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Bile salt manipulation in Crohn's disease

Submission date 01/04/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 08/04/2009	**Overall study status** Completed	
Last Edited 23/05/2016	**Condition category** Digestive System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
08/0285

Study information

Scientific Title

Bile salt manipulation as a novel treatment for Crohn's disease: a single-centre open-label pilot study of atorvastatin and colesevalam in patients with active terminal ileal Crohn's disease

Acronym
BISMAC

Study objectives
We hypothesise that the mucosal breaches and/or increased intestinal permeability may be caused by bile salts. Various in vitro, in vivo and biopsy studies have shown that bile salts can disrupt the intestinal mucosa and increase permeability, by loosening tight junctions, or inducing apoptosis of gut epithelial cells. Therefore, it is possible that bile salts contribute to intestinal barrier dysfunction, allowing ingress of antigenic material into the bowel wall. In a patient with impaired acute inflammation, as has been established to be the case in Crohns disease, this may act as the trigger for the development of small bowel Crohns disease.

If bile salts are important in the pathophysiology of terminal ileal Crohns disease, then therapies that alter the composition of the bile salt pool may be of benefit. Statins (HMG CoA reductase inhibitors) are currently widely used in the treatment of cardiovascular disease. Their main mechanism of action is inhibition of cholesterol biosynthesis, although they also have pleiotropic effects such as immunomodulation. Cholestyramine is a bile acid binding resin used in the treatment of hyperlipidaemias, primary prevention of coronary heart disease, as well as in the treatment of bile salt malabsorption. It is also often used in patients with Crohns disease who have had bowel resection surgery to treat the diarrhoea that can occur as a result of bile salts irritating the colon. It has been demonstrated that combined administration of simvastatin and cholestyramine (at doses of 20 mg/day and 8 g/day respectively) results in a decreased concentration of duodenal bile salts, and that changes in bile salt composition occur after use of cholestyramine alone or in combination therapy. Use of these agents should therefore result in a reduction in bile salt concentration at the mucosal surface, thereby limiting damage to the mucosa and enabling healing.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Single-centre open-label pilot study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

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
Crohn's disease localised to the terminal ileum

Interventions
Atorvastatin 10 mg orally once daily plus Colesevelam 1875 mg orally twice daily taken for six weeks.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Atorvastatin, colesevelam

Primary outcome measure
Response, as defined by a 100 point fall in the Crohn's Disease Activity Index (CDAI) score at week 6 compared to baseline

Secondary outcome measures
1. Remission (defined as an absolute Crohn's Disease Activity Index (CDAI) score of less than or equal to 150) at week 6
2. Mucosal healing (as defined by a faecal calprotectin level of less than or equal to 50 mg/kg) at week 6
3. Serum C-reactive protein level at week 6 compared with baseline

Overall study start date
01/05/2009

Completion date
01/09/2009

Eligibility

Key inclusion criteria
1. Able to give informed consent
2. Greater than 18 years of age, either sex
3. Diagnosis of Crohn's disease confined to the terminal ileum (but may involve the ileocaecal valve)
4. Mild to moderate disease activity, defined as a Crohn's Disease Activity Index (CDAI) score of 220 - 400
5. Negative SeHCAT scan within 6 months of enrolment into the study
6. Patients:
6.1. On no medication
6.2. Who have received aminosalicylates or nutritional supplements for at least 8 weeks prior to

screening with no clinically relevant change in dose (as determined by the investigator) within 4 weeks
6.3. Are receiving immunosuppressants (except steroids) commenced at least 12 weeks prior to screening and been on a stable dose for at least 4 weeks
7. Able to comply with trial requirements (drug taking and visits)
8. Negative serum pregnancy test in females of child-bearing potential, who must agree to use an adequate method of contraception for the duration of trial
9. Stool sample negative for pathogenic bacteria and C. difficile toxin (if clinically indicated) during current episode of disease flare

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
13

Key exclusion criteria
1. Fasting triglyceride level greater than 3.4 mmol/L
2. Use of oral or parenteral steroids within four weeks or infliximab within eight weeks of start of trial medication; use of any investigational medication within the preceding 3 months
3. Use of antibiotics as treatment for the Crohn's disease within 4 weeks of screening
4. Current use of a 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase inhibitor or bile acid sequestrants, or use within 12 weeks of screening
5. Known intolerance to either HMG CoA reductase inhibitors or bile acid sequestrants
6. Taking any of the prohibited medications listed in protocol
7. Existing colostomy or ileostomy; current symptoms of bowel obstruction; any other severe concurrent morbidity including bleeding disorders or active upper gastrointestinal peptic ulceration; likely need for hospitalisation during the period of the study
8. Significant hepatic or renal dysfunction (alanine aminotransferase [ALT] greater than twice the upper limit of normal [ULN]; creatinine greater than 150 µmol/L)
9. Women who are currently or attempting to become pregnant, or those who are breast-feeding

Date of first enrolment
01/05/2009

Date of final enrolment
01/09/2009

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
University College London Hospitals
London
United Kingdom
WC1E 6DB

Sponsor information

Organisation
University College London (UK)

Sponsor details
Joint UCLH/UCL Biomedical research (R&D) Unit
Research & Development (1st Floor Maple House)
Ground Floor Rosenheim Building
25 Grafton Way
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England
United Kingdom
WC1E 6DB

Sponsor type
University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded (UK) - University College London Hospital will not be charging for any routine care in this trial

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