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Evaluation of the capacity of a drinkable vaccine against entertoxigenic E. coli diarrhoea to elicit immunological memory

Submission date
25/11/2013

Recruitment status
No longer recruiting

Registration date
16/12/2013

Overall study status
Completed

Last Edited
07/10/2021

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Infection with enterotoxigenic E. coli bacteria (ETEC) is a common cause of diarrhoea among children in developing countries and in travellers to such countries. However, there is no vaccine available against ETEC disease. Our research team has developed a drinkable vaccine against ETEC infection which consists of killed bacteria and a toxin antigen (a protein from the bacteria). A first generation of our ETEC vaccine has been tested in several thousand people around the world. This ETEC vaccine was shown to provide protection against severe ETEC diarrhoea in adult travellers but did not protect young children in a developing country. We have now developed an improved vaccine against ETEC diarrhoea which was recently shown to be well tolerated and to produce robust intestinal immune responses when tested in 95 healthy Swedish adults. We will now assess whether the vaccinations in the previous study have given rise to immunological memory responses, i.e. responses that last for an extended time after immunization.

Who can participate?
Adults aged between 18 and 47 years in good health who have been vaccinated with the new ETEC vaccine in the previous study, or individuals who have never been immunized with ETEC or cholera vaccines.

What does the study involve?
All volunteers will be given one dose of the ETEC vaccine. The vaccine will be given as a drink. Participants will visit the vaccination unit four times over a period of 2-7 weeks for physical examination (two times) and to provide blood samples (four times). Participants will be asked to keep a diary in which they should report how they are feeling and whether they are taking any medicines throughout the study.

What are the possible benefits and risks of participating?
Participants will receive a free medical check-up, and immunized participants may develop some protection against ETEC and cholera infection. Participation will promote the development of a new vaccine, which will hopefully diminish the risk for both children and adults of developing

ETEC diarrhoea in the future. The vaccine has been well tolerated when given in two oral doses in the previous study and similar ETEC vaccines have also been shown to be safe when given in three doses. Side effects are rare in adults, but if there are any they would consist of mild and transient diarrhoea, nausea, occasional vomiting, bloating and abdominal pain.

Where is the study run from?
Sahlgrenska University Hospital, Gothenburg, Sweden.

When is the study starting and how long is it expected to run for?
The study is planned to start in December 2013 and is due to end in June 2014.

Who is funding the study?
The Swedish Research Council and the Sahlgrenska University Hospital, Gothenburg, Sweden.

Who is the main contact?
Prof. Ann-Mari Svennerholm,
ann-mari.svennerholm@microbio.gu.se

Contact information

Type(s)
Scientific

Contact name
Prof Ann-Mari Svennerholm

Contact details
Dept. of Microbiology and Immunology
University of Gothenburg
Box 435
Gothenburg
Sweden
405 30
+46 (0)31 7866202
ann-mari.svennerholm@microbio.gu.se

Additional identifiers

EudraCT/CTIS number
2013-003693-28

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OEV-121A

Study information

Scientific Title
A phase I study to evaluate the capacity of an oral inactivated tetravalent ETEC vaccine alone and in combination with dmLT adjuvant to induce immunological memory to toxin and colonization factor antigens in the vaccine

Study objectives
We have recently developed a new oral inactivated tetravalent ETEC vaccine (TEV) which contains four different inactivated E. coli strains expressing the most prevalent ETEC colonization factors (CFs), i.e. CFA/I, CS3, CS5 and CS6, plus a LTB/CTB hybrid protein (LCTBA). This vaccine was recently shown to be safe and highly immunogenic when tested alone or together with two different dosages, i.e. 10 µg and 25 µg, respectively, of the mucosal adjuvant dmLT in adult Swedish volunteers (Study OEV-121, ISRCTN91363076). The aim of the present study is to evaluate if the TEV given alone or together with the lower dose of dmLT adjuvant in the OEV-121 trial has induced immunological memory.

Primary study hypothesis:
Orally administered TEV, the non-adjuvanted and/or adjuvanted vaccine formulations, has induced mucosal memory responses to LTB and CFs that may be detected by accelerated, higher and/or more frequent circulating antibody secreting cell (antibodies in lymphocyte supernatants; ALS) responses to a single booster dose of TEV in previously vaccinated subjects than to a single dose of TEV in naive volunteers.

Secondary study hypotheses:
1. The late booster dose and the single oral dose of TEV given to non-immunized subjects will be safe and not induce any serious adverse events or vaccine-related severe adverse events.
2. Orally administered TEV, the non-adjuvanted and/or adjuvanted vaccine formulations, has induced systemic memory responses that may be detected after immunization with a single dose of TEV given 1-2 years after the primary two-dose vaccinations.
3. The single late booster dose will induce antibody responses with higher avidity than the responses induced by the primary first or second vaccinations with TEV.
4. The primary vaccinations with TEV alone or together with dmLT have induced vaccine-specific memory B cells in the circulation that may be detected after 1-2 years.
5. Primary immunization with the dmLT adjuvanted vaccine has induced stronger immunological memory responses than the non-adjuvanted vaccine.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Independent Ethics Committee in the Gothenburg region in Sweden, 07/11/2013 and 20/11 /2013, ref no: 714-13

Study design
Three-armed open-label non-randomised single-center phase I study

Primary study design
Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Enterotoxigenic E. coli (ETEC) diarrhoea

Interventions
One oral dose of TEV will be given to healthy adult Swedes previously vaccinated with TEV ± dmLT adjuvant (10 µg) or age-matched non-vaccinated subjects. The vaccine consists of approximately 8x10e10 formalin-inactivated E. coli bacteria that over-express the colonization factors CFA/I, CS3, CS5 and CS6 and are combined with 1 mg LCTBA hybrid protein. The vaccine will be given orally in buffer.

The following three groups of totally 45-60 subjects will be immunized:
First group: previously non-vaccinated subjects (n = 15-20)
Second group: subjects previously given 2 doses of TEV alone (n = 15-20)
Third group: subjects previously given 2 doses of TEV + 10 ug dmLT (n = 15-20)

The follow up will be 7-8 days from immunization.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Inactivated tetravalent ETEC vaccine

Primary outcome measure
To determine if primary vaccination with an inactivated tetravalent ETEC vaccine (TEV), given in two oral doses two weeks apart ± dmLT adjuvant to adult volunteers, has induced immunological memory responses against toxin (LTB) and colonization factor (CF) vaccine antigens.

Memory will be assessed as accelerated, higher and/or more frequent intestinally derived immune responses (antibodies in lymphocyte supernatants; ALS) to a single oral booster dose of TEV given to primed subjects vaccinated 1-2 years before than to a single dose of TEV given to naïve subjects.

Secondary outcome measures
1. To evaluate the safety of a single booster dose of TEV given to subjects previously vaccinated with a primary 2-dose series of TEV alone or TEV + dmLT and to further evaluate the safety of a single dose of TEV given to naive subjects.

2. To evaluate if TEV previously given in two oral doses ± dmLT has induced systemic immunological memory as measured by accelerated and/or higher and/or more frequent serum IgA and /or IgG antibody responses against LTB to a single oral dose of TEV given after 1-2 years than to a single dose of TEV given to naive volunteers.
3. To evaluate if the avidity of the antibody responses induced by the late booster immunization with TEV is higher than the avidity of the responses induced by the first or the second primary vaccinations or after a single dose given to naive subjects.
4. To evaluate if primary vaccinations with TEV alone and/or TEV + dmLT have induced vaccine-specific memory B-cell responses that are detectable in the circulation (using polyclonal B-cell stimulation methods); this includes evaluating if there is a relationship between circulating memory B-cell responses prior to vaccination and memory antibody responses to a single booster dose determined by ALS analyses.
5. To evaluate if primary vaccination with TEV + dmLT adjuvant has induced accelerated, higher and/or more frequent immunological memory responses than priming with TEV.

Gastrointestinal and systemic adverse events will be assessed post-vaccination through day 7 using physical examination, vital signs and clinical laboratory tests, diary cards and interviews.

Overall study start date
02/12/2013

Completion date
30/06/2014

Eligibility

Key inclusion criteria
1. Male or female aged 18-47 years
2. Healthy constitution as established by medical history, medical examination and clinical chemistry and haematology testing
3. Willing and able to communicate with the investigators/physicians and understand the requirements of the study
4. Give written informed consent to participate
5. Sexually active females should, unless being menopausal, agree to use reliable contraception during the study as assessed by the investigator/physician, and should have a negative urine pregnancy test at screening and also negative urine pregnancy tests before vaccination.
6. For recruitment to group A: has never received any ETEC vaccine
For recruitment to group B: has received two doses of TEV in the OEV-121 study
For recruitment to group C: has received two doses of TEV + 10 µg dmLT in the OEV-121 study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
47 Years

Sex
Both

Target number of participants
45-60

Key exclusion criteria
1. An acute or chronic medical condition that, in the opinion of the investigator/physician, would render ingestion of the investigational products unsafe or would interfere with the evaluation of responses. This includes, but is not limited to, gastrointestinal diseases and autoimmune diseases.
2. Gastroenteritis within two weeks prior to vaccination
3. Antibiotic therapy within six weeks prior to vaccination
4. Known hepatitis A, B, C and/or HIV infection
5. Concomitant intake of immune-modulating drugs during the study period or less than three months prior to the first immunization
6. Psychiatric symptoms and treatments during the last year deemed by the investigator /physician to be relevant for participation in the OEV-121A study.
7. Intends to receive any other vaccine during the study period, or within two weeks prior to trial vaccination
8. Any known hypersensitivity to any ingredient in the vaccines
9. Has received Dukoral or any other ETEC vaccine than the TEV
10. Brought up in ETEC-endemic areas (e.g., Central and South America, Caribbean, most countries in Asia, Africa, etc)
11. Has travelled to ETEC-endemic areas within the last 3 years or spent > two months in ETEC-endemic areas during the last 10 years
12. Known or suspected history of drug, chemical or alcohol abuse, as deemed by the investigator/physician
13. Receipt of any other investigational product in the month before study entry or during the study deemed by the investigator/physician to be relevant for the OEV-121 study
14. Concomitant participation in any other clinical study deemed by the investigator/physician to be relevant for the OEV-121A study
15. Blood donation less than two weeks before immunization until one month after immunization
16. Females who are pregnant
17. Females who are nursing
18. Unable to participate in all study visits
19. Any condition or circumstance which would make the subject unsuitable for participation in the study in the opinion of the investigator/physician

Date of first enrolment
02/12/2013

Date of final enrolment
30/06/2014

Locations

Countries of recruitment
Sweden

Study participating centre
Dept. of Microbiology and Immunology
Gothenburg
Sweden
405 30

Sponsor information

Organisation
Gothenburg University Vaccine Research Institute (GUVAX) (Sweden)

Sponsor details
c/o Prof Jan Holmgren
Dept. of Microbiology and Immunology
University of Gothenburg
Box 435
Gothenburg
Sweden
405 30
+46 (0)31 7866201
jan.holmgren@microbio.gu.se

Sponsor type
University/education

Website
http://www.biomedicine.gu.se/ominst/avd/mikrobio/forskare/GUVAX/

ROR
https://ror.org/01tm6cn81

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Sahlgrenska University Hospital (ALF; Agreement on Medical Education and Research) (Sweden)

Funder Name
Swedish Research Council (Sweden)

Alternative Name(s)
Swedish Research Council, VR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Sweden

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	08/06/2016	23/01/2019	Yes	No
Results article		22/03/2021	07/10/2021	Yes	No