ERJ Express. Published on March 12, 2009 as doi: 10.1183/09031936.00009509

A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in MDR-TB

Giovanni Battista Migliori*, Barbara Eker† Morgan D'Arcy Richardson§, Giovanni Sotgiu#, Jean-Pierre Zellweger##, Alena Skrahina§§, Johannes Ortmann‡, Enrico Girardi¶, Harald Hoffmann**, Giorgio Besozzi^, Nazario Bevilacqua¶, Detlef Kirsten^^, Rosella Centis* and Christoph Lange† for the TBNET Study Group[∞]

Authors Affiliations

*WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy;

† Div. of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany;

§ HIV/TB Global Program, PATH, Seattle, Washington, USA;

Hygiene and Preventive Medicine Institute, University of Sassari, Sassari, Italy;

TB Clinic, Department of ambulatory care and community medicine, University of Lausanne, Switzerland;

§§ Research Institute of Pulmonology and Tuberculosis, Minsk, Belarus;

‡Pulmonary Clinic, Karl-Hansen-Clinic, Bad Lippspringe, Germany;

¶ National Institute for Infectious Diseases (INMI) L. Spallanzani, Rome, Italy;

** Supranational Reference Laboratory of Tuberculosis, Asklepios Clinic Munich-Gauting, Munich-Gauting, Germany;

^ E. Morelli Hospital, Reference Hospital for MDR and HIV TB, Sondalo, Italy;

^^ Hospital Großhansdorf, Center for Pneumology and Thoracic Surgery, Großhansdorf, Germany

Corresponding Author:

Christoph Lange MD, Tuberculosis Network European Trialsgroup (TBNET), Clinical Infectious Diseases, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany, Tel. +49 4537 188 332, Fax + 49 4537 188 313, email: clange@fz-borstel.de

Funding/Support: The study was supported by the current research funds of the participating institutions. The data collection system was initiated in 1996 with funding obtained by AIPO (Italian Association of Hospital Polmunologists) through a Ministry of Health/ Superior Institute of Health (Istituto Superiore di Sanità) grant (National TB Project, Grant N°1, 641/96). The study is partially funded by European Respiratory Society as Clinical Research Collaboration (CRC).

Running Head:

Linezolid safety and efficacy in MDR-TB

Key Words:

Multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, linezolid, tolerability, efficacy, safety

[∞] The additional participating members of the TBNET Study Group (Tuberculosis Network European Trialsgroup) are:

Belarus: Hennadz Hurevich, Research Institute of Pulmonology and Tuberculosis; Aliaksandr Skrahin, Belarus State Medical University.

Germany: R. Muetterlein, Regional Hospital, Pasberg; T. Schaberg, Pulmonary Clinic, Deakoness Hospital, Rotenburg; R. Eberhardt, Division of Pulmonary Medicine, Thorax-Clinic-Heidelberg; H. Flick, Div. of Infectious Diseases, Charité Berlin, Berlin; M. Hamm, Pulmonary Clinic, Hospital Diekholzen; H. Hang, Pulmonary Clinic, Hospital Schillerhöhe; P. Hannemann, Pulmonary Clinic, Deakoness Hospital, Neustadt; D. Hillemann, Div. of Mycobacteriology, Research Center Borstel, Borstel; B. Kretz, Asklepios Pulmonary Hospital, Gauting; C. Laumanns, Bethania Hospital, Solingen; A. Paulick, Pulmonary Clinic-Coswig, Coswig; M.W. Pletz, Div. of Pulmonary Medicine, Hannover Medical School; M. Rau, Pulmonary Clinic,Wangen; A. de Roux, Pulmonary Clinic, Protestant Pulmonary Clinic, Berlin; C. Schaudt, Pulmonary Clinic, Hospital St.Blasien

Italy: A. Matteelli, Brescia University, Brescia; A. Spanevello, Insubria University, Varese; O. Toungoussova, Fondazione S. Maugeri, Cassano delle Murge; Lia D'Ambrosio, Fondazione S. Maugeri, Tradate; S. De Lorenzo, P. Troupioti and G. De Iaco, Sondalo Hospital, Sondalo; A. Gualano, P. De Mori and F. N. Lauria, INMI L. Spallanzani, Rome; G. Ferrara, University of Perugia, Perugia; D. Cirillo, S. Raffaele Hospital, Milan

Switzerland: J. P. Janssens, University Hospital Geneva, Geneva

ABSTRACT

Linezolid is used to treat MDR/XDR-TB cases, although clinical data on its safety, tolerability and efficacy are lacking.

We performed a retrospective, non-randomised, unblinded observational study evaluating the safety and tolerability of linezolid at 600 mg once (OD) or twice daily (BD) in MDR/XDR-TB treatment in four European countries. Efficacy evaluation compared endpoints of 45 linezolid-treated against 110 linezolid non-treated cases.

Eighty-five of 195 MDR/XDR-TB patients were treated with linezolid for a mean of 221 days. Of these, 35/85 (41.2%) experienced major side effects attributed to linezolid (anemia, thrombocytopenia, polyneuropathy) requiring discontinuation in 27 (77%) cases. Most side effects occurred after 60 days of treatment. BD administration produced more major side effects ($p=0.0004$) than OD dosing, with no difference in efficacy found. Outcomes were similar in patients treated with/without linezolid ($p=0.8$), even though linezolid-treated cases had more first-line ($p=0.002$) and second-line ($p=0.02$) drug resistance and a higher number of previous treatment regimens (4.5 versus 2.3, $p=0.07$).

Linezolid 600 mg OD added to an individualized multidrug-regimen may improve the chances of bacteriological conversion, providing a better chance at treatment success in only the most complicated MDR/XDR-TB cases. Its safety profile does not warrant use in cases for which there are other, safer, alternatives.

INTRODUCTION

Tuberculosis (TB) is a leading cause of death worldwide. The World Health Organization (WHO) estimates that approximately 9.2 million new TB cases and 1.5 million TB-related deaths occurred in 2006 [1]. The prevalence of multidrug-resistant (MDR) *Mycobacterium tuberculosis* (defined as *in vitro* resistance to isoniazid and rifampicin, the two most potent first-line drugs for TB treatment) is increasing globally [2,3]. Multidrug-resistant strains are now found in more than 15% of all TB cases in some countries of the Former Soviet Union, Israel and areas of China [4-6]. *M. tuberculosis* resistant to second-line drugs is also emerging. Cases of extensively drug-resistant TB (XDR-TB) (defined by WHO as *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable drugs - capreomycin, kanamycin, or amikacin) have been described in most regions of the world [7,8]. This manuscript is part of a larger effort by TBNET to characterize the clinical epidemiology of MDR- and XDR-TB in Europe and thus strengthen the evidence base for clinical and public health recommendations for MDR- and XDR-TB control.

Treatment outcomes for complicated MDR-TB cases (those with additional resistance beyond isoniazid and rifampicin) and cases with XDR-TB are poor [9-15], thus information on safety, tolerability and efficacy of other antibiotics potentially useful in treatment is urgent to improve individual outcomes and control the spread of MDR- and XDR-TB. *In-vitro* and pharmacological data suggest that linezolid, an oxazolidinone antibiotic, could be useful in treating mycobacterial infections, including MDR-TB [16-23]. However, clinical experience with linezolid for purposes outside the drug's approved uses has been restricted mainly to case-reports in non-tuberculous mycobacterial diseases [24-29]. Linezolid is used in both Eastern and Western Europe to treat MDR/XDR-TB, a purpose outside the drug's approved uses, but treatment costs are high. In a recent epidemiological study on MDR-TB in Germany

[15] linezolid was widely used: 33.8% of the patients reported side effects, with 56% of those experiencing severe anemia. However, these data and other previous studies [22, 30-33] did not provide sufficient detail to evaluate safety, tolerability and efficacy of linezolid in MDR/XDR-TB treatment. The aim of this study was to evaluate the safety, tolerability and efficacy of linezolid using a sizable cohort of patients with MDR/XDR-TB from four European countries.

METHODS

Study design

Safety and tolerability were analyzed in this retrospective cohort study of MDR/XDR-TB patients from 21 participating centres in Belarus, Germany, Italy and Switzerland from 2001 to 2007. To assess the efficacy of linezolid in MDR/XDR-TB treatment, we compared only patients who had definitive treatment endpoints recorded (cured, completed, died, or failed). Patients who were still on treatment at the time of the data collection were excluded from the analysis as no follow-up information was available for these cases.

The data collection tool was pre-tested in Germany [15], providing the following information: previous treatment, HIV status, drug-resistance profile, time to sputum and culture conversion, length of hospital stay, adverse effects (yes/no), treatment interruption (yes/no), and treatment outcome. This tool was refined to include linezolid dosage and details on adverse effects, linezolid re-introduction (including dosage) and anti-TB drugs used in treatment regimens. The final dataset included complete information on 59 of the 74 MDR/XDR-TB cases from Germany and on 26 additional cases from Italy, Belarus and Switzerland.

Approval for collection of study data was provided by the ethical committee of the clinical coordinating centre at Sondalo Hospital in Sondalo, Italy and the statistical coordinating

centre, Fondazione S. Maugeri in Tradate, Italy. All participating centres complied with national regulations and organizational requirements for human subjects protection. All data were coded and individual identifiers were available only to treating physicians.

Definitions

Standard treatment outcome definitions were used as proposed by Laserson et al. [11, 34-35]. A patient who completed treatment and was consistently culture-negative with at least five results for the final 12 months of treatment was defined as cured. If bacteriological results were lacking (i.e., <5 cultures performed), the case was defined as treatment completed. Treatment failure was defined as two or more positive cultures in the last 12 months of treatment, or if a medical decision was made to terminate treatment due to poor response or adverse events.

Safety and tolerability endpoints included major and minor side effects. A major side effect was defined as any adverse reaction that resulted in temporary or permanent discontinuation of linezolid, while a minor side effect required only dose adjustment and/or addition of concomitant treatment. All patients in the cohort treated with linezolid were included in the safety and tolerability analysis.

Efficacy endpoints included time to and proportion of sputum smear and culture conversions, and treatment outcome. Sputum conversion was defined as two consecutive negative sputum smears in patients who were smear-positive at diagnosis. Time to culture conversion was defined as time from treatment start to date of the first of two consecutive negative cultures.

Data collection

Data were extracted from clinical records of all culture-confirmed MDR/XDR-TB cases diagnosed consecutively by the participating centres and verified by the study review panel. Drug susceptibility testing for first- and second-line anti-TB drugs was performed by laboratories quality-assured by WHO's Supranational Reference Laboratories (Rome/Milan,

Borstel, Stockholm) [9-11]. All participating centres performed sputum smear weekly until negative and then monthly. Cultures were performed monthly.

Treatment regimens

In all countries, regimens to treat MDR/XDR-TB cases were tailored to drug susceptibility test (DST) results according to WHO recommendations, using fluoroquinolones; injectable agents; and other second-line oral agents. Linezolid was available without any limitation except in Belarus where it was prescribed for a maximum of three months to optimise the use of the drug, given its limited availability in the country.

Statistical analyses

Categorical variables were compared by χ^2 test and continuous variables by Student's t test for unpaired data. A p-value of ≤ 0.05 was considered statistically significant. Data were collected on standardised e-forms and analysed using Stata 9.0 (StataCorp, Stata Statistical Software Release 9, College Station, TX, USA, 2005).

RESULTS

Within the cohort of 195 MDR/XDR-TB cases, 85 patients were treated with an individualized regimen including linezolid and 110 were treated without linezolid. In the linezolid group, 45 patients had a definitive treatment endpoint and 40 patients did not: 1/40 (2.5%) defaulted, 1/40 (2.5%) transferred out, and 38/40 (95%) were still on treatment.

Safety and tolerability

Safety and tolerability were evaluated for all 75 MDR-TB patients (88.2%) and 10 XDR-TB patients (11.8%) treated with linezolid. Of these, 28 patients received linezolid at 600 mg once daily, and 57 patients received 600 mg twice daily (1,200 mg). No differences in the main sociodemographic variables or in drug resistance profiles were observed between these two groups (data not shown).

Linezolid was administered for a mean (±SD) period of 222 (±249) days (median time, 93 days).

Adverse events appeared after a median of 69 days (range, 1-596) of linezolid treatment. In total, 35 of 85 (41.2%) patients experienced 52 episodes of side effects attributable to linezolid. Of the 35 patients experiencing side effects, 27 (77.1%) experienced major side effects requiring temporary or permanent discontinuation of linezolid, while 8 (22.9%) patients experienced minor side effects.

Side effects were primarily represented by anaemia (23 of 52 episodes, 44.2%). Out of 23 patients experiencing anaemia, 5 (21.7%) were severely affected, requiring blood transfusion as haemoglobin level was < 8 mg/dl; 2 of these patients had haemolytic anaemia. Other side effects were thrombocytopenia (7/52, 13.5%), nausea/vomiting (4/52, 7.7%) and polyneuropathy (3/52, 5.7%). In 8/27 (29.6%) patients experiencing major side effects, linezolid was successfully reintroduced and in 19/27 (70.4%) it was permanently discontinued. No linezolid-related deaths were observed.

A significant difference in side effects was observed between those receiving 600 mg versus 1,200 mg daily. Only 4/28 (14.3%) patients receiving 600 mg of linezolid experienced any side effects versus 31/57 (54.4%) who received 1,200 mg (p-value: 0.0004) (Figure 1). Patients prescribed linezolid at 600 mg daily had a lower risk of major side effects as well as a lower risk of any side effects than those prescribed 1,200 mg. (Table 1).

Efficacy endpoints analysis

No significant differences were found in efficacy between 45 patients treated with linezolid and 110 patients not treated with linezolid for the main demographic and clinical variables. There were 41 MDR-TB cases (91.1%) among the 45 linezolid-treated patients and 102 among 110 patients not treated with linezolid (92.7%; p-value: 0.83), while there were 4 (8.9%) and 8 (7.3%; p-value: 0.82) XDR-TB patients in the two groups, respectively. The

mean number of first-line drugs to which those treated with or without linezolid were resistant was 4.3 and 3.8 (p-value: 0.002), and 1.5 and 0.9 for second-line drugs (p-value: 0.02), respectively. Both groups included retreatment patients, but the mean number of treatment regimens previously prescribed (> 1 month) was almost doubled in the linezolid-treated group (4.5 vs. 2.3, respectively; p-value, 0.07). Both linezolid–treated and non-treated patients were prescribed a mean number of five drugs.

Those treated with linezolid took significantly longer for both sputum smear and culture conversion than those without, but they achieved a higher (although not significant) percentage of conversion overall (Table 2). The mean time to smear conversion (± SD) was 102.9 ± 74 days in the linezolid group and 65.4 ± 80.1 days in the non-linezolid group (p-value: 0.007), while the mean time to culture conversion (± S.D.) was 109 ± 71 and 69 ± 63 days, respectively (p-value: 0.0007). The proportion achieving sputum smear conversion was 69% for the linezolid versus 54% in the non-linezolid group (RR=1.28; 95% CI: 0.99-1.6; p-value: 0.08). The proportion achieving culture conversion was 87% versus 78% (RR=1.1; 95% CI, 0.95-1.28; p-value, 0.22). There was no significant difference in treatment outcomes for those with definitive treatment endpoints: 36/45 linezolid-treated patients (80%) achieved treatment success versus 90/110 non-linezolid-treated patients (81.8%, p-value: 0.88), and there was no difference in the risk of failure or death between the two groups.

Efficacy was similar for patients who were prescribed 600 mg versus 1,200 mg of linezolid: the proportion achieving sputum smear conversion was 71.4% in the 600 mg versus 67.7% in the 1,200 mg group (p-value: 0.8). The proportion achieving culture conversion was 92.9% in those receiving 600 mg per day versus 83.9% in the 1,200 mg/day group (p-value, 0.4). The mean time to sputum smear conversion (± SD) was 101.5 ± 79.3 days in 600 mg/day group and 103.6 ± 73.4 days in 1,200 mg/day group (p-value: 0.9), while the mean time to culture conversion (± S.D.) was 109 ± 74.6 and 108.8 ± 70 days, respectively (p-value: 0.9). No

significant difference in efficacy endpoints (sputum and culture conversion, positive treatment outcome) was observed related to the presence or absence of cavities on chest radiographs.

Efficacy endpoint analysis stratified by resistance patterns

When stratified by the number of drugs to which isolates were resistant, the proportion of sputum smear and culture converters in the linezolid group was higher than for the non-linezolid group for all strata, reaching statistical significance only for cases harbouring strains resistant to >7 drugs (p=0.009 for smear; p=0.004 for culture, Table 3). There was no clear trend in time to conversion related to the number of drugs to which isolates were resistant (data not shown).

Risk of adverse outcome

The logistic regression analysis presented in Table 4 showed a significant risk of adverse outcome (failure or death) related to increasing age, resistance to >5 drugs, and the presence of XDR-TB, and was not influenced by linezolid treatment (crude odds ratios). Adjusted odds ratios, however, showed a significant risk of adverse treatment outcome only for increasing age and the presence of XDR-TB.

DISCUSSION

In the absence of new drugs for TB treatment, curing patients with MDR/XDR-TB critically depends on the pattern of drug resistance and on the availability of second- and third-line anti-TB drugs that have reasonable safety, tolerability, and efficacy [13-14]. Anecdotal reports suggest that linezolid may be an effective option to treat complicated cases of MDR/XDR-TB. However, serious concerns have been raised regarding safety and tolerability. Results of the five studies available with more than one case described suggest that adverse events may range from 43% [30] up to 80% or more [22, 29, 32, 33, 35]. Results of the present study

augment findings of the previous study [15], where adverse effects were observed in 33.8% of the cases but no information on doses prescribed or details on side effects were available.

Our results confirm a high frequency of major adverse side effects associated with linezolid, particularly in the higher 1,200 mg dose and in treatment longer than eight weeks. Although results from our study are more encouraging than most of those described previously [22, 30, 31, 32, 33] and adverse events seemed reversible shortly after timely drug discontinuation or dose reduction [30], they are still extremely relevant. More than one out of three cases treated (35/85, 41.2%) experienced side effects, with 27 (31.8%) having adverse reactions serious enough to indicate drug discontinuation.

Our data showed a significant difference in side effects between a 600 mg and 1,200 mg daily dosage of linezolid: they were less frequent when the lower dosage was prescribed, while no significant difference was seen in efficacy between the two doses. These data suggest that a lower dose is sufficient to convey the possible benefits of linezolid while reducing the risk of major side effects. In contrast, based on a case series of eight patients treated with 600 mg daily of linezolid, Park et al. [33] suggested that this "daily half dose" was effective in treating intractable MDR/XDR-TB cases, but did not prevent appearance of major adverse events.

In our cohort, linezolid was administered for a mean duration exceeding 32 weeks. Thirteen (37.1%) episodes of linezolid-attributed adverse effects occurred in the first eight weeks of treatment. Only 1/28 (3.6%) patients who received 600 mg of linezolid daily experienced adverse drug effects in the first eight weeks of treatment. Adverse effects appeared after a median time of approximately 10 weeks (69 days), suggesting that after approximately two months of linezolid treatment, the risk of adverse events increases.

Our data show that patients treated with linezolid (at either dose) achieved similar treatment outcomes to those in the non- linezolid group, even though those treated with linezolid had a

more frequent history of previous treatment and were resistant to more first- and second-line drugs than patients who were not. Patients treated with linezolid achieved a higher proportion of sputum smear and culture conversion (significant for resistance to >7 drugs only), but took significantly longer to convert than patients who were not treated with linezolid. This apparent increase in treatment success in XDR-TB patients might represent an opportunity for decreasing transmission of XDR-TB strains. It would be useful to improve the methodology in future studies (e.g. prospective, randomized, blinded evaluation) in order to assess the safety, efficacy and quality of the drug more thoroughly. These findings suggest that linezolid may confer a benefit for treatment of the most complicated cases of MDR/XDR-TB, and warrants further study in a randomized, controlled trial.

To our knowledge, this is the first study allowing a comprehensive evaluation of linezolid tolerability and a first report on its long-term efficacy in a clinical setting. The study strengths include a relatively large sample size, the quality of laboratory data (all XDR-TB defining drugs tested and quality-controlled DST) and the capacity to provide representative data from four European countries.

The study has several limitations associated with its retrospective, observational nature. Although the described adverse effects were reversible in all cases when therapy with linezolid was discontinued, cause and effect of linezolid therapy and adverse effects are not proven, as they may also be due to other drugs. Another bias is the non-randomized allocation of patients to linezolid treatment. As a consequence of the linezolid-treated patients being resistant to more drugs than those not treated with linezolid (and therefore presumably having a poorer chance of treatment success), the effect of linezolid on treatment outcome may have been diminished in these data. In addition, even with a relatively sizable cohort of patients, numbers of patients when data were stratified by resistance pattern became small, challenging our ability to evaluate the potential effects of linezolid on efficacy in a definitive manner.

The study results are important in that they 1) confirm the substantial risk of adverse effects noted in other studies of linezolid, but suggest a safer dosage that could be prescribed without losing the potential benefits of linezolid; 2) provide documentation for cautiously justifying the use of linezolid in clinical practice for only the most complicated MDR/XDR-TB cases; 3) contribute evidence for regulatory authorities to develop clear indications for the use of linezolid in MDR/XDR-TB treatment; 4) represent a baseline against which future studies can be compared; and 5) allow for justification and improved planning of prospective, controlled clinical trials. Overall, the study results have both a clinical and public health relevance.

In conclusion, the data suggest that linezolid may be useful in improving the chances of smear and culture conversion and may provide a better chance at treatment success in only the most complicated cases of MDR/XDR-TB when other treatment alternatives are not available, but that its safety profile does not warrant its use in cases for which other, safer second-line or third-line drugs are available. The side effects associated with linezolid are frequent and often serious, and require careful monitoring, particularly when treatment extends beyond eight weeks. The potential benefits of linezolid can likely be achieved using a lower dosage of 600 mg OD, which appeared to reduce the risk of side effects in this cohort of patients and to reduce costs without changing efficacy. Additional randomized, controlled trials of linezolid for difficult-to-treat cases of MDR/XDR-TB should be conducted to confirm these findings.

REFERENCES

1. World Health Organization. Global Tuberculosis Control 2008, Surveillance, Planning Financing: WHO Report 2008. WHO/HTM/TB2008.393. Geneva, Switzerland: World Helath Organization...
2. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, Williams BG, Dye C. Global incidence of multidrug-resistant tuberculosis. *J Infect Dis* 2006;194:479-485.
3. Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, Wells C, Nunn P, Blanc L, Raviglione M.. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet* 2006;368:2142-2154.
4. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, Hoffner S, Rieder HL, Binkin N, Dye C, Williams R, Raviglione MC. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 2001;344:1294-1303.
5. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet* 2006;367:952-955.
6. World Health Organization. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-tuberculosis drug resistance in the world: fourth global report. WHO/HTM/TB/2008.394. Geneva, Switzerland: World Health Organization; 2008.
7. World Health Organization. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. *Wkly Epidemiol Rec* 2006;81:430-432.

8. Centers for Disease Control and Prevention. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs — worldwide, 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006;55:301-305.
9. Migliori GB, Ortmann J, Girardi E, Besozzi G, Lange C, Cirillo DM, Ferrarese M, De Iaco G, Gori A, Raviglione MC; SMIRA/TBNET Study Group. Extensively drug-resistant tuberculosis, Italy and Germany. *Emerg Infect Dis* 2007;13:780-782.
10. Migliori GB, G. Besozzi, E. Girardi, Kliiman K, Lange C, Toungoussova OS, Ferrara G, Cirillo DM, Gori A, Matteelli A, Spanevello A, Codecasa LR, Raviglione MC; SMIRA/TBNET Study Group. Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur Resp J* 2007;30:623-626
11. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, Ortmann J, Matteelli A, Spanevello A, Cirillo DM; SMIRA/TBNET Study Group. Extensively drug-resistant tuberculosis is worse than multidrug-resistant tuberculosis: different methodology and settings, same results. *Clin Infect Dis* 2008;46:958-959.
12. Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW, Han SK, Shim YS, Yim JJ. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. *Clin Infect Dis* 2007;45:1290-1295.
13. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, Codecasa LR, Spanevello A, Cirillo DM; SMIRA/TBNET Study Group. Fluoroquinolones: are they essential to treat multidrug-resistant tuberculosis? *Eur Respir J* 2008;31:904-910.
14. Migliori GB, Lange C, Centis R, Sotgiu G, Mütterlein R, Hoffmann H, Kliiman K, De Iaco G, Lauria FN, Richardson MD, Spanevello A, Cirillo DM, TBNET Study Group. Resistance to second-line injectables and treatment outcomes in MDR and XDR-TB cases. *Eur Respir J* 2008;31:1155-1159.

15. B. Eker, J. Ortmann, G.B. Migliori, Sotgiu G, Muetterlein R, Centis R, Hoffmann H, Kirsten D, Schaberg T, Ruesch-Gerdes S, Lange C; German TBNET Group. Multidrug- and extensively-drug resistant tuberculosis: a TBNET survey in Germany. *Emerg Infect Dis* 2008;14:1700-1706

16. Molicotti P, Ortu S, Bua A, Cannas S, Sechi LA, Zanetti S. In vitro efficacy of Linezolid on clinical strains of Mycobacterium tuberculosis and other mycobacteria. *New Microbiol*. 2006;29:275-280.

17. Tato M, de la Pedrosa EG, Canton R, Gómez-García I, Fortún J, Martín-Davila P, Baquero F, Gomez-Mampaso E. In vitro activity of linezolid against Mycobacterium tuberculosis complex, including multidrug-resistant Mycobacterium bovis isolates. *Int J Antimicrob Agents* 2006;28:75-78.

18. Erturan Z, Uzun M. In vitro activity of linezolid against multidrug-resistant Mycobacterium tuberculosis isolates. *Int J Antimicrob Agents* 2005;26:78-80.

19. Alcala L, Ruiz-Serrano MJ, Perez-Fernandez Turegano C, García De Viedma D, Díaz-Infantes M, Marín-Arriaza M, Bouza E. In vitro activities of linezolid against clinical isolates of Mycobacterium tuberculosis that are susceptible or resistant to first-line antituberculous drugs. *Antimicrob Agents Chemother* 2003;47:416-417.

20. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against Mycobacterium tuberculosis. *Int J Antimicrob Agents* 2002;20:464-467.

21. Diekema DJ, Jones RN. Oxazolidinone antibiotics. *Lancet* 2001;358:1975-1982.

22. Fortun J, Martin-Davila P, Navas E, Pérez-Elías MJ, Cobo J, Tato M, De la Pedrosa EG, Gómez-Mampaso E, Moreno S. Linezolid for the treatment of multidrug-resistant tuberculosis. *J Antimicrob Chemother* 2005;56:180-185.

23. Dietze R, Hadad DJ, McGee B, Molino LP, Maciel EL, Peloquin CA, Johnson DF, Debanne SM, Eisenach K, Boom WH, Palaci M, Johnson JL. Early and Extended Early Bactericidal Activity of Linezolid in Pulmonary Tuberculosis. *Am J Respir Crit Care Med* 2008;178:1180-1185.

24. Nannini EC, Keating M, Binstock P, Samonis G, Kontoyiannis DP. Successful treatment of refractory disseminated Mycobacterium avium complex infection with the addition of linezolid and mefloquine. *J Infect*. 2002;44:201-203.

25. Brown-Elliott BA, Wallace RJ Jr, Blinkhorn R, Crist CJ, Mann LB. Successful treatment of disseminated Mycobacterium chelonae infection with linezolid. *Clin Infect Dis* 2001;33:1433-1434.

26. Morales P, Ros JA, Blanes M, Perez-Enguix D, Saiz V, Santos M. Successful recovery after disseminated infection due to mycobacterium abscessus in a lung transplant patient: subcutaneous nodule as first manifestation - a case report. *Transplant Proc* 2007;39:2413-2415.

27. Hoetzenecker W, Ulmer A, Klingel K, Kempf VA, Schanz S, Metzler G, Fierlbeck G. Dissemination of a localized cutaneous infection with Mycobacterium chelonae under immunosuppressive treatment. *Arch Dermatol* 2007;143:951-952.

28. Kyle SD, Porter WM. Mycobacterium chelonae infection successfully treated with oral clarithromycin and linezolid. *Br J Dermatol* 2004;151:1101.

29. Ntziora F, Falagas M.E. Linezolid for the treatment of patients with atypical mycobacterial infection: a systematic review. *Int J Tuberc Lung Dis* 2007;11:606-611.

30. Condos R, Hadgiangelits N, Leibert E, Jacquette G, Harkin T, Rom WN. Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. *Chest* 2008;134:187-192.

31. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2008;12:345-346.
32. von der Lippe B, Sandven P and Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)-a report of ten cases. *J Infect* 2006;52:92-96.
33. Park IN, Hong SB, Oh YM, Kim MN, Lim CM, Lee SD, Koh Y, Kim WS, Kim DS, Kim WD, Shim TS. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. *J Antimicrob Chemother* 2006;58:701-704.
34. Laserson K, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, Zarovska E, Rich ML, Fraser HS, Alarcón E, Cegielski JP, Grzemska M, Gupta R, Espinal M. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005;9:640-645.
35. Sotgiu G, Ferrara G, Matteelli A, Richardson MD, Centis R, Ruesch-Gerdes S, Toungoussova O, Zellweger JP, Spanevello A, Cirillo D, Lange C, Migliori GB. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Resp J* 2009;32:in press

Table 1. Safety and tolerability of linezolid (presented separately as number of episodes and patients) in patients treated for MDR-/XDR-TB in Belarus, Germany, Italy and Switzerland, 2001 - 2007.

	Number of patients (%)			p-value*
	Total n = 85	**600 mg OD n = 28**	**600 mg BD n = 57**	
No adverse event	50 (58.8)	24 (85.7)	26 (45.6)	0.0004
Total (any adverse event)	35 (41.2)	4 (14.3)	31 (54.4)	0.0004
Minor adverse event	8 (9.4)	0	8 (14)	--
Major adverse event	27 (31.8)	4 (14.3)	23 (40.4)	0.01
Episodes	**Number of episodes (%)**			**p-value***
	Total n = 52	**600 mg OD n = 5**	**600 mg BD n = 47**	
Anemia	23 (44.2)	3 (60)	20 (42.5)	0.44
Thrombocytopenia	7 (13.5)	0 (0)	7 (14.9)	--
Nausea/vomiting	4 (7.7)	1 (20)	3 (6.4)	0.25
Polyneuropathy	3 (5.8)	1 (20)	2 (4.3)	0.13
Others	15 (28.8)	0 (0)	15 (31.9)	--

** Comparison between 600 mg OD group and 600 mg BD group*

Table 2. Comparison of efficacy endpoints for the treatment of MDR/XDR-TB with or without linezolid in cases with known outcome

Variables	Cases treated with linezolid (N = 45)	Cases treated without linezolid (N = 110)	*p-value*
Sputum smear conversion time (days, mean ± S.D.)	102.9 ± 74 n = 31 (69%)	65.4 ± 80.1 n = 59 (54%)	0.007
Culture conversion time (days, mean ± S.D.)	109 ± 71 n = 39 (87%)	69 ± 63 n = 86 (78%)	0.0007
Treatment outcome (%)			
Treatment success	36/45 (80.0)	90/110 (81.8)	0.88
Cured	23/45 (51.1)	75/110 (68.2)	0.04
Treatment completed	13/45 (28.9)	15/110 (13.6)	0.02
Failure	-	1/110 (0.9)	-
Death	9/45 (20)	19/110 (17.3)	0.65

Table 3. Proportion of converters according to the number of antituberculous drugs to which isolates were resistant among patients treated with and without linezolid in Belarus, Germany, Italy and Switzerland, 2001 - 2007 (LZD: linezolid).

	Proportion of converters (%)					
N° of drugs (resistance)	**Sputum smear conversion**		***p-value***	**Culture conversion**		***p-value***
	LZD treated	**No LZD**		**LZD treated**	**No LZD**	
< 5	6/9 (66.7)	35/59 (59.3)	0.68	8/9 (88.9)	50/59 (84.7)	0.75
5-7	16/26 (61.5)	23/43 (53.5)	0.51	22/26 (84.6)	34/43 (79.1)	0.6
>7	9/10 (90)	1/8 (12.5)	0.0009	9/10 (90)	2/8 (25)	0.004
TOTAL	31/45 (68.9)	59/110 (53.6)	0.07	39/45 (86.7)	86/110 (78.2)	0.22

Table 4. Logistic regression analysis of potential independent variables associated with adverse treatment outcome (failure or death) in MDR/XDR-TB cases.

Variables	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Gender (male)	1.11 (0.43 - 2.85)	0.82	1.8 (0.56 - 5.78)	0.32
Increasing age (years)	1.03 (1.008 - 1.06)	0.01	1.03 (1.003 - 1.07)	0.03
Previous TB-treatment > 30 days	1.8 (0.76 - 4.27)	0.18	1.01 (0.38 - 2.65)	0.98
Resistance to >5 anti-TB drugs	2.67 (1.17 - 6.1)	0.01	1.78 (0.59 - 5.34)	0.29
Linezolid treatment	0.88 (0.36 - 2.13)	0.79	1.1 (0.39 - 3.1)	0.85
XDR-TB	11.6 (3.2 - 42.05)	< 0.0001	8.3 (1.74 - 40.28)	0.008

Figure 1. Frequency of adverse effects attributed to linezolid during combined treatment against MDR/XDR-TB at different time points after treatment initiation with a 600 mg once daily or a 600 mg twice daily regimen (denominator is the total number of individuals per group; 600 mg/day n=28; 1200 mg/day =57).