La tuberculose XDR

Dr Matteo Vassallo
Centre hospitalier de Cannes

Meta-Analysis of XDR TB Treatment Outcomes • CID 2010; 51: 6-14.

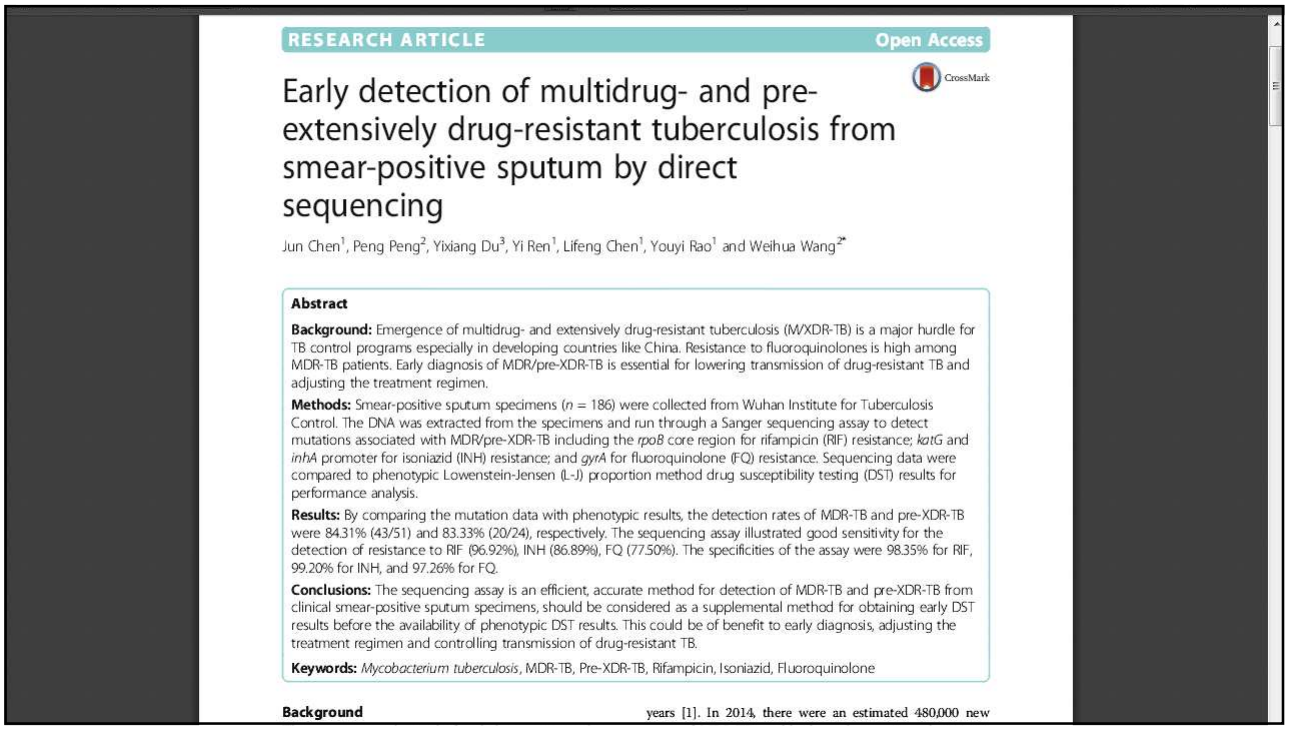
- Estimation du taux de succès dans le modèle à 43.7% (95% CI, 32.8%–54.5%), en dessous des 62%–70% pour les patients avec TB MDR [1,2].
- Mortalité à 20.8% (95% CI, 14.2%–27.3%)—plus élevée que pour TB-MDR [2].

1- Nathanson E, Lambregts-van Weezenbeek C, Rich ML, et al. Multidrug-resistant tuberculosis management in resource-limited settings.Emerg Infect Dis 2006; 12:1389–97.

2- Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009; 9:153–61.

Epidémiologie MDR et XDR

- Chine, Inde, Russie : = 60% du total des cas MDR
- XDR: Azerbaïdjan (13%), Biélorussie (12%), Estonie (19%), Lettonie (13%), Lituanie (17%), Tadjikistan 21%)



RESEARCH ARTICLE Open Access

Early detection of multidrug- and pre-extensively drug-resistant tuberculosis from smear-positive sputum by direct sequencing

Jun Chen[1], Peng Peng[2], Yixiang Du[3], Yi Ren[1], Lifeng Chen[1], Youyi Rao[1] and Weihua Wang[2*]

Abstract

Background: Emergence of multidrug- and extensively drug-resistant tuberculosis (M/XDR-TB) is a major hurdle for TB control programs especially in developing countries like China. Resistance to fluoroquinolones is high among MDR-TB patients. Early diagnosis of MDR/pre-XDR-TB is essential for lowering transmission of drug-resistant TB and adjusting the treatment regimen.

Methods: Smear-positive sputum specimens (n = 186) were collected from Wuhan Institute for Tuberculosis Control. The DNA was extracted from the specimens and run through a Sanger sequencing assay to detect mutations associated with MDR/pre-XDR-TB including the *rpoB* core region for rifampicin (RIF) resistance; *katG* and *inhA* promoter for isoniazid (INH) resistance; and *gyrA* for fluoroquinolone (FQ) resistance. Sequencing data were compared to phenotypic Lowenstein-Jensen (L-J) proportion method drug susceptibility testing (DST) results for performance analysis.

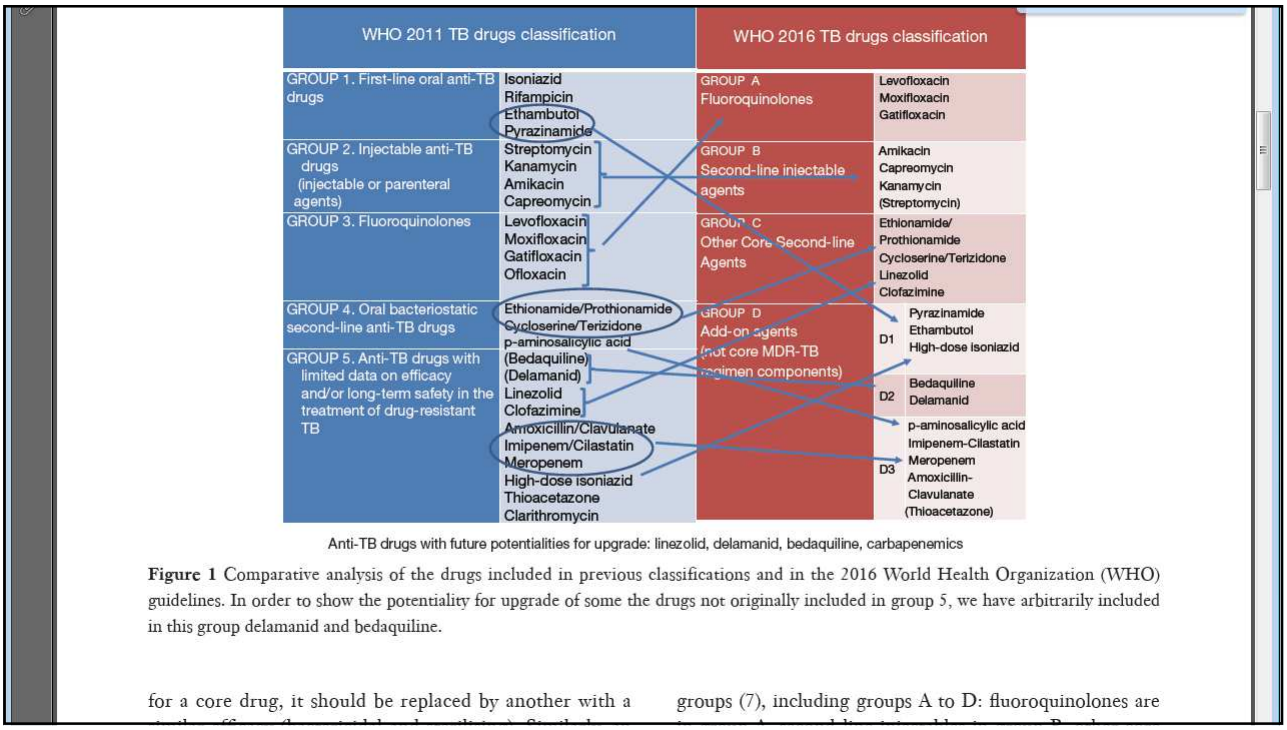
Results: By comparing the mutation data with phenotypic results, the detection rates of MDR-TB and pre-XDR-TB were 84.31% (43/51) and 83.33% (20/24), respectively. The sequencing assay illustrated good sensitivity for the detection of resistance to RIF (96.92%), INH (86.89%), FQ (77.50%). The specificities of the assay were 98.35% for RIF, 99.20% for INH, and 97.26% for FQ.

Conclusions: The sequencing assay is an efficient, accurate method for detection of MDR-TB and pre-XDR-TB from clinical smear-positive sputum specimens, should be considered as a supplemental method for obtaining early DST results before the availability of phenotypic DST results. This could be of benefit to early diagnosis, adjusting the treatment regimen and controlling transmission of drug-resistant TB.

Keywords: *Mycobacterium tuberculosis*, MDR-TB, Pre-XDR-TB, Rifampicin, Isoniazid, Fluoroquinolone

Background

years [1]. In 2014, there were an estimated 480,000 new



Anti-TB drugs with future potentialities for upgrade: linezolid, delamanid, bedaquiline, carbapenemics

Figure 1 Comparative analysis of the drugs included in previous classifications and in the 2016 World Health Organization (WHO) guidelines. In order to show the potentiality for upgrade of some the drugs not originally included in group 5, we have arbitrarily included in this group delamanid and bedaquiline.

for a core drug, it should be replaced by another with a

groups (7), including groups A to D: fluoroquinolones are

Ethionamide

Bactériostatique, il agit seulement sur les microorganismes extracellulaires

500-1000 mg/j

Résistance croisée avec R à l'Isoniazide à bas niveau (gène InhA)

Effets secondaires possibles gastro-intestinaux, convulsions, neuropathies périphériques, déséquilibre glycémique, hypotiroidie

ATU nominative

Prothionamide

Similaire à l'ethionamide

15-20 mg/kg/j

Toxicité hépatique (surtout) et gastro-intestinale

Non disponible en France

Cycloserine

Bactériostatique, action sur les microorganismes intra- et extra-cellulaires

Pas de R croisée avec les autres antituberculeux

750-1000 mg/j, en 2-4 doses journalières

Effets secondaires: neuropathie périphérique (rajout de vitamine B6), psychoses, crises d'epilepsie

ATU nominative

Linezolid

Oxadolidinone

Action anti gram+(SASM et SARM) à la dose de 600 mg 2/j
Excellente diffusion pulmonaire

A la dose de 600 mg/j il est adapté comme trt antituberculeux

Toxicité médullaire, neuropathies périphériques, diarrhée

Clofazimine

100 mg/j pendant les repas

Effets secondaires: coloration de la peau, infarctus spléniques, effets gastro-intestinaux

90% de réussite quand utilisé dans des schéma thérapeutiques courts (Bangladesh)

Disponible sans ATU (Lamprene)

Pyrazinamide

Bactéricide pour les microorganismes intracellulaires

25 mg/kg/j en une prise

toxicité hépatique (il n'est plus conseillé comme traitement de la tuberculose latente), arthralgies, crises de goute

Ethambutol

Bactériostatique, action sur microorganismes intra- et extracellulaires

Toxicité oculaire (névrite optique), neuropathie périphériques

Isoniazide a haute dose

Dans les tuberculose MDR ou XDR, en cas de résistance à bas niveau (gène InhA), l'isoniazide à haute dose peut être encore efficace

Importance de garder l'Isoniazide dans le schéma therapeutique grâce à son action sur les deux compartiments (intra- et extracellulaire)

Isoniazide (2)

En cas de mutation de haut niveau (gène kat G), l'Isoniazide semble encore avoir un intérêt, car présence de souches à sensibilité différente (Cambau et al. JAC 2015)

Associer la vit B6 pour réduire le risque de neuropathie périphérique

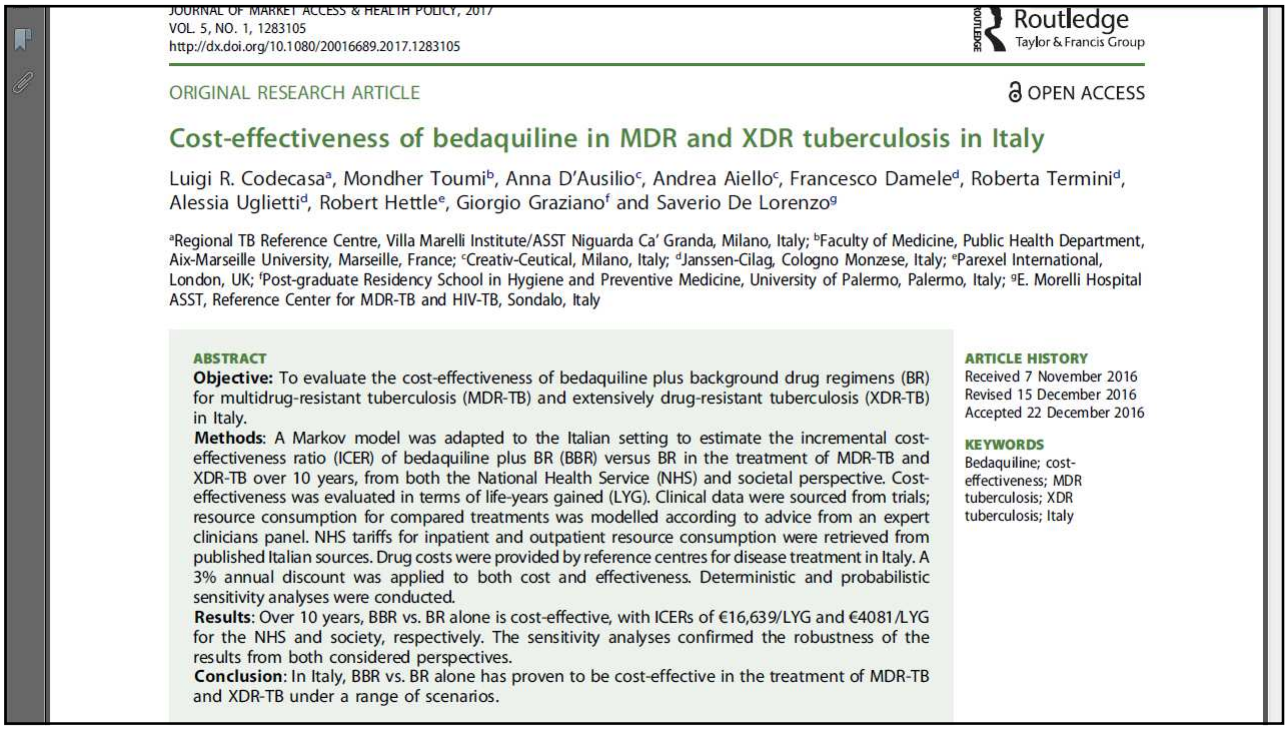
Bedaquiline (SIRTURO, ex. TMC 207)

Dyarilquinoléine. Excellente action bactéricide, sur les compartiments intra- et extra-cellulaires

Synergie d'action avec la pyrazinamide

400 mg/j pendant 14 jours, puis 200 mg 3 fois/semaine pendant 22 semaines

toxicité cardiaque (allongement QT: contrôles réguliers de l'ECG)



JOURNAL OF MARKET ACCESS & HEALTH POLICY, 2017
VOL. 5, NO. 1, 1283105
http://dx.doi.org/10.1080/20016689.2017.1283105

Routledge
Taylor & Francis Group

ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

Cost-effectiveness of bedaquiline in MDR and XDR tuberculosis in Italy

Luigi R. Codecasa[a], Mondher Toumi[b], Anna D'Ausilio[c], Andrea Aiello[c], Francesco Damele[d], Roberta Termini[d], Alessia Uglietti[d], Robert Hettle[e], Giorgio Graziano[f] and Saverio De Lorenzo[g]

[a]Regional TB Reference Centre, Villa Marelli Institute/ASST Niguarda Ca' Granda, Milano, Italy; [b]Faculty of Medicine, Public Health Department, Aix-Marseille University, Marseille, France; [c]Creativ-Ceutical, Milano, Italy; [d]Janssen-Cilag, Cologno Monzese, Italy; [e]Parexel International, London, UK; [f]Post-graduate Residency School in Hygiene and Preventive Medicine, University of Palermo, Palermo, Italy; [g]E. Morelli Hospital ASST, Reference Center for MDR-TB and HIV-TB, Sondalo, Italy

ABSTRACT

Objective: To evaluate the cost-effectiveness of bedaquiline plus background drug regimens (BR) for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in Italy.

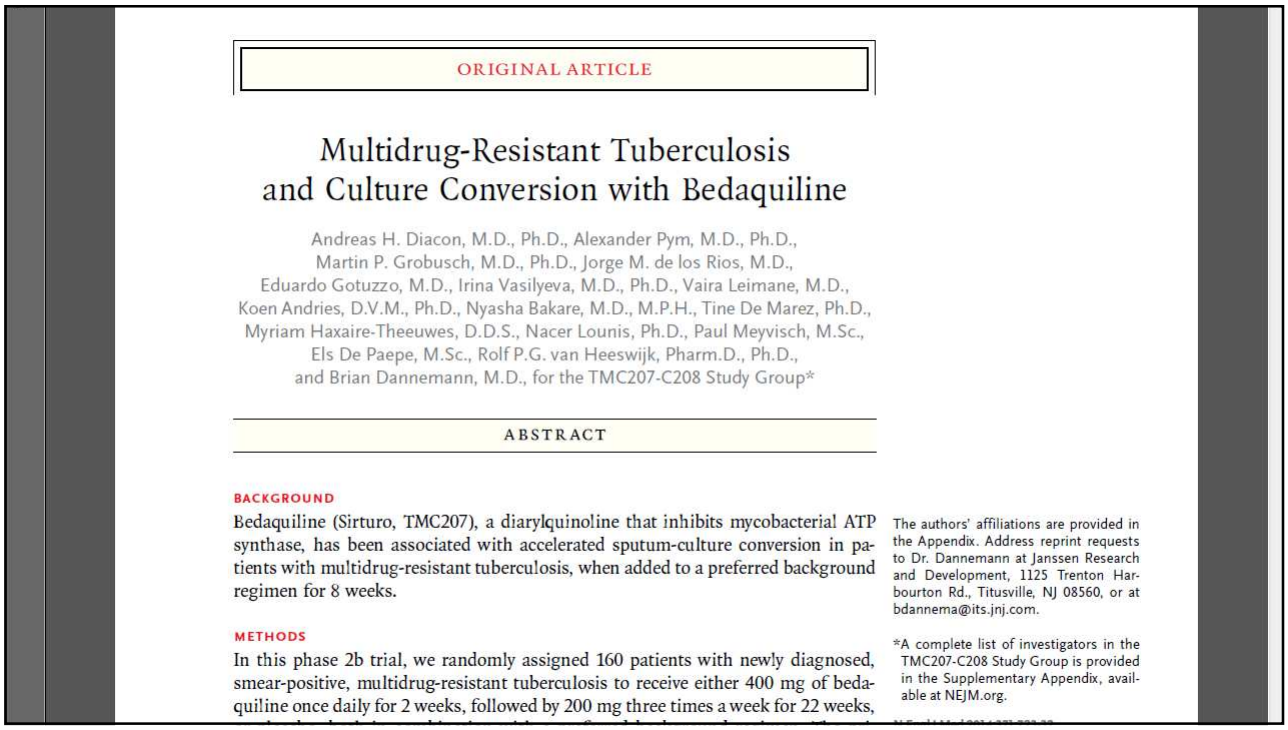
Methods: A Markov model was adapted to the Italian setting to estimate the incremental cost-effectiveness ratio (ICER) of bedaquiline plus BR (BBR) versus BR in the treatment of MDR-TB and XDR-TB over 10 years, from both the National Health Service (NHS) and societal perspective. Cost-effectiveness was evaluated in terms of life-years gained (LYG). Clinical data were sourced from trials; resource consumption for compared treatments was modelled according to advice from an expert clinicians panel. NHS tariffs for inpatient and outpatient resource consumption were retrieved from published Italian sources. Drug costs were provided by reference centres for disease treatment in Italy. A 3% annual discount was applied to both cost and effectiveness. Deterministic and probabilistic sensitivity analyses were conducted.

Results: Over 10 years, BBR vs. BR alone is cost-effective, with ICERs of €16,639/LYG and €4081/LYG for the NHS and society, respectively. The sensitivity analyses confirmed the robustness of the results from both considered perspectives.

Conclusion: In Italy, BBR vs. BR alone has proven to be cost-effective in the treatment of MDR-TB and XDR-TB under a range of scenarios.

ARTICLE HISTORY
Received 7 November 2016
Revised 15 December 2016
Accepted 22 December 2016

KEYWORDS
Bedaquiline; cost-effectiveness; MDR tuberculosis; XDR tuberculosis; Italy



ORIGINAL ARTICLE

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*

ABSTRACT

BACKGROUND

Bedaquiline (Sirturo, TMC207), a diarylquinoline that inhibits mycobacterial ATP synthase, has been associated with accelerated sputum-culture conversion in patients with multidrug-resistant tuberculosis, when added to a preferred background regimen for 8 weeks.

METHODS

In this phase 2b trial, we randomly assigned 160 patients with newly diagnosed, smear-positive, multidrug-resistant tuberculosis to receive either 400 mg of bedaquiline once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks,

The authors' affiliations are provided in the Appendix. Address reprint requests to Dr. Dannemann at Janssen Research and Development, 1125 Trenton Harbourton Rd., Titusville, NJ 08560, or at bdannema@its.jnj.com.

*A complete list of investigators in the TMC207-C208 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Bedaquiline

Associé à une négativation plus rapide des cultures

Mais plus de mortalité dans cette étude dans le groupe Bedaquiline

La cause de la surmortalité n'est pas éclaircie

Possibilité d'associer Bedaquiline et Delamanid (Tadolini et al. 2016)

Quelques données sur l'extension de la durée du traitement de la Bedaquiline au-delà des 6 mois

Delamanid (Deltyba, comprimé de 50 mg)

Bactéricide rapide, pas de résistance croisée

100 mg 2 fois/j pendant 24 semaines

Stérilise rapidement les cultures (Gler et al. 2012)

Réduit la mortalité (Skripconoka et al. 2013, Wells et al. 2015)

allongement du QT: nécessité d'une surveillance cardiaque comme pour la Bedaquiline

PAS (acide para-amino salycilique)

Bactériostatique, action seulement sur les microorganismes extracellulaires

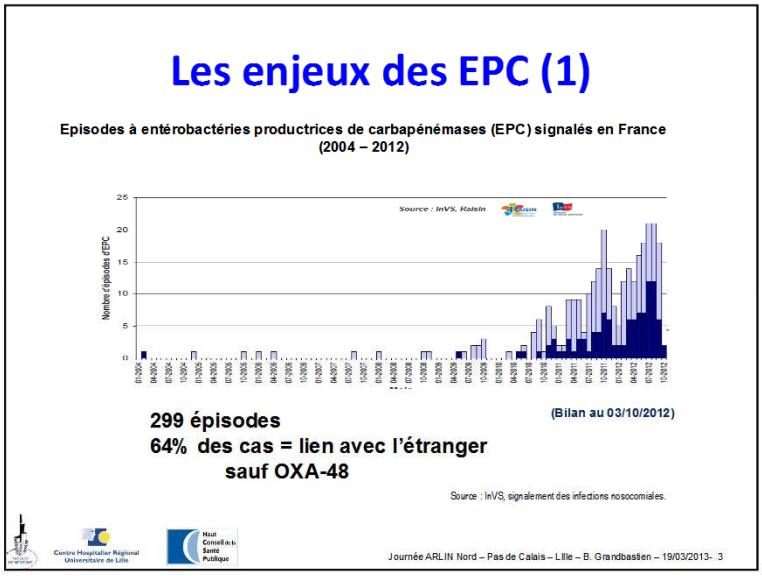
Posologie 200 mg/kg/j en deux fois
Gros comprimés de 4 gr

Pas pratique du tout

Carbapenemes

Meropenem > Imipenem (Tiberi et al. 2016)

Intérêt de l'ertapenem, surtout pour le traitement à domicile (1 fois/j, possibilité i.m.)



Mais de l'autre coté la politique actuelle est de l'épargne des carbapenèmes à cause des bactéries BHRE!

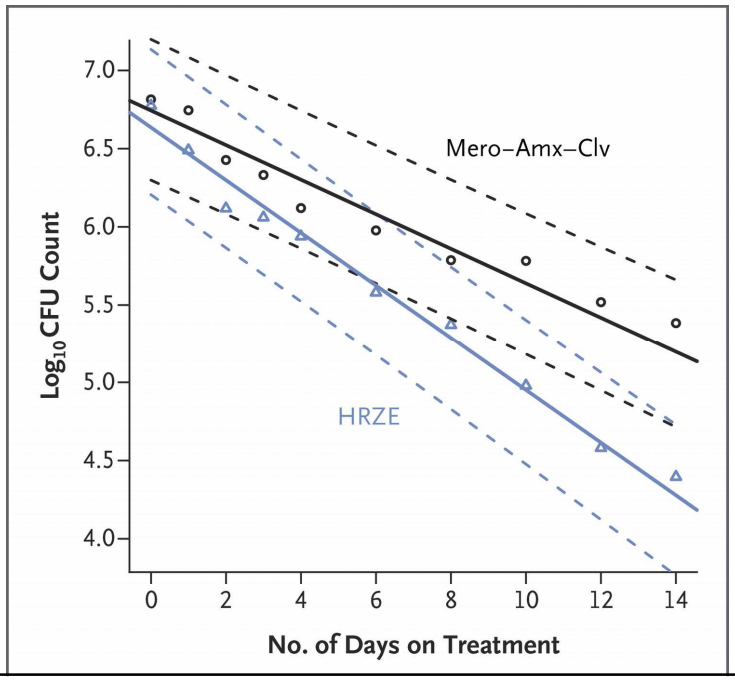
Amoxilline-acide clavulanique

Efficacité in vitro de l'acide clavulanique sur M. tuberculosis (nombreuses Beta-lactamases produites par les Mycobactéries)

Efficacité in vivo incertaine car échec dans deux essaies cliniques aux USA, Turquie et Afrique du Sud

Synergisme avec les carbapenemes

NEJM 2016



Futures scenarii pour le trt des TB XDR

De moins en moins d'utilisations des anciennes molécules (Amox/ac. clav, Carbapenémes, PAS, Clofazimine)

De plus en plus de prescription de Linezolid, Bedaquiline et Delamanid, chez l'enfant et l'adulte

International Journal of
Molecular Sciences

MDPI

Review

Combined Use of Delamanid and Bedaquiline to Treat Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: A Systematic Review

Giovanni Battista Migliori [1], Emanuele Pontali [2], Giovanni Sotgiu [3], Rosella Centis [1], Lia D'Ambrosio [1,4], Simon Tiberi [5], Marina Tadolini [6] and Susanna Esposito [7,8,*]

1 World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Maugeri Institute, IRCCS Tradate 21049, Italy; giovannibattista.migliori@icsmaugeri.it (G.B.M.); rosella.centis@icsmaugeri.it (R.C.); liadambrosio59@gmail.com (L.D.)
2 Department of Infectious Diseases, Galliera Hospital, Genoa 16128, Italy; pontals@yahoo.com
3 Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari, Sassari 07100, Italy; gsotgiu@uniss.it
4 Public Health Consulting Group, Lugano CH-6904, Switzerland
5 Division of Infection, Royal London Hospital, Barts Health NHS Trust, 80 Newark Street, London E1 2ES, UK; simon.tiberi@bartshealth.nhs.uk
6 Unit of Infectious Diseases, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna 40138, Italy; mtadolini@hotmail.com
7 Pediatric Clinic, Department of Surgical and Biomedical Sciences, Università degli Studi di Perugia, Perugia 06129, Italy
8 Pediatric Highly Intensity Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy
* Correspondence: susanna.esposito@unimi.it; Tel.: +39-075-5784417; Fax: +39-075-5784415

Schéma XDR

- **TMC 207 (bédaquiline)**: 400 mg 1X/j 2 sem puis 200 mg 3 X/sem 22 sem avec aliments. Cp 100 mg.
- Ethambutol ou Pyrazinamide ou FQ (izilox-ciprofloxacine)
- 1 injectable actif 6 mois (Streptomycine > capréomycine (Capastat®) > kanamycine > amikacine)
- Thioamides (**Trécator** 250 mg, 15-20 mg/kg/j) (± bactéricide, peu cher, peu toxique), à dose progressivement croissante
- Cyclosérine (tendance suicidaire) ou PAS (**Paser®** 4g sachet X 3/J; mauvaise tolérance gastrique)
- **Linezolid**: 300-1200 mg/J préférentiel: 600 mg/j
- 18 mois après < 0 des cultures (sauf injectable: 6 mois)

Sputum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis

David J Horne, Sarah E Royce, Lisa Gooze, Masahiro Narita, Philip C Hopewell, Payam Nahid, Karen R Steingart

Lancet Infect Dis 2010; 10: 387–94

WHO has previously recommended sputum-smear examination at the end of the second month of treatment in patients with recently diagnosed pulmonary tuberculosis, and, if positive, extension of the intensive therapy phase. We did a systematic review and meta-analysis to assess the accuracy of a positive sputum smear or culture during treatment for predicting failure or relapse in pulmonary tuberculosis. We searched PubMed, Embase, and the Cochrane Library for studies published in English through December, 2009. We included randomised controlled trials, cohort, and case-control studies of previously untreated pulmonary tuberculosis patients who had received a standardised regimen with rifampicin in the initial phase. Accuracy results were summarised in forest plots and pooled by use of a hierarchical regression approach. 15 papers (28 studies) met the inclusion criteria. The pooled sensitivities for both 2-month smear (24% [95% CI 12–42%], six studies) and culture (40% [95% CI 25–56%], four studies) to predict relapse were low. Corresponding specificities (85% [95% CI 72–90%] and 85% [95% CI 77–91%]) were higher, but modest. For failure, 2-month smear (seven studies) had low sensitivity (57% [95% CI 41–73%]) and higher, although modest, specificity (81% [95% CI 72–87%]). Both sputum-smear microscopy and mycobacterial culture during tuberculosis treatment have low sensitivity and modest specificity for predicting failure and relapse. Although we pooled a diverse group of patients, the individual studies had similar performance characteristics. Better predictive markers are needed.

Meta-Analysis of XDR TB Treatment Outcomes • CID 2010; 51: 6-14.

- Pubmed et Embase
- 13 études, 560 patients
- Ont un effet favorable sur la survie:
  - * âge jeune
  - * administration de moxifloxacine (même si BK-R à ciprofloxacine, ofloxacine)
- Trop faibles effectifs pour apprécier le Linezolid, la chirurgie

Durée de traitement des TB XDR

Généralement au moins 18 mois de traitement après négativation des cultures

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transmission of Extensively Drug-Resistant Tuberculosis in South Africa

N. Sarita Shah, M.D., M.P.H., Sara C. Auld, M.D., James C.M. Brust, M.D., Barun Mathema, Ph.D., Nazir Ismail, Ph.D., Pravi Moodley, M.D., Koleka Mlisana, M.D., Ph.D., Salim Allana, M.B., B.S., M.D., Angela Campbell, M.A., Thuli Mthiyane, M.Sc., Natashia Morris, M.Sc., Primrose Mpangase, B.A., Hermina van der Meulen, Shaheed V. Omar, Ph.D., Tyler S. Brown, M.D., Apurva Narechania, M.A., Elena Shaskina, Ph.D., Thandi Kapwata, M.Sc., Barry Kreiswirth, Ph.D., and Neel R. Gandhi, M.D.

ABSTRACT

BACKGROUND

Drug-resistant tuberculosis threatens recent gains in the treatment of tuberculosis and human immunodeficiency virus (HIV) infection worldwide. A widespread epidemic of extensively drug-resistant (XDR) tuberculosis is occurring in South Africa, where cases have increased substantially since 2002. The factors driving this rapid increase have not been fully elucidated, but such knowledge is needed to guide public health interventions.

METHODS

We conducted a prospective study involving 404 participants in KwaZulu-Natal Province, South Africa, with a diagnosis of XDR tuberculosis between 2011 and 2014. Interviews and medical-record reviews were used to elicit information on the participants' history of tuberculosis and HIV infection, hospitalizations, and social networks. *Mycobac-*

From the Emory University Rollins School of Public Health and School of Medicine (N.S.S., S.C.A., S.A., A.C., N.R.G.) and the Centers for Disease Control and Prevention (N.S.S.) — both in Atlanta; Albert Einstein College of Medicine and Montefiore Medical Center (N.S.S., J.C.M.B., N.R.G.), Columbia University Mailman School of Public Health (B.M., T.S.B.), and the American Museum of Natural History (A.N.) — all in New York; the National Institute for Communicable Diseases, Johannesburg (N.I., H.M., S.V.O.), University of KwaZulu-Natal and National Health

tory of tuberculosis and HIV infection, hospitalizations, and social networks. *Mycobacterium tuberculosis* isolates underwent insertion sequence (IS)*6110* restriction-fragment–length polymorphism analysis, targeted gene sequencing, and whole-genome sequencing. We used clinical and genotypic case definitions to calculate the proportion of cases of XDR tuberculosis that were due to inadequate treatment of multidrug-resistant (MDR) tuberculosis (i.e., acquired resistance) versus those that were due to transmission (i.e., transmitted resistance). We used social-network analysis to identify community and hospital locations of transmission.

RESULTS

Of the 404 participants, 311 (77%) had HIV infection; the median CD4+ count was 340 cells per cubic millimeter (interquartile range, 117 to 431). A total of 280 participants (69%) had never received treatment for MDR tuberculosis. Genotypic analysis in 386 participants revealed that 323 (84%) belonged to 1 of 31 clusters. Clusters ranged from 2 to 14 participants, except for 1 large cluster of 212 participants (55%) with a LAM4/KZN strain. Person-to-person or hospital-based epidemiologic links were identified in 123 of 404 participants (30%).

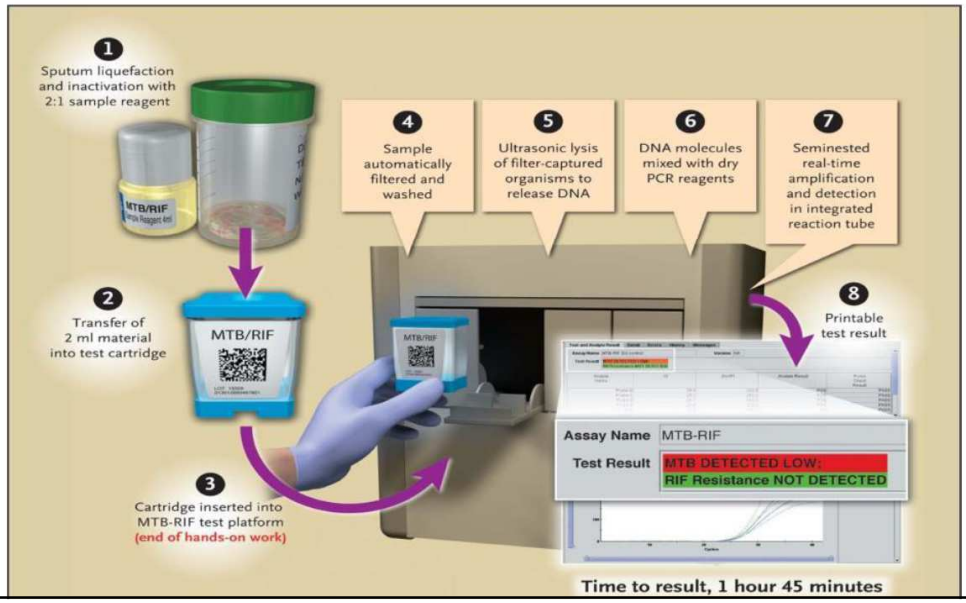
CONCLUSIONS

The majority of cases of XDR tuberculosis in KwaZulu-Natal, South Africa, an area with a high tuberculosis burden, were probably due to transmission rather than to inadequate treatment of MDR tuberculosis. These data suggest that control of the epidemic of drug-resistant tuberculosis requires an increased focus on interrupting transmission. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

sity of KwaZulu-Natal and Na
Laboratory Service, Durban
K.M., T.M., P. Mpangase), a
African Medical Research C
Town (N.M., T.K.) — all in
and the Public Health Resea
New Jersey Medical School–
versity, Newark (E.S., B.K.). A
requests to Dr. Gandhi at
School of Public Health, E
sity, 1518 Clifton Rd. NE, Cl
Rollins Bldg., Rm. 3031, Atlan
or at neel.r.gandhi@emory.e

N Engl J Med 2017;376:243-53
DOI: 10.1056/NEJMoa160454

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance
Catharina C. Boehme, et al. N Engl J Med Volume 363(11):1005-1015



AVIS

La tuberculose se propageant surtout par les germes contenus dans les crachats desséchés,

il est absolument défendu

DE

CRACHER A TERRE

sous peine de punition disciplinaire.