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Efficacy of moxifloxacin combined with levofloxacin in the treatment of drug-resistant tuberculosis

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Abstract: Drug-resistant tuberculosis is a clinically common respiratory-borne chronic infectious disease. Fluoroquinolone drugs can inhibit the replication and transcription of bacterial DNA and cause bacteria to die, and the antibacterial spectrum of such drugs is broad, especially for *Mycobacterium tuberculosis*-induced diseases. This article observes and compares the clinical efficacy of levofloxacin and moxifloxacin in the treatment of multidrug-resistant tuberculosis (MDR-TB). At the end of the course of treatment, the treatment success rate was 76.4% in the control group and 68.2% in the treatment group. The difference between the two groups was not statistically significant (P>0.05). The cavity reduction rate was 70.1% in the control group and 62.5% in the treatment group. Adverse reaction rate, the control group was 14.7% and the treatment group was 18.1%. There was no significant difference between the two groups (P <0.05). For multidrug-resistant tuberculosis, levofloxacin tablets and moxifloxacin tablets have similar effects in the treatment of multidrug-resistant tuberculosis, adverse drug reactions, and economically difficult multidrug-resistant patients. Drug sensitivity indicates that they are sensitive to levofloxacin.

Keywords: Levofloxacin, moxifloxacin, multidrug-resistant tuberculosis, adverse reactions.

INTRODUCTION

Multidrug-resistant tuberculosis refers to tuberculosis bacteria infected by patients with tuberculosis. Drug resistance *in vitro* has proven to be at least simultaneously resistant to isoniazid and rifampicin (Bagatini *et al.,* 2011; Cristina *et al.,* 2018). Isoniazid and rifampicin are the two most important drugs for the treatment of tuberculosis. Multidrug-resistant tuberculosis is one of the main reasons for the rise in the global tuberculosis epidemic, and it is also a difficult problem for global tuberculosis control (Subar, 2006; Aparicio *et al.,* 2018). According to a 2019 World Health Organization report estimate, there were an estimated 480,000 new multidrug-resistant cases and 100,000 rifampicin-resistant TB cases worldwide in 2017 (Bergmann *et al.,* 2016). India, China and Russia account for 45% of all 580,000 cases. China has a severe epidemic of drug-resistant tuberculosis and is one of the 30 countries with a high burden of MDR-TB in the world (Chtourou *et al.,* 2015; Otify *et al.,* 2019). The results of a national baseline survey of tuberculosis resistance in China from 2007 to 2008 showed that the rate of drug resistance among patients with bacilli-positive tuberculosis in China was 37.79%, the rate of multidrug resistance (MDR-TB) was 8.32%, and the rate of extensive resistance (XDR-TB) The ratio is 0.68%. According to this estimate, China has 560,000 new cases of drug-resistant tuberculosis, 120,000 multidrug-resistant tuberculosis patients, and nearly 10,000 patients with extensively drug-resistant tuberculosis. Multidrug-resistant tuberculosis has a long treatment time, high cost of treatment, high incidence of adverse reactions, and low cure rate (Ceylan *et al.,* 2016). The average global successful cure rate for multidrug-resistant patients who started treatment in 2013 is 52%. Fluoroquinolones are important drugs for the treatment of multidrug-resistant tuberculosis (Selvin, 2004; Carroll *et al.,* 2012). The WHO guidelines recommend that fluoroquinolones should be included in the treatment of multidrug-resistant patients and that newer generations of fluoroquinolones (levofloxacin, moxifloxacin) should be used (Martins *et al.,* 2018).

Drug-resistant tuberculosis is a clinically common tuberculosis (Dabash *et al.,* 2015; Ajami *et al.,* 2016). The abuse of drugs such as isoniazid and streptomycin is an important reason for drug resistance (Patel, 2016; Pereira *et al.,* 2018). At present, the incidence of drug-resistant tuberculosis in China is getting higher and higher, and the attention of related medical staff is also increasing (Dindo *et al.,* 2004; Ayinuer *et al.,* 2019). The disease itself has a certain degree of drug resistance, and the treatment plan has a situation of long medication time, high cost, and poor treatment effect (Carloto *et al.,* 2019; Maria *et al.,* 2019). Conventional medicines have a poor effect in treating the disease. At present, clinical trials of anti-tuberculosis drugs such as levofloxacin and moxifloxacin have gradually begun. To this end, this article explores the efficacy and safety of levofloxacin and moxifloxacin in the treatment of drug-resistant tuberculosis.

MATERIALS AND METHODS

Selection criteria

(1) Volunteer to participate in this study and sign the informed consent; (2) Aged between 18 and 65 years; (3)

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Drug susceptibility test results show that it is multidrug-resistant and sensitive to levofloxacin and moxifloxacin; (4) Non-XDR-TB patients; (5) Chest radiograph Examination showed tuberculosis lesions; (6) The previous treatment with fluoroquinolones and injections did not last more than 3 months or used alone for less than 6 months.

Exclusion criteria

(1) People who have a history of allergies to the research drug or any of its components, or who cannot form an effective regimen;(2) Currently have severe comorbidities (such as: respiratory failure, cardiac insufficiency, etc.)[or liver and kidney function impairment (serum creatinine level, ALT and / Or the AST level is greater than 3 times the upper limit of the reference value); (3) Clinically significant ECG abnormalities (the QT interval of male patients is longer than 430 milliseconds, and the QT interval of female patients is longer than 450 milliseconds); (4) Severe heart and cerebrovascular diseases; (5) Pregnant or lactating women; (6) Those who participated in any other clinical trials within 3 months before clinical research; (7) HIV antibody positive and AIDS patients.

General Information

According to the above criteria, 90 multi-drug resistant tuberculosis patients admitted from January 2018 to June 2019 were selected, and the patients were randomly included in the treatment group and the control group according to the random number table method. In the treatment group, there were 30 males and 15 females, aged 20-60 years, with an average age of (45.3±4.8) years. There were 28 males and 17 females in the control group, aged 19-58 years, with an average of (44.5±4.3) years.

Treatment options

Control group: 3 Z Am Mfx Pto E / 3 Z Am3 Mfx Pto E / 18Z Mf x Pto E. Treatment group: 3 Z Am Lfx Pto E / 3 Z Am3 Lfx Pto E/18Z Lfx Pto E. Description: Z-pyrazinamide Am-amikacin Mfx-moxifloxacin Lfx-levofloxacin Pto-promethionin E-ethylamine butanol, in which amikacin is injected daily for the first 3 months and the last three Months are given every other day.

Moxifloxacin was selected from Bayer Pharma's moxifloxacin tablets, 0.4/day and levofloxacin was selected from levofloxacin hydrochloride tablets produced by Nanjing Zhengke Pharmaceutical Co., Ltd., 0.5 / day. The other two groups of patients were selected from Specification drug, calculated based on kilogram body weight.

Observations

Efficacy monitoring: Bacteriology: All patients undergo sputum smears every month to look for acid-fast bacilli and sputum mycobacterium tuberculosis culture examinations. At 6 months of treatment, the drug sensitivity test was re-examined for patients whose sputum had not been negatively converted. Imaging: All patients undergo chest radiography or CT examination every 2 to 3 months.

Safety monitoring: Blood, urine routine (injection period), liver and kidney function and other biochemical indicators should be checked at least once a month for all patients; Adverse reaction monitoring should be performed for all patients; Application of moxifloxacin Star patients were tested by electrocardiogram; Periodic monitoring of TSH in patients using propylisotonicotin; Periodic monitoring of hearing in patients using injections; Periodic testing of vision and visual field in patients using ethambutol (Santeliz *et al.,* 2019).

Efficacy Evaluation

In this study, sputum mycobacterium tuberculosis culture and imaging examination were used as methods and indicators for evaluating the efficacy of multidrug-resistant tuberculosis.

According to literature reports, the imaging criteria are divided into: Lesions: significant absorption: lesion absorption ≥ 1/2 of the original lesion; absorption: lesion absorption, but <1/2 of the original lesion; unchanged: no significant change in lesion ; Deterioration: enlargement or dissemination of the lesion; Cavity: closed: closed or disappeared; reduction: cavity reduction ≧original cavity diameter 1/2; unchanged: cavity reduction <original cavity diameter 1/2 or cavity increase <original cavity diameter 1/2; increase: the cavity becomes larger than the original cavity diameter 1/2.

Bacteriology determination criteria, according to the World Health Organization standards, are divided into six levels of cure, completion of treatment, failure, death, loss, and inability to evaluate: Cure: the patient completed the course of treatment without evidence of treatment failure, and was in the intensive period After the end, the sputum culture was negative for 3 consecutive times or more, at least 30 days apart. Completion of treatment: The patient completed the course of treatment without evidence of treatment failure, and after the end of the intensive period, there was no evidence that the sputum culture was negative for 3 consecutive times or more, with each interval at least 30 days. Failure: The patient needs to terminate treatment or change the plan permanently (replacement of more than 2 drugs) due to the following reasons, including the inability of the sputum to be negative at the end of the intensive period, the sputum to be re-positive and the fluorine to be found after the continuation period Evidence of resistance to quinolone and injectable drugs and adverse drug reactions. Death: The patient died due to any reason during the treatment. Loss: The patient was untreated or

Table 1: Comparison of the success of the two groups after treatment

Group	n	Number of successful cases after treatment	Success rate after treatment (%)
Control group	42	33	78.57
Therapy group	41	29	70.73

Note: X2 = 0.6747, P = 0.4114> 0.05

Table 2: Comparison of lesion absorption between two groups after treatment

Group	n	Number of lesions absorbed (absorptive + absorbed) after treatment	Lesion absorption rate after treatment (%)
Control group	42	35	83.30
Therapy group	41	32	78.04

Note: X2 = 0.6071, P = 0.4359> 0.05

Table 3: Comparison of cavity shrinkage between two groups after treatment

Group	n	Cavity shrinkage after treatment	Cavity reduction rate after treatment (%)
Control group	42	30	71.42
Therapy group	41	26	63.41

Note: X2 = 0.4811, P = 0.4879> 0.05

Table 4: Comparison of cavity closure between two groups after treatment

Group	n	Number of cavities closed after treatment	Cavity reduction rate after treatment (%)
Control group	42	12	28.57
Therapy group	41	9	21.95

Note: X2 = 0.0583, P = 0.6513> 0.05

Table 5: Comparison of adverse reactions between two groups after treatment

Group	n	Number of cases of drug liver after treatment	Number of gastrointestinal reactions after treatment	Incidence of adverse reactions after treatment (%)
Control group	42	3	4	16.67
Therapy group	42	3	3	14.63

Note: X2 = 0.0649, P = 0.7989> 0.05

the treatment was interrupted for any reason for 2 consecutive months or more. Cannot be evaluated: Including patients referred to other prevention institutions or their treatment outcomes are unknown. Treatment success: including cure and completion of treatment.

Ethical approval

All patients were approved by Ethics Committee of our hospital and signed on the informed consent. Ethical approval number as 18SPCHJ-16.

STATISTICAL ANALYSIS

The treatment data of the two groups were checked with SPSS 21.0 statistical software, the measurement data were expressed with mean ± standard deviation (x±s), and t test was used, the count data were expressed with [n%%], x2 test was used, $P < 0.05$ was statistically significant.

RESULTS

Sputum negative conversion (successful treatment) in both groups

During treatment, 3 patients in the control group were lost to follow-up, and 4 patients in the treatment group were lost to follow-up. There were 42 patients in the control group and 41 patients in the treatment group.

After the course of treatment, the success rate of treatment (including cure and completion of treatment) was judged according to the negative conversion of sputum bacteria. The control group was 78.57% and the treatment group was 70.73%. There was no significant difference between the two groups, P> 0.05 (as show in table 1).

Absorption of lesions in the two groups

After the treatment course, the rate of lesion absorption (absorptive absorption + absorption) was 83.3% in the control group and 78.04% in the treatment group. There was no significant difference between the two groups, P> 0.05 (as show in table 2).

Hole shrinkage in two groups

After the course of treatment, the hollow reduction rate was 71.42% in the control group and 63.41% in the treatment group. There was no significant difference between the two groups, P>0.05 (as show in table 3).

Two groups of holes closed

After the course of treatment, the rate of cavity closure was 28.57% in the control group and 21.95% in the treatment group. There was no significant difference between the two groups, P> 0.05 (as shown in table 4).

Adverse reactions in the two groups

The main adverse reactions during the treatment were drug-induced liver damage and gastrointestinal reactions. The adverse reaction rate was 16.67% in the control group and 14.63% in the treatment group. After symptomatic treatment, it returned to normal and completed the treatment plan. The difference between the two groups was not statistically significant (P>0.05) (table 5).

DISCUSSION

Drug-resistant tuberculosis is a clinically common respiratory-borne chronic infectious disease. Most of the reasons are caused by the unreasonable and irregular administration of antituberculosis drugs and tuberculosis mutations in patients, which makes patients infected with tuberculosis bacteria have data on-or-more than one anti-tuberculosis drug(Touvier *et al.,* 2005; Danir *et al.,* 2017). Studies show that there are more than 20 million tuberculosis cases worldwide, of which there are more than 6 million patients in China, 76% of whom are young and middle-aged, and the drug resistance rate of tuberculosis patients in China has reached 27.8% (Fardeau *et al.,* 2014; Kohlrausch *et al.,* 2018). Tuberculosis has a long treatment time, a low cure rate, an expensive treatment and a high mortality rate (Verdot *et al.,* 2017).

With the occurrence of incompatible use or abuse of related drugs, the drug resistance of *Mycobacterium tuberculosis* has gradually increased, the relapse rate of patients after treatment has increased, the difficulty of treatment has been increased, and the physical health and life safety of patients have been seriously affected (Forero *et al.,* 2018). At present, more and more attention is paid to the treatment of drug-resistant tuberculosis in clinical practice. Both traditional Chinese medicine and western medicine have tried different drug treatment schemes to explore effective treatment methods. Fluoroquinolone drugs can inhibit the replication and transcription of bacterial DNA and cause bacteria to die, and the antibacterial spectrum of such drugs is broad, especially for *Mycobacterium tuberculosis*-induced diseases (Gatter *et al.,* 2015; Isabel *et al.,* 2019). It is worth mentioning that these drugs do not cause mutations in pathogenic bacteria and do not cause cross-resistance with other anti-tuberculosis drugs. They have become the drug of choice for clinical treatment of drug-resistant tuberculosis patients (Ji *et al.,* 2015; Kanninen *et al.,* 2018).

Moxifloxacin (MxFx) is a fourth-generation new buenolone antibacterial drug and its hydrochloride is used clinically (Kellermann *et al.,* 2011; Latino *et al.,* 2012). It was approved by the US FDA in December 1999. In 1997, we applied for clinical research in China. In 2001, the use of 0 moxifloxacin (MXFX) was performed by inhibiting the activity of bacterial DNA gyrase A subunit and topoisomerase IV, blocking the replication of DNA and exerting bactericidal effects (Gao *et al.,* 2010; Henkel *et al.,* 2018). Its chemical structure is characterized by the introduction of a methoxy group at the 8 carbon atom, which increases the drug's ability to bind to bacteria and its ability to penetrate and destroy cell membranes, and it has a strong and long-lasting antibacterial effect (PAE). The bactericidal curve shows that the bactericidal activity of moxifloxacin (MXFX) is concentration-dependent, and its minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) are basically the same (Pilar *et al.,* 2018). MXFX was completely absorbed soon after oral administration, and the absolute bioavailability totaled about 92%. After oral administration of 400 mg, the peak t1 /2 was 0.5-4h (12.0±1.3) h. Moxifloxacin (MXFX) can be quickly distributed to various tissues in the body and mainly binds to plasma albumin (Goldberg *et al.,* 2015). Due to the low protein binding rate, the free peak concentration is> 10 times the MIC (Ohannessian, 2016; Karen *et al.,* 2017). Moxifloxacin (MXFX) can reach high concentrations in the following tissues: lungs (alveolar fluid, alveolar macrophages, bronchial tissues), sinuses (ethmoidal sinus, upper collar sinus, nasal polyps) and inflammatory lesions (spotted scars) Liquid), whose drug concentration exceeds the blood drug concentration (Joanna *et al.,* 2019). MXFX has a high bactericidal activity against Mycobacterium tuberculosis (Norgren *et al.,* 2007; Negron *et al.,* 2019). Its MIC value against anti-M. Tuberculosis is 0.125-0.5μg/mL, and its MIC value against drug-resistant strains is 2-4μg/mL, and it can improve RPT weekly- Times of efficacy. After oral administration of 400 mg, the Cmax value reached 3.42μmL and the concentrations of alveolar epithelial surface lining fluid, alveolar macrophages, and bronchial membranes were 5.9, 54.1, and 2.0μg/mL, respectively, and the AUC value was (39.3±5.35) μg/h /mL. Studies have shown that the early bactericidal activity (EBA) of moxifloxacin (MXFX) is 0.273 1og10 CFU / ml sputum per day, which is similar to that of isoniazid (INH) (0.209 log10 CFU / ml sputum per day)], which is better than ciprofloxacin And ofloxacin. Its 50% live bacteria kill time (vtso) is 0.88 days, which is similar to rifampicin (RFP), but longer than INH (0.46 days). Tanzanian scholar Pletz MW and German scholar Gosling RD (Kohlrausch *et al.,* 2018) also confirmed that moxifloxacin (MXFX) has early bactericidal activity similar to isoniazid (INH) or rifampicin (RFP).

Some scholars also conducted a randomized open single-blind trial in patients with tuberculosis to evaluate the early and prolonged early-stage prolongation of levofloxacin (LVFX), gatifloxacin (GAFX), and moxifloxacin (MXFX) in patients with tuberculosis. Bactericidal activity (Meydani *et al.,* 1998). It is concluded that the early bactericidal activity and prolonged early bactericidal activity of three fluorinolone drugs, LVFX, MXFX, and GAFX, are similar to INH.

Animal experiments have shown that high-dose moxifloxacin (MXFX) intermittent treatment of rat tuberculosis has achieved good results (Tooze *et al.,* 2006; Goldstone *et al.,* 2017). Although the in vitro activity of MXFX is roughly equivalent to that of sparfloxacin ((SPFX), studies of experimental tuberculosis in mice have shown that MXFX has higher in vivo activity than SPFX, and some studies have also shown that moxifloxacin MXFX is the strongest sterilization activity of MTB and it has been proven to have rapid sterilization activity after several months of combined treatment with current -line antituberculosis drugs.

For the lowest inhibitory concentration of *M. tuberculosis*, moxifloxacin (MIC 0.25ug/mL) is better than levofloxacin (MIC 0.5ug/ mL) and the antibacterial activity of moxifloxacin is twice that of levofloxacin. However, moxifloxacin currently only has imported preparations and the price is much higher than domestic levofloxacin tablets. Many multidrug-resistant patients are repeatedly treated for many years, and economic difficulties are difficult. Moxifloxacin is not easily accepted by such patients. And domestic levofloxacin tablets are cheap, and the monthly cost is only 1/8 of that of moxifloxacin tablets.

CONCLUSION

This study shows that moxifloxacin tablets are superior to levofloxacin tablets in sputum negative conversion rate, focus absorption rate, cavity reduction rate, cavity closure rate, etc. in the treatment of MDR-TB, but there is no statistical difference between the two, and there is no statistical difference in adverse reactions between the two, indicating that the curative effect of moxifloxacin tablets in the treatment of MDR-TB is basically the same. This brings hope to the majority of patients with MDR-TB who are suffering from economic difficulties. Drug sensitivity suggests that patients with MDR-TB who are sensitive to levofloxacin can choose levofloxacin with lower price, which will greatly reduce the economic burden of patients and improve the treatment compliance of MDR-TB patients.

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