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Antibody avidity and immunological memory induced by oral cholera vaccination

Submission date
03/09/2016

Recruitment status
No longer recruiting

Registration date
06/09/2016

Overall study status
Completed

Last Edited
07/10/2021

Condition category
Infections and Infestations

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

Plain English Summary
Background and study aims
Diarrhoea caused by the bacteria enterotoxigenic Escherichia coli (ETEC) and Vibrio cholerae are important health problems, particularly for children in developing countries and for people travelling to these areas. . Both ETEC and V. cholerae are found in the small intestine, where they make the toxins (the enterotoxins E. coli heat-labile toxin, LT, heat stabile toxin, ST or cholera toxin, CT) that cause diarrhoea. Here, researchers have been focusing on the development of a vaccine called ETVAX. They have run several studies to test the safety of this vaccine and how well it works in adult Swedish volunteers. However, several remaining scientific questions remain regarding the mucosal immune responses (that is, the immune response to protect mucous membranes, such as the inner lining in the intestine) to vaccines taken by mouth (oral) which are difficult to address during early clinical development. This study is investigating the immune response of the vaccine Dukoral® to see if it can be used as a model for oral enteric vaccines (that is vaccines taken in pill form that stops diarrhoea). It aims to investigate whether the long term antibody responses (immune response) to this vaccine may be influenced by late booster vaccinations with reduced dosages in people that have been previously given the vaccine at a higher dose (primed) , as compared to late booster vaccination with a full dosage. B cell and T cell responses (white cells involved in the immune response) will be investigated for both cases. In addition, the researchers will investigate whether vaccine responses differ in people with the non-secretor or secretor blood group phenotypes; this means whether a person secretes their blood type into bodily fluids, such as saliva or semen. The results of these studies will provide important information about how efficient and long lived immune responses are when caused by oral vaccination in humans and will help to establish methods which may help test of novel oral enteric vaccines.

Who can participate?
Healthy adults aged between 18-55.

What does the study involve?
All participants are given the same treatment during the first part of the study. They are all given two full doses of Dukoral® two weeks apart. During the second part, the participants are randomly allocated to one of three groups. Those in group 1 are given another full dose of the vaccine 3-6 months later. Those in group 2 are given 1/5th of a full dose of the vaccine 3-6

months later. Those in group 3 are given 1/25th of a full dose of the vaccine 3-6 months later. The immune response for all three groups are then analysed.

What are the possible benefits and risks of participating?
Participants will receive financial compensation for participation in the study, as well as free immunisation with the vaccine Dukoral, which can be beneficial during travel to cholera or ETEC endemic countries. Based on previous studies on Dukoral, the risk for individuals participating in this study is assessed to be very small.

Where is the study run from?
Department of Microbiology and Immunology, University of Gothenburg (Sweden)

When is the study starting and how long is it expected to run for?
March 2016 to June 2017

Who is funding the study?
Swedish Research Council

Who is the main contact?
Dr Susannah Leach

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2016-002080-33

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
1.1

Study information

Scientific Title
Clinical trial to study antibody avidity and immunological memory induced by oral cholera vaccination

Study hypothesis
1. Primary hypothesis
1.1. Primary vaccinations with the oral cholera vaccine Dukoral will induce significant vaccine-specific memory B cell responses in the circulation early after vaccination
1.2. Booster vaccination with reduced dosages (1/5 and/or 1/25) of the oral cholera vaccine Dukoral in fully primed subjects will induce significantly increased avidity of antibodies in serum and/or lymphocyte secretions compared to vaccination with a full booster dose

2. Secondary hypothesis
2.2. Primary vaccination with the oral cholera vaccine Dukoral will induce circulating memory B cell responses which correlate with the antibody serum and/or ALS responses induced by a single late booster dose
2.3. Primary and/or booster vaccinations with the oral cholera vaccine Dukoral will:
2.3.1. Induce ASCs and/or circulating memory B cells expressing gut homing markers
2.3.2. Induce TFH cell responses in the circulation
2.3.3. significantly alter the receptor diversity and transcriptional profile of circulating B cells and /or CD4+ T cells
2.3.4. Induce serum and/or ASC responses of increased quantity and/or quality in individuals who carry the secretor compared to non-secretor phenotype

Ethics approval required
Old ethics approval format

Ethics approval(s)
Regional Ethical Review Board in Gothenburg (IECGR), 22/08/2016, ref: 611-16

Study design
Single centre three-armed open label phase II study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Prevention

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

Condition
Diarrhoea caused by enterotoxigenic Escherichia coli (ETEC) and Vibrio cholerae bacteria

Interventions
All subjects will receive identical treatment during the first stage (primary two dose vaccination) and hence this part of the study will not be randomised or blinded.

During the second stage (late booster vaccination), subjects will be randomised into three arms and receive a booster dose at either full dosage (group A), 1/5th dosage (group B) or 1/25th dosage (group C). The second stage will also not be blinded due to difficulties in masking the difference in appearance and taste between the full dosage and lower dosages.

The three dosing regimes are as follows:
1. Give two full doses of Dukoral two weeks apart followed by a full dose of Dukoral 3-6 months later
2. Give two full doses of Dukoral two weeks apart followed by 1/5th of full dose of Dukoral 3-6 months later
3. Give two full doses of Dukoral two weeks apart followed by 1/25th of full dose of Dukoral 3-6 months later

There is no follow up period.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
Dukoral

Primary outcome measure
The antibody avidity and immunological memory in fully primed subjects, measured using KSCN elution and/or limiting antigen dilution and ELISA, measured day 19 after primary vaccination (i. e. 5 days after the second dose) and day 5 after booster vaccination.

Secondary outcome measures
1. Immunological responses in fully primed subjects, quantified using flow cytometric and RNAseq techniques, assessed on day 5 post booster vaccination
2. The immunological responses to oral cholera vaccine Dukoral in subjects with secretor or non-secretor phenotype, as measured using ELISA at day 0, 19 and day 44 post vaccination

Overall study start date
01/03/2016

Overall study end date
01/02/2018

Eligibility

Participant inclusion criteria
1. Male or female aged 18-55 years
2. Healthy constitution as established by medical history
3. Give written informed consent to participate
4. Willing and able to communicate with the investigators and understand the requirements of the study

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
60 participants

Total final enrolment
44

Participant 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. Gastroenteritis within two weeks prior to the first vaccination or during vaccination.
2. Antibiotic therapy within six weeks prior to the first vaccination or during the study period.
3. Known Hepatitis A, B, C and/or HIV infection.
4. Concomitant intake of immunomodulating drugs during the study period or less than four weeks prior to the first immunisation.
5. Psychiatric symptoms and treatments during the last year deemed by the investigator /physician to be relevant for participation in the study.
6. Intends to receive any other vaccine during the study period, or within two weeks prior to trial vaccination.
7. Any known hypersensitivity to any ingredient in the vaccine.
8. Has received Dukoral or any ETEC vaccine.
9. Brought up in ETEC-endemic areas (e.g., Central and South America, Caribbean, most countries in Asia, Africa, etc.).
10. Has travelled to ETEC-endemic areas within the last 3 years, or travelled repeatedly and/or spent > two months in ETEC endemic areas during the last 10 years.
11. Known or suspected history of drug, chemical or alcohol abuse, as deemed by the investigator/physician.
12. 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 OVM study.

13. Concomitant participation in any other clinical study deemed by the investigator/physician to be relevant for the OVM study.
14. Intends to donate blood during the study.
15. Females who are pregnant or nursing.
16. Sexually active females who unless being menopausal do not agree to use reliable contraception as assessed by the investigator, from inclusion to last study visit.
17. Unable to participate in all study visits.
18. Any condition or circumstance which would make the subject unsuitable for participation in the study in the opinion of the investigator/physician.

Recruitment start date
21/09/2016

Recruitment end date
05/10/2016

Locations

Countries of recruitment
Sweden

Study participating centre
Department of Microbiology and Immunology, University of Gothenburg
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Sponsor information

Organisation
Göteborg University Vaccine Research Institute (GUVAX)

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Sponsor type
University/education

ROR
https://ror.org/01tm6cn81

Funder(s)

Funder type
Government

Funder Name
Vetenskapsrådet

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
To be confirmed at a later date

Intention to publish date
31/07/2019

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	16/01/2020	11/11/2019	Yes	No
Results article		22/03/2021	07/10/2021	Yes	No