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Original article

Retrospective study of tolerability and efficacy of linezolid in patients with multidrug-resistant tuberculosis (1998–2014)

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ABSTRACT

Introduction: Although linezolid is known to be effective when used as an adjunct therapy in the treatment of patients with multidrug-resistant tuberculosis (MDR-TB), the clinical experience is limited. In this study the efficacy and adverse effects of linezolid treatment were evaluated.
Methods: A retrospective study of tolerability and efficacy of linezolid in MDR-TB patients was performed in Madrid, Spain. Demographic characteristics, microbiological and clinical features and data on treatment tolerability were collected. Regimens were constructed with a target of prescribing, at least, five anti-tuberculosis agents likely to be effective. Linezolid, at a dosage of 1200 or 600 mg daily, was included to complete the treatment if no other sensitive drugs were available. Vitamin B6 was used to reduce toxicity. Treatment outcome and clinical status at last contact were compared between patients with linezolid-containing regimens and with those without linezolid-containing regimens.
Results: During the period 1998–2014, 55 patients with MDR-TB received treatment. In 21 of these patients, linezolid was added. The median of linezolid administration was 23.9 months (IQT 13.1–24.7). Patients using linezolid showed a greater resistance to drugs, with a median of 6 (IQR 5–7) compared with those who did not use it, with a median of 4 drugs (IQR 3–5) ($p < 0.001$). The median time to sputum culture conversion of the patients in the linezolid group (73.5 days) did not differ significantly from those in the non-linezolid group (61 days) ($p = 0.29$). There were no significant differences in the outcomes of the two patient groups. There were no reported adverse events in 81% of patients assigned to linezolid therapy. Only four patients developed toxicity attributed to linezolid. The most serious adverse event in these patients was anemia observed in the two patients treated with 1200 mg per day. One of them also developed moderate paresthesia. In both cases the dosage was reduced to 600 mg per day, with improvement of the anemia and paresthesias. No patients stopped linezolid therapy.
Conclusion: A daily dosage of 600 mg of linezolid was well tolerated without stopping treatment in any case. The efficacy of the treatment and the outcomes were similar in both the linezolid and non-linezolid group.

Estudio retrospectivo sobre la tolerabilidad y eficacia de linezolid en pacientes con tuberculosis multirresistente (1998–2014)

Palabras clave:
Linezolid
Tuberculosis multirresistente
Evolución
Efectos adversos

RESUMEN

Introducción: Aunque es conocida la utilidad y la eficacia de linezolid cuando se administra para el tratamiento de pacientes con tuberculosis multirresistente (TB-MR), la experiencia clínica actual sigue siendo limitada. En este estudio se analiza la evolución, la eficacia y los efectos adversos del tratamiento con linezolid en pacientes con diagnostico de TB-MR.

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Método: Se realizó un estudio retrospectivo sobre la tolerabilidad y la eficacia de linezolid en pacientes diagnosticados de TB-MR en Madrid, España. Los regimenes de tratamiento se constituyeron con al menos 5 fármacos antituberculosos efectivos. Linezolid (a dosis de 1200 o 600 mg por día) se añadió para completar el tratamiento en los pacientes en los que no existían otros fármacos alternativos sensibles. Se utilizó vitamina B6 para reducir la toxicidad al tratamiento. Se comparó la evolución clínica de los pacientes y los resultados del tratamiento entre el grupo de pacientes tratados con linezolid y el grupo de pacientes que no fueron tratados con este fármaco.
Resultados: Entre 1998 y 2014, 55 pacientes fueron diagnosticados de TB-MR y recibieron tratamiento. En 21 pacientes fue necesaria la administración de linezolid. La media de tiempo de administración de linezolid fue de 23.9 meses (IQR 13.1-24.7). Los pacientes del grupo de linezolid presentaron mayor número de resistencias a fármacos con una mediana de 6 (IQR 5-7), respecto al grupo que no tomó Linezolid [4 fármacos (IQR 3-5)] (p < 0,001). No hubo diferencias significativas entre el tiempo de conversión del cultivo de esputo de los pacientes del grupo de linezolid (73,5 días) frente al del grupo sin linezolid (61 días) (p = 0,29). Tampoco hubo diferencias significativas en la evolución de los dos grupos de pacientes. El 81% de los pacientes que tomaron linezolid no experimentaron efectos adversos atribuidos a la administración de Linezolid. Sólo cuatro pacientes desarrollaron toxicidad secundaria al uso de linezolid. El efecto adverso más importante fue anemia que se presentó en los dos pacientes tratados con 1200 mg al día. Uno de ellos también desarrolló parestesias de grado moderado en miembros inferiores. En ambos casos, la dosis se redujo a 600 mg al día, con mejoría de la anemia y de las parestesias.
Conclusión: La dosis de 600 mg al día de linezolid fue bien tolerada sin necesidad de interrumpir el tratamiento en ningún caso. La eficacia del tratamiento y la evolución de los pacientes fueron similares en ambos grupos.

Introduction

Linezolid is the first oxazolidinone approved for clinical use, which has proved to be effective when added to the treatment of patients with multidrug-resistant tuberculosis (MDR-TB). Linezolid inhibits protein synthesis by binding to the 50S ribosomal subunit of mycobacteria. The drug is rapidly absorbed and well distributed in tissues. The minimal inhibitory concentration of linezolid to *Mycobacterium tuberculosis* is 0.5–1 μg/ml.[1] Although linezolid has a moderate early bactericidal activity against *M. tuberculosis*, it has shown to have excellent efficacy in vitro as well as in mouse model studies against *M. tuberculosis*, including multidrug-resistant and extensively resistant strains.[1] In spite of this discrepancy, linezolid has been used successfully in the treatment of patients with MDR-TB and XDR-TB, with favorable outcome in up to 73–80% of the patients. However, the information was mainly based on retrospective data on patient material.[2,3] Nevertheless these good results, its high price in many countries and the appearance of adverse effects, such as bone marrow toxicity or neuropathy, have resulted in the avoidance of its widespread use. Due to these side events, treatment discontinuation has been necessary in many cases, reaching up to 77% of the patients. When administered in a smaller dosage, an important decrease of adverse effects has been observed and no differences have been found in the patient's outcome.[2]

The aim of this study was to analyze the tolerability and efficacy of the administration of linezolid, when it is used as part of a multidrug-resistant tuberculosis treatment and to compare it with a no linezolid-containing regimen.

Materials and method

Study patients

A retrospective study of a series of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) diagnosed patients was performed in Madrid. We included patients older than 17 years. Standard definitions were used for MDR-TB (i.e., tuberculosis with confirmed phenotypic resistance to at least isoniazid and rifampicin) and XDR-TB-MR (i.e., MDR-TB with additional resistance to any fluoroquinole and at least, 1 of the 3 injectable drugs: capreomycin, kanamycin or amikacin). The patients came from other hospitals, emergency department or primary care in Madrid and they were admitted in the Isolation Ward of Internal Medicine of La Paz-Cantoblanco Hospital in Madrid. At first, the physician responsible performed a clinical questionnaire. Data included demographic characteristics, comorbidity conditions, clinical features and radiographic information.

Microbiological data

Sputum staining and culture were done monthly during the first 6 months and once every two months afterwards until treatment completion. Sputum culture conversion was defined as two consecutive negative sputum samples on solid (Lowenstein–Jensen) medium in patients who were sputum culture positive at diagnosis. Time to culture conversion was defined as time from treatment start to date of the first of two consecutive negative cultures. Surgery was performed in cases of localized disease refractory to medical treatment.

Sputum smear, culture and drugs-susceptibility testing (DST) for first- and second-line drugs of all patients were tested by absolute concentration method on Lowenstein–Jensen medium, in three different microbiology departments (National Center of Microbiology of Majadahonda, in the Mycobacterial Microbiology Department of Gregorio Marañón and La Paz Hospital in Madrid). The MIC of linezolid against *M. tuberculosis* was 1 μg/ml.

Treatment regimens

Regimens were constructed in an individualized treatment determined on the basis of DST results and the prior treatment history. Treatments consisted of four to six active first- or second-line anti-tuberculosis drugs (pyrazinamide and ethambutol whenever it was possible, one injectable agent, one fluoroquinolone and two or more second-/third-line anti-tuberculosis drug).

Linezolid was included when additional drug was needed to complete the treatment and no other sensitive drugs were available. It was administered orally at a dosage of 600 mg to all, but two patients received doses of 600 mg twice a day.