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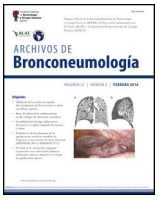

Editorial

New Perspectives in Latent Tuberculosis Infection☆

Nuevas perspectivas en infección tuberculosa latente

Miguel Arias Guillén,[a,*] Patricio Escalante,[b] y Juan José Palacios Gutiérrez[c]

[a] Servicio de Neumología, Hospital Universitario Central de Asturias, CIBER Enfermedades Respiratorias, Instituto de Salud Carlos III, Oviedo, Asturias, Spain
[b] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA
[c] Unidad de Referencia Regional de Micobacterias, Servicio de Microbiología, Hospital Universitario Central de Asturias, Oviedo, Spain

The management of latent tuberculosis infection (LTI) is still both a clinical and public health challenge. Approximately 1,700 million people, 23% of the world's population, are thought to be infected by *Mycobacterium tuberculosis* (MTB), mostly in asymptomatic and latent forms. Immunocompetent individuals have a 5%–10% risk of developing active tuberculosis (TB) during their lifetime, and this risk rises in situations of immunosuppression.[1] It is estimated that in 2017 approximately 10 million people developed TB and 1.6 million died with TB, including 300,000 deaths in patients coinfected with HIV.[2] TB control has improved in many countries, including Spain and other European states.[2] However, in order to achieve levels of TB eradication, preventive measures will have to be reinforced with the optimal detection and management of LTI.[3]

The classical dichotomy between active disease and LTI has been rethought as a dynamic and continuous spectrum that encompasses sterilization of latent infection, LTI in the strict sense, incipient and subclinical tuberculosis infection, and finally active TB in its different forms.[1,4] The host immune response can prevent MTB infection by eliminating the bacilli immediately after entry, thanks to the work of the innate immune system or an effective adaptive immune response, which can eliminate the infection within a short time (transient infection) or years later.[1] This immune response to MTB is complex, dynamic, and multifocal: different immune system cells participate by forming granulomas in the infected organs and activating regional nodes, which can contain and even sterilize the infection, although they might also fail to impede the progress of the disease. In addition to T cells, NK cells play a leading role in controlling disease progression or reactivation.[1,5]

Generally, people at high risk of developing active TB disease belong to one of 2 categories: those who have been infected recently by MTB, or those with medical conditions that weaken the immune system in different clinical settings. Biological agents, such as TNF-α antagonists, used in the treatment of chronic inflammatory diseases, and the immunosuppressive drugs used to prevent rejection in transplanted patients, come under the second category.[6]

LTI is diagnosed using immunological tests that detect the sensitization of the individual to MTB antigens in the absence of clinical and/or radiological findings consistent with active TB disease.[6] The purified protein derivative (PPD) or tuberculin test has been widely used, and its limitations are well-known: false negatives in immunosuppressed patients (lower sensitivity) and false positives in subjects vaccinated with BCG or sensitized with nontuberculous mycobacteria (lower specificity).[6]

Interferon gamma release assays (IGRA) that measure the production of gamma interferon in response to CFP-10 and ESAT-6 specific antigens expressed in MTB were introduced just over 10 years ago. The interpretation of the results is objective, although there are sources of variability, and false positives and negatives have been detected.[6,7] Two types of IGRA are available: QuantiFERON® and T-SPOT.TB®. QuantiFERON® TB Gold Plus is the latest version; in addition to positive and negative control tubes, the kit includes a TB1 tube that contains peptides derived from ESAT-6 and CFP-10, designed to generate a response from $CD4^+$ helper T cells, and a TB2 tube, in which those peptides have been optimized to induce responses of $CD4^+$ and $CD8^+$[6,8] cytotoxic T cells.

The T-SPOT.TB® is an enzyme-linked immunospot assay (ELISPOT); peripheral blood mononuclear cells are stimulated with ESAT-6 and CFP10 antigens in 2 separate wells, allowing the number of effector T cells to be visualized by counting the number of spots. The QuantiFERON® (In-Tube version) and SPOT.TB® have an estimated sensitivity of 80% and 90%, and a specificity of 97% and 95%, respectively, for the diagnosis of LTI.[7] In contrast, the PPD has a sensitivity of 79% and a specificity of 97% when the criterion of positivity is an induration ≥10 mm in individuals unexposed to the BCG vaccine.[7] However, neither the IGRA nor the PPD differentiate between LTI and active TB, and they have a predictive value of progression to disease of less than 5%. In general, special recommendations apply to the use of these techniques in countries of low incidence due to their high specificity.[1,7]

Recent studies have examined new immunological tests and RNA signatures that can differentiate LTI from active TB. New evidence in the future might allow us to stratify individuals at high risk of progression (incipient infection) to active TB, as well as to assess response to preventive treatment, but more longitudinal val-

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* Corresponding author.
E-mail address: mag@crit-lab.org (M. Arias-Guillén).

idation studies will first be needed.[4,9] Other advances include the development of new diagnostic techniques. The C-Tb skin test using ESAT-6/CFP-10 antigens has proved to be a safe technique with positivity rates similar to the traditional PPD and QuantiFERON in children and HIV-infected patients.[10] The detection of antigens expressed in latency (for example, DosR regulon-encoded antigens) and the use of IP-10 and lymphocyte differentiation markers (e.g., CD27) can distinguish between recent and remote infection, and/or between active tuberculosis and LTI; however, very little comparative experience has been published.[4,9]

There has also been significant progress with shortened, effective therapies for LTI. For example, the effectiveness of rifapentine (not yet marketed in Spain) plus isoniazid weekly for a period of 3 months was similar to 9 months of daily isoniazid, and had a better rate of adherence.[11] Recent studies also showed that the effectiveness of rifampin daily for 4 months was similar to 9 months of isoniazid, and was associated with better adherence and less toxicity.[12] Another study in patients coinfected with HIV in areas endemic for TB showed that the combination of rifapentine and isoniazid for 1 month was equivalent to the use of isoniazid for 9 months, but these results, while very promising, still need to be validated.[13]

There has also been progress in the field of new vaccines to prevent pulmonary TB. A recent multicenter study showed 54% efficacy among individuals residing in TB-endemic areas who had previously been vaccinated with BCG.[14] The M72/AS01E vaccine includes 2 MTB proteins that are administered with adjuvant AS01E. Another recent study showed a 45% protection rate with BCG revaccination in South African adolescents.[15] These developments underline the importance of collaboration at an international level to introduce new effective vaccines against TB into clinical practice in the not too distant future.

In conclusion, the detection of LTI and effective prevention of TB are increasingly gaining importance, which justifies dedicating the necessary resources to both research and the implementation of new diagnostic techniques and preventive strategies in clinical practice.

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