Malaria Vaccines

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COMPTES RENDUS
HEBDOMADAIRES
DES SÉANCES
DE L'ACADÉMIE DES SCIENCES,

PUBLIÉS,
CONFORMÉMENT À UNE DÉCISION DE L'ACADÉMIE
EN DATE DU 13 JUILLET 1835,
PAR MM. LES SECRÉTAIRES PERPÉTUELS.

TOME CENT-CINQUANTE-ET-UNIÈME.
JUILLET — DÉCEMBRE 1910.

PATHOLOGIE. — Sur l'immunité dans le paludisme des Oiseaux. Conservation in vitro des sporozoïtes de Plasmodium relictum. Immunité relative obtenue par inoculation de ces sporozoïtes. Note de MM. ÉTIENNE SERGENT et ÉDMOND SERGENT, présentée par M. É. ROUX.
Candidates

• RTS,S
• Live sporozoite based vaccines
• And many others
Early clinical development

- First in man: 1997
  - Vaccine efficacy: 6/7 protected

- Overall efficacy in controlled human infections ~40% (phase II)

- Vaccine efficacy in African trials 25–66% (phase II)
Malaria Day: 25 April 2015

Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial

RTS,S Clinical Trials Partnership*

http://dx.doi.org/10.1016/S0140-6736(15)60721-8
Mal-055

• 8922 children (5–17 months)
• 6537 infants (6–12 weeks)

• RTS,S/AS01 schedule:
  • RTS,S  R0 – R1 – R2 – R20
  • RTS,S  R0 – R1 – R2 – C20
  • Co      C0 – C1 – C2 – C20

• Up to 48 months follow-up
Protective efficacy

• Children
  • 36% (28%) malaria (1774 prevented episodes per 1000 vaccinees)
  • 32% (1%) severe malaria

• Infants
  • 26% (18%) malaria (1363 prevented episodes per 1000 vaccinees)
  • 17% (10%) severe malaria
European Medicines Agency

- Review by Committee for Medicinal Products for Human Use (CHMP) under Article 58
- 24 July 2015: Positive scientific opinion
- RTS,S → Mosquirix
WHO

• Joint review by:
  • Strategic Advisory Group of Experts (SAGE) on Immunization
  • Malaria Policy Advisory Committee (MPAC)
• January 2016:
• Pilot implementation in selected African countries
  • Feasibility (4 injections)
  • Impact on mortality
  • Safety (meningitis)
Others

- PfSPZ
- GMZ2
- AMA1
- Viral vectors
- ...

PfSPZ

Sanaria Inc.
Plasmodium falciparum sporozoite vaccines

- Chemoattenuation
- Radioattenuation
- Genetic attenuation
TÜCHMI-002 (chemoattenuation)

Intravenous inoculation with 3200, 12800 and 51200 sporozoites

4 week intervals

10 week chloroquine chemoprophylaxis

Challenge 10 weeks after last injection
Study flow

Assessed for eligibility: 73

Received CQ loading dose: 44

Excluded
Not meeting criteria: 11
Refusal: 1
Other: 7

Excluded
CQ intolerance: 2

3,200 PfSPZ
Randomized: 14

Allocated to PfSPZ: 9
Received PfSPZ: 9

Allocated to Placebo: 5
Received Placebo: 5

Received CHMI: 9
Lost to follow-up: 0
Analysed: 9
Excluded: 0

12,800 PfSPZ
Randomized: 14

Allocated to PfSPZ: 9
Received PfSPZ: 9

Allocated to Placebo: 5
Received Placebo: 5

Received CHMI: 9
Received CHMI: 4
Consent withdrawal: 1
Lost to follow-up: 0
Analysed: 9
Excluded: 0

51,200 PfSPZ
Randomized: 14

Allocated to PfSPZ: 9
Received PfSPZ: 9

Allocated to Placebo: 5
Received Placebo: 4
Consent withdrawal: 1

Received CHMI: 4
Lost to follow-up: 0
Analysed: 4
Excluded: 0

* Participant received only the first Placebo injection
Safety and tolerability: Immunization
Efficacy

33%  
67%  
100%
Invasion inhibition
Post-immunisation parasitaemia

![Graph showing the logarithmic parasite equivalents per mL over time for different time points.](image-url)
Conclusions

• PfSPZ-CVac is a highly efficacious, safe and well tolerated vaccine
• Striking dose-response
• Parasitaemia post-immunization predicts protection
• Proteome-wide arrays reveal relevant immune-signatures
• Immune responses are heterogeneous
• Heterologous protection
• Regimen optimization
Radioattenuated sporozoites

• Up to 100% protective efficacy
• Requires intravenous injection of PfSPZ
• Current trials:
  • Durability
  • Heterologous protection
  • Immunisation schedule and dose
Genetically attenuated sporozoites

- Animal models: high protective efficacy
- First trials in humans: breakthrough infection
- First double knock-out GAP vialled (PfΔb9Δslarp)
- First-in-man planned in 2017
Overall conclusions

• First antiparasitic vaccine in humans: RTS,S/Mosquirix (not yet ready for implementation)
• Promising results with sporozoite-based vaccines (licensure foreseen in 2019)
• Successful asexual and sexual blood stage vaccines pending
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