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Human challenge studies of vaccines

Possibilities and requirements

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Possible?

„Human challenge studies might also provide valuable information. However, such studies are appropriate only for selected diseases for which successful treatment is available and if ethically acceptable. Applicants are advised to seek specific advice from EU Competent Authorities on the need for and design of such studies"

GUIDELINE ON CLINICAL EVALUATION OF NEW VACCINES, EMEA/CHMP/VWP/164653/2005

"In some situations, it may be possible to conduct challenge studies in human subjects during early development or in lieu of clinical trials in an endemic area. ... provided that studies were adequate and well-controlled and conducted under the provisions of GCP . Of note, use of challenge studies to demonstrate efficacy does not preclude the requirement for adequate safety data. As human challenge studies may present unique considerations, we recommend that the sponsor discuss its development plan with CBER... "

General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases, FDA 2011

Why human challenge studies?

- Proving a vaccine's beneficial effect increasingly difficult:
  - Efficacy studies (huge subject numbers required)
  - correlate of protection not known/ no clear threshold
  - higher regulatory standards
  - higher demand from recommendation boards (and public)
- Challenge shows protection:
  - Within shorter time
  - Smaller group size compared to real-life studies
  - Under very controlled conditions

Is this a new approach?

- “Self-challenge” by Wolters and Dehmel after self-inoculation with tetanus vaccine (1942)
- Intranasal challenge using different Rubella strains (1978)
- Oral challenge with S. typhi testing “killed” oral antigens (1971)
- Current projects include:
  - Helicobacter pylori
  - Malaria

Is it possible with infection X?

- Infectious agent needs to be known
- Disease must not be:
  - Invariably fatal
  - Immediately severe (time for diagnosis + therapy)
- Diagnosis relatively simple
- Therapy possible and safe
- NC models not feasible
- Humans:
  - “Healthy adult (male) subjects”...
  - Compliance of subjects
  - Highly motivated personnel

The Case: H. pylori vaccine candidate

- Candidate vaccine: purified antigens + adjuvant
- Challenge bacterium H.pylori:
  - 10^6 to 10^7 cfu
  - Susceptible to amicillin, clarithromycin and metronidazole
  - Prepared under GMP
- Setting:
  - observer-blinded, Placebo-controlled
  - Staggered design + interim analysis
  - UGE for screening and 12w post challenge
  - UBT and stool antigen weekly

Outcome

- Low rate of infections in placebo-group (<50%)
- No difference in infection rate between groups
  - Study stopped for futility
  - not all subjects challenged
  - HP positives (UBT): eradication therapy

The End ?

Follow-up revealed trouble...

- Persistance of infection in all challenged subjects:
  - Mucosal inflammation 12 weeks post challenge (moderate - severe)
  - Urea breath test negative in all subjects
  - BUT: H.pylori culture positive in 50%!
    - Screening methods (UBT and stool antigen) not sufficient?

Follow-up explorative and safety study

- Exploration:
  - H. pylori still present?
    - Bacteria found „sanctuary site“
    - Not detected (by standard diagnostics of original study)
  - Intensified Diagnostics:
    - Histology
    - Gene expression profiling of inflammatory medicators
    - Rapid urease test and 13C-UBT
    - Culture
    - Fecal stool antigen test
- Eradication repeated

Safety, safety, safety...

- Challenge agent:
  - Highly susceptible to established therapy (Guidelines!)
  - Produced ideally under GMP
- Detection methods:
  - Established medical practice
  - As easy as possible, as invasive as necessary
  - More than one...
- Intense Surveillance (weekly, daily etc. as needed)
- Long surveillance using best detection method

Which development phase should we pick?

- Early phase
  - saves costs (of futile development)
  - Clearly shows possibilities and pitfalls of product
    - Additional „vulnerable“ populations
    - Additional target populations
  - Dose finding tricky (range) but clear answers
- Later phases
  - Clear data on expected (S)AEs of product
  - Immunogenicity data (correlate/surrogate of protection)
  - Better idea of „ideal“ dose

Benefit and risks of the human challenge approach

- Clear answer on protection from infection / disease
- No children allowed:
  - Bridging to non-adult age groups needed
    - Bridging from healthy to risk groups
  - Need for surrogate / correlate of protection
- Usually small numbers -> further studies needed (3000 subjects for new vaccines)
- Artificial?
  - Mimic route of infection
  - Different infection sites for male/ female e.g. STDs?
  - Ususally not tested under “real-life” conditions :

    ⟹ Public health impact of vaccine still unclear

When in doubt…

(generally)

…ask for advice!

PEI:

- DZIF-OSRA
- Sections for Microbiological or Viral Vaccines
- Office for Innovation

Thank you for your attention!

Questions?