Will We Be Treating Tuberculosis With Vaccines in the XXI Century?²

¿Trataremos la tuberculosis con vacunas en el siglo xxi?

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The pillars for the control of tuberculosis are early diagnosis, appropriate treatment and prevention. After the discovery of the bacteriologically based treatment of tuberculosis halfway through the last century, various therapeutic regimens were established, allowing us to cure the vast majority of patients. However, it must be said that very little progress has been made in this area in recent decades. Prevention of tuberculosis remains focused on measures for avoiding contagion, chemoprophylaxis and BCG vaccination. Unlike the situation with other diseases such as smallpox, poliomyelitis, etc., where vaccines have led to control and even, in some cases, eradication, the role of the BCG vaccine has been constantly under discussion since it was introduced because, in addition to interfering with the predictive value of the tuberculin test, it has not managed to significantly modify the epidemiology of tuberculosis. The efficacy of the vaccine is very variable (0%–80%), it does not prevent tuberculosis infection and it does not protect the infected patient. The protection it does confer consists basically in preventing severe complications which may follow on from primary infection, such as meningitis and miliary tuberculosis. It is not recommended for systematic use in Spain.

Despite this, we still believe that, as has already occurred with other diseases, an effective vaccine may be the right tool for achieving the anxiously awaited worldwide eradication of tuberculosis. In this respect, the discovery of the Mycobacterium tuberculosis genome and improved knowledge of the bacillus’ immunopathology has opened new avenues of research into new vaccines for the prevention and treatment of tuberculosis.

Over the past 20 years, enormous efforts and public and private financial resources have been poured into the search for and development of new vaccines in order to improve or replace the BCG. Great progress has been made in the last 15 years that has produced a good number of vaccines now in the clinical development phase. Furthermore, various centers, including some in Spain, have specialized in the evaluation of candidate molecules in both animal models and in humans in clinical trial settings.

Existing candidate vaccines comprise the classic prophylactic and therapeutic vaccines. Most vaccines are prophylactic, and aim to prevent infection either by “priming” (those that hope to replace the BCG) or “boosting” (those that improve BCG efficacy when both are administered in a combined regimen 1). Therapeutic vaccines are in the minority, and are designed to prevent latent infection or the development of infection into disease or to reduce chemotherapy requirements. The scant interest in these compounds probably dates from the time when widespread use of tuberculin in Europe as a treatment for tuberculosis caused severe side effects, and the idea of a therapeutic vaccine against the disease was shelved. Nevertheless, a few success stories, such as the RUTI vaccine that has obtained positive results in a phase 1 clinical trial and in another phase 2 study in subjects with and without HIV infection, have encouraged the scientific community to regard these strategies with less suspicion and even to include them among their short-term priorities.

With regard to design, candidate vaccines currently in clinical development are grouped into viral vector vaccines (MVA85A, AERAS-402, AdAg85A), proteins plus adjuvants (M72, Hybrid-1, Hyvac-4, H56), recombinant BCG vaccines (VPM 1002, AERAS-422) or dead bacillus extracts (Mw, RUTI).

Producing vaccines is not an easy task, at least not in the area of tuberculosis. There are no biomarkers correlated with protection, there is little consensus on the design of clinical trials and the sites capable of carrying them out, and the selection and evaluation of new candidates needs to be rationalized. The ethical and regulatory requirements that accompany vaccine development can also cause problems. As with all medications, 15 years can elapse between design and marketing approval, and the process is extremely costly. Moreover, experience with BCG in HIV-infected subjects and the introduction of genetically engineered vaccines call for extra efforts to guarantee vaccine safety, an issue that has started to be addressed in regulatory guidelines and successfully implemented in research groups.

Initiatives such as the TBVAC and NEWTBVAC projects (funded by the European Union Seventh Framework Program) and the GC12 project from the Bill and Melinda Gates Foundation have fostered collaboration between the main players in the development of TB vaccines.

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vaccines. However, there is still room for improvement in methodological harmonization and, unfortunately, an effective TB vaccine remains elusive.  

The great hopes invested in TB vaccines faded when the most promising and outstanding candidate, MVA85A, was shown to be incapable of protecting against tuberculosis infection and disease in a clinical trial conducted in 2794 children in South Africa.  

Yet the enormous effort made in recent years has not been in vain. Knowledge of the disease and vaccine design and development has deepened considerably, and a very high degree of international collaboration with a single common objective has been achieved. However, from now on, vaccine strategies will have to be redesigned, and the scientific community will have to be prepared to consider new less orthodox proposals, such as therapeutic vaccines, and proposals rejected long ago, such as those focusing on humoral immunity, may have to be reexamined.

It is safe to say that we have not yet achieved our dream of finding a really effective vaccine against tuberculosis, but considering the pace of recent developments, it is not unreasonable to believe that this may occur in the not too distant future.

References