International Journal of Antimicrobial Agents 49 (2017) 554–557

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Themed Issue: Resurrection of old antibiotics

# Old antibiotics for emerging multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB)

Philippe Brouqui [a,b], Fanny Quenard [a,b], Michel Drancourt [a,b,*]

[a] Institut Hospital-Universitaire (IHU) Mediterranée Infection, AP-HM, Marseille, France
[b] Aix-Marseille Université, Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes (URMITE), UM63, CNRS 7278, IRD 198, INSERM 1095, Marseille, France

ARTICLE INFO

*Keywords:*
Antibiotics
Multidrug-resistant tuberculosis
MDR-TB
Extensively drug-resistant tuberculosis
XDR-TB

ABSTRACT

Recently, multidrug-resistant tuberculosis (MDR-TB) has become a therapeutic challenge. In addition to drug resistance, drug adverse events, intravenous delivery, cost and availability of some antibiotics in low-income countries have led to a look back to old drugs, especially those efficient against closely related organisms such as *Mycobacterium leprae*. Here we review the available drugs that respect the conditions above and could be upgraded to first-line therapy for treating MDR-TB and extensively drug-resistant tuberculosis (XDR-TB).



## 1. State of the art

Drug-resistant strains of *Mycobacterium tuberculosis* pose a serious obstacle to progress in global tuberculosis (TB) control. Globally in 2015, an estimated 580,000 people developed multidrug-resistant TB (MDR-TB), and among them several hundred were extensively drug-resistant TB (XDR-TB) cases [1]. Some cases of totally drug-resistant TB (TDR-TB) have been reported [2,3]. MDR-TB is defined as a strain that is resistant to both isoniazid and rifampicin, and XDR-TB is defined as a MDR-TB strain that is resistant to any fluoroquinolone and at least one of the three second-line injectable drugs (SLIDs) (i.e. amikacin, capreomycin or kanamycin) [4]. Treatment options are severely limited; the higher the total number of appropriate drugs used in the treatment regimen, the better the outcome. Based on clinical evidence, the World Health Organization (WHO) has recommended a standardised MDR-TB treatment regimen consisting of pyrazinamide plus four drugs including a fluoroquinolone, a SLID, a thionamide and one oral bacteriostatic drug (cycloserine) [4,5]. Owing to the delay between diagnosis and antibiotic susceptibility testing as well as the restricted availability of such testing in developing countries or in developed countries without adapted BSL3/4 laboratory facilities, patients may be treated for a period of weeks up to the entire treatment duration without knowing the antibiotic susceptibility of the causative *M. tuberculosis* strain. It is therefore necessary to take into account the epidemiology of TB resistance in endemic countries in the initial choice of MDR-TB therapy. In Europe, susceptibility testing showed that 16–18% of MDR-TB strains are resistant to quinolones, with 82% and 76% showing intermediate-level resistance to moxifloxacin and ofloxacin, respectively, suggesting that inappropriate quinolone therapy would likely select for highly resistant strains [6]. Rates of antibiotic resistance to ethionamide, pyrazinamide and para-aminosalicylic acid (PAS) were 41%, 47% and 8%, respectively. Among SLIDs, the resistance rate was reported as 77% for streptomycin, 17% for capreomycin and 16% for amikacin [6].

A part from the challenge posed by the choice of an effective empirical antituberculous therapy, another major challenge in these situations is the adverse events due to multiple-antibiotic regimens and their negative impact on the duration of treatment and final outcome [7]. In a recent meta-analysis, adverse events leading to discontinuation of linezolid therapy were observed with a pooled proportion of 15.81% (95% confidence interval = 9.68–23.11%; $P < 0.0001$), with no significant difference between linezolid daily doses (≤600 mg vs. >600 mg) [8]. In another systematic review, peripheral neuropathy was recorded in 31% of patients receiving linezolid [9]. The prevalence of adverse events due to PAS in its new granulated formulation (GranuPAS®) has recently been reported to be of 9%, mainly gastrointestinal [10], leading to therapy interruption in 6% of cases. The mean duration of treatment recommended by the WHO is not more than 8 months of intravenous (i.v.) therapy. Whilst MDR-TB regimens including amikacin are successful, they are associated with 62% hearing loss related to longer length of amikacin therapy and higher dosage [11]. We did not find any report on catheter-related adverse events in MDR-TB treatment, nor related sequelae or death, but a rate of catheter-related bloodstream infection similar to that observed in other situations is likely. In a recent prospective cohort study of peripherally inserted central catheters (PICCs) in oncology, PICC complications occurred in 24.7% of patients (11.7% thrombosis, 2.1% septicaemia, 4.8% site infection, 2.4%

* Corresponding author. Institut Hospital-Universitaire (IHU) Mediterranée Infection, 19-21 Boulevard Jean Moulin, 13885, Marseille, France. Fax: 33(0)04.13.73.20.52.
*E-mail address:* michel.drancourt@univ-amu.fr (M. Drancourt).

http://dx.doi.org/10.1016/j.ijantimicag.2017.02.008
0924-8579/

occlusion and 15.1% catheter removal) [12]. In our experience with 10 MDR-TB patients treated with i.v. amikacin, 6 presented with catheter-related adverse events leading to 3 interruptions of i.v. treatment, with a mean duration of amikacin treatment of 3.6 months (P. Brouqui, unpublished observations). Finally, among 115 XDR-TB patients in South Africa, 161 adverse events were recorded in 67 patients (58%); 23/67 (34%) required modification of treatment and the causative drug was stopped in 19/67 (28%) [7]. One may appreciate that with the few antituberculous drugs available, such adverse events quickly lead to a therapeutic impasse. One study recorded a high rate of loss to follow-up among MDR-TB patients (19.2%; year-wise range 18.3–23.3%), and patients lost to follow-up were more likely to die or to develop more severe and resistant forms of TB [13]. Daily injection, pill burden and adverse drug reactions among others have been reported as major barriers to treatment adherence [14]. Finally, TB and MDR-TB are essentially challenging low-income developing countries.

This situation poses the question of the optimisation of MDR/XDR-TB treatment and the revival of old antibiotics [15]. Ideally, treatment of MDR/XDR-TB should be efficient (optimised TB clearance), with few adverse events (no regimen changes), available orally, with inexpensive, easily available and affordable drugs (feasible in poor social conditions).

## 2. Search strategy

A step-by-step search strategy was performed using several 'open access' databases to emphasise the sensitivity and specificity of the request (PubMed, Web of Science and Google scholar). ClinicalTrials.gov (https://clinicaltrials.gov) was used to assess the most recent ongoing trials. Keywords included MDR-TB, XDR-TB and 'compound'. As compound, old drugs were selected that are available orally and are affordable (a few Euros/day and worldwide availability) [i.e. excluding those that are only deliverable intravenously such as imipenem [16] and expensive drugs (up to €5 daily treatment)] and that have been reported to be evaluated in vitro and/or used in TB treatment at least one time and those used in closely related micro-organisms such as other mycobacteria. Papers were selected based on quality (journal impact factor above 2 and cited half-life), accuracy and their Internet availability free of charge.

## 3. Antibiotics and other non-antibiotic treatments

The following antibiotics were selected for review: clofazimine; sulfonamides; minocycline; amoxicillin/clavulanic acid (AMC); and macrolides. In addition, other non-antibiotic treatments were reviewed.

### 3.1. Clofazimine

Clofazimine is a lipophilic riminophenazine antibiotic first synthesised in 1954 by Barry et al as an antituberculosis drug (Table 1). Whilst in vitro studies showed high anti-TB activity, in the mid-1950s reports of poor in vivo results in animal models, including monkeys, discouraged the use of this drug in TB treatment, but its clinical use in the early 1970s was extended to fight the emergence of *Mycobacterium leprae* resistant to sulfones [17]. Clofazimine does not induce resistance and also inhibits the emergence of resistance to isoniazid in *M. tuberculosis*. In the challenge to fight MDR-TB, this antibiotic has been re-used recently in an MDR-TB treatment observational study in Bangladesh, where regimens containing clofazimine showed high efficacy (69% cure rate) [18]. In a Korean study, 32 patients with MDR-TB and additional resistance to ofloxacin (11 with XDR-TB) were treated with clofazimine-containing regimens, with a lower cure rate (48.4%) [19]. Another recent report showed a cure rate of 38.5% with combination regimens including clofazimine for the treatment of MDR-TB, with mild adverse events [20]. Among 861 patients with MDR/XDR-TB who received a clofazimine-containing regimen, the pooled proportion of adverse reactions requiring discontinuation was reported to be 0.1% and the median frequency of adverse reaction was 5.1%, which is comparable with first-line TB treatment [21]. Adverse reactions most frequently concern skin discolouration (75–100% of cases) and ichthyosis (66% of cases) and are slowly reversible at discontinuation of treatment [22]. Adequate dose management would help to control adverse events, especially photosensitivity and gastric intolerance. However, low market availability [4] and cost are currently important barriers that need to be overcome for universal use of this drug [21].

### 3.2. Sulfonamides

Between the late 1930s and early 1950s, sulfonamides and sulphanilamide were used as monotherapy in the treatment of TB with some success [23]. However, because streptomycin and isoniazid were better antituberculous drugs, sulphonamide use was not prolonged [15]. The revival of sulphamethoxazole (SMX) in TB was first suggested by its efficacy in preventing TB in patients with human immunodeficiency virus (HIV) infection receiving trimethoprim/sulphamethoxazole (TMP/SMX) to prevent *Pneumocystis jirovecii* infection [24]. In a trial evaluating the efficiency of MDR-TB treatment in two cohorts of Nigerian HIV-negative and HIV-positive patients, TMP/SMX prophylaxis demonstrated a significantly shorter time to sputum conversion [25]. Death in TB/HIV co-infected patients during TB treatment was associated with not receiving TMP/SMX prophylaxis (adjusted odds ratio = 3.35) [26]. Several recent studies confirmed the in vitro susceptibility both of sensitive and resistant TB strains to TMP/SMX [27] and that susceptibility does not appear to change with time [28]. It was further demonstrated that the sulphonamide compound (SMX) only is efficient and that the minimum inhibitory concentrations (MICs) of SMX for *M. tuberculosis* range between 4.75 μg/mL and 25 μg/mL [28–30]. Moreover, a synergistic effect of SMX has been reported in vitro with rifampicin [30]. Clinical evidence of the efficacy of SMX regimens in MDR-TB is scarce [27,31]. In a study of 10 HIV-negative patients infected with MDR-TB, Alsaad et al report that at a dose of 480 mg of TMP/SMX (median dosage 6.5 mg/kg) once daily for a median treatment period of 381 days, 8 of 10 patients successfully completed treatment with no sign of recurrence and 2 patients were still under treatment on the day of paper release. The treatment was safe and well tolerated [32]. Trials on the efficacy of TMP/SMX are underway. As SMX alone is efficient and some adverse events are link to the TMP compound, we tested in the laboratory 5 type strains and 55 clinical isolates of *M. tuberculosis* for susceptibility to TMP, TMP/SMX and sulfadiazine.

**Table 1**
Summary of the main characteristics of the most well described drugs available for multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB) treatment.

| Drug | In vitro activity | Reported cure in MDR-TB | Daily dose (mg) | Adverse events | Discontinuation | Worldwide availability | Daily cost (€) in France |
|---|---|---|---|---|---|---|---|
| Clofazimine | Good | Yes | 100 mg | Mild (5%) | 0.1% | Low | 0.35 |
| Sulfadiazine | Very good | Yes | 500 mg × 8 | Low | Unknown | Good | 1.12 |
| Minocycline | Good | Yes | 100 mg × 2 | Low | Unknown | Good | 0.80 |