

PMDT in Japan

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Proportion of drug resistance, Japan (Ryoken sampling survey)

Without treatment	1977	1982	1987	1992	1997	2002	2007
INH0.1(1997=0.2)		5.8%	3.9%	3.7%	4.4%	2.8%	3.1%
INH1	2.2%	2.0%	1.4%	1.6%	2.5%		
RFP	0.4%	0.7%	0.5%	0.8%	1.4%	1.0%	0.7%
SM	3.1%	5.1%	4.7%	3.8%	7.5%	7.0%	5.6%
EB	3.0%	2.4%	0.9%	0.7%	0.4%	1.2%	1.3%
H0.1+R		0.9%	0.5%	0.3%	0.8%	0.7%	0.4%
H1+R	0.3%	0.4%	0.1%	0.1%			
LVFX							3.2%

Proportion of drug resistance by surveillance (MDR and INH resistance)

	total			new		retreatment	
	MDR	H res	proportion of exam	MDR	H res	MDR	H res
2007	1.2%	6.2%	41.8%				
2008	1.1%	4.9%	45.7%				
2009	0.8%	5.0%	63.5%				
2010	0.8%	4.7%	72.9%				
2011	0.7%	4.1%	73.7%				
2012	0.7%	4.6%	74.1%	0.5%	4.0%	4.0%	12.1%
2013	0.6%	4.8%	73.2%	0.4%	4.5%	3.7%	8.0%
2014	0.7%	4.6%	74.5%	0.56%	4.1%	3.34%	12.7%

Surveillance

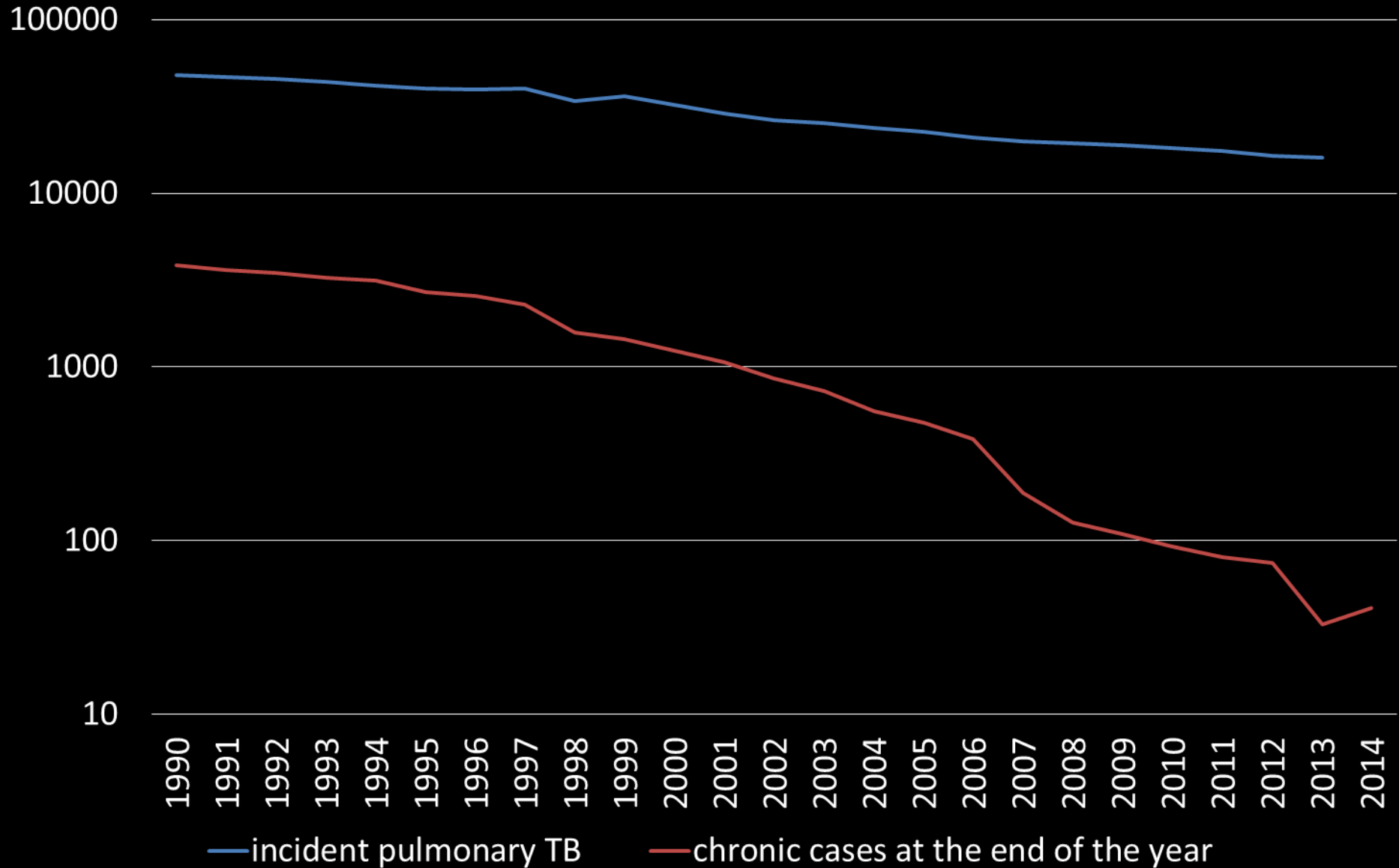
TB surveillance of Japan is not treatment based but disease-activity based. If failure, continue to be registered.

Cohort analysis started only in 2000s and no specific cohort analysis of MDR TB.

Chronic TB in Japan

Year	prevalent chronic TB	TB incidence
1990	3859	51821
1995	2698	43078
2000	1244	39384
2006	387	26384
2007	188	25311
2008	127	24760
2009	109	24170
2010	92	23261
2011	80	22681
2012	74	21283
2013	33	20681
2014	41	

FChronic cases in Japan



Treatment of MDR TB

Treatment upon individual DST to each drug (Japan)

priority drugs 4-5: PZA-EB-FQ-AG-TH-PAS-CS

DLM / LZD: potent drugs but second choice in Japan
now

Quality of DST (first line drugs) was assured by the periodical QC by Japan Tuberculosis Society. (no QC for the DST to second line drugs)

Management

Hospitalization of TB cases are basically done at the TB beds. All sputum smear positive TB cases are basically hospitalized in Japan. (total 6000-7000 cases per year and around 200 hospitals are qualified for the hospitalization of TB cases). All 200 hospitals can hospitalize any kind of TB cases. Around 20 hospitals hospitalize MDR TB cases. Total detected MDR TB cases are around 60-100 and 10-20 cases of these are hospitalized in Fukujuji hospital.

Supervision

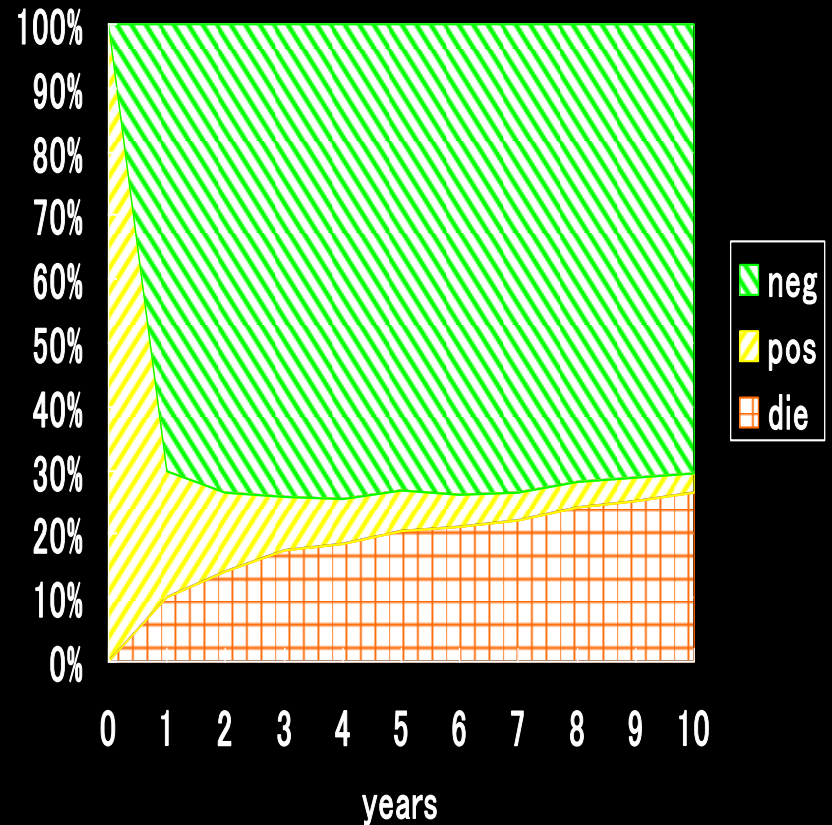
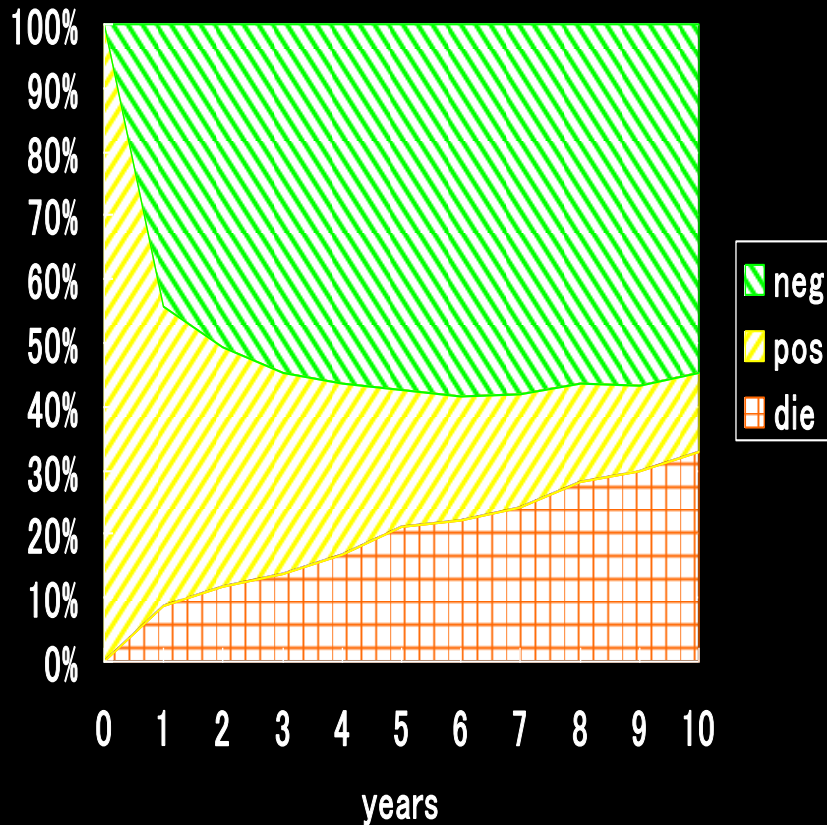
Difficult TB cases are either referred to specialist hospitals treated at the local hospital and consulted to specialist hospitals.

All TB cases are supervised by government (public health centers) and regimen is consulted at the committee in the public health centers.

Fate of MDR TB in F hospital

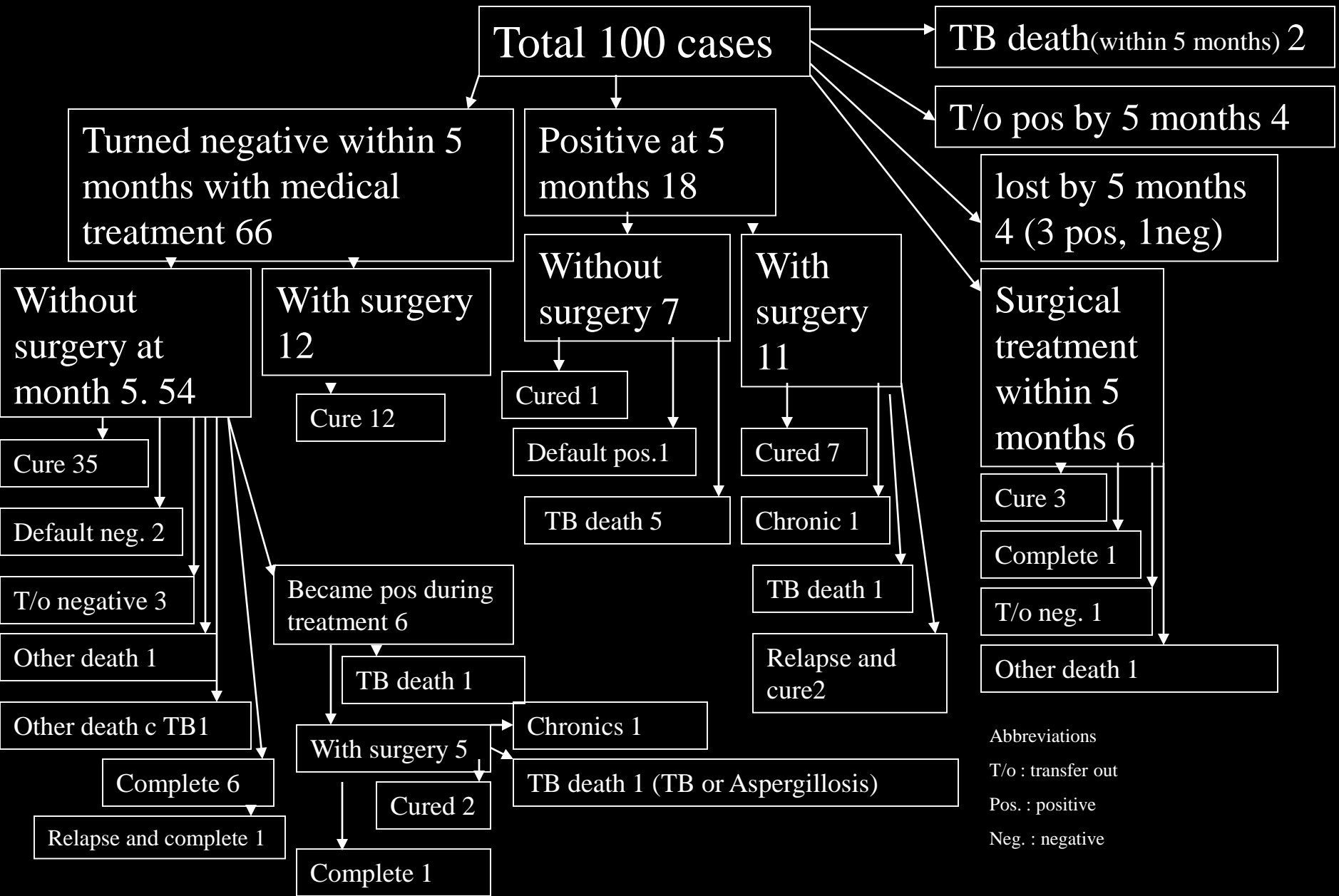
1970-97

1990-2009



Treatment result of 100 MDR cases, 1990s,

Fukujuji hospital, this data is confidential as yet



Comparison between 200-05 vs 1990s

		2000-05 (102)	1990s(100)
cure (and negative during 2 year fu)		33	62
cure (without follow up)		26	8
unknown	return to home country	1	0
(after	die	6	3
conversion)	transfer	14	4
	lost	4	3
	without information	1	0
Fail	chronic	2	2
(without	die	9	10
Conversion)	lost	2	4
	transfer out	2	4
Relapse and cure later		2	0

Before and after LZD

	before		afer
	1990-2001	2002-2011	2011-
Resistant drug		5.05	4.85
XDR		21/158(13%)	5/28(18%)
Cure%	65%	54%	39%
Cure+t/o neg.	74%	74%	82%
Fail %	19%	15%	7%

Experiences in Fukujuji hospital

	-1988	1989-2000	2000-2011	2011-2014
Age	48	47	48	48
Resistant drug (without PZA/LVFX)	4.6	3.9	4.4	4.1
(with PZA/LVFX)			4.9	5.0

Treatment result in Fukujuji hp

	-1988	1989-2000	2000-2011	2011-2014
cure	52(relapse1)	77(relapse2)	107(relapse 3)	24
t/o with negative	20(maybe lost)	6	38(relapse1)	23
(total favorable)	52-72(50-69%)	83(73%)	144(75%)	47(76%)
Died with positive	9	11	18	2
t/o positive	0	4	6	2
Lost, positive	0	6	4	0
Failure	16	0	1	2
(total unfavorable)	25 (24%)	21(19%)	29(15%)	6(10%)
Died with negative	8	4	9	3
Lost, negative	0	3	8(2 relapse)	1
Turned negative	0	0	0	5
Unknown	1	1	0	0

Infection control

Modern TB infection control is based upon US-CDC recommendation in 1994 and in Japan started in 2000s.

All sputum smear positive TB cases are hospitalized and infection control is done to these all. Most of the current infection of TB occur before diagnosis of TB.

1. Delamanid

Drug information

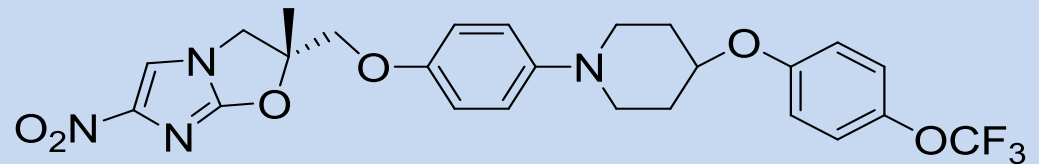
Generic name

Delamanid

Structure

剂形

Oral drug



有效成分

Delamanid 50mg/tab

mechanism

Inhibition of mycolic acid
synthase

效能·效果

Indication (bacilli)
susceptible M. tb
indication
MDR - TB

Dosage

100mg bid

Restrictions for use, Institutional criteria

- 1 QC of DST (INH and RIF resistance : sensitivity and specificity >95% by panel testing of Japan TB society QC)
- 2 Japanese DOT is done
- 3 Air born infection isolation room
- 4 Human resources : with experiences of MDR treatment

4. Responsible access program

Before starting treatment

Applicant (doctor)

4 Request of data follow up. Drug distribution after consent

③ judgement result

① registration after IC and application of the use of delamanid

Otsuka Pharmaceutical company

⑤ after use data collection on Pharmacovigilance and effectiveness

database of all cases

RAP

Otsuka

computer

② judgement and advise

Judgement committee
Judgement on the use of delamanid and advise To prescribing doctors

* Consent and confirmation

- indication - all cases will be monitored
- DST to Delamanid
- agree to the RAP, follow recommended treatment by JTS
- Institutions must meet the JTS criteria
- Cases must agree that the information will be sent to RAP

Responsible access program

The screenshot shows the Daiichi Sankyo website's 'Responsible Access Program' page. The page is titled '医薬関係者向け情報サイト' (Information site for medical professionals) and features a search bar, navigation menu, and a main content area. The main content area includes a '製品情報' (Product Information) section with a table of products. The table has columns for '医薬品名' (Product Name), '添付文書情報' (Product Information Leaflet), '改訂案内' (Revision Notice), 'インタビューフォーム' (Interview Form), '副作用発生頻度' (Frequency of Adverse Effects), '使用上の注意解説' (Explanation of Precautions), '適正使用に関する情報' (Information on Proper Use), 'くすりのしおり' (Medicine Reminder), '製剤写真' (Photograph of the Preparation), '配合変化情報' (Information on Formulation Changes), '包装・流通コード' (Packaging and Distribution Code), and 'その他' (Others). The '医薬品名' column lists '医療用医薬品' (Medical Products), '体外診断用医薬品' (In Vitro Diagnostic Products), and '医療機器' (Medical Devices). The '適正使用に関する情報' column has a red circle around a right-pointing arrow icon, with a red arrow pointing to a callout box that says 'こちらをクリック' (Click here). Below the table, there is a 'タ行' (T) section with a row for 'デルティバ錠50mg' (Delteiba 50mg) and a link to '輸液・栄養製品は大家製薬工場へ' (For infusions and nutritional products, please go to the Daiichi Sankyo factory).

医薬品名	添付文書情報	改訂案内	インタビューフォーム	副作用発生頻度	使用上の注意解説	適正使用に関する情報	くすりのしおり	製剤写真	配合変化情報	包装・流通コード	その他
医療用医薬品 体外診断用医薬品 医療機器											
タ行											
デルティバ錠50mg	PDF	→	PDF	-	-	→	-	→	-	→	-
ナ行											

輸液・栄養製品は大家製薬工場へ

こちらをクリック

Judgement result, Jan 29, 2016

requested	59
appropriate	46
inappropriate	10
pending	3
treated	?

10 cases not accepted with RAP

1. Non MDR :2
2. No information of DST
3. extrapulmonary
4. Culture negative for 2 years and not necessary
5. Turned to negative with LSEZ and add DLM
6. Add EVM + DLM to failing regimen
7. Add only LZD+DLM
- 8 add CS+DLM
9. Add only DLM

Japanese experiences in Fukujuji hospital

SN	sex	age	Nationality	culture	resist at start	drugs	regimen	outcome	ADR
1	M	43	Chi	neg		HREZTL(pre)	KLzdCs		
2	M	55	Jap	neg		HRSEZL(pre)	TCsPas		
3	F	32	Afgan	neg		HRSZ	H9KPas		
4	F	29	Jap	pos		HRSEZL(pre)	KTLzdPas		
5	M	72	Jap	neg		HRSEZKTL(X)	HECsPasEvm		
6	M	63	Jap	neg		HREK	ZLLzdCsPas		plt<70T
7	M	57	Jap	neg		HREST	HRbtEKLzdCsPas		
8	M	52	Jap	neg		HR	EZLTPas		
9	M	49	Jap	pos		HR	ZELS		
10	M	49	Jap	pos		HR	ZLPasCs		
11	M	60	Phil	pos		HRSEZT	ZLLzdCsPas		

(all cases turned to negative during treatment)

Monitor

Every 3-6 month, company request information for

- Effectiveness – sputum smear / culture
- ADR – symptom / blood test ECG

Cost of MDR TB treatment

Total TB medical cost in Japan in 2012 was 27 billion Yen (around 250 million US\$, 11 thousand US\$/person). We have no differentiation between MDR and non MDR TB. The majority of the cost was hospitalization cost.

The proportion of MDRTB among newly diagnosed cases is around 0.7% and the average duration of hospitalization of MDR TB is around 3 times higher than non MDR TB. There are around 40 chronic cases that are hospitalized. Roughly speaking, the medical cost of MDR TB will be around 4% of all TB cost, that is around 1 Billion Yen (around 9 million US\$).

Cost of MDR TB treatment

There is a threat of increase of drug cost.

Linezolid : 7000 Yen / 600mg. 1 260 000 Yen with 6 months treatment.

Delamanid : 26000 Yen / 200mg. 4 680 000 Yen with 6 months treatment.

If both drugs are used, 6 million Yen = 50-60 000 US\$

If 30 cases are treated with this regimen, total amount will be 180 million Yen with these drugs only. (around 0.7% of all TB cost). With the introduction of Linezolid, the proportion of failure decreased by 5%. To avoid one failure case, the cost will be 20-40 million Yen? (admission of one chronic case will cost around 7 million Yen / year)