Multicentre, open-label, randomised, parallel-group, superiority study to compare the efficacy of octreotide therapy 40 mg monthly versus standard of care in patients with refractory anaemia due to gastrointestinal bleeding from small bowel angiodysplasias: a protocol of the OCEAN trial

K V Grooteman, E J M van Geenen, J P H Drenth

ABSTRACT

Introduction: Gastrointestinal angiodysplasias are an important cause of difficult-to-manage bleeding, especially in older patients. Endoscopic coagulation of angiodysplasias is the mainstay of treatment, but may be difficult for small bowel angiodysplasias because of the inability to reach them for endoscopic intervention. Some patients are red blood cell (RBC) transfusion dependent due to frequent rebleeding despite endoscopic treatment. In small cohort studies, octreotide appears to decrease the number of bleeding episodes in patients with RBC transfusion dependency due to gastrointestinal angiodysplasias. This trial will assess the efficacy of octreotide in decreasing the need for RBC transfusions and parenteral iron in patients with anaemia due to gastrointestinal bleeding from small bowel angiodysplasias despite endoscopic intervention.

Study design: Randomised controlled, superiority, open-label multicentre trial.

Participants: 62 patients will be included with refractory anaemia due to small bowel angiodysplasias, who are RBC transfusion or iron infusion dependent despite endoscopic intervention.

Intervention: Patients will be randomly assigned (1:1) to standard care or 40 mg long-acting octreotide once every 4 weeks for 52 weeks, in addition to standard care. The follow-up period is 8 weeks.

Main outcome measures: The primary outcome is the difference in the number of blood and iron infusions between the year prior to inclusion and the treatment period of 1 year. Important secondary outcomes are the per cent change in the number of rebleeds from baseline to end point, adverse events and quality of life.

Ethics and dissemination: The trial received ethical approval from the Central Committee on Research Involving Human Subjects and from the local accredited Medical Research Ethics Committee of the region Arnhem-Nijmegen, the Netherlands (reference number: 2014-1433). Results will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number: NCT02384122; Pre-results.

INTRODUCTION

Angiodysplasias (ADs) are the most common vascular anomalies of the gastrointestinal tract and the second leading cause of gastrointestinal bleeding in the elderly. The presentation extends from absence of symptoms to occult and sometimes overt gastrointestinal bleeding. Approximately 90% of haemorrhagic ADs cease spontaneously, but recurrence is high. The impact on the patient may be large with a need for multiple red blood cell (RBC) transfusions, frequent hospitalisations and surgery. Decreased
quality of life and the financial burden on healthcare systems are legitimate concerns.

There are different treatment options for symptomatic ADs: (1) conservative management with iron supplementation and, when necessary, RBC transfusions, (2) endoscopic intervention with argon plasma coagulation (APC), (3) radiological intervention with artery coiling, (4) pharmacological therapies and (5) surgical resection. Endoscopic APC is the preferred treatment. Recurrent bleeding rates in patients treated with APC remain high, with rates up to 20% over a 2-year follow-up.\(^\text{4–6}\) ADs located in the small bowel are associated with an even higher rebleeding rate, up to 45%. This could be related to their relative inaccessibility with standard endoscopy.\(^\text{7}\) As a result, some of these patients develop refractory anaemia and become dependent on symptomatic treatment with parenteral iron supplementation and RBC transfusions.

Determining the most effective pharmacological treatment in these patients with small bowel AD-associated refractory anaemia is challenging. Oestrogen and progesterone are not effective and while\(^\text{8–12}\) thalidomide has been advocated for bleeding ADs, side effects are considerable.\(^\text{13}\)

Therapy with octreotide is promising, because of its antiangiogenic properties, decrease in splanchic blood flow and enhanced platelet aggregation.\(^\text{14–15}\) Moreover, it is easy to use and has a relative mild side effect profile. There is limited evidence for the efficacy of octreotide in reducing AD bleeding.\(^\text{16–21}\) A non-randomised study compared 32 refractory AD patients treated with octreotide to an external placebo control group, which showed a significant decrease in rebleeding rate and need for oral iron.\(^\text{16}\) Recently, a small randomised controlled trial (RCT) was performed with the somatostatin analogue pasireotide, with promising results.\(^\text{22}\) However, no statistical difference in RBC transfusions was observed. Other cohort studies showed a significant decrease of more than 50% in RBC transfusion requirements.\(^\text{17–21}\) Extrapolation of these results is difficult in view of the very small size of cohorts and absence of control groups.

We designed a randomised, open-label controlled trial to evaluate the clinical efficacy of octreotide. We hypothesise that octreotide decreases the need for RBC transfusions and iron supplementation in patients with refractory anaemia due to small bowel ADs. The primary aim of this study is to assess the efficacy of octreotide to decrease the RBC and iron transfusions in patients with refractory anaemia due to small bowel ADs. Also, we determine if octreotide decreases the number of rebleeds and assess safety and cost-effectiveness compared with standard care.

METHODS AND ANALYSIS

Study design

We will conduct a phase III, randomised, open-label, parallel-group, superiority, multicentre trial of standard care plus octreotide, compared with standard care in 62 patients with anaemia despite endoscopic intervention due to small bowel ADs (OCEAN). This protocol is according to the standard protocol items for randomised trials (SPIRIT) statement.

Study population

Patients older than 45 years that are diagnosed with refractory anaemia due to small bowel ADs. Refractory anaemia is defined as a haemoglobin level of <7.5 mmol/L with intravenous iron or blood transfusion dependency despite ≥1 endoscopic intervention in the year after diagnosis (or unsuitable for/refusing endoscopy or surgery) and oral iron supplementation. It is known that gastrointestinal AD is mostly a disease of the elderly; younger patients with symptomatic AD might have another aetiology (eg, Rendu-Osler-Weber). Therefore, we exclude patients younger than 45 years, to obtain a homogeneous patient group.

Inclusion criteria

- Older than 45 years;
- Proven small bowel ADs: single or multiple 2–5 mm flat bright red spots with round uniform or slightly irregular margins; or lesions appearing as raised and reddened areas with a distinctly irregular margin, when larger than 5 mm; found during upper, lower gastrointestinal endoscopy and video capsule or enteroscopy;
- Intravenous transfusion dependency: at least four blood transfusions and/or iron infusions in the year before inclusion, despite an attempt to supplement iron orally;
- Failure of endoscopic therapy: at least one endoscopic attempt to coagulate the ADs within the year of diagnosis or unsuitable for/refusing endoscopy or surgery;
- Able to provide informed consent (IC).

Exclusion criteria

- Liver cirrhosis Child-Pugh C, liver failure or diagnosed portal hypertension;
- Any other possible source of gastrointestinal bleeding found during diagnostic endoscopy;
- Previous unsuccessful treatment with octreotide for the same indication (refractory anaemia due to ADs);
- Current thalidomide treatment which is effective (no parenteral iron or RBC transfusion dependency);
- Normalisation of haemoglobin level under oral iron supplementation alone;
- Patients with chronic renal failure who have an estimated glomerular filtration rate (eGFR) <30 mL/min;
- Life expectancy <1 year;
- Patients with left ventricular assist devices;
- Hereditary haemorrhagic telangiectasia;
- Pregnant or nursing women;
- Uncontrolled diabetes as defined by glycated haemoglobin >64 mmol/mL, despite adequate therapy;
► Hereditary haemorrhagic diseases or haematological disorders with active treatment;
► Patients with a known hypersensitivity to somatostatin analogues or any component of the octreotide (Sandostatin) LAR formulations;
► Symptomatic cholecystolithiasis;
► Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardised by the treatment with this study treatment;
► Cancer currently undergoing chemotherapy or radiation therapy.

Randomisation and treatment allocation
Patients will be randomised in a 1:1 ratio to receive standard care or open-label octreotide plus standard care for 1 year. Stratification will be based on two variables with each of the two groups: (1) the use of anticoagulants and platelet aggregation inhibitors versus no anticoagulant drugs; (2) only iron infusion dependent versus iron and blood infusion dependency. Therefore, block randomisation will consist of block sizes of 4. The trial is not blinded for patients and treating physicians, but the outcome adjudication committee is.

A web-based patient randomisation service for clinical trials will be used (Castor Electronic Data Collection (EDC)). When the screening visit data are entered in the electronic case record form (eCRF), and information regarding use of anticoagulants and/or platelet aggregation inhibitors is given, randomisation will be performed.

Trial treatments
Octreotide
Patients in the intervention group will simultaneously receive two injections of 20 mg Sandostatin LAR (octreotide) intramuscular every 28 days on top of standard of care. Treatment duration is 1 year with 2 months follow-up for all patients. Long-acting octreotide (LAR formulation) is chosen for patient comfort to only have injections once monthly and thereby optimise patient adherence. This dose is higher than existing evidence on octreotide for this indication. The reason is that it is still not proven with an RCT that somatostatin analogues (SST) is effective in these patients and this is a proof-of-principle study rather than a dose-finding study. Moreover, for other indications, higher monthly dosages of somatostatin analogues are more effective. When patients develop severe but not life-threatening adverse events (AEs; ie, grade 3; hospitalisation required or limitation of patient’s ability to care for himself/herself), we will reduce the dosage with 10 mg until AEs disappear. When a grade 3 AE persists despite dosage reduction, Sandostatin LAR will be discontinued. Those patients will be followed after discontinuation and will not be excluded from analyses. If patients are unresponsive to octreotide (Sandostatin) LAR 40 mg monthly, we will not increase the dose any further. Sandostatin LAR will be administered at the patients’ home by experienced nurses from Novanurses, a service provided by Eurocept Homecare.

Standard care
To align clinical practices in the participating centres, a standard of care protocol is developed to treat patients similarly during the treatment phase of this trial. A summary of this protocol is given below.

Anticoagulant therapy can be modified after randomisation according to local practice of the attending physician and is registered as adjustment in the standard of care. However, in most patients with such severe AD bleeding, the option of withdrawal antplatelet and/or anticoagulant therapy would have been considered prior to entry in the trial.

The first choice of therapy is oral iron supplementation and must be initiated prior to starting parenteral iron as maintenance therapy. When oral iron is insufficient and iron deficiency anaemia persists, parenteral iron may be administered (maximum 20 mg/kg bodyweight).

RBC transfusion is only indicated when anaemia persists despite parenteral iron supplementation. A distinction is made between patients with and without haemodynamic instability:
► Occult gastrointestinal bleed or acute gastrointestinal bleed without haemodynamic instability: RBC transfusion is given following the ‘4-5-6’ rule (see online supplementary additional file 1) or when symptoms associated with anaemia arise.
► Acute gastrointestinal bleed with haemodynamic instability: haemoglobin target value >5.0 mmol/L. In case of symptoms of hypoxia, the target value is >6 mmol/L.

Study procedures
This study consists of seven visits including one screening visit, five visits during treatment and one follow-up visit (figure 1). Data will be collected into an eCRF (Castor) designed to capture all visit information including medical history, results from laboratory analysis and AEs. The study duration for all patients is 60 weeks in total, divided into a screening phase, a 52-week treatment phase and a 8-week follow-up phase (figure 1). At screening, each participant will be screened for eligibility after written IC is obtained. In women with childbearing potential, a pregnancy test is performed. Within the treatment phase of the trial, patients are seen at weeks 0, 4, 16, 28 and 52. One week after the first injection, the patient will receive a phone call to assess AEs. The follow-up visit takes place 2 months after the octreotide concentration is below therapeutic doses, which is 8 weeks after the last treatment phase visit. This study visit aims to detect late AEs rather than establish the long-term effect of octreotide after discontinuation. During each visit, medical history, medication use, AEs, tolerability and drug accountability are assessed. In addition, a physical examination is performed and blood samples are drawn. Glucose, liver enzymes and lipid
profile are checked to assess the possible side effects of octreotide. Patients have to fill out two questionnaires (SF-36 and PSQ-An) three times, that is, at the start (week 0) and end of treatment (week 52), and at follow-up (week 60). The requested parameters at the different visits are listed below:

Screening visit
- Written IC
- Eligibility criteria check
- General AD characteristics
- Pregnancy test in premenopausal females.

Baseline, end of treatment and follow-up visit
- 36-item short form survey (SF-36) questionnaire: quality of life

Every visit
- AEs;
- Concomitant therapy;
- Drug accountability;
- Physical examination, including vital signs and weight;
- Laboratory tests: haematology (haemoglobin, haematocrit, leucocytes, platelets, absolute neutrophil count, prothrombin time), biochemistry (serum iron, ferritin, transferring and transferring saturation, calcium, phosphate, glucose, alanine aminotransferase, aspartate aminotransferase, total bilirubin, γ-glutamyl transpeptidase, alkaline phosphatase, albumin, creatinine) and lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides).

Secondary outcomes
- The percentual decrease in blood and iron requirements between the year prior to inclusion and the treatment period of 1 year in the intervention arm compared with the control group;
- Percentage of haemoglobin increase from baseline until end of treatment for patients treated with octreotide compared with the control group;
- The mean difference in haemoglobin level from baseline until end of treatment for patients treated with octreotide compared with the control group;
- Number of patients requiring RBC transfusions from baseline until end of treatment for patients treated with octreotide compared with the control group;
- Number of patients requiring other transfusions or medication to correct coagulation between baseline until end of treatment for patients treated with octreotide compared with the control group;
- The change in number and severity of bleeding episodes between start and end of treatment for patients treated with octreotide compared with the control group;
- The change in number of patients free of rebleeding between start and end of treatment for patients treated with octreotide compared with the control group;
- Reduction in oral iron requirement between start and end of treatment for patients treated with octreotide compared with the control group;
- The change in level of serum ferritin between baseline until end of treatment for patients treated with octreotide compared with the control group;
- The number and type of AEs (cardiac, pulmonary, neurological, other) between the control and treatment arms during the treatment period;
- Difference in number of hospitalisations, intensive care unit admissions and duration of hospitalisation between the control and treatment arms during the treatment period;
- The need for rescue therapy using APC, coiling or surgery compared between the control and treatment arms during the treatment period;
- Change in quality of life as measured by SF-36 between baseline and end of treatment for patients treated with octreotide compared with the control group;

Study end points
Primary outcome
The mean/median difference in blood and parenteral iron requirements between the 1 year prior to inclusion and the treatment period of 1 year compared between the intervention and control arm. All blood transfusions that are given with another indication than gastrointestinal blood loss are registered, but excluded for analysis for the primary outcome.
Mortality and cause of death compared between the control and treatment arms during the treatment period.

Study withdrawal
Participants can withdraw IC and leave the study at any time. The investigator will withdraw a participant from the study for any of the following reasons: pregnancy, consistent failure to adhere to protocol requirements, unacceptable toxicity of study medication, surgical interventions during the study or any other reason in the best interest of the patient. In case of withdrawal by the physician, all data generated from the study will be analysed and the reason(s) for discontinuation will be recorded.

Sample size considerations
We aim to analyse 56 patients based on a sample size calculation with 80% power to detect a difference of two RBC transfusions or iron infusions in 1 year. This accounts for an expected decrease of two transfusions in the intervention arm and no decrease in the control arm, with an estimated SD of 2.6 and a significance level of 0.05 using a Mann-Whitney U test. The estimated mean difference is based on the five available prospective cohort studies at the time of designing the study and the difference in blood transfusion requirements before and after treatment with octreotide. Those studies show a decrease of more than 50% of the blood transfusion requirements. We estimate a baseline dependency of four blood or iron transfusions in the last year, as this is intermediate of the studies of Junquera et al. Those studies have a dropout rate of 10%, the total sample size has to be 62 for the complete cohort with 31 patients in each treatment group.

Data management
All data are entered electronically according to Good Clinical Practice in the data management system Castor EDC at the participating site where the data are originated. Checks will be applied at the time of data entry and reviewed at the time of data entry. All data are entered electronically according to Good Clinical Practice in the data management system Castor EDC at the participating site where the data are originated. Checks will be applied at the time of data entry. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password. A complete back-up of the database is regularly performed. After study completion, the data will be locked and transferred to SPSS. Data are stored for at least 15 years after study completion.

Statistical analysis
Each patient who received at least one injection of Sandostatin LAR or has been included in the observational arm for 1 month will be included in the intention-to-treat analysis. Parallel analyses will be performed on the per-protocol population. The per-protocol population is defined as all patients who have received at least 80% of the total amount of dosages of octreotide at 52 weeks from baseline.

Data on demographic and baseline characteristics will be summarised for continuous variables, depending on distribution, and values will be presented as mean±SD or as median±IQR. Discrete variables (eg, sex) will be summarised by proportions (percentages). Differences between the intervention and standard of care will be analysed using Student’s t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Pearson’s χ² test will be used to compare dichotomised outcomes between the two arms. Frequency tables will be compiled for (serious) AEs classified according to the standard WHO—Adverse Reaction Terminology (WHO-ART) Body System Dictionary and preferred terms. All statistical analyses will be two-sided with a critical significance level of 5%. Missing data and loss to follow-up will be reported as percentage and, if known, the reason will be reported. Analyses will be performed with IBM SPSS Statistics V22.0 (SPSS, Chicago, Illinois, USA).

Subgroup analysis will be performed for stratified variables: (1) use of anticoagulants, (2) iron infusion or iron and blood transfusion dependent. The SF-36 will be used to calculate quality-adjusted life years to determine cost-effectiveness.

Monitoring
Site monitoring
Two independent monitors of St Antonius Hospital will visit the sites to review the records, compare with source documents, and observe and discuss the conduct of the trial with the investigators and site coordinator. The monitors are responsible for monitoring adherence to the protocol and guidelines, as well as ensuring completion of the eCRF and other documentation. In order to ensure the accuracy of data, the monitors, regulatory agencies and members of the Steering Committee have direct access to source documents. Anonymity of participants will be maintained at all times.

Trial monitoring
An independent Data Safety Monitoring Board (DSMB) will meet periodically to monitor the safety and progression of the trial. The responsibilities and procedures of the board are included in a DSMB Charter. Once 31 participants have completed the trial, an interim analysis of effectiveness and safety end points will be performed. The DSMB may recommend continuing the trial, early termination of the trial or modification of the trial. A
recommendation to terminate the trial early will only be made if there is clear evidence of a clinically important beneficial or harmful effect.

Ethics and dissemination
Ethical considerations
Ethical approval of the study protocol was given by the Central Committee on Research Involving Human Subjects and by the local accredited Medical Research Ethics Committee of the region Arnhem-Nijmegen, the Netherlands (reference number: 2013/354). An independent DSMB has been constituted to monitor patient safety and treatment efficacy during the trial.

Dissemination plan
Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the sponsor has published its report. The sponsor will have access to the final data set, form the basis of the Writing Committee and advise on the nature of publications. The trial will be presented at regional and national conferences. The final results will be presented at scientific meetings and published in a peer-reviewed journal (authorship will be according to the journal’s guidelines).

DISCUSSION
The OCEAN study is the first to prospectively investigate the efficacy of octreotide in patients with small bowel AD-associated refractory anaemia in an RCT. It is designed to determine whether and to what extent octreotide treatment can decrease parenteral iron and RBC transfusion requirements. This trial has a relevant clinical end point, that is, 50% reduction in parenteral iron and/or RBC transfusions, with an adequate powered sample size. A statistically significant outcome has direct implications for current practice of patients with refractory anaemia due to gastrointestinal ADs. Furthermore, this design provides an opportunity to study the safety of octreotide in a monthly dose of 40 mg in patients with ADs. Finally, we incorporate patient-reported outcome measurements to investigate the effect of octreotide on quality of life and cost-effectiveness. A retrospective study suggests that octreotide LAR treatment is cost-effective in these patients, but no previous studies evaluated treatment of ADs from the most important perspective: the patient’s perspective.

Some possible concerns need to be addressed. First, although a double-blind, placebo-controlled designed trial would have been superior in minimising the chance of information bias, an advantage of this current design is that it resembles the effect in clinical practice more after implementation of the intervention in comparison to a blinded trial. Second, the primary outcome at baseline (parenteral iron and RBC transfusion requirements before start of treatment phase) is determined retrospectively in both groups, which could lead to regression to the mean and information bias. However, comparing the outcomes between the two groups should wash out any effect of regression to the mean. We think the risk of information bias as a consequence of the retrospective retrieval is low due to the fact that parenteral iron administration or RBC transfusion must be registered and therefore retrievable in the patient’s electronic record. Third, with other somatostatin analogues (eg, pasireotide), intramuscular use could cause haematomas, especially in patients on anticoagulants. This might lead to a reduction in injections compared with the protocol and could influence the results. Fourth, the strict inclusion and exclusion criteria will slow down our inclusion rate with possible delay in gaining the final results. Finally, we did not stratify for any possible differences between centres. Owing to the small number of patient inclusions per centre, centre stratification might lead to more unbalanced randomisation than it would correct for an influence due to differences in practice.

Despite these concerns, our study will add significant value to the existing body of literature on treatment of patients with refractory anaemia resulting from small bowel ADs bleeds. The rigorous design of the OCEAN trial will address the efficacy of octreotide in therapy-resistant anaemia from small bowel ADs.

Trial status
The Medical Ethics Committee of the Radboud University Medical Center Nijmegen approved the protocol in August 2015. Patient recruitment started in September 2015.

By the medical ethical committee approved amendment
Inclusion criteria
▸ ADs at any location in the gastrointestinal tract, which are transfusion dependent and fail endoscopic therapy;
▸ Owing to the broadening in localisation of the ADs, it is not always necessary to perform a video capsule endoscopy.

Exclusion criteria
Patients with chronic renal failure who have a eGFR<30 mL/min is removed as exclusion criterion.

Study procedures
▸ The PSQ-An questionnaire is replaced for the validated Multidimensional Fatigue Inventory (MFI-20);
▸ Physical examination is only performed at the baseline, visit T28 and end of study visit;
▸ No blood samples are taken at the follow-up visit (week 60);
▸ The following laboratory tests are not measured: haemocrit, absolute neutrophil count, prothrombin time, transferring, calcium, phosphate, alanine transaminase, cholesterol (total, HDL, LDL), triglycerides.
Author affiliations
Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands

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Collaborators

Contributors
KVG carried out the trial, participated in the design and coordination of the study and drafted the first version of this manuscript. EJMvG and JPHD participated in the design of this study and gave important intellectual input. JPHD conceived the study and participated in its design and coordination. EJMvG and JPHD helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interests
None declared.

Patient consent
Obtained.

Ethics approval
The Central Committee on Research Involving Human Subjects and by the local accredited Medical Research Ethics Committee of the region Arnhem-Nijmegen, the Netherlands (reference number: 2014-1433).

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REFERENCES

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