Treatment of tuberculosis: have we turned the corner?

The number of multidrug-resistant (MDR) tuberculosis cases officially reported to WHO increased from 29 000 to 53 000 between 2008 and 2010, still representing only 18% of the estimated 290 000 patients potentially identifiable if drug susceptibility testing was done in all notified cases of tuberculosis. A recent study done in Belarus showed a new global record for prevalence of MDR tuberculosis with 35·3% of new patients and 76·5% of previously treated patients diagnosed with the disease. This finding clearly shows how far case mismanagement can affect the chances to control (and eventually eliminate) the disease. Unfortunately, since only a quarter of patients with tuberculosis are treated according to established standards and the proportion of treatment success does not exceed 50%, extensively drug-resistant (XDR) tuberculosis has already been reported in 77 countries and totally drug resistant cases (ie, Mycobacterium tuberculosis strains with resistance to all known drugs) have been recently described in Italy, Iran, and India.

The urgent need for new drugs is obvious. The question the tuberculosis community is anxiously posing is whether, in addition to existing drugs, the most promising compounds in the development pipeline (delamanid, bedaquiline, and PA-824) are as effective as preliminary studies suggested. Gler and colleagues and Diacon and colleagues provided part of the answer when they reported that delamanid in combination with a background regimen developed according to WHO guidelines, is associated with an increase in sputum-culture conversion at 2 months in patients with MDR tuberculosis.

In The Lancet, Andreas Diacon and colleagues point to a new direction in tuberculosis treatment with a universal regimen that would be equally effective against Mycobacterium tuberculosis susceptible and MDR strains. Diacon and colleagues assessed the 14-day early bactericidal activity (EBA) of PA-824-moxifloxacin-pyrazinamide. The mean 14-day EBA of this combination (n=13; 0·233 [SD 0·128]) was significantly higher than that of bedaquiline alone (n=14; 0·061 [0·068]), bedaquiline-pyrazinamide (n=15; 0·131 [0·102]), bedaquiline-PA-824 (14; 0·114 [0·050]), but not PA-824-pyrazinamide (n=14; 0·154 [0·040]), and was comparable with standard treatment (ie, rifampicin, isoniazid, and pyrazinamide with streptomycin or ethambutol; n=ten; 0·140 [0·094]), as reported previously.

Importantly, the...
addition of pyrazinamide increased the activity of bedaquiline and PA-824.

Diacon and colleagues’ study makes several important contributions to the existing body of knowledge. First, treatments seem to be well tolerated and safe, although their study design and sample size does not allow assignment of adverse events to a specific agent. The exclusion of tuberculosis patients with comorbidities and the poor sample-size-related inferential strength are methodologically justified by the early clinical research phase and underline the need for further trials that enrol more heterogeneous and larger cohorts.

Second, the new experimental regimen PA-824-moxifloxacin-pyrazinamide does not include three of the current four first-line drugs, yet still retained activity at least comparable with the current standard WHO category I regimen over the first 2 weeks of treatment. Third, the new regimen seems to have a low potential for interactions with antiretrovirals. New regimens without rifampicin could be beneficial for HIV positive or negative individuals at risk of drug-drug interactions. The lack of activation of the nuclear receptor PXR by rifamycins slows down the transcription of the cytochrome CYP3A4, allowing safe administration of several medicines (eg, prednisolone, hormonal contraceptives) in patients with serious disorders.20 Furthermore, a major advantage of the new rifampicin-sparing regimens will rely on averting the pharmacological interactions between rifampicin and protease inhibitors, CCR-5 receptor antagonists, and non-nucleoside reverse transcriptase inhibitors.21 Fourth, the new regimen seems to have the characteristics necessary to treat both drug-susceptible as well as isoniazid-resistant and rifampicin-resistant tuberculosis cases.

However, two pivotal issues remain to be addressed. First, this novel approach of regimen development will require a careful assessment of toxic effects in future studies. This kind of assessment is of crucial importance before embarking on regulatory approval and, particularly, if one or more novel, unapproved compounds are included in the regimen. Second, in future trials it would be ideal to develop and adopt biomarkers or surrogate markers able to rapidly detect the microbiological efficacy of a new single drug or of a new combination of antmycobacterial drugs, following the successful use of this approach in other infectious diseases such as HIV/AIDS and hepatitis C virus infection.

Although EBA-based studies allow investigation of the sterilising activity of available antituberculosis drugs (assessing the ability to prevent the emergence of resistant strains, in the early stages of the treatment and when the load of viable mycobacteria is elevated), they might be affected by intrinsic unpredictability (related to selected patients’ clinical features and sputum-sampling methods).22 Furthermore, the long-term effect (ie, the reduced rate of relapses) of the regimens cannot be directly investigated.

The next question to pose is whether the new drugs could rapidly treat individuals with latent infection as well as 90% of patients with XDR tuberculosis within 2 months. These outcomes need to be achieved by the new antituberculosis regimens to embark on the elimination phase, which WHO is currently debating.23 The rational use of antibiotics has attracted major attention and was selected as the topic of the 2011 World Health Day.24 Mistakes that have been made with the most effective drugs we have to treat tuberculosis (rifampicin and fluoroquinolones) should be kept in mind.25 The international community has the chance to prevent the misuse of new drugs and regimens. To protect the investment in these drugs, the rational use of antibiotics within strengthened health systems is necessary to avoid the real risk of losing these new agents in a time shorter than that needed to develop them.

*Giovanni Battista Migliori, Giovanni Sotgiu*
World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S Maugeri, Care and Research Institute, Tradate 21049, Italy (GBM); and Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari, Sassari, Italy (GS)

We declare that we have no conflicts of interest.

In The Lancet, Martin Elliott and colleagues report the successful surgical management of an aortotracheal fistula in a 10-year-old boy with congenital tracheal stenosis. The child had undergone patch tracheoplasty and bare metal stent placement 6 days after birth, emergency repair of an aortotracheal fistula and tracheal homograft at age 3 years, subsequent replacement of the homograft for mediastinitis, and multiple interventions and stent placements up until the age of 10 years, when a tracheal stent eroded into the thoracic aorta. Because of the length of the lesion and previous operations, slide tracheoplasty or tracheal resection and primary reconstruction were not possible.

The authors elected to use a tissue-engineered tracheal graft based on a decellularised tracheal scaffold, as previously reported by the same group. At the time of implantation, the scaffold was saturated with granulocyte colony stimulating factor, erythropoietin, and transforming growth factor β and seeded with bone-marrow-derived autologous mesenchymal stem cells and mucosal free grafts. An absorbable polydioxanone stent was used to ensure mechanical stability. During the initial 6 months, the patient maintained a patent airway but needed repeated bronchoscopies and stent placements for tracheomalacia. Over the course of 2 years, the trachea fully epithelialised and reached mechanical stability to the point where no further intervention was necessary 18 months after surgery. Elliott and colleagues report a follow-up of 2 years, during which time the patient returned to school without respiratory complaints and grew over 10 cm in height.

Elliott and colleagues not only report the successful surgical management of a life-threatening disease, but also highlight the clinical need for tissue replacement in children. Most tissue and organ engineering efforts are targeted at adult patients, who suffer from tissue loss because of injury or resection. However, a substantial number of paediatric patients need surgical reconstruction because of congenital malformations. About 3% of newborn babies have structural abnormalities that are present at birth and seriously interfere with viability or physical wellbeing. Among those, congenital heart defects affect about 2% of livebirths, with over 10 000 children per year needing reconstructive surgical intervention. Congenital tracheal and bronchopulmonary malformations occur in about 2% of livebirths and defects involving the genitourinary tract affect 4% of livebirths.

Tissue engineering has been proposed as an alternative technology to provide graft material for surgical augmentation and reconstruction. Translation of this technology in paediatric patients provides a unique set of challenges and opportunities. Clinical use of tissue-engineered vascular grafts as extracardiac total cavopulmonary connection in children with single ventricle physiology has resulted in preserved graft patency without mortality during 5 years of follow-up; stenosis in a subgroup of patients was managed percutaneously. Findings from studies of the use of tissue-engineered heart valves for right ventricular outflow reconstruction showed preserved graft function and adaptive growth during follow-up of 3·5 years. The use of tissue-engineered grafts for cystoplasty in about 2% of livebirths and defects involving the genitourinary tract affects 4% of livebirths.

These initial results show that tissue-engineered grafts can be safely used in paediatric surgery, and that children...