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Rational Use of Anti-Tuberculosis Drugs in the Chemotherapy Era of Drug-Resistant Tuberculosis

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Abstract

The rational use of existing anti-TB drugs to design a regimen with high efficacy is the premise and guarantees to prevent the occurrence of acquired drug-resistance. The fundamental element is not only to follow the label strictly, but also to give patients off-label use of some drugs according to the principles of guidelines and reliable clinical trial evidences.

Keywords: Infectious disease; Mortality; MDR-TB; Drug-resistant

Mini Review

The chemotherapy of tuberculosis has been facing stern challenge since 1930s. The regimens have developed gradually from single anti-tuberculous (TB) drug in early stage of chemotherapy to the combination of four first-line drugs in 1970s based on biological characteristics of Mycobacterium tuberculosis. Since the standard short-term chemotherapy regimen was recommended by WHO, such fundamental treatment principles as early use, combined drugs, regularly administration, appropriate dose and full-course had run through the whole procedure, which also guaranteed the rational use of anti-TB drugs. Global TB Reports 2013 suggested that the incidence, prevalence and mortality have been falling down worldwide [1]. As one of the 22 TB high-burden countries, China has made tremendous contributions to this favorable declining. According to results of national epidemiological survey between 1990 and 2010 in China, the incidence, prevalence or mortality represented a remarkable decrease [2]. Such a brilliant achievement is closely related to promotion of standard short-term chemotherapy regimen and rational use of anti-TB drugs.

Although some progress has been made in reducing the global TB burden, the increasing incidence of drug-resistant TB (DR-TB) cannot be ignored. The emergence of multi-drug resistance (MDR-TB) is a major threat to global tuberculosis care and control, especially for the extensively drug-resistant tuberculosis (XDR-TB). According to the results of the 2007-2008 Chinese national survey on DR-TB and 5th national epidemiological sample survey of TB in 2010, the prevalence of XDR-TB were 0.68% [3] and 2.1% [2] respectively, which was very shocking. In fact, the rise on MDR-TB epidemic can be traced back to the late 1980s. In 1996, WHO formally proposed chemotherapy of multidrug-resistant tuberculosis [4]. In August of 2002, Chinese Anti-tuberculosis Association published the first guideline for treatment of MDR-TB named "Proposal of MDR-TB Chemotherapy (Trial version)" [5]. To facilitate the treatment of DR-TB, anti-TB drugs had been divided into five groups by the WHO in 2006 for the first time in the "Guidelines for the programmatic management of drug-resistant tuberculosis" [6]. Thereafter WHO revised and made some update in 2008 [7] and in 2011 [8] respectively. In 2013, WHO revised some definitions of tuberculosis and separate rifampicin resistant tuberculosis (RR- TB) [9] from other types of DR-TB because WHO-approved rapid diagnostics (WRD) are being introduced globally? At the same time, studies showed RR-TB usually had poor outcome, even worse than resistant to second-line anti-TB drugs [10]. We can say that the focus of TB treatment has been shifting to the treatment of drug-resistant TB since the beginning of this century, which means chemotherapy of tuberculosis history has turned into a new but tough time. Confronted with the new challenges, we need a new vision to look at the rational use of anti-TB drugs in order to eliminate the drug resistance from the source, which is to cure newly diagnosed TB and drug-resistant TB other than MDR-TB patients.

Following the label

When a prescription medicine is approved, careful attention is paid to the prescription drug labelling [11], also known as the "package insert", which contains all the data from preclinical and clinical trials. Taking medication strictly following the label is the fundamental element of rational use of anti-TB drugs, and it is also an effective safeguard to prevent the occurrence of drug-resistant TB. The typical example is that taking lower-dosage of rifampicin could lead to rifampicin-resistance. In China, according to the label instruction, rifampicin should be taken 0.45 g per day when the body weight<50 kg or 0.6 g per day when the body weight 50 kg. However, it frequently occurred that all the patients take 0.45 g/d regardless of their body weights in practice, which means those who are over 50 kg would take low doses of rifampicin and thus have higher risk of rifampicin-resistance if they keep taking for a long time. Conversely, if those who under 50 kg take rifampicin 0.6 g/d, the adverse effects related to rifampicin like liver injury would very much likely happen, which may cause the discontinuation or irregular use of rifampicin and thus cause failure of chemotherapy. Similar situation happened when fixed-dose combinations (FDCs) are used. Chiang et al. investigated 506 patients prescribed a three-drug FDC, the dosage was too low in 100 (19.8%) and too high in 32 (6.3%). Of 75 patients prescribed a two-drug FDC, the dosage was too low in 15 (20.0%) and too high in 3 (4.0%) [12]. In China, for convenience sake, the dosage of anti-TB drugs usually be labeled into two grades: <50 kg or 50 kg, instead of being calculated

according to the body weight. Physicians who are not well trained or considering poor tolerate of patients to high dose may prescribe low dose. The inadequate intake of the anti-tuberculosis medicines is one of the main factors that associated with emergence of drug-resistant strain in community settings [13].

Off-label use of anti-TB drugs

It is not appropriate to take medicine stick to labels regardless of individual differences of TB patients. For RR-TB, MDR- TB and XDR-TB patients, off-label uses will be inevitable. Several clinical off-label experiences demonstrated the efficacy, safety, and tolerability profile of some antibiotics prescribed for other infectious diseases [14,15]. Among them, the drug most frequently prescribed is the linezolid, which is originally an antibiotic to treat infection caused by Gram-positive bacteria. It has shown good activity against drug-resistant Mycobacterium tuberculosis (*M. tuberculosis*) both in vitro and in vivo [16-18]. A number of case reports and respective studies have been performed to evaluate the efficacy of the regimens containing linezolid in the treatment of MDR and XDR TB [19-21]. The systematic review suggested that linezolid use significantly increased the probability of a favourable outcome [22]. However, it is lacking of dosage instruction during treatment. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ≤ 600 mg versus >600 mg) [22], even a lower linezolid dosage of 300 mg daily apparently achieved good efficacy [23]. Moreover, the optimum duration of linezolid use to treat MDR-TB is still unknown. Fluoroquinolones (FQs) are core drugs in treatment of MDR-TB. They have been proved to have excellent anti-tuberculosis effects since 1980s [24,25] and been used in clinical against tuberculosis including MDR-TB [26] for nearly 20 years. However this indication has never been labeled. One example is that in Japan [27], FQs have not yet been approved for tuberculosis treatment and therefore are not included in "the Standards of Tuberculosis Treatment" established by the government. The costs for FQs are not covered by public subsidies for medical treatment, thus increasing the economic burden for patients, which may in turn cause drop-out.

Second-line injections, like kanamycin and amikacin, are important drugs to treat MDR-TB. The treatment duration can be up to 6-8 months for MDR patients and to 12 months for XDR patients, recommended by guideline [8], which is not instructed by labels. Therefore, MDR-TB patients often receive a very large cumulative dose of injectable agents with significant toxicity. Ototoxicity and nephrotoxicity are both well-recognized adverse effects of injectable treatment, this adverse effect may positively related to the long-term using. A retrospective study in UK of patients initiating injectable antimicrobials for MDR-TB treatment showed among 50 patients, 14(28%) experienced ototoxicity, 9/50(18%) left with long-term hearing loss. Increased age, use of amikacin and decreased renal function were significantly associated with ototoxicity [28].

The other example of off-label use is over-dosage of some anti-TB drugs. As early as eight years ago, WHO suggested the use of high doses (16-20 mg/kg/d) of isoniazid for the treatment of MDR-TB [6]. Though its effect remains debatable, high dose of INH had been used in China as well as other countries, especially when lacking of enough anti-TB drugs to constitute an effective regimen according to the DST results. With an excellent drug concentration in lung and high achievable serum drug levels, high-dose isoniazid may be beneficial when the isoniazid MIC is below 1 mg/L and possibly below 5 mg/L, but there is no beneficial for XDR-TB or FQs-resistant MDR-TB patients [29]. Katiyar's clinical trial [30] suggested MDR-TB patients who received high-dose INH became sputum negative more rapidly than those who did not receive it as well as significantly better radiological improvement without an increased risk of INH toxicity. The data of high-dose isoniazid containing regimen for MDR-TB patients were so limited that the optimal dose and duration are still unknown.

Finally, there is a confusing phenomenon that the tolerance of patients to high dose medicine may differ because of different drug producing place. According to the investigate of Chinese CDC (data not published), MDR-TB patients could tolerate imported amikacin with a dose of 0.5 g-0.75 g/d (<50 kg) or 1 g (50 kg),which differed greatly from domestic amikacin dose, empiracal dosage of which was 0.4 g/d (<50 kg) or 0.6 g/d (50 kg).However, there was no difference of adverse drug reactions rate between these two doses.

Off-label use of an antibiotic was defined as use in an off-label indication or dose or age or duration of administration. Whatever pattern is used to treat TB, the rational approach of anti-TB drugs use should base on the label instruction and integrate with the standard procedures and guidelines. Because off-label indications efficacy is always not tested in large-sample clinical trial and the safety data are also absent for MDR-TB patients, the therapeutic drug monitoring might represent a helpful tool to improve the safety of a drug and, then, the adherence of the patient.

To choose appropriate anti-TB drugs designing effective regimen

How to choose anti-tuberculosis drugs rationally to design an effective regimen for DR-TB is not solely depend on complying with drug labels. There are some general principles should be following recommended by WHO and Chinese anti-TB association [8,31,32]. (1) Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. (2) Never add a single anti-TB drug to a failed regimen, since this "pseudo-combination" is the common cause of multidrug-resistant [33]. (3) Fluoroquinolones and second-line anti-TB injections are first two choices for MDR-TB if the DST result shows no resistance to these drugs. (4) Orally first-line anti-TB drugs: Rifapentine and rifabutin can be used for rifampin-sensitive single or poly-drug resistant tuberculosis, mainly for co-infected patients with by MTB and human immunodeficiency virus (HIV); Pyrazinamide could be chosen as conventional treatment under the condition that drug sensitive test (DST) proved pyrazinamide sensitive. (5) Injections: If DST shows a single- or poly-drug resistant patient is sensitive to streptomycin, streptomycin could be used as priority. But for the RR-TB patients, streptomycin should be avoided because of the high rates of streptomycin resistance in DR-TB patients and higher incidence of ototoxicity even if DST suggests susceptibility. (6) Fluoroquinolones: Add a fluoroquinolone based on DST and treatment history. In cases where resistance to ofloxacin or XDR-TB is suspected, use a higher-generation fluoroquinolone, but do not rely upon it as one of the four core drugs. (7) The sequence for selecting orally second-line drugs is like the following: cycloserine, protionamide and then p-aminosalicylic acid. If two combined drugs are needed, cycloserine plus protionamide are the best option. If three combined drugs are needed, cycloserine+protionamide +aminosalicylate are chosen. (8) Using more than one drug belonged to the same class of drugs at the same time is forbidden. (9)Do not use the drugs for which there is the possibility of cross-resistance. For

example, rifamycin, including rifambutin should not be used for RR-TB patients.

Management of DR-TB, especially MDR-TB and XDR-TB is a major problem from both clinical and public health perspective. Today, under the circumstance that lacking of new highly sterilizing anti-TB drugs, the rational use of existing anti-TB drugs is the precondition to prevent the amplification of drug-resistance as well as design an effective individualized regimen. It is important for physicians of TB to comprehensively understand the characteristics printed on the labels of all five groups anti-TB drugs including their indications, contraindications, dosage, adverse effects administration route and the drug interactions. It is also crucial for them to be familiar with the guidelines of WHO and China, especially the principles of drug selection as well as off-label use of when designing a rational regimen for DR-TB, which will ensure the safety of patients and obtain the maximum therapeutic efficacy.

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