Clinical Note

Pulmonary Tuberculosis Associated to Adalimumab: a Study of 3 Cases

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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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Introduction

Tumour necrosis factor-alpha (TNF-α) is a proinflammatory cytokine produced by macrophages and T lymphocytes, which intervene in the pathogenicity of several chronic inflammatory diseases. It is an important component in the immunological response inducing the differentiation of monocytes to macrophages, and has a role in the formation and maintenance of the granuloma. 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 G1, which functions by neutralising the TNF) and adalimumab (recombinant human monoclonal antibody that binds to TNF-α, 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. There is less data in relation to adalimumab, although some studies have recorded similar risks.

We present three cases of patients under treatment with adalimumab who developed tuberculosis, despite following the recommendations in the clinical guidelines.
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 positive. 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 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 micronodular 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 it is probable that it is 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.

Discusison

We present three cases of patients under treatment with adalimumab who developed tuberculosis despite following the prevention recommendations of the Spanish Rheumatology Society. Treatment with anti-TNF-α 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. 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 usually occurs a short time after the start of the anti-TNF and it is probable that it represents a reactivation of a latent infection, while when it appears

Figure 1. Computerised chest tomography displaying parenchymal consolidation in the lower right lobe and pleural effusion.
later usually represents a new infection that progresses directly to active disease. The Spanish and international rheumatology societies recommend, when the tuberculin test is positive (>5 mm 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 (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. 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 has been observed, even though in the Sichletidis et al. 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; however, more research is needed to determine its sensitivity 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. Adalimumab has not been reintroduced in any of our patients to date. After interrupting the anti-TNF-α, 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.

References