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ARTICLE

Preliminary, Real-world, Multicenter Experience With Omadacycline for *Mycobacterium abscessus* Infections. Open Forum Infectious Diseases, Volume 8, Issue 2, February 2021, ofab002, https://doi.org/10.1093/ofid/ofab002.

CLINICAL QUESTION

What is the real-world experience with omadacycline as part of multidrug regimens for *M. abscessus* pulmonary and extrapulmonary infections?

SUMMARY

Patients with *M. abscessus* complex pulmonary and extrapulmonary disease have challenging infections involving significant antibiotic resistance and requiring prolonged regimens with drugs that have limited effectiveness. Due to a lack of clinical trial data there is variation in how patients are treated. Omadacycline is a newer semisynthetic aminomethylcycline within the tetracycline class that has been shown to have potent in vitro activity against *M. abscessus* complex clinical isolates. However, there have been few studies of real-world cases in which omadacycline is used as part of the drug regimen.

Twelve adult patients from 6 geographically distinct medical centers were analyzed in a retrospective observational study (January to August 2020). Patients needed to have been on omadacycline (as part of a combination regimen) for 3 or more months and to have 3 or more months of follow-up. Early clinical success was defined as a composite of survival, lack of worsening (clinical or radiographic), lack of microbiological relapse, and lack of culture persistence for 3 positive cultures after omadacycline initiation. Relapse was defined as 2 consecutive cultures positive for the same pathogen following sputum culture conversion (respiratory) or microbiologic clearance (nonrespiratory). Sputum culture conversion involved 3 consecutive negative cultures over 12 months. (Non-respiratory) microbiological clearance involved any negative culture following a positive index culture.

Sixteen patients were identified but 4 were excluded based off of insufficient drug exposure time or insufficient duration of follow-up. All patients received oral therapy. Demographics of the 12 patients who met criteria included median age 58 years (IQR 54-63), median BMI 23.6 (IQR 21.1-28.9), even split by sex (50% male, 50% female), and 91.7% Caucasian. Seven of the 12 had pulmonary disease and common comorbidities included interstitial lung disease (5/7), COPD (2/7), asthma (2/7), and solid or blood malignancy (2/7). There were no patients with cystic fibrosis or autoimmune disease. Of the 5 patients with extrapulmonary disease, 2 had bone/joint infections, and the others intra-abdominal, skin and soft tissue, and intravenous catheter-related infection. Of all 12 cases, 5 underwent surgery and 7 had sub-speciation performed (6 of 7 being subspecies abscessus and only 1 subspecies massiliense). Erm gene genotyping was performed in 9/12 cases with a functional erm gene detected in 6 of 9 cases.

Most patients had already been started on antibiotics before omadacycline was added (10/12) for a median of 4.7 (IQR 3.4-12.7) months. There were positive cultures in 6/9 patients for whom data was available, at the time of omadacycline initiation. The total median duration of omadacycline was 6.2 (IQR 4.2-11.0) months with median follow-up after omadacycline initiation of 5.1 (IQR 3.4-7.2) months.

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Omadacycline MICs were obtained for just one case but tigecycline MICs were available for all but one case. Clinical success was achieved in 9/12 cases. Failures involved 3 cases with radiographic fibrocavitary and nodular bronchiectatic (plus dissemination) sources and skin and soft tissue sources. In 6/12 cases omadacycline was added for previous antibiotic failure. Three patients experienced adverse events including gastrointestinal upset, temporary serum creatinine increase >=0.5 mg/dL and AST/ALT elevations >3x the upper limit of normal. In all 3 cases omadacycline was able to be continued/resumed.

This report of the largest group of real-world clinical cases to date shows that most patients (75%) on combination regimens including omadacycline were able to achieve clinical success. Moreover, adverse events were few and temporary. Acknowledged limitations included potential selection bias in a retrospective observational study, relatively short durations of omadacycline treatment and follow-up, confounding from nonpharmacologic management (e.g., device removal), lack of erm gene detection for all cases, and use of combination regimens. Prospective and larger real-world studies are needed.

GROUP OPINION

Omadacycline has promise for difficult-to-treat *M. abscessus* complex infections, based on both *in vitro* data and increasingly anecdotal experience when used in combination regimens. Omadacycline is useful especially as an oral drug that can be retained even after the discontinuation of IV therapy and, thus far, side effects appear to be limited. The ability to judge effectiveness however is complicated by a number of factors: a lack of prospective real-world studies with large numbers, uncertainties regarding minimum inhibitory concentrations, and the presence of multiple confounding factors spanning host-related factors, organism-related factors, and therapeutic variations (i.e., different companion drugs, different durations, non-pharmacologic interventions). Importantly, many infections cannot be cured without adequate source control and although 5 of the 12 patients in this study required a surgical intervention, it was unclear when this occurred in relation to omadacycline initiation. Also, the presence or absence of immune suppression could have been better elucidated. Moreover, the ability to use a macrolide is a key question that must be answered by clarifying subspecies and especially erm gene status; too often this crucial information is lacking. Such confounding factors will need to be better studied in larger prospective trials, with longer durations of follow up going forward – since early clinical success may not be durable. Finally, the authors did not address the fact that cost is a prohibitive factor for many patients, as insurance coverage of this expensive drug has been limited.