EXPERIENCE FROM ONGOING PHAGOBURN CLINICAL TRIAL

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DISCLOSURE

» None
PLAN

1. Background
2. Clinical study
3. Adjustments
OUR MEDICAL OBJECTIVES

» Main objective: Proof of concept
  » Use of phages in human bacterial infections

» Secondary objectives
  » Causes of failure
  » Evolution of local flora
  » Healing improvement

PubMed (Mesh):
Bacteriophages = 51,662 references
Bacteriophages/therapeutic use = 20 references
OTHER OBJECTIVES

» Interaction with antibiotics
» MRD bacteria

» Modulation of immune response
» Impact on gut flora

» Bio distribution: absorption, clearance, elimination...

131 referenced publications in the last 5 years

Brüssow, 2005 Microbiology
Sarker 2012, Virology

In only 36 months
CHOICE 1: BURN UNITS

» Topical application: BMJ, 1970

» IV is more complicated

» Topical application instead of antibiotics

» Numerous adverse effects with topics currently used

» Strong policy about use of antibiotics

» Skilled environment: Medical, nurses...
CHOICE 2: 2 BACTERIA

» **E** *coli*:
  » in charge of 60% of burned skin infection
  » Many published data on phages Vs *E.coli*

» **P** *aeruginosa*:
  » *One the most difficult strain to cure*
Comparative proportion of fluoroquinolones resistant Escherichia coli isolates in EU during the last ten years. | Credit: European Centre for Disease Prevention and Control (ECDC).
CHOICE 3: COCKTAILS

» Reduce risk of failure +++
» Reduce risk of emergence of phage resistant strains
» Natural Vs modified lytic phages: regulatory tolerance
» Pre-clinical tests available (efficacy and safety)
ORGANIZATION

» International
» Multi centric study
» In-hospital patients
» Critical care environment
» Cooperation with regulatory agencies:
  » French / Swiss / Belgian / EMA
» Respect of good medical practices
» Standardization of care +++
**DESIGN**

Infection suspected

- **Povidone**
- **PP0121 E. coli**
- **Control Silver Sulfadiazine**
- **PP1131 P. aeruginosa**

Daily dressing and samples for 7 days

Usual treatment

D0  D1  D2  D3  D4  D5  D6  D7  D21
DESIGN

Povidone

- PP0121 E. coli
  - Control Silver Sulfadiazine

PP1131 P. aeruginosa

Suspected Infection/ Samples

Daily dressing and samples for 7 days

Usual treatment

D0  D1  D2  D3  D4  D5  D6  D7

D21
CLINICAL CRITERIA OF INFECTION

» Local or loco-regional inflammatory reaction

» Adverse or Unexpected local evolution

» Purulent wound

» Fast debridement or delayed healing of donor site

» Blackish spot

» Conversion of superficial wound in a deeper wound

SFETB, guidelines
DESIGN

Povidone

PP0121 *E. coli*

Control Silver Sulfadiazine

PP1131 *P. aeruginosa*

Usual treatment

Infection suspected

D0  D1  D2  D3  D4  D5  D6  D7

Daily dressing and samples for 7 days

Local Probabilistic treatment for 2 days
POVIDONE IODINE

» Usual probabilistic topical treatment
» Pathogen none yet identified: Cocci Plus Vs Gram Negative Bacillus
» Adverse effects / restiction of use
» No negative interaction with phages
DESIGN

Povidone

PP0121 *E. coli*

Control Silver Sulfadiazine

PP1131 *P. aeruginosa*

Usual treatment

Daily dressing and samples for 7 days

D0 D1 D2 D3 D4 D5 D6 D7 D21

Infection suspected

Eligibility?
INCLUSION CRITERIONS

» Man or woman
» Adult
» Informed consent obtained
» In-hospital patient in a burn unit
» Infected wound: SFETB standards
» *E. coli* or *Pseudomonas aeruginosa*, whatever antimicrobial resistance
EXCLUSION CRITERIA

» Child under 18

» Pregnant or breastfeeding woman

» Undercurrent condition requiring a treatment which may interfere with analysis results: such as high dose of chronic corticotherapy, immunosuppressive medication, oncologic chemotherapy

» Patient included in an interventional research protocol with therapeutic intervention still ongoing upon inclusion time or having participated into anti-infective drug trials during the previous month. Patient previously included in the study

» Vulnerable population

» Patient for whom treatment limitation or withdrawal during study period is considered

» General or local Known sensitization to sulfamides
**DESIGN**

Infection suspected

- **Povidone**
- **Control Silver Sulfadiazine**
- **PP0121 E. coli**
- **PP1131 P. aeruginosa**

**Randomization**

Daily dressing and samples for 7 days

D0  D1  D2  D3  D4  D5  D6  D7  D21

Usual treatment
PP0121 AND PP1131

- **PP0121**: Mix of 13 lytic phages lytiques against *Escherichia coli*

- **PP1131**: Mix of 12 lytic phages lytiques against *Pseudomonas aeruginosa*
CHARACTERIZATION

Morphotypage

Genomic Sequencing

Action profile

Genomic analysis

Classification:
- Ordre: Caudoviridae
- Family: Myoviridae
- Gender: PB1/KPP12-like
- Genomic Sequencing
  - 66 212 pairs of bases
  - Genre PB1/KPP12-like Lytic phage
    - No toxin gen
    - No integrase

Integrity tests
## PRE CLINICAL SUMMARY

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<thead>
<tr>
<th>Characterization of φ</th>
<th>Cocktail anti COLI</th>
<th>Cocktail anti PYO</th>
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PK OF PP0121

Injection of 100µl of cocktail at $10^8$ PFU

With PP1131, identical results were observed
### Conclusions PP0121

- No treatment Survival rate : 20%
- Treated J0 (infection+6h) via SC : SR = 100%
- Dilution of cocktail from $10^8$ to $10^5$ PFU/ml

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<tr>
<th>Jour</th>
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<td>1,5mg Cy</td>
<td>Burn</td>
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<td>Infection</td>
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<td>Mode injection</td>
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<td>SC $10^7$cfu</td>
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<td>PHAGE</td>
<td></td>
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<td>SC 6h post-infection</td>
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CONTROL GROUP

» Silver sulfadiazine
» Broad spectrum antiseptic activity
» Instead of :
  – Sulfamylon®: Temporary use
  – Colimycin preparation : Local preparation
  – Hypochlorite Bath
» Expert agreement
» Several Known adverse effects
DESIGN

Povidone

PP0121 *E. coli*

Control Silver Sulfadiazine

PP1131 *P. aeruginosa*

Infection suspected

D0  D1  D2  D3  D4  D5  D6  D7  D21

Daily dressing and samples for 7 days

Daily dressing

Usual treatment
<table>
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<tr>
<th>Study procedure</th>
<th>V0</th>
<th>V1</th>
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<th>V7 End of treatment</th>
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<th>V9 End of study</th>
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<td>Treatment (phage cocktails or silver sulfadiazine)</td>
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ADJUSTMENTS

» Increase duration of study 36 months

» Increase number of investigation sites 11 centers

NNT = 220 patients / 1 year

» Adjustment in cocktail use to reduce workload of teams and errors in re-composition
REGULATORY DISCUSSIONS

» Management of adverse effects:
  » control group: Silver Sulfadiazine
  » study group: GRAS (Generally Recognized As Safe)

» Interactions with ongoing antibiotics
  » With or without effect on the treated strain

» Education and information of teams
NEXT DEVELOPMENTS

» First inclusion expected before 1\textsuperscript{st} July
» DSMB every 3 months, 50 patients
» Open data to agencies
» Specific management of potential \textit{adverse effects}
» Non blind for investigator, so inclusions would be easy whether clinical results are positive
» Results will be known in 1 year
WHAT HAVE WE LEARNT?

» Many questions to answer in a single study: efficacy, safety, metabolism...

» In vivo/vitro, Animal/human differences

» Collaborative work with many different components
CONCLUSIONS

» PHAGOBURN is the first multi centric clinical study ever done on human phage therapy

» Whatever the results, after PHAGOBURN further studies will be necessary

» It’s now time to move from a belief to scientific evidence