Is there any role for injectable agents in management of MDR/RR-TB?

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Outline of the lecture

- Role of the injectable agent
- Are all-oral regimens based on Group A drugs sufficient
- Using the 2021 WHO recommended regimens in patients that may have had renal disease (due to the injectable agent or other causes)

Some recent history of WHO recommendations around the use of the injectable agent.

- Prior to August 2018, MDR/RR-TB treatment guidelines recommended that a member of the aminoglycoside (amikacin or kanamycin) or polypeptide (capreomycin) class be administered parenterally as part of treatment.
- For the patient, this meant painful daily intramuscular injections for many months, and the risk of irreversible deafness and other harms, such as renal dysfunction and electrolyte disturbance.
- In 2019, the World Health Organisation (WHO) changed the guidelines, de-prioritising the injectable-containing regimens and recommending use of both longer (18-20 month) and shorter all-oral regimens.

Evidence from the endTB Observational Study

- In the endTB Observational Study, we did a sub-study to answer a question related to injectable use within RR/MDR-TB treatment regimens, namely: **“Among individuals receiving a bedaquiline- and/or delamanid-containing regimen, do injectable-containing regimens offer greater effectiveness than all-oral regimens?”**

- We analyzed 1,120 RR-/MDR-TB patients treated in 16 countries.

EUROPEAN RESPIRATORY journal
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All-oral longer regimens are effective for the management of multidrug resistant tuberculosis in high burden settings

Palwasha Y. Khan, Molly F. Franke, Catherine Hewison, Kwonjune J. Seung, Helena Huerga, Sidney Atwood, Saman Ahmed, Munira Khan, Tanha Sultana, Mohammad Manzur-ul-Alam, Luan N.Q. Vo, Leonid Lecca, Kalkidan Yae, Serik Kozhabekov, Meseret Tamirat, Alain Gelin, Stalz C. Vilbrun, Marina Kikvidze, Jamil Faqirzai, Abdullaat Kadyrov, Alena Skrahina, Anita Mesic, Nana Avagyan, Mathieu Bastard, Michael L. Rich, Uzma Khan, Carole D. Mitnick

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- We compared the effectiveness of an injectable-containing regimen to that of an all-oral regimen among patients with drug-resistant tuberculosis who received bedaquiline- and/or delamanid as part of their multidrug regimen in the endTB Observational Study.
- Culture conversion was observed in 83.8% (526/628) of patients receiving an all-oral regimen and 85.5% (425/497) of those receiving an injectable-containing regimen.
- There was no significant difference between those who received an injectable and those who did not regarding culture conversion within six months.
- Conclusion: Our study supports the de-prioritisation of the injectable agents and most MDR-TB patients can be treated effectively with all-oral regimens and with less toxicity

More evidence from the endTB Observational Study:
Outcomes among patients receiving WHO-conforming individualized longer all-oral multidrug-resistant tuberculosis regimens (part 1 of 2)

- To date, treatment outcomes among patients receiving WHO-conforming individualized longer all-oral regimens that use new grouping of TB drugs in their design have not been published.
- We did a sub-analysis in the endTB Observational Study to determine if having more Group A drugs in the regimen effected the outcomes.

Groups & Steps	Medicine
Group A: Include all three medicines	Levofloxacin (Lfx) or moxifloxacin (Mfx)
	Bedaquiline (Bdq)
	Linezolid (Lzd)
Group B: Add one or both medicines	Clofazimine (Cfz)
	Cycloserine (Cs) or terizidone (Trd)
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol (E)
	Delamanid (Dlm)
	Pyrazinamide (Z)
	Imipenem/cilastatin (Imp/Cln) or meropenem (Mpm)
	Amikacin (Am) or streptomycin (S)
	Ethionamide (Eto) or prothionamide (Pto)
	p-aminosalicylic acid (PAS)

- Note: The analysis is ongoing, and the data presented in the next slide has not been finalized.

More evidence from the endTB Observational Study:
Outcomes among patients receiving WHO-conforming individualized longer all-oral multidrug-resistant tuberculosis regimens (part 2 of 2)

- In in FQ-susceptible MDR-TB, patients that received **exactly 3 Group A drugs** plus at least one Group B drug, plus or minus Group C drugs had a 75 to 85% success rate
- In in FQ-resistant MDR-TB, patients that received **exactly 2 Group A drugs** plus at least one Group B drug plus or minus Group C drugs a similar success rate as the exactly 3 Group A drugs
- In in FQ-resistant MDR-TB, patients that received **exactly 1 Group A drugs** plus at least one Group B drug plus or minus Group C drugs had a lower success rate than the exactly 2 or exactly 3 Group A drugs (analysis is ongoing and preliminary, a lower statistical significance has NOT yet been determined)

Note: Further analysis is ongoing and will examine which combinations of drugs has the best effectiveness

Conclusion: WHO-conforming individualized longer all-oral that contain Group A drugs do appear effective.

Dose adjustment in renal insufficiency

	Изменение периодичности приема	Рекомендуемые дозы и периодичность приема для пациентов с клиренсом креатинина <30 мл/мин, а также для пациентов, проходящих гемодиализ†‡§¶
Левофлоксацин	Да	Суточная доза 750-1000 мг/кг, 3 раза в неделю
Моксифлоксацин	Без изменения	400 мг один раз в день, ежнедневно
Bedaquiline	No change in mild to moderate renal insufficiency	No dose adjustment needed for mild to moderate renal insufficiency but should be used with caution in patients requiring peritoneal or hemodialysis. Drug level monitoring may be useful, once available.
Linezolid	No change	No dose adjustment is recommended, but metabolites may accumulate. Use with caution in severe renal insufficiency.
Клофазимин	Без изменения	No dosage adjustment required
Циклосерин	Да	250 мг один раз в день, ежедневно или 500 мг на прием в сутки, 3 раза в неделю‖
Этамбутол	Да	Суточная доза 15-25 мг/кг, 3 раза в неделю
Delamanid	No change in mild to moderate renal insufficiency	No dose adjustment needed for mild to moderate renal insufficiency, but delamanid is not recommended for patients with severe renal impairment.
Пиразинамид	Да	Суточная доза 25-35 мг/кг, 3 раза в неделю
Imipenem/cilastatin	Yes	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/ min
Meropenem	Yes	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/ min
Амикацин	Да	Суточная доза 12-15 мг/кг, 2 или 3 раза в неделю
Стрептомицин	Да	Суточная доза 12-15 мг/кг, 2 или 3 раза в неделю
Этионамид	Без изменения	Суточная доза 250-750 мг, ежедневно
Парааминосалициловая кислота	Без изменения	4 г на прием, два раза в день. Avoid in sever renal failure

- Note: Severe renal insufficiency = Creatinine Clearance (milliliters/ minutes) less than 30 mL/min

Dose adjustment in renal insufficiency

	Изменение периодичности приема	Рекомендуемые дозы и периодичность приема для пациентов с клиренсом креатинина <30 мл/мин, а также для пациентов, проходящих гемодиализ[†‡§¶]
Levofloxacin	Yes	750-1000 mg three times per week (not daily)
Moxifloxacin	Без изменения	400 mg daily
Bedaquiline	No change in mild to moderate renal insufficiency	No dose adjustment needed for mild to moderate renal insufficiency but should be used with caution in patients requiring peritoneal or hemodialysis. Drug level monitoring may be useful, once available.
Linezolid	No change	No dose adjustment is recommended, but metabolites may accumulate. Use with caution in severe renal insufficiency.
Clofazimine	No change	No dosage adjustment required
Cycloserine	Yes	250 mg once daily or 500 mg three times per week
Ethambutol	yYs	15–25 mg/kg three times per week (not daily)
Delamanid	No change in mild to moderate renal insufficiency	No dose adjustment needed for mild to moderate renal insufficiency, but delamanid is not recommended for patients with severe renal impairment.
Pyrazinamide	Yes	25–35 mg/kg three times per week (not daily)
Imipenem/cilastatin	Yes	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/ min
Meropenem	Yes	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/ min
Amikacin	Да	12–15 mg/kg two or three times per week (not daily)
Streptomycin	Да	12–15 mg/kg two or three times per week (not daily)
Ethionamide	No change	250 – 750 mg daily
PAS	No change	(PASER®) 8 g/day in two divided doses. . Avoid in sever renal failure

- Note: Severe renal insufficiency = Creatinine Clearance (milliliters/ minutes) less than 30 mL/min

Thank you

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