Open Forum Infectious Diseases
CORRESPONDENCE

Comment on "Long-term Safety and Tolerability of Omadacycline for the Treatment of *Mycobacterium abscessus* Infections"

To the Editor—*Mycobacterium abscessus* (MAB) diseases, especially MAB lung disease (MAB-LD), are extremely difficult to treat, with sustained sputum culture conversion (SSCC) rates of only 34% in macrolide-containing regimens as initial therapy, and in 20% of patients with refractory disease [1]. Omadacycline is a promising drug for MAB diseases with both an oral and intravenous (IV) formulation. Two recent case series' reported a 75% response rate in patients with MAB infections treated with omadacycline combination regimens [2, 3]. Omadacycline achieves a 1.5-fold higher 0 to 24-hour area under the concentration-time curve (AUC_{0-24}) in the lung than plasma [4, 5]. Thus far, the 117-patient (95 with MAB-LD) multicenter study by Mingora et al is the largest to examine the efficacy and tolerability of omadacycline-based multidrug regimens in refractory disease [6]. In the study by Mingora et al, patients were treated for an average of 8 months [6]. Only 8 patients had treatment-limiting adverse events, whereas 42% achieved 1 or more negative culture and 18% SSCC. However, 50% of the patients were still on therapy at the time of data analysis presented by Mingora et al [6].

Here we reexamined the results of Mingora et al from a pharmacokinetics/pharmacodynamics (PK/PD) consideration. Mingora et al found that 48% of patients treated with a 300 mg/day omadacycline dose achieved negative culture, while 0% of those at a 150 mg/day dose demonstrated microbial response [6]. We recently published a PK/PD study of omadacycline in the hollow fiber system model of MAB, which identified omadacycline AUC_{0-24} to minimum inhibitory concentration (MIC) of 23.76 as exposure mediating optimal microbial effect [7]. Monte Carlo experiment dose-finding for the clinical use to treat MAB-LD was performed using the published PK parameters for the dose of 300 mg once daily. In Figure 1, we provide the probability of target attainment for 150-mg and 300-mg doses for both MAB-LD and disseminated disease [7]. We assumed, based on the findings of Brown-Elliott and Wallace [8], that the omadacycline and tigecycline MIC distributions for MAB are similar, which led to a higher MIC distribution by 2-tube dilution as reported by Mingora et al compared to our own previously published omadacycline MIC values for MAB [7]. The cumulative fraction of response (CFR) is the proportion of 10 000 patients that will achieve target exposure, and is calculated taking an expectation over the MIC distribution (ie, technically a summation over the joint probability distribution). Based on Figure 1, the CFR was 29.99% for an oral dose of 150 mg/day, 49.43% for an oral dose of 300 mg/day, 40.14% for an IV dose of 150 mg/day, and 86.59% for an IV dose of 300 mg/day. For nonpulmonary disease (disseminated), based on plasma concentrations, the cumulative fraction of response was 12.68% for an oral dose of 150 mg/day, 34.97% for an oral dose of 300 mg/day, 46.40% for an IV dose of 150 mg/day, and 70.44% for an IV dose of 300 mg/day. These results are concordant with the microbial response rates reported by Mingora et al [6].

We also performed a retrospective case-control study of patients with MAB-LD on omadacycline 300 mg/day-based combinations versus comparators. SSCC was achieved in 80% versus 11%, symptom

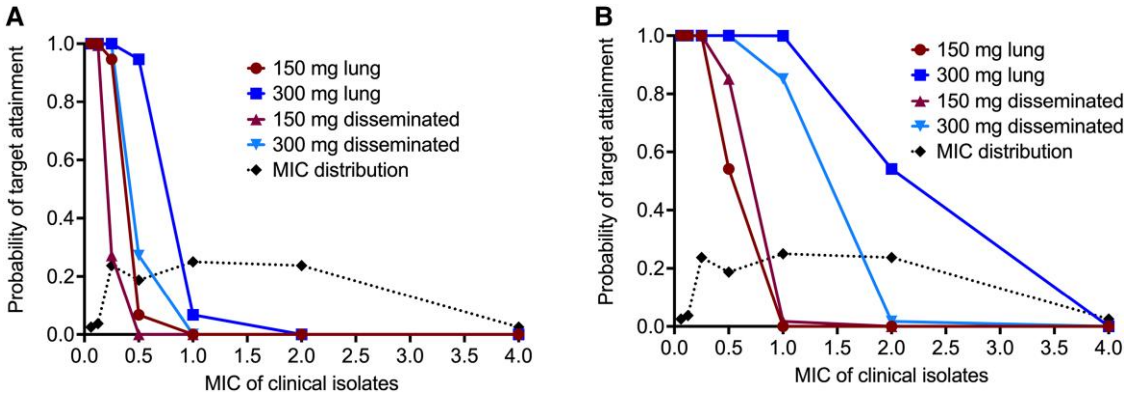

Figure 1. Probability of target attainment with different omadacycline doses. *A*, The probability of target attainment with 300 mg oral administration was higher, up to a minimum inhibitory concentration (MIC) of 0.5 mg/L, in *Mycobacterium abscessus* lung disease compared to disseminated disease. *B*, Intravenous drug administration was predicted to achieve exposure in the lungs. Hence, the susceptibility breakpoint MIC was calculated as 1 mg/L. In other words, the route of administration and the MIC of the infecting strain will affect the treatment outcome.

improvement in 100% versus 56%, and adverse events in 0% versus 100%, respectively [7]. Based on our MIC distribution, the Monte Carlo experiment-based dose-finding for MAB-LD revealed a cumulative fraction of response of 96.56% for an oral dose and 99.99% for an IV dose of 300 mg/day, with a loading dose of 450 mg. However, the results of Mingora et al [6] show a lower response rate than ours, though the responses were higher than seen in the past with other drugs, which suggests that omadacycline MICs will play a pivotal role in how patients respond to therapy. Unfortunately, the MIC distribution results vary from laboratory to laboratory: our own MICs were 4-tube dilutions different from those others identified [8, 9].

Therefore, it is crucial to develop good omadacycline MIC assays that take into account the omadacycline degradation, and hopefully, that could also eliminate the trailing effects [10].

Notes

Author contributions. T. G. wrote the first draft of the manuscript. S. S. read and edited the manuscript.

Potential conflicts of interest. T. G. is founder and CEO of Praedicare Inc, and founder of Praedicare Africa. S. S. reports no potential conflicts.

Shashikant Srivastava[1,2] and Tawanda Gumbo[3,4]

[1]Department of Medicine, University of Texas School of Medicine, Tyler, Texas, USA; [2]Department of Cellular and Molecular Biology, University of Texas Health Science Center at Tyler, Tyler, Texas, USA; [3]Quantitative Preclinical and Clinical Sciences Department, Praedicare Inc, Dallas, Texas, USA; and [4]Hollow Fiber System and Experimental Therapeutics Laboratories, Praedicare Inc, Dallas, Texas, USA

References

1. Pasipanodya JG, Ogbonna D, Ferro BE, et al. Systematic review and meta-analyses of the effect of chemotherapy on pulmonary *Mycobacterium abscessus* outcomes and disease recurrence. Antimicrob Agents Chemother **2017**; 61:9.
2. Morrisette T, Alosaimy S, Philley JV, et al. Preliminary, real-world, multicenter experience with omadacycline for *Mycobacterium abscessus* infections. Open Forum Infect Dis **2021**; 8:ofab002.
3. Pearson JC, Dionne B, Richterman A, et al. Omadacycline for the treatment of *Mycobacterium abscessus* disease: a case series. Open Forum Infect Dis **2020**; 7:ofaa415.
4. Gotfried MH, Horn K, Garrity-Ryan L, et al. Comparison of omadacycline and tigecycline pharmacokinetics in the plasma, epithelial lining fluid, and alveolar cells of healthy adult subjects. Antimicrob Agents Chemother **2017**; 61:e01135-17.
5. Gumbo T, Cirrincione K, Srivastava S. Repurposing drugs for treatment of *Mycobacterium abscessus*: a view to a kill. J Antimicrob Chemother **2020**; 75: 1212–7.
6. Mingora CM, Bullington W, Faasuamalie PE, et al. Long term safety and tolerability of omadacycline for the treatment of *Mycobacterium abscessus* infections. Open Forum Infect Dis **2023**; 10:ofad335.
7. Singh S, Wang J-Y, Heysell SK, et al. Omadacycline pharmacokinetics/pharmacodynamics in the hollow fiber model and clinical validation of efficacy to treat pulmonary *Mycobacterium abscessus* disease. Int J Antimicrob Agents **2023**; 62:106847.
8. Brown-Elliott BA, Wallace RJ. In vitro susceptibility testing of omadacycline against nontuberculous mycobacteria. Antimicrob Agents Chemother **2021**; 65:e01947-20.
9. Nicklas DA, Maggioncalda EC, Story-Roller E, et al. Potency of omadacycline against *Mycobacteroides abscessus* clinical isolates in vitro and in a mouse model of pulmonary infection. Antimicrob Agents Chemother **2022**; 66: e0170421.
10. Chapagain M, Pasipanodya JG, Athale S, et al. Omadacycline efficacy in the hollow fibre system model of pulmonary *Mycobacterium avium* complex and potency at clinically attainable doses. J Antimicrob Chemother **2022**; 77:1694–705.

Received 06 July 2023; editorial decision 24 July 2023; accepted 04 August 2023; published online 7 August 2023

Correspondence: Shashikant Srivastava, PhD, Department of Medicine, UT Tyler School of Medicine, 11937 US Highway 271, Tyler, TX 75708 (shashi.kant@uthct.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad423