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Efficacy and safety of a new short regimen for treatment of tuberculosis resistant to rifampicin. A pilot study

Eficacia y seguridad de un nuevo esquema corto para el tratamiento de la tuberculosis resistente a rifampicina. Estudio piloto

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ABSTRACT. Introduction: a fundamental problem in the treatment of drug-resistant tuberculosis has been the long duration of treatment regimens; globally successful treatment rates are less than 60%. The World Health Organization has proposed that through operational research new shortened all-oral regimens be tested for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis. **Objectives:** a pilot study was conducted to determine the efficacy of a 4-drug all-oral regimen, through the conversion time of the culture, and the safety based on the presence of adverse reactions grade ≥ 3. **Material and methods:** twenty-six consecutive patients who have received this regimen, were included. Rigorous clinical and bacteriological follow-up was carried out to evaluate efficacy and safety. **Results:** the culture conversion time from the start of treatment was 1.42 ± 0.82 months (six weeks) and the smear microscopy conversion time was 1.75 ± 0.95 months (seven weeks). Regarding the safety of the regimen, 73.1% of the patients reported some type of adverse effect. **Conclusions:** this all-oral regimen shows excellent effectiveness with culture conversion within two months and by including three drugs with sterilizing activity (bedaquiline, levofloxacin, and clofazimine), it offers the possibility of reducing the duration of treatment, which could reduce losses to follow-up. The toxicity of the regimen is significant, and its implementation requires expert management in drug-resistant TB, and rigorous clinical and laboratory monitoring.

Keywords: tuberculosis, drug-resistant, short-course, treatment, efficacy.

RESUMEN. Introducción: un problema fundamental en el tratamiento de la tuberculosis resistente a fármacos ha sido la larga duración de los esquemas de tratamiento; globalmente las tasas de éxito son inferiores a 60%. La Organización Mundial de la Salud ha propuesto la aprobación de nuevos esquemas acortados, todos orales, a través de investigación operacional para el tratamiento de la tuberculosis resistente a rifampicina y multidrogorresistente. **Objetivos:** este estudio piloto fue realizado para determinar la eficacia de un esquema de cuatro fármacos, todos orales, a través del tiempo de conversión del cultivo, y seguridad con base en la presencia de reacciones adversas grado ≥ 3. **Material y métodos:** se incluyeron a 26 pacientes consecutivos que han recibido este esquema. Se llevó a cabo un riguroso seguimiento clínico y bacteriológico para evaluar la eficacia y seguridad. **Resultados:** el tiempo de conversión del cultivo desde el inicio del tratamiento fue de 1.42 ± 0.82 meses (seis semanas) y el tiempo de conversión de la baciloscopia fue de 1.75 ± 0.95 meses (siete semanas). En cuanto a la seguridad del esquema, 73.1% de los pacientes reportaron algún tipo de efecto adverso. **Conclusiones:** este régimen todo oral muestra excelente efectividad con conversión del cultivo antes de dos meses, al incluir tres fármacos con actividad esterilizante (bedaquilina, levofloxacino y clofazimina), ofrece la posibilidad de reducir la duración del tratamiento, lo que disminuirá las pérdidas a seguimiento. La toxicidad es significativa y su uso requiere manejo experto en tuberculosis resistente a fármacos y riguroso monitoreo clínico y de laboratorio.

Palabras clave: tuberculosis, resistente a fármacos, acortado, tratamiento, eficacia.

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INTRODUCTION

A fundamental problem in the treatment of drug-resistant tuberculosis (TB) has been the long duration of treatment regimens.[1] This is one of the factors that contribute to a success rate in the Americas region of less than 60% with traditional treatment regimens and rates of loss to follow-up above 20%.[2] The World Health Organization (WHO) has proposed that, through operational research projects, new shortened all-oral regimens be tested for the treatment of rifampicin-resistant (RR-TB) and multidrug-resistant (MDR-

TB) tuberculosis. The Special Programme for Research and Training in Tropical Diseases (TDR) in close collaboration with the Global TB Programme at WHO has developed ShORRT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis), an operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on health-related quality of life).[3]

The National Tuberculosis Program of Mexico plans to implement a new shortened standardized nine-month regimen with four oral drugs under operational research conditions. To this end, a pilot study was conducted to determine the efficacy of the drug regimen, evaluated through the conversion time of the culture, and the safety based on the presence of adverse reactions grade ≥ 3.

MATERIAL AND METHODS

The subjects with RR-TB/MDR were diagnosed and treated at the Tuberculosis Clinic of the Tijuana General Hospital. The diagnosis was established by molecular (Xpert® MTB/RIF, Cepheid, Sunnyvale, CA) and phenotypic (MGIT, Becton-Dickinson, NJ) methods. The standardized regimen includes four oral drugs, three from group A and one from WHO group B:[4] bedaquiline, levofloxacin, linezolid, and clofazimine. Twenty-six consecutive subjects who have received this regimen, currently indicated in Mexico for 18 months, were included. Subjects underwent a strict protocol to determine the effectiveness of the regimen by smear microscopy and monthly cultures during treatment; to determine the safety of the regimen, clinical evaluation (including visual acuity test and color discrimination ability) and safety laboratory tests (blood count, biochemical profile) were performed monthly. In addition, electrocardiograms at baseline, on day 15 of treatment, and monthly thereafter while the subjects were receiving bedaquiline.

The study was approved by the Institutional Review Board of the Tijuana General Hospital (CONBIOETICA-02-CEI-001-20170526) and performed under the principles of the declaration of Helsinki. Written informed consent was obtained from every participant.

RESULTS

The mean age of the group was 38.2 ± 17.7 years; the majority were male (65.4%). Nineteen subjects (73%) had rifampicin-resistant (RR) tuberculosis and seven multidrug-resistant tuberculosis (MDR-TB). Sixteen subjects (61.5%) had some comorbidity, the most frequent being diabetes (12 cases, 46.1%) and infection by the human immunodeficiency virus (HIV; six cases, 23.1%). Most of the subjects with diabetes presented uncontrolled glucose levels at the time of diagnosis, with a baseline glycosylated hemoglobin (HbA1c) of 7.51 ± 2.9%; 60% of subjects with diabetes had a baseline HbA1c of ≥ 9%. Eleven subjects (42.3%) reported addictions, methamphetamine being (27.7%) the most frequent.

The culture conversion time from the start of treatment was 1.42 ± 0.82 months (six weeks) and the smear microscopy conversion time was 1.75 ± 0.95 months (seven weeks).

Regarding the safety of the regimen, 73.1% of the subjects reported some type of adverse effect, with gastrointestinal adverse reactions being the most frequent (42.3%). Hematologic toxicity attributable to linezolid occurred in six subjects (23.1%) as anemia and/or thrombocytopenia.

During the monthly follow-up, five subjects had a corrected QT interval (QTc) value ≥ 490 ms on at least one occasion; these five subjects (19.2%) required a temporary suspension of bedaquiline due to prolongation of the QTc interval. Twelve subjects (46.1%) presented an increase of ≥ 60 ms compared to the baseline QTc. In general, an adverse reaction made it necessary to adjust the dose of one of the drugs in nine subjects (34.6%) and to suspend a drug in seven cases (26.9%) *(Table 1)*.

DISCUSSION

Globally, only 59% of subjects with rifampicin-resistant tuberculosis who started treatment in 2018 were successful and this figure has not improved much in the last five years.[5] As mentioned, one of the contributing factors to this low success rate is the long duration of traditional RR/MDR TB treatment of 18-20 months. For this reason, shortened oral treatments have been proposed; the results of the TB-PRACTECAL study were recently published, which included a 24-week all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin, with higher success rates than those of the traditional regimen.[6]

The regimen proposed for the treatment of RR-TB/MDR in Mexico as an operational research protocol includes the

Table 1: Most frequent adverse reactions associated with the anti-tuberculosis drugs that make up the regimen.

Adverse reaction	n (%)
Gastrointestinal (nausea, vomiting)	11 (42.3)
Elevated liver enzymes (< 3 times the upper limit of normal)	8 (30.8)
Skin adverse reactions	7 (26.9)
Visual (green/red color discrimination/visual acuity)	7 (26.9)
Hematologic (anemia/thrombocytopenia)	6 (23.1)
QTc prolongation ≥ 490 ms	5 (19.2)
Elevated liver enzymes (≥ 3 times the upper limit of normal)	3 (11.5)

three drugs from WHO group A (bedaquiline, levofloxacin, and linezolid) and one drug from group B (clofazimine) for nine months. This combination demonstrated in our pilot test an excellent bactericidal effect with culture conversion in only six weeks.

As with all second-line drug treatment regimens, adverse effects are reported in the majority of subjects[7-9] when active pharmacovigilance is carried out. The most toxic medication in the regimen is linezolid,[4] with hematologic and neurologic toxicity. Hematological toxicity attributable to linezolid occurred in one out of every four subjects in the form of anemia and/or thrombocytopenia, which in some cases forced the definitive suspension of the drug; similarly, in cases with optic neuritis (26.9%), it was necessary to reduce the dose or permanently suspend linezolid. Bedaquiline, fluoroquinolones (especially moxifloxacin), delamanid, pretomanid, and clofazimine, drugs currently used to treat drug-resistant TB, prolong the QTc interval of the cardiac electrical cycle. QTc prolongation is a risk factor for life-threatening polymorphic ventricular tachycardia (torsade de pointe), and sudden death.[10]

CONCLUSION

This all-oral regimen shows excellent effectiveness with culture conversion within two months, and by including three drugs with sterilizing activity (bedaquiline, levofloxacin, and clofazimine), it offers the possibility of reducing the duration of treatment, which could reduce losses. To follow-up[4] by shortening the treatment from 18 to 9 months. However, the toxicity of the regimen is significant, and its implementation requires expert management in drug-resistant TB, and rigorous clinical and laboratory monitoring. It is important to emphasize that this is a pilot study whose results cannot be extrapolated to the national level.

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