Amikcacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT)

Background

- There is an interest in developing therapeutic options for treatment-refractory nontuberculous mycobacterial lung disease due to Mycobacterium avium complex (MAC) infections.
- Subtypes of MAC infections include Fibrocavitary disease and Nodular/Brochiectatic disease.
- The liposomal formulation was developed for biofilm and macrophage penetration.
- Macrophages are a frequent site of MAC residence in the lung.

Objective

- To evaluate the efficacy and safety of daily amikacin liposome inhalation suspension (ALIS) added to standard guideline-based therapy (GBT) in patients with refractory MAC lung disease.

Methods

- 336 patients with MAC lung disease infections (amikacin MIC <64ug/mL) that had had at least 6 months of stable GBT were randomized 2:1 to receive either ALIS + GBT (n = 224) or GBT (n = 112).
- The study duration was up to 28 months.
- Patients had to be 18 years old with active MAC lung disease within 6 months before screening and MAC positive in spite of stable GBT.
- The primary endpoint was sputum culture conversion, which was defined as three consecutive months of MAC-negative cultures by month 6 of treatment. Treatment-associated adverse events were analyzed as well.
- Patients couldn't have had Cystic Fibrosis, active TB, Immunodeficiency syndromes, or MAC isolates with amikacin resistance.
- A 20% conversion of the treatment group and 5% for the GBT-alone group with 261 evaluable patients at 6 months would provide at least 90% power.
- Data were collected by the investigators and analyzed by the sponsor.

Results

- The primary endpoint of culture conversion was achieved by 65/224 (29.0%) of patients in the ALIS+GBT arm and 10 of 112 (8.9%) patients in the GBT arm (OR = 4.22; 95% CI: 2.08-8.57; P<0.001).
- Adverse events, especially respiratory adverse events, were more prevalent in the ALIS+GBT arm than the GBT arm (87.4% vs 50.0%), likely due to the liposomal formulation of ALIS.

Strengths

- The trial is prospective and randomized.

- The trial addresses a needed therapeutic intervention (treatment-resistant MAC infections.)

Limitations

- Compliance wasn't addressed.
- The trial was open-label.
- Dosing and duration could've been too little/short.
- Authors and funding affiliation could've biased the interpretation of results and is evident in some of the wording of the discussion.

Conclusion

- Daily amikacin liposome inhalation suspension (ALIS) did appear to have increased culture conversion rates in patients with refractory MAC disease compared to usual therapy.
- Compliance is a possible issue due to the irritation from the liposomal formulation. Although ALIS + GBT was statistically significantly better than GBT alone at culture conversion, the conversion rate was still low (29%), especially given that one of the exclusion criteria was amikacin resistant strains (MIC >64ug/mL).
- This could be explained by poor compliance described above (since patients were likely not monitored at home) improper nebulization technique, and/or the nebulized dosing of amikacin not being high enough.
- There also might be a difference in efficacy based on the subtype of MAC infection the patient has (Fibrocavitary vs Nodular).
- Investigators should compare rates of conversion in Fibrocavitary disease vs Nodular/Brochiectatic disease in future studies.

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