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EXPERT OPINION

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Fighting *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: orphan drug designation for a novel PcrV antibody

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Impaired mucociliary clearance in patients with cystic fibrosis (CF) may often lead to chronic recurrent respiratory tract infection. *Pseudomonas aeruginosa* (*Pa*) is a common bacterium found in many natural environments and hypoxic conditions and is frequently found in adult CF patients. Despite improving success rates for the treatment of infection with antibiotics, the bacterium has developed strategies, which may allow persistence thus warranting the discovery and development of alternative pharmacological interventions. KB-001, a first-in-class monoclonal antibody directed against the PcrV protein of the type III secretion system, has entered clinical trials for patients with *Pa* infection, in patients with ventilator-assisted pneumonia and in patients with CF. KB-001-A, the successor to KB-001, has recently been granted orphan drug designation by the FDA and European Medicines Agency for the treatment of *Pa* infection in patients with CF and is currently in Phase II clinical development.

Keywords: antibody, cystic fibrosis, orphan drug designation, PcrV, *Pseudomonas aeruginosa*, type three secretion system

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1. The challenge

Pseudomonas aeruginosa (*Pa*) airway infection is the principle cause of chronic respiratory tract infection and is associated with increased morbidity and mortality in patients with cystic fibrosis (CF) [1,2]. It is a human pathogen that exists in biofilms and that often demonstrates increased resistance to environmental stress including microgravity in spaceflight [3] and attenuation by host defense mechanisms [4]. Despite advances in the treatment of *Pa* with antibiotics [2], resistance to the current standard-of-care antibiotics such as beta-lactams, aminoglycosides, polymixins and fluoroquinolones is increasing [5], even in regimes where coadministration of at least two antibiotics is commonplace. A recent study in patients with CF demonstrates that multi-drug-resistant *Pa* infection is not associated with a significant decline in lung function and is more likely to be a marker of greater disease severity [6]. This finding further suggests the need to combat mechanisms of resistance, which include intervention at targets other than those associated with bacterial persistence.

A feature of *Pa* and several gram-negative bacteria that enables its virulence is utilization of the type three or III secretion system (TTSS or T3SS [7]), also termed the injectisome or injectosome. This is a needle-like structure, which functions as a sensory probe to detect the presence of eukaryotic target cells for infection. The TTSS is a complex composed of approximately 30 different proteins, making it one of the most complex secretion systems in nature. The role of TTSS has been validated as a target for *Pa* virulence in animal studies of acute *Pa* infection [8] using antibodies

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directed against *Pa* PcrV. PcrV is a structural translocation protein located at the tip of the TTSS, and secretion of PcrV enables intracellular delivery of a number of cytotoxic proteins, which interfere with host-cell signal transduction mechanisms, which result in either attenuation of the host's ability to orchestrate an immune response or an exaggerated pro-inflammatory response, and both processes may include cell death [9,10]. Thus, it is hypothesized that blockade of PcrV may neutralize TTSS activity and may protect cells from endotoxin-mediated cytotoxicity. Further evidence for the importance of this protein is derived from a recent study suggesting that anti-PcrV immunotherapy may protect against infection in *in vitro* cell culture systems containing strain variants harboring mutations in PcrV from disparate global regions [11].

2. The drug, clinical Phase I and Phase II data

KB-001-A (KaloBios Pharmaceuticals, Inc.) is a 'humaneered' PEGylated Fab' antibody that lacks the IgG Fc region. KB-001-A is directed against the *Pa* PcrV protein and is designed to inhibit TTSS activity, and, as a consequence, it may demonstrate anti-inflammatory properties. PEGylation extends the serum half-life and protects the antibody against inactivation in the lung, which may extend the pharmacodynamic (PD) range of the antibody. KB-001-A, which is the molecule now under investigation in Phase II clinical studies in CF patients with *Pa* infection, is a modification of KB-001 that binds to the same target on PcrV protein and facilitates the PEGylation step of the production process. KB-001 has been studied in two clinical trials [12,13]. In a Phase IIa multicenter, randomized, placebo-controlled, double-blind trial, the safety, pharmacokinetics (PK) and ability of KB-001 to prevent *Pa* infection in ventilator-assisted pneumonia (VAP) were investigated in 39 *Pa*-colonized, but not infected, mechanically ventilated patients [12]. In this study, patients received a single intravenous infusion of KB-001, 3 mg/kg (n = 13), 10 mg/kg (n = 14) or placebo (n = 12). The primary endpoints were safety and tolerability and secondary endpoints included serum and lung PK measurements and determination of *Pa* pneumonia rate within 28 days of KB-001 infusion. KB-001 was shown to be well tolerated and no anti-KB-001 antibodies were detected at days 0, 14 and 28 of the treatment regime. The 3 – 10 mg/kg patient groups had mean elimination half-lives of 8.1 – 9.3 days, respectively. KB-001 was detected in endotracheal aspirates from all patients receiving it, as early as day 1 and up to 28 days post-treatment. Respective mean endotracheal aspirate/serum concentration ratios were reported as 0.092 – 0.085 for the 3 – 10 mg/kg groups, who developed *Pa* pneumonia less frequently (33 and 31%, respectively) than patients receiving placebo (60%). It should be noted, however, that the patient groups in the efficacy population were small and that these results did not reach statistical significance (n = 4/12, n = 4/12 and n = 6/10 patients dosed at 3, 10 mg/kg and placebo, respectively).

In a Phase I study, the safety, PK and PD properties of KB-001 were studied in CF subjects with chronic *Pa* infection [13]. Twenty-seven eligible CF subjects (≥ 12 years of age, forced expiratory volume in 1 s (FEV_1) ≥ 40% of predicted, and sputum *Pa* density > 105 colony-forming units/g) received a single intravenous dose of KB-001 (3 or 10 mg/kg) or placebo. Safety, PK, *Pa* density, clinical outcomes and inflammatory markers were assessed. KB-001 demonstrated an acceptable safety profile with a mean serum half-life of 11.9 days. All subjects had *Pa* TTSS expression detected in the sputum, and there were no significant differences between KB-001 and placebo for changes in *Pa* density, symptoms or spirometry after a single dose of the drug. However, compared to baseline, at day 28, there was a trend toward a dose-dependent reduction in sputum myeloperoxidase (MPO), IL-1 and IL-8, and there were overall differences in the change in sputum neutrophil elastase and neutrophil counts favoring the KB-001 10 mg/kg group versus placebo (-0.61 $\log^{10}$ and -0.63 $\log^{10}$, respectively; $p < 0.05$).

3. The potential

In the Phase IIa study in patients with VAP, KB-001 was shown to be safe and well tolerated with an acceptable PK profile. KB-001 demonstrated the potential for reducing *Pa* pneumonia incidence in intensive care unit mechanically ventilated patients colonized with this bacterium; however, the clinical data report an effect in a small number of patients, which did not achieve statistical significance. The potential of this approach to be a new standard of care in VAP patients with *Pa* infection requires further investigation in larger studies. These may include more extensive investigation of PK/PDs in pulmonary airway secretions from VAP patients infected with *Pa* and in patients undergoing bronchoscopy for noninfective lung conditions.

A clinical Phase I data in *Pa*-infected CF patients was conducted with KB-001 to reduce airway inflammation and lung damage. In this first study, there was a tendency for a reduction of a number of inflammatory biomarkers in the KB-001-treated patients and an increase in the same biomarkers in the patient group receiving the placebo. Although there were no significant changes in biomarkers from baseline within subject groups, there was a consistent trend toward a KB-001 dose-dependent reduction in sputum MPO, IL-8, IL-1β and neutrophil elastase. The study used an extensive set of efficacy measures; however, the study did not adjust for multiple comparisons when calculating statistical significance with these variables. Reductions compared with placebo were observed at day 14 (IL-1β and NE for KB-001 at 3 mg/kg group, $p < 0.05$). At day 28, there was a median increase of NE in the placebo group (n = 8) of 0.38 $\log^{10}$ and a median decrease in the KB-001

10 mg/kg group (n = 6) of 0.23 $\log^{10}$ (p = 0.039). There was a reduction in median percentage from baseline compared to placebo for sputum macrophages at day 28 for the KB-001 3 mg/kg group (p = 0.024) and at day 56 for the 10 mg/kg group (p = 0.023). At day 28, there was a median increase in neutrophils per gram of sputum of 0.25 $\log^{10}$ in the placebo group, a decrease of 0.03 $\log^{10}$ in the KB-001 3 mg/kg group (p = 0.073) and a decrease of 0.38 $\log^{10}$ in the KB-001 10 mg/kg group (p < 0.05 compared to placebo). At day 28, there was a numerical reduction from baseline in median mucoid *Pa* density in the KB-001 10 mg/kg group (-0.4 $\log^{10}$) compared with placebo (+0.8 $\log^{10}$). However, these changes were not statistically significant and this trend was not observed in non-mucoid or total *Pa* density over 28 or 56 days. There were no significant differences between active treatment and placebo groups for ANC, C-reactive protein, cystic fibrosis questionnaire-revised respiratory domain scores, spirometric parameters (FEV_1, forced expiratory $flow_{25\ -\ 75}$ or forced vital capacity) at any time point.

Repeat-dosing studies are necessary to evaluate the durability of the anti-inflammatory effects and how these observations may translate into clinical benefit for CF patients with *Pa* infection. Given the need to combat the rise of antibiotic resistance in this disease, immunotherapy against protein constituents of the *Pa* TTSS may hold promise as a potential new treatment. KB-001-A as a first-in-class molecule directed against this target is currently being studied in a 180-patient Phase II, multiple-dose, randomized, double-blind placebo-controlled trial in CF patients chronically infected with *Pa.* The study will evaluate both the safety and efficacy of repeat doses of KB-001-A, with the primary endpoint being time-to-need for antibiotic intervention.

On October 30, 2013, the FDA granted orphan drug designation for KB-001-A for the treatment of *Pa* infection in CF patients [14,15].

Declaration of interest

M Braddock is an employee of AstraZeneca and they support his work on this manuscript. The author has no conflict of interest and received no payment in preparation of this manuscript.

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