

Bile salt manipulation in Crohn's disease

Submission date 01/04/2009	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 08/04/2009	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 23/05/2016	Condition category Digestive System	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Dr Stuart Bloom

Contact details
Department of Gastroenterology
Ground Floor Rosenheim Building
25 Grafton Way
London
United Kingdom
WC1E 6DB

Additional identifiers

Protocol serial number
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 colestevam 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

Study type(s)

Treatment

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(s)

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

Key secondary outcome(s)

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

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

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

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

United Kingdom

England

Study participating centre

University College London Hospitals

London

United Kingdom

WC1E 6DB

Sponsor information

Organisation

University College London (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

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration