Jean-Paul Pirnay

Bacteriophages: It’s a Medicine, Jim, but Not as We Know It

Introduction

Bacteriophage (phage) therapy is increasingly put forward as a promising tool to help curb the global antimicrobial resistance crisis. By definition, phages are medicinal products (biologicals), but they have a number of peculiarities (eg, target specificity and antagonistic coevolution), which makes them quite different from the ones we are used to [1]. After more than two decades of so-called "phage therapy renaissance", no industrially manufactured phage medicinal products have made it to the EU and US markets. In addition, the business purpose–driven phage products that are currently navigating the pharma development and marketing funnel mainly target commercially viable bacterial species and clinical indications, using defined phage cocktails or engineered phages. Hospitals or phage therapy centers aiming to help all patients with difficult-to-treat infections urgently need phage preparations targeting all bacterial pathogens, in all indications. An analysis of phage therapy requests submitted to the Center for Innovative Phage Applications and Therapeutics (IPATH) in San Diego (n = 488) [2] and to the Queen Astrid Military Hospital in Brussels (n = 260) [3] revealed that the concerned infections involved no fewer than 35 and 30 bacterial species, respectively.

Methods

In 2018, Belgium developed a national phage therapy framework based on the magistral preparation of personalized (preadapted) phage products, which to date provided an immediate solution for more than 150 patients and could complement future industrially manufactured products. We performed a retrospective, observational analysis of the first 100 consecutive cases of personalized bacteriophage therapy of difficult-to-treat infections facilitated by the Belgian consortium [4]. The most common indications were lower respiratory tract, skin & soft tissue, and bone infections, and involved combinations of 26 bacteriophages (targeting 14 bacterial species), individually selected and sometimes pre-adapted to target the causative bacterial pathogens.

Results

Clinical improvement and eradication of the targeted bacteria were reported for 77.2% and 61.3% of infections, respectively. Eradication was 70% less probable when no concomitant antibiotics were used (odds-ratio = 0.3; 95% confidence interval = 0.127–0.749). In vivo selection of bacteriophage resistance and in vitro bacteriophage-antibiotic synergy were documented in 43.8% (7/16 patients) and 90% (9/10) of evaluated patients, respectively. Bacteriophage immune neutralization was observed in 38.5% (5/13) of screened patients. (BT100 study, ClinicalTrials.gov registration: NCT05498363).

Discussion

Just like Belgium, other (European) countries could develop a magistral phage preparation framework that would exist next to the conventional medicinal product development and licensing pathways. However, it is important that the current producers of personalized phage products are provided with pragmatic quality and safety assurance requirements, which are preferably standardized (at least at the European level) and are tiered based on benefit–risk assessments at the individual patient level.

References

[1] Pirnay JP and Kutter E. Bacteriophages: it's a medicine, Jim, but not as we know it. Lancet Infect Dis. 2021 Mar;21(3):309-311. doi: 10.1016/S1473-3099(20)30464-3.
[2] Aslam S, Lampley E, Wooten D, Karris M, Benson C, Strathdee S, Schooley RT. Lessons Learned From the First 10 Consecutive Cases of Intravenous Bacteriophage Therapy to Treat Multidrug-Resistant Bacterial Infections at a Single Center in the United States. Open Forum Infect Dis. 2020 Aug 27;7(9):ofaa389. doi: 10.1093/ofid/ofaa389.
[3] Djebara S et al. Processing Phage Therapy Requests in a Brussels Military Hospital: Lessons Identified. Viruses. 2019 Mar 17;11(3):265. doi: 10.3390/v11030265.
[4] Pirnay JP et al. Retrospective, observational analysis of the first one hundred consecutive cases of personalized bacteriophage therapy of difficult-to-treat infections facilitated by a Belgian consortium. medRxiv 2023.08.28.23294728; doi: https://doi.org/10.1101/2023.08.28.23294728.