Phage Therapy: Considerations and Challenges for Development

Rebecca Reindel and Cara R. Fiore
Office of Vaccines Research and Review, Center For Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

(See the Major Article by Dufour et al on pages 1582–8.)

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Bacteriophage therapy (phage therapy) involves the use of live, lytic bacteriophages to treat bacterial infections via bacterial cell lysis. Lytic bacteriophages mediate their antimicrobial effect by way of specific attachment to bacterial cell wall receptors, injection of bacteriophage DNA into the bacterium, recruitment of bacterial host cell machinery for bacteriophage protein production, and subsequent lysis of the bacterial cell with release of bacteriophage progeny [1, 2]. Phage therapy has a century-old origin [3], and while the interest in this treatment modality waned with the development of antibiotics, medical practice in some Eastern European countries has continued the clinical use of phage therapy. The emergence of multidrug-resistant (MDR) bacterial infections has renewed interest in phage therapy [2, 4]. However, published data in the English literature on controlled trials of phage therapy that rigorously measure safety and efficacy are sparse.

In addition to the potential for phage therapy to treat MDR bacterial infections, some of the proposed benefits of phage therapy include the reduced risks of drug interactions between antibiotics and other medications, avoidance of antibiotic toxicities, and the prospects of retained activity in the presence of biofilms [5–7]. Concerns with phage therapy can include the potential for transduction of genetic material to the microbiome, such as virulence factors or genes that confer antibiotic resistance; development of bacterial resistance to the phage; and rapid release of endotoxin due to bacterial cell lysis [2, 7, 8]. Data that address these concerns are important to advance product manufacturing and evaluation of phage therapy products in controlled clinical trials. The Office of Vaccines Research and Review (OVRR) within the Center for Biologics Evaluation and Research at the US Food and Drug Administration regulates the development of investigational bacteriophages for infectious diseases indications. OVRR reviews information regarding the composition, manufacture, and control of investigational bacteriophages and protocols for planned clinical studies of phage therapy within the regulatory framework for biological products.

In this issue, Dufour et al [9] present comparative in vitro data on endotoxin release (ER) during bacterial cell lysis after exposure to bacteriophages in order to address one of the clinical safety concerns of phage therapy. The authors measured ER, metabolic growth, and cell viability of 2 pathogenic Escherichia coli strains over 180 minutes following exposure to bacteriophages, β-lactam antibiotics, or amikacin. While bacterial cell growth and the number of metabolically active cells decreased faster after exposure to bacteriophage than to β-lactam antibiotics, the cumulative endotoxin concentrations were higher in the β-lactam–treated bacterial strains than in either the amikacin- or bacteriophage-treated strains. Amikacin- and bacteriophage-treated strains produced similar concentrations of endotoxin and exhibited a greater decrease in metabolically active cells than the β-lactam–treated strains. The authors state that their study provides novel data regarding ER that may occur with phage therapy but acknowledge that the in vivo relevance of the study findings may be limited.

Bacteria–bacteriophage interactions in the context of active infection and the human immune system involve complexities that are not easily reproduced in vitro. In transitioning the study of phage therapy from the bench to the clinic, issues to be considered include product composition, mode of administration, and the underlying disease (including site of infection). Since bacteriophages replicate only in the presence of their host bacteria, first-in-human data with phages in healthy participants may not address safety concerns that are unique to bacteriophage–bacteria interaction in the setting of active infection, such as tolerability of therapy, immune response to therapy, and ER. Assessment of bacteriophage pharmacokinetics and pharmacodynamics in otherwise healthy patients who are colonized by the target strain(s) may provide some insights, such as the...
impact on the microbiome, but may still not predict what happens in the setting of higher bacterial burden associated with infection. Studies conducted in a population of patients with active infections (ideally at the same sites and by the same bacterial species) may overcome some of these limitations. However, differences in bacterial burden, bacterial susceptibility to bacteriophages, host immune factors, and concomitant antibiotic therapy within the enrolled population will complicate interpretation of the data. Interpretation of pharmacokinetic data may also be affected by immune clearance of the bacteriophages [10, 11], such that blood levels of bacteriophages may not accurately represent the activity of bacteriophages at the site of infection.

The design of an appropriate clinical development plan should consider the intended use and indication of the product. If the product is an individual bacteriophage, or a standardized cocktail of bacteriophages, clinical trials would be designed to support the proposed indication (ie, treatment of a specified infection or infections caused by specified species or strains of bacteria). The clinical development program for personalized phase therapy (ie, selection of specific phages based on susceptibility of bacterial isolates from infected patients) becomes much more complex [8], as it relies on the premise that safety and efficacy data from clinical studies can be generalized more broadly to account for potential differences in the bacteriophage products, the targeted bacterial strains, and the sites of infection. It is unclear at this time whether data from individual patients treated with a personalized phase product (as opposed to a standardized product) for a limited spectrum of infections due to a limited range of bacteria species can be extrapolated to predict the safety and effectiveness of a personalized phage therapy approach to treatment for a wide variety of infectious disease indications.

Product characterization of investigational drugs and biologics includes measurements to assess identity, quality, purity, and potency. Product safety and characterization profiles are needed for the bacteriophage(s) and the host bacteria used for its propagation. Important parameters could include genomic analysis for determination of clinically relevant antibiotic-resistant genes, virulence factors, and transduction genes [12]. Product purity may be evaluated by assessing endotoxin and bioburden content. The phages should be lytic (the virulent life stage) and not capable of lysogeny (the dormant life stage where the phage incorporates itself into the bacterial chromosome) [2, 12]. Stability in specified storage conditions is another important component of product characterization. Manufacturing and product development will be more challenging for personalized bacteriophage products, depending on the number of individual bacteriophages included in the product. Propagation of bacteriophages on a background of pathogenic (and possibly MDR) bacterial host strains may be challenging for manufacturers and would require them to address safety related to transmissible genetic elements and contamination of the final product with host bacterial products. Therefore, some investigators may plan for initial clinical trials with a defined set of phages, with appropriate selection of participants, before proceeding to clinical development of personalized phase therapy.

Development of bacteriophage(s) for use in treating bacterial infections presents many challenges. Addressing issues related to bacteriophage product manufacturing and characterization and to designing early clinical trials that reliably assess product safety and tolerability are prerequisites for advancing development to trials designed to demonstrate effectiveness and assess clinical benefit. The utility of the use of animal studies for the proof of concept of phage therapy is unclear at this time. Despite these challenges, phage therapy is an exciting field that may have potential to address serious conditions for which treatment options are increasingly limited.

Note

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References