Diagnosis and Prevention of Tuberculosis in Patients With Inflammatory Rheumatic Disease, Is There Anything New?

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Patients with inflammatory rheumatic disease have an increased risk of aquiring tuberculosis. The incorporation during the past decade of biologic therapy has led to an increase in that risk.[1] In the majority of cases, the disease is produced as a consequence of the reactivation of a latent infection, making its incidence highly variable with regard to the prevalence of infection in the area under study. The systematic practice of an evaluation before the start of biologic therapy, which intends to root out those patients with infection and tuberculosis, has allowed for a reduction in its incidence in this population. The experience of the Spanish cohort of patients treated with biologic agents (BIOBADASER), an effort of the Spanish Society of Rheumatology, shows a reduction in the cases of tuberculosis since the implementation of the official recommendations in 2002 with respect to the previous period (117 vs 522 cases/100 000 person-year, respectively).[2] However, it must be pointed out that an important increase in the use of etanercept during the second period of the study, as compared to a reduction in the use of infliximab, could partially explain the reduction in its incidence. Even when assuming the effectiveness of these measures, the incidence of tuberculosis in this group of patients continues to be almost 5 times that of the general Spanish population. Several causes could explain this fact: an inadequate implementation of protocols, a lack of control on the treatment for infectious tuberculosis compliance, exogenous reinfection, and the limitations of the TT (tuberculin test) for the identification of latent infection in these circumstances. The TT is a widely used, cheap and easy to apply test which has a prognostic value in the development of tuberculosis. However, its lack of sensitivity in situations of immune compromise, malnutrition or severe disease and the positive results associated with vaccination with BCG and infection by other mycobacteria are its most important limitations. These factors concur frequently in patients with chronic inflammatory rheumatic disease, who are presumed to present a determined degree of immunodeficiency due to the underlying disease, the treatment or both. The sensitivity of the TT in this context is greatly reduced.[3] In order to improve its effectiveness, it should be performed in a 2 tiered approach, allowing the clinician to take advantage of the booster effect of the first application. However, this strategy has yet to prove ideal. In the unpublished experience of the Tuberculosis Clinic of the University Hospital at Bellvitge, of those patients who were candidates to receive biologic treatment, 15% with the first TT resulting negative and who then recover with the second test, which is performed 1 week later (positive booster). The greatest inconvenience of this practice is the increase in the number of false positives among patients vaccinated with BCG, among which positive cases are duplicated (22% of positivity with the first TT and 41% when repeated in the initially negative cases). Taking into account that the prevalence of tuberculosis infection in our population is lower than the numbers presented above, a remarkable number of positive cases must be produced by a response to vaccine. On the other hand, the positive boosters did not take place, as would have been expected, in older patients, those who theoretically would have a more profound immune compromise, and an opposite phenomenon was seen, something that brings into question the convenience of maintaining this practice.

The new diagnostic techniques for the detection of tuberculosis, based on the quantification of the specific cellular immune response directed against *Mycobacterium tuberculosis,* can complement and even substitute TT in different clinical situations. This can complement and even substitute TT in different clinical situations. These techniques, denominated Interferon Gamma Release Assays (IGRA) as a group, are based on the principle that primed T cells in infected individuals produce inteferon (IFN) gamma when rechallenged with the *M tuberculosis* antigens. The antigens used are coded in the RD1 genomic

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region, present in *M tuberculosis* and absent in BCG and in most of the non-tuberculosis mycobacteria. The secretion of IFNγ can be quantified through ELISA (Quanti-FERON-TB Gold in Tube, Cellestis) or ELISPOT (T-SPOT.TB, Oxford Immunotec) after in vitro stimulation of the mycobacterium bearing lymphocytes. An elevated concentration of IFNγ indicates tuberculosis infection. In general, IGRA has shown more specificity and sensitivity as well as a better correlation with the time of exposure to a case of tuberculosis than TT. In addition, available data indicates its usefulness in specific situations, such as the case of children and the diagnosis of active disease.[4]

In spite of the overwhelming amount of information accumulated in the past few years on IGRA, there are still many doubts on the value of these techniques and on their application. Recently, Ponce de León et al[5] demonstrated that QuantiFERON-TB Gold in Tube (QFT) Is more sensitive than TT for the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis, when compared to healthy controls: positive QFT in 44.6% of patients, versus 59.1% of controls; meanwhile TT was positive in 26% of patients versus 65.6% of controls. In the Clinical Tuberculosis Unit of the University Hospital at Bellvitge, we performed TT and QuantiFERON-TB Gold in Tube to those patients considered candidates to biologic treatment. In our experience, of the 155 patients who were to be subjected to biologic therapy, agreement between TT and QFT was 81% (κ=0.52). However, if we only consider subjects with one or both positive tests, agreement is reduced to 48%, indicating that each one of the tests, done separately, detects less than half of those theoretically infected.[6]

The question is wether, with the current knowledge, IGRA could substitute TT for the evaluation of tuberculosis in patients who are to be subjected to biologic therapy. In my opinion, currently it could complement it but not substitute it. There is no data available on the development of tuberculosis in the long term that would allow us to decide treatment based exclusively on the result of IGRA. Not only that, but the theoretical basis of the IGRA indicate that these techniques measure a type of immune response which is different than that provided by the delayed hypersensitivity to PPD. In other words, the information provided by each one of the tests does not necessarily have to be the same. In contrast to what occurs in the follow-up of contacts—something with the objective of identifying individuals with recent tuberculosis infection and, therefore, at a higher risk of contracting the active disease—, in patients who are to be submitted to immune suppression, both the recent and older infection are of importance. From a theoretical standpoint, and the clinical data attests to this, IGRA have a good capacity for detecting recent infection, but are less effective for the detection of older infection. IFNγ detected is produced by memory effector T cells, while central memory T cells, which do not produce IFNγ, need longer periods of incubation time for proliferation and differentiation into effector cells. It is possible that, in infected individuals, the profile of the immune response changes with time and effector memory T cells reduce their numbers but maintain, under normal circumstances, the delayed hypersensitivity response to PPD.[7] Following this line of thought, faced with a long term infection, response to PPD would be maintained (delayed hypersensitivity) while the absence or a reduction in number of effector memory T cells would make the result of the IGRA tests negative (effector response). This could explain the often found discrepancies between TT and IGRA (positive TT and negative IGRA) in subjects who have not been vaccinated with BCG, in which the positive result of TT could not be attributed to vaccination. It is possible that this speculation, although well founded, constitutes a simplification of the problem and that determined discrepancies between both tests have an as of yet unknown significance.

There is no doubt, in any case, that IGRA represent a notable advance in the diagnosis of tuberculosis. The place it occupies in the evaluation of persons at risk, among them those who are candidates to tumor necrosis factor inhibitors, is still to be determined. Therefore, longitudinal studies that provide solid evidence on its prognostic value on the development of long-term tuberculosis are needed. Meanwhile, we should employ these techniques as a complement, with the guidance of a clinical sense that must always guide medical performance. We mustn't forget other elements in decision-making which, apart from TT, include the evaluation of infection risk factors, previous treatment, vaccination with BCG and the careful evaluation of the chest x-ray. Finally, it is important to remember that, in order to achieve the final objective of preventing the deveopment of tuberculosis, it is fundamental to achieve an adequate compliance to prescribed treatment. Periodic controls should specifically consider this aspect and include an interview and determination of isoniazide metabolites (or color as in the case of riphampicin) in urine.

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