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ORIGINAL ARTICLE

Long-term efficacy of 6-month therapy with isoniazid and rifampin compared with isoniazid, rifampin, and pyrazinamide treatment for pleural tuberculosis

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Abstract

Research into anti-tuberculosis treatment has mainly focused on pulmonary tuberculosis (TB), with few studies on pleural-TB. The aim of the study is to compare the long-term efficacy of a 6-month treatment regimen with isoniazid and rifampicin (6HR) with treatment regimen of isoniazid, rifampicin, and pyrazinamide (6HR2Z) for pleural-TB. A case-control study of 200 HIV-negative patients with pleural-TB prospectively followed in our TB-unit from 1995 to 2018. The primary resistance to isoniazid is < 4% in our geographic area. Pleural-TB diagnosis was based on a positive culture for *M. tuberculosis* (84 patients), presence of caseating granulomas in pleural biopsy (28), or characteristics of pleural fluid (88). A comparative study of demographic and clinical characteristics between the treatment groups was carried out. Out of the 200 patients followed, (112 males, 88 females; mean age 32.9 ± 18.4 years), 99 patients were treated with 6HR regimen and 101 with 6HR2Z. The groups were comparable, except the 6HR2Z had larger size of pleural effusion. All patients completed the treatment. The group treated with 6HR presented fewer adverse effects (15.3%) than 6HR2Z group (33%), $p = 0.005$, and lower frequency of severe hepatic toxicity (5% vs 10.9%). Four patients died from causes other than TB during treatment with 6HR2Z, and all other patients were cured during a monitoring period for 8.4 years (IQRs, 3.3–14.3). Six patients in 6HR and 10 in 6HR2Z developed residual pachypleuritis. 6HR is as effective as 6HR2Z treatment for pleural-TB, with fewer adverse effects.

Keywords Tuberculosis · Epidemiology · Tuberculosis · Pleural tuberculosis · Therapy

Introduction

The effective treatment for tuberculosis (TB) requires the combination of several drugs and an extended treatment duration [1–3]. It is necessary to associate at least three drugs at the beginning to ensure a correct coverage in case there is resistance to some of them [4–6].

M. tuberculosis appears to show chromosomal resistance against drugs, probably through spontaneous mutations. The probability of developing resistance depends on the bacterial population and is different for each drug [7].

Tuberculous pleuritis is triggered by an inflammatory reaction, mediated by T helper type 1 cells, with a few tuberculous bacilli invading the pleural space [8]. It is for this reason that the probability of developing mutations that confer drug resistance is low and the association of isoniazid and rifampin could be a suitable alternative, if the primary resistance to the treatment is unlikely.

Research into anti-tuberculosis treatment has mainly focused on pulmonary TB, with few studies on pleural-TB. Studies conducted years ago did not compare patterns of 3 to 4 drugs, but showed that a 6-month regimen of isoniazid and rifampicin (6HR) was effective in pleural-TB and in the forms of pulmonary-TB with negative acid-fast smears and

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positive sputum culture for *M. tuberculosis* [9–12]. Although these strategies have been disputed as conferring a higher risk of relapse and possibly fuelling the emergence of drug resistance.

The incidence of TB in our healthcare area has decreased over time from 65 per 100,000 in 1995 to 14.7 in 2018, and primary isoniazid resistance is low [13].

The aim of our study is to compare the long-term efficacy of a 6-month treatment regimen of isoniazid and rifampicin (6HR) with treatment regimen of isoniazid, rifampicin, and pyrazinamide (6HR2Z) for pleural-TB.

Methods We have a specific unit to monitor patients with TB in our hospital and an active search of all diagnosed cases of TB is performed in our healthcare area, which has a Caucasian population of 200,000 inhabitants in the Northwest of Spain. From 1995 to 2018, 1700 new cases of TB were diagnosed (212 (12.5%) were pleural-TB). The incidence decreased over time from 65 per 100,000 in 1995 to 14.7 in 2018. Out of 1700 cases, 1023 were confirmed to have a *Mycobacterium tuberculosis*–positive culture and drug sensitivity testing was performed on 1008 of them. Primary resistance was 8/876 (0.9%; CI 95%, 0.3–1.5) for isoniazid and 3/876 (0.3%; CI 95%, 0–0.7%) for rifampicin.

We conducted a case-control study of 200 HIV-negative patients with pleural-TB to compare the long-term efficacy of a 6-month treatment regimen of isoniazid and rifampicin (6HR) with a treatment regimen of isoniazid, rifampicin and pyrazinamide (6HR2Z). When we started the study, the guidelines considered it was not necessary to associate a fourth drug, ethambutol or streptomycin, for the treatment of pulmonary TB when the primary resistance to isoniazid in the community is less than 4% [14]. As the primary resistances in our geographical area remained low, we treated patients with pulmonary TB with three-drug regimens. Treatment options for pleural TB were reported from the infectious unit, and the choice of the regimen was at the discretion of the physician who made the diagnosis of pleural TB.

Patients were prospectively followed in our TB-unit from 1995 to 2018, with informed consent under protocols approved by the Institutional Ethics Review Boards. The trial was performed in accordance with the principles of the Declaration of Helsinki.

For each case, data were collected on underlying disease, symptoms, complete physical examination, pleural fluid analysis, BCG vaccination, tuberculin skin test (TST) status, method of diagnosis, radiographic findings, as well as evaluation of treatment tolerance, compliance, and evolution of the disease.

Confidentiality of the data was ensured by use of an unique, coded survey identification number for each patient. A descriptive and comparative study of the variables between the treatment groups was carried out.

The diagnosis of tuberculous pleuritis was based on the following: (1) positive culture for *Mycobacterium tuberculosis* from pleural fluid or biopsy specimen (84 cases); (2) caseating granulomas in pleural biopsy (28 cases); or (3) characteristics of pleural fluid: pleural exudate with lymphocyte predominance and ADA > 45 IU/L in patients with positive TST (88 cases). We have not used molecular tests for rapid diagnosis and resistance detection before the culture results were available.

Patients with previous anti-TB treatment, purulent pleural effusion suggestive of empyema, and those with associated pulmonary infiltrates on chest x-ray were not eligible to be included.

The treatment regimen consisted of H 5 mg/kg, R 10 mg/kg, and Z 30 mg/kg daily for 6 months.

The treatment was self-administered every day, given as two (Rifinah®) or three-drug coformulated capsules (Rifater®). Therapeutic thoracocentesis and respiratory physiotherapy were performed on patients with extensive effusion that caused dyspnea.

Pleural effusions were classified as mild if they affected less than one-fifth of the hemithorax, moderate if they affected between one-fifth and one-third, and extensive if they affected more than one-third of the hemithorax.

Drug side effects were clinically monitored. Baseline liver enzymes were performed on every patient before treatment was started, on the first and second month of treatment, and if the patient developed symptoms of hepatitis. Severe hepatic toxicity was considered to be an increase of transaminase values more than five times in asymptomatic patients, or more than three times if they presented symptoms suggesting hepatitis.

A chest x-ray was performed in the first month and at the end of treatment. Residual pachypleuritis was defined in a posteroanterior chest x-ray as a pleural space of > 10 mm measured in the lower lateral chest at the level of an imaginary horizontal line intersecting the diaphragmatic dome. A spirometry was performed on patients with residual pachypleuritis; those who developed moderate-severe ventilatory insufficiency were considered for pleural decortication.

After the treatment was completed, a follow-up of the patients was performed by means of telephone consultation and review of the electronic medical record in December 2018 to know if there were any relapses in the illness.

Statistical analysis

Analyses were performed with the use of SPSS software, version 22.0 (IBM). Variables were compared between the 6HR and 6HR2Z groups. Continuous variables are presented as mean and standard deviations or median and interquartile ranges, as appropriate, and were compared with the use of

Student's *t* test or the Mann-Whitney *U* test. Categorical variables are expressed as absolute numbers and frequencies and were compared with the chi-square test, or Fisher's exact test, as appropriate. Two-sided *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Out of 200 patients with tuberculous pleuritis that were followed, (112 (56%) males and 88 females, mean age 32.9 ± 18.4 years (11–95 years)), 99 were treated with the 6HR regimen and 101 with 6HR2Z.

The patients' characteristics were similar between the two treatment groups, except for greater frequency of cough, fever, and greater extension of pleural effusion in those treated with 6HR2Z. The risk factors for developing TB, pleural fluid characteristics, TST status, and method of diagnosis were similar between the two groups treated (Table 1). All strains of *M. tuberculosis* with sensitivity tests performed (48, 57.1%) were susceptible to first-line agents.

All patients completed the treatment. The group treated with 6HR presented fewer adverse effects (15.3%) (rash-pruritus, 4 (4%); digestive intolerance, 6 (6.1%); acne, 5 (5.1%)) than those treated with 6HR2Z (33%) (rash-pruritus, 15 (14.9%); $p = 0.014$; digestive intolerance, 11 (10.9%); acne, 4 (4%); arthralgias, 1 (1%); gout, 1 (1%)] $p = 0.005$, and there was a lower frequency of severe hepatic toxicity (5/99 (5%) vs 11/101 (10.9%)), non-significant difference (Table 2).

There was no difference between the 88 patients with probable TB and those with confirmed pleural TB diagnosis regarding the frequency of adverse effects (17/87 (19.5%) vs. 31/111 (27.9%), $p = 0.18$) or regarding the frequency of severe hepatic toxicity (8/88 (9.1%) vs. 8/112 (7.1%), $p = 0.61$)).

In the 6HR group, it was necessary to modify the regimen and prolong the duration of treatment in four patients (4%): in two, isoniazid was withdrawn due to liver toxicity; in one, rifampicin was discontinued due to fever and rash; and in another patient, rifampicin was discontinued due to drug interaction with other drugs. In the 6HR2Z group, it was necessary to modify the regimen and prolong the duration of treatment in three patients (3%): in one, pyrazinamide was

Table 1 Characteristics of the patients in the therapy groups

Variables	6HR *N* = 99 (%)	6HR2Z *N* = 101 (%)	*p*
Male	57 (57.6)	55 (54.5)	0.67
Female	42 (42.4)	46 (45.5)	
Age, mean ± SD	33.3 ± 17.1	33.1 ± 20.2	0.99
Diabetes	4 (4)	3 (3)	0.72
Gastrectomy	0 (0)	1 (1)	1.00
COPD	2 (2)	2 (1.9)	1.00
Neoplasia	0 (0)	0 (0)	
Immunosuppression	1 (1)	2 (2)	1.00
Etilism	5 (5.1)	7 (6.9)	0.77
Smoking	33 (33.3)	22 (21.8)	0.08
IDUs	2 (2)	1 (1)	0.62
CRI	1 (1)	2 (2)	1.00
Cirrhosis	0 (0)	1 (1)	1.00
Pregnant	3 (3)	1 (1)	0.37
Contact with TBP	30 (30.3)	24 (21.8)	0.20
BCG vaccinated	17 (17.2)	11 (11)	0.23
Cough with expectoration	7 (7.1)	18 (17.8)	0.03
Fever	36 (36.7)	66 (66.7)	< 0.001
Tuberculin skin test positive	83/93 (89.2)	75/95 (78.9)	0.054
Extensive pleural effusion	41 (41.4)	71 (71.0)	< 0.001
Acid-fast staining positive	2 (2)	5 (4.9)	0.45
Culture positive for *M. tuberculosis*	37 (37.4)	47 (46.5)	0.97
Culture negative and caseating granulomas	14 (14.2)	14 (13.9)	0.95

COPD, chronic obstructive pulmonary disease; *Etilism*, drank more than 60 g ethanol at day; *Smoking*, smoked more than 5 cigarettes at day; *IDU*, intravenous drug user; *CRI*, chronic renal insufficiency; *TBP*, pulmonary tuberculosis

Table 2 Evolution of the patients in the therapy groups

Variables	6HR *N* = 99 (%)	6HR2Z *N* = 101 (%)	*p*
Treatment adherence	99 (100)	101 (100)	
Pyridoxine supplement	5 (5)	9 (8.9)	0.41
Adverse effects	15/98 (15.3)	33/100 (33)	0.005
Rash/itching	4 (4)	15 (14.9)	0.014
Digestive intolerance	6 (6.1)	11 (10.9)	0.31
Acne	5 (5.1)	4 (4)	0.45
Arthralgias	0 (0)	1 (1)	1.00
Gout	0 (0)	1 (1)	1.00
Polyneuropathy	0 (0)	0 (0)	
Severe transaminases alteration	5 (5)	11 (10.9)	0.19
Need to modify the regimen	4 (4)	3 (3)	0.72
Corticoids	0 (0)	5 (5)	0.06
Respiratory physiotherapy	20 (20.2)	11 (10.9)	0.08
Death for cause other than TB	0 (0)	4 (4)	
Healing	99 (100)	97 (96)	0.12
Residual pachypleuritis	6/99 (6.1)	10/97 (10.3)	0.31
Relapses	0/99 (0)	0/97 (0)	
Subsequent development of drug-resistant pulmonary TB	0/99 (0)	0/97 (0)	
Follow-up time (years)			
Media ± SD	9.7 ± 4.9	7.5 ± 6.4	0.01
Median (IQ)	10.3 (5.8–14.2)	5 (1.7–14.8)	

withdrawn due to liver toxicity; in one, pyrazinamide and isoniazid were removed due to liver toxicity; and in one, rifampicin was discontinued for jaundice.

No patients died from TB, 4 patients died from causes other than TB during treatment with 6HR2Z, and all other patients were cured, without any case of relapse or subsequent development of drug resistant pulmonary TB during a monitoring period of 8.6 ± 5.8 years (0.5–19.4 years); median 8.4 years; IQR, 3.3–14.3; 66% of the patients were monitored during more than 5 years, and 42% more than 10 years. The monitoring time was longer for the group of patients treated with 6HR (9.7 ± 5 years) than for the group treated with 6HR2Z (7.5 ± 6.4 years).

Sixteen patients (8%), 6 with 6HR and 10 with 6HR2Z, developed residual pachypleuritis, but none of them required decortication.

Discussion

Our results show that 6HR regimen has long-term efficacy equal to the treatment regimen with 6HR2Z for pleural-TB in an HIV-negative population, in a geographic area with low incidence of primary drug resistance. All the patients completed the treatment and relapses or subsequent development of drug-resistant pulmonary TB did not occur during the long monitoring period of the patients.

An extensive experience does not exist with this 6HR treatment regimen with which to compare the results. Some non-comparatives studies performed at the end of the last century showed similar results in a shorter follow-up [11, 12]. Our clinical results are so good that it is difficult to imagine that they can be improved with any other treatment regimen than in the present study.

The adverse effects were similar in frequency and type to those from other reported studies [11, 15, 16]. In general, they were trivial and were corrected with symptomatic treatment or with a temporary discontinuation of the drugs, it was only necessary to modify the treatment in 4 patients [17]. However, we should consider the advantages of using the 6HR treatment regimen which is simpler due to lower number of tablets and it has half of severe hepatotoxicity than 6HR2Z.

Pleural-TB is caused by a few tuberculous bacilli, and although tuberculous pleurisy can resolve spontaneously within a few weeks or months, 43 to 65% of untreated patients will subsequently develop a more serious form of pulmonary or extrapulmonary TB in the following years [18].

Pleural-TB is the most frequent site of extrapulmonary TB in geographic areas with intermediate or high incidence of disease, and it happens mostly in young people as a manifestation of early post-primary TB [19, 20]. Although the drug resistance seems to be an increasing problem [21–24], our results indicate that in many patients with pleural-TB, in areas where resistance to first-line drugs is low, it is not necessary to

treat them with the same recommended treatment guidelines for pulmonary TB [2, 3, 17, 25–28].

Research into anti-tuberculosis treatment has mainly focused on pulmonary TB, with few studies on pleural-TB. More studies are needed to confirm the results of our study.

Limitations of the study

Only 56% of the cases were confirmed by culture or histological study; however, it is well known that despite extensive investigations, in a considerable number of patients, the diagnosis may not be confirmed in 24 to 88% of them [29, 30]. In this situation, most authors recommend anti-tuberculous treatment for patients with positive TST and compatible pleural fluid characteristics, after reasonable exclusion of other diagnoses, and then carefully to follow the response of treatment [8].

Patients with large effusions in whom it was not possible to rule out underlying parenchymal involvement on chest x-ray were allocated by the patient's physician more frequently to the 3 drug regimen group. However, none of these patients had a positive smear or sputum cultures, when available.

There was no difference in the indication of treatment with corticosteroids and/or respiratory physiotherapy, although there is a tendency to report them more frequently in patients with more extensive pleural effusion. Corticosteroids and respiratory physiotherapy can contribute to a faster initial improvement of the process but do not seem to influence the degree of residual thickening at the end of treatment [17], as our results reflect.

The open-label design of the study could have introduced bias, but the good clinical evolution in long-term monitoring reinforces the strength of the results.

This study was carried out in a geographic area with a low incidence of primary resistance to drugs and our results may not be generalized to geographical areas with a greater incidence of resistance or with a lack of knowledge about them.

Conclusions

A 6-month treatment regimen with isoniazid and rifampicin (6HR) is as effective as 6HR2Z treatment for pleural-TB in HIV-negative patients, if the likelihood of resistance to treatment and pulmonary involvement are low, and it has the advantages of a lower number of doses, excellent patient compliance, and less frequent drug adverse effects.

Compliance with ethical standards The study has been approved by the institutional research ethics committee and has been carried out in accordance with the ethical standards established in the Declaration of Helsinki of 1964. The informed consent of all the individual participants included in the study was obtained.

Conflict of interest The authors declare that they have no competing interests.

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