

## THE USE OF DELAMANID

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The Treatment Committee of the Japanese Society for Tuberculosis

### 1. Background

Drug resistance poses a major problem in the treatment of tuberculosis (TB). For example, multidrug-resistant TB (MDR-TB) appeared following the introduction of rifampicin. Furthermore, extensively drug-resistant TB (XDR-TB) appeared following the subsequent introduction of aminoglycosides and fluoroquinolones. These resistant strains of TB are a major problem worldwide. Japan is also potentially facing an inability to administer effective treatment, resulting in many TB patients becoming chronic carriers. Drug resistance to TB, which is a category 2 infectious disease, is a major medical problem.

Since the introduction of rifampicin in the 1970s, no new class of anti-TB drug has been developed. Rifabutin, which was approved in 2008, is the same class of agent as rifampicin. Rifabutin is used when the use of rifampicin poses problems due to drug interactions or side effects. However, there is cross-resistance between rifabutin and rifampicin, and the efficacy of rifabutin against rifampicin-resistant TB is limited. The quinolone ofloxacin became available in the 1980s, followed by linezolid in the 2000s; however, neither these agents nor subsequently introduced fluoroquinolones have been approved as anti-TB drugs. Although fluoroquinolones are widely used in clinical settings as anti-TB drugs, some patients who need them may be unable to afford them. Furthermore, improper use may induce resistance<sup>1)</sup>.

Accordingly, many new drugs are currently under development. In 2012, an application was filed in Europe for the use of delamanid for the treatment for MDR-TB; approval was granted by the European Medicines Agency in April 2014. In Japan, a new drug application was filed for delamanid in March 2013, and it has recently been approved as an agent for use in combination therapies with other second-line drugs for the treatment of MDR-TB. Bedaquiline was approved in the United States in December 2012, and usage guidelines were announced by the WHO in June 2013<sup>2)</sup>.

The main reason why usage guidelines are required for these new drugs is that if used improperly, they are very likely to induce increased resistance in the same manner as previous drugs. Preparations have been advanced for the clinical application of not only delamanid and bedaquiline, but also other drugs such as sutezolid. However, in patients who are very likely to be successfully treated with a combination of these drugs, delamanid monotherapy is predicted

to induce resistance in a high percentage of cases. Therefore, the use of delamanid in combination therapies with new drugs may result in the loss of opportunity for cure. In order to avoid the loss of the effectiveness of valuable new drugs effective against MDR-TB and XDR-TB, new drugs must be managed strictly and appropriately. In order to ensure the appropriate use of delamanid once it is approved in Japan, we, the Japanese Society for Tuberculosis, have decided to publish our views on the use of delamanid.

These guidelines are provisional, and we will consider revising them roughly 2 years after the introduction of delamanid for the following reasons:

1) The application for delamanid filed was for its use as a concomitant drug with other existing second-line drugs for MDR-TB. However, subsequent applications have been filed for many other new anti-TB drugs; the effects of combinations of these drugs with delamanid are unknown. It is very likely that new knowledge will be obtained in the near future.

2) Although the indications for delamanid are limited to MDR-TB, its indications could be expanded, for example, cases in which standard anti-TB drugs cannot be used because of side effects.

### 2. Drug Overview

Delamanid is a novel nitro-dihydro-imidazooxazole derivative developed for TB treatment. The usage and dosage of delamanid is 100 mg, twice per day, administered orally after breakfast and dinner.

A comparison of delamanid combined with other second-line drugs as an MDR-TB treatment versus the use of second-line drugs not including delamanid shows that combination therapy with delamanid and other second-line drugs significantly improves the negative conversion of bacilli after 2 months, demonstrating its efficacy<sup>3)</sup>. In addition, subsequent observations showed that a group of patients who used delamanid for 6 months exhibited improved prognosis and reduced mortality rate<sup>4)</sup>.

Regarding adverse events, the combination of delamanid with other second-line drugs is reported to significantly prolong the QT interval<sup>3)</sup>. Therefore, follow-up via electrocardiogram (ECG) as well as caution regarding the use of other drugs that may prolong the QT interval are required.

### 3. Principles of Delamanid Use

The Japanese Society for Tuberculosis stipulates the following principles regarding the treatment of MDR-TB<sup>5)</sup>:

1) Initial treatment consists of administration of at least 3 agents (4 or 5 if possible) to which the patient's TB is susceptible; this initial treatment lasts for 6 months following negative conversion of bacilli. Treatment is subsequently continued, except for agents for which long-term administration is problematic.

2) In cases in which bacteriological relapse occurs during treatment and drug resistance acquisition is strongly suspected, replacing only one agent suspected of inducing resistance (among all agents in use) is very likely to effectively result in monotherapy with a new agent. There is a high risk of inducing resistance to this agent; therefore, such a replacement of an agent is contraindicated. Thus, changes of therapeutic agents should involve multiple effective agents simultaneously.

3) Agents are selected from among the following in order, beginning with those to which TB is deemed least resistant: pyrazinamide (PZA), streptomycin (SM), ethambutol (EB), levofloxacin (LVFX), kanamycin (KM), ethionamide (TH), enviomycin (EVM), para-aminosalicylic acid (PAS), and cycloserine (CS). However, SM, KM, and EVM, which are aminoglycosides, cannot be used in combination with each other. Considering their antimicrobial activity and cross-resistance, SM is chosen first, followed by KM and then EVM. Moxifloxacin (MFLX) is another fluoroquinolone besides LVFX that can be used; however, multiple fluoroquinolones cannot be used in combination. After considering their respective antimicrobial activities and side effects, one of the abovementioned drugs is chosen. Fluoroquinolones, PZA, aminoglycosides, and EB should be used if possible; including TH, PAS, and CS, at least 3 agents (4 or 5 if possible) are used.

The use of delamanid for MDR-TB currently involves combination with other second-line anti-TB drugs<sup>1)</sup>. However, there has been no assessment of how treatment outcomes change if delamanid is replaced with another drug. In other words, information about whether delamanid ultimately contributes to treatment outcomes beyond demonstrating a bactericidal effect has been gathered but not consolidated. Therefore, there is currently no information regarding which 3 agents (4 or 5 if possible) in section 1) above can be used as replacements. Therefore, the suitability of delamanid use is judged according to the following principles:

(1) Delamanid should be used when no existing anti-TB drugs can be used as the fourth or fifth agent because of drug resistance or side effects.

(2) In cases in which the existing 5 drugs can be used, there is no conclusion as to whether delamanid should be used; in either case, the use of delamanid is not ruled out.

(3) When 1 or 2 existing agents can be used, the use of delamanid as a second or third agent is not ruled out; how-

ever, delamanid must be handled carefully because of the risk of inducing resistance.

(4) Although it is permissible to use drugs that are not listed in the Standards for Tuberculosis Care or have not been recommended as effective against TB by the Treatment Committee of the Japanese Society for Tuberculosis<sup>5)</sup>, such drugs are basically not counted among the existing drugs listed above. However, the following drugs can be considered to have similar efficacy to the existing drugs listed above: prothionamide (in cases susceptible to ethionamide or prothionamide), capreomycin (in cases susceptible to capreomycin), and thiazide (in cases in which Tb1 or thiazide have not been previously used), and linezolid (which has not been approved for tuberculosis in Japan) in cases in which it has not been previously used. The Japanese Society for Tuberculosis does not recommend the use of clofazimine, AMPC/CVA, or meropenem because of the dearth of evidence for their use.

### 4. Conditions for Suitable Use of Delamanid

In order to ensure the appropriate use of delamanid, the following 2 conditions must be met: the selection of a medical institution that meets certain criteria, and an assessment of suitability for each case.

#### 4.1. Criteria for Medical Institutions

The 4 institutional criteria listed below are required for the application of delamanid; these conditions are well known in advance as necessary conditions when first applying the drug in a case. When transferring from the medical institution where treatment began to another institution in order to continue treatment, the new institution will continue to supply drugs regardless of whether they meet the necessary institutional conditions.

1) Performance of drug susceptibility tests at a laboratory with at least 95% sensitivity and specificity for isonicotinic acid hydrazide and rifampicin in a drug sensitivity panel test performed by the Antibacterial Testing Methods Examination Committee of the Japanese Society for Tuberculosis or at a laboratory deemed to demonstrate equivalent capacity.

2) Established drug compliance confirmation system (i.e., Japanese DOTS); namely, the execution of DOTS within the institution and the establishment of a coordination system with health centers and other institutions to confirm drug compliance in outpatient treatment.

3) Consideration of measures against MDR-TB infection within the institution; specifically, negative-pressure rooms for isolating MDR-TB patients.

4) Physicians on staff (either full- or part-time) with sufficient experience and knowledge regarding MDR-TB treatment (e.g., a medical instructor in TB and mycobacterial infections certified by the Japanese Society for Tuberculosis).

#### 4.2. Conditions for Suitability in Individual Cases

Delamanid has been approved only for the treatment of MDR-TB and is considered unsuitable for other types of TB.

Considerations for the use of delamanid in individual cases are based on the following information: the possibility of successful treatment when using delamanid based on (1)–(4) in section 3 *Principles of Delamanid Use*, the risk of side effects from delamanid, and the risk of inducing resistance to delamanid.

The following information is necessary when assessing the suitability of using delamanid:

- \*Lesion site, patient age, TB treatment history, and comorbidities
- \*Sputum (or another suitable specimen) smear and culture findings, and drug susceptibility test results
- \*Previously used drugs (drugs used in the last 3 months, and drugs used in the past)
- \*Concomitant drugs
- \*Risk of discontinuing treatment during hospitalization and during post-discharge outpatient care, and methods for confirming drug adherence
- \*ECG findings

#### 4.3. Course of Cases of Delamanid Use and Conditions for Continuing Use

The risk of inducing resistance to delamanid is high in cases in which negative conversion of bacilli has not been achieved after 3 months of treatment; thus, an expert must decide whether to continue administration. Proper consultation and advice are also necessary when side effects are suspected.

Therefore, in all cases treated with delamanid, after 90 days of treatment, an expert should decide the suitability of continuing delamanid use on the basis of the following information: sputum (or another specimen) smear and culture results, drug susceptibility test results, and concomitant drugs.

In addition, in cases in which cultures are still positive on day 90 of delamanid use, a delamanid susceptibility test must be performed using the most recently isolated strain.

Delamanid use should be continued in cases exhibiting negative conversion of bacilli without side effects; however, there are no clinical trials in which delamanid use was continued for more than 6 months. If delamanid use continues for more than 6 months, an expert must be consulted again at that point.

#### 5. Investigating the Efficacy of Delamanid

Delamanid treatment outcomes have been reported in a limited number of cases. However, in the future, the efficacy and safety of delamanid must be confirmed in clinical set-

tings. For at least 2 years after the conclusion of delamanid treatment, the following information regarding clinical efficacy should be gathered and analyzed:

- \*Lesion site, patient age, TB treatment history, and comorbidities
- \*Sputum (or another suitable specimen) smear and culture findings, and drug susceptibility test results
- \*X-ray findings : classification of pulmonary tuberculosis according to the Japanese Society for Tuberculosis, sites with infiltrative shadows and cavities, cavity size, and wall thickness
- \*History of drugs used prior to delamanid
- \*Use of concomitant drugs (including adherence status)
- \*Presence of side effects (including ECG)
- \*History of surgical treatment

#### 6. Conclusions

Delamanid has recently been approved in Japan for the treatment of MDR-TB. The widespread use of this new drug may result in unexpected side effects and interactions. In addition, the gathering and analysis of clinical information may reveal that delamanid is superior to existing TB drugs in terms of efficacy and side effects, thus leading to its use in a wider array of conditions. This will require proper use starting from its introduction on the market as well as the accumulation and analysis of information from cases of delamanid use. We sincerely hope this statement serves as a reference for the proper use of delamanid and we hope for your cooperation in gathering information about cases delamanid use.

#### References

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