Prevalence of adverse electrophysiological and audiometric changes in nontuberculous mycobacterium treatment regimens

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To the Editor:

Nontuberculous mycobacteria (NTM) are opportunistic pathogens capable of causing pulmonary disease [1]. Antimicrobial regimens are complex and lengthy, requiring multidrug treatment for 18–24 months [1]. Drug choices are limited due to NTM resistance profiles and interactions with other medications [2]. These medications can be associated with adverse events including prolonged corrected QT (QTc) intervals (macrolides, fluroquinolones and clofazimine), hearing loss and ototoxicity (macrolides and aminoglycosides) [3, 4].

The American Thoracic Society and Infectious Diseases Society of America practice guidelines recommend serial monitoring with ECGs for QTc prolongation and audiograms for ototoxicity [4]. Due to limited data, the optimal frequency of monitoring is unknown, even amongst NTM experts, making management changes following treatment-related adverse events challenging [5]. In this study, we aimed to identify the frequency of adverse electrophysiological and auditory events in patients treated for NTM and the impact of routine ECG and audiology monitoring on management.

A retrospective chart review at the Southern Alberta NTM clinic (Calgary, AB, Canada) was performed, consisting of 106 patients either currently receiving or having previously received NTM treatment between the years 2003 and 2021. ECGs at or prior to therapy initiation and follow-up ECGs while receiving NTM treatment were available for 78 patients. Patients with prolonged QTc at baseline (defined as ⩾500 ms based on the Bazett formula) were excluded. Included patients had a mean±SD age of 71.4±12.7 years and were predominantly female (n=52; 67%). 75 out of 78 patients (96.2%) received macrolides in their regimen and 34 out of 78 (43.59%) had NTM therapy primarily consisting of two QTc-prolonging agents. The mean QTc for these patients at baseline was 438.45±27.31 ms. Patients on average received 2.79±2.44 follow-up ECGs, with a mean±SD time between ECGs of 178.72±450.04 days. There was a significant increase ($p<0.0005$) in mean QTc while on therapy (to 451.33±32.11 ms) compared to baseline ECGs (table 1). Sex-based differences in QTc prolongation were noted, with females demonstrating a significantly greater increase in QTc ($p<0.0005$) compared to males ($p=0.056$); however, this may in part be due to the small available sample size with unevenly distributed groups. When separated by medications, there was no significant QTc prolongation amongst the four patients treated with fluoroquinolones ($p=0.11$). In contrast, significant QTc prolongation was observed more frequently with clofazimine-containing regimens ($p<0.0005$). QTc prolongation to ⩾500 ms occurred in only one patient (1.3%) not treated with clofazimine. Although not statistically significant, there was a trend towards greater odds of QTc prolongation (OR 6.81, 95% CI 0.77–60.79; $p=0.08$) in those on clofazimine.

Importantly, QTc prolongation had a minimal effect on treatment regimens for affected individuals. Only five out of 36 patients (13.8%) with a clofazimine-containing protocol had at least one QTc interval ⩾500 ms with an associated period prevalence of 6.41% over 16 years, based on the earliest baseline ECG available. Treatment was altered by the physician in only two instances due to QTc prolongation. In the first, NTM medications were held and later resumed without domperidone, an additional QTc-prolonging agent. In the second, treatment was adjusted and additional QTc-prolonging medications were removed due to persistent QTc prolongation. Our results are similar to a retrospective study of multidrug-resistant tuberculosis patients, where 0.6% of individuals required clofazimine discontinuation due to QTc ⩾500 ms [6].

Shareable abstract (@ERSpublications)
QTc prolongation was associated with clofazimine treatment and in two cases resulted in a treatment change. Audiometric deterioration was found but had limited clinical impact. Frequent ECG and audiometry monitoring may be unnecessary in all patients. https://bit.ly/3uI244P

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We also evaluated the incidence and prevalence of hearing impairment during NTM treatment. 29 patients had both baseline (defined as performed within 30 days of treatment initiation) and follow-up audiology performed. Similarly, this cohort was predominantly female (22 females *versus* seven males; 75.9% *versus* 24.1%) and older (mean±SD of 71.4±9.86 years). Significant audiometric deterioration was observed between baseline and follow-up audiograms, with a mean±SD hearing reduction for both ears of 3.19±5.84 dB ($p<0.0005$; range −30 to 30 dB). Both males and females had significant audiometric deterioration, with an increase of 3.75±6.23 dB and 2.89±5.72 dB ($p<0.0005$), respectively.

According to criteria set by the American Speech–Language–Hearing Association (ASHA), 18 patients (62.1%) in our study developed ototoxicity during treatment (table 1) [7, 8]. These criteria aim to identify early ototoxicity using small threshold changes that exceed test–retest variability [9]. However, a criticism regarding oversensitivity of these criteria is that they result in premature treatment changes without a clear clinical impact [9, 10]. Furthermore, ASHA criteria recommend repeat testing within 24 h to confirm changes, which is not a common practice in our clinic [8]. In contrast, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) use gradable hearing loss, which decreases sensitivity but may be more relevant to day-to-day practice [9, 11]. Using the NCI CTCAE criteria, six patients (20.7%) met grade 1 criteria and two patients (6.90%) met grade 2 criteria in at least one ear in follow-up audiology testing (table 1).

Given the duration of therapy for NTM treatment and older patient demographics, age-related hearing loss is an important confounder. Although threshold changes due to age are poorly established, it is predicted

TABLE 1 Corrected QT (QTc) intervals in 78 patients at baseline and on different types of nontuberculous mycobacterial therapy, and hearing change at follow-up compared to baseline audiology and corresponding ototoxicity criteria for 29 patients

Therapy	Patients, n	Baseline QTc, ms	QTc on therapy, ms	p-value[#]	QTc >500 ms	Management changes[¶]
All therapy types	78	438.45±27.31	451.33±32.11	<0.0005	5 (6.4)	2 (2.6)
Clofazimine	36[+]	446.81±25.83	466.16±29.41	<0.0005	5[§] (13.9)	2 (5.6)
Non-clofazimine	52[+]	434.89±27.77	436.32±27.80	0.52	1[§] (1.9)	0
Macrolide	75	437.34±27.09	448.08±29.06	<0.0005	4 (5.3)	1 (1.3)
Macrolide without clofazimine	54	435.89±28.02	436.08±26.90	0.60	1 (1.6)	0
Macrolide with clofazimine	33	445.24±25.24	462.48±24.66	<0.0005	3 (9.1)	2 (6.1)
Fluoroquinolone	4	449.75±13.07	456.4±32.25	0.11	1 (25.0)	0
	Patients, n	**dB change[f] right/ left ear**	**p-value[#] right/ left ear**	**NCI CTCAE grade 1/2[##]**	**ASHA[¶¶]**	**Management changes[¶]**
All therapy types	29	3.56±7.14/2.78±6.43	<0.0005/<0.0005	6 (20.7)[§§]/ 2 (6.9)[§§]	18 (62.1)	3 (10.3)
Azithromycin, ethambutol, clofazimine	7	6.28±6.87/2.10±6.31	<0.0005/<0.0005	3 (42.9)/1 (14.2)	5 (71.4)	1 (14.2)
Rifampin/rifabutin, azithromycin, ethambutol	17	2.20±5.59/2.75±5.80	<0.0005/<0.0005	1 (5.9)/0	8 (47.1)	1 (5.9)
Fluoroquinolone	2	5.00±9.16/7.00±7.59	NC	1 (50.0)[§§]/ 1 (50.0)[§§]	1 (50.0)	0
Aminoglycoside	3	0.42±5.59/0.64±3.55	NC	0/0	1 (33.3)	0
Other drug regimens[++]	6	3.06±9.29/3.55±8.12	NC	2 (33.3)/0	4 (66.7)	1 (16.7)

Data are presented as mean±SD or n (%), unless otherwise stated. NC: not calculated (as the number of samples was small). [#]: p-values were calculated using paired difference t-tests with R (version 4.1.1). [¶]: management changes consisted of any alterations to antibiotic therapy. [+]: antibiotic changes occurred in multiple patients, resulting in inclusion in both the clofazimine-containing and non-clofazimine-containing regimens. [§]: QTc prolongation seen in one patient when receiving both clofazimine-containing and non-clofazimine-containing regimens at different time-points. [f]: mean dB change for each ear was calculated by summing the change at each threshold and dividing by the number of thresholds tested; mean dB for both ears was calculated by summing the mean change for both ears at each threshold and dividing by the number of thresholds tested. [##]: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) define grade 1 hearing loss as a shift or loss of 15–25 dB relative to baseline averaged at two or more contiguous frequencies [11]; grade 2 consists of a threshold shift or loss of >25–90 dB averaged at two contiguous frequencies; grade 3 is defined as hearing loss sufficient to indicate therapeutic intervention, including hearing aids, with loss >25–90 dB averaged at three adjacent test frequencies; grade 4 is defined by indication of requirements for cochlear implant and additional speech–language-related services by hearing loss of >90 dB. [¶¶]: American Speech–Language–Hearing Association (ASHA) criteria define hearing loss as a decrease of 20 dB at one test frequency, >10 dB decrease at any two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained [8]. [++]: other drug regimens consisted of azithromycin, ethambutol, rifampin and clofazimine; azithromycin and ethambutol; or ethambutol and clofazimine. [§§]: one patient identified who satisfied both grade 1 and 2 NCI CTCAE criteria at different follow-up audiograms.

that, on average, hearing thresholds increase approximately 1 dB per year [12]. The average time on therapy at a follow-up audiology appointment was 254.18±182.19 days, indicating that threshold increases of approximately 1 dB would be expected. The average increase observed of 3.19 dB is greater than expected for simply age-related deterioration; however, this falls within the range of test–retest variability of ±5 dB at a single threshold [8,9].

Identified audiology changes resulted in medication changes in only three patients (10.3%). No patients met grade 3 NCI CTCAE criteria, which necessitate therapeutic intervention [11]. Although ototoxicity was a factor in management changes, it was often coupled with concerns of other adverse events including weight loss, visual side-effects and hearing-related adverse events of tinnitus and hearing loss. Associations of macrolides, such as azithromycin, with hearing toxicity have been identified in a large study of COPD patients [13]. In contrast to our findings, there was a significant decrease in hearing resulting in high rates of treatment discontinuation [13]. However, the authors suggested the employed criteria may have overestimated the incidence of hearing decrements [13]. Azithromycin was discontinued if patients had ⩾95th percentile age-adjusted hearing loss at 500, 1000, 2000 or 4000 Hz in either ear or patients with ⩾10 dB hearing loss at two frequencies in either ear when compared to previous audiometry testing [13]. When applying this to our patient cohort, 16 patients on azithromycin (57.1%) would have met criteria for discontinuation, whereas treatment cessation occurred in only 10.3%. These findings suggest a need for standardisation of criteria for monitoring hearing-related adverse events during NTM therapy.

This was a small single-centre exploratory retrospective study, with all the limitations inherent in such methodology. While we found that there was no significant QTc prolongation for those on macrolides not receiving clofazimine (p=0.60), we may have been unable to discern the significance of macrolide QTc prolongation due to the small cohort size and nearly all patients' therapies consisting of macrolides (75 out of 78; 96.2%). This warrants further investigation as macrolides are clearly identified as a causative agent in QTc prolongation [14]. Our analysis does not account for certain confounders such as the use of other QTc-prolonging agents or ototoxic medications. A recent cohort study using a large healthcare database found that short courses of azithromycin were not associated with prolonged QTc, but those with concurrent QTc-prolonging agents had significantly higher odds of cardiac events with azithromycin compared to amoxicillin [14]. Thus, in the NTM patient population, who are often complex and multimorbid, use of additional QTc-prolonging agents may occur and serial monitoring should be considered. With these limitations in mind, these findings suggest that frequent regular ECG and audiometry monitoring may be unnecessary in all patients. We recommend an initial ECG at therapy initiation to identify those patients with baseline prolonged QTc interval (such as >450 ms) and a minimum of one follow-up after initiation of therapy for those treated with a macrolide and/or clofazimine. In individuals with baseline QTc <450 ms, follow-up ECGs are likely to be unnecessary. While our study did not find the degree of ototoxicity to necessitate treatment discontinuation according to the NCI CTCAE, we did find that 6.9% had hearing loss in the moderate range of severity. Long-term outcomes of those with ototoxicity will be an important avenue of future study to discern the extent of permanent hearing loss. Serial monitoring may not be required in all patients but should be considered when symptoms appear or worsen (*i.e.* grade 3), as recommended in the tuberculosis treatment guidelines or for those on high-risk agents including systemic aminoglycosides [15]. Given the limited effective drug therapies for NTM, clinicians should consider regular risk assessments where ototoxicity and QTc prolongation are weighed against the risk of treatment failure or discontinuation. With that in mind, we suggest that reducing unnecessary testing is possible and should be considered a priority for this complex patient population.

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