Biofilm Eradication from Bioprosthetic Aortic Valve

In-vitro Biofilm Eradication

Background. Prosthetic valve endocarditis (PVE) is a major treatment challenge associated with biofilm formation. It requires intensive infectious diseases consultations and prolonged therapy. Nevertheless, high mortality rates are reported even with timely diagnosis and optimal management. Bacteriophage (phage) therapy, the use of bacterial viruses as antimicrobial agents, has been suggested as a potential adjunctive treatment for PVE. This is due to the ability of lytic phages to synergize with antibiotics and to destroy biofilms. However, due to the challenge associated with biofilm formation, it requires intensive infectious diseases consultations and prolonged therapy. Nevertheless, high mortality rates are reported even with timely diagnosis and optimal management.

Methods. In this study we demonstrate this matching using an in-vitro model of vancomycin-resistant Enterococcus faecalis (VRE). We have looked at the ability of the phage EFLK1, alone or in combination with antibiotics, to destroy mature biofilms with high specificity, it is crucial to match the phages by prescribing the phages to synergize with antibiotics and to destroy biofilms. However, due to the challenge associated with biofilm formation, it requires intensive infectious diseases consultations and prolonged therapy. Nevertheless, high mortality rates are reported even with timely diagnosis and optimal management.

Results. We found that the phage EFLK1 presents a significant inhibitory effect against planktonic cultures of VRE, both alone or in combination with ampicillin or ceftriaxone. We then tested the effect of these combinations on mature biofilm grown on a standard 96-well plate. We found that the phage, or its combination with ceftriaxone, led to a two-log reduction in the bacterial viability. In contrast, the addition of ampicillin to the phage caused interference with this antibacterial effect. When tested against biofilm grown on a pericardial patch, the combination of EFLK1 and ceftriaxone was found most efficient. Finally, when tested on the whole prosthetic aortic valve, we found that the phage EFLK1 alone was even more efficient than its combination with ceftriaxone.

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A) Representation of E. faecalis biofilm formation on bioprosthetic valves. (B) Following 48-hours of growth, the valves were treated for five days by the phage EFLK1, alone or in combination with antibiotics, to destroy mature biofilms with high specificity, it is crucial to match the phages by prescribing the phages to synergize with antibiotics and to destroy biofilms. However, due to the challenge associated with biofilm formation, it requires intensive infectious diseases consultations and prolonged therapy. Nevertheless, high mortality rates are reported even with timely diagnosis and optimal management.

Session: P-61. Novel Agents

Background. HSV recurrent infections are usually managed effectively with existing anti-inflammatory drugs (nucleoside analogs such as acyclovir). However, in immunocompromised patients (e.g., malignancy, HIV, transplant), if lesions persist or recur while receiving antiviral treatment, acyclovir resistance should be suspected. In this population, there are limited treatment options. The helicase-primease inhibitor pritelivir is a novel antiviral, with a new mode of action and is active against both HSV-1 and HSV-2, including acyclovir and foscarnet-resistant strains. In this case series, we report the first clinical experiences with pritelivir in the treatment of immunocompromised patients with acyclovir resistant HSV infection.

Methods. All patient reported in this case series received pritelivir in a Phase 2 study. There were treated in an open-label design with a 400 mg pritelivir oral loading dose followed by 400 mg bid for up to 28 days.

Results. Of the 23 patients, 11 had HSV infection and 12 had malignancy, transplant or an autoimmune disease. Of this cohort, 19 patients showed full resolution of their HSV-related lesions during the 28 day treatment period, while in 4 subjects lesions persisted or relapsed completely during the observation period. Pritelivir was well tolerated without significant adverse effects. Reasons for incomplete lesion resolution of the 28 day treatment period, were extensive lesions in one patient, one patient was noncompliant during the course of the study, one patient with lesions in the oral cavity. Three patients subsequently experienced recurrence of HSV, while one patient required further treatment due to delayed resolution of lesions.

Conclusion. Pritelivir is a promising novel treatment option for patients with severe mucocutaneous HSV-1/2 infections that are resistant to acyclovir and foscarnet. As an international Phase 3 study is underway to evaluate pritelivir efficacy in immunocompromised patients.
ceftriaxone or their combination. The valves were then washed from any planktonic cells and the biofilm biomass was established by CFU enumeration.

Conclusion. This study demonstrates that a proper in vitro testing is essential in the development of the treatment for gonorrhea and uncomplicated urinary tract infections (UTIs). This study reports on the in vitro activity of gepotidacin and other oral antibiotics when tested against contemporary Escherichia coli and Staphylococcus aureus clinical isolates collected from patients with UTIs for a gepotidacin phase 1 clinical global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Methods. A total of 3,562 E. coli and 344 S. aureus isolates were collected between 2019 and 2020 from 92 medical centers located in 25 countries. Most isolates were tested and were isolated from patients who were seen in ambulatory, emergency, family practice, and outpatient medical services. Identifications were confirmed by MALDI-TOF. ESIs were tested for susceptibility by CLSI methods at a central laboratory (JMI Laboratories). MICs results for oral antibiotics licensed for the treatment of UTI and drug-resistant subsets were interpreted per CLSI guidelines.

Results. Gepotidacin (MIC90 2/2 mg/L) displayed good activity against 3,562 E. coli isolates, with 98.0% of all observed gepotidacin MICs ≤4 mg/L (Table). Susceptibility (S) rates for the other oral agents tested against these isolates were: amoxicillin-clavulanate (79.6% S), ampicillin (45.6% S), ciprofloxacin (72.5% S), fosfomycin (99.0% S), mecillinam (91.4% S), nitrofurantoin (97.3% S), and trimethoprim-sulfamethoxazole (68.2% S). When tested against the drug-resistant subsets, gepotidacin resisted cephalosporins values (2/4 mg/L), except against isolates resistant to fosfomycin (2/8 mg/L). Against S. aureus isolates, gepotidacin (MIC90 0.06/0.12 mg/L) inhibited all isolates at ≤0.25 mg/L. Most oral agents showed S results of >97% against S. aureus isolates, except for penicillin (3.5%).

Conclusion. Gepotidacin demonstrated potent in vitro activity against contemporary E. coli and S. aureus urine isolates. This activity was largely unaffected among isolates demonstrating drug resistance to other oral standard of care antibiotics.

Disclosures. Ran Nir-Paz, MD, BiomX (Consultant) Technophage (Scientific Research Study Investigator, Advisor or Review Panel member)

1063. ARGONAUT-V: Susceptibility of Multidrug-Resistant (MDR) Pseudomonas aeruginosa to Cefepime-Taniborbactam
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Session: P-61 Novel Agents

Background. P. aeruginosa is a Gram-negative pathogen responsible for many serious infections. MDR, both intrinsic and acquired, presents major clinical challenges. Taniborbactam (formerly VNRX-5133; Fig 1) is a β-lactamase inhibitor (BLI) characterized as a bicyclic boronate, uniquely possessing activity toward all four Ambler classes of β-lactamases, both serine and metallo, with the exception of class B IMP β-lactamases. The β-lactam-β-lactam combination cefepime-taniborbactam (FTB; Fig 1) is currently in phase 3 clinical trials.

Table

| Organism (No. Isolates) | % of isolates inhibited by cephalosporin (MIC ≤ 6 µg/mL) | Cefepime | Taniborbactam | CEF-TAN |
|-------------------------|-------------------------------------------------------|----------|--------------|--------|
| E. coli                  | 97                                                   | 100      | 100          | 100    |
| S. aureus               | 99                                                   | 100      | 100          | 100    |

Conclusion. This study demonstrates that a proper in vitro testing is essential in the development of the treatment for gonorrhea and uncomplicated urinary tract infections (UTIs). This study reports on the in vitro activity of gepotidacin and other oral antibiotics when tested against contemporary Escherichia coli and Staphylococcus aureus clinical isolates collected from patients with UTIs for a gepotidacin phase 1 clinical global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Methods. A total of 3,562 E. coli and 344 S. aureus isolates were collected between 2019 and 2020 from 92 medical centers located in 25 countries. Most isolates were tested and were isolated from patients who were seen in ambulatory, emergency, family practice, and outpatient medical services. Identifications were confirmed by MALDI-TOF. ESIs were tested for susceptibility by CLSI methods at a central laboratory (JMI Laboratories). MICs results for oral antibiotics licensed for the treatment of UTI and drug-resistant subsets were interpreted per CLSI guidelines.

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