

RECOMMENDATIONS TO LOWER THE RISK OF TUBERCULOSIS IN PATIENTS TREATED WITH TUMOUR NECROSIS FACTOR ALPHA ANTAGONISTS

Juan Gómez-Reino*, Loreto Carmona**

Now and then, the place and the time matter. When Tumour Necrosis Factor (TNF) antagonists were on clinical development, it was not clear that they were to increase the risk of tuberculosis as much as they did once on the market. In fact, a warning was not included in the primary Summary of Product Characteristics. These new agents had to be widely used in places where the background risk of tuberculosis were high enough as to reach a statistically significant increase. Spain was one of those places. With a background rate of tuberculosis several times higher than that of other developed countries—around 25 cases per 100,000 inhabitants each year,¹ as a matter of fact in the range of Portugal—and a wealthy universal health system that permitted the use of TNF antagonists in many patients, Spain was just the right place for demonstrating the trigger of tuberculosis reactivation by blocking TNF. Fortunately, and thanks to the establishment of a drug register, we knew early enough that tuberculosis was a true threat, and we put an end to it.

BIOBADASER, the Spanish Register for Adverse Events of Biological Therapies in Rheumatic Patients, was launched one year after the first TNF-antagonist appeared in the Spanish market for rheumatoid arthritis, infliximab, in February 2001. By the time the first report came out, in July 2001, it was already clear that the rate of tuberculosis in patients treated with TNF antagonists was several times higher than the Spanish general population rate.² It took a few more months to find out whether it was rheumatoid arthritis itself or the use of anti-TNF that triggered tuberculosis.³ We went to our national cohort of rheumatoid arthritis and analysed the rate of tuberculosis, which was four times the expected in the general population,⁴ and then compared it to that of the BIOBADASER cohort, and it was clear cut then that blocking TNF put patients in an additional risk.⁵ We knew all these data by November

2001. At that time, a crisis committee got together and developed strict guidelines to be followed in all patients undergoing treatment with TNF antagonists, in order to prevent tuberculosis reactivation. The expert panel took the example of HIV patients, with a risk rate in the range of the TNF blocked patients, and so included among the recommendations: 1) considering a skin test positive if over 5 mm of reaction—and not 10 mm as usual—and 2) using isoniazide as chemoprophylaxis for nine months, instead of four. The expert panel, composed of rheumatologists, infectologists, and members the Spanish Medicines Agency, went further and recommended the repetition of the skin test after a week if the first one was negative, as a way to override anergic reactions, typical in patients who receive long term immune suppressive therapy, especially glucocorticoids. These recommendations were finally issued and rapidly widespread among treating physicians in February 2002.

When we repeated the analysis of BIOBADASER one year after, the recommendations had been clearly effective, and the rate of tuberculosis had lowered dramatically among patients starting on biological therapies after February 2002.⁶ A full investigation of all patients registered was done, with special attention to the adherence to the recommendations prior to the initiation of TNF antagonists. Full adherence was considered when 1) isoniazide treatment was started in patients with skin tests (either the first or the re-test) greater than 5 mm, or in patients with a chest radiograph compatible with past tuberculosis; and 2) a skin test was repeated after one week following a negative test, or a chest radiograph was performed despite negative skin tests. In all other cases, recommendations were considered to be incompletely followed.

What we found was that none of the tuberculosis cases appearing after February 2002 had strictly attached to the recommendations (manuscript in press). Moreover, the rate of tuberculosis in patients treated with TNF antagonists whose physicians adhered tightly to the recom-

*Servicio de Reumatología, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, España

**Unidad de Investigación, Sociedad Española de Reumatología, Madrid, España

mendations has lowered to Spanish background rate.

Spain and Portugal share an abnormally high rate of tuberculosis for developed countries, but are different in that BCG vaccination is mandatory in Portugal, but not in Spain, which may have some implications on the assessment of the skin tests. The Spanish recommendations to prevent tuberculosis reactivation ignore BCG status consciously. The result of the skin test is taken as positive if over 5 mm, in any case. Other guidelines developed in high rate countries, such as Japan, have set a cut-off for the skin test that is higher based on BCG status.

The Portuguese Society of Rheumatology (SPR) has issued guidelines based on the epidemiological particularities of tuberculosis in Portugal.⁷ The major differences with the Spanish guidelines regard to the initiation of chemoprophylaxis in all patients that are going to start anti-TNF treatment and are already immunosuppressed, regardless the skin test result. In practical terms, all rheumatoid arthritis patients who need treatment with TNF antagonists must be on chemoprophylaxis. Additional particularities are related to the recommendation of screening for latent tuberculosis at the time of the diagnosis of an inflammatory joint disease and to the use, in selected cases, of two drugs regime for chemoprophylaxis. All these differences are based on specific epidemiological problems such as a 30% greater incidence of tuberculosis, more resistance to isoniazide and, probably, a weaker primary care service.

An issue that may drive back when applying recommendations in which isoniazide has to be given to so many people is the toxicity associated to tuberculosis treatment. In our experience, with over one thousand patients put prophylactically on isoniazide, only 1% presented relevant liver enzymes increase and none was fatal or led to hospitalization.

Ambiguity and softly supported evidence contribute largely to the failure to follow recommendations. Two-step skin test helps to eliminate false negative results by up to 80% in previously BCG vaccinated people in other settings.⁸ Eight percent of the BIOBADASER patients in whom a second test was performed following a negative skin test, became positive. In a population as ours, with a high background annual rate of tuberculosis, this may represent a true prior exposure to mycobacterium infection rather than vaccination. Cost effective alternatives to skin tests in selected populations are Quantiferon and Quantiferon-gold

tests.⁹ However, these tests have not been validated in immune-compromised populations, something that is critical in rheumatoid arthritis and other chronic inflammatory diseases.

Another important issue is whether we should consider all three available molecules equal. It has been suggested that infliximab and adalimumab carry a higher risk than etanercept. Nonetheless, direct comparison has never been reported. At the time of our first report, all patients with tuberculosis had been treated with infliximab, accessible earlier than etanercept and adalimumab in our setting, but some of the most recent cases have occurred in patients treated with any of the three antagonists. Any recommendation to prevent tuberculosis should not make distinction between molecules.

The value of a recommendation lies on its applicability, on the capacity of the clinicians to follow them and, at the end, on the practical results that its implementation has produced. Our experience has shown that, in our setting, our guidelines were highly effective. No other guidelines have proved any effect whatsoever in preventing tuberculosis reactivation.

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Corresponding author

Loreto Carmona
Unidade de Investigação da Fundação Espanhola de Reumatologia
Sociedad Española de Reumatología, Calle Marqués de Duero, 5 - 1º C, 28001 Madrid
Tel: 91 576 7799, 902 193 102, Fax: 91 578 1133
E-mail: lcarmona@ser.es

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