Therapeutic Vaccination: Hope for Untreatable Tuberculosis?

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(See the major article by Coler et al on pages 1242–52.)

Although tuberculosis remains a major public health threat globally [1], promising advances have been made in the past several years in the development of new tools to control the pandemic. These include rapid diagnostic tests [2], new drug regimens that may shorten the total treatment time and improve compliance [3], and novel drug delivery systems that may allow sustained therapeutic levels with lower drug doses [4]. There are currently more than a dozen tuberculosis vaccines in human trials that are based upon a variety of platforms, including viral-vectorized, recombinant bacille Calmette-Guérin, and protein/peptide vaccines [5]. Thus, the progress made in recent years in the battle against this ancient scourge is remarkable.

Unfortunately, control of tuberculosis is complicated by a number of factors, not the least of which are the interactions with human immunodeficiency infection and the development of multi-drug-resistant and extensively drug-resistant strains [6]. In parts of the world where these resistant strains are common, treatment of patients with tuberculosis is difficult, if not impossible, because of the paucity of effective drugs. For such patients, an immune-stimulatory therapy that effectively engages patients’ own immune systems to assist the drugs in controlling the infection would be a major asset in the clinic setting. The therapeutic vaccine described by Coler et al [7] in this issue of the Journal of Infectious Diseases appears to have many of the qualities that one would want as an adjunct to chemotherapy for tuberculosis.

Although a massive effort is underway to develop and test new tuberculosis vaccines, virtually all of them are designed as prophylactic vaccines to prevent progression to pulmonary disease in newly infected individuals. In the recently published Blueprint for Tuberculosis Vaccine Development [8], nearly all of the emphasis was on the use of vaccination to prevent, not to treat, tuberculosis. The use of vaccination as an adjunct to chemotherapy for tuberculosis, however, is not a new idea. Two of the vaccines currently in human trials, RUTI [9] and Mw (Mycobacterium indicus pranii) [10], are proposed as therapeutic vaccines. Investigators have been studying the therapeutic effect of Mycobacterium vaccae for many years [11]. The results of experimental studies of such vaccines have been mixed [12, 13], likely reflecting the lack of well-standardized animal models in which to test therapeutic tuberculosis vaccines.

Coler et al [7] describe the use of mouse and cynomolgus monkey models of tuberculosis in which to test the ability of a vaccine that incorporates 4 mycobacterial antigens into a synthetic nano-emulsion adjuvant containing a Toll-like receptor-4 agonist (Infectious Disease Research Institute [ID] 93/glucoopyranosil lipid A-stable water-in-oil emulsion [GLA-SE]) [14] to augment the therapeutic effect of rifampin (RIF) and isoniazid (INH). The hypersusceptible inbred mouse strain based upon a Swiss background (SWR) mouse strain was chosen for these studies because of the rapid progression to lethal disease following pulmonary infection and the inability of RIF and INH to completely eliminate bacilli from the tissues. These features gave the investigators a window within which to detect the effect of immunizing the infected, drug-treated mice 3 times with their vaccine and to measure a significant improvement in the response of the mice to the 2 drugs. Indeed, therapeutic vaccination did result in a remarkable improvement in survival, a significant reduction in lung bacillary loads and pathology, and a shortening by one-third of the treatment duration required to achieve a beneficial outcome compared with mice treated with RIF and INH alone. This latter observation is important because it suggests that therapeutic vaccination might be useful in the treatment of drug-sensitive tuberculosis to reduce the duration of
chemotherapy and improve compliance. The therapeutic vaccine’s mechanism of action appeared to be related to the induction of polyfunctional antigen-specific CD4+ and CD8+ T cells. Promising results were also obtained in cynomolgus monkeys, although the magnitude of the added benefit of therapeutic vaccination was modest at best, and the monkeys appeared to divide into responsive and nonresponsive subgroups when lung bacillary loads were measured.

The enthusiasm generated by these promising results should be tempered by the fact that tuberculosis in the SWR mouse is very different from tuberculosis in other mouse strains, let alone humans. The model has not been characterized to the same extent as more commonly used mouse strains, and this limitation makes the extrapolation of the results somewhat problematic. The underlying defects in disease resistance, the unusual nature of the histopathological response (eg, alveolar edema, necrosis), the unknown anatomical location (ie, intracellular vs extracellular), and metabolic activity of the mycobacteria may be very different in the SWR mouse and could influence significantly the response to therapy. The fact that the effect of therapeutic vaccination was much more dramatic in the SWR mice than in the more human-like cynomolgus monkeys further justifies caution in extrapolating these results to humans.

Obviously, investigators of therapeutic vaccination in tuberculosis are caught on the horns of a dilemma, namely, to create animal models in which the therapeutic effects of the drugs alone have been blunted enough to detect an additional vaccine effect, without compromising the human-like aspects of the disease being modeled. Ideally, one would use a well-established, conventional animal model infected with a drug-resistant strain of Mycobacterium tuberculosis since this most directly approximates the clinical condition in which the therapeutic vaccine is likely to be most useful. However, most institutions have little enthusiasm for allowing investigators to infect animals with drug-resistant M. tuberculosis, especially by the respiratory route. The approach by Coler et al [7] to create a natural “drug failure model” is certainly novel, notwithstanding the caveats mentioned above.

One aspect of therapeutic vaccination that has been raised as a potential clinical complication, namely, the induction of serious hypersensitivity reactions at the site of vaccination (the so-called Koch phenomenon) was apparently not observed in the Coler study [7]. The authors reported no significant injection site reactions and no fever or weight loss in the tuberculosis-infected cynomolgus monkeys that had received 3 doses of the therapeutic vaccine. Unfortunately, the same detailed studies of the T-cell responses conducted in the mice were not performed in the monkeys, so the nature of the immune response to the vaccine in the context of an ongoing infection remains to be determined. Based upon these initial observations, however, the ID93/GLA-SE vaccine appears to be safe for use in M. tuberculosis-infected individuals.

These encouraging results should form the basis for additional therapeutic studies with ID93/GLA-SE in small animal tuberculosis models that more closely approximate the disease in humans. In addition, further characterization of the tuberculosis disease process in the SWR mouse will help to clarify the relevance of the authors’ findings in that novel model. Additional immunological studies in the cynomolgus monkey model will likely reveal the mechanistic basis for the vaccine effect and may provide an explanation for the very clear dichotomous response in the authors’ bacillary load data.

Note

Potential conflict of interest. The author declares no conflicts of interest.

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References