Tuberculosis elimination, patients’ lives and rational use of new drugs: revisited

To the Editor:

The World Health Organization (WHO) has recently published a framework on tuberculosis (TB) elimination opening debates on elimination and multidrug-resistant (MDR)-TB [1, 2]. The document highlights MDR-TB as a core area, emphasising the moral duty of preventing the selection of MDR-TB (by treating susceptible cases correctly with first-line drugs) and the necessary efforts to treat it when diagnosed. Unfortunately, treating MDR- and extensively drug-resistant (XDR)-TB is much more onerous, lengthy and terribly expensive; treatment outcomes remain suboptimal, adverse events being frequent and severe [3–6]. The availability of new drugs has offered new possibilities for saving patients who were not previously treatable and posed new challenges related to their rational use in order to prevent selection of resistant strains of Mycobacterium tuberculosis [7–10].

The aim of this report is to describe a patient’s 22-year ordeal with TB. He was treated for two decades unsuccessfully until the advent of new active drugs. We hope that this case will serve as a scenario to emphasise the importance and moral obligations of physicians not to foster resistance, as well as to conserve new drugs for subsequent generations.

In the 1990s, the approach to the treatment of resistant TB differed greatly and was based on the second-line TB drugs available at the time, in an era preceding the development of specific guidelines [11], and before the availability of new “off-label” drugs (linezolid and imipenem).

The patient in question is a HIV-negative Italian man, who was 32 years of age at the time of MDR-TB diagnosis (March 1991). He had been previously treated for pulmonary nodular TB between 1985 and 1991. He had no known risk factors or contacts for TB. He was transferred to the MDR-TB reference hospital in Sondalo, Italy, in March 1991 when his condition deteriorated following retreatment with first-line drugs and ciprofloxacin (table 1), a single active drug added to a failing regimen.

On admission he was sputum smear positive (grade 4+) and culture positive (20 colonies in solid medium); he was resistant to all first-line drugs, para-aminosalicylic acid (PAS) and terizidone, with susceptibility to ofloxacin and capreomycin. The disease had progressed, with bilateral nodular infiltrates with cavities in the upper left lobe. The initial regimen included amikacin, clofazimine, ofloxacin and PAS; he also underwent bisegmentectomy of the left upper lobe in November 1991.

During his treatment, the patient was admitted 24 times (664 days) between 1991 and 2005, remaining sputum smear and culture positive throughout, while adhering strictly to therapy. In August 1992 (10th admission), he developed resistance to kanamycin; in October 1999, to ethionamide; in October 2000, to pyrazinamide; and in July 2001, to ciprofloxacin. In November 2001 (24th admission), exhausted, he refused to be treated any further and was isolated in his home.

In March 2005, he was admitted in a critical condition (26th admission) with disseminated TB, a miliary pattern on chest radiography, epididymitis and Pott’s disease, as well as sputum smear (4+) and culture positivity (200 colonies). However, the patient did manage to survive till new active and effective drugs became available.

A salvage regimen was initiated composed of linezolid (600 mg twice a day), imipenem (500 g four times a day), terizidone, ethambutol and clarithromycin. The first two drugs in the regimen were introduced in the TB armamentarium for salvage therapy in 2005 [12].

After 404 days of the salvage regimen, linezolid was stopped due to development of severe anaemia, while imipenem was interrupted after 428 days (hospital administered) without adverse events reported (28th admission); continuation-phase treatment continued with terizidone, ethambutol, clarithromycin and moxifloxacin. The latter was newly available and added despite ciprofloxacin resistance. The patient sputum smear converted 72 days and culture converted 127 days (table 1) after starting the salvage regimen.

At the end of August 2007, 29 months after commencing the salvage treatment with two unlicensed drugs in his optimised background regimen, the patient was declared cured according to the WHO definition [11]. As of today, the patient (who has since fathered two children) is well and has long since resumed a normal working life.
# Table 1: Treatment history of a patient diagnosed with multidrug-resistant (MDR) tuberculosis (TB) in 1991, with available drugs till 2005, then with a salvage regimen approach, finally being cured after 707 days of hospital admission, surgery and administration of 15 different drugs

<table>
<thead>
<tr>
<th></th>
<th>Chest radiography</th>
<th>Resistance pattern on drug susceptibility test</th>
<th>Treatment</th>
<th>Sputum smear (grading)</th>
<th>Culture (colonies n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When TB was probably susceptible to all drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Nodular monolateral lesions (upper left lung)</td>
<td>Not performed</td>
<td>H, R, E</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>1986</td>
<td>Cavity (upper left lung)</td>
<td>Not performed</td>
<td>H and R, then E and Cfx</td>
<td>Positive on bronchoaspirate</td>
<td>Positive</td>
</tr>
<tr>
<td>1991</td>
<td>Cavities (worsening)</td>
<td>Not performed</td>
<td>Transfer to Sondalo reference hospital</td>
<td>Not performed</td>
<td>Not performed</td>
</tr>
<tr>
<td><strong>From MDR- to XDR-TB, treating with second-line anti-TB drugs available at the time</strong></td>
<td></td>
<td></td>
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<tr>
<td>August 1992</td>
<td>Same as previous</td>
<td>+Km</td>
<td></td>
<td>Positive for the entire period</td>
<td></td>
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<tr>
<td>October 1999</td>
<td>Same as previous</td>
<td>+Eto</td>
<td></td>
<td>Positive for the entire period</td>
<td></td>
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<tr>
<td>October 2000</td>
<td>Same as previous</td>
<td>+Z</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>July 2001</td>
<td>Bilateral cavities</td>
<td>+Cfx</td>
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<tr>
<td><strong>When XDR-TB, with a salvage regimen comprising newly available off-label drugs</strong></td>
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<tr>
<td>March 2005 to August 2007</td>
<td>Bilateral cavities</td>
<td>H, R, S, E, Z, Cfx, Eto, Km, PAS, Trd</td>
<td>E, Mfx, Clr, Imi, Trd, Lzd, Negative after 72 days</td>
<td>Negative after 127 days</td>
<td></td>
</tr>
</tbody>
</table>

First-line anti-TB drugs are as follows. Group 1 oral drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), rifapentine and rifabutin. The second-line anti-TB drugs are as follows. Group 2 injectable aminoglycosides: streptomycin (S), kanamycin (Km) and amikacin (Amk); group 2 injectable polypeptides: capreomycin and viomycin. Group 3 oral and injectable fluoroquinolones: ciprofloxacin (Cfx), levofloxacin, moxifloxacin (Mfx), ofloxacin (Ofx) and gatifloxacin. Group 4 oral drugs: para-aminosalicylic acid (PAS), cycloserine, terizidone (Trd), ethionamide (Eto), prothionamide, thiopetazone and linezolid (Lzd). The third-line anti-TB drugs are as follows. Group 5: clofazimine, Lzd, amoxicillin plus clavulanate, imipenem (Imi) plus cilastatin and clarithromycin (Clr). XDR-TB: extensively drug-resistant.
This patients’ story, spanning three decades since his first diagnosis with TB, with a total of 707 days in hospital split into 29 hospital admissions, demonstrates the ease of developing MDR- and XDR-TB if initial treatment is not correctly managed. Unfortunately, at the time, many clinicians had relegated the emergence of resistance to streptomycin and isoniazid to the history books, and had forgotten the dangers of adding a single active drug to a failing regimen; the addition of ciprofloxacin to his failing regimen led to resistance and to a cascade effect endangering other agents in the second-line regimen (ethionamide and kanamycin), to which his TB later became resistant.

The causation of TB resistance is multiple and complex. MDR- and XDR-TB can be primary; caused by lack of adherence, drug quality or stock outs; iatrogenic; or related to bacillary burden. The patient was previously treated for TB and may have had resistance from three potential sources, namely primary infection with resistant bacilli, acquisition of resistance during treatment and re-infection with resistant bacilli. Adding single active drugs to a regimen, either through lack of experience or unknowingly from the unavailability of drug susceptibility, is a iatrogenic cause of MDR TB, which is avoidable.

This report highlights how limited treatment options were until recently, and how new drugs offer hope to patients and the importance of using them well. That being said, history runs the risk of repeating itself and we risk losing the precious few new drugs we have through lack of experience in their use. The importance of ensuring adequate treatment in specialised reference centres with infection control measures in place needs to be stressed.

Historically, this was, to our knowledge, the first patient to receive imipenem and linezolid in combination and off label for the treatment of MDR/XDR-TB [12]. Today, we salvage patients with either bedaquiline or delamanid; we are awaiting safety data for their combined use and hope that we will not select resistance to either of them beforehand [13, 14]. It is of utmost importance to use these latter drugs effectively if elimination is ever to be a reality and to stop history from repeating itself [15].

Although the MDR-TB burden is low in absolute terms in low TB incidence countries, similar cases sustained by resistant strains of M. tuberculosis are likely to be seen more frequently in the future. Europe needs to prepare itself to manage them correctly in order to reach elimination.

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The importance of not fostering resistance and conserving new TB drugs for subsequent generations

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Simon Tiberi1,5, Lia D’Ambrosio2,3,5, Saverio De Lorenzo4,5, Pietro Viggiani4, Rosella Centis3 and Giovanni Battista Migliori3

1Division of Infection, Barts Healthcare NHS Trust, London, UK. 2Public Health Consulting Group, Lugano, Switzerland. 3WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Tradate, Italy. 4Eugenio Morelli MDR-TB Reference Hospital, AOVV, Sondalo, Italy. 5These authors contributed equally.

Correspondence: Giovanni Battista Migliori, WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Via Roncaccio 16, Tradate, Varese 21049, Italy. E-mail: giovannibattista.migliori@fsm.it

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References


