Amikacin treatment for multidrug resistant tuberculosis: how much monitoring is required?

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem. The World Health Organization (WHO) guidelines state that all patients suspected of MDR-TB should be given a group 2 injectable agent, usually an aminoglycoside. However, when taken for extended periods, these can cause nephrotoxicity, neurotoxicity and irreversible ototoxicity [1, 2].

Aminoglycoside-associated progressive hearing loss, from high to low conversational frequency sounds (0.5–2 KHz), affects at least 19% of MDR-TB patients [3, 4]. Most assessments are based on self-reported hearing loss, which is likely to significantly under-estimate the true proportion affected. Although both cochlear and vestibular functions can be impaired, the cochlea is predominantly damaged. This makes audiology testing, in particular serial audiograms that detect tone threshold changes, a useful way to assess ototoxicity, especially for non-conversational ultra-high frequency losses [3–5].

Despite this, there is no widely accepted protocol to monitor for ototoxicity in aminoglycoside-treated MDR-TB patients. Weekly to fortnightly audiograms are recommended after baseline evaluation, though financial and logistical barriers can limit this to monthly assessment [4].

We sought to determine the practicality of intensive assessments in subjects using long-term amikacin, and whether we detected early changes in high frequency hearing loss that could assist in clinical management and so avoid subjective ototoxicity.

A retrospective data review of all MDR-TB patients treated with amikacin at a single site London MDR-TB service between 2009 and 2011 was performed. This included information on audiology testing, renal assessments and serum trough level drug concentration. Amikacin was administered intravenously at 15 $mg \cdot kg^{-1}$ body weight (maximum 1 g) once daily in the morning, with dosing frequency later revised where indicated by toxicity or clinical decision. This case series is part of service evaluation of our drug resistant tuberculosis management and therefore ethical review was not required.

Audiological assessments were performed according to a standard local protocol, testing eight frequencies from 250 Hz to 8000 Hz. Hearing loss from a pre-treatment baseline was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) guidelines. Grade 1 hearing loss was defined as 15–25 dB loss at two different audiological frequencies. Baseline records taken within 5 days of commencing therapy were considered valid given that the earliest ototoxic manifestations from amikacin are generally not seen over this time [5, 6].

12 patients (10 males, median (interquartile range) age 27 (24–33) years) were reviewed. Eight were South Asian, three Eastern European and one East African. All were HIV negative, with no evidence of chronic renal or hepatic disease.

The median (interquartile range) dose of amikacin received was 98.2 (80.8–111.2) g over a median (interquartile range) period of 122 (92–144) days. Amikacin trough levels were measured a median (interquartile range) of every 7 (3–10) days and were consistently within target range. During treatment, patients had a median (interquartile range) of 6.5 (4–7.3) audiograms at 2.3 (2–3.3) weekly intervals. Seven (58%) received valid baseline audiograms, which were a median (interquartile range) 3 (-2–3) days after starting amikacin treatment. The remaining five patients had their baseline or first audiogram a median (interquartile range) of 11 (8–22) days from start of treatment.

Audiologically detectable hearing loss occurred in 7 (58%) subjects (table 1). Four had NCI CTCAE gradable hearing loss, while three had persistent changes at one frequency and hence were of concern to the audiologists. In two cases, hearing loss was also reported by the patient. Three (25%) complained of tinnitus. 10 (83%) stopped amikacin earlier than planned at the start of treatment. In eight cases this was due to audiological complaints (one discontinued amikacin because of severe tinnitus). Two stopped the drug for non-hearing related reasons (table 1). No patients had amikacin substituted with a different injectable. There have been no cases of TB reactivation since treatment completion.

TABLE 1 Amikacin use, ototoxicity detected during treatment and rationale for discontinuation of treatment

Hearing loss	Age years	Tinnitus	Maximal hearing loss[#] dB	Frequencies[¶] n (NCI CTCAE grade)	Stopped amikacin early (reason)	Progression of hearing loss after amikacin cessation?	Total treatment period days	Total dose g
Gradable hearing loss	29	Yes	50	2 (2)	Yes (hearing loss)	Yes	139	104.3
	26	Yes	75	6 (3)	Yes (hearing loss)	Yes	160	160
	37	No	55	1 (2)	Yes (hearing loss)	No	91	81.9
	23	No	75	4 (3)	Yes (hearing loss)	Yes	125	87.5
Early non-gradable hearing loss	31	No	15	1 (-)	Yes (hearing loss)	Unknown	75	75
	26	No	15	1 (-)	Yes (hearing loss)	No	123	115
	42	No	25	1 (-)	Yes (hearing loss)	No	178	109.9
No hearing loss	28	Yes	20	1 (-)	Yes (tinnitus)	No	119	107
	20	No	10	0 (-)	Yes (eczematous drug reaction[+])	No	121	77.5
	19	No	5	0 (-)	Yes (morning fatigue[§])	Unknown	78	54.6
	50	No	0	0 (-)	No	Unknown	92	92
	24	No	10	0 (-)	No	No	180	119.4

''Gradable hearing loss'' indicates pure tone audiogram changes sufficient to be categorised as grade 1 hearing loss (loss of 15–25 dB averaged at two or more contiguous frequencies in at least one ear) or higher. ''Early non-gradable hearing loss'' indicates audiogram changes insufficient to be gradable, but of clinical concern. Tinnitus self-reported by patients. [#]: from baseline at 8000 Hz; [¶]: at which sustained loss $\geqslant$15 dB detected, with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade allocated in parentheses; [+]:adverse event immediately following *i.v.* injection of amikacin; [§]: distressing morning fatigue resolving only after discontinuation of amikacin.

All four subjects with gradable hearing loss had further pure tone audiometry after amikacin was stopped. Three showed post-cessation progression to higher grades of hearing loss. Five of the other eight patients had one-off post-treatment audiograms; none demonstrated progression (table 1).

Patients' renal assessments (estimated glomerular filtration rate, eGFR) were performed at a median (interquartile range) interval of 7 (3–10) days. Renal function was consistently $\geqslant$90 mL·min^{-1} before, during and after treatment.

New WHO guidelines recommend at least 8 months of aminoglycoside treatment in MDR-TB [1, 7]. This reflects the importance of these drugs despite their toxicity. The guidance, however, does not advise on strategies to test for, classify or avoid hearing loss.

In the belief that early detection of ototoxicity and appropriate clinical management could minimise the adverse effects of treatment, we instituted a policy of baseline audiometry followed by fortnightly assessment when using amikacin. With some effort, this was generally achieved, and led to treatment modification if high frequency ototoxicity were observed.

Despite this, plus regular trough drug level monitoring, our strategy did not avoid ototoxicity: after about 4 months, over half the patients had audiologically detectable hearing loss and one-quarter developed subjective tinnitus. Of concern, the one-third that could be classified as having gradable (*i.e.* $\geqslant$15 dB at two frequencies) hearing loss continued to deteriorate despite amikacin cessation. This has been reported previously; and as patients with less severe hearing loss did not appear to run a similar course, our data suggest that early, small but sustained changes at higher frequencies should trigger the use of hearing preservative strategies, as outlined below [2].

In contrast to previous work reporting nephrotoxicity as a frequent adverse event of aminoglycoside therapy, our cohort had sustained normal renal function [2]. Our unit's policy is to give single dose, morning amikacin treatment with regular drug level monitoring.

Pending further data, to minimise ototoxicity we propose that where possible all patients starting amikacin have a baseline audiogram within 5 days of commencing treatment. Where, on therapy, early, sustained changes are demonstrated on audiograms, amikacin could be discontinued, the dose or frequency modified, or an alternative injectable agent used [8].

The American Speech-Language-Hearing Association (ASHA) have recommended an ototoxic threshold of $\geqslant$20 dB loss at one frequency or $\geqslant$10 dB loss at two [1]. This would have detected all cases of ototoxicity, though would have shortened amikacin treatment duration in two thirds of subjects, and by an overall

median of 71 days. Given the importance of aminoglycosides within a treatment regimen, this threshold appears oversensitive, and it may be better to use a loss of $\geqslant$15 dB at 6 kHz or 8 kHz on either any single audiogram plus tinnitus, or two consecutive audiograms in the absence of symptoms. From our data, this would avoid long term hearing loss but not lead to very early amikacin cessation. The proposed strategy can be evaluated prospectively.

Testing for changes at even higher frequencies (up to 20 000 Hz) may also assist in detecting earlier impairment and so avoid symptomatic, potentially irreversible hearing loss that affects speech frequencies [9]. However, this is not routinely available; neither is the use of preventive strategies with agents such as *N*-acetyl cysteine [10], nor testing for specific mitochondrial mutations associated with aminoglycoside-induced hearing loss. Of note, when applied to a South African MDR-TB population, the latter generated significant cost with no discernible benefit [11].

In summary, amikacin-associated ototoxicity appears common despite frequent audiological assessments and, in our experience, often led to treatment discontinuation after around 3–5 months. Avoidance of short- and long-term audiological damage in MDR-TB requires a combination strategy that includes systematic high frequency assessment and tailored drug dose optimisation. How to achieve this simply and effectively for the majority of patients with potentially life-threatening MDR-TB remains a significant and important global challenge.

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