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All-Trans Retinoic acid as an Oral Adjuvant

Submission date
06/05/2013

Recruitment status
No longer recruiting

Registration date
24/06/2013

Overall study status
Completed

Last Edited
10/07/2015

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The purpose of this study is to find a way to overcome the poor immune responses to oral vaccines seen in developing countries. We have previously found that all-trans retinoic acid (ATRA) can increase the intestinal antibody response to oral typhoid vaccine. The purpose of this study is to determine if ATRA can do this with other vaccines, how long a course of treatment is required, whether the effect depends on vitamin A status, and how it works. We also intend to find the most suitable dose which would be required to take this into studies in children, who most need the benefit of oral vaccines.

Who can participate?
Men and children under 5 years of age who are residents of Lusaka, Zambia, and all will be healthy volunteers.

What does the study involve?
Participants will be given one of five vaccines (against typhoid, cholera, polio, enterotoxigenic E. coli or rotavirus) with or without ATRA. In initial studies, a group of 20 men will be given ATRA alone to evaluate its immune effects, and these men will have intestinal biopsies for measurement of expression of relevant genes. In all cases, blood will be collected for studies of cellular and antibody responses. Participants who receive vaccines will also undergo whole gut lavage for quantification of intestinal antibody responses.

What are the possible benefits and risks of participating?
Participants will benefit from vaccination, and from screening and monitoring programmes. There are minimal adverse effects of ATRA at this dose; the serious adverse effects are observed in patients with leukaemia, when ATRA is used at much higher doses. While blood sampling carries minimal discomfort and risk, gut lavage involves modest discomfort, and endoscopy requires sedation and carries finite (though low) risk of procedure-related effects.

Where is the study run from?
There is only one study centre - the University of Zambia School of Medicine, Lusaka.

When is the study starting and how long will it run for?
The study started in May 2013 and will continue until late 2014. Participant recruitment will continue until December 2013.

Who is funding the study?
The study is funded by the Bill & Melinda Gates Foundation (USA).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
TROPGAN004v1

Study information

Scientific Title
Retinoic acid as an oral adjuvant: is it generalisable and realistic?

Acronym
ATROA

Study objectives
That all-trans retinoic acid (ATRA) can act as an oral adjuvant.

The overall aim of this proposed work is to determine if this finding has general applicability to oral vaccination in human populations, particularly those living in the tropics. In order to determine if ATRA could ever be a useful adjuvant in large scale vaccination programs we need

to know much more about its effects on mucosal immune system and their responses to vaccines. We intend to build on the work we carried out in the previous study, using similar techniques, in order to answer five questions:
1. Can we reduce the frequency of administration, perhaps to a single dose given just before the vaccine?
2. Can the effect of ATRA on responses to oral typhoid vaccine be generalised to other vaccines?
3. Is this effect only, or predominantly, seen in individuals with overt or borderline vitamin A deficiency?
4. How does it work?
5. Are we ready to take this intervention forward to trials in children?

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Zambia Biomedical Research Ethics Committee, 12/10/2012, ref: 012-06-12

Study design
Interventional phase 1 single-centre non-blinded randomised trial with immunological endpoints

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Prevention

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
Vaccine responses

Interventions
All-trans retinoic acid 10mg daily for 10 days against 20mg as single dose, using oral vaccines against typhoid, cholera, rotavirus, polio and enterotoxigenic E. coli.

Second part of the study we will do some preliminary pharmacokinetics in children, designed to lead up to formal phase 2 studies in children. A key goal of this proposal is to define a minimal dose schedule to use in children which is likely to be safe and can be rolled out into phase 1, phase 2 and phase 3 studies in Africa. In order to design such studies, it would be highly desirable to have relevant pharmacokinetic data in children, and it would be useful to make an early assessment whether faecal specific IgA concentrations are of any value in assessing the adjuvanticity of ATRA in children. To our knowledge there are no data on the disposition of ATRA in children.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
All-trans retinoic acid

Primary outcome measure
Specific sIgA secreted into gut lavage fluid directed against LPS and other vaccine antigens measured 14 days after vaccination

Secondary outcome measures
Changes in expression of alphabeta7-integrin, and changes of polymeric Ig receptor in small intestinal biopsies measured 14 days after vaccination

Overall study start date
01/06/2013

Completion date
30/05/2014

Eligibility

Key inclusion criteria
1. Adult male volunteers, aged 18-60 from our community cohort in Misisi, Lusaka
2. Naïve to the vaccine to be administered
3. Children under 5 years of age, who will be included in the second part of the study only. In the second part of the study we will do some preliminary pharmacokinetics in children.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Male

Target number of participants
5 groups of 20 adult men

Key exclusion criteria
1. Diarrhoea within the previous month
2. Antibiotics within the previous 2 weeks
3. Vaccination within the previous 6 months
4. Helminth infection
5. Ethanol dependency (i.e. the full clinical syndrome)
6. Inclusion in another research study

Date of first enrolment
01/06/2013

Date of final enrolment
01/12/2013

Locations

Countries of recruitment
England

United Kingdom

Zambia

Study participating centre
Blizard Institute
London
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Sponsor information

Organisation
Queen Mary, University of London (UK)

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Sponsor type

University/education

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ROR
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Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

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