A randomized, single-blind, placebo-controlled study to evaluate an oral cholera vaccination with intranasal rechallenge as adaptive immune challenge model

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• To characterize the systemic response to mucosal immunization with an oral cholera vaccination challenge.• To characterize the local response to intranasal rechallenge after cholera vaccination as outcome measure for nasal mucosal immunity.• To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON53390

Source
ToetsingOnline

Brief title
Cholera vaccination challenge

Condition

- Bacterial infectious disorders

Synonym
There will be no specific condition investigated in this study

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Clinical Research Organization (investigator initiated)

Intervention

Keyword: cholera, healthy volunteers, immune challenge, intranasal

Outcome measures

Primary outcome

• Serum cholera antigen specific IgA levels at Day 1, 14, 18, 20 and 28.

• Serum cholera antigen specific IgG levels at Day 1, 14, 18, 20 and 28.

Secondary outcome

• Cholera antigen specific IgA in nasal secretion (measured by nasosorption) at

-2 hours before and 1, 2, 7 and 10 days after nasal rechallenge.

• Treatment-emergent (serious) adverse events (S)AEs.

• Clinical safety laboratory measurements.

• Vital signs measurements.

• Physical examinations.

Study description

Background summary

The mucosal immune system is a relatively new and promising target for IMPs. These mucosa-associated lymphoid tissues (MALT), containing a specialized innate and adaptive immune system, are located in all mucous membranes covering the digestive, respiratory and urogenital tracts. Amongst the MALT are anatomically defined lymphoid compartments that are the main mucosal inductive sites for initiating the immune response, such as the Peyer*s patches, mesenteric lymph nodes and the appendix (gastrointestinal tract), tonsils and adenoids (nose and airway). The mucosal immune system protects against

colonization and invasion by pathogenic microbes, but also provides tolerance against non-pathogenic antigens from commensal bacteria or food. Contrary to the systemic immune reaction, the mucosal immune system functions in surroundings containing several foreign antigens and therefore immunological reactions have to be strictly regulated. The mucosal immune reaction is regulated by nature of the antigen, type of antigen presenting cell (APC) and the local microenvironment. Another difference between the mucosal immune system and systemic immune system is the production of secretory IgA (SIgA) as most abundant immunoglobulin. SIgA is a dimer of two IgA monomers coupled by a J-chain, which also protects against the breakdown by proteolytic enzymes present in the digestive system.
When luminal antigens are taken up by absorptive epithelial cells (M cells) and presented by antigen presenting cells (APCs), cytokines and B cell stimulating factors will be produced, after which activation and class switching by B cells is induced. Non-pathogen antigens (such as food proteins) usually result in suppression of the immune reaction (tolerance), while pathogenic antigens are recognized by mucosal APCs (e.g. by toll-like receptors) and will lead to a broader humoral and cellular immune response. After sensitization, B- and T cells leave the mucosal site where they have encountered the antigen, and enter the circulation via the lymph vessels. Next, they return to the MALT (*homing*), where differentiation into memory or effector cells takes place.
The principal location where lymphocytes are homing is determined by expression of their homing receptors, and locally produced chemokines. More specifically, the homing receptor integrin α4β1 binds to vascular cell adhesion molecule 1 (VCAM-1), that is mainly expressed at the bronchial and nasal mucosa. Integrin α4β7 binds to the mucosal addressin cell adhesion molecule 1 (MAdCAM-1), that is mainly located in the gastrointestinal mucosa. Local chemokines such as chemokine (C-C motif) ligand (CCL)-25 and CCL28 further attract lymphocytes via their chemokine receptors (C-C motif Chemokine Receptor [CCR]-9, CCR10). The presence of retinoic acid (RA) imprints IgA-producing cells with gut-homing properties; without RA homing receptors to other parts of the MALT are formed.
Despite the extensive functions of the mucosal immune system, which provide new opportunities for IMPs targeting - amongst others - gut immunity, possibilities for quantifying the mucosal immune reaction are still limited. Measuring the effect of novel immunomodulatory drugs targeting the mucosal immune system is challenging, as the immune reaction first needs to be activated to be able to measure pharmacodynamic effects, and measuring local response is not possible. Therefore, a well-characterized immune challenge driving a mucosal immune response is needed.
Oral vaccinations such as the cholera vaccine interact with the mucosal immune system, particularly the Waldeyer*s ring in the oral cavity and the Peyer*s patches in the small intestine. Therefore, inducing the mucosal immune system by oral cholera vaccination may be used to measure the effect of new compounds on the mucosal immune system. In order to study the effect of IMPs on the mucosal immune response via oral cholera vaccination, firstly the effect of well-known compounds should be characterized. It is already known that use of immunosuppressive medication by renal transplant recipients results in a much

lower increase in IgA antibody level after oral cholera vaccination. More specifically, in healthy controls the anti-cholera toxin subunit B (CBT) titer is 13.4 times higher post-vaccination compared to pre-vaccination, while it is 4.3 times higher post-vaccination in renal transplant recipients using immunosuppressive medication (prednisolone and either a calcineurine inhibitor or mycophenolate).
Although the mucosal immune system is spread all over the internal mucosa, particular mucosal inductive sites are associated with corresponding effector sites. Differences in expression of chemokines, integrins (the aforementioned *homing receptors*) and cytokines over the mucosal surface result in a compartmentalization of the mucosal immune system. Therefore, the mucosal immune response can be induced by different vaccination routes, resulting in segmentalized antibody production. Oral vaccination mainly induces antibody responses in the small intestine, ascending colon and salivary glands, but there is little IgA production in the tonsils or genital tract. Conversely, nasal immunization results in an antibody response in the upper airway, saliva and nasal secretion and does not have much effect on immune responses in the gut. Therefore, nasal vaccinations may be used to study compounds targeting the nasal cavity and upper respiratory tract. Nasal vaccinations have already been investigated with a diphtheria and tetanus vaccination8, influenza vaccination9 and cholera toxin vaccination. It has been shown that nasal vaccination is superior to oral vaccination in obtaining local antibodies in the respiratory tract. In this study, the use of nasal cholera rechallenge as model for compounds targeting the nasal mucosa will be investigated.

Study objective

• To characterize the systemic response to mucosal immunization with an oral cholera vaccination challenge.
• To characterize the local response to intranasal rechallenge after cholera vaccination as outcome measure for nasal mucosal immunity.
• To evaluate safety and tolerability of nasal rechallenge after oral cholera vaccination.

Study design

The study will be a single-blind, randomized, placebo controlled, single center study including 12 healthy subjects (groups: 6 MMF, 6 placebo). Subjects will receive an oral cholera vaccination at Day 1 and Day 14. Intranasal rechallenge will take place at Day 18. Immunosuppression (MMF or placebo) will be administered for 6 days around the initial oral cholera vaccination (i.e. 2 days before, 4 days after).

Intervention

For oral cholera vaccination Dukoral will be used, combined with recombinant

cholera toxin subunit B. Subjects will receive a dose (3 mL) at Day 1 and at Day 14. At Day 18, nasal rechallenge with the cholera vaccination will take place. For nasal rechallenge, 0.375 mL containing 125 µg recombinant cholera toxin subunit B, a total dosage of 250 ug in 0.75 mL will be administered in two nostrils.
As immunosuppressive agent, MMF will be used. Dosing will be 2 dd 1g, according to standard treatment protocols.
As comparative drugs, placebo tablets will be used.

Study burden and risks

The oral cholera vaccination (Dukoral®) that is used in this study is already registered and is known to have good safety profile with few side effects. Also, the intranasal administration of the cholera vaccination has already been performed in earlier studies, with mild and self-limiting adverse events. More risks are involved in the use of MMF as benchmarking drug. MMF will be used for a short period (6 days) and in healthy subjects. During the study, subjects will be monitored closely for signs of infection by the study physician, and will be instructed to contact the study physician in case of any complaints. After MMF use, haematology blood tests will be performed to ensure lymphocytes have returned to their normal levels. Given the short use of MMF and the close monitoring of subjects, the risks of administration to healthy volunteers is acceptable in this study. To limit the period of immunosuppression, MMF will only be used around the initial oral cholera vaccination, to inhibit the initial immune response. It was hypothesized that the lack of initial immune priming and inhibited T and B cell proliferation will result in a substantially lower response to the second oral cholera vaccination and intranasal rechallenge. In case an infection occurs within a subject, MMF treatment will be stopped immediately. If needed, infections may be treated with antibiotics or antiviral medication. As shown in the CHDR1902 study, proliferation will be restored rapidly. Lastly, both MMF and the oral cholera vaccination may cause gastrointestinal side effects, which may also result in interaction between these drugs. However, the oral cholera vaccination has already been administered to different patient groups under immunosuppressive therapy and to patients with inflammation of the gut, where no serious safety concerns were raised.

For a structured risk assessment see Section 10 of the protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed informed consent prior to any mandated procedure.
2. Healthy male and female subjects, 18 to 45 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 35 kg/m2, inclusive, and with a minimum weight of 50 kg.
4. All subjects must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
5. The participant has clinical laboratory evaluations (including clinical chemistry, haematology and complete urine analysis) within the reference range for the testing laboratory, unless the results are deemed not clinically significant by the investigator.
6. Participants who are overtly healthy as determined by medical evaluation including medical history, vital signs, physical examination, laboratory tests and ECGs at Screening and on Day -2.
7. The participant should be able to take MMF / placebo 2 times per day for 6 days, and to refrain from eating 2 hours before intake.
8. Has the ability to communicate well with the Investigator in the Dutch

language and willing to comply with the study restrictions.

Exclusion criteria

1. The participant has signs and/or symptoms of an infection 2 weeks prior to dosing, or recurrent infection, or has had an infection requiring antibiotic treatment (e.g. sepsis, pneumonia, abscess) within 42 days prior to start of MMF / placebo administration.
2. The participant has (a history of) autoimmune disease such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis or other immune-inflammatory disease.
3. The participant has a history of trauma with likely damage to the spleen, or has had surgery to the spleen or splenectomy.
4. The participant has a known immunodeficiency.
5. Positive Hepatitis B surface antigen (HBsAg), anti-hepatitis B core, hepatitis C, or human immunodeficiency virus antibody (HIV-Ab) at screening.
6. Serious psychiatric or medical conditions that, in the opinion of the investigator, could interfere with treatment, compliance, or the ability to give consent.
7. The participant has taken any over-the-counter (OTC) or any prescription medication (with the exception of paracetamol) less than 5 half lives prior to the first oral cholera vaccination, and considered as relevant by the investigator.
8. Participant has received live attenuated vaccination within 42 days prior to Screening or intends to have vaccinations during the course of the study. SARS-CoV-2 vaccinations are not allowed 1 week prior to Screening and from 2 weeks before dosing until EOS.
9. Participant has received any investigational drug of experimental procedure within 90 days or 5 half-lives, whichever is longer, prior to study intervention administration, or participant was enrolled in an investigational drug or device study within 90 days prior to first IMP dosing.
10. The participant has a history of hypersensitivity or allergies to any drug or to any of the components of the study interventions (i.e. Dukoral oral cholera vaccination, MMF or placebo).
11. The participant has lost or donated more than 400 mL of blood or blood products within 90 days prior to start of MMF or placebo treatment (Day -2) or plans to donate blood during the study.
12. The participant has had an acute, clinically significant illness or intervention by surgeon or dentist within 14 days prior to screening.
13. Current (or within past 6 months) nicotine use in excess of 5 cigarettes per day, or unable not to smoke during visits.
14. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 14 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent.
15. Previous vaccination against cholera or enterotoxigenic Escherichia coli.

16. Travel in the last 3 years to a country where cholera or enterotoxigenic E. coli is prevalent.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-04-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CellCept
Generic name:	mycophenolate mofetil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Dukoral

Ethics review

Approved WMO

Date:	21-02-2023
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2023-000084-31-NL
CCMO	NL83700.056.23