INFORMATION FOR RESEARCH SUBJECTS

Faecal transplant recipients

Faecal transplant for the treatment of active ulcerative colitis

The Department of Gastroenterology at the Royal Adelaide Hospital would like to invite you to participate in a study investigating the role of faecal transplantation (FT) as a treatment for active ulcerative colitis (UC). The research will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research.

Purpose of this study

The purpose of this study is to determine whether FT improves symptoms as well as bowel inflammation in patients with active UC. There is evidence that patients with UC have a reduced diversity of colonic bacteria. This has led some investigators to attempt to replenish the colonic bacteria in UC patients with FT from a faecal donor with the aim of reducing the disease severity. There are case reports of success with this technique in the literature, however no structured scientific trials have investigated its effectiveness.

The aim of this study is to see whether any clinical change in symptoms following FT is accompanied by an alteration in the bacteria in the bowel and whether this change persists. We also aim to assess whether there are changes in the immune system following FT and whether these are influenced by any change in bacteria. It is important for us also to establish patient satisfaction with FT as a therapy for ulcerative colitis. People recruited for this study will include those with active ulcerative colitis as well as healthy volunteer stool donors.

Your rights

This is a research project and you do not have to be involved. If you do not wish to participate, your usual medical care will not be affected in any way. Please remember you can withdraw from the study at any time. If you decide to participate, your personal data will be treated as confidential except as required by law and you will not be personally identified in any published results.

Standard of care for patients with ulcerative colitis

The management of ulcerative colitis involves both maintenance medication and medication used to control flares of the disease. The goal of maintenance therapy in UC is to maintain disease remission without the use of steroids. This requires regular clinical assessment including history, physical examination and at times colonoscopic examination. Other tools of assessment include blood and stool testing for inflammation and at times imaging including MRI, CT or ultrasound scans.

The choice of maintenance treatment in UC is determined by disease extent as well as
the frequency and severity of flares. Other factors taken into account include the response to previous therapy and safety of the therapy. The mainstay of maintenance medications are the 5-aminosalicylic acid compounds (5-ASA) such as mesalazine or sulphasalazine. These compounds are commonly taken orally in preparations that predominantly deliver the active 5-ASA component to the site of the disease in the colon. Alternatively, or in addition, mesalazine preparations can be delivered topically via enema or suppository if the disease only involves the left side of the colon. The majority of patients can be managed with maintenance 5-ASA compounds most of the time.

For patients who have repeated flares of disease on 5-ASA maintenance therapy, thiopurine medication such as Azathioprine or 6-mercaptopurine can be used. These medications suppress the immune system thereby, reducing the incidence and severity of flares of colitis. However, immune suppression can lead to an increased risk of some infections and malignancy.

Anti-TNF agents such as infliximab or adalimumab have been shown to have benefit in maintaining remission in UC however these agents are expensive and not funded by the pharmaceutical benefits scheme in Australia and so are not readily available. The anti-TNF agents also give an increased risk of infection, particularly latent tuberculosis reactivation.

Patients in whom colonic inflammation cannot be controlled adequately may undergo surgical removal of the large bowel or “total colectomy”. This may be done electively or as emergency surgery in acute severe colitis. Colectomy is associated with surgical risk that is higher when the surgery is done as an emergency. The risks of surgery include infection, wound breakdown and rarely death. Colectomy is considered “curative” for ulcerative colitis especially if patients have an ileostomy stoma created. This results in the need for a stoma bag attached to the abdominal wall to collect the faeces. This surgery, however, does frequently still lead to other short- and long-term complications. In patients in whom the bowel is connected to the anus via a pouch procedure up to 50% of patients will subsequently develop chronic inflammation of the pouch after surgery.

Mild flares of ulcerative colitis can be managed with higher doses of oral 5-ASA compounds or the addition of topical agents given via enema or suppository. More severe flares are usually managed with a short courses of systemic corticosteroid. These can be given intravenously in acute, severe disease or orally in less severe flares. The steroids are then tapered over time and discontinued. There is no indication for long term steroid use in ulcerative colitis and prolonged steroid use is associated with a number of complications including infection, osteoporosis, obesity, diabetes, poor wound healing, thinning skin, mood changes and insomnia.

**Inclusion criteria**

You should have mild-moderately active ulcerative colitis that has been active (in flare) for at least 1 week.
Exclusion criteria

It is important that you do not participate in the study if you have severe ulcerative colitis. The severity of disease will be assessed clinically and at colonoscopy and if the disease is assessed as severe then appropriate management outside of the trial will be advised to you.

Potential participants should not

- be taking more than 25mg of prednisolone (or equivalent steroid) per day
- have had previous colonic resection surgery.
- have an active gastrointestinal infection (testing will be undertaken to exclude this)
- be pregnant
- on anticoagulant therapy such as warfarin or dual antiplatelet therapy (i.e. aspirin and clopidogrel)

Description of the procedure

Faecal transplantation involves the delivery of bacteria derived from donor faeces into the bowel of a patient for therapeutic purposes. This will be conducted using a colonoscope to deposit the donor faeces deep into the colon in the first instance and then two subsequent faecal enemas in the following week.

Faecal donors will be anonymous healthy volunteers similar to how blood donation is conducted in the community. Donors will be thoroughly screened for infection or any potentially transmissible disease. Following screening donor stool from four donors will be pooled and then frozen for use as a FT at a later date.

Prior to faecal transplantation

At the beginning of the study you will provide a stool sample. A small portion of this will be tested to exclude infection and to analyse for bacterial content and inflammatory markers, the remainder of the stool sample that will be frozen and stored. You will be asked to complete a questionnaire regarding your perception and expectation of FT. A detailed history of your ulcerative colitis will be taken and current symptoms recorded by a study investigator. Stool will be collected. A blood test will be taken to test inflammatory markers. A flexible sigmoidoscopy will be undertaken to assess your disease activity and a biopsy taken to exclude infection. This is a shorter and less invasive procedure than a colonoscopy that requires minimal preparation (an enema or no preparation) and minimal sedation. It is a standard procedure in the assessment of a patient with ulcerative colitis (see attached standard RAH leaflet explaining flexible sigmoidoscopy).

Faecal transplantation

You will be randomly assigned into one of two groups. If you are assigned to the first group, you will receive a pooled donor stool FT. If you are assigned to the second group, you will receive your own stool that had previously been collected and frozen. The FT will be delivered via colonoscopy with both groups undergoing standard bowel preparation with 3 litres of colonlytely. Colonoscopy will be conducted under conscious sedation (see standard RAH colonoscopy information leaflet as attached).
You will then receive two faecal transplant enemas in the next week. One on day 3 or 4 and a second on day 6 or 7.

A 2mg tablet of loperamide will be given to you following the colonoscopy or stool enema(s) to help with retention of the transplanted stool. Loperamide can cause constipation, however one tablet is not expected to have a duration of action longer than 24 hours.

If you are assigned to the second group and receive your own stool at the initial colonoscopy you will then receive a donor faecal transplant at the 8 week colonoscopy and two faecal transplant enemas in the next week. One on day 3 or 4 and a second on day 6 or 7. In this way every patient enrolled in the study will receive the donor faecal transplant within the first 9 weeks of their enrolment.

Medical care during the trial

During this study you will continue to receive your usual medical care and treatment. However, you will additionally meet with the researcher who is responsible for this study.

Follow up

You will be followed-up for a 12 month period during the trial. You will be asked to give a stool sample, a blood test and complete a disease activity questionnaire at 2 weeks, 4 weeks, 8 weeks, 6 months and 12 months after transplant. We will provide you with a portable freezer and bags to allow immediate freezing of samples at home. If you complete the questionnaire at home a reply paid envelope will be provided. You will undergo repeat colonoscopy and biopsies at 8 weeks and 12 months post FT. Biopsies will be taken for routine assessment of disease activity as well as to assess for bacteria and immune studies.

Colonoscopy

In general all subject with ulcerative colitis have had a colonoscopy and understand the procedure. Colonoscopy is performed to examine the large bowel, usually under sedation and it involves sliding a narrow, flexible tube (colonoscope) up through the anus and around the large bowel. The colonoscope has a small camera on the end of it. The procedure usually taken between 15 to 30 minutes. The faecal transplant can be delivered through the channel within the colonoscope. Biopsies of the bowel wall can also be taken through the colonoscope. You will be provided with a standard information sheet on colonoscopy and the risks are discussed below.

Retention enema

An enema is a liquid that is inserted into the rectum via the anus with a small hand held introducer. The liquid is then retained by the recipient with voluntary contraction of the anal sphincter. An enema is a relatively quick procedure that does not require sedation.

Bowel preparation
Bowel preparation is a liquid drink that is taken to clear the bowel of solid faeces so that the colon can be visualised during colonoscopy. The bowel preparation also has the effect of lowering the bacterial content of the colon prior to faecal transplant. The bowel preparation is consumed the day prior or on the morning of the colonoscopy. You will be asked to drink 3 litres of colonlytely bowel preparation for this study.

**Biopsy**

A biopsy is a tiny piece of tissue which is removed by forceps at the time of colonoscopy. Biopsies are routinely taken during diagnostic colonoscopy to allow additional diagnostic information to be obtained when these tests are performed. For this study 20 extra biopsies will be taken.

**Medication use during the trial**

Your usual maintenance medication for ulcerative colitis will be managed as it usually would by your doctor. In this way you will receive the standard of care for ulcerative colitis with the faecal transplant in addition to this.

The only required change to medications within the trial is a mandated attempt at a steroid taper. Steroids such as oral prednisolone are used routinely in the short term to manage flares of ulcerative colitis. The prolonged use of systemic steroids, however, is associated with a large number of potential side effects. It is therefore now the standard of care to minimize steroid exposure. For this reason, if you are taking oral prednisolone at the time of FT you will have the dose reduced by 5mg per week until down to 15mg and then taper by 2.5mg per week. If you are taking more than 25mg of prednisolone per day you be excluded from the trial.

**Risk and Discomforts of the Study**

There have not been any serious adverse effects attributed to FT in the medical literature to date from more than 300 recorded cases. The vast majority of recorded FT procedures have occurred in the last 10 years, however, and so long term risks are not known. The major potential risks include transmission of infection from donor to recipient. There is an association between some medical conditions such as obesity and certain bacterial profiles in stool. It is for this reason that we are rigorously screening donors for any medical conditions that could potentially impact on the recipient.

Blood sampling will be performed by an experienced member of our medical staff. Taking blood from a vein can be associated with pain and bruising and on rare occasions infection can occur. It is not anticipated that completing the questionnaires will cause distress and you can choose to decline to answer specific questions.

Colonoscopy is associated with some potential risks. The major risk of colonoscopy, bowel perforation, occurs in approximately 1 in 1000 colonoscopies. Other risks include dehydration from bowel preparation, over-sedation, aspiration, bleeding and splenic laceration. Up to 20 colonic biopsies may be taken during this study. Taking biopsies has a very small (less than 1:1000) risk of relevant bleeding. If you are on strong blood thinning medication (e.g. Warfarin), or have a bleeding disorder the risk
of bleeding may be greater and you should not participate in the trial. Colonoscopy may require you to take 2 days away from work including a day for the bowel preparation and a day for the procedure and recovery. In the event that you suffer an injury as a result of the study, you will receive care within the public hospital system.

Possible benefits

This is a study looking at an experimental new therapy for ulcerative colitis. There are case reports of successful treatment of ulcerative colitis with FT. Participation in this trial could possibly improve your symptoms and reduce your medication requirement and medication related side effects. There are no guarantees of success with this potential new therapy however. Participation in this study may also help our understanding of the disease and help to develop new therapies for the treatment of ulcerative colitis.

Confidentiality

The data that we collect from your involvement in the trial will be de-identified. You will be assigned a study number and this will only be linked to your name in a single secure document. The data collected regarding the microbial composition of your stool and clinical response during the trial will be identified only by your number on the data sheet and in publication. You will not know the identity of the stool donors and the stool donor will not know the identity of any recipient of their donated stool.

Approval and further information

This study has been approved by the Research Ethics Committee of the Royal Adelaide Hospital

A description of this clinical trial will be available on www.anzctr.org.au/. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you have any questions, you can contact:

1. Dr. Samuel Costello Tel: 0413311793  
   Email: sam.costello@health.sa.gov.au
2. Associate Professor Jane Andrews, Gastroenterologist, Head of RAH IBD Service,  
   Tel: 8222 5207 (BH) or 8222 4000 (AH) in emergency. Email: Jane.Andrews@health.sa.gov.au
3. Professor Ian Roberts Thomson, Gastroenterologist, 82226234 or 82226000  
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If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairperson, Research Ethics Committee, Royal Adelaide Hospital on 82224139.

Thank you,

Dr. Samuel Costello