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RAPID study: Rifaximin for preventing relapse of Clostridium associated diarrhoea

Submission date
25/10/2012

Recruitment status
No longer recruiting

Registration date
26/10/2012

Overall study status
Completed

Last Edited
30/07/2019

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Clostridium difficile associated diarrhoea is a serious health problem with over 14,139 cases reported in 2015-16 in England and Wales. There are lots of beneficial gut bacteria which help suppress the growth of Clostridium difficile bacteria. However, taking antibiotics can kill these beneficial bacteria, allowing C. difficile to grow and causing inflammation of the bowel. Standard antibiotics used to treat C. difficile are vancomycin or metronidazole which kill C. difficile but also suppress the beneficial bacteria, meaning relapse of C. difficile occurs in around 1 in 3 patients. Rifaximin is an antibiotic which prevents C. difficile growth but only partly inhibits the growth of beneficial gut bacteria, allowing them to recover. A recent small study found that for patients successfully treated for C. difficile, relapse could be reduced from 31% to 15% by taking a course of Rifaximin. The aim of this study is to evaluate the effectiveness of Rifaximin for preventing relapse of C. difficile in a large study.

Who can participate?
Patients aged 18 or over who have been diagnosed with C. difficile infection and are currently being or have recently been successfully treated with a course of Metronidazole and/or Vancomycin. Adults who lack mental capacity who have a legal representative are also included.

What does the study involve?
Participants are randomly allocated to be treated with 2 weeks of Rifaximin 400mg three times daily, followed by 2 more weeks of 200mg three times daily or identical looking tablets which have no active ingredient (placebo). Blood and stool samples (serum to assess antibody response to C. difficile toxins, apart from participants with legal representative consent) are collected for those patients who have consented to provide these. Neither the doctors or the nurses or the patient know which treatment the patient received. Patients are interviewed at 12 weeks to see if they have had a relapse.

What are the possible benefits and risks of participating?
One in four patients completing a successful course of Metronidazole and Vancomycin may experience a return of their infection. It is anticipated that this will be lower in the group receiving Rifaximin but this cannot be guaranteed. Rifaximin works differently from other antibiotics because it passes through the stomach and into the intestines without being

absorbed into the blood stream, so it is very safe. Most people have no side effects though rarely nausea and headache have been reported and there is a very low risk of an allergic reaction developing. Giving a blood sample may cause discomfort or bruising though this usually resolves within a few days. Adults who lack mental capacity are not required to provide a blood sample.

Where is the study run from?
The NIHR Nottingham Digestive Diseases Biomedical research unit at Nottingham University Hospitals is organising the research; trial coordination takes place at the Nottingham Clinical Trials Unit, University of Nottingham (UK).

When is the study starting and how long is it expected to run for?
December 2012 to July 2016

Who is funding the study?
NIHR Research for Patient Benefit Programme (UK)

Who is the main contact?
Kirsty Sprange
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Contact information

Type(s)
Scientific

Contact name
Ms Kirsty Sprange

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-003205-10

Protocol serial number
12990

Study information

Scientific Title
A randomised placebo controlled trial of "follow on" Rifaximin for the prevention of relapse of Clostridium associated diarrhoea

Acronym
RAPID

Study objectives
Rifaximin is a poorly absorbed antibiotic which has been used for many years in Italy and the USA for the treatment of traveller's diarrhoea and IBS. It has an excellent safety record and has been shown to achieve high concentrations in the bowel. It has been used effectively to treat Clostridium difficile infection and has a low rate of antibiotic-resistance development. It has also been suggested as beneficial when used after an effective course of the antibiotic, metronidazole since it is said to disturb the normal gut bacteria less than metronidazole and vancomycin and hence might be predicted to reduce the incidence of relapse. This hypothesis is tested in this study. A reduction in recurrence rate of C. difficile from 30% to 10% would significantly reduce the burden of this disease in hospitals and the community and provide an inexpensive solution to this serious illness.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East Midlands - Leicester, First MREC approval date 31/08/2012, ref:12/EM /0292

Study design
Multicentre two-arm parallel-group double-blind randomised placebo-controlled trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Clostridium difficile-associated diarrhoea

Interventions
Patients randomised to receive either Rifaximin (200mg tablets) or placebo.

Dosage: Treatment is for 4 weeks. The initial trial daily dose will be 2 x 200mg tablets three times a day for first 2 weeks then, 1 x 200mg tablet three times a day for the final 2 weeks.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
The difference in % relapse between Rifaximin and placebo at week 12

Key secondary outcome(s))
Current secondary outcome measures as of 30/04/2015:
Clinical:
1. Proportion with relapse of CDAD within 6 months
2. Proportion rehospitalised for CDAD within 6 months
3. Length of in-hospital stay following start of treatment

Exploratory:
1. Stool frequency and consistency during 12 weeks after start of treatment
2. Microbiological assessments

Previous secondary outcome measures:
1. Bowel symptoms measured at weeks 1-4 and weeks 11-12
2. Length of stay on active versus placebo measured at week 12
3. Microbiological exploratory assessments measured at week 12
4. Safety/Adverse events measured at 6 months
5. The difference in relapse of CDAD within 6 months of start of therapy

Completion date
14/07/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/04/2015:
1. Men/women aged 18 and over (adults who lack mental capacity for whom there is a legal representative are included)
2. Successful treatment of clinically diagnosed CDAD using standard therapy (metronidazole or vancomycin given according to standard local hospital guidelines)

Previous inclusion criteria:
1. Men/women aged 18 and over (adults who lack mental capacity for whom there is a legal representative are included)
2. Successful treatment of clinically diagnosed C. difficile-associated diarrhea (CDAD) using standard therapy (metronidazole or vancomycin given according to standard local hospital guidelines
3. Able to swallow tablets
4. Able to stop chronic antibiotic use
5. Women of child bearing potential willing and able to use at least one highly effective contraceptive method throughout the study. Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
151

Key exclusion criteria
Current exclusion criteria as of 24/02/2016:
1. Woman of childbearing potential and not willing to use at least one highly effective contraceptive method throughout the study*
2. Male with spouse/partner of childbearing potential and not willing to use condoms
3. Pregnant or breastfeeding
4. Unable to swallow tablets
5. Life expectancy of <4 weeks
6. Hypersensitivity to the active substance, to any rifamycin (e.g. rifampicin or rifabutin) or to any of its excipients (tablet core: sodium starch glycolate type A, glycerol distearate, colloidal anhydrous, silica, talc and microcrystalline cellulose. Tablet coating: hypromellose, titanium dioxide (E171), disodium edentate, propylene glycol and red iron oxide E172)
7. >5 days post standard therapy (metronidazole or vancomycin) for clinically diagnosed CDAD
8. Taking ciclosporin

* Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Exclusion criteria from 30/04/2015 to 24/02/2016:
1. Woman of childbearing potential and not willing to use at least one highly effective contraceptive method throughout the study*
2. Male with spouse/partner of childbearing potential and not willing to use condoms
3. Pregnant or breastfeeding
4. Unable to swallow tablets
5. Life expectancy of <4 weeks
6. Hypersensitivity to the active substance, to any rifamycin (e.g. rifampicin or rifabutin) or to any of its excipients (tablet core: sodium starch glycolate type A, glycerol distearate, colloidal anhydrous, silica, talc and microcrystalline cellulose. Tablet coating: hypromellose, titanium dioxide (E171), disodium edentate, propylene glycol and red iron oxide E172)
7. >5 days post standard therapy (metronidazole or vancomycin) for clinically diagnosed CDAD

* Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS);

condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Original exclusion criteria:
1. Pregnant or breast feeding
2. Hypersensitivity to the active substance, to any rifamycin (e.g. rifampicin or rifabutin) or to any of its excipients (Tablet core: Sodium starch glycolate type A, glycerol distearate, colloidal anhydrous, silica, talc and microcrystalline cellulose. Tablet coating: hypromellose, titanium dioxide (E171), disodium edentate, propylene glycol and red iron oxide E172)
3. >5 days post standard therapy (metronidazole or vancomycin) for clinically diagnosed CDAD

Date of first enrolment
11/12/2012

Date of final enrolment
10/03/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Nottingham University Hospitals
Nottingham
United Kingdom
NG7 2UH

Study participating centre
King's Mill Hospital
Sutton-in-Ashfield
United Kingdom
NG17 4JL

Study participating centre
Royal Derby Hospital
Derby
United Kingdom
DE22 3NE

Study participating centre
Northern General Hospital
Sheffield
United Kingdom
S5 7AU

Study participating centre
Chesterfield Royal Hospital
Chesterfield
United Kingdom
S44 5BL

Study participating centre
Royal Shrewsbury Hospital
Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
County Durham and Darlington NHS Foundation Trust
Darlington
United Kingdom
DL3 6HX

Study participating centre
Sunderland Royal Hospital
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Kettering General Hospital
Kettering
United Kingdom
NN16 8UZ

Study participating centre
Dorset County Hospital
Dorchester

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DT1 2JY

Study participating centre
James Cook Hospital
Middlesbrough
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Study participating centre
North Cumbria University Hospitals
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Hampshire Hospitals NHS Foundation Trust
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Study participating centre
New Cross Hospital
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WV10 0QP

Study participating centre
Doncaster Royal Infirmary
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United Kingdom
DN2 5LT

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Russells Hall Hospital
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DY1 2HQ

Study participating centre
Stepping Hill Hospital
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SK2 7JE

Study participating centre
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RM7 0AG

Study participating centre
King's College Hospital
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Sponsor information

Organisation
University of Nottingham (UK)

ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Government

Funder Name
National Institute of Health Research (NIHR) (UK) - Research for Patient Benefit (RfPB) Grant Codes: PB-PG-1010-23257

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Nottingham Clinical Trials Unit (NCTU) (ctu@nottingham.ac.uk) once the results of the trial have been published.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2019		Yes	No
Results article	results	01/07/2019	30/07/2019	Yes	No
HRA research summary			28/06/2023	No	No