Rev Port Pneumol. 2011;17(2): 94-95

revista portuguesa de
PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org

CASE SERIES DISCUSSION

Comment to the article: In iximab for treating sarcoidosis patients, Portuguese experience

ComentÆrio ao artigo: In iximab no tratamento da Sarcoidose - ExperiŒncia de um hospital central

The treatment of sarcoidosis encompasses a series of different issues which are related with a variety of clinical presentations, organ involvement and different follow-up. [1] At the time of diagnosis the first treatment decision is which patients to treat, since not every patient needs to be treated. In fact, half of the patients recover spontaneously without any treatment. [1,2] The main indications for systemic treatment include ophthalmologic, neurologic, cardiovascular, renal or laryngeal involvements, severe pulmonary manifestations, lupus pernio and marked hypercalcaemia. [2,3] Corticosteroids are the rst choice when treatment is decided and usually induce disease remission. However some cases are refractory to corticoids, in other circumstances patients need longer time of treatment and/or high doses of this drug or in some cases corticoid toxicity is not tolerated. In these patients, concurrent use of immunosuppressive drugs to increase ef cacy or as a steroid sparing agent should be considered. [1,4] Low-dose methotrexate and azathioprine are the most useful and widely used immunosuppressive drugs in sarcoidosis and are indicated in these circumstances. [4] Moreover, there are patients in which the disease persists in spite of the therapeutic approach or have unacceptable side effects related with the immunosuppressive agents. In this case, an anti-TNF agent may be considered and this constitutes the most frequent reason for prescription in the available literature. [5,6]

Three anti-TNF agents are approved for use in rheumatoid arthritis, ankylosing spondylitis, Crohns disease and psoriasis mainly for its anti-in ammatory effect. While in iximab and adalimumab are monoclonal antibodies targeted against TNF-alpha, etanercept is a direct TNF receptor antagonist. [5,6] TNF-alpha has been shown to play a major pathogenic pro-inflammatory role in inflammatory cell recruitment and activation and in granuloma formation, which makes its therapeutic use in sarcoidosis plausible. [7] In addition to isolated case reports and a few series, two double blind randomized trials have been published showing the bene t of in iximab in sarcoidosis. [8,9] In another study etanercept failed to show any ef cacy in patients with sarcoidosis. [10] Although there are some clinical cases describing a good response to adalimumab there is a scarce amount of data to sustain its use. [11] Based on the current literature, the best anti-TNF agent for treatment of sarcoidosis appears to be in iximab. Aguiar et al describe ten patients with different clinical presentations of sarcoidosis treated with in iximab. This paper adds information about the most relevant issues concerned with the use of anti-TNF alpha in sarcoidosis, such as its ef cacy, doses and duration of the treatment, toxicity, the role in the therapeutic approach and which phenotypes are more likely to respond to this drug. [12] All the patients had failed previously to respond to corticoids and other conventional drugs or had unacceptable side effects, according to the usual procedures. Regarding efficacy, Baughmann et al in 2006 described a randomized placebo controlled trial of 135 chronic pulmonary sarcoidosis patients which received either placebo or infliximab at either 3 mg/kg or 5 mg/kg. All patients were receiving concomitant corticosteroids or immunosuppressive therapy. After 24 weeks and five treatments with infliximab or placebo, the primary end point was achieved with a significant improvement in Forced Vital Capacity (FVC) of 2.5 % in the infliximab arm. Interestingly patients experiencing more severe disease seemed to have a better response to in iximab therapy since their improvement in FVC exceeded 3 %. This result was also achieved in another randomized placebo controlled phase II study realized in 2006 with only 19 patients with pulmonary sarcoidosis, in which patients with lower initial FVC treated with 5 mg/kg of infliximab, assessed at weeks 0 and 2 and open-label infliximab at weeks 6, 14 and 19 had an improvement of 6 % in their absolute vital capacity. [9] Besides the amount

of information related to pulmonary sarcoidosis, there are several case reports and series suggesting TNF-alpha ef cacy in extrapulmonary sarcoidosis. Several case reports confirm that infliximab has been effective especially in neurosarcoidosis and chronic cutaneous disease, including lupus pernio. [13,14] Infliximab has been also described as ef cacious for the treatment of refractory ocular disease in one series of chronic ocular sarcoidosis where other drugs include etanercept had failed. [15] In Baugmann trial, the majority of the patients had extrapulmonary disease, and the clinical improvement was also signi cant. [8] John Doty et al described ten patients with several extrapulmonary involvement in which nine had an objective response to infliximab after conventional treatment had failed. [13] This data is according with Aguiar et al paper, in which ve patients with cutaneous sarcoidosis had an objective response and two out of three patients with neurosarcoidosis had a signi cant response to in iximab. All the patients had thoracic involvement, eight felt improvement and complete resolution was achieved in four. However since the majority of patients had slight pulmonary impairment it is impossible to know if the therapeutic effect was more signi cant in severe patients although one patient with stage IV had a major improvement.

In the in iximab trial by Baughman et al, patients were randomized to receive either 3 mg/kg or 5 mg/kg and the response rate both in pulmonary and extrapulmonary disease was similar.[8] However there are reports of a better response with higher doses either reducing the interval or increasing the dose of in iximab. Otherwise the duration of anti-TNF therapy for a responding patient it is unclear. Besides the risk, the rate of relapse after drug withdrawal remains unknown. Some cases may need a maintenance treatment. In other cases, after discontining infliximab, the return of symptoms can be the sign for reintroducing the drug. In this series of clinical cases, the standard dose was 5 mg/kg and when patients tolerated treatment the duration was up to one year. Since the aim of the paper was primarily the description of the in iximab ef cacy, there is little data about the time after withdrawal, except the mention of two cases in which there was a follow up over eighteen months without need to reintroduce the drug.

Toxicity includes allergic reaction in up to ve percent of patients. [1,8] However the most serious side effect is the increased risk for opportunistic infections and all the patients have to be previously screened for tuberculosis. Aguiar et al reported an overall good tolerance to in iximab, with the exception of one patient who developed organizing pneumonia. All the patients had a negative tuberculin test and bronchoscopy was performed to rule out tuberculosis. The latter procedure is controversial and not recommended in patients with no clinical or radiological signs suggesting tuberculosis according to current documents. At the time these patients were treated the use of tuberculin test to investigate latent tuberculosis was the method of choice but now the use of interferon gamma release assay seems to be more adequate. [16]

Although the role of speci c TNF-alpha-blocking therapies in sarcoidosis is not well defined, the demonstration of complex involvement of TNF-alpha pathway in granulomatous inflammation and also in disease progression adds to the available data regarding its efficacy in sarcoidosis. Infliximab can be considered in cases refractory to the standard therapy or in cases of drug toxicity. However, this approach needs to be supported by a more robust body of clinical evidence not only related with ef cacy and which patients to treat, but also in relation to appropriate doses and treatment duration. These series of cases are therefore a useful contribution.

References

1. Lazar CA, Culver DA. Treatment of sarcoidosis. Semin Respir Crit Care Med. 2010;31:501-18.
2. Keir G, Wells AU. Assessing Pulmonary Disease and Response to Therapy: Which Test? Semin Respir Crit Care Med. 2010;31:501-18.
3. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357:2153-65.
4. Nunes H, Soler P, Valeyre D. Pulmonary Sarcoidosis. Allergy. 2005;60:565-82.
5. Baughman RP. Tumor necrosis factor inhibition in treating sarcoidosis: the American experience. Revista Portuguesa de Pneumonologia. 2007;13:S47-50.
6. Baughman RP, Drent M, Kavuru M, et al. In iximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174:795-802.
7. Antoniu SA. Targeting the TNF-alpha pathway in sarcoidosis. Expert Opin Ther Targets. 2010;14:21-9.
8. Baughman RP, Drent M, Kavuru M, et al. In iximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174:795-802.
9. Rossman MD, Newman LS, Baughman RP, et al. A double-blind, randomized, placebo-controlled trial of in iximab in patients with active pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23:201-8.
10. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest. 2003;124:177-85.
11. Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, et al. Treatment of therapy-resistant sarcoidosis with adalimumab. Clin Rheumatol. 2006;25:596-7.
12. Aguiar M, Maral N, Mendes AC, et al. A. In iximab for treating Sarcoidosis patients, Portuguese Experience. Revista Portuguesa de Pneumologia. 2011;17:85-93.
13. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with in iximab. Chest. 2005;127:1064-71.
14. Rosen T, Doherty C. Successful long-term management of refractory cutaneous and upper airway sarcoidosis with periodic in iximab infusion. Dermatol Online J. 2007;13:14.
15. Smith JR, Levinson RD, Holland GN, et al. Differential ef cacy of tumor necrosis factor inhibition in the management of in ammatory eye disease and associated rheumatic disease. Arthritis Rheum. 2001;45:252-7.
16. Girlanda S, Mantegani P, Baldissera E, et al. ELISPOT-IFN-gamma assay instead of tuberculin skin test for detecting latent Mycobacterium tuberculosis infection in rheumatic patients candidate to anti-TNF-alpha treatment. Clin Rheumatol. 2010;29:1135-41.

A. Morais

Associated Editor, Portuguese Journal of Pulmonology

E-mail: amorais3@hotmail.com