

## Clinical Note

### Pulmonary Tuberculosis Associated to Adalimumab: a Study of 3 Cases

José J. Blanco Pérez,<sup>a,\*</sup> Ángel Aranda Torres,<sup>a</sup> José M. Pego Reigosa,<sup>b</sup> Manuel Núñez Delgado,<sup>a</sup> Enrique Temes Montes,<sup>a</sup> and José Luis Guerra Vales<sup>a</sup>

<sup>a</sup>Servicio de Neumología, Hospital Meixoeiro, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain

<sup>b</sup>Servicio de Reumatología, Hospital Meixoeiro, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain

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#### ABSTRACT

Tumour necrosis factor-alpha antagonist drugs represent a significant advance in the treatment of inflammatory diseases, such as rheumatoid arthritis, spondyloarthropathies, and intestinal inflammatory disease. The increase in tuberculosis with infliximab is known, but there is less data available that specifically associates tuberculosis with adalimumab. We present the cases of 2 patients with rheumatoid arthritis and one patient with ankylopoietic spondylitis on treatment with adalimumab, who developed pulmonary and disseminated tuberculosis, despite following the screening and prophylaxis measures recommended in guidelines. We also review the association between treatment with tumour necrosis factor-alpha antagonists and tuberculosis.

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#### Tuberculosis pulmonar en relación con adalimumab: estudio de 3 casos

#### RESUMEN

Los fármacos antagonistas del factor de necrosis tumoral alfa representan un importante avance en el tratamiento de enfermedades inflamatorias como la artritis reumatoide, las espondiloartropatías y la enfermedad inflamatoria intestinal. Se reconoce el incremento de tuberculosis con infliximab, pero disponemos de menos datos que relacionen la tuberculosis específicamente con adalimumab. Presentamos los casos de 2 pacientes con artritis reumatoide y un paciente con espondilitis anquilopoyética en tratamiento con adalimumab, que desarrollaron tuberculosis pulmonar y diseminada a pesar de seguir las medidas de cribado y profilaxis recomendadas por las guías, y revisamos la asociación entre el tratamiento con antagonistas del factor de necrosis tumoral alfa y tuberculosis.

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#### Introduction

Tumour necrosis factor-alpha (TNF- $\alpha$ ) is a proinflammatory cytokine produced by macrophages and T lymphocytes, which intervene in the pathogeny of several chronic inflammatory diseases.<sup>1</sup> It is an important component in the immunological response inducing the differentiation of monocytes to macrophages, and has a key role in the formation and maintenance of the granuloma.<sup>2</sup> This group of biological drugs includes infliximab (mouse-human chimeric monoclonal antibody), etanercept (fusion protein of the

soluble portion of the human TNF receptor and the Fc portion of immunoglobulin G<sub>1</sub>, which functions by neutralising the TNF) and adalimumab (recombinant human monoclonal antibody that binds to TNF- $\alpha$ , preventing it from activating its p55 and p75 membrane receptors). Multiple complications and adverse effects have been identified with the use of infliximab, some insufficiently proven, such as demyelinating encephalopathy, neoplasia and heart failure and others such as infections (bacterial, fungal and tuberculosis) with more conclusive data.<sup>3-8</sup> There is less data in relation to adalimumab, although some studies have recorded similar risks.<sup>5</sup> We present three cases of patients under treatment with adalimumab who developed tuberculosis, despite following the recommendations in the clinical guidelines.

\*Corresponding author.

E-mail address: josejesus.blanco.perez@sergas.es (J.J. Blanco Pérez).

## Clinical Observation

### Case 1

The patient is a 49 year old woman, diagnosed with rheumatoid arthritis (RA) at 40, treated with methotrexate and low dose steroids and, from February 2006, with adalimumab (subcutaneous route - 40mg fortnightly). The RA was in remission. The tuberculin test and boosted reaction were both negative. The dose of steroids had been increased to 10mg of prednisone after the presence of a condition indicative of erythema nodosum 3 months earlier. She attended the emergency service with coughing, profuse sweating and fever, reaching 38° C and a development of 4 weeks. She was diagnosed with community-acquired pneumonia and was treated with amoxicillin-clavulanic acid, with no improvement and returned to the emergency service. The chest x-ray displayed a consolidation in the lower right lobe. The computerised tomography (CT) displayed a parenchymal consolidation in the lobe (fig. 1). Treatment with levofloxacin resulted in partial clinical and radiological improvement. The fever reappeared seven days later. A sample was taken through sputum induction where acid-alcohol resistant bacilli were detected and the *Mycobacterium tuberculosis complex* culture was positive. Treatment was established with isoniazid, rifampicin and pyrazinamide. The patient was readmitted a week later with vomiting, abdominal pain and jaundice; the hepatic biochemical displayed 7.3U/L bilirubin, at the expense of direct bilirubin; 146U/L aspartate transaminase, 158U/L alanine transaminase, 515U/L alkaline phosphatase and 136U/L gamma-glutamyltransferase. Tuberculostatic treatment was discontinued. Eleven days after admittance, the isoniazid and rifampicin were progressively restored, and streptomycin administered until the sensitivity tests enabled its withdrawal. Posterior evolution of the patient was good and the RA is in remission.

### Case 2

A male 37 year old patient, diagnosed with ankylosing spondylitis at 21. In the previous year adalimumab (subcutaneous route - 40mg fortnightly) had been administered. Previously, after presenting a positive tuberculin test, he had received isoniazid for 9 months. He attended the emergency services three times in one month with



**Figure 1.** Computerised chest tomography displaying parenchymal consolidation in the lower right lobe and pleural effusion.

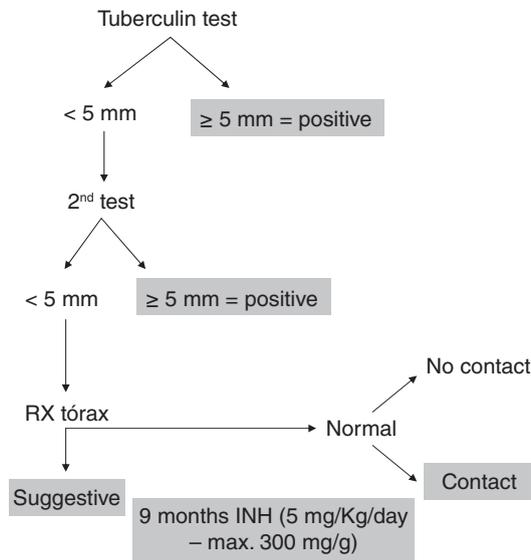
general discomfort, night sweats, dry cough and low fever. His body temperature was 37.8° C in the physical examination and the impression was of gravity. The chest x-ray showed a left parahilar infiltrate and a diffuse bilateral micronoduli pattern. The infiltrate was observed in the posterior segment of the upper left lobe in the CT, as well as bilateral micronodules, bilateral hilar and mediastinal adenopathies, left pleural effusion and spleen and liver with micronodular lesions of up to 1.5cm, all indicative of miliary tuberculosis. The pleural tap revealed clear pleural liquid with 95% lymphocytes, 104U/L adenosine deaminase and 623U/L lactate dehydrogenase. The sputum and urine AFB-smear were negative and the culture positive in sputum and bronchoalveolar lavage for *M. tuberculosis complex*. Treatment was commenced with 3 drugs (isoniazid, rifampicin and pyrazinamide) in low doses, since the transaminase levels were high (aspartate transaminase: 49U/L; alanine transaminase: 132U/L; alkaline phosphatase: 766U/L; gamma-glutamyltransferase: 308U/L). Throughout one month, the transaminase levels progressively normalised and the treatment was continued at full dosage for 6 months; the endurance tests resulted in sensitivity to first-line drugs. The patient's clinical evolution, both from a point of view of the tuberculosis and the spondylitis, has been good.

### Case 3

A 62 year old male patient, diagnosed with RA aged 51. He had a background of pleuropulmonary affectionation with bilateral bullosa disease and spontaneous pneumothorax 5 years earlier. Both the tuberculin test and the booster reaction were negative. He was prescribed subcutaneous adalimumab (40mg a fortnight) 10 months earlier and had also received prednisone (10mg/day). He attended the clinic with an increase in the dyspnoea and 2 month development, which had come about from small efforts and occasional hemoptoic expectoration. He presented bilateral crepitation in the physical examination. The CT displayed bilateral and diffuse micronodular interstitial affectionation of subpleural preponderance, as well as multiple blisters and areas of emphysema of subpleural and centrilobular preponderance. A positive sputum culture was obtained for *M. tuberculosis complex* and treatment was established with 4 drugs, with a good level of tolerance and clinical response.

## Discussion

We present three cases of patients under treatment with adalimumab who developed tuberculosis despite following the prevention recommendations of the Spanish Rheumatology Society.<sup>9</sup> Treatment with anti-TNF- $\alpha$  increases the risk of active tuberculosis up to 5 times. According to the Food and Drug Administration database, the rates of tuberculosis in patients treated with infliximab and etanercept were 54 and 28 per 100,000, respectively, for rates of tuberculosis in the same period of 5.2 to 6.8 cases per 100,000.<sup>6</sup> Most of the cases manifested as extra pulmonary disease, occurring an average of 12 weeks after the first drug infusion and having as additional factors favouring the tuberculosis the administration of other immunosuppressive drugs, a latent or active history of tuberculosis and endemic area origin.<sup>7,8</sup> In a national study based on the BIOBADASER register (Spanish Rheumatology Society Biological Products Database), from a total number of 5,198 patients treated with biotherapy, there were 15 cases of tuberculosis (all in patients with infliximab and only one with adalimumab), which constitutes a rate of 172 per 100,000 patients/years.<sup>3,4</sup> Treatment with immunosuppressive drugs<sup>8</sup> as well as anti-TNF- $\alpha$ , which occurred with 3 of our patients, is not considered sufficient to explain the increase in the reported tuberculosis.<sup>2</sup> Tuberculosis usually occurs a short time after the start of the anti-TNF<sup>7</sup> and it is probable that it represents a reactivation of a latent infection, while when it appears



**Figure 2.** Algorithm of recommendations of the Spanish Rheumatology Society for the prevention of tubercular infection in patients treated with antagonists of the tumour necrosis factor alpha. Shading indicates treatment recommendation. INH: isoniazid.

later usually represents a new infection that progresses directly to active disease.

The Spanish and international rheumatology societies<sup>9</sup> recommend, when the tuberculin test is positive (= 5mm induration), 9 months of isoniazid. If the test is negative, prophylaxis is also recommended when there is remote evidence of disease in the chest x-ray or if there has been close contact with a case of tuberculosis<sup>9-11</sup> (fig. 2). According to the experience accumulated with infliximab, the interval from the start of treatment to the development of tuberculosis is increasing, probably due to the prophylaxis with isoniazid.<sup>7</sup> The time intervals from the introduction of the adalimumab in our 3 patients (of 30, 12 and 10 months) make us think about the possibility of a new infection. Based on these recommendations, a descent of up to 74% of the cases of tuberculosis in patients with RA treated with infliximab<sup>3,9</sup> has been observed, even though in the Sichletidis et al.<sup>12</sup> study, 22.2% of the patients developed tuberculosis despite the appropriate prophylaxis protocol. Our case 2, given that the tuberculin test was positive, received the recommended chemoprophylaxis, although unsuccessfully. The new diagnostic method based on in vitro production of interferon gamma in response to *M. tuberculosis* antigens (IGRA, of *interferon-gamma release assay*) would be especially useful in these patients, in which a negative tuberculin test should not exclude the existence of latent infection,<sup>13-16</sup> and could be used to distinguish true positives from false positives caused by the antitubercular vaccine; however, more research is needed to determine its sensibility and specificity.

The best moment to recommence anti-TNF treatment in the cases of active tuberculosis has not been determined but, in general, it should wait until specific treatment is established, once the sensitivity tests are known and an evident clinical improvement is verified.<sup>10,11</sup> Adalimumab has not been reintroduced in any of our patients to date. After interrupting the anti-TNF- $\alpha$ , a paradoxical worsening of the tuberculosis has been reported (immune reconstitution inflammatory syndrome), that was not observed in any of our patients.

In conclusion, we can point out that neither the appropriate chemoprophylaxis when the tuberculin test is positive (case 2) nor the negativity of this (cases 1 and 2) are an impediment for a close supervision aimed at detecting the presence of tuberculosis. The atypical presence of tuberculosis could cause diagnostic delay. The presence of panniculitis and slight radiological changes in case 1 should have led us to a thorough search for tuberculosis from the start. More data is needed to verify whether the patients with tuberculosis taking adalimumab develop greater hepatic toxicity than the rest (2 of our patients presented it), and if an analytical follow-up is necessary faced with the risk of toxic hepatitis. Communication with a pharmacovigilance service is of maximum importance aimed at gathering all the cases and listing each of the anti-TNFs including the presence of the different complications.<sup>3,17</sup>

**References**

- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med.* 2001;344:907-16.
- Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis.* 2003;3:148-55.
- Gómez-Reino JJ, Carmona J, Descalzo MA, BIOBADASER Group. Risk of tuberculosis in patients with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.* 2007;57:756-61.
- Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.* 2003;48:2122-7.
- Fonseca JE, Canhao H, Silva C, Miguel C, Mediavilla MJ, Teixeira A, et al. Tuberculosis in rheumatic patients treated with tumour necrosis factor alpha antagonists: the portuguese experience. *Acta Reumatol Port.* 2006;31:247-53.
- Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer D. Granulomatous infections diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis.* 2004;38:1261-5.
- Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345:1098-104.
- Raval A, Akhavan-Toyserkani G, Brinker A, Avigan M. Brief communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Ann Intern Med.* 2007;147:699-702.
- Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005;52:1766-72.
- British Thoracic Society Standards of care committee. BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF- $\alpha$  treatment. *Thorax.* 2005;60:800-5.
- Saag KG, Teng GG, Patkar NM, Anuntiylo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008. Recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis and Rheumatism* 2008;59:762-84.
- Sichletidis L, Settas L, Spyrtatos D, Chloros D, Patakas D. Tuberculosis inpatients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lun Dis.* 2006;10:1127-32.
- Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A; the Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, and the Centers for Disease Control and Prevention (CDC). Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR Recomm Rep.* 2005;54:49-55.
- Chen DY, Shen GH, Hsieh TY, Hsieh CW, Lan JL. Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. *Arthritis Rheum.* 2008;59:800-6.
- Malaviya AN, Kapoor S, Garg S, Rawat R, Shankar S, Nagpal S, et al. Preventing tuberculosis flare in patients with inflammatory rheumatic diseases receiving tumor necrosis factor- $\alpha$  inhibitors in India. An audit report. *J Rheumatol.* 2009;36:1414-20.
- Coaccioli S, Di Cato L, Marioli D, Patucchi E, Pizzuti C, Ponteggia M, et al. Impaired cutaneous cell-mediated immunity in newly diagnosed rheumatoid arthritis. *Panminerva Med.* 2000;42:263-6.
- Tubach F, Salmon-Ceron D, Ravaud P, Mariette X, for the RATIO Study Group. French registry of opportunistic infections, severe bacterial infections, and lymphomas complicating anti-TNF- $\alpha$  therapy. *Joint Bone Spine.* 2005;72:456-60.