BCG vaccine for clinically isolated syndrome and MS

Infections and protective immunity

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Infections may be harmful for people with multiple sclerosis (MS), resulting in fever, "pseudo-exacerbations," and increased risk of relapses.[1] Can infections ever be beneficial for MS? The long-held yet unproven "hygiene hypothesis" proposes that certain infections early in life might reduce the risk of developing autoimmune diseases by inducing protective immunity.[2] In addition, parasitic intestinal infections in people with MS may reduce disease activity.[3] It follows that better sanitation and common use of disinfectants and antibiotics may account in part for the increased prevalence of MS and other autoimmune diseases in North America and much of Europe, compared with Africa, South America, and parts of Asia. If true, might we harness this natural phenomenon to develop new treatments for MS?

In this issue of *Neurology*®, Ristori et al.[4] report results of a clinical trial of the live attenuated Bacille Calmette-Guérin (BCG) vaccine in people with a clinically isolated syndrome (CIS) at high risk for developing MS. Following a single intracutaneous injection of BCG or placebo, participants underwent monthly gadolinium-enhanced brain MRI. After 6 months, the mean number of total gadolinium-enhancing lesions was substantially lower in subjects receiving BCG vs placebo (3.1 vs 6.6 lesions), with a relative risk reduction of 0.54 after correction for baseline variables ($p = 0.03$). All participants then received interferon-β-1a for 12 months per study protocol. After 18 months from study entry, they could receive any disease-modifying therapy (DMT) per the recommendations of their neurologists, while continuing regular clinical assessments. Over the course of 60 months after entering the trial, more subjects receiving BCG + DMT remained relapse-free and therefore did not meet criteria for clinically definite MS (CDMS) than did those receiving placebo + DMT (19/33, 57.6% vs 12/40, 30%, $p = 0.018$). The cumulative probability of the BCG + DMT group developing CDMS after adjustment for baseline variables was lower than that of the placebo + DMT group (hazard ratio = 0.52, $p < 0.05$). Thus, a single injection of BCG appeared to affect not only the total number of gadolinium-enhancing lesions for 6 months in persons at high risk of developing MS following a CIS but also was associated with decreased clinical activity for up to 5 years.

What are the possible mechanisms of action of BCG? BCG is a live vaccine composed of an attenuated strain of *Mycobacterium bovis* and is used to reduce the risk of tuberculosis in many parts of the world. Injection with BCG induces an immune response directed at the mycobacterium, in addition to other potential immune-stimulatory effects. These postvaccination immunologic responses might induce short- and long-term protective immunity in CIS and MS by downregulating proinflammatory T-cell responses, stimulating regulatory T cells, and altering cells of the innate immune system. These mechanisms of action are speculative, and further investigation of immune responses in people receiving BCG is needed to better understand how BCG might be protective in MS.

Ristori et al. suggest that BCG could prove to be a "safe, inexpensive, and handy" treatment for MS. Given the high cost of DMT for relapsing MS, we would welcome one that was inexpensive, and this might be accomplished by repurposing a generic agent. BCG has potential to do more than prevent tuberculosis, as it is utilized to treat bladder cancer and is undergoing early clinical trials in type I diabetes mellitus.[5,6] However, there are potential problems with BCG as a treatment for MS.

Despite the apparent long-term effects suggested by the present study, it seems unlikely that a single injection of BCG would be highly effective in a disease that lasts decades. The safety of repeated administration of BCG is unclear, and in the case of repeated bladder injections for cancer treatment, serious side effects can include a systemic BCG immune reaction and localized or systemic BCG infection.[5] Studies in the murine model of MS, experimental autoimmune encephalomyelitis (EAE), demonstrated that administration of BCG can be therapeutic but requires an active *M bovis* infection,[7] an approach that seems imprudent in MS. In addition, disseminated

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BCG infections can occur following a single injection, particularly in people who are immunocompromised.[8] Thus, one should be concerned about the safety of BCG if used in conjunction with immunosuppressive drugs for MS.

A safer approach might lie in using killed BCG or components of *M bovis* as a therapeutic vaccine. This approach has been successful in EAE using heat-inactivated *Mycobacterium tuberculosis* and proteins isolated from the mycobacterium,[9] and BCG killed by freeze-drying appears to inhibit inflammation in some murine models of human diseases.[10] Characterizing the protective immune response that BCG induces in people would help in developing therapeutic approaches that do not require repeated treatment with live *M bovis*.

Clinicians should not use BCG to treat CIS or MS off-label, as its efficacy is not established; further, its safety with repeated dosing is unknown. This study provides Class I evidence based on design methods, as a randomized, placebo-controlled, double-blind study with a defined primary outcome. However, the sample size was small, the controlled part of the study was relatively short, and one would require a larger trial demonstrating similar results with acceptable safety before deciding whether or not BCG is truly effective. We should encourage investigations into understanding how BCG might induce immunoprotection and hope that this knowledge leads to the development of a "safe, inexpensive, and handy" therapy for MS.

This study and others suggest that infections are not always deleterious for people with MS. Some may be beneficial and even open doors to new therapies for MS.

AUTHOR CONTRIBUTIONS

Dennis Bourdette: drafting/revising the manuscript, study concept or design. Robert Naismith: drafting/revising the manuscript.

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D. Bourdette serves on a scientific advisory board for the nonprofit entity NYSTEM; has received speaker honoraria from Biogen Idec, Teva Neurosciences, and Genzyme; holds a use patent for the treatment of MS with cyclic peptide derivatives of cyclosporine, for which he receives royalty payments from DebioPharma; served as a consultant to Teva Neurosciences and Biogen Idec in the past 12 months; has received support for patient and physician education programs from Teva Neuroscience, Biogen Idec, EMD Serono, Acorda, and Novartis; and has received research support from the Department of Veterans Affairs. R. Naismith has received speaker, travel, or consulting honoraria from Acorda Therapeutics, Bayer Healthcare, Biogen Idec, Genzyme Corporation, National MS Society, Consortium MS Centers, EMD Serono, and Questcor Therapeutics; serves on speakers' bureaus for Acorda Therapeutics, Bayer Healthcare, Biogen Idec, and Genzyme Corporation; and receives research support from Acorda Therapeutics, the NIH, and the National MS Society. Go to Neurology.org for full disclosures.

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