (non-caseating epithelioid granulomas with Langhans giant cells) hepatitis may be concurrently associated with lung involvement. Cultures, PCR analysis and Ziehl-Neelsen staining performed in blood, bone marrow, urine, feces, biopsy samples, and broncho-alveolar lavage failed to isolate *Mycobacterium* species. [58-60]. A granulomatous, sterile hepatitis is also described as single complication of intravesical BCG, although much more rarely than infectious one [61]. Even the kidney may be the target of hypersensitivity reaction to intravesical BCG, which may induce an interstitial nephritis with non-necrotizing, sterile granulomas responsive to steroid therapy [62,63]. Anecdotally, renal

involvement may be observed in association with pneumonitis and hepatitis in the same patient [64]. In these cases corticosteroid therapy was always effective either as monotherapy or second line treatment after the failure of anti-tubercular drugs.
An interesting report suggested a possible involvement of both pathogenetic mechanisms, namely infection and hypersensitivity, in the same patient with multi-organ involvement and a significant time course. Firstly, granulomatous hepatitis with positive PCR for mycobacterial DNA and aortic valve vegetations occurred after intravesical BCG; these manifestations were successfully treated with 3-drug anti-tubercular therapy. Several days after, cutaneous leucocytoclastic vasculitis, leucopenia, thrombocytopenia, antinuclear antibodies, and rheumatoid factor appeared together with a persistent impaired cholestasis. For a possible hepatotoxic effect, ethambutol and rifampin were stopped while ofloxacine was added to isoniazid. Three months later, the granulomatous lesions were spread to lungs (interstitial micronodular pattern on chest CT), spleen (multiple foci on abdominal ultrasound), bone marrow, and liver (extensive no caseating granulomata at liver biopsy, with negative stains and cultures for acid-fast bacilli). In addition, marked hypercalcemia was documented for the first time. Therefore, corticosteroid therapy was given with complete recovery of the systemic features after 15-month follow-up. The Authors suggested both an early infective phase (PCR positive and response to anti-TB treatment), probably triggered by too short time interval between surgery and intravesical BCG, and a late, hypersensitivity reaction (vasculitis, cytopenias, antinuclear antibodies, and rheumatoid factor seropositivity) with disseminated, sterile granulomatosis, responsible for hypercalcemia due to activation of reticuloendothelial system as in sarcoidosis. Concordantly with their pathogenetic hypothesis, this second phase of disease showed a marked response to low-dose corticosteroid therapy [65].

4.2.3 Skin

Not otherwise specified “rash” are reported in 0,3% of patients [52]; however, cutaneous complications of intravesical BCG have been seldom described in anecdotal observations [11]. Id reaction or auto-eczematization (a dermatitis appearing at a distance from an initial site of infection or sensitization) was referred in a patient as an intensely pruritic, scaly, erythematous eruption involving all extremities 2 weeks after starting weekly intravesical use of BCG therapy. The skin biopsy showed spongiotic dermatitis with overlying scaling and an eosinophilic infiltrate. The eruption resolved with topical corticosteroids [66]. Finally, vitiligo has been also reported as autoimmune side-effect of intravesical BCG [67].

4.2.4 Ophthalmopathy

Uveitis can be caused by intraocular infections or as a result of autoimmune stimulation. Several reports, also after BCG vaccination, focused on ocular complications of intravesical BCG but not infrequently a clear-cut exclusion of infective origin is lacking, probably due to low sensitivity of diagnostic tools. However, some cases show a complete recovery with topical or oral steroid therapy. Of interest, when searched, HLA B27 was negative [68-70], contrarily to that observed in patients with uveitis and reactive arthritis (7.7%), invariably HLA B27-positive [11]. An autoimmune retinopathy associated with intravesical BCG therapy has been also reported [71].

4.2.5 Others

Among the very rare reports may be worthy to note one case of anaphylactoid purpura in the lower legs and another case of Henoch-Schönlein purpura occurring after intravesical BCG therapy in the absence of any concomitant possible cause, [72,73].

5. BCG vaccination in autoimmune diseases

In spite of the global tuberculosis control achieved in Central Europe, the disease represents currently one of the major health problems, particularly in development countries, high-income countries, Latin America, and the Western Pacific region [74]. Although with variable efficacy and largely ineffective on the most common lung infection, the BCG vaccination remains the only currently licensed TB vaccine. In this context, the relationship between BCG vaccination and autoimmune diseases is another not negligible aspect. In fact, the risk of getting TB, the protective effect of BCG and the possible harms of vaccination are, as for any vaccine, the main issues to take in account in patients with systemic autoimmune disorders. The inherent risk of the single disease, the geographic risk for TB and the use of immunosuppressive therapy in rheumatic diseases are all factors that create a new scenario. In patients with rheumatoid arthritis corticosteroids, disease-modifying drugs and, especially, TNFα blocking agents are associated with increased risk of TB although reduced by the screening procedures for latent TB. In ankylosing spondylitis patients treated with infliximab, etanercept, and adalimumab no cases of active TB has been reported [75]. The BCG vaccination in patients with autoimmune rheumatic diseases has been recently evaluated in the EULAR evidence-based review where it is stated that BCG vaccination is not recommended in patients with auto-immune inflammatory rheumatic diseases. This advice relies upon the following considerations: the incidence of active TB is increased in patients with autoimmune rheumatic diseases especially when are treated with immunosuppressive drugs (mainly TNFα blocking agents), these cases are mostly reactivations on latent TB that could not be prevented by the vaccine, the protective effect of BCG vaccination in adults is not clearly demonstrated, BCG vaccine carries attenuated, live, mycobacteria that, in immunocompromised patients might increase the risk of disseminated TB [76]. However, some exceptions should be evaluated as the case of health care workers exposed to resistant TB [77].

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Legend to the Figures.

Figure. 1. Clinical applications of BCG. Apart from its current use in the vaccination against tuberculosis and leprosy, BCG has been proposed as a possible immunotherapy treatment in both neoplastic and autoimmune diseases.

Figure. 2.Summary of the main pathogenetic mechanisms correlated with BCG vaccination or intravescical BCG immunotherapy for bladder cancer, as well as the possible BCG-driven autoimmune disorders.

* cross-reaction between BCG heat-shock protein HSP65 and cartilage proteoglycan link protein represents one example of possible molecular mimicry pathogenetic mechanism.