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Comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis

Submission date 15/05/2008	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 16/05/2008	**Overall study status** Completed	
Last Edited 10/03/2023	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Ulcerative colitis is a long-term condition where the colon and rectum become inflamed, causing diarrhoea and abdominal pain. It often leads to frequent and long inpatients stays and emergency colectomy (surgery to remove the colon), and is therefore a major burden on patients and NHS resources. Recent studies have reported that two new drugs, infliximab and ciclosporin, are often effective at treating steroid-resistant ulcerative colitis in the short term, but there is a lack of evidence in the longer-term. The aim of this study is to compare the clinical and cost effectiveness of infliximab and ciclosporin in acute severe steroid-resistant ulcerative colitis.

Who can participate?
Patients aged 18 and over with steroid-resistant ulcerative colitis (i.e., does not respond to steroid treatment)

What does the study involve?
Participants are randomly allocated to be treated with either infliximab or ciclosporin. All participants are then followed up for two years (and using routine records for a further eight years) to assess quality of life, death rates, colectomy rates, severe illness, NHS and patient borne costs, and patient views of these treatments.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Swansea University (UK)

When is the study starting and how long is it expected to run for?
September 2008 to August 2014

Who is funding the study?
NIHR Health Technology Assessment Programme - HTA (UK)

Who is the main contact?
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Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
HTA 06/78/03; NRES: 08/MRE09/42

Study information

Scientific Title
Comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis: a randomised controlled trial

Acronym
CONSTRUCT

Study objectives
To determine the clinical and cost effectiveness of infliximab and ciclosporin in acute severe steroid resistant ulcerative colitis.

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/067803
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0005/51476/PRO-06-78-03.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Research Ethics Committee (REC) for Wales, July 2008, ref: 08/MRE09/42

Study design
Two-arm pragmatic multi-centre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Acute severe steroid resistant ulcerative colitis

Interventions
Current interventions as of 22/10/2012:
Infliximab:
Infliximab as 5mg/kg intravenous infusion over a 2 hour period, at baseline and at 2 and 6 weeks after the first infusion, in accordance with local prescribing guidelines and policies.
Ciclosporin:
IV ciclosporin (2 mg/kg/day) by continuous infusion for up to 7 days (aiming for trough levels

100 200 ng/ml) followed by oral ciclosporin (5.5 mg/kg/day in two divided doses) for up to 12 weeks. Whole blood ciclosporin levels measured according to local practice ideally 48 hours after oral therapy and then approximately every two weeks.
For both treatments:
Azathioprine or 6-mercaptopurine should be started at therapeutically appropriate doses in both groups at week 4, at the discretion of the supervising consultant.
Steroids must be tapered to zero by week 12 in both groups in patients that remain well but should be re-escalated in patients that become symptomatic.
Septrin should be given as prophylaxis against Pneumocystis jiroveci (carinii) pneumonia in both groups, at the discretion of the supervising consultant.
After 12 weeks, treatment is at the discretion of the supervising consultant.

Previous interventions until 22/10/2012:
Patients will be randomised to either infliximab (Remicade®) or ciclosporin (Sandimmun®/ Neoral®).
Both infliximab and ciclosporin will be used in accordance with normal routes of administration, dosage, dosage regimen and treatment periods as detailed below. Relapse or failure to respond at any stage will prompt surgical referral.
Infliximab:
Infliximab (5 mg per kg as a single intravenous infusion) at time 0 and further doses at 2 and 6 weeks followed by infusions every 8 weeks up to 6 months. The addition/continuation of azathioprine or 6-mercaptopurine is necessary if tolerated (to reduce likelihood of antibody formation). Steroids will be tapered over a 3 month period.
Ciclosporin:
Intravenous ciclosporin (2 mg per kg) for 7 days (aiming for trough levels of 150-250 ng/ml) will be followed by oral ciclosporin (8 mg/kg) for 3 months while the effect of either azathioprine or 6-mercaptopurine is allowed (commenced on discharge). During that 3 month period, steroids are also tapered and Septrin® should be given to cover for pneumocystis carinii pneumonia.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
infliximab, ciclosporin

Primary outcome measure
Current primary outcome measures as of 22/10/2012:
The primary outcome measure is quality-adjusted survival, weighted by scores on the disease-specific CCQ.

Previous primary outcome measures until 22/10/2012:
Quality of life, measured at 3, 6, 12 and 24 months with the following:
1. Disease specific questionnaire: UK-Inflammatory Bowel Disease Questionnaire (IBDQ)
2. Generic questionnaires: The 12-item short form health survey (SF-12) and EQ-5D

Secondary outcome measures
Current secondary outcome measures as of 22/10/2012:
1. Generic SF-12 and EQ-5D QoL questionnaires.

2. Emergency and planned colectomy; centres report all colectomies undertaken based on clinical judgement and patient agreement, both emergency and elective.
3. Mortality.
4. Re-admissions, including those for non-UC-specific causes.
5. Incidence of malignancies, subdivided between colorectal, other GI and other malignancies.
6. Incidence of serious infections during treatment, including bacterial infections, pneumonia, abscesses, and other serious infections.
7. Incidence of renal disorders during treatment.
8. Incidence of new symptoms during or attributable to treatment.
9. Incidence of adverse events, grouped as SUSARs, SARs, SAEs, ARs or AEs and including all relevant events described in 3. to 8. above.
10. Disease activity, measured by the criteria proposed by Truelove and Witts: to this end we seek to measure full blood count, inflammatory markers and albumin at baseline and three, six, 12, 18, 24, 30 and 36 months.
11. Quality of life, measured by the CCQ.
12. NHS costs, measured by a healthcare resource use questionnaire and hospital activity data; the economic analysis will combine these with quality adjusted survival.
13. Patient borne costs, including number of days off work and travel costs to healthcare; we shall report these separately from NHS costs because the main economic analysis takes the perspective of the NHS.
14. Patient views, of the alternative drugs elicited through 12 (10%) telephone interviews in each arm following discharge from hospital about three months and 12 months after randomisation.
15. Healthcare professional views about the drugs and their administration; a minimum of 8 clinicians and 4 nurses will be interviewed.

Previous secondary outcome measures until 22/10/2012:
1. Emergency and planned colectomy; colectomy may be undertaken based on clinical judgement and patient agreement. The incidence of emergency colectomy will be measured up to 2 years post-admission during the research data collection and up to 10 years during the clinical data collection and record linkage phase. Similarly, elective colectomy will be measured separately up to 2 years and 10 years follow-up.
2. Concomitant medical therapy; continuing steroid treatment, and/or the addition of azathioprine (or other immunosuppressive therapy) will be at the discretion of the attending team. Oral ciclosporin, or a second infusion of infliximab may be given. Data on treatment will be recorded by the patient after discharge up to 3 months after entry to the trial, and recorded at each hospital visit.
3. Mortality; which will be measured by case fatality and standardised mortality ratios up to 2 and 10 years follow-up.
4. Quality adjusted survival; to combine the effects of quality of life and mortality, will be measured up to 2 years follow-up and then modelled for lifetime Quality Adjusted Life Years
5. Disease activity; Full blood count, inflammatory markers and albumin will be measured at baseline and at 3, 6, 12 and 24 months.
6. Re-admissions; including for non-UC specific causes. Data will be collected for two years but monitored using routine data for a further eight years.
7. Total NHS costs; measured up to 2 years follow-up.
8. Patient borne costs; including number of days off work per year and travel costs for health care, up to 2 years follow-up. These will be reported separately from the NHS costs and will not be included in the cost utility estimates.
9. Patient views; elicited through telephone interviews, following discharge from hospital at approximately 2 to 3 and 6 to 8 months into follow-up. These will be conducted for 24 patients, 12 (5%) in each of the two trial arms.

Overall study start date
01/09/2008

Completion date
31/08/2014

Eligibility

Key inclusion criteria
Current inclusion criteria as of 22/10/2012:
1.1. Patients admitted acutely (ie an emergency admission) with severe colitis (as evidenced by eg a Mayo score of at least 2 on endoscopic finding) who fail to respond to approximately 2-5 days of intravenous hydrocortisone therapy, who also have either:
1.2. A histological diagnosis of ulcerative colitis in this episode
OR
1.3. A histological diagnosis of indeterminate colitis in this episode, where clinical judgement (based on macroscopic appearance, disease distribution or previous history) suggests a diagnosis of ulcerative colitis rather than Crohns disease
OR
1.4. Typical symptoms of ulcerative colitis but histology awaited
OR
1.5. A history of ulcerative colitis (previously confirmed histologically)

Previous inclusion criteria until 22/10/2012:
1. Patients with ulcerative colitis (UC) diagnosed on histological evidence
2. Inpatients with documented evidence of acute severe UC (based on sigmoidoscopic appearances and Truelove and Witts' criteria)
3. Continuing acute severe UC (according to Truelove and Witts criteria) after three days intravenous hydrocortisone

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
250 (125 in each arm)

Total final enrolment
270

Key exclusion criteria
Current exclusion criteria as of 22/10/2012:
1. Patient aged under 18 years of age on admission
2. Patient with histological diagnosis inconsistent with ulcerative colitis (indeterminate colitis is

not necessarily inconsistent with ulcerative-see inclusion criteria b)
3. Patient with enteric infection confirmed on stool microscopy or culture or histology (includes salmonella, shigella, clostridium difficile, campylobacter and CMV)
4. Patient from a vulnerable group
5. Patient unable to consent for themselves
6. Patient who are pregnant (as evidenced by +ve pregnancy test) or currently lactating
7. Women of child-bearing potential who are not prepared to use adequate contraception during treatment with infliximab and for 6 months afterwards in line with the Summary of Product Characteristics
8. Patient with current malignancy, excluding basal cell carcinoma
9. Patient with serious co-morbidities, including:
9.1. Immunodeficiency
9.2. Myocardial infarction (within last month)
9.3. Moderate or severe heart failure (NYHA class III or IV)
9.4. Acute stroke (within last month)
9.5. Respiratory failure
9.6. Renal failure
9.7. Hepatic failure
9.8. Active, or suspected active tuberculosis
9.9. Other severe infections (as determined by the investigator) such as sepsis, abscesses and opportunistic infections
10.1. Patient with a history of hypersensitivity to
10.2. Infliximab (Remicade)
10.3. Ciclosporin (Sandimmun and Neoral)
10.4. Polyethoxylated oils (Sandimmun Concentrate for IV Infusion)
11. Concomitant use of tacrolimus or rosuvastatin
12. Patients who do not speak English well enough to take part in the study, and for whom local translation services cannot be provided
13. Where clinical need determines the patient should undergo emergency colectomy without further medical treatment
14. Patients currently taking part in other clinical trials
15. Patients who have received treatment with either infliximab or ciclosporin in the three months before admission
16. Patient with contraindication(s) to treatment with Infliximab or Ciclosporin

Previous exclusion criteria until 22/10/2012:
1. Age under 18 years on the day of admission
2. Treatment with either infliximab or ciclosporin in the three months before admission
3. Positive stool microscopy or culture for enteric infection, including salmonella, shigella and Clostridium difficile
4. Pregnancy and lactation
5. Malignancy, excluding basal cell carcinoma
6. Other serious co-morbidities, including immunodeficiency, myocardial infarction, acute stroke, respiratory, renal or hepatic failure
7. Severe cognitive impairment
8. Patients unable to consent for themselves
9. Patients who do not speak English well enough to take part in the study
10. Where clinical need determines the patient should undergo emergency colectomy without further medical treatment
11. Patients currently taking part in other clinical trials
12. Patients from vulnerable groups with the exception of severe illness as this will be the reason for their acute admission and treatment

Date of first enrolment
01/09/2008

Date of final enrolment
31/08/2014

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Swansea University
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ROR
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Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
01/04/2016

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	29/04/2014		Yes	No
Results article	results	01/06/2016		Yes	No
Results article	results	01/09/2016		Yes	No
Results article	results of nested qualitative study in healthcare professionals	22/02/2017		Yes	No
Results article	results of nested qualitative study in patients results	15/10/2019		Yes	No

Other publications	Model-based cost-utility analysis	08/03/2023	10/03/2023	Yes	No