A Pilot, Multicenter, Randomized, Non Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee Prosthetic Joint Infection due to Staphylococcus aureus Treated with DAIR and Antibiotic Therapy

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Considering the paucity and the variability of data regarding the clinical control of infection in patients presenting a prosthesis Joint Infection (PJI) later than 1 month after the arthroplasty and treated with DAIR + suppressive antibiotics...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON53569

Source
ToetsingOnline

Brief title
PhagoDAIR I

Condition

- Bacterial infectious disorders

Synonym
knee or hip prosthetic infection, Prosthetic joint infection

Research involving

Human

Sponsors and support

Primary sponsor: Phaxiam Therapeutics
Source(s) of monetary or material Support: Phaxiam Therapeutics

Intervention

Keyword: Hip Prostetic Joint Infection, Knee Prostetic Joint Infection, Phage therapy, Staphylococcus aureus

Outcome measures

Primary outcome

Clinical control of infection at week 12±2 defined by:

- no clinical signs of evolutive infection:

o no fever (defined by a temperature less than 38°C) due to prosthesis infection

o no recurrence, no worsening pain assessed with an Visual Analog Scale (VAS)

and defined by an VAS at Week 12 below VAS prior to D0

- Peri articular Inflammatory and infectious Clinical signs will be collected :

o No local post surgical recurrence or worsening of local articular swelling

o No unusual aspect of scar as erythema or abnormal flow or a fistula or

inflammatory or local necrosis or no healing

- and no new surgical procedure requested before Week 12±2 and no

Staphylococcus aureus detected in joint fluid in case of aspiration for

suspicion of relapse before Week 12±2

Secondary outcome

1. Safety parameters: adverse events, physical examination, biological tests as

hematology and biochemistry during the whole study;

2. Initial activity of phages: active bacteriophages (PP1493 and/or PP1815)

according to phagogram results in regard of the clinical outcome (infection control or relapse) of patients at Week 12±2

3. Clinical control of the infection (as described in primary endpoint) at Week 12±2 for superinfected patients (other species isolated during the surgical procedure)

4. In case of failure before Week 12±2, aspiration of joint fluid at time of failure for microbiological test and identification of Staphylococcus aureus strain: antibiogram and phagogram

5. Microbiology:

- Joint fluid: Staphylococcus aureus quantification (CFU and qPCR) at D0 for THA and TKA at D14±1 only for TKA

6. Immunology:

- Serum: anti Staphylococcus aureus phage antibodies, at D0, D2, D4, D14±1, D28±2 and Week 12±2 and IL-6 at D0, D14±1 and W12±2

- Joint fluid: anti Staphylococcus aureus phage antibodies at D0 and at D14±1 only for patients with TKA

7. Pharmacokinetics:

- Serum: quantification of the phages by qPCR at D0, D0T4H, D2, D4, D14±1, D28±2 and Week 12±2

- Blood: quantification of the phages by plaque assay at D0, D0T4H, D2, D4, D14±1, D28±2 and Week 12±2 for patients in sites in Paris, Nantes and Lyon

- Joint Fluid: quantification of the phage by qPCR and plaque assay at D0 and at D14±1 only for patients with TKA; the plaque assay will be performed only for patients in sites in Paris, Nantes and Lyon;

8. Duration of hospitalization

9. Questionnaire EQ-5D-5L for quality of life at each visit (except D14±1 and

D28±2);

10. Evaluation of joint function during the pre-inclusion period or at D-1,

Week 12±2, Month 6 ±2 weeks, Month 12±1, Month 18±1 and Month 24±2 with:

- Knee: KOOS 12-Knee Survey

- Hip: HOOS 12-Hip Survey;

11. Clinical control of the infection (as described in primary endpoint) at

Month 6±2 weeks, Month 12±1, Month 18±1 and Month 24±2;

12. X Ray during the pre-inclusion period or at D-1, Week 12±2, Month6 ±2

weeks, Month 12±1, Month 18±1 and Month 24±2: to check potential appearance of

abnormal loosening (border with shifting of the prosthesis), or an abnormal

periprosthetic border;

13. In case of rescue treatment: clinical infection control at Week12-RT±2

after the first ultra-guided injection, safety parameters, pharmacokinetics,

bacteriological and immunological tests.

Study description

Background summary

The main causality of PJIs in THA and TKA are Gram-positive cocci, which are largely driven by infection with Staphylococcus aureus and coagulase-negative staphylococci. Together, these bacteria contribute to 50-60% of PJIs; streptococci and enterococci only account for 10% of cases (8;11) and in 90% of cases, infections are monomicrobial (5).
Beside the antibiotic resistance, the ability of a bacterium to form biofilm largely contributes to treatment failure (14). Biofilms are formed when microorganisms such as Staphylococcus spp. adhere to a substratum or interface

to form an aggregate. They have been reported to account for more than 80% of microbial infections in the body, including prosthesis and internal fixation devices (15). Bacteria, such as Staphylococcus aureus and Staphylococcus epidermidis, can form biofilms on stainless steel and titanium orthopaedic screws with ease (16). Therefore, when considering new anti-infectious treatment, especially to fight PJI, the anti-biofilm activity is of major concern.

Bacteriophage therapy, also referred to as phage therapy, could be an improvement for treating PJIs. Phages are naturally occurring, highly specific bacterial viruses that invade bacterial cells and disrupt metabolism, causing lysis and destroying the microbe. There are limited nonclinical in vivo studies published on phage therapy for bone-related infections. In a PJI model using MRSA, in which the antibiotic and phages were incorporated in a biopolymer coated on the implant before implantation. It was demonstrated that a phage-antibiotic combination led to an effective control of the bacterial burden and inflammatory response. The animals treated with phages showed a faster restoration of locomotion as compared to the individual treatments. Another preclinical model of implant related infection showed that the phage-antibiotic combination decreased the biofilm thickness as compared to the antibiotic alone (26).
In vitro anti-Staphylococcus aureus bacteriophages were shown to be effective in reducing viable biofilm-associated cells and synergistic properties of phages with certain antibiotics have been reported (27).
In a clinical setting, phage therapy is currently used as standard practice in Georgia and Poland (28) and consequently, studies have been concentrated in Eastern Europe. There is currently no phage therapy approved for use in Western countries; however, some phage studies have been conducted in France, Belgium, United States of America, United Kingdom and Switzerland (29,30, 31,32), for chronic leg venous ulcer, chronic otitis media and burn wound infections. Additional studies are in the pipeline (33).
Although some positive results have been published from in vivo studies using implant-related infection models (25,26), an adequate model for PJIs is still to be perfected. Indeed, Kaur et al. demonstrated phage efficacy when phages were coated on the implant (25), and Yilmaz et al (26) demonstrated activity of the phages on the biofilm thickness but not on the control of the bacterial burden.
Lastly, as with all biological therapies, there are immunogenicity concerns. Numerous studies have demonstrated in various animal species that repeated phage injections trigger an antibody response with anti-phage IgM and IgG production (34,35). Some studies have also shown in vitro that in some cases they correspond to neutralizing antibodies, meaning that they decrease the phage activity. However, it remains unclear whether the presence of neutralizing antibodies has an impact on the therapeutic outcome of the phage therapy. In samples from 20 patients having been administered a Staphylococcus aureus phage cocktail orally and locally to treat a variety of infections, most patients did not present with high levels of anti-phage antibodies in the

sampled serum. In patients with an increased immune response (induction of IgG and IgM antibodies), in general, the clinical response was not greatly affected (36,37).
Pherecydes Pharma is a French Biotechnology Company specializing in the research and development of anti-infective therapies based on the use of bacteriophages (phages). It currently owns collections of phages against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.
Currently Pherecydes Pharma has two anti-Staphylococcus aureus phages in development: PP1493 and PP1815. To date, these phages have undergone extensive physiochemical tests, studies of anti-infective activity in vitro and in vivo, pharmacokinetic (PK), and toxicity studies in laboratory animals. These phages have shown promising in vitro efficacy as well as in vivo tolerance. The anti-Staphylococcus aureus phages will be tested in vitro against the patient*s specific Staphylococcus aureus strain: this will be referred to as a phagogram. This allows the selection of phages active against a particular patient*s infecting bacteria and only active phages will be administered to the patient.

Until now, no clinical trial has been carried out with the Pherecydes anti-Staphylococcus aureus bacteriophages in prosthetic joint infection (PJI) nor any other pathology.
PhagoDAIR I
Prosthesis exchange could be associated with a considerable loss of function, especially if the patient needs a prosthesis revision with a complex reconstruction, a resection arthroplasty of the hip (removal of the prosthesis without possibility of a reimplantation), arthrodesis of the knee or amputation. For these patients, using locally an antibiofilm agent facilitating the rescue could be of importance, to limit the loss of function and the considerable additional cost associated with complex surgeries. As anti-Staphylococcus aureus bacteriophages demonstrated in vitro antibiofilm activity, we hypothesized that they could facilitate the efficacy of DAIR with antibiotics to control the infection, and to avoid prosthesis revision and considerable loss of function.
PhagoDAIR I will be the first phagotherapy clinical trial in this indication.

Study objective

Considering the paucity and the variability of data regarding the clinical control of infection in patients presenting a prosthesis Joint Infection (PJI) later than 1 month after the arthroplasty and treated with DAIR + suppressive antibiotics therapy and the absence of efficacy data in patients treated by phagotherapy, a pilot study is necessary.
Then, the overall objective of this pilot study is to generate data which will allow to optimize the design of future comparative studies on the efficacy of phage therapy in patients presenting a prosthesis Joint Infection (PJI) later than 1 month after the arthroplasty.

To estimate the rate of clinical control of infection due to Staphylococcus

aureus at Week 12±2 of two different therapeutic regimens: DAIR + curative antibiotics therapy combined with bacteriophages or solution of NaCl 0.9%; in patients presenting a Prosthesis Joint Infection (PJI) later than 1 month after the arthroplasty, with the indication of DAIR + Suppressive Antibiotics Therapy (SAT) which will allow to calculate the sample size for future comparative studies.

Study design

This is a pilot, randomized, non-comparative, double-blind study in patients with knee or hip prosthetic joint infection (PJI) due to Staphylococcus aureus, with the indication of DAIR and suppressive antibiotic therapy. A stratification will be based on the affected area of arthroplasty: knee, hip and on study site.

Intervention

anti- Staphylococcus aureus bacteriophages

Study burden and risks

- Chance of measurements during examination (blood sampling, puncture)
- Extra visits to the hospital (9)
- Keep to agreements that are part of the research
- There are no known risks for the use of bacteriophages

Contacts

Public
Phaxiam Therapeutics

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female >= 18 years
2. Staphylococcus aureus monomicrobial knee or hip PJI *1 month after prosthesis implantation with clinical signs of infection and with indication of DAIR with direct closure (if associated flap, arthrotomy must be sealed), and Suppressive Antibiotics Therapy (SAT)
3. Staphylococcus aureus only in joint fluid within 6 months before randomization or in case of relapse of infection under antibiotics therapy after a DAIR performed within 6 months before pre-inclusion visit
4. Without preoperative diagnosis of superinfection due to another pathogen if treatment is administered at the end of the DAIR
5. Without diagnosis of superinfection due to another pathogen identified within 72h after a bacteriological sample performed during a DAIR if treatment is administered 14±2 days after a DAIR.
6. Phagogram displaying the susceptibility of the strain to at least one of the phages.
7. Patient with a life expectancy of 2 years and more as determined by the principal investigator
8. Females of childbearing potential/Sexually active males with partner of childbearing potential: commitment to consistently and correctly use an acceptable effective method of birth control (oral, transdermal, systemic or implant contraception birth control, intrauterine devices, condom) for 1 month after the last study drug administration
9. Females of non-childbearing potential: either surgically sterilized or at least 1 year postmenopausal (amenorrhea duration at least 12 months)
10. Negative pregnancy test
11. Signing a written informed consent before any study related procedures including phagogram
12. Affiliated to a national social security system and / or private health

insurance in compliance with the

Exclusion criteria

1. Early Staphylococcus aureus Prosthesis Joint infection (*1month after the prosthesis implantation)
2. Other germ found in culture of joint fluid sample
3. Phagogram displaying no susceptibility of the strain to anti-Staphylococcus aureus bacteriophages
4. Patients with ASA score >= 4
5. Severe sepsis or Septic shock or hemodynamic instability
6. Patients with an indication to prosthesis replacement or amputation
7. Immunosuppressed patients
8. Known allergic reactions to components of phages products
9. Relapse between DAIR and treatment administration planned 14±2 days after a DAIR
10. Medical history which in the opinion of the investigator would mean that the patient is unsuitable for participation in the study
11. Patient who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development
12. Currently in exclusion period from a previous study
13. Concomitant participation to another interventional clinical trial or previous participation with active drug levels still present, i.e. the last medication intake is less than 4 half-lives ago
14. Patients who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the treatment period and up to 1 month after the last administration of study drug
15. Women/Men refusing to use an acceptable effective contraception during 1 month after the last administration of study drug
16. No possibility of contact in case of emergency
17. Minors, persons deprived of liberty by judicial or administrative decision, persons receiving psychiatric care and persons admitted to a health or social institution, to adult patient under legal protection or unable to express consent.

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	16
Type:	Anticipated

Ethics review

Approved WMO Date:	23-02-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-08-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	25-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-004469-11-NL
ClinicalTrials.gov	NCT05369104
CCMO	NL83287.000.23

Study results

Summary results
Trial never started