Efficacy of prolonged antimicrobial chemotherapy for brucellar spondylodiscitis

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Abstract

The standard treatment of brucellar spondylitis with a combination of two antibiotics for 6–12 weeks is associated with high rates of treatment failure and relapse. The present study aimed to assess the safety and efficacy of a treatment strategy based on the prolonged administration of a triple combination of suitable antibiotics. Eighteen patients with brucellar spondylitis were treated with a combination of at least three suitable antibiotics (doxycycline, rifampin, plus intramuscular streptomycin or cotrimoxazole or ciprofloxacin) until the completion of at least 6 months of treatment, when clinical, radiological and serology re-evaluation was performed. If necessary, the treatment was continued with additional 6-month cycles, until resolution or significant improvement of clinical and radiological findings, or for a maximum of 18 months. At presentation, the median age was 66 years (range, 42–85 years) with male predominance. The median duration of therapy was 48 weeks (range 24–72 weeks). Treatment was discontinued early because of side-effects in only one patient. Surgical intervention was required for three patients. At the end of treatment all patients had a complete response. After completion of treatment, all patients were followed up with regular visits. During the follow-up period (duration 1–96 months, median 36.5 months), no relapses were observed. In conclusion, prolonged (at least 6 months) administration of a triple combination of suitable antibiotics appears to be an effective treatment for brucellar spondylitis.

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Introduction

Brucellar spondylitis might be a devastating complication because, quite often, it is associated with neurological complications, requires spinal surgery, and results in permanent functional sequelae [1]. Even though it was described back in 1932 [2], there is still controversy regarding major treatment issues, such as the optimal antibiotic regimen, the duration of treatment and the criteria by which to consider the disease as cured [3]. The reason for this confusion is that the existing studies comprise small series of cases, treated and followed very heterogeneously.

In the largest published studies [4–8], various combinations of two antibiotics with known efficacy against *Brucella* were administered for 6–12 weeks, with disappointing results. Alp and coworkers reported that the standard regimen (doxycycline combined with streptomycin) for at least 12 weeks remains the first choice [3]. Solera *et al* treated 35 patients for a median duration of antimicrobial therapy of 120 days, but with high relapse and failure rates (5/35, and 9/35 respectively) [9]. Nevertheless, all these series and a recent meta-analysis [10] made clear that failure rates are much higher when the duration of treatment is 6 weeks or less than when treatment is continued until 12 weeks (43.66% vs. 17.43%). Therefore the duration of treatment suggested by the World Health Organization for acute, uncomplicated brucellosis (6 weeks) is clearly not sufficient for patients with spondylitis. Yet, even 12 weeks of treatment

is not optimal; a recent retrospective study of 96 patients treated for at least 3 months with suitable combinations of antibiotics reported treatment failure rate 20%, attributable mortality 2.6% and 6% of the patients had severe functional sequelae [7]. On the other hand, there are some small, early studies, suggesting that a triple combination of suitable antibiotics administered for 6–8 weeks achieves more acceptable cure rates [11,12].

The high failure and relapse rates observed in patients treated for 6–12 weeks urged three Greek centres to adopt a different treatment and follow-up strategy for brucellar spondylitis based on the several principles: the minimum duration of treatment should be 24 weeks; if there is no clear resolution of clinical and radiological findings the treatment should be continued for up to 72 weeks; the regimen should contain three suitable antibiotics; a complete clinical, serology and imaging work-up should be performed every 6 months, to rule out relapse and to assess the need for further treatment. In the present study, we report the efficacy of this treatment strategy in 18 consecutive patients with brucellar spondylitis.

Materials and Methods

Study population and setting

From October 2000 until December 2009, 11 cases of brucellar spondylitis were diagnosed and followed up prospectively at the Laikon General Hospital, Athens; one case at the General Hospital of Arta, a city in north-western Greece; and six cases at the General Hospital of Tripolis, a city which lies in southern Greece; the last hospital serves an area with a long tradition of sheep farming.

Diagnosis

The diagnosis of brucellosis was established by the clinical findings compatible with brucellosis, positive standard agglutination test (SAT, 1:160 or higher) [13], and/or by isolating *Brucella* species from blood or bone marrow, other body fluids, or tissue specimens. An ELISA for *Brucella*-specific IgM and IgG serum antibodies, as well as the Coombs test, were used as additional diagnostic tools where available. In five cases, computed tomography-guided biopsy of the affected spinal region was performed.

Demographics and laboratory evaluation

The demographic variables recorded at presentation were age, sex, occupation, type of exposure to *Brucella melitensis*, associated illnesses, clinical presentation and diagnostic delay. The baseline haematology studies included total and differential white blood cell counts, haemoglobin levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and biochemistry profile.

Radiographic studies

Diagnosis of spondylitis was confirmed by magnetic resonance imaging (MRI). Findings suggestive of spinal involvement were decreased signal intensity in the vertebral bodies on T1-weighted images, increased signal in the vertebral bodies on T2-weighted images, increase in signal in discs on T2-weighted images, loss of end-plate definition on T1-weighted images and contrast enhancement in the discs on T1-weighted images with gadolinium [14].

Definitions

Spondylitis was defined as infection of the intervertebral disk and the adjacent vertebrae, with or without associated epidural or psoas abscesses [15].

Therapeutic failure was defined as persistent or worsening symptoms and signs of the disease and increasing MRI findings, at the completion of 24 weeks of therapy [4]. Partial remission was considered to have clinical improvement and stable or improved MRI findings (i.e. no new lesions and stable or improved initial lesions). Complete remission was considered as the resolution of all clinical findings (with the exception of mild residual mechanical pain) and resolution or significant improvement of radiological findings of spondylitis.

Relapse was defined as the reappearance of symptoms, new positive blood cultures, and/or worsening imaging findings during the follow-up, after the discontinuation of antibiotics [4].

Sequelae were considered to have occurred when pain, neurological deficits or functional limitation persisted for longer than 6 months after the end of treatment. The severity of clinical sequelae was categorized according to the patient's functional status: mild sequelae, no neurological deficits but pain with exercise, not preventing the patients from performing their usual work or daily activities; moderate sequelae, mild neurological deficits and pain, interfering with patient's ability to work; and severe sequelae, permanent pain requiring bed rest and analgesics, and/or motor or sensorial deficits [4].

Indications for surgery were severe mechanical instability of the affected spine, treatment failure after 24 weeks of antibiotic therapy, large paravertebral or epidural abscesses not responding to medical treatment, cauda equina syndrome, and severe weakness of muscle as a result of collapse of the vertebral body [4,9].

Adverse effects that could result in treatment modification included: hepatotoxicity, defined as a more than five-fold