Management of drug toxicity in *M. avium* complex pulmonary disease – an expert panel survey

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Abstract

Adverse events are frequent in NTM pulmonary disease treatment, but evidence to support their management is scarce. An expert panel survey on management of adverse events shows consistent opinions on management of hepatoxicity, ocular toxicity, ototoxicity, tinnitus and GI upset. These opinions can provide assistance in individual patient management decisions.

Keywords: antibiotic treatment; nontuberculous mycobacteria; adverse events; *Mycobacterium avium* complex; azithromycin

Treatment of *Mycobacterium avium* complex pulmonary disease (MAC-PD) requires prolonged courses of potentially toxic antimicrobials and has suboptimal outcomes, with culture conversion rates of 65% in patients treated for >1 year [1]. Across published cohorts, up to 70% of all treated patients reported a treatment-related adverse event [2-4] and 30-70% of patients receiving daily antimicrobial treatment permanently discontinue at least one drug in their initial regimen because of adverse events [2-4]. These regimen modifications may contribute to development of macrolide-resistance [5] or suboptimal outcomes.

There are very limited published data to support management decisions even for the most frequent adverse events in MAC-PD treatment and management of drug toxicity is poorly addressed in current guidelines. To know the opinions of clinicians with expertise treating MAC-PD, we designed a survey on adverse event management in MAC-PD, using the SurveyMonkey online tool (http://www.surveymonkey.com). The survey presented common adverse events in MAC-PD treatment (hepatotoxicity, ocular toxicity, gastro-intestinal upset, tinnitus and ototoxicity) and a choice of management strategies; the adverse events were selected by a during a face-to-face meeting at the European Respiratory Society conference (Paris, September 2018). Experts were selected from the NTM-NET (www.ntm-net.org) membership on basis of publication records of cohort studies of MAC-PD management. We sought to include experts from geographically diverse settings to capture the full range of opinions and underlying cultural differences and drug availabilities.

Twenty-three experts were identified and invited; 21 completed the survey. A summary of the questions and answers is presented in the Table. The full questions and answers of the survey are available in the Supplementary file.

There was almost unanimous agreement that mild, rifampicin-associated, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations do not require action beyond ongoing surveillance; treatment interruption or a switch to a rifamycin-free regimen was preferred by most respondents only with severe hepatotoxicity (ALT and/or AST concentrations >5 times the upper limit of normal). Hepatotoxicity, which may manifest as AST/ALT elevations or cholestasis [6], occurred in 19% of MAC-PD patients in two recent cohorts [4,7]. This hepatotoxicity is mostly an idiosyncratic (i.e. concentration/dose-independent) event, with spontaneous resolution and no recurrence after rifampicin reintroduction in >90% of MAC-PD patients [7], which mirrors previous experiences and recommendations in tuberculosis treatment [6].

Ocular toxicity by ethambutol was considered a reason to stop ethambutol or switch to another antibiotic class for 95% of the experts; 5% would interrupt and attempt a re-challenge. This aligns well with the available data. In two cohorts of MAC-PD treatment, ophthalmologist-confirmed ocular toxicity occurred in 26/364 (8%) and 8/229 (3%) patients on daily ethambutol therapy (15mg/kg/dose) [7,8] and 0 of 90 patients on thrice weekly dosing (25mg/kg/dose) [8]. Yet, in the Griffith *et al.* cohort, 99/229 patients (43%) had symptoms that warranted an ophthalmology consult and 24 (10%) stopped ethambutol at least temporarily [8]. The risk of ethambutol ocular toxicity increases with total drug exposure and thus it typically occurs late, i.e. after >6 months, in therapy [7,8]. Blurred vision and color vision disturbance are the most frequent manifestations, and these are mostly reversible after stopping ethambutol; four patients were re-challenged with ethambutol thrice weekly (25mg/kg/dose) and none developed recurrent ocular toxicity [8]. Stopping ethambutol without adding a third drug to the regimen occurs frequently [3,5,7], but is a known risk factor for development of macrolide-resistance [5] and should be avoided.

Azithromycin was uniformly considered most likely responsible for bloating and diarrhea. Its management differed in the panel, with switching to clarithromycin, continuing azithromycin with supportive treatment and lowering the azithromycin dose as the most frequent strategies. These strategies evolve around maintaining macrolide therapy and highlight the key role of macrolides in MAC-PD treatment [1]. Lowering azithromycin dose or offering supportive treatments (e.g. nighttime administration, anti-emetics) both proved successful in a previously published cohort [9]. Similarly, lowering the azithromycin dose or switching to clarithromycin were the preferred strategies for azithromycin-treatment-emergent tinnitus (65% and 20% of votes). Tinnitus occurred in 18 and 46% of patients in two cohorts of high-dose (500-600 mg/day) azithromycin therapy for MAC-PD [4,9]. One study reported good outcome of lowering azithromycin doses from 600mg to 300mg/day [9].

Lowering azithromycin doses may increase the risk of treatment failure in patients with severe or fibro-cavitary disease in whom regular doses may already be subtherapeutic [10,11]. A switch to clarithromycin can be successful, but it is unproven whether this is due to clarithromycin causing less bloating and diarrhea or being less ototoxic [4,9] or due to lower macrolide exposure because of shorter half-life and greater reduction in serum clarithromycin (68%) than azithromycin (23%) concentrations caused by rifampicin-induced cytochrome p450 metabolism [10].

Ototoxicity with hearing loss is a notorious adverse event of parenteral aminoglycoside therapy and was observed in 42% (10/24) patients treated with streptomycin and 27% (3/11) of patients treated with amikacin for macrolide-resistant MAC-PD [12]. Our panel preferred to lower the amikacin dosing frequency to thrice weekly or stop amikacin, as ototoxicity risk is associated with total aminoglycoside exposure. Switching to an alternative drug was not a common strategy, likely because no alternative drugs with proven efficacy in severe MAC-PD exist [5,9,12]. Because aminoglycoside antimicrobial activity is exposure-dependent [10], lower dosing is likely to negatively impact microbiologic outcomes. Switching to amikacin liposome inhalation suspension (ALIS) or

inhalation of conventional amikacin could be a rational strategy; in the CONVERT trial, only 10/223 (4.5%) of patients receiving ALIS reported hearing loss versus 7/112 (6.3%) in the control arm [13]. However, the safety of switching to inhaled formulations of amikacin has not been investigated in the setting of proven amikacin ototoxicity.

The panel was also asked to rank five antimicrobials (amikacin, clofazimine, moxifloxacin, linezolid and bedaquiline) as their preferred replacements for ethambutol and rifamycins; clofazimine and amikacin (or streptomycin) were preferred replacements for both the rifamycins and ethambutol. This selection is in part driven by local availability and patient preferences, particularly for clofazimine [4], but also reflects *in vitro* activity and *in vivo* treatment outcomes [4,5,9,12]; the high ranking of the parenteral and toxic amikacin and streptomycin emphasizes the limited options available. The outcome of MAC-PD treatment with regimens in which amikacin replaces rifampicin or ethambutol or in which clofazimine replaces ethambutol has not been addressed in clinical studies.

This survey focused on MAC-PD treatment and only addressed a set number of adverse events; several other important adverse events, e.g. vestibular toxicity, nephrotoxicity and QTc interval prolongation, may arise during MAC-PD treatment [8,10,12]. Toxicities and outcomes are different in treatment of other NTM species, e.g. *M. abscessus*. Also, the members of the panel, whilst managing large numbers of NTM patients, are in frequent contact as members of numerous committees and projects. As a result, the topics addressed in the survey have likely been discussed previously between the experts, which may explain some of the level of agreement. This level of agreement contrasts with the very limited published data available to support these management decisions and a previous survey of other aspects of MAC-PD treatment where agreement among an expert panel was low [14].

In summary, this survey summarizes the opinions of MAC-PD experts on treatment-related adverse event management. Hepatoxicity of rifampicin was preferentially managed by watchful waiting or -if severe- interruption and reintroduction of normal doses. Azithromycin-associated diarrhoea and tinnitus were preferentially managed by lowering the dose or switching to clarithromycin, with caveats. Ethambutol was discontinued in case of ocular toxicity; with careful monitoring, reintroduction using a thrice weekly regimen might be safe in selected patients but our panel does not recommend this based on the low level of evidence and the potential associated risk. In the event of amikacin-induced hearing loss the panel preferred lowering the dosing frequency or discontinuation. If rifampicin or ethambutol needs to be discontinued, clofazimine and amikacin were the favoured replacements. These opinions can provide assistance in clinical decision making, but should not be used as an alternative to expert consultation.

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Potential Conflicts of Interest

SA reports advisory board membership from Insmed, outside the submitted work. CA reports consulting fees from Insmed, outside the submitted work. JC reports research grants from GlaxoSmithKline, Boehringer-Ingelheim, AstraZeneca, Pfizer, Bayer Healthcare, Grifols, and Insmed; and personal fees from GlaxoSmithKline, Boehringer-Ingelheim, Pfizer, Bayer Healthcare, Grifols, Napp, Aradigm corporation, and Insmed, outside the submitted work. CD reports grants from Insmed, Spero, and Beyond Air; and personal fees from Insmed, Paratek, Spero, Horizon, Mieji, Johnson and Johnson, Matinas Biopharma, Cipla, and Beyond Air, outside the submitted work. NH reports consulting fees from Insmed, outside the submitted work. JvI reports manuscript preparation support from Physicians World, advisory board membership from Insmed, and a Veni personal grant from ZonMW / Ministry of Health, Netherlands, during the conduct of the study. JvI also reports advisory board membership from Janssen pharmaceuticals, Spero Therapeutics, and Paratek, outside the submitted work. ML reports personal fees from Savara, Insmed, and Meiji, outside the submitted work. TM reports: Site PI for clinical trial in NTM lung disease, consultant re studies in NTM lung disease, and funds paid to institution from Insmed; Honoraria for CME presentations in mycobacterial disease, funds paid to institution from AstraZeneca and Novartis; Consultant fees paid to institution from Horizon Therapeutics, Spero Therapeutics, and RedHill Biopharma, all outside the submitted work. KM reports personal fees from Insmed, outside the submitted work. EP reports advisory board fees from Insmed, outside the submitted work. FCR reports grants from Bayer Healthcare, Grifols SA, Insmed Inc, Novartis, and InfectoPharm; personal fees from Bayer Healthcare, Grifols SA, Insmed Inc, AstraZeneca, Novartis, Chiesi, PARI, Vertex, and Boehringer Ingelheim; and clinical trial participation from Insmed Inc, Novartis, Chiesi, Vertex,

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Table: Summary of survey questions and responses

Q	Type	Disease severity	Event	Culprit	Option	Vote (%)
1	NB	Moderate-severe	AST/ALT 2xULN	Rifampicin	Repeat test	86
					Lower dose	0
					Thrice weekly	0
					Interrupt rifampicin	4
					Interrupt regimen	0
					Switch to rifabutin	0
					Switch to other class	10
2	NB	Moderate-severe	AST/ALT 5xULN	Rifampicin	Repeat test	0
					Lower dose	0
					Thrice weekly	5
					Interrupt rifampicin	20
					Interrupt regimen	40
					Switch to rifabutin	5
					Switch to other class	30
3	NB	Moderate-severe	Blurry vision	Ethambutol	Thrice weekly	0
					Lower dose	0

					Stop ethambutol Interrupt ethambutol Switch to other class	11 5 84
4	FC	severe	Bloating/diarrhoea	?	Rifampicin Ethambutol Azithromycin Amikacin	0 0 100 0
5	FC	severe	Bloating/diarrhoea	Azithromycin	Lower dose To clarithromycin Switch to other class Supportive Rx	21 47 5 26
6	FC	severe	Slight hearing loss	Amikacin	Lower dosing frequency Switch to ALIS Stop amikacin Switch to other class Continue iv amikacin	70 0 25 5 0
7	NB	moderate	Tinnitus	Azithromycin	Lower dose To clarithromycin Switch to other class Interrupt azithromycin Continue regimen	65 20 0 15 0
8	NB / FC	Mild-moderate	Need class switch	Rifampicin	Clofazimine Amikacin/streptomycin Moxifloxacin /other FQ Linezolid	4.40* 4.21* 2.30* 2.15*

					Bedaquiline	2.10*
9	NB / FC	Mild-moderate	Need class switch	Ethambutol	Clofazimine Amikacin/streptomycin Moxifloxacin /other FQ Linezolid Bedaquiline	4.30* 4.05* 2.25* 2.25* 2.16*

Note: *= mean preference score; NB= nodular-bronchiectatic; FC= fibrocavitary; xULN= times upper limit of normal; Rx= treatments; FQ= fluoroquinolone antibiotic