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General review

Screening of tuberculosis before biologics

Le dépistage de la tuberculose avant mise sous biothérapie

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Abstract

Using anti-TNF has significantly improved the management of chronic inflammatory rheumatism. However, there is clear evidence that this treatment increases the risk of reactivating tuberculosis. The intradermal tuberculin skin test (ITT) and interferon-γ-release assays (IGRAs) are currently used to detect latent tuberculosis infection. The results of ITT are difficult to analyze in patients vaccinated with Bacille Calmette-Guérin (BCG) and because of variation in test administration and reading. Numerous authors have compared the sensitivity and specificity of IGRA and ITT, including in two recent meta-analyses and one literature review. These authors, however, compared different populations with different ITT positive thresholds (5, 10, and 15 mm). We performed a meta-analysis of studies in which the threshold was 15 mm, the recommended level in France. The sensitivity of QuantiFERON, T-spot, and ITT was 79% (IC 76%–83%), 84% (IC 75%–95%), and 69% (IC 65%–73%), respectively. In France, it is recommended to detect latent tuberculosis infection on the basis of history taking, physical examination, 5-unit ITT, and lung X-ray. This screening leads to treating 20%–30% of patients, with considerable adverse-effects. Because of the sensitivity and specificity of IGRAs, it is no longer justified to systematically perform TST for detection of tuberculosis before initiating anti-TNF treatment.

Keywords: Biologics; Tuberculosis; IGRA; ITT; Chronic inflammatory rheumatisms

Résumé

L'utilisation des anti-TNF représente une avancée considérable dans la prise en charge des rhumatismes inflammatoires chroniques. L'augmentation du risque de réactivation tuberculeuse est clairement démontrée lors de l'utilisation de ces traitements. Les outils actuellement disponibles pour dépister la tuberculose latente sont l'intradermoréaction à la tuberculine (IDR) et les interferon-gamma release assays (IGRA). À la différence des IGRA, l'interprétation de l'IDR est rendue délicate par l'utilisation de la vaccination par le BCG, et par les différences lors de sa réalisation et de sa lecture. De nombreuses études ont comparé la sensibilité et la spécificité des IGRA et de l'IDR, et notamment deux méta-analyses et une revue de la littérature récente. Ces études comparent cependant des populations différentes avec des seuils de positivité de l'IDR différents (5, 10 et 15 mm). Nous avons repris les différentes études pour lesquelles le seuil de positivité de l'IDR était de 5 mm (seuil recommandé en France) dans une méta-analyse: la sensibilité du Quantiféron est de 79 % (IC 76 %–83 %), celle du T-spot.TB de 84 % (IC 75 %–95 %) et celle de l'IDR de 69 % (IC 65 %–73 %). En France, il est recommandé de rechercher une tuberculose latente par l'interrogatoire, l'examen physique, la réalisation d'une IDR à cinq unités et d'une radiographie pulmonaire. Ce dépistage conduit à traiter 20 à 30 % des patients, avec des effets indésirables non négligeables. La sensibilité et la spécificité des IGRA ne semblent plus justifier la réalisation systématique de l'IDR dans le dépistage de la tuberculose avant de débuter un traitement par anti-TNF.

Mots clés : Biothérapie ; Tuberculose ; IGRA ; IDR ; Rhumatismes inflammatoires chroniques

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Anti-TNF have greatly improved the management of chronic inflammatory rheumatism, whether for rheumatoid polyarthritis (RP) or spondylarthropathy, psoriasis, and Crohn's disease [1]. Abatacept, a costimulatory inhibitor of T lymphocyte, and tocilizumab, an anti-interleukin-6 receptor antibody, is also indicated for RP in therapeutic failure with conventional long-term treatment and anti-TNF [2,3]. Screening for latent tuberculosis must be performed before initiating anti-TNF, abatacept, and tocilizumab [1–3]. It must be performed if abatacept or tocilizumab treatment is re-initiated after anti-TNF-a failure, if negative screening was more than a year old [2,3].

1. Tuberculosis and biologics

The risk of reactivating latent tuberculosis increases when initiating an anti-TNF treatment. In 2001, Keane reported a 24/100,000 incidence of tuberculosis in patients with RP treated by infliximab, whereas it was only 6.2/100,000 for RP under common long-term treatment [1,4]. Tuberculosis occurs shortly after treatment initiation (average 12 weeks). This data was confirmed by Wolfe, in 2004, with an incidence of tuberculosis at 52.5/100,000 for RP treated by infliximab and 6.2/100,000 for RP treated without anti-TNF [1,4]. The ARTIS data in 2005 and BSR data in 2006 confirm an increased risk of tuberculosis with anti-TNF with a higher risk for monoclonal antibodies (infliximab and adalimumab) compared to a soluble receptor (etanercept) when BSBR data was updated [1,4]. This difference was also observed by the RATIO observatory [5]. Tuberculosis cases were collected for 3 years, in patients treated by anti-TNF whatever the disease. Sixty-nine cases of tuberculosis were observed (36 under infliximab, 28 under adalimumab, and 5 under etanercept) with a relative risk of 13.3 [95% CI 2.6–69.0] for infliximab, and 17.1 [95% CI 3.6–80.6] for adalimumab compared to etanercept [5].

There is no clearly identified increase of risk for tuberculosis in trials on abatacept and tocilizumab [2–4]. This does not mean there is no increase of risk since in all trials tuberculosis was screened for.

2. Screening for tuberculosis before anti-TNF treatment

Screening for latent tuberculosis is performed with intradermal tuberculin test (ITT) and IGRA [1,4].

ITT is considered positive beyond 5 mm. Several factors influence ITT results: its administration, and analysis. It may be a false positive in patients vaccinated with Bacille Calmette-Guérin (BCG) or in patients previously infected by another mycobacterium. Conversely, its sensitivity may be weaker in patients presenting with RP [4].

IGRA currently include the Quantiferon and T-spot.TB tests [4,7]. The Quantiferon test is performed on whole-blood with Elisa. It allows measuring the capacity of the patient's lymphocytes to secrete interferon-gamma after protein mycobacterium tuberculosis ESAT6, CFP10, and TB7.7 stimulation. The T-spot.TB test is performed on mononuclear cells and detects lymphocyte T secretion of interferon-gamma by the specific ESAT6 and CFP10 as Spot. These tests are reproducible and do not interfere with BCG vaccination. Nevertheless, they may be non-informative when the result not determined and there is a potential cross-reaction with some atypical mycobacteria (N. Kansasii, M. Marinum, M. Szulgai). Their cost, given the cost of biologics, seems a weak argument from our point of view.

The sensitivity and specificity of IGRA compared to ITT has been largely studied. Two meta-analyses and systematic literature review have been recently published [6–8]. They concern the sensitivity and the specificity of available tests on the market: quantiferon (Quantiferon-TB Gold, Quantiferon-TB gold in-Tube, Cellestis, Victoria, Australia), and the T-spot.TB test (Oxford immunotech, Oxford, United Kingdom). The sensitivity was determined in populations with bacteriologically proved tuberculosis and in which not all patients were immunodepressed. The specificity was determined in populations with low tuberculosis endemic. There is no gold standard method to define latent tuberculosis. In Pai's meta-analysis [6], the sensitivity of T-spot.TB, determined from 13 studies, was the strongest (90% IC 86%–93%). The sensitivity of quantiferon tests determined from 22 studies was 78% (IC 73% to 82%) for Quantiferon-TB Gold and 70% (IC 63% to 78%) for Quantiferon-TB Gold In-tube. The sensitivity de ITT, determined from 20 studies was 77% (IC 71% to 82%). Seven studies were made on the same population to assess the sensitivity of quantiferon and T-spot.TB. It was higher for T-spot.TB in six of these (difference ranging from 3% to 25%) and identical in the last one. The specificity of Quantiferon without BCG was 99% (IC 98%–100%), and with BCG 96% (IC 94%-98%), and the specificity of T-spot.TB was 93% (IC 86%–100%). The specificity of ITT without BCG was 97% (IC 95%–99%); with BCG it was 59% (46%–73%). The second meta-analysis, made in 2011 par Diel [7] shows the negative predictive value of quantiferon IT (risk of progression of tuberculosis) for 2 years was 99.8% and 97.8% for T-spot.TB. The positivity of IGRA was clearly associated with exposure to tuberculosis patients and not influenced by BCG vaccination contrary to ITT. Nevertheless, in these two meta-analyses the ITT threshold for positivity varied (5 mm, 10 mm, or 15 mm). WE repeated the using the same method than Pai, choosing the studies in which the ITT threshold for positivity was 5 mm [9–18]. The sensitivity of quantiferon was 79% (IC 76%–83%), that of T-spot.TB was 84% (IC 75%–95%), and that of ITT was 69% (IC 65%–73%).

Chang and Leung in their systematic literature review used a different methodological approach [8]. With a threshold set at 90%, the diagnosis of latent tuberculosis may be made using the Quantiferon-TB Gold test or Quantiferon-TB gold in-Tube when positive and excluded by a negative T-spot.TB or quantiferon test (Quantiferon-TB Gold or Quantiferon-TB gold in-Tube).

Numerous studies were dedicated to the concordance analysis of ITT and IGRA in patients with inflammatory rheumatism before anti-TNF treatment [4]. It is difficult to draw conclusions. Indeed, the studied populations are very different concerning: tuberculosis endemic (Turkey, United Kingdom), and BCG vaccination (4% to 100%), the treated disease (RP or all diseases treated by anti-TNF), combined treatments (methotrexate combined with corticotherapy, but also anti-TNF, azathioprine or