Pulmonary Pharmacology & Therapeutics 32 (2015) 144–148

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Facing multi-drug resistant tuberculosis

Giovanni Sotgiu [a], Giovanni Battista Migliori [b,*]

[a] Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari, Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy
[b] WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, via Roncaccio 16, 21049 Tradate (VA), Italy

ARTICLE INFO

Article history:
Received 20 March 2014
Accepted 17 April 2014
Available online 30 April 2014

Keywords:
Mycobacterium tuberculosis
MDR-TB
XDR-TB
Second-line drugs
Elimination
Stop TB strategy

ABSTRACT

Multi-drug resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* strains resistant to at least two of the most effective anti-tuberculosis drugs (*i.e.*, isoniazid and rifampicin). Therapeutic regimens based on second- and third-line anti-tuberculosis medicines showed poor efficacy, safety, and tolerability profiles. It was estimated that in 2012 the multi-drug resistant tuberculosis incidence ranged from 300,000 to 600,000 cases, mainly diagnosed in the Eastern European and Central Asian countries. The highest proportion of cases is among individuals previously exposed to anti-tuberculosis drugs. Three main conditions can favour the emergence and spread of multi-drug resistant tuberculosis: the poor implementation of the DOTS strategy, the shortage or the poor quality of the anti-tuberculosis drugs, and the poor therapeutic adherence of the patients to the prescribed regimens.

Consultation with tuberculosis experts (e.g., consilium) is crucial to tailor the best anti-tuberculosis therapy.

New therapeutic options are necessary: bedaquiline and delamanid seem promising drugs; in particular, during the development phase they demonstrated a protective effect against the emergence of further resistances towards the backbone drugs. In the recent past, other antibiotics have been administered off-label: the most relevant efficacy, safety, and tolerability profile was proved in linezolid-, meropenem/clavulanate-, cotrimoxazole-containing regimens.

New research and development activities are needed in the diagnostic, therapeutic, preventive fields.

1. Introduction

Tuberculosis is an important, mainly airborne, infectious disease caused by gram-positive bacteria, essentially by *Mycobacterium tuberculosis* [1,2].

It is currently deemed an archaic, never-ending clinical and public health issue. After the Second World War several anti-tuberculosis drugs were produced. Their prescription to tuberculosis patients, concomitantly with significant public health interventions, favoured the improvement of the global epidemiological scenario [3].

An efficacious anti-tuberculosis therapy is equal to a prognostic improvement (*i.e.*, reduction of the mortality) and to a decreased infection rate, and, consequently, to a decreased tuberculosis incidence rate [4].

Unfortunately, the expected epidemiological improvement following the distribution of the anti-tuberculosis drugs has been hindered by several negative variables, including the emergence and spread of *M. tuberculosis* resistant strains [5–9].

2. Epidemiology

HIV/AIDS, tuberculosis, and malaria are considered the most important epidemiological issues worldwide. The possibility of a co-infection, including at least two of them, could represent a further clinical and public health problem, particularly in low- and middle-income countries, where the poverty and the poor organization of the health-care systems are the denominator favouring the persistent spread of those diseases [7,10].

The 2013 World Health Organization global report on tuberculosis highlighted the recent clinical and public health achievements in the control of the disease worldwide, following successful global strategies (*i.e.*, Directly Observed Therapy Short course – DOTS – and Stop TB strategy) [7,11–16].

However, several shortcomings in the implementation and scale-up of the above-mentioned strategies in the national tuberculosis programs, as a consequence of political, social, economic,

* Corresponding author. Tel.: +39 (0)331829404; fax: +39 (0)331829402.
E-mail address: giovannibattista.migliori@fsm.it (G.B. Migliori).

http://dx.doi.org/10.1016/j.pupt.2014.04.006
1094-5539/

and medical issues, hampered the expected epidemiological achievements. Therefore, the goal of the tuberculosis elimination, equal to a tuberculosis incidence rate <1 case per million population cannot be obtained by 2050 without a comprehensive strategy addressing the risk factors associated with the negative outcomes of the national tuberculosis programs [5,7,9,17].

One of the most relevant problems, pointed out in the World Health Organization Stop TB strategy, has been the emergence and spread of the multi-drug resistant tuberculosis (MDR-TB), that is pulmonary and/or extra-pulmonary forms of tuberculosis caused by *M. tuberculosis* strains resistant to at least two of the most potent anti-tuberculosis drugs (*i.e.*, isoniazid and rifampicin). The first case of this form of tuberculosis was described about two decades ago and it was clear the poor prognostic evolution of the patients if compared with those infected by drug-susceptible strains [6,8,14,15,18,19].

The issue of the antibiotic resistance was described more than 60 years ago; however, some infectious diseases caused by drug-resistant strains are successfully treated because clinicians can prescribe effective therapeutic alternatives [20]. In the tuberculosis field, the therapeutic armamentarium is significant, but the efficacy of the anti-tuberculosis drugs cannot be deemed equivalent: drugs which should be administered in cases of drug-resistant tuberculosis forms are less efficacious, expensive, and more toxic. From a clinical perspective, the main consequence is a poor prognosis (*i.e.*, increased mortality), a poor adherence because of the adverse events, a longer duration of drug exposure linked to personal and social problems. From a public health perspective, more human and economic resources should be involved to control the disease and the transmission of the *M. tuberculosis* strains is more difficult to be interrupted because of the long duration of the contagiousness of the index patients [4,7,19,21].

The issue of the drug-resistance is not associated with only one variable and the public health solution should be comprehensive, including numerous stakeholders. Recently, Caminero tried to systematically analyse the etio-pathogenesis of the multi-drug resistant cases in the community settings [22]. He stated that three main factors can be associated with the emergence of drug-resistant strains: the non-implementation of DOTS and DOTS expansion strategies, the insufficient supply or the poor quality of the anti-tuberculosis drugs, and the inadequate intake of the anti-tuberculosis medicines. The first above-mentioned condition is related to the public health system; in particular, the national tuberculosis programs, which are poorly funded and/or managed, cannot favour the implementation or the scale-up of the DOTS Strategy. Missing or inadequate guidelines for the therapeutic approach of the tuberculosis patients, with or without a poor or a missing training of the health-care workers, the non-standardized treatment or the missing monitoring of the bacteriological evolution of the anti-tuberculosis therapy can be the basis of the emergence and spread of drug-resistant strains. On the other side, the inadequate quality or quantity of the anti-tuberculosis drugs, managed by the national tuberculosis programs, or the inadequate administration of an inadequate drug combinations and/or their dosages can be the background of poor drug levels: sub-inhibitory concentrations of the anti-tuberculosis drugs can select the sample of drug-resistant *M. tuberculosis* strains. Together with the health system factors, patient-related variables can be considered: side effects can decrease the quality of life and, consequently, the adherence to the anti-tuberculosis medications; stigma for the disease can represent a factor that could reduce the adherence, particularly when the symptoms improve and the clinical recovery is more evident. Co-morbidities, such as those which give dependency, can decrease the adherence, as well as the economic causes related to the payment of the drugs, or to the transport towards the urban health centres. In some countries a crucial role can be played by the private sectors, which could be significantly influent in the management of the tuberculosis patients.

The additive and/or synergistic effect of two or more variables may explain the current epidemiological estimates, issued by the World Health Organization. The global tuberculosis incidence rate in 2012 was 122 per 100,000, equivalent to a best-estimated incident burden of 8.6 million new cases, ranging from 8.3 to 9.0 million new patients [7].

The multi-drug resistant tuberculosis incidence was estimated to be 450,000 ranging from 300,000 to 600,000 new patients. The mortality attributed to multi-drug resistant tuberculosis was equivalent to 170,000 cases. The majority of the cases are diagnosed in Eastern European and Central Asian countries: it was estimated that in some countries the proportion of multi-drug resistant tuberculosis in previously treated individuals is higher than 50% and higher than 20% in new treated cases (Figs. 1 and 2). It was estimated that 3.6 and 20% of new and previously treated patients are affected by multi-drug resistant tuberculosis. About 84,000 cases were bacteriologically confirmed as MDR-TB and about 10,000 with new molecular diagnostic techniques (*i.e.*, Xpert MTB/RIF): all of them could be treated with second- or third-line anti-tuberculosis regimens; however, only 77,000 patients were administered *ad hoc* drugs. Approximately 10% of the total MDR-TB cases are classified as XDR-TB (extensively drug-resistant tuberculosis, *i.e.* MDR-TB with additional resistances to any fluoroquinolones and to at least 1 s-line injectable anti-tuberculosis drugs – amikacin, capreomycin, and kanamycin-): 92 countries have notified at least one patient with this serious form of the disease [7,18,19]. However, only 48% of those individuals with MDR-TB exposed to anti-tuberculosis drugs were successfully treated; only 34/107 countries reached a treatment success rate of at least 75%. Poor treatment outcomes were frequently high, particularly the death rate and the loss to follow-up [7].

3. Treatment issues

As previously underlined, the secondary anti-tuberculosis drug options show several shortcomings, which could favour the clinical deterioration of the treated patients and relevant public health issues linked to the persistence of the contagiousness, and, then, to a persistent transmission of drug resistant *M. tuberculosis* strains.

It was clearly proved that they are less effective, associated with a higher percentage of adverse events, higher costs, longer exposure duration [4,7,19,21,23].

World Health Organization guidelines recommend complicated anti-tuberculosis therapeutic regimens during the intensive and the continuation phases: in the former pyrazinamide should be administered with a later generation of fluoroquinolone, ethionamide or prothionamide, cycloserine or para-aminosalicylic acid, and second-line injectable drug (*i.e.*, amikacin, capreomycin, kanamycin); one of those drugs can be replaced by a group 5 drug in case of resistance. The conventional drug susceptibility testing for first- and second-line drugs, which requires a quality-assured laboratory, is required to tailor the treatment regimen, though more than one month for the definitive results is requested. In the meantime, patients could be treated on the basis of the suggested World Health Organization standardized regimens, of the most prevalent epidemiological resistance pattern in the setting where the infection presumptively occurs, and of the resistance pattern of the index case (Table 1) [24–26].

The duration of the intensive and of the continuation phases depends on the culture conversion; therefore, a strict bacteriological culture-based follow-up should be in place in the hospital and in the community (*i.e.*, outpatient tuberculosis centres).