Addendum to the FDA Briefing Document for the

Antimicrobial Drugs Advisory Committee Meeting

Amikacin liposome inhalation suspension (ALIS)
Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

August 7, 2018

Addendum to the FDA briefing document for the Antimicrobial Drugs Advisory Committee Meeting, August 7, 2018 for NDA 207356, Amikacin liposomal inhalational suspension (ALIS)

Discussion of the surrogate endpoint of 3 consecutive negative monthly sputum cultures within 6 months of treatment

In the Phase 3 Study 212, the primary endpoint was sputum culture conversion, a microbiologic surrogate endpoint. A successful outcome was defined as 3 consecutive negative monthly sputum cultures at any time within the first 6 months of treatment.

We have performed a review of the literature to assess the relationship between sputum culture conversion and clinical outcomes in patients with MAC lung disease. We are reviewing the available information to assess whether the information supports a relationship between sputum culture conversion and clinical outcomes. We focused our review on studies that included patients with infections due to MAC only or those that included MAC along with other nontuberculous mycobacterial species.

There are limited data available, based mainly on retrospective, non-randomized studies or exploratory analyses from non-randomized subgroups that evaluate the relationship of sputum culture conversion and clinical outcomes. The main limitation of these studies is the difficulty in assessing if there are differences in patient characteristics between the converters and non-converters that might have an impact on the clinical outcomes. We examined the findings reported in each of 6 publications referenced in this document and also considered the strengths and limitations of the data or publications to address if there is a relationship between sputum culture conversion and clinical benefit.

Griffith et al. (2006) reported on a case series of 51 patients with macrolide-resistant MAC lung disease from a single institution suggesting that 1-year mortality was lower in those who converted to culture negative after salvage therapy that included but was not limited to injectable aminoglycosides and/or lung resection surgery compared to those who remained culture positive. Of note, patients had to be fit enough to undergo surgical resection and compliant enough to tolerate ≥ 6 months of injectable aminoglycoside therapy. In the group that converted, more patients underwent surgery and received an injectable for ≥6 months. Thus, the assessment of outcomes is confounded by the surgery and by selection of patients who were surgical candidates and or ability to tolerate ≥ 6 months of injectable aminoglycoside therapy. The report does not allow one to discern if culture negativity is a marker for an intrinsically less ill patient population or if the negative culture is leading to improved outcomes.

In a retrospective, non-randomized study of patients with pulmonary MAC lung disease, Ito et al. (2012) reported in a univariate analysis that 5-year mortality was lower in treated MAC patients who achieved sputum culture conversion; however, the result was not statistically significant. Of note, the authors clarified that some patients were left untreated due to lack of symptoms, patient refusal or severe disease suggesting that these patients were inherently different from those that were treated. The authors also note that ~62% of untreated patients had sputum culture conversion and that patients in the MAC-treated group had more cavitary lesions and positive smears than untreated patients, indicating that the two groups were likely not comparable. Also,

if all 117 patients with microbiologic and survival outcome data were included in the analysis, the mortality rates were similar between the treated and untreated groups. The findings from this study suggest that sputum culture conversion may be associated with clinical benefit; however, the inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome.

A report on 180 patients from a single center in patients with nodular/bronchiectatic disease suggests an association between early improvement in a semi-quantitative sputum culture scale and subsequent long-term sputum culture conversion and improvement in sputum production and radiologic findings (Griffith 2015). This study was from a single center of a group of patients who were treated with a standard macrolide-containing regimen per the IDSA/ATS treatment guidelines and had 12 months of follow up. As the authors note, some aspects of the study can impact on the generalizability of the findings as the single center is highly experienced in the management of MAC lung disease and the study was limited to nodular/bronchiectatic MAC. As noted by Koh et al. (2017), treatment outcomes, relapse and reinfection may differ based on clinical phenotype of MAC lung disease (nodular/bronchiectatic (NB), fibrocavitary, or cavitary NB) and host factors).

Moon et al. (2016) describe 34 cases of macrolide-resistant MAC from a registry at a single institution. No evidence was provided in the study that achieving culture conversion translates to a clinical benefit/reduction in mortality. The authors note that patients with unfavorable outcomes were more likely to have a sputum smear positive for acid fast bacilli (AFB) at the time of detection of macrolide resistance.

In one randomized, open-label, multicenter trial that assessed two multidrug regimens for the treatment of NTM lung infections (including but not limited to MAC), the authors note that deaths attributed to NTM disease were more frequent in those who were still sputum culture positive for NTM after 12 months of therapy as compared with patients who converted to sputum culture negative (Jenkins et al. 2008). Determining attributable mortality with any degree of certainty in this patient population can be difficult. The mortality analysis was based on the post-randomization event of sputum culture remaining positive at 12 months and not by the randomized group. Also, no difference was reported in all-cause mortality between patients who remained culture positive and those who became culture negative.

The goals of therapy as outlined by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) are symptomatic, radiographic, and microbiologic improvement (Griffith et al. 2007). Though symptomatic improvement is important, differentiating the benefit of MAC treatment is complicated by progression or exacerbation of underlying lung diseases such as bronchiectasis and COPD. Similarly, although radiographic improvement is anticipated and desirable, assessment can be difficult both because of concomitant lung disease and limited potential improvement of MAC-related abnormalities. Additionally, the radiographic evolution of nodular/bronchiectatic MAC lung disease in either treated or untreated patients is not well defined. The microbiological goal is sustained culture conversion, defined as 12 months of consistently negative sputum cultures while on treatment.

The following is a brief review of the relevant literature discussed above.

Publication: Griffith DE, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2006 Oct 15;174(8):928-34.

Design: Retrospective chart review of 51 patients at a single medical center over a 15-year period identified as having clarithromycin-resistant MAC lung disease.

Primary objective: Assessment of risk factors for macrolide resistance.

Reported Finding: The 1-year mortality in patients who remained sputum culture positive was 34% (13/38) vs. 0% (0/13) of patients who became culture negative.

Information on the relationship of sputum culture conversion and clinical outcome: The 1-year mortality in patients who remained sputum culture positive was 34% (13/38) vs. 0% (0/13) of patients who became culture negative.

Limitations of the available data: Potential confounders include that patients had to be fit enough to undergo surgical resection and compliant enough to tolerate ≥6 months of injectable aminoglycoside therapy. Such patients may be more likely to convert their sputum cultures to negative as compared with those that were not surgical candidates and were not compliant or able to tolerate ≥6 months of injectable aminoglycoside therapy. The inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome due to other patient characteristics.

Summary: This was a retrospective analysis of 51 patients at a single medical center over a 15-year period identified as having clarithromycin-resistant MAC lung disease. Twenty-four had nodular/bronchiectatic disease and 27 had upper lobe cavitary disease. Optimal salvage therapy generally included: ethambutol, rifabutin, and either streptomycin or amikacin IV plus surgical resection (if deemed a surgical candidate). Sputum conversion occurred in 11/14 (79%) patients who received >6 months of injectable aminoglycoside therapy and lung resection compared with 1/27 (4%) who did not receive an injectable aminoglycoside or have surgery. One additional patient who received an injectable aminoglycoside but no surgery experienced sputum culture conversion. The 1-year mortality in patients who remained sputum culture positive was 34% (13/38) vs. 0% (0/13) of patients who became culture negative.

Publication: Moon SM, et al. Clinical Characteristics, Treatment Outcomes, and Resistance Mutations Associated with Macrolide-Resistant *Mycobacterium avium* Complex Lung Disease. Antimicrob Agents Chemother. 2016 Oct 21;60(11):6758-6765.

Design: Retrospective chart review.

Primary objective: Assessment of the clinical characteristics, treatment outcomes and resistance mutations associated with macrolide-resistant MAC lung disease in 34 patients from a single medical center.

Reported Finding: During a median follow-up period of 39.3 months (IQR, 22.9 to 43.4 months) after detection of macrolide resistance, all-cause mortality was 50% (17/34), mortality attributed to MAC-lung disease was reported as 26% (9/34). Mortality was more frequent in patients with fibrocavitary disease at 68% (13/19), than in those with NB [27% (4/15)]. The 1-, 3-, and 5-year mortality was 9% (3/34), 24% (8/34), and 47% (16/34), respectively.

Information on the relationship of sputum culture conversion and clinical outcome: None.

Limitations of the available data: While those with unfavorable outcomes were more likely to be AFB smear positive at the time of detection of macrolide resistance, no evidence is provided that achieving culture conversion translates to a clinical benefit/reduction in mortality. The presence of AFB smear positivity might reflect more severe disease or be a marker for a poorer outcome.

Summary: This retrospective analysis describes clinical characteristics, treatment outcomes and resistance mutations associated with macrolide-resistant MAC lung disease in 34 patients from a single medical center. The median age of the patients was 65 years, 23 (68%) were males, 25 (74%) had a history of prior TB, and 11 (32%) had COPD. Their disease was characterized as fibrocavitary in 19 (56%) patients and nodular/bronchiectatic (NB) in 15 (44%). *M. intracellulare* was the etiologic organism in 21 (62%) patients and *M. avium* in 13 (38%). None had received macrolide monotherapy prior to the detection of macrolide-resistant MAC and 65% (22/34) had been treated with a multidrug regimen consisting of a macrolide, ethambutol, and rifamycin. Only 5 (15%) had a favorable treatment outcome including 2 who had lung resection surgery. During a median follow-up period of 39.3 months (IQR, 22.9 to 43.4 months) after detection of macrolide resistance, all-cause mortality was 50% (17/34), mortality attributed to MAC-lung disease was reported as 26% (9/34). Mortality was more frequent in patients with fibrocavitary disease at 68% (13/19), than in those with NB [27% (4/15)]. The 1-, 3-, and 5-year mortality was 9% (3/34), 24% (8/34), and 47% (16/34), respectively. They noted that the continuation of macrolides or the addition of moxifloxacin, clofazimine, or streptomycin did not improve treatment success. Surgical resection was associated with a more favorable outcome; however, they also reported that most of the patients in the study were not surgical candidates due to poor generalized health status.

Publication: Jenkins PA, et al. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. Thorax. 2008 Jul;63(7):627-34.

Design: Randomized, open-label, prospective, multicenter trial.

Primary objective: Assessment of mortality due to mycobacterial disease, failure of treatment, and relapse comparing the addition of clarithromycin (REClari arm) or ciprofloxacin (RECipro arm) as third drugs to a backbone regimen of rifampicin and ethambutol for two years for NTM pulmonary disease due to MAC, *M. malmoense*, and *M. xenopi*.

Type of analysis: Mortality analysis in those with sputum culture conversion vs. those who did not convert to negative was based on a post randomization event.

Reported Finding: Of the 32 patients (13 REClair, 19 RECipro) requiring a 4th drug at the end of their first year because they did not convert to sputum culture negative, 13% (4/32) died from mycobacterial disease, compared with 1% (2/219) who did not require a 4th drug.

Information on the relationship of sputum culture conversion and clinical outcome: Of the 32 patients (13 REClair, 19 RECipro) requiring a 4th drug at the end of their first year because they did not convert to sputum culture negative, 13% (4/32) died from mycobacterial disease, compared with 1% (2/219) who did not require a 4th drug.

Limitations of the available data: Determining attributable mortality with any degree of certainty in this patient population can be difficult. Also, no difference was reported in all-cause mortality between patients who remained culture positive and those who became culture negative. The mortality analysis was based on the post-randomization event of sputum culture remaining positive at 12 months and not by the randomized group. The inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome. Additionally, the assessment of mortality due to mycobacterial disease based on the requirement of a 4th drug at the end of the first year does not take into account 120 of the 371 patients enrolled in the study.

Summary: This was a randomized, open-label, prospective, multicenter trial conducted by the Research Committee of the British Thoracic Society comparing the addition of clarithromycin (REClari arm) or ciprofloxacin (RECipro arm) as third drugs to a backbone regimen of rifampicin and ethambutol for two years for pulmonary disease due to MAC, *M. malmoense*, and *M. xenopi*. The antibacterial drugs were taken daily, but were not directly observed by healthcare providers. An optional comparison of immunotherapy with *M. vaccae* vs. no immunotherapy was also performed. Patients were monitored annually during the 2 years of therapy, and then for 3 years in follow-up. If patients were not improving at 1 year, their regimen was supplemented with the addition of a 4th drug (the drug not received in the original allocation). The coordinating physician determined the cause of death based on the account of the treating physician and/or autopsy report. 371 patients (186 in REClari, 185 in RECipro) were enrolled: 170 with MAC, 167 with *M. malmoense*, and 34 with *M. xenopi*. The 5-year all-cause mortality was: 44% for REClari, 43% RECipro. Mortality rates were also reported stratified on pathogen: MAC: 48% for REClari, 29% RECipro; *M. malmoense*: 42% for REClari, 56% RECipro; and *M. xenopi*: 29% for REClari, 47% RECipro. The authors reported that 3% (n=12) of patients died due to their mycobacterial disease with similar proportions in REClari and RECipro arms (n=6 in each arm), and that 148 deaths were attributed to non-mycobacterial causes. The authors noted that, "No difference was found in all-cause mortality between those requiring the fourth drug and those in whom it was not deemed necessary." However, the authors also stated that of the 32 patients (13 REClair, 19 RECipro) requiring a 4th drug at the end of their first year, 13% (4/32) died from mycobacterial disease, compared with 1% (2/219) who did not require a 4th drug.

Publication: Ito Y, et al. Predictors of 5-year mortality in pulmonary *Mycobacterium avium-intracellulare* complex disease. Int J Tuberc Lung Dis. 2012;16(3):408-14.

Design: Retrospective study.

Primary objective: Assessment of predictors of 5-year mortality in patients with pulmonary MAC lung disease.

Type of analysis: Non-randomized univariate analysis.

Information on the relationship of sputum culture conversion and clinical outcome: In a univariate analysis, 5-year mortality was lower in treated MAC patients who achieved sputum culture conversion (5/29=17%) vs. those who did not convert (7/25=28%); however, the result was not statistically significant. Based on FDA calculations of information found in the article, the mortality rates for those who remained sputum culture positive vs. those who were sputum culture negative were 30.6% (15/49) and 17.6% (12/68), respectively.

Reported Finding: 5-year mortality was lower in treated MAC patients who achieved sputum culture conversion (5/29=17%) vs. those who did not convert (7/25=28%); however, the result was not statistically significant.

Limitations of the available data: Some patients were left untreated due to lack of symptoms, patient refusal or severe disease raising concerns that these patients were inherently different from those treated. However, if all 117 patients with microbiologic and survival outcome data were included in the analysis, the mortality rates were similar between the treated and untreated groups. Additionally, the inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome.

Summary: This was a retrospective study of 164 patients with pulmonary MAC lung disease (LD) between 1999 and 2005 who were followed for 5 years. Out of 164 patients with MAC LD, 117 had microbiologic outcome data. 54 were treated and 63 were not treated. The sputum culture conversion rates were 53.7% (29/54) for treated patients (referred to as the "treated MAC patients") and 62% (39/63) for untreated patients. The authors consider the untreated patients who spontaneously converted to be colonized rather than infected with MAC. It should be noted that 7/39 (18%) of the "colonized" patients who were untreated and experienced sputum culture conversion died during follow-up. The remaining 24 patients who were untreated and did not convert were considered "untreated chronic MAC patients". These 24 patients were left untreated due to "…patient refusal or symptomatology…" Out of which 8 patients had disease that was "…too severe to tolerate treatment, which included advanced malignancy or interstitial lung disease…" and 16 patients who "had minimal symptoms that did not warrant treatment". 8/24 died: 6 due to malignancy and 2 due to "pneumonia due to an aetiology unrelated to MAC". The authors stated that the mortality rate for "treated patients" was 22% (12/54) and 33% (8/24) "untreated chronic MAC" patients (p=0.30). Additionally, in a univariate analysis, 5-year mortality was lower in treated MAC patients who achieved sputum culture conversion (5/29=17%) vs. those who did not convert (7/25=28%); however, the result was not statistically significant.

Publication: Griffith DE, et al. Semiquantitative Culture Analysis during Therapy for *Mycobacterium avium* Complex Lung Disease. Am J Respir Crit Care Med. 2015 Sep 15;192(6):754-60.

Design: Retrospective study.

Primary objective: Evaluation on whether sputum AFB cultures assessed using a semiquantitative scale in 180 patients with nodular/bronchiectatic MAC lung disease at a single medical center, treated according to ATS/IDSA guidelines with standard macrolide-based treatment and at least 12 months of follow-up, correlates with clinical disease status and if the semiquantitative sputum AFB culture scores were predictive of long-term sputum AFB culture conversion and treatment success.

Reported Finding: After 12 months of treatment, 148/180 (82%) had sputum conversion to culture negative. With each additional point improvement (i.e., a lower value) in culture scores from baseline to Month 2, the odds of a patient converting were 7 times greater (univariate logistic regression model). With each one-point decrease in culture score, a patient was 20% more likely to convert to negative by 1 year of follow-up time. (RR=1.2, 95%CI=1.1-1.3; $p<0.0001$, univariate generalized linear model). Patients who showed improvement in cough between baseline and their next visit were more likely to convert to negative ($p<0.0001$). With exception of sputum production, all other symptoms evaluated (fatigue, hemoptysis, fever) were weakly correlated with semiquantitative culture result when evaluated at monthly intervals throughout the follow-up study period. (correlation coefficient=0.1-0.2). Converters demonstrated greater radiologic improvement from baseline to next radiologic assessment in chest imaging.

Information on the relationship of sputum culture conversion and clinical outcome: Study suggests an association between improvement in a semi-quantitative sputum culture scale and sputum culture conversion and improvement in sputum production and radiologic findings.

Limitations of the available data: As noted by the authors, the data for this study were obtained from a single center with more than 20 years of experience with performing semiquantitative sputum acid fast bacilli cultures. Additionally, the patient population studied was limited to those with nodular/bronchiectatic MAC lung disease. The study did not include patients with fibrocavitary MAC LD. It has also been noted that treatment outcomes, relapse and reinfection may differ based on clinical phenotype of MAC lung disease (nodular/bronchiectatic (NB), fibrocavitary, or cavitary NB) and host factors (Koh et al. 2017).

Summary: The objective of this study was to determine if a semiquantitative mycobacterial culture scale correlated with clinical disease status and was predictive of long-term sputum mycobacterial culture conversion to negative in a cohort of 180 patients with nodular/bronchiectatic MAC lung disease undergoing standard macrolide-based treatment. The following were monitored: symptoms, radiography, microbiologic data (including semiquantitative culture data). The data were analyzed to evaluate clinical and microbiologic predictors of long-term sputum culture conversion to negative. After 12 months of treatment,

148/180 (82%) had sputum culture conversion to negative. The change in sputum culture semiquantitative score from baseline to Month 3 was reported as predictive of subsequent sputum long-term conversion status, as was improvement in cough and early radiographic improvement. Regarding symptom evaluations, nearly all patients presented with cough, sputum and fatigue. Patients who showed improvement in cough between baseline and their next visit were more likely to convert ($p<0.0001$). With the exception of sputum production, all other symptoms evaluated (fatigue, hemoptysis, fever) were weakly correlated with semiquantitative culture results when evaluated at monthly intervals throughout the follow-up study period (correlation coefficient=0.1-0.2). Converters had greater radiologic improvement from baseline to the next radiologic assessment in CT scans and chest x-rays.

Publication: Koh WJ, et al. Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype. Eur Respir J. 2017 Sep 27;50(3).

Design: Retrospective study using registry data from a single center.

Primary objective: The aim of the study was to assess the effect of clinical phenotype of MAC LD on treatment outcomes and re-development of NTM LD after treatment completion.

Type of analysis: Non-randomized.

Reported Finding: Out of the 481 treatment-naïve patients with MAC LD who underwent antimycobacterial treatment for ≥12 months, 278 (58%) had noncavitary nodular/bronchiectatic (NB) disease, 80 (17%) had cavitary NB, and 123 (25%) had fibrocavitary disease. Favorable outcomes were more frequent in those with non-cavitary disease (88%) than in those with cavitary disease (76% for fibrocavitary and 78% for cavitary NB disease, $P< 0.05$). Cavitary disease was found to be independently associated with unfavorable outcomes ($P<0.05$). Out of 402 with favorable outcomes, 118 (29%) experienced redevelopment of NTM LD during a median follow-up of 13.6 months and 65 (55%) patients had the same MAC species isolated. In patients with recurrent MAC LD due to the same species, bacterial genotyping revealed that 74% were attributable to reinfection and 26% to relapse. Relapse occurred within a median of 6 months, and reinfection within median time of 13 months. Relapse with the same MAC genotype occurred more frequently in patients with fibrocavitary disease, and clarithromycin resistance was noted in 2/7 (29%) of relapse cases. Reinfection with a new MAC genotype occurred more commonly in those with NB disease. The NB form was an independent risk factor for re-development of NTM LD ($P<0.05$).

Information on the relationship of sputum culture conversion and clinical outcome: Not the focus of the paper. Mortality among patients with sputum culture conversion to negative was not provided to compare with those who remained culture positive. We know from the paper that 79 patients had unfavorable outcomes and 24 (30%) of those patients died. Favorable outcome: sputum culture conversion after initiation of treatment and maintenance of a negative culture for >12 months on treatment. Unfavorable outcome: no culture conversion or death. Therefore, if a patient converted to sputum negative, but died, they would still be in the unfavorable category.

Limitations of the available data: Mortality among patients with sputum culture conversion to negative was not provided to compare with those who remained culture positive. Retrospective design.

Summary: This was a retrospective cohort study using registry data from a single center. The aim of the study was to assess the effect of clinical phenotype of MAC LD on treatment outcomes and re-development of NTM LD after treatment completion. The authors evaluated 481 treatment-naïve patients with MAC LD who underwent antimycobacterial treatment for ≥12 months between 1/2002 and 12/2013. Out of the 481 patients, 278 (58%) had noncavitary nodular/bronchiectatic (NB) disease, 80 (17%) have cavitary NB, and 123 (25%) had fibrocavitary disease. Genotypic analysis was performed on all MAC isolates. Favorable outcomes were more frequent in those with non-cavitary disease (88%) than in those with cavitary disease (76% for fibrocavitary and 78% for cavitary NB disease, $P< 0.05$). Cavitary disease was found to be independently associated with unfavorable outcomes ($P<0.05$). Out of 402 with favorable outcomes, 118 (29%) experienced redevelopment of NTM LD during a median follow-up of 13.6 months and 65 (55%) patients had the same MAC species isolated. In patients with recurrent MAC LD due to the same species, bacterial genotyping revealed that 74% were attributable to reinfection and 26% to relapse. Relapse occurred within a median of 6 months, and reinfection within median time of 13 months. Relapse with the same MAC genotype occurred more frequently in patients with fibrocavitary disease, and clarithromycin resistance was noted in 2/7 (29%) of relapse cases. Reinfection with a new MAC genotype occurred more commonly in those with NB disease. The NB form was an independent risk factor for re-development of NTM LD ($P<0.05$). The authors discuss that NB MAC LD typically occurs in postmenopausal women with a unique body morphotype, slender marfanoid body habitus (scoliosis, pectus excavatum and mitral valve prolapse), altered immunophenotype and mucociliary dysfunction making them susceptible to environmental NTM infection/re-infection. They suggest that patients with NB MAC LD should have lifelong follow-up to assess for recurrence of MAC or other NTM LD.

The following is a summary of additional literature that was reviewed.

Park TY, et al. Natural course of the nodular bronchiectatic form of *Mycobacterium avium* complex lung disease: Long-term radiologic change without treatment. PLoS One. 2017 2;12(10):e0185774.

The aim of this retrospective cohort study was to evaluate long-term radiologic changes in 40 untreated nodular/bronchiectatic MAC LD patients with serial CT scans. Data were obtained from a single center from 1/2005 to 5/2012. The authors assessed changes in lung pathology on initial chest CT scan and final follow-up CT prior to initiating MAC treatment using a scoring system. Patients were followed for a mean of 6 years. Regarding demographic information, 33 (82.5%) patients were female, the mean age was 64 years, and mean BMI was 20.9 kg/m^2. *M. intracellulare* was isolated from 20 patients, *M. avium* from 15, and 5 patients had both organisms isolated. All patients had at least one respiratory symptom at baseline: 31 (77.5%) had cough, 31 (77.5%) had sputum production, 11 (27.5%) had hemoptysis, 5 (12.5%) had dyspnea. Over a mean follow-up time of 6 years, 97.5% (39/40) experienced worsening CT changes. Chest CT score increases were noted as follows: 33 (82.5%) had score increases related to bronchiectasis, 28 (70%) patients related to cellular bronchiolitis, 24 (60%) related to cavities, 27 (67.5%) patients due to consolidation, and 16 (40%) due to nodules. The authors noted that these patients did not receive treatment for their MAC LD during the follow-up period due to minimal or mild symptoms.

Comment: This was a retrospective study. The study did not contain a treated group of comparable patients to assess whether treatment alters the progression of lung pathology as assessed by chest CT scans. Additionally, the patients included in the study were apparently not treated during the follow-up period (mean=6 years) because they had minimal or mild symptoms despite changes on CT scans.

Park HY, et al. Lung Function Decline According to Clinical Course in Nontuberculous Mycobacterial Lung Disease. Chest. 2016 Dec;150(6):1222-1232.

The aim of the authors was to assess the impact of NTM LD on lung function decline. Data were obtained from an NTM registry cohort. Treatment outcomes and spirometry data at diagnosis and at least 3 years later (median follow-up=5 years) were collected from 358 patients with NTM LD between 1/1999 and 11/2011. Spirometry was assessed at two timepoints: baseline and last follow-up. Patients were divided into three groups for analysis: patients observed without treatment (n=118), patients who were successfully treated (n=172), and patients who failed treatment (n=68) including 10 patients who prematurely discontinued antibacterial treatment within 12 months. At baseline, a higher proportion of female patients were in the treatment-success group compared to the other two groups. Patients in the observation group had a higher BMI, lower incidences of prior TB, cavities on CT scans, and positive sputum smears at diagnosis than in the treated groups. At baseline, the treatment-failure group had a higher proportion of fibrocavitary disease and cavities on chest CT than the other two groups. Additionally, the treatment-failure group as compared with the observation group had a higher proportion of subjects with a positive sputum smear at baseline, prior history of TB, and lower BMI. At baseline, the treatment-failure group as compared to the treatment-success group had a

higher incidence of fibrocavitary disease and cavities on chest CT and more male patients. The treatment-failure group had a more rapid decline in FEV1 and FVC compared with the observation group and the treatment-success group. Patients in the treatment-success group had declines in FEV1 and FVC similar to those in the observation group.

Comment: This was a non-randomized cohort study. Patients who did not require treatment and those who were successfully treated may have been intrinsically different (e.g., less fibrocavitary disease and cavities on chest CT) than those patients who were treatment failures.

Pan SW, et al. Microbiological Persistence in Patients with *Mycobacterium avium* Complex Lung Disease: The Predictors and the Impact on Radiographic Progression. Clin Infect Dis. 2017 Sep 15;65(6):927-934.

The aim of the study was to evaluate predictors of persistent culture-positivity for MAC (MAC-PP) and its impact on radiographic deterioration in MAC LD. The authors retrospectively evaluated patients with MAC LD from two centers from 2011 to 2016. Microbiological persistence of MAC was defined as continuously culture positive for >1 year. Radiographic progression was defined as an increase in the number of involved areas or cavity formation. Patients were included if they had at least 2 positive MAC sputum cultures within a 12-month period. Exclusion criteria included HIV positivity, no microbiological follow-up information after the first year, or not found to have MAC LD at screening. Among 126 patients with MAC-LD, the mean age 67.4 years, 46% male, 72% with nodular/bronchiectatic pattern, and 15 (12%) received anti-MAC treatment in the first year. 75/126 (60%) were considered MAC-PP. Patients with MAC-PP had a higher proportion of radiographic progression (54%) than converters (OR 3.3, 95% CI:1.146-9.612). Independent predictors of MAC-PP were low BMI, nodular/bronchiectatic pattern on radiological studies, and higher grade sputum acid fast bacilli smear (AFS). Patients with BMI <21 kg/m^2, NB pattern, and positive AFS had OR of 17.7 for MAC-PP, those with > or = 2 factors had 4.5-fold increased OR for MAC-PP. The authors noted the following from the literature: (1) low BMI has been reported as a risk factor for NTM LD and correlates with low leptin, a deficiency that may affect immune modulation. (2) Low BMI was reported as an independent risk factor for poor long-term outcomes and MAC LD specific mortality. (3) In patients with NB pattern MAC LD, initial extensive involvement was independently associated with subsequent radiographic deterioration. The authors noted the following limitation in their study: "…in contrast to the patients with MAC-PP, a high proportion of those with MAC-NC [patients who converted to negative sputum culture] (41%) had no radiographic follow-up, which may be a potential confounder of the association between MAC-PP and radiographic progression. In addition, the anti-MAC treatment effect and long-term outcomes, including pulmonary function and mortality of patients with MAC LD, could not be fully recovered because the study design was observational and retrospective."

Comment: The MAC-PP group was different from the converter group in that they had lower BMI and persistently acid fast bacilli smear positive. It is unclear if culture negativity or some other inherent characteristic of the converted patients was responsible for reduced progression on radiographic studies. Additionally, the authors noted differential radiologic follow-up between the MAC-PP group and the patients who converted sputum cultures to negative.

Min J, et al. Determinants of recurrence after successful treatment of *Mycobacterium avium complex* lung disease. Int J Tuberc Lung Dis. 2015 Oct;19(10):1239-45.

The authors performed a retrospective analysis using an NTM patient registry to evaluate for determinants of microbiological recurrence after successful treatment of MAC LD. 91 patients who maintained negative sputum culture conversion during treatment and had a minimum of 10 months of follow-up post treatment were included. The median duration of follow-up was 25 months. 71 (78%) patients remained culture negative, while 20 (22%) had microbiological recurrence. Variables associated with microbiological recurrence were: longer intervals between initial diagnosis and administration of medication, increased number of lobes affected, and failure of sputum conversion within 6 months of initiating treatment. Additionally, 15/20 (75%) of the patients with microbiological recurrence had bronchiectatic disease vs. 35/71 (49%) of patients without recurrence. The authors also noted that, "Early conversion to negative culture may be attributed to reduced bacterial burden and increased susceptibility to antimicrobial agents in MAC LD, which subsequently affected long-term outcomes."

Comment: This was a retrospective analysis registry data. The number of patients in the analysis was relatively small. Patients who had microbiological recurrence may have been inherently different (e.g., higher incidence of nodular/bronchiectatic disease) from those who remained culture negative during the follow-up period. Additionally, susceptibility testing for macrolide resistance was not uniformly assessed.

Research Committee of the British Thoracic Society. First randomised trial of treatments for pulmonary disease caused by *M avium intracellulare*, *M malmoense*, and *M xenopi* in HIV negative patients: rifampicin, ethambutol and isoniazid versus rifampicin and ethambutol. Thorax. 2001 Mar;56(3):167-72.

This was an open-label, randomized trial assessing two treatment regimens (rifampicin + ethambutol (RE) vs. rifampicin + ethambutol + isoniazid (REH)) for patients with NTM lung disease due to *M. malmoense*, MAC, and *M. xenopi*. From October 1987 to December 1992, 223 patients were enrolled: 106 with *M. malmoense*, 75 with MAC, and 42 with *M. xenopi*. Patients were treated for 2 years and then followed for an additional 3 years. For MAC, 37 patients were randomized to RE and 38 to REH. In the subgroup of MAC patients, the number that completed treatment as allocated and were considered alive and cured at 5 years was: 10/37 (27%) for RE and 13/38 (34%) for REH. For the MAC patients, all-cause mortality was 9/37 (24%) for RE and 14/38 (37%) for REH, and mortality attributed to MAC was 0/37 for RE and 3/38 for REH. The authors reported that there was no correlation between failure of treatment/relapse and in vitro resistance.

Comment: The proportion of patients with MAC LD per treatment arm was relatively small in this study to draw any meaningful conclusions related to whether culture conversion predicted survival or another clinically meaningful endpoint.

Andréjak C, et al. *Mycobacterium xenopi* pulmonary infections: a multicentric retrospective study of 136 cases in north-east France. Thorax. 2009 Apr;64(4):291-6.

Jeon K, et al. Antibiotic treatment of *Mycobacterium abscessus* lung disease: a retrospective analysis of 65 patients. Am J Respir Crit Care Med. 2009 Nov 1;180(9):896-902.

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