ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

Amikacin Liposome Inhalation Suspension Clinical Benefit-Risk Assessment for Refractory MAC Lung Disease

Theodore K. Marras, Mariam Hassan, Kevin C. Mange, Monika Ciesielska, Shilpa Dhar Murthy, Zhanna Jumadilova, Anjan Chatterjee

Please cite this article as: Marras TK, Hassan M, Mange KC, *et al*. Amikacin Liposome Inhalation Suspension Clinical Benefit-Risk Assessment for Refractory MAC Lung Disease. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00623-2021).

Amikacin Liposome Inhalation Suspension Clinical Benefit-Risk Assessment for Refractory MAC Lung Disease

Authors: Theodore K. Marras, MD, MSc[1], Mariam Hassan, PhD, BPharm[2], Kevin C. Mange, MD, MSCE[2], Monika Ciesielska, MS, MA[2], Shilpa Dhar Murthy, MBBS, MS[2], Zhanna Jumadilova, MD, MBA[2], Anjan Chatterjee, MD, MPH, MBA[2]

[1]Department of Medicine, University of Toronto and Toronto Western Hospital, Toronto, ON, Canada; [2]Insmed Incorporated, Bridgewater, NJ, USA

Corresponding author information:

Theodore K. Marras, MD
Toronto Western Hospital
7E-452, 399 Bathurst St.
Toronto, ON M5T 2S8, Canada
Email: Ted.marras@uhn.ca

Take home message for social media (256/256 characters):

Marras et al. report a low number needed to treat and high number needed to harm, supporting addition of amikacin liposome inhalation suspension to guideline-based treatments in patients with treatment-refractory *Mycobacterium avium* complex lung disease.

To the Editor:

Mycobacterium avium complex (MAC) is the leading cause of nontuberculous mycobacterial lung disease, which can be associated with progressive lung damage and increased mortality [1]. Patients with MAC lung disease have substantial disease burden and limited treatment options [1]. Up to 40% of patients experience failure with lengthy multidrug treatments, relapse, or reinfection [2]. For patients with treatment-refractory MAC lung disease (persistent MAC-positive sputum despite ≥6 months of guideline-based therapy [GBT]), international guidelines recommend the addition of amikacin liposome inhalation suspension (ALIS) to GBT regimens [3]. In clinical trials, patients with treatment-refractory MAC lung disease had improved culture conversion with ALIS + GBT vs GBT [4, 5].

To facilitate benefit and risk interpretation for clinical care, the number needed to treat (NNT) and number needed to harm (NNH) values indicate how many patients would need to receive treatment over a comparator until 1 patient experienced that benefit or risk, respectively [6]. These post hoc analyses of ALIS clinical trial data aimed to assess the NNTs and NNHs for ALIS + GBT compared with GBT in patients with treatment-refractory MAC lung disease.

We studied results from adults with confirmed MAC lung disease diagnoses [7] and persistently positive sputum cultures despite ≥6 months of GBT who were enrolled in clinical trials evaluating the efficacy and safety of adding ALIS (or placebo) to continued GBT [5]. Our analyses included the phase 3, open-label, randomised (2:1) CONVERT study (NCT02344004) [5, 8], an open-label safety extension of CONVERT (study INS-312; NCT02628600) [8, 9], and a phase 2, double-blind, placebo-controlled study with an open-label extension (study TR02-112; NCT01315236) [4, 9]. Patient inclusion and exclusion criteria for these studies have been reported [4, 5, 8, 9]. Study protocols and patient informed consent forms were reviewed and approved by an independent ethics committee or institutional review board at each site in these studies [4, 5, 8, 9].

The benefit of ALIS over GBT was assessed using CONVERT data (ALIS + GBT [n=224] vs GBT alone [n=112]) [5, 8]. NNTs were calculated for culture conversion by month 6, sustained culture conversion by month 12, and durable culture conversion 3 months off all MAC treatments in patients completing 12 months of postconversion treatment [6]. For the risk of adverse events of special interest with ALIS compared with GBT alone or with placebo, pooled data from all 3 clinical trials (ALIS + GBT [n=404] vs GBT ± placebo [n=157]) [4, 5, 8, 9] were assessed, including ototoxicity, nephrotoxicity, neuromuscular effects, and allergic alveolitis.

Due to varied durations of treatment across studies, unadjusted and exposure-adjusted NNH values were calculated [6]. The risk difference between treatment arms was calculated with 95% CIs for NNT and NNH. When the 2-sided 95% CI for the risk difference included 0, as may occur in the case of rare events in very small populations, the 95% CI for NNH included infinity. In these cases, the worst-case scenario for the lower bound of the NNH has been reported. The upper bounds of the 95% CI for most reported NNH values were infinite (ie, an infinite number of patients would be required to show any harm within the 95% CI).

The NNTs were determined from results in the CONVERT study (N=336) and are presented in**Table 1A** [8]. In patients achieving culture conversion by month 6 of treatment, the NNT was 5 (95% CI, 3.6-8.2) with 29.0% of patients achieving culture conversion when treated with ALIS + GBT vs 8.9% of patients treated with GBT alone. At 12 months of sustained conversion, the NNT was 6 (95% CI, 4.6-10.3), and a higher proportion of patients had sustained culture conversion with ALIS + GBT vs GBT alone (18.3% vs 2.7%). For durable culture conversion at 3 months off all MAC treatments, the NNT was 6 (95% CI, 4.8-8.9), and a higher proportion of patients had durable culture conversion with ALIS + GBT vs GBT alone (16.1% vs 0%).

Risk estimates of adverse events of special interest with ALIS were determined using pooled safety data from all 3 clinical trials (N=561) [4, 5, 8, 9]. The unadjusted NNH values were 13 for ototoxicity, 60 for nephrotoxicity, 43 for neuromuscular effects, and 51 for allergic alveolitis (**Table 1B**). Exposure-adjusted NNHs were calculated to account for differences in treatment durations across studies (327 patient-years [PYs] for ALIS + GBT; 87 PYs for GBT ± placebo). The exposure-adjusted NNHs were 28 for ototoxicity, 166 for nephrotoxicity, 40 for neuromuscular effects, and 60 for allergic alveolitis (**Table 1C**). Ototoxicity was reported in 72 of 404 patients treated with ALIS + GBT (17.8%), mainly comprising tinnitus (6.9%) and dizziness (5.9%). Other ototoxicity symptoms (deafness, deafness neurosensory, deafness unilateral, hypoacusis, balance disorder, presyncope, and vertigo) were each reported in <3% of patients treated with ALIS + GBT. The exposure-adjusted NNHs for ototoxicity symptoms were 20 for tinnitus, 36 for dizziness, and >40 for other ototoxicity symptoms (data not shown).

In evaluating the benefit and risk of a treatment, NNT and NNH measures help clinicians intuit statistical data to understand how treatments can impact specific numbers of patients and how clinical trial data relates to real-world practice [6]. This report highlights the substantial benefits observed in the phase 3 CONVERT study and safety extension due to a low NNT for culture conversion in the ALIS + GBT group (vs the GBT-alone group) (NNT=5 by 6 months of

treatment). In addition, the low NNTs for sustained conversion at 12 months of postconversion treatment (NNT=6) and durable conversion at 3 months off all MAC treatment (NNT=6) support the long-term benefit of ALIS + GBT over GBT alone. Because NNTs are typically higher in difficult-to-treat populations and when active comparators are compared with placebo, the low NNTs reported here for the addition of ALIS to a multidrug regimen are particularly notable [10].

Unadjusted NNHs for adverse events of special interest ranged from 13 for ototoxicity to 60 for nephrotoxicity. When NNH values were exposure adjusted for the greater treatment duration with ALIS + GBT vs GBT across studies (327 vs 87 PYs), exposure-adjusted NNHs ranged from 28 for ototoxicity to 166 for nephrotoxicity. The lowest NNH was for ototoxicity and was largely driven by tinnitus and dizziness. The low single-digit NNT and higher NNH values observed in these analyses support the favourable safety profile of ALIS + GBT in offering a clinically meaningful treatment for patients with treatment-refractory MAC lung disease.

Acknowledgements

The authors thank the patients who participated in these studies and their families. This study was financially sponsored by Insmed Incorporated (Bridgewater, NJ). Medical writing and editorial assistance was provided by Jenna Kotak, PhD, of SciMentum, Inc., a Nucleus Holding Ltd company, and was funded by Insmed Incorporated (Bridgewater, NJ). The authors are responsible for all content and editorial decisions for this manuscript.

Author Contributions

All authors critically reviewed and approved the final manuscript. TKM was an investigator in the CONVERT and INS-312 trials, interpreted data, and drafted the manuscript. MH conducted the analysis, interpreted data, and drafted the manuscript. KCM and SDM interpreted data. MC, ZJ, and AC conducted the analysis and interpreted data.

Summary conflict of interest statements: TKM reports, within the past 24 months, research support from Insmed Incorporated, consultant fees from Spero and RedHill, and speaker fees from AstraZeneca and Novartis. MH, KCM, MC, SDM, ZJ, and AC are employees of Insmed Incorporated.

Funding information: This study was financially sponsored by Insmed Incorporated (Bridgewater, NJ). Medical writing and editorial assistance was provided by Jenna Kotak, PhD, of SciMentum, Inc., a Nucleus Holding Ltd company, and was funded by Insmed Incorporated (Bridgewater, NJ).

Table 1. NNT and NNH for ALIS + GBT vs GBT ± Placebo

A. NNT for ALIS + GBT vs GBT Alone in the CONVERT Trial and Safety Extension [5, 8]			
	ALIS + GBT (n=224), n (%)	**GBT** (n=112), n (%)	**NNT** (95% CI)
Culture conversion by month 6	65 (29.0)	10 (8.9)	5 (3.6-8.2)
Sustained conversion at 12 months of treatment	41 (18.3)[a]	3 (2.7)	6 (4.6-10.3)
Durable conversion at follow-up 3 months off treatment	36 (16.1)[b]	0	6 (4.8-8.9)
NNH for ALIS + GBT vs GBT ± Placebo in a Pooled Safety Population [4, 5, 8, 9]			
B. Unadjusted			
	ALIS + GBT (n=404), n (%)	**GBT ± Placebo** (n=157), n (%)	**NNH** (95% CI)
Ototoxicity	72 (17.8)	16 (10.2)	13 (7.3-62.3)
Nephrotoxicity	17 (4.2)	4 (2.5)	60 (>20.8[e])
Neuromuscular effects	12 (3.0)	1 (0.6)	43 (22.7-381.1)
Allergic alveolitis	13 (3.2)	2 (1.3)	51 (>22.7[e])
C. Exposure-Adjusted[c]			
	ALIS + GBT (PY=327), n (%[b])	**GBT ± Placebo** (PY=87), n (%[d])	**NNH** (95% CI)
Ototoxicity	72 (22.0)	16 (18.4)	28 (>7.7[c])
Nephrotoxicity	17 (5.2)	4 (4.6)	166 (>17.8[e])
Neuromuscular effects	12 (3.7)	1 (1.1)	40 (>18.0[e])
Allergic alveolitis	13 (4.0)	2 (2.3)	60 (>18.3[e])

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex; NNH, number needed to harm; NNT, number needed to treat; PY, patient-year.

[a] At 12 months of treatment, 5 patients experienced relapse of MAC lung disease with the same species and strain, 3 patients had reinfection with a different MAC species or strain, and 16

patients had no sputum data at this time point [8]. [b] At 3 months off treatment, 1 additional patient experienced relapse of MAC lung disease with the same species and strain, and 4 patients had no sputum data at this time point [8]. [c] Data were adjusted for difference in exposure time to ALIS vs GBT. [d] Incidence rate per 100 PYs was calculated as (number of patients with events/total exposure in years) × 100. [e]The 2-sided 95% CI of risk difference includes 0; therefore, noncontinuous 95% CIs are generated when the upper bounds of the 95% CI are infinite. The lower bound of NNH (unadjusted) was 20.8 for nephrotoxicity and 22.7 for allergic alveolitis; for NNH (adjusted), the lower bounds were 7.7 for ototoxicity, 17.8 for nephrotoxicity, 18.0 for neuromuscular events, and 18.3 for allergic alveolitis.

References

1. Diel R, Lipman M, and Hoefsloot W. High mortality in patients with Mycobacterium avium complex lung disease: a systematic review. BMC Infect Dis 2018; 18: 206.

2. Kwak N, Park J, Kim E, et al. Treatment outcomes of Mycobacterium avium complex lung disease: a systematic review and meta-analysis. Clin Infect Dis 2017; 65: 1077-1084.

3. Daley CL, Iaccaino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline Clin Infect Dis 2020; 71: e1-e36.

4. Olivier KN, Griffith DE, Eagle G, et al. Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. Am J Respir Crit Care Med 2017; 195: 814-823.

5. Griffith DE, Eagle G, Thomson R, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). Am J Respir Crit Care Med 2018; 198: 1559-1569.

6. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013; 67: 407-411.

7. Griffith DE, Aksamit T, Brown BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007; 175: 367-416.

8. Griffith DE, Thomson R, Flume PA, et al. Amikacin liposome inhalation suspension for refractory MAC lung disease: sustainability and durability of culture conversion and safety of long-term exposure. Chest 2021; 160: 831-842.

9. Winthrop KL, Flume PA, Thomson R, et al. Amikacin liposome inhalation suspension for *Mycobacterium avium* complex lung disease: a 12-month open-label extension clinical trial. Ann Am Thorac Soc 2021; 18: 1147-1157.

10. Caro JJ, Ishak KJ, Caro I, et al. Comparing medications in a therapeutic area using an NNT model. Value Health 2004; 7: 585-594.