Infection (2019) 47:665–668
https://doi.org/10.1007/s15010-019-01319-0

CASE REPORT

Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant *Pseudomonas aeruginosa* infection in a cystic fibrosis patient

Nancy Law[1] · Cathy Logan[1] · Gordon Yung[2] · Carrie-Lynn Langlais Furr[3] · Susan M. Lehman[3] · Sandra Morales[3] · Francisco Rosas[3] · Alexander Gaidamaka[3] · Igor Bilinsky[3] · Paul Grint[3] · Robert T. Schooley[1,4] · Saima Aslam[1,4]

Received: 29 January 2019 / Accepted: 9 May 2019 / Published online: 17 May 2019

Abstract

Introduction We describe the use of bacteriophage therapy in a 26-year-old cystic fibrosis (CF) patient awaiting lung transplantation.

Hospital Course The patient developed multidrug resistant (MDR) Pseudomonas aeruginosa pneumonia, persistent respiratory failure, and colistin-induced renal failure. We describe the use of intravenous bacteriophage therapy (BT) along with systemic antibiotics in this patient, lack of adverse events, and clinical resolution of infection with this approach. She did not have recurrence of pseudomonal pneumonia and CF exacerbation within 100 days following the end of BT and underwent successful bilateral lung transplantation 9 months later.

Conclusion Given the concern for MDR P. aeruginosa infections in CF patients, BT may offer a viable anti-infective adjunct to traditional antibiotic therapy.

Keywords Bacteriophage therapy · Multidrug-resistant *Pseudomonas aeruginosa* · Cystic fibrosis · Lung transplant · Antimicrobial · Antibiotic

Introduction

Chronic respiratory infections are an important cause of morbidity, progressive respiratory failure, and mortality in cystic fibrosis (CF) patients. Due to continued exposure to antibiotics, CF patients are at increased risk of developing infections with multidrug-resistant (MDR) bacteria. *Pseudomonas aeruginosa* is a common pathogen recovered from respiratory specimens in CF patients, with colonization reported in up to 80% of adults; there are increasing rates of colonization with MDR *P. aeruginosa* as the patients age. Thus, the development of new antimicrobial therapies for treatment of MDR *P. aeruginosa* infections in this population is a high priority.

The use of lytic bacteriophages for treatment, bacteriophage therapy (BT), represents an exciting anticipated option to fight MDR bacteria. Lytic bacteriophages are viruses that infect, replicate within, and lyse bacteria, causing bacterial cell death and have been shown in vitro to have activity against *P. aeruginosa* biofilms [1]. There is growing evidence to support the use of BT alone and synergistically with antibiotics in patients suffering from *P. aeruginosa* infections [2]. BT directed against biofilms is of increasing interest in CF patients suffering from persistent infections [3]. Here, we describe the successful use of BT in a patient with CF awaiting lung transplantation.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s15010-019-01319-0) contains supplementary material, which is available to authorized users.

✉ Nancy Law
nalaw@ucsd.edu

[1] Division of Infectious Diseases and Global Health, University of California, San Diego, 4510 Executive Drive, Suite P7, La Jolla, San Diego, CA 92121, USA

[2] Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego, La Jolla, CA, USA

[3] Ampliphi Biosciences Corporation, San Diego, CA, USA

[4] Center for Innovative Phage Applications and Therapeutics, University of California, San Diego, La Jolla, CA, USA

Case presentation

A 26-year-old female with CF on the lung transplant waitlist was admitted with a pulmonary exacerbation leading to acute-on-chronic respiratory failure requiring mechanical ventilation for 12 days. Her course was complicated by a pneumothorax requiring long-term chest tube placement. On admission, she was colonized with two distinct MDR *P. aeruginosa* phenotypes (Supplemental Table 1; non-mucoid strain sensitive to colistin and mucoid strain sensitive to meropenem and piperacillin/tazobactam). She was treated with antibiotics for 4 weeks: colistin and azithromycin for the entire period, piperacillin–tazobactam for the first 2 weeks and a carbapenem for the latter 2 weeks (based on clinical response and antibiotic susceptibilities of recovered organisms). At the end of 4 weeks, the patient was on supplemental oxygen via nasal cannula (NC) at 6 L/min flow rate. She was deconditioned, unable to ambulate independently, and had developed acute kidney injury (AKI) with a serum creatinine (Cr) of 1.5 mg/dL and estimated creatinine clearance (CrCl) of 43 mL/min. She was transitioned to inhaled colistin as suppressive therapy. Of note, multiple *P. aeruginosa* strains were sensitive only to colistin.

As shown in Fig. 1, 1 week after discontinuation of intravenous (IV) antibiotics, the patient developed fever, increased sputum production, and oxygen requirements. She was restarted on IV antibiotics (vancomycin, colistin, and meropenem which were then switched to piperacillin–tazobactam due to susceptibility profiles). Despite antibiotic therapy, she worsened over the following week with progressive respiratory and renal failure; oxygen requirement was 70 L/min with fraction of inspired oxygen (FIO_2) of 50% on heated high-flow blender and serum creatinine of 2.26 mg/dL with associated serum CrCl of 26 mL/min. AKI was attributed to colistin. Due to worsening clinical status and limited antimicrobial options, she was made inactive on the transplant waitlist.

At this time, we obtained approval under emergency Investigational New Drug #17710 by the US Food and Drug Administration for AB-PA01 (combination of 4 lytic phages produced in a Good Manufacturing Practices certified facility by AmpliPhi Biosciences Corporation [AMP]) for treatment of MDR *P. aeruginosa* infection. After informed consent, AB-PA01 was administered every 6 h (4×10^9 plaque-forming units in 5 mL, IV syringe) for 8 weeks.

At the start of BT, the patient was receiving supplemental oxygen via a heated high-flow blender at 40% FIO_2 and at a rate of 30 L/min. Colistin was discontinued and the patient received concomitant ciprofloxacin and piperacillin–tazobactam for 3 weeks. By Day 7 of BT, the patient was afebrile and had a dry cough with difficulty in expectorating sputum. Figure 2 provides a baseline chest X-ray image; no radiographical changes were seen in her follow-up chest X-rays as her baseline image was severely abnormal and she had a chronic pneumothorax; however, her pneumonia clinically resolved and she transitioned to NC 10 L/min. For the latter portion of BT, ciprofloxacin was discontinued and doripenem was added based on updated PA sensitivity profiles; the isolates remained sensitive to BT. At the end of the 8-week BT course, the patient was on 3 L/min NC supplemental oxygen, without sputum production and was ambulatory. AKI resolved with return to baseline renal function (peaked at 2.26 mg/dL 1 week before starting BT therapy; 0.83 at the end of therapy, EOT). Her white blood cell count (WBC) normalized to 7.7 1000/mm^3 from 15 1000/mm^3 prior to BT initiation; and her fever (maximum temperature prior to BT was 102.3 °F) resolved and did not recur while on BT. She did not have recurrence of *P. aeruginosa* pneumonia and CF exacerbation within 100 days following the end of BT; she underwent successful bilateral lung transplantation 9 months later.

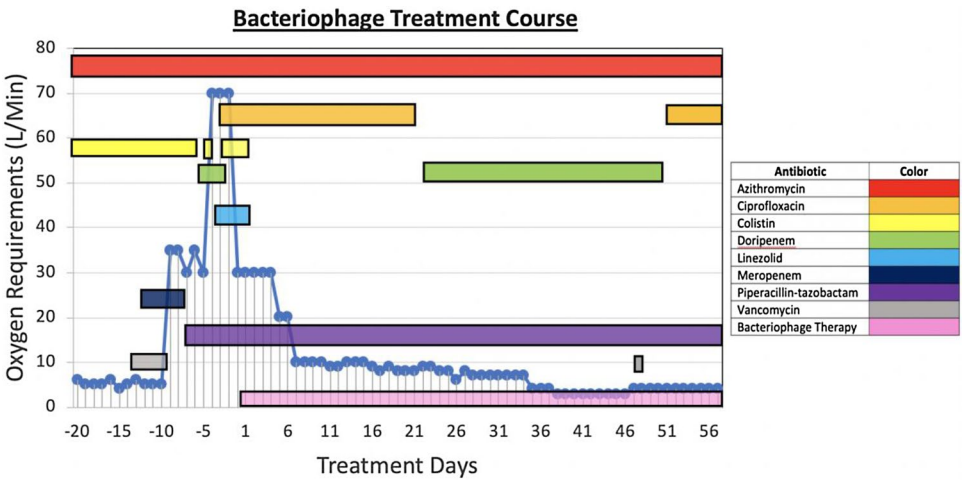

Fig. 1 Oxygen saturation and antibacterial use during the clinical course of our case patient

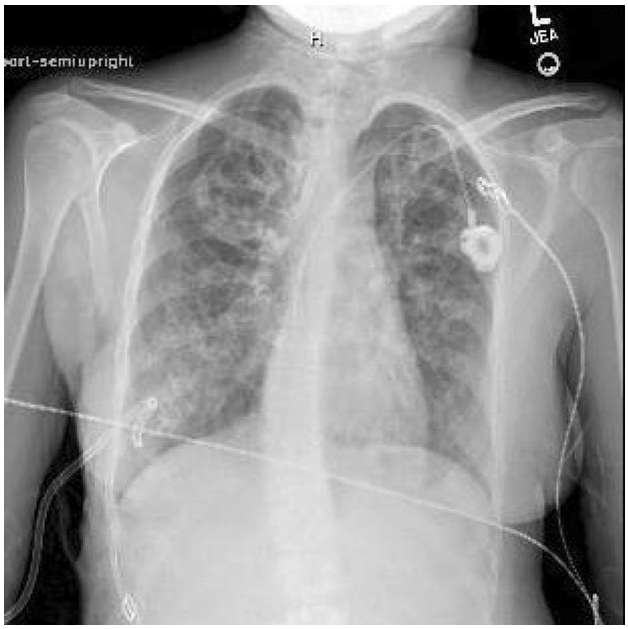

Fig. 2 Patient's chest X-ray on admission

No adverse events related to BT were noted clinically or on laboratory monitoring (liver function tests, complete blood counts, electrolytes). At baseline, patient's *P. aeruginosa* isolates were susceptible to AB-PA01. Serial *P. aeruginosa* isolates remained mostly sensitive throughout treatment except for the transient appearance of one non-sensitive isolate on Day 9 (Supplemental Table 1).

Discussion

Bacteriophage therapy is an innovative antimicrobial treatment option against *P. aeruginosa* infections, especially MDR strains, and deserves more attention. We report the first case in the US that we are aware of in which IV BT was used as an adjunctive treatment for MDR *P. aeruginosa* infection in a CF patient.

Given the common occurrence of *P. aeruginosa* in CF patients, there has been burgeoning interest in using BT in this particular population. AB-PA01 is active against approximately 80% of > 400 global clinical *P. aeruginosa* isolates, including a panel of 65 genotypically different CF isolates (AMP, unpublished). French researchers tested bacteriophages from a Georgian commercial phage preparation against *P. aeruginosa* isolates from 47 CF patients and reported activity against 70% of the strains [4]. Another in vitro study noted that approximately 50% of *P. aeruginosa* isolates from CF patients were susceptible to a combination of 10 lytic phages [5]. Bacteriophages can also produce enzymes that hydrolyze biofilms, further validating their use in chronic *P. aeruginosa* infections in CF patients [3].

The Eliava Institute of Bacteriophages, Microbiology and Virology in Georgia successfully used nebulized BT as an adjunct to antibiotics, antimucus medications, and vitamins in 8 CF patients [6]. The treatment led to a decrease in bacterial concentration in all patients' sputum samples, as well as improved clinical status. This correlates with our experience, as the patient had difficulty in producing sputum after 5 weeks of BT. Similar to our case patient, they noted a prolonged infection-free period between colonization episodes in all patients.

The goal of using a combination of phages rather than a single phage at a time is that multiple *P. aeruginosa* isolates may be targeted simultaneously, and within-product complementation can limit resistance development. This is specifically important in the complex microbiological milieu of the CF respiratory tract, which usually contains a genetically and phenotypically heterogeneous *P. aeruginosa* population. We observed that sensitivity to individual AB-PA01 component phages shifted over time in our patient and included the transient appearance of a resistant isolate, while still ultimately leading to clinical resolution. Clinical trials evaluating the utility of such an approach are urgently needed and microbiome assessments need to be carried out as well.

Our case report demonstrates that intravenous BT is safe and well tolerated and can be used as an adjunct to antibiotics. No adverse events related to BT were noted and the patient had a successful clinical outcome. There was no recurrent pneumonia or CF exacerbations within 100 days of follow-up after the end of BT.

Conclusion

We describe the safe and efficacious use of intravenous bacteriophage therapy in a CF patient awaiting lung transplant. Given the concern for MDR *P. aeruginosa* in CF patients, BT may offer a viable adjunct to antibiotic therapy in CF patients and further study in clinical trials is urgently needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Fong SA, Drilling A, Morales S, et al. Activity of bacteriophages in removing biofilms of *Pseudomonas aeruginosa* isolates from chronic rhinosinusitis patients. Front Cell Infect Microbiol. 2017;7:418.

2. Hurley MN, Camara M, Smyth AR. Novel approaches to the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis. Eur Respir J. 2012;40:1014–23.
3. Hraiech S, Bregeon F, Rolain JM. Bacteriophage-based therapy in cystic fibrosis-associated *Pseudomonas aeruginosa* infections: rationale and current status. Drug Des Dev Ther. 2015;9:3653–63.
4. Essoh C, Blouin Y, Loukou G, et al. The susceptibility of *Pseudomonas aeruginosa* strains from cystic fibrosis patients to bacteriophages. PLoS ONE. 2013;8:e60575.
5. Saussereau E, Vachier I, Chiron R, et al. Effectiveness of bacteriophages in the sputum of cystic fibrosis patients. Clin Microbiol Infect. 2014;20:O983–90.
6. Kutateladze M, Adamia R. Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends Biotechnol. 2010;28:591–5.