

Amikacin Inhale: the therapeutic potential of a new aerosol treatment for mechanically ventilated patients with Gram-negative pneumonia

Introduction

Pneumonia is the second most common infection affecting patients in hospital intensive care units (ICUs),¹ and its most serious manifestation, in mechanically ventilated patients, occurs at a rate of 250,000 cases per year in the US with associated treatment costs of 10 billion USD.² Pneumonia in mechanically ventilated patients increases the risk of mortality by 1.7- to 4.4-fold³ and average length of hospital stay by 7–9 days per patient (compared to patients without pneumonia),⁴ and results in estimated excess treatment costs of 40,000 USD per patient.⁵ This document provides a summary as of July 2008 of the development status of Amikacin Inhale, an innovative aerosolized antibiotic therapy for serious and life-threatening pneumonia in patients undergoing mechanical ventilation. Amikacin Inhale is a proprietary drug-device combination consisting of a specially formulated liquid antibiotic with an excellent antibacterial spectrum coupled with a highly efficient aerosol delivery platform. It is being developed through an exclusive collaboration between Bayer and Nektar to assess the potential efficacy benefits of delivering targeted antibiotic treatment directly to the site of infection for mechanically ventilated patients with pneumonia.

Overview

Pneumonia caused by invasive pathogens is characterized by inflammation and consolidation of lung tissue. It is the most serious form of respiratory tract infection and contributes to substantial morbidity and mortality worldwide.³ In ICU settings, pneumonia is particularly prevalent in patients requiring artificial breathing support (mechanical ventilation), because the invasive process of intubation and the consequent reduction in patient immune defences predispose the lower respiratory tract to infection by pathogenic organisms. In general, mechanically ventilated patients are already critically ill and many have diseases or require medications that compromise the immune system, such that pneumonia is a

potentially much a more dangerous complication in these patients than in less severely ill patients.

A group of microbes called Gram-negative bacteria are responsible for approximately 80% of cases of pneumonia in hospitalized patients (this contrasts with bloodstream infections, for example, which are mainly caused by Gram-positive bacteria, of which methicillin-resistant *Staphylococcus aureus* [MRSA] is one species).⁶ The emergence and spread of antimicrobial drug resistance is a well-documented phenomenon that jeopardizes clinician's ability to treat infections and raises concerns about potentially untreatable 'superbugs', especially in the context of declining innovation in the field of antimicrobial drug development. However, because of the reduced numbers of new drugs being developed for Gram-negative as opposed to Gram-positive pathogens, the outlook is particularly bleak for serious Gram-negative infections such as pneumonia.

Amikacin Inhale is an innovative and proprietary drug-device combination that is being developed through an exclusive collaboration between Bayer Schering Pharma/Bayer HealthCare and Nektar Therapeutics. The system combines a special preservative-free liquid antibiotic (amikacin) formulated for efficient aerosol delivery, with Nektar's Liquid Pulmonary Technology (LPT), a targeted aerosol delivery platform that can be integrated with conventional mechanical ventilators or used as a stand-alone hand-held inhaler to enable direct antibiotic treatment of infected areas deep in the lungs. Amikacin Inhale represents a new strategy for the treatment of pneumonia that can be added to standard-of-care intravenous (i.v.) antibiotic therapy to provide a potent antimicrobial agent targeted directly to the site of infection.

Amikacin Inhale will enter pivotal phase III clinical trials in 2009 to assess its potential value as an adjunct to standard-of-care i.v. antimicrobial therapy for pneumonia in mechanically ventilated patients. If approved, Amikacin Inhale could be the first aerosolized antibiotic licensed for the treatment of pneumonia, and it will form a complimentary addition to the Bayer Schering Pharma/Bayer HealthCare specialist anti-infective portfolio.

Hospital treatment of pneumonia

In 2005, the American Thoracic Society (ATS) published expert guidelines for the diagnosis and management of pneumonia in hospitalized patients,⁴ which are widely considered to reflect the current standard of care for pneumonia in the in-patient setting. It is notable that because treatment options are currently limited to systemic therapies, the current guidelines do not differentiate between ventilated and non-ventilated patients in terms of treatment

recommendations, despite the significantly increased risks of adverse outcomes (including mortality) in mechanically ventilated patients.

Significance of mechanical ventilation in pneumonia

Patients in the ICU who are intubated and mechanically ventilated are 7–20-fold more likely to contract pneumonia than spontaneously breathing patients,³ and nearly 90% of pneumonia cases in this setting occur in mechanically ventilated patients.⁷ This is in part because intubating a patient replaces a section of the respiratory tract with an artificial airway that lacks the natural defences of the real airway, and which promotes the accumulation of respiratory secretions that are prone to colonization with potentially infective pathogens. In addition, mechanically ventilated patients are generally more severely ill, and often have additional co-morbidities compared with non-ventilated patients. Duration of mechanical ventilation of more than 7 days has been identified as a predictor of MDR infection in patients with pneumonia, along with prior antibiotic treatment and use of broad-spectrum antimicrobials.⁸ Accordingly, pneumonia in mechanically ventilated patients is often the most difficult form of the disease to treat, and is associated with the poorest patient outcomes.⁹

Current treatment strategies

Urgent treatment, consisting of i.v. antimicrobial therapy with or without supplemental oxygen and fluids, is necessary for patients diagnosed with pneumonia. The ATS guidelines recommend taking respiratory secretion and blood samples for microbiological culture and initiating immediate empiric (i.e. selected on the basis of suspected pathogens rather than on microbiological results) antibiotic therapy pending the results of the sample cultures.⁴

For patients considered to be at risk of infection with MDR pathogens, the ATS guidelines currently recommend that empiric therapy should include a combination of i.v. antibiotics (consisting of a β -lactam plus either an antipseudomonal quinolone or an aminoglycoside) to provide a broad spectrum of antibacterial coverage with known activity against MDR strains. When microbiology results are known, de-escalation is advocated to refine or narrow the spectrum of antimicrobial activity to match the causative pathogens. However, the guidelines acknowledge that the selection of appropriate empiric therapy is becoming more difficult because of increasing antimicrobial resistance, and note that the outcomes for patients with pneumonia who do not receive appropriate empiric therapy include significantly increased hospital mortality.⁴

Potential role of inhaled antibiotics for pneumonia

In patients with pneumonia, many systemically administered drugs fail to reach the same levels in lung tissues as are observed in blood or serum.^{10,11} For safety reasons, it is often not possible to simply increase the dose to achieve the desired level in relevant tissues. It follows that some infections are considered 'resistant' to certain drugs because of the difficulties in safely achieving relevant concentrations at the site of infection, rather than because of the antimicrobial activity of the drug *per se*. For patients with pneumonia, aerosolized antibiotic delivery could potentially circumvent the problems associated with systemic administration by providing high concentrations directly to infected lung tissues while avoiding or minimizing systemic drug exposure. However, because there are currently no inhaled products licensed for treating pneumonia, the available evidence is limited and based mainly on off-label use of 'homebrew' antibiotics intended for i.v. administration. The potential value of aerosol therapy for pneumonia is nonetheless recognized in the current ATS guidelines.⁴

Bayer–Nektar collaboration

History

In August 2007, Bayer HealthCare and Nektar Therapeutics embarked on an exclusive collaboration to develop a unique drug-device combination for aerosolized treatment of Gram-negative pneumonia in mechanically ventilated patients. The project draws together Nektar's expertise in developing pulmonary drug delivery platforms with Bayer's heritage in anti-infectives and strong sales force in the specialist secondary care field. The adopted development name for the product of the collaboration is 'Amikacin Inhale' (the trade name[s] under which the product will be marketed has yet to be determined).

Amikacin Inhale: an innovative drug-device combination

Amikacin Inhale consists of the aminoglycoside antibiotic amikacin, which has an excellent spectrum of activity against the key respiratory tract pathogens (including Gram-negative bacteria and MRSA) as a liquid specially formulated for inhalation, and Nektar's LPT, a microprocessor-controlled vibrating mesh nebulizer designed to provide highly efficient aerosol delivery direct to the site of infection – the deep lung – in mechanically ventilated patients with pneumonia. For added flexibility, the delivery platform can either be integrated within mechanical ventilator circuits, or used as a stand-alone hand-held inhaler, so that patients making the transition from mechanical ventilation to spontaneous breathing are able

to complete their course of aerosol treatment. This innovative drug-device combination is protected under international patents and relevant intellectual property legislation until 2026.

Development status

An extensive programme of clinical and laboratory research underpins the development of Amikacin Inhale. Phase II studies in mechanically ventilated patients with pneumonia were completed in March 2008, and the results were positive. Key among the findings was that in a majority of patients, the administration of Amikacin Inhale 400 mg twice daily achieved concentrations in lung fluid of more than 25 times the minimal inhibitory concentration for the key respiratory tract pathogens,^{12,13} and serum amikacin levels well below the accepted safety threshold in all patients.¹⁴ Furthermore, 7–14 days of treatment with Amikacin Inhale was associated with a decrease in the requirement for i.v. antibiotics for pneumonia during the course of the study (compared with an aerosol placebo).¹⁵

These promising phase II findings helped to guide the phase III dosage selection and study design, which is intended to establish whether the addition of Amikacin Inhale to standard-of-care i.v. therapy can demonstrate superiority over i.v. antibiotics alone in mechanically ventilated patients with Gram-negative pneumonia. Two phase III randomized, placebo-controlled studies of identical design will commence recruitment in 2009. With approximately 130 investigational sites in the US, Europe and Asia and a planned total enrolment of 1300 patients, these trials will be among the largest ever conducted of an antibiotic intervention for pneumonia in mechanically ventilated patients. Specific design features of both studies include:

- All patients will receive standard-of-care i.v. antibiotics (per ATS guidelines⁴) and will then be randomized to receive a 10-day course of either Amikacin Inhale 400 mg twice daily or an aerosolized placebo
- On day 10, efficacy will be assessed by the need for continued antibiotic treatment. Patients will be eligible to continue treatment if clinically required, but these patients will be considered treatment failures for analysis purposes
- Safety and tolerability assessments and sample culture microbiological investigations will be conducted at a central laboratory

Why choose amikacin for this drug-device combination?

Amikacin is a well-characterized generic aminoglycoside antibiotic that has been available for i.v. and intramuscular use for several decades and has an excellent spectrum of activity against the main Gram-negative pathogens responsible for respiratory tract infections, including MDR strains, particularly *P. aeruginosa*, *Enterobacter* species and

K. pneumoniae.¹⁶ It has a concentration-dependent bactericidal effect, meaning that the antibacterial efficacy of the drug can be improved by increasing its concentration at the site of infection. Unfortunately, however, aminoglycosides administered by the i.v. route exhibit poor lung penetration, and this situation is compounded by the risks of severe side-effects with high doses, including permanent nervous system and kidney damage. Consequently, despite recognizing its potency, clinicians are cautious about using amikacin, and when it is prescribed, patients are carefully monitored to ensure serum drug levels remain within safe ranges. By targeting aerosol delivery directly to the lungs, it may be possible to circumvent the systemic side-effects of amikacin while achieving high local concentrations at the site of infection, thereby providing potent antibacterial coverage exactly where it is most needed. Support for this hypothesis comes from experience with inhaled tobramycin (TOBI[®]), another antibiotic in the aminoglycoside class, which has been licensed since 1998 for the treatment of chronic *P. aeruginosa* infections in patients with cystic fibrosis. In pneumonia, the approach of using a combination of i.v. systemic therapy with a targeted adjunctive aerosol holds promise for eradicating resistant pathogens by achieving concentrations at the site of infection several-fold higher than is possible with i.v. administration alone.

Liquid Pulmonary Technology™

The delivery platform used for Amikacin Inhale employs Nektar's proprietary LPT aerosol generator, which has been developed to provide highly efficient delivery of liquid drug formulations. LPT uses a vibrating mesh nebulizer to aerosolize liquid amikacin without the need for a pressurized jet of gas or a heat-generating piezoelectric element. The key components of the system include a reservoir for liquid amikacin, the aerosol generator, a control unit and a set of adapters that enable two modes of use (on-vent or handheld). The aerosol generator is fed by gravity from the reservoir, and has specially designed apertures in the mesh that produce a high proportion of fine particles in the aerosol (3–5 µm diameter), which are an optimal size for deposition in the deep lung. The average delivery efficiency of LPT is 43% of the nominal dose,¹⁷ compared with a maximum of around 10–15% with other nebulizers. The device can be easily integrated with most mechanical ventilator systems, or configured to work with a hand-held adaptor. The aerosol generator is breath-actuated, being controlled by a microprocessor linked to a pressure monitor to detect breathing patterns. For optimal delivery efficiency during mechanical ventilation, the generator is only active during the first 75% of the inspiratory cycle.

Further development opportunities

We plan to also investigate the potential benefits of Amikacin Inhale in neonatal/paediatric patients. The study protocol(s), number of patients to be enrolled, and the geographical

locations of the study sites are currently under discussion. A life-cycle management approach will be taken to assess potential development of Amikacin Inhale in other indications, including pneumonia caused by MRSA.

Conclusions

- Pneumonia in mechanically ventilated patients is a leading cause of death and a major complication in many patients hospitalized for other causes, and is associated with a substantial burden on healthcare resources
- The need for new therapies to treat MDR pathogens is growing, and few novel antimicrobials are in development for Gram-negative bacteria
- Amikacin Inhale represents an innovative approach to the treatment of pneumonia in mechanically ventilated patients that has shown promising results in phase II clinical trials as an adjunct to i.v. antimicrobial therapy
- Phase III clinical trials will commence in 2009 to assess whether Amikacin Inhale can offer additional efficacy benefits over standard-of-care i.v therapy for pneumonia in mechanically ventilated patients
- If approved, Amikacin Inhale could be the first licensed aerosolized antibiotic therapy for the treatment of pneumonia

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Nektar Therapeutics is a biopharmaceutical company developing novel therapeutics based on its advanced polymer conjugate chemistry technology platform. Nektar technology and drug development expertise have enabled nine approved products for partners, which include leading biopharmaceutical companies. Nektar is also developing a robust pipeline of its own high-value therapeutics that addresses unmet medical needs by leveraging and expanding its technology platforms to improve and enable molecules. For more information on Nektar Therapeutics, please visit www.nektar.com.

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