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Article Summary by: David E. Griffith, MD

ARTICLE

Amikacin liposome inhalation suspension for Treatment-Refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study. Am J Repir Crit Care Med 2018; 198: 1559-1569. https://www.atsjournals.org/doi/10.1164/rccm.201807-1318OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

CLINICAL QUESTION

For patients with treatment refractory Mycobacterium avium complex (MAC) lung disease, does the addition of amikacin liposome inhalation suspension to standard, guidelines-based therapy (GBT) improve microbiologic treatment outcome over continuation of the standard GBT alone?

SUMMARY

This was an international (127 clinical centers in 18 countries), multi-site, randomized open-label trial. Subjects were ≥ 18 years of age with active MAC lung disease as documented by MAC-positive sputum or bronchoscopy cultures within 6 months before screening and at screening. Eligible patients were MAC culture positive while on stable guidelines-based therapy (GBT) for at least 6 months or had stopped GBT less than 12 months before screening. Key exclusion criteria included cystic fibrosis, active pulmonary tuberculosis, immunodeficiency syndromes, MAC isolates with amikacin resistance on culture screening (MIC > 64 µg/ml) and active malignancies. Patients were randomly assigned in a 2:1 ratio to receive ALIS 590 mg by nebulizer once daily added to GBT (ALIS + GBT) or GBT alone (see Figure 1). The primary endpoint was the proportion of patients achieving culture conversion based on assessment of monthly sputum cultures from baseline through Month 6. Culture conversion was achieved if patients had three consecutive monthly negative sputum cultures, with all sputum samples collected at each visit required to be culture negative. To meet the primary endpoint, Month 4 was the latest visit at which a negative sputum culture could be first detected. Sputum analysis at each monthly clinic visit included sputum collection in triplicate. Secondary endpoints at 6 months were change in baseline in the 6-minute-walk test, time to culture conversion, and change from baseline in St. George's Respiratory questionnaire (SGRQ).

A total of 492 patients were enrolled, 336 were randomized (intention to treat), 224 to ALIS + GBT and 112 to GBT alone. More patients withdrew from the study in the ALIS + GBT arm (19.6%) than the GBT alone arm (8.9%). The most common reasons for study discontinuation in the ALIS + GBT arm were withdrawal by patient (8.5%), adverse event (3.6%), and death (3.1%). The study population was mean age 64.7 years, 69.3% female, mean BMI 21, 70% µwhite, 62.5% underlying lung disease (primarily bronchiectasis), 10.7% clarithromycin resistant, 10.7% current smoker. The primary endpoint of sputum culture conversion by Month 6 was achieved by significantly more patients in the ALIS + GBT arm (65/224 patients, 29%) versus 10/112 patients, 8.9%) in the GBT alone arm ($p<0.001$) (Figure 2). Only one patient with an amikacin MIC > 64 µg/ml converted sputum to negative. At baseline 73/335 patients (21.8%) had clarithromycin-resistant

MAC isolates. Culture conversion was achieved by 7/51 patients (13.7%) in the ALIS + GBT arm and 1/22 patients (4.5%) in the GBT alone arm. Patients with culture conversion from both arms demonstrated greater improvement in 6MWT distance than patients without culture conversion ($p = 0.011$). At Month 6 there was a numerical difference in SGRQ score change from baseline favoring the GBT alone arm. Treatment emergent adverse events (TEAEs) were reported in 98.2% and 91.1% of patients in the ALIS + GBT and GBT alone arms, respectively. Most events were moderate severity in the ALIS + GBT group, and 17.4% of patients had TEAEs leading to discontinuation of ALIS. The most common TEAEs overall were respiratory events reported in 87.4% of patients in the ALIS + GBT group: dysphonia (45.7%), cough (37.2%), dyspnea (21.5%), hemoptysis (17.5%), fatigue (16.1%), exacerbation of COPD or bronchiectasis (5.3%), tinnitus (7.6%), hearing loss (4.5%), diarrhea (12.6%). Most events were initially reported in the first month of ALIS treatment, with declining incidence of new onset thereafter. Serious TEAEs included pneumonia/respiratory infection and hypersensitivity pneumonitis (not listed in this manuscript). The mean estimated amikacin steady state Cmax (1-4 hours after dosing) was 2.32 µg/ml.

GROUP OPINION

Significance of the study: Since the advent of the macrolides for treatment of MAC infections in the 1990's there have been no further significant advances in MAC therapy. MAC treatment success was disappointing even with macrolide-containing regimens. This study demonstrated that the addition of ALIS to GBT significantly improved microbiologic treatment outcomes for treatment refractory MAC patients who had received at least 6 months of GBT without attaining sputum conversion. This trial, along with the preceding multi-site, randomized placebo-controlled Phase II trial of ALIS for refractory MAC lung disease were among only a handful of randomized controlled trials (RCTs) for any agent with MAC lung disease over a 3-decade span. The two studies also formed the basis for the FDA to grant limited approval to ALIS for treatment refractory MAC lung disease thereby making ALIS the first and only drug with any level of FDA approval for MAC lung disease therapy. ALIS is indicated for MAC lung disease patients with positive sputum cultures after at least 6 months of guidelines-based therapy. Administration of ALIS is associated with frequent adverse events, primarily respiratory events, especially dysphonia. Most of the respiratory adverse events are manageable without discontinuation of ALIS. Serious adverse events such as pneumonia and hypersensitivity pneumonitis can also occur.

Two additional studies from this cohort have subsequently been published. First, patients who had sputum conversion within 6 months either with or without ALIS were evaluated for sustainability (evaluation of sustained sputum culture negativity while on therapy) and durability (evaluation of sputum culture negativity for 3-12 months after completion of therapy) of sputum culture conversion. Patients receiving ALIS + GBT had significantly greater sustainability and durability of sputum conversion compared with GBT alone. Second patients on ALIS + GBT who did not convert sputum to negative in the CONVERT trial were offered continued follow-up on ALIS + GBT. Patients on GBT alone were offered unblinded therapy with ALIS + GBT. Patients started on ALIS who were previously ALIS naïve had approximately 30% sputum conversion rate after ALIS was added to GBT.

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