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GI BLEEDING

Standard of Care Versus Octreotide in Angiodysplasia-Related Bleeding (the OCEAN Study): A Multicenter Randomized Controlled Trial

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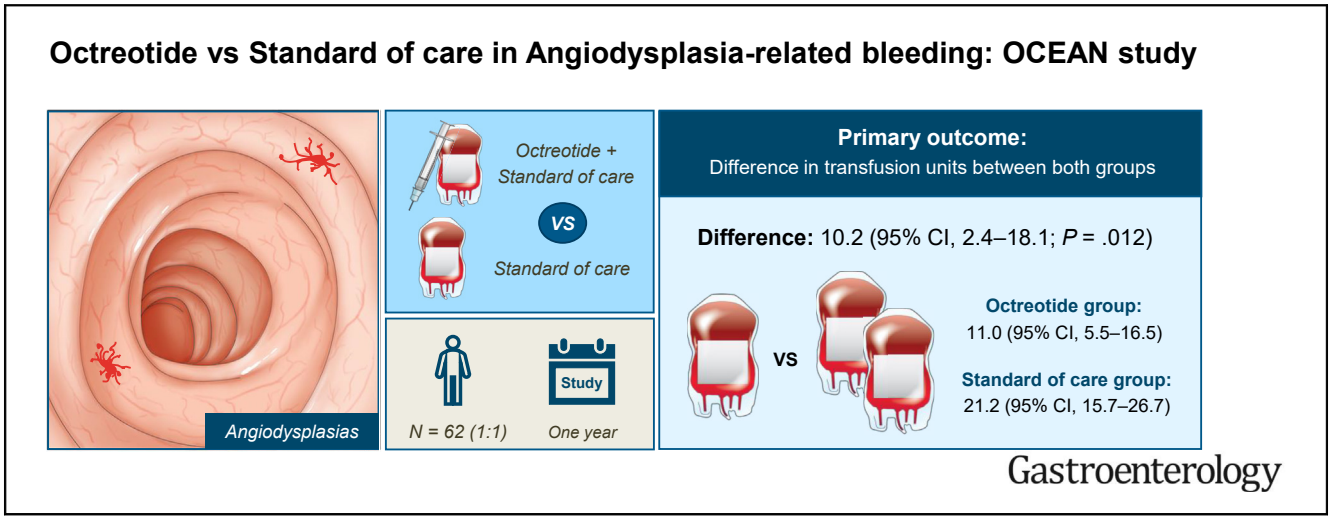

BACKGROUND & AIMS: Gastrointestinal angiodysplasias are vascular anomalies that may result in transfusion-dependent anemia despite endoscopic therapy. An individual patient data meta-analysis of cohort studies suggests that octreotide decreases rebleeding rates, but component studies possessed a high risk of bias. We investigated the efficacy of octreotide in reducing the transfusion requirements of patients with angiodysplasia-related anemia in a clinical trial setting. **METHODS:** The study was designed as a multicenter, open-label, randomized controlled trial. Patients with angiodysplasia bleeding were required to have had at least 4 red blood cell (RBC) units or parental iron infusions, or both, in the year preceding randomization. Patients were allocated (1:1) to 40-mg octreotide long-acting release intramuscular every 28 days or standard of care, including endoscopic therapy. The treatment duration was 1 year. The primary outcome was the mean difference in the number of transfusion units (RBC + parental iron) between the octreotide and standard of care groups. Patients who received at least 1 octreotide injection or followed standard of care for at least 1 month were included in the intention-to-treat analyses. Analyses of covariance were used to adjust for baseline transfusion requirements and incomplete follow-up. **RESULTS:** We enrolled 62 patients (mean age, 72 years; 32 men) from 17 Dutch hospitals in the octreotide (n = 31) and standard of care (n = 31) groups. Patients required a mean number of 20.3 (standard deviation, 15.6) transfusion units and 2.4 (standard deviation, 2.0) endoscopic procedures in the year before enrollment. The total

number of transfusions was lower with octreotide (11.0; 95% confidence interval [CI], 5.5–16.5) compared with standard of care (21.2; 95% CI, 15.7–26.7). Octreotide reduced the mean number of transfusion units by 10.2 (95% CI, 2.4–18.1; P = .012). Octreotide reduced the annual volume of endoscopic procedures by 0.9 (95% CI, 0.3–1.5). **CONCLUSIONS:** Octreotide effectively reduces transfusion requirements and the need for endoscopic therapy in patients with angiodysplasia-related anemia. ClinicalTrials.gov, NCT02384122.

Keywords: Angiodysplasia; Gastrointestinal Bleeding; Octreotide; Somatostatin Analogues.

Angiodysplasias are tortuous, dilated small blood vessels that lack a smooth muscle layer and are located in the gastrointestinal (sub)mucosa.[1] Angiodysplasias are the most common vascular malformation found in the gastrointestinal tract and a frequent source of intractable small-bowel bleeding, particularly in the elderly population.[1,2] The typical clinical picture consists of recurrent overt or occult bleeding episodes resulting in iron-deficiency anemia.[3] Patients with recurrent anemia are often managed with iron supplementation and red blood cell (RBC) transfusions.[1,4] However, the resulting transfusion dependency reduces patient quality of life and is associated with substantial (cardiovascular) morbidity and mortality as well as substantial health care costs.[5,6]

Endoscopic ablation of angiodysplasias with argon plasma coagulation (APC) is the treatment of choice, but efficacy is limited, and rebleeding rates are considerable. A meta-analysis found that 34% of patients experience rebleeding episodes within 2 years after an endoscopic intervention.[7]

Pharmacotherapy is an attractive alternative for patients with angiodysplasias who have transfusion-dependent anemia.[3] Somatostatin analogues, such as octreotide and lanreotide, have entered this space because they possess multiple beneficial effects against angiodysplasia-related bleeding. Octreotide decreases duodenal and splanchnic flow through vasoconstriction, which mitigates bleeding, improves platelet aggregation, and reduces the nutrient and oxygen supply required for angiogenesis. Angiogenesis is also directly repressed by inhibiting several growth factors, including vascular endothelial growth factor (VEGF).[8,9]

A recent individual patient data meta-analysis (IPDMA) suggests that long-acting octreotide increases hemoglobin concentrations while greatly reducing the need for blood transfusions.[8] Although promising, risk of bias in the studies that informed this meta-analysis was high due to the retrospective designs, small cohorts (<20 patients), and lack of formal control groups.[8] This emphasizes the need for a controlled study to provide a robust measure of effectiveness. To this end, we designed this investigator-initiated, randomized, controlled study, Efficacy of Octreotide on Blood and Iron Requirements in Patients With Anemia Due to Angiodysplasias (OCEAN) to assess the efficacy of long-acting octreotide in patients with refractory anemia due to bleeding gastrointestinal angiodysplasias.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Angiodysplasia-related bleeding often results in transfusion dependency associated with substantial morbidity and mortality. Multiple cohort studies suggest a beneficial effect of octreotide, but evidence from randomized controlled trials was lacking. We designed the Efficacy of Octreotide on Blood and Iron Requirements in Patients With Anemia Due to Angiodysplasias (OCEAN) study to provide a robust measure of effectiveness.

NEW FINDINGS

The first randomized controlled study, with adequate power, to show the efficacy of long-acting octreotide in patients with transfusion-dependent, angiodysplasia-related anemia.

LIMITATIONS

The open-label design caused 5 patients allocated to standard of care to switch to octreotide. A relatively high dose of octreotide was used, possibly resulting in more adverse events. Endoscopic treatment was more frequently applied in patients assigned to standard of care.

CLINICAL RESEARCH RELEVANCE

Octreotide treatment effectively reduces transfusion requirements and healthcare utilization of patients with angiodysplasia-related anemia, significantly increasing patients' quality of life. Adverse events were mostly mild and self-limiting, seldom leading to octreotide discontinuation.

BASIC RESEARCH RELEVANCE

Octreotide treatment was effective in most patients, but the benefits are not uniform. Clinical characteristics did not predict treatment response. The development of angiogenesis biomarkers may help to tailor treatment strategies.

Materials and Methods

The OCEAN trial was registered in The Netherlands National Trial Register and at ClinicalTrials.gov (NCT02384122) in 2014. The registration is accessible on the international clinical trials registry platform of the World Health Organization (EUCTR2014-004032-19-NL).[10] The trial protocol was approved by the Central Committee of Human-related Research in the Netherlands (CCMO), the Medical Ethics Committee of East Netherlands (METC Oost-Nederland), and independent

Abbreviations used in this paper: **AE, adverse event; APC, argon plasma coagulation; CI, confidence interval; EDC, Electronic Data Collection; SF-36, 36-Item Short Form Health Survey; IPDMA, individual patient data meta-analysis; ITT, intention-to-treat; IQR, interquartile range; LAR, long-acting release; MFI-20, Multidimensional Fatigue Inventory (20 items); RBC, red blood cell; SAE, serious adverse event; VEGF, vascular endothelial growth factor.**

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Ethics Committees at each of the other participating centers.[11] Reference to the online trial protocol can be found in the Supplementary Material (page 2). The study was conducted in accordance with good clinical practice, the Declaration of Helsinki, and all applicable national laws. All patients provided written informed consent. The study was reported following the Consolidated Standards of Reporting Trials guidelines for reporting parallel-group, randomized trials.[12] All authors had full access to the study data and reviewed and approved the final manuscript.

Patients

Patients aged ≥18 years with transfusion-dependent anemia due to angiodysplasias who had received at least 1 endoscopic treatment attempt (if not contraindicated) were recruited from 17 hospitals in the Netherlands. Patients with endoscopically confirmed angiodysplasias were eligible if they received at least 4 transfusion units in the preceding year (baseline). This threshold was arbitrarily selected to include patients with a substantial transfusion dependency, because this would better resemble the intended target population, given the associated costs and medical implications.[6] Transfusion units consisted of parental iron infusions (500 mg) and red blood cell (RBC) transfusions (500 mL). Recruitment was initially limited to patients with small-bowel angiodysplasias, because they are less accessible for endoscopic therapy.[13] However, in view of the unmet need for patients with APC-unresponsive angiodysplasias located elsewhere in the gastrointestinal tract, we expanded the inclusion criteria in February 2016 to allow patients with angiodysplasias in the stomach or colon to enter the trial.[11]

Patients with liver cirrhosis Child-Pugh C or liver failure, uncontrolled diabetes mellitus (defined by glycohemoglobin >64 mmol/mL), symptomatic cholecystolithiasis, and pregnant or lactating women were regarded as ineligible because of the pharmacologic profile of octreotide.[14] Patients with hereditary hemorrhagic diseases or hematologic disorders on active treatment, other alternative causes of gastrointestinal bleeding, presence of left ventricular assist devices, patients with cancer under active treatment, and those with a life expectancy <1 year were excluded from enrollment.[1,3]

Study Design

The trial was designed as an investigator-initiated, multicenter, open-label, randomized, parallel-group, superiority study to compare the efficacy of long-acting octreotide vs standard of care. Patients were randomly assigned to receive 2 intramuscular long-acting octreotide (Sandostatin long-acting release [LAR] formulation; Novartis) injections of 20 mg (40 mg in total) every 28 days as an adjunct to standard of care or standard of care alone for 52 weeks. A relatively high dose of octreotide was selected because we aimed to perform a proof-of-principal study, and higher monthly dosages were found to be more effective for other indications while still being safe.[10,15,16] Dose reduction was considered in case of adverse events (AEs) that were serious (SAEs), but not life-threatening.[10] Octreotide was administered by experienced nurses at the patient's home, a service provided by Eurocept Homecare.

Standard of care consisted of parental iron and RBC transfusions prescribed at the discretion of the treating physician. We developed a standard of care protocol to manage anemia, which consisted of oral iron supplementation and, if ineffective, parenteral iron substitution, followed by RBC transfusion. RBC transfusion was only recommended if anemia persisted despite parenteral iron supplementation.[11] The thresholds for RBC transfusion followed the prevailing national guideline on gastrointestinal bleeding.[17] The guideline adheres to the "4-5-6" rule, which states that patients with severe comorbidities should have a hemoglobin level >6 mmol/L or 9.5 g/dL, whereas healthy patients with an active bleeding source and those with fewer severe comorbidities should be kept >5 mmol/L or 8 g/dL. Healthy patients with asymptomatic anemia should not fall <4 mmol/L or 6.5 g/dL.[17]

Patients in both groups were allowed to receive concomitant care, including endoscopic application of APC, discontinuation of antithrombotics, and use of tranexamic acid. We urged treating physicians to exclusively prescribe concomitant care if active bleeding was suspected, severely compromising the patients' health. The use of drugs with antiangiogenic properties (ie, thalidomide and bevacizumab) was not allowed during the study.

If treatment with standard of care alone was no longer deemed medically appropriate by the treating physician, patients in the standard of care group could initiate octreotide during the study year. However, initiating octreotide was considered a protocol violation, and as a result, participants were removed from specific analyses (see Statistical Methods and Data Analysis). Octreotide was also counted as concomitant care for patients in the standard of care group.

Patients visited the outpatient clinic 5 times during the trial period, at weeks 0, 4, 16, 28, and 52. In addition, a screening and follow-up visit at week 60 took place in person or by telephone. Medical history, medication use, and AEs were assessed during each visit. Pancreatic enzymes were prescribed if the patient had bothersome gastrointestinal AEs, because octreotide is known to affect the secretion of digestive enzymes.[14] Dose adjustments to antidiabetes medications were advised in case of glucose intolerance, because octreotide inhibits insulin and glucagon secretion.[14] Physical examinations were performed, and blood samples were drawn during each clinic visit. The study design is illustrated in Supplementary Figure 1.

Data were stored in the data management system Castor Electronic Data Collection (EDC) and compared with source documents at the participating site by an independent monitor. Drug accountability was registered in the electronic medication management registry of Eurocept Homecare.

Safety Assessment

Investigators assessed the safety at each patient visit through physical examination, laboratory tests, and symptoms reported by patients and nurses administering the octreotide. Because cholecystolithiasis and impaired glucose tolerance are known AEs of octreotide, liver enzymes, glucose, and glycohemoglobin were determined at every visit.[8,14] SAEs, as defined by the European Medicines Agency, were reported within 24 hours of onset through the web portal ToetsingOnline to the Medical Ethics Committee.[18] AEs were classified according to the standard World Health Organization Adverse Reaction Terminology and were recorded in Castor EDC.[19] Development Safety Update Reports were annually monitored by the METC Oost-Nederland.

Clinical Outcomes

The primary outcome of this study was defined as the mean difference in blood (RBC transfusions per 500 mL or packed cells) and parenteral iron (intravenous iron infusions per 500 mg) requirements between the intervention and standard of care groups. Initially, the primary outcome was defined as the mean within-patient difference in blood and parental iron requirements between groups. However, this was later revised in consultation with a statistician, because group differences in baseline transfusion requirements could influence results.[10]

Secondary outcomes included the proportion of patients in both groups that experienced a ≥50% (defined as a good response) and 100% (defined as a full response) reduction in the number of transfusion units received during the study year compared with baseline, the proportion of patients that required concomitant care during the study, the mean difference in endoscopic procedures between both groups and the mean difference in bleeding episodes (defined as each noncontiguous episode in which hospital care was sought for anemia), and health care utilization, consisting of hospital admissions, ambulatory care, and emergency care. Secondary outcomes also included serum hemoglobin and ferritin levels.[10]

Patient-Reported Outcome Measures and Adverse Events

Patient-reported outcome measures included fatigue levels and quality of life. Fatigue was measured by the 20-item Multidimensional Fatigue Inventory (MFI-20), which covers 5 dimensions of fatigue affect and tolerability. MFI-20 summary scores range from 20 (best) to 100 (worst).[20] Quality of life was assessed by the 36-Item Short Form Health Survey (SF-36), which uses 8 subdomains to evaluate physical and mental health. Subdomain scores range from 0 (worst) to 100 (best). The physical and mental component summary scores are generated from the subdomain scores. Summary scores were normalized, meaning that a score of 50 resembles the mean score of the general population.[21] The MFI-20 and SF-36 were distributed at week 0 and 52. Mean questionnaire scores at week 52 were compared between the intervention and standard of care groups.

AEs were reported by patients at weeks 4, 16, 28, and 52. The type and number of AEs were assessed. The proportion of patients that experienced ≥1 AEs was compared between the intervention and standard of care groups.

Randomization

Patients were randomly assigned to octreotide or standard of care (1:1) according to a web-based patient randomization service (Castor EDC) with a maximum block size of 4. Stratification was performed based on the use of antithrombotic therapy (none vs any) at the time of inclusion and the type of transfusion units received in the year preceding inclusion (only parental iron vs RBC transfusions). The trial was blinded for the outcome adjudication committee but not for patients or attending physicians. The week of the first octreotide LAR injection was set as week 0 of the clinical trial.

Statistical Methods and Data Analysis

The primary outcome was the difference in transfusion units between both groups during the study year. With 28 patients per group, the study was calculated to have 80% power to detect a difference of 2 transfusion units between the octreotide and standard of care groups. The power calculation was based on previous cohort studies that showed a median decrease of 2.2 transfusion units, which equates to a ≥50% reduction in the number of transfusion units required by patients.[8] We set out to recruit 31 patients per group, considering a 10% dropout rate. Analyses were performed based on both intention-to-treat (ITT; all patients who were randomized) as well as per-protocol (all patients who received ≥80% of the total octreotide dosages or only received standard of care for ≥80% of the study year) rules.

Analyses of covariance were used to compare the number of transfusion units, endoscopic procedures, bleeding episodes, health care utilization, fatigue levels, and quality of life between groups. We used analyses of covariance to adjust for baseline differences between groups in the respective outcome variables because this could influence results.[22,23] We also adjusted for reduced follow-up time due to death.

The models included 2 covariates, the respective baseline value (eg, transfusion units for the primary outcome) and follow-up in days. Covariates were preselected and included regardless of significance levels.[22] A pre-post design was used to assess treatment response. The number of transfusion units each patient received during the study year was determined and converted to a proportion based on their baseline numbers.[8]

A linear mixed random-effects model was used to examine whether the effect of octreotide treatment on transfusion requirements varied during follow-up. In this model, the interaction term group × time was determined. Study group and follow-up time (made categorical using the 4 study visits) were included as independent variables, and a random intercept was added to control for individual differences in transfusion requirements.

Component summary scores of the SF-36 were calculated using standard scoring algorithms with validated scores from the United States general population.[24] Subgroup analyses were performed for RBC transfusion dependency during baseline and use of antithrombotic medications. An analysis with correction for the use of concomitant care was performed, in which transfusion units administered before the application of concomitant care were counted and multiplied in proportion to the reduced follow-up time. Exploratory analyses were performed on patients in the octreotide group with and without a good response. Separate ITT and per-protocol analyses were executed in which patients who died before completing the trial were excluded.

All statistical analyses were 2-sided, with a critical .05 significance level. Missing data and loss of follow-up were reported. Baseline characteristics are presented as mean ± standard deviation or median (interquartile range [IQR]) in case of nonnormally distributed continuous variables. Binary and categorical variables are presented as frequencies and percentages. Analyses were performed with IBM SPSS Statistics 22.0 software (IBM Corp). Figures were made using the seaborn library in Python 3.8.5 (Python Corp).

Results

Patient Characteristics

From September 2015 to April 2021, 79 consecutive eligible patients from 15 peripheral and 2 academic medical

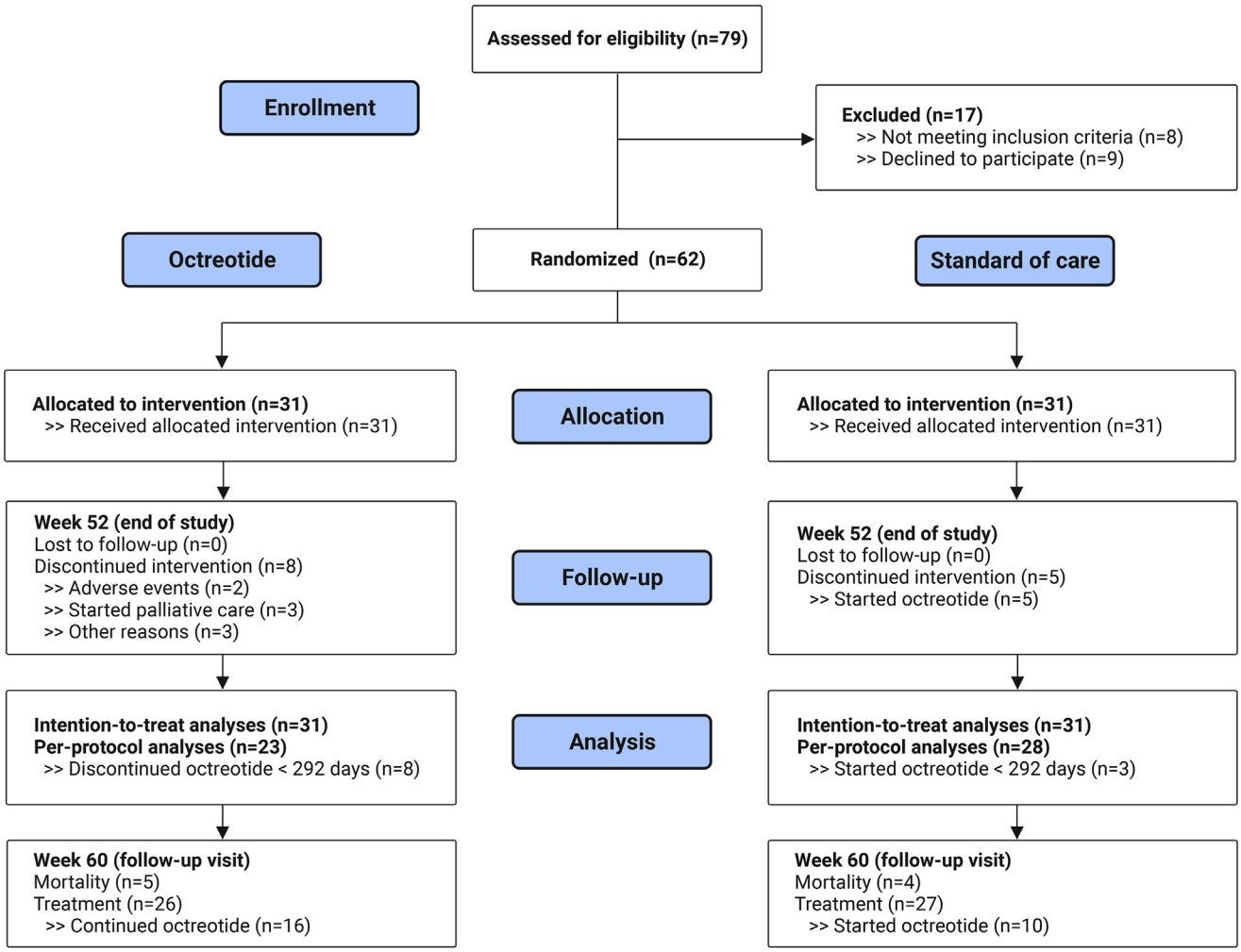

Figure 1. Study flowchart illustrates how patients were included and evaluated during study participation. The Consolidated Standards of Reporting Trials guidelines were followed.[12] Of 79 who were screened, 8 were screening failures, and 9 did not want to participate. Sixty-two patients were randomized (n = 31 in each group). No patients withdrew from the study. Eight patients in the octreotide group discontinued treatment (all within 292 days). Five patients on standard of care started with octreotide (3 within 292 days). At 60 weeks of follow-up, 16 patients in the octreotide group had continued octreotide. Ten patients in the standard of care group had started octreotide (5 during the study year). Five patients in the octreotide group had died (all during the study year), and 4 patients in the standard of care group died (2 during the study year).

centers were considered for inclusion, and 62 patients (aged 72 ± 11 years, 32 men) were randomized. Seven patients died before completing the trial. No patients withdrew from the study (Figure 1).[12]

In total, 31 patients were treated with octreotide, and 31 received standard of care. Most of the 62 patients had 1 or multiple associated comorbidities, including valvular heart disease (29 [47%]), diabetes mellitus (22 [35%]), and chronic renal failure (10 [16%]). Antithrombotics were used by most patients (49 [79%]), especially antiplatelet (28 [45%]) or anticoagulant (18 [29%]) monotherapy.

Angiodysplasias were predominantly located in the small bowel (54 of 62 [87%]), followed by the colon (30 [48%]) and stomach (17 [27%]). Patients experienced anemia for a median period of 6 years (IQR, 3–10 years), in which they underwent 8.0 (IQR, 7.0–21.5) endoscopic procedures (Table 1). In the year before study participation, patients required a mean number of 20.4 ± 15.6 transfusion units and underwent 2.4 ± 2.0 endoscopic procedures (Table 1).

Primary Outcome: Difference in Transfusion Units

Patients on octreotide required a mean adjusted number of 11.0 (95% confidence interval [CI], 5.5–16.5) transfusion units during the study year compared with 21.2 (95% CI, 15.7–26.7) transfusion units for patients on standard of care. Octreotide thus reduced the number of transfusion units by 10.2 (95% CI, 2.4–18.1; $P = .01$). Patients on octreotide required a mean adjusted number of 8.2 (95% CI, 3.2–13.2) RBC transfusions and 2.8 (95% CI, 1.3–4.3) iron infusions compared with 16.8 (95% CI, 11.8–21.8) and 4.6 (95% CI, 3.1–6.0), respectively, for patients receiving standard of care (Table 2). There was no significant interaction effect between the study groups and follow-up time on the primary outcome, indicating that the difference was unrelated to the treatment duration ($P = .76$) (Figure 2).

Table 1. Patient Characteristics at Baseline and During the Baseline Year

Variable	Octreotide (n = 31)	Standard of care (n = 31)
Patient characteristics at baseline		
Male sex	15 (48)	17 (55)
Age, *y*	72.5 ± 9.9	71.8 ± 12.6
Comorbidities	29 (94)	29 (94)
Valvular heart disease	14 (45)	15 (48)
Ischemic heart disease	12 (39)	5 (16)
Arrhythmia	11 (35)	10 (32)
COPD	8 (26)	8 (26)
Chronic renal failure	7 (26)	3 (10)
Liver cirrhosis	1 (3)	1 (3)
Coagulopathies	1 (3)	2 (6)
Diabetes mellitus	10 (32)	12 (39)
Antithrombotic agent	25 (81)	24 (77)
Antiplatelet agent	19 (76)	11 (35)
Single-antiplatelet therapy	18 (95)	10 (91)
Dual-antiplatelet therapy	1 (5)	1 (9)
Anticoagulants	6 (24)	13 (54)
Single therapy	6 (100)	12 (92)
Dual therapy	0 (100)	1 (8)
Prothrombin time, *s*	14.0 (12.2–15.2)	15.0 (12.8–23.3)
Abnormal	6 (19)	9 (29)
Angiodysplasia characteristics		
Years with anemia	7.7 (3.5–11.5)	5.4 (2.2–8.7)
Years with diagnosis	2.5 (0.6–5.2)	2.0 (1.3–6.5)
Multiple angiodysplasias	27 (87)	28 (90)
One group	2 (7)	3 (11)
Diffuse lesions	25 (93)	25 (89)
Location		
Multiple locations	13 (42)	17 (55)
Stomach	7 (23)	10 (32)
Isolated	1 (14)	2 (20)
Small bowel	27 (87)	27 (87)
Isolated	15 (56)	11 (41)
Colon	14 (45)	16 (52)
Isolated	2 (14)	1 (13)
Treatment characteristics		
Previous surgical treatment	1 (3)	0 (0)
Previous pharmacologic treatment	5 (16)	3 (10)
Thalidomide	4 (80)	2 (67)
Tranexamic acid	1 (20)	1 (33)
Characteristics during the baseline year		
Bleeding and health care utilization		
Total number of bleeding episodes	13.0 (7.0–21.8)	13.0 (7.0–23.0)
Bleeding episodes at baseline[a]	9.8 ± 8.0	7.2 ± 5.3
Total transfusion units received	33.0 (15.0–53.3)	32.0 (20.0–55.0)
Transfusion units at baseline[a]	22.6 ± 18.2	18.0 ± 12.5
RBC transfusions (per 500 mL)	18.9 ± 19.2	12.6 ± 12.9
Intravenous iron infusions (per 500 mL)	3.9 ± 5.7	5.4 ± 4.7
Total endoscopic procedures	8.0 (6.0–11.0)	8.0 (5.0–13.0)
Endoscopic procedures at baseline[a]	2.6 ± 2.2	2.2 ± 1.8
Treatment modalities applied	1.0 ± 1.2	1.0 ± 1.1
Last treatment applied, *d*	142 ± 114	109 ± 72
Hospital admissions at baseline[a]	2.1 ± 2.8	1.5 ± 1.8
Length of stay, *d*	6.3 ± 7.6	5.6 ± 7.9
Emergency care at baseline[a]	1.3 ± 1.7	1.0 ± 1.4
Ambulatory care at baseline[a]	9.7 ± 9.8	7.2 ± 6.1
Biochemical analyses		
Hemoglobin levels, *mmol/L*	6.3 ± 1.1	6.3 ± 1.3
Ferritin levels, μg/L	161.8 ± 238.0	165.1 ± 231.6
Patient-reported outcome measures		
Fatigue (MFI-20)	71.3 ± 16.9	68.9 ± 15.8
Physical component summary (SF-36)[b]	33.1 ± 8.4	36.9 ± 8.3
Physical functioning	33.7 ± 27.4	43.5 ± 28.0
Role-physical	18.5 ± 32.3	27.4 ± 39.5
Bodily pain	53.1 ± 26.4	60.8 ± 31.9
General health	30.6 ± 19.9	36.6 ± 18.0
Mental component summary (SF-36)[b]	40.6 ± 14.2	41.3 ± 11.4
Vitality	37.5 ± 19.6	39.8 ± 16.7
Social functioning	47.6 ± 26.7	54.4 ± 27.1
Role-emotional	40.9 ± 44.5	53.1 ± 26.4
Mental health	57.0 ± 28.8	62.2 ± 24.9

NOTE. Data are mean ± standard deviation, n (%), or median (IQR).
COPD, chronic obstructive pulmonary disease.
[a]Baseline refers to the year preceding randomization.
[b]Summary scores are normalized, meaning that a score of 50 resembles the mean score of the general population.

Secondary Outcomes

Treatment response and concomitant care. A good treatment response (≥50% reduction in transfusion units compared with baseline) was seen in 19 of 31 patients (61%) on octreotide compared with 6 of 31 patients (19%) on standard of care. Patients on octreotide were also more likely to experience a full response (6 of 31 [19%] vs 1 of 31 [3%]). Individual differences in transfusion requirements are depicted in Figure 3. Concomitant care was provided to 4 of 31 patients (13%) on octreotide compared with 14 of 31 patients (45%) on standard of care and was applied after a mean period of 218 days (range, 25–339 days) and 166 days (range, 1–338 days), respectively (Table 2). Individual use of concomitant care is reported in Supplementary Figure 2.

Table 2. Outcomes of the Intention-to-Treat Analyses

Variable	Octreotide (n = 31)	Standard of care (n = 31)	Difference	*P* value
Primary outcome[a]				
Transfusion units	11.0 (5.5–16.5)	21.2 (15.7–26.7)	10.2 (2.4–18.1)	**.012**
RBC transfusion	8.2 (3.2–13.2)	16.8 (11.8–21.8)	8.6 (1.4–15.7)	
Intravenous iron infusions	2.8 (1.3–4.3)	4.6 (3.1–6.0)	1.8 (0.3–3.9)	
Treatment response				
Transfusion decrease ≥50%	19/31 (61)	6/31 (19)	13/31 (42)	
Decrease 100%	5/19 (26)	1/6 (17)		
Concomitant care				
Required concomitant care	4/31 (13)	14/31 (45)		
Endoscopic APC	3/4 (75)	7/14 (50)	4/10 (40)	
Discontinue antithrombitics	1/4 (25)	4/14 (29)	3/10 (30)	
Start other treatment	0/4 (0)	7/14 (57)	7/10 (70)	
Endoscopic procedures[a]	0.3 (−0.1 to 0.7)	1.2 (0.8–1.6)	0.9 (0.3–1.5)	
Applied interventions	0.1 (−0.1 to 0.4)	0.7 (0.4–0.9)	0.5 (0.2–0.9)	
Healthcare utilization[a]				
Bleeding episodes	5.3 (2.9–7.6)	8.5 (6.1–10.8)	3.2 (−0.2 to 6.6)	
Hospital admissions	0.5 (−0.2 to 1.1)	1.8 (1.2–2.5)	1.3 (0.4–2.3)	
Length of stay, *d*	2.3 (−0.4 to 5.0)	6.0 (3.3–8.7)	3.7 (−0.2 to 7.6)	
Emergency care	0.3 (−0.4 to 0.9)	1.6 (0.9–2.2)	1.3 (0.4–2.2)	
Ambulatory care	4.5 (2.5–6.5)	6.9 (4.9–8.9)	2.4 (−0.4 to 5.2)	
Biochemical analyses				
Hemoglobin, *mmol/L*	7.1 (6.6–7.6)	6.8 (6.3–7.2)	0.3 (−0.3 to 1.0)	
Ferritin, *μg/L*	199 (83–316)	180 (69–289)	20 (−140 to 180)	
Patient-reported outcome measures[a]				
Fatigue (MFI-20)	56.0 (49.3–62.8)	69.4 (63.0–75.8)	13.4 (4.1–22.6)	
Physical component score (SF-36)[b]	41.5 (37.6–65.3)	36.5 (32.8–40.2)	5.0 (−0.4 to 10.4)	
Physical functioning	58.4 (48.6–68.2)	39.2 (30.0–48.4)	19.2 (5.7–32.7)	
Role-physical	45.2 (30.1–60.4)	31.0 (16.6–45.4)	14.3 (−6.7 to 35.2)	
Bodily pain	69.9 (58.5–81.3)	62.3 (51.6–73.1)	7.6 (−8.1 to 23.3)	
General health	49.8 (41.1–58.6)	37.4 (29.1–45.6)	12.4 (0.4–24.5)	
Mental component score (SF-36)[b]	49.1 (44.6–53.6)	41.9 (37.6–46.2)	7.2 (1.0–13.4)	
Vitality	53.3 (44.7–62.0)	38.8 (30.6–47.0)	14.6 (2.6–26.5)	
Social functioning	73.5 (61.6–85.4)	57.7 (46.5–69.0)	15.8 (−0.7 to 32.2)	
Role-emotional	59.3 (43.5–75.1)	41.1 (26.1–56.1)	18.2 (−3.5 to 40.0)	
Mental health	75.8 (67.1–84.5)	62.2 (54.0–70.5)	13.6 (1.6–25.6)	
Adverse events				
Total number	22/31 (71)	21/31 (68)	1/31 (3)	
Drug-related	20/22 (91)	7/21 (33)		
Gastrointestinal	15/20 (75)	6/7 (86)		
Pain administration	9/20 (45)	0/7 (0)		
Glucose intolerance	3/20 (15)	2/7 (29)		
Anemia-related	12/22 (55)	20/21 (95)		
Other	6/22 (27)	2/21 (10)		
Mortality	5/31 (16)	2/31 (6)	3/31 (10)	
Unrelated to octreotide	4/5 (80)	2/2 (100)		
Unknown	1/5 (20)	0/2 (0)		

NOTE. Data are mean (95% CI) or n (%). The bold *P* value is statistically significant ($P < .05$).
[a]Results were adjusted for by the covariates (respective baseline values and follow-up time in days). Patient-reported outcome measures were only adjusted for by their baseline values.

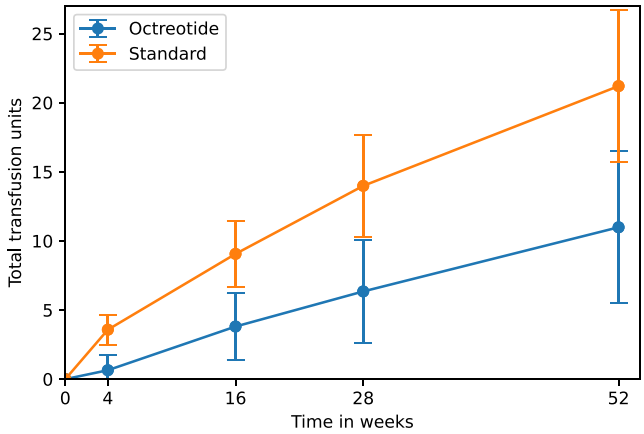

Figure 2. The mean number of transfusion units patients in the octreotide group and standard of care group received during the study is shown. The difference in transfusion units between groups was unrelated to the treatment duration ($P = .76$). The error bars indicate the standard deviation.

Endoscopic procedures and argon plasma coagulation. During the study year, patients on octreotide underwent a mean number of 0.3 endoscopic procedures compared with 1.2 for those on standard of care (adjusted difference of 0.9; 95% CI, 0.3–1.5). Similarly, patients on octreotide and standard of care received 0.1 and 0.7 rounds of APC, respectively (adjusted difference of 0.5; 95% CI, 0.2–0.9). Treatment modalities other than APC were not applied (Table 2).

Bleeding episodes, health care utilization, and laboratory results. During the study year, patients on octreotide experienced fewer bleeding episodes than patients on standard of care (adjusted difference of 3.2; 95% CI, −0.2 to 6.6) and required fewer health care services, including hospital admissions (adjusted difference of 1.3; 95% CI, 0.4–2.3), emergency care (adjusted difference of 1.3; 95% CI, 0.4–2.2), and ambulatory care (adjusted difference of 2.4; 95% CI −0.4 to 5.2). Hemoglobin levels were numerically higher for patients on octreotide at the end of the study year (7.1 [95% CI, 6.6–7.6] mmol/L vs 6.8 [95% CI, 6.3–7.2] mmol/L), whereas ferritin levels were comparable between groups (199 [95% CI, 83–316] μg/L vs 180 [95% CI, 69–289] μg/L) (Table 2).

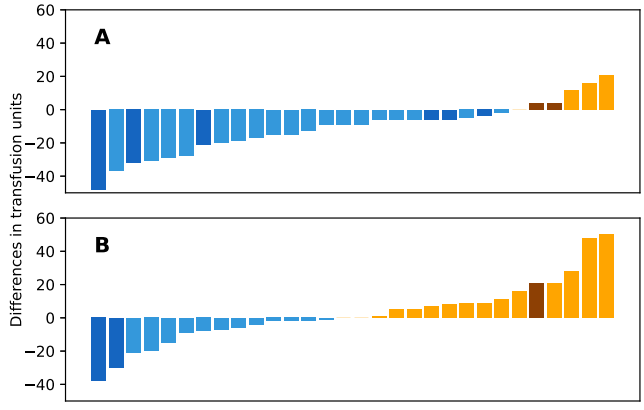

Figure 3. Difference in transfusion units patients received between the year before and after randomization is shown. Blue bars represent patients who experienced a decrease, and orange bars represent patients who experienced an increase. The darker bars represent patients who were excluded from the per-protocol analyses. (*A*) Octreotide group. Two patients did not experience a difference in transfusion units (not depicted). (*B*) Standard of care group. Three patients did not experience a difference in transfusion units (not depicted).

Patient-Reported Outcome Measures: Fatigue and Health

We explored 5 dimensions of fatigue and found that patients on octreotide had a lower adjusted MFI-20 score than those on standard of care (56.0 [95% CI, 49.3–62.8] vs 69.4 [95% CI, 63.0–75.8]), suggesting they experienced less fatigue (Table 2). We examined 8 domains of health measured by the SF-36 and found that patients on octreotide had a higher adjusted physical component summary scores (41.5 [95% CI, 37.6–65.3] vs 36.5 [95% CI, 32.8–40.2]) and significantly higher adjusted mental component summary scores (49.1 [95% CI, 44.6–53.6] vs 41.9 [95% CI, 37.6–46.2]) than those on standard of care. Patients on octreotide experienced an increase in all 8 subdomain scores (Table 2).

Adverse Events

During the study period, 50 AEs were reported in 22 of 31 patients (71%) on octreotide compared with 37 in 21 of 31 patients (68%) on standard of care. Most AEs reported by patients on octreotide were likely related to the study drug (31 of 50). Drug-related AEs included gastrointestinal AE (19 of 50), pain at the administration site (9 of 50), and glucose intolerance (3 of 50). Five patients started pancreatic enzymes because of bothersome gastrointestinal AEs (diarrhea and abdominal pain). Two patients adjusted the dose of their antidiabetes medication. Patients on standard of care also reported gastrointestinal AEs (6 of 37) and glucose intolerance (2 of 37).

Anemia-related AEs, including fatigue and dyspnea, were reported by patients from both groups, especially by those on standard of care (14 of 50 vs 27 of 37). Other AEs were only registered once and deemed unrelated to the study drug and anemia (5 of 50 vs 2 of 37) (Table 2). Individual AEs are displayed in Supplementary Figure 3. In the octreotide group, AEs were primarily mild and self-limiting. At the end of the study, 10 of 26 patients (38%) on octreotide reported having AEs, of which 5 were drug-related. Pancreatic enzymes were no longer used, and antidiabetes medications were resumed at the original dose. The course of drug-related AEs throughout the study period is illustrated in Figure 4. In comparison, 13 of 29 patients (45%) on standard of care reported (anemia-related) AEs at the end of the study.

Serious Adverse Events and Mortality

An SAE developed in 2 patients on octreotide (acute cholangitis and a hypoglycemic episode with loss of

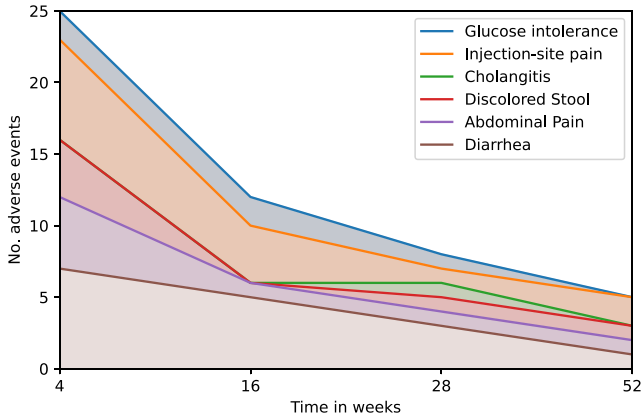

Figure 4. The number of drug-related AEs in patients in the octreotide group experienced during the study year is shown. AEs were reported at weeks 4, 16, 28, and 52.

consciousness). Both patients fully recovered, and octreotide was directly discontinued in the patient with cholangitis. In the patient with a hypoglycemic episode, octreotide was initially reduced to 20 mg and discontinued 1 month later because glucose levels remained unstable.

During the study year, 5 patients on octreotide died compared with 2 on standard of care (16% vs 6%). Three patients from the octreotide group died of unrelated causes, of which 2 had discontinued octreotide several months prior. One patient died after an acute bleeding episode, and the cause of death of 1 patient was unknown. Two patients on standard of care died of unrelated reasons. Annual Development Safety Update Reports reviews resulted in continuation of the study without change.

Two additional patients in the standard of care group died during follow-up. Individual causes and time until death are reported in Supplementary Figure 4. Analyses excluding those who died during the study year provided comparable results (Supplementary Table 1).

Per-Protocol Analyses

The per-protocol analyses excluded 11 patients (8 octreotide, 3 standard of care). Four patients from the octreotide group discontinued octreotide for unrelated reasons: 2 because of drug-related AEs, 1 because of assumed lack of efficacy, and 1 because of assumed recovery. Three patients from the standard of care group started octreotide because of untenable disease severity. Individual reasons and time until exclusion are provided in Supplementary Figure 5.

After we adjusted for covariates, 23 patients on octreotide required a mean number of 8.7 (95% CI, 2.4–15.1) transfusion units compared with 21.5 (95% CI, 15.8–27.3) transfusion units for 28 patients on standard of care. Octreotide reduced the number of transfusion units by 12.8 (95% CI, 4.2–21.4) units. Patients on octreotide required a mean adjusted number of 6.1 (95% CI, 0.3–12.0) RBC transfusions and 2.6 (95% CI, 0.9–4.2) iron infusions compared with 17.1 (95% CI, 11.8–22.4) and 4.5 (95% CI, 3.1–6.0) for patients on standard of care, respectively (Table 3). In total, 16 of 23 patients (70%) on octreotide had a good treatment response compared with 4 of 28 patients (14%) on standard of care. Figure 3 distinguishes patients based on inclusion in the per-protocol analyses. Other secondary outcomes were comparable to the ITT analyses (Table 3). Analyses excluding those who died during the study year provided similar results (Supplementary Table 2).

Subgroup and Exploratory Analyses

Subgroup analyses on patients who required ≥1 RBC transfusions at baseline and on patients that used antithrombotics before randomization yielded similar results (Supplementary Table 3). Analyses with adjustments for concomitant care revealed a greater difference between both groups compared with the main analyses (16.4 [95% CI, 6.9–25.8] vs 10.2 [95% CI, 2.4–18.1]) (Supplementary Table 4). Exploratory analyses, which compared the 19 patients with and the 12 without a good response to octreotide, indicated no apparent differences between both subgroups. Patients with a good response to octreotide were more likely to have multiple angiodysplasias (18 of 19 [95%] vs 9 of 12 [75%]) and had received more transfusion units over the years (45.0 [IQR, 18.0–54.0] transfusion units vs 27.0 [IQR, 14.0–40.0] transfusion units) (Supplementary Table 5).

Discussion

In this investigator-initiated, randomized, multicenter trial, we found that octreotide is superior to standard of care in reducing transfusion requirements of patients with angiodysplasia-related anemia. Patients on octreotide required 11.0 transfusion units during the study year compared with 21.2 for those receiving standard of care. The beneficial effect became apparent within the first month and persisted consistently during the study year. Overall, 61% of patients on octreotide experienced a ≥50% decrease in transfusion requirements, which compared favorably to 19% of those who received standard of care. In parallel to the lower transfusion requirements with octreotide, patients experienced fewer bleeding episodes and required fewer health care services.

Octreotide treatment provided other benefits. Patients had a reduced need for endoscopic procedures, were less fatigued, and experienced better physical and mental health. Moreover, although octreotide-related AEs are common (65%), their mild and self-limiting nature rarely elicits treatment discontinuation. These results support the concept that octreotide should be part of the treatment algorithm for gastrointestinal angiodysplasias.

This adequately powered randomized controlled trial was designed to provide a robust point estimation of the efficacy of octreotide in patients with angiodysplasia-related anemia.[25] Octreotide reduced annual transfusion requirements by 10.2 (95% CI, 2.4-18.1) units, which aligns with the results of a recently published IPDMA.[8] There, pretreatment and posttreatment data from 11 cohorts (N = 212) revealed that somatostatin analogues reduced

Table 3. Outcomes Per-Protocol Analyses

Variable	Octreotide (n = 23)	Standard of care (n = 28)	Difference
Primary outcome[a]			
Transfusion units	8.7 (2.4–15.1)	21.5 (15.8–27.3)	12.8 (4.2–21.4)
RBC transfusion	6.1 (0.3–12.0)	17.1 (11.8–22.4)	8.6 (1.4–15.7)
Intravenous iron infusions	2.6 (0.9–4.2)	4.5 (3.1–6.0)	1.8 (0.3–3.9)
Treatment response			
Transfusion decrease ≥50%	16/23 (70)	4/28 (14)	NA
Decrease 100%	5/16 (31)	1/4 (25)	NA
Concomitant care			
Required concomitant care	3/23 (13)	11/28 (45)	NA
Endoscopic APC	2/3 (67)	7/11 (64)	
Discontinue AT	1/3 (33)	4/11 (14)	
Start other treatment	0/3 (0)	4/11 (14)	
Endoscopic procedures[a]	0.3 (−0.3 to 0.8)	1.2 (0.7–1.7)	1.0 (0.2–1.7)
Applied interventions	0.1 (−0.2 to 0.5)	0.7 (0.4–1.0)	0.5 (0.1–1.0)
Healthcare utilization[a]			
Bleeding episodes	3.4 (1.0–5.8)	8.4 (6.2–10.5)	5.0 (1.8–8.3)
Hospital admissions	0.5 (−0.3 to 1.4)	1.9 (1.1–2.7)	1.4 (0.2–2.5)
Length of stay, *d*	2.1 (−1.2 to 5.4)	6.4 (3.5–9.4)	4.4 (−0.1 to 8.8)
Emergency care	0.3 (−0.5 to 1.2)	1.8 (1.0–2.5)	1.4 (0.3–2.5)
Ambulatory care	3.1 (0.9–5.3)	6.7 (4.7–8.7)	3.6 (0.6–6.6)
Biochemical analyses			
Hemoglobin, *mmol/L*	7.2 (6.7–7.8)	6.6 (6.1–7.1)	0.6 (−0.1 to 1.3)
Ferritin, *μg/L*	183 (62–304)	155 (50–259)	28 (−132 to 189)
Patient-reported outcome measures[a]			
Fatigue (MFI-20)	58.3 (50.9–65.7)	70.2 (63.7–76.7)	11.9 (2.0–21.8)
Physical component score (SF-36)[b]	40.6 (35.9–45.2)	36.3 (32.2–40.4)	4.3 (−2.0 to 10.6)
Physical functioning	55.5 (43.8–67.2)	38.2 (28.0–48.5)	17.3 (1.6–33.0)
Role-physical	42.6 (25.6–59.6)	31.6 (16.7–46.6)	11.0 (−11.7 to 33.7)
Bodily pain	64.6 (51.3–77.9)	58.8 (47.2–70.5)	5.8 (−12.0 to 23.6)
General health	48.8 (38.6–59.0)	37.5 (28.5–46.4)	11.4 (−2.3 to 25.0)
Mental component score (SF-36)[b]	47.7 (42.6–52.7)	40.9 (36.4–45.3)	6.8 (0.06–13.6)
Vitality	51.9 (42.0–61.7)	38.4 (29.7–47.0)	13.5 (0.4–26.7)
Social functioning	68.4 (54.3–82.5)	55.3 (42.9–67.6)	13.1 (−5.7 to 32.0)
Role-emotional	56.7 (39.4–74.0)	39.7 (24.5–54.9)	17.0 (−6.1 to 40.1)
Mental health	72.1 (61.9–82.3)	59.9 (51.0–68.9)	12.2 (−1.4 to 25.8)
Adverse events			
Total number	17/23 (74)	19/28 (68)	NA
Drug-related	16/17 (94)	5/19 (26)	
Gastrointestinal	11/16 (69)	5/5 (100)	
Pain administration	8/16 (50)	0/5 (0)	
Glucose intolerance	2/16 (13)	0/5 (0)	
Anemia-related	9/17 (53)	18/19 (95)	
Other	4/17 (24)	1/19 (5)	
Mortality	3/23 (13)	2/28 (7)	NA
Unrelated to octreotide	2/3 (67)	2/2 (100)	
Unknown	1/3 (33)	NA	

Data are mean (95% CI) or n (%).
IV, Intravenous; NA, not applicable.
[a]Results were adjusted for by the covariates (respective baseline values and follow-up time in days). Patient-reported outcome measures were only adjusted for by their baseline values.
[b]Summary scores are normalized, meaning that a score of 50 resembles the mean score of the general population.

RBC transfusion requirements by 10.5. However, the proportion of patients with a ≥50% (19 of 31 [61%] vs 177 of 212 [83%]) and 100% (5 of 31 [16%] vs 109 of 212 [51%]) decrease in transfusion requirements was much lower in the current trial compared with previous cohort studies part of the IPDMA.[8]

The randomized design of our trial helps to explain these differences. Angiodysplasia-related bleeding naturally varies over time, accounting for the ≥50% reduction in transfusion units received by 6 of 31 of our control patients (19%).[26] Most studies included in the IPDMA were observational, which lowers the bar for selection bias.[10] Baseline transfusion dependency was low compared with the current study, and use of endoscopic therapy shortly before inclusion was often not mentioned.[8] Similarly, 2 nonrandomized trials reported remarkably high bleeding cessation rates after initiation of octreotide but failed to show a difference in transfusion requirements compared with external controls.[27,28] One additional randomized trial has been published on the efficacy of somatostatin analogues in angiodysplasia-related bleeding. Patient characteristics were comparable to the present study, including the relatively high transfusion requirement before participation (≥1 units per month). Similarly, transfusion requirements decreased more substantially in the intervention group compared with the placebo group (67% vs 18% reduction). However, the study was not designed for group comparisons, which explains why only 14 participants completed the study protocol.[25]

Multiple pharmacologic agents have been evaluated for angiodysplasia-related bleeding, but most do not confer benefits, including tranexamic acid and hormonal preparations.[29,30] Alternative antiangiogenic drugs include thalidomide, which suppresses plasma VEGF. A 4-month randomized clinical trial compared thalidomide (n = 28) with oral iron (n = 27) in patients with angiodysplasias.[31] Thalidomide was highly effective, as 71% experienced a >50% decrease in bleeding episodes compared with only 4% with oral iron.

However, thalidomide comes with a poor safety profile. Drug-related AEs, such as fatigue, constipation, and dizziness, were reported by 71% of patients in the aforementioned trial.[31] Moreover, studies of longer duration have established that thalidomide causes sensorimotor length-dependent axonal neuropathy in ∼80% of patients after 6 months of treatment.[32] These safety concerns preclude the prolonged use of thalidomide. Octreotide compares favorably here. Although mild treatment-emergent AEs are frequent (20 of 31 [65%]), this led to discontinuation in only 6%.[8]

Octreotide is effective in most patients with angiodysplasia-related anemia, but the benefits are not uniform. Indeed, 12 of 31 patients (39%) had a suboptimal response (<50% reduction in transfusion requirements), including 7 who remained on octreotide for the entire study period. In contrast to earlier studies, the location of angiodysplasias did not determine response to octreotide.[8] In fact, exploratory analyses based on treatment response did not reveal any apparent differences between groups (Supplementary Table 5). Patients who responded to octreotide were somewhat more likely to have multiple angiodysplasias (18 of 19 [95%] vs 9 of 12 [75%]) and had received a higher total number of transfusion units (45 vs 27).

Because octreotide is believed to possess antiangiogenic properties, it might be more effective against multiple, smaller angiodysplasias compared with 1 or a few larger lesions. Correspondingly, 2 previous studies on the efficacy of octreotide endoscopically reassessed lesions after treatment. Both found that smaller angiodysplasias had mostly disappeared, and larger lesions had decreased in size.[30,33] Perhaps select patients would benefit more from combination therapy with endoscopic APC rather than octreotide alone.[34]

Identification of biomarkers would be beneficial to guide angiodysplasia management, because these are currently lacking.[2,9] Angiogenic factors could potentially fulfill this role, because several studies on the efficacy of octreotide in hepatocellular carcinoma found that the difference in VEGF levels independently predicted tumor progression.[35,36] Moreover, patients with angiodysplasias that responded to thalidomide treatment had a more significant decrease in VEGF than those who did not.[31]

Mortality was higher in the octreotide group (5 of 31 vs 2 of 31) (Figure 1). The cause of death was known for 4 of 5 patients and deemed unrelated to the study drug, especially because 2 patients had previously discontinued octreotide (Supplementary Figure 4). Angiodysplasias often occur secondary to heart and renal disorders, emphasizing the frailty of this patient group.[37,38] High doses of continuous intravenous infusion with octreotide infrequently cause cardiac conduction abnormalities.[39] Although cardiac arrhythmias have not been documented after intermittent therapy, some case reports describe the occurrence of arrhythmia in those with long-QT syndrome-associated genetic variants.[39]

In our cohort, there was a median delay of 4 years (Table 1) between the onset of anemia and the endoscopic diagnosis of angiodysplasias, even though these vascular malformations constitute the leading cause of small-bowel bleeding and the second leading cause of gastrointestinal bleeding among the elderly.[40] Conservative measures are inadequate, as patients in our randomized controlled trial received ∼35 transfusion units and required at least 3 endoscopic procedures with APC in the years (one or multiple) preceding enrollment (Table 1). Apparently, our current clinical practices are insufficient to identify these patients and provide proper care.[6]

We found that patients on octreotide were less fatigued than patients on standard of care (56 of 100 vs 69 of 100 on MFI-20) and possessed better physical (42 of 100 vs 37 of 100 on SF-36) and mental (49 of 100 vs 42 of 100 on SF-36) health.[41] Patients treated with octreotide experienced more fatigue (42 of 100 pm the MFI-20) compared with their peers in the general population but had similar SF-36 physical (42 of 100) and mental (52 of 100) health scores.[20] Moreover, patients on octreotide required fewer health care services, including endoscopic procedures, than

those on standard of care (Table 2). These differences help to explain why previous research established cost-effectiveness of octreotide despite the relatively high price (€824 per 20 mg of Sandostatin LAR in the Netherlands).[6]

The main strength of our study is the randomized clinical trial design that, as a result of its multicenter approach, tapped into a diverse population of patients from a wide range of health care settings. This favors the generalizability of the obtained results. There was complete follow-up, and drug adherence was assured by deploying a medical homecare service.

A limitation of this study is that patients and physicians were not blinded to treatment allocation. As a result, 5 patients allocated to standard of care switched to octreotide during the trial. Moreover, concomitant care (including APC) was more frequently used for patients assigned to standard of care (14 of 31 [45%]) than for those on octreotide (4 of 31 [13%]), possibly skewing the results. Indeed, analysis with corrections for concomitant treatment revealed an even larger difference in transfusion requirements between both groups (between-group difference in the main analyses: 10.2 [Table 2] vs between-group difference in the adjusted analyses: 16.4 [Supplementary Table 4]). Concomitant care might also account for the slight decrease in transfusion requirements experienced by patients on standard of care between weeks 28 and 52 (Figure 2).

Another limitation was that patients on octreotide required more transfusion units in the year before study participation (22.6 vs 18.0). Analyses of covariance were used to control for this difference.

Finally, compared with earlier studies, a relatively high dose of octreotide was used. A previous meta-analysis found no association between the dose of octreotide and treatment effects, but AEs were more common at a higher dose.[8] This could explain why we reported substantially more drug-related AEs compared with previous research (65% vs 18%). However, this difference could also be related to the retrospective design of these studies, because the discontinuation rate after AEs was comparable (6% vs 5%).[8] Nevertheless, if patients experience AEs that are not adequately resolved by adjustments in antidiabetes medications (as glucose dysregulation was experienced by 20% with diabetes mellitus) or by pancreatic enzyme supplementation (as gastrointestinal AEs were reported by 16%), dose reduction should be contemplated.[14]

The number needed to treat of only 2 for 1 patient to experience a reduction in transfusion requirements of at least 50% supports the use of octreotide in patients with transfusion-dependent, angiodysplasia-related bleeding. Based on our findings, octreotide LAR should be considered if (1) rebleeding occurs after APC, (2) if bleeding persists after endoscopic treatment, or (3) if endoscopic treatment is contraindicated. Initiation of octreotide may be combined with a second course of APC if the patient has few or actively bleeding angiodysplasias accessible by endoscopy.[34]

Conclusion

Octreotide treatment effectively reduces the transfusion requirements and health care utilization, including endoscopic procedures, of patients with angiodysplasia-related anemia. Physicians should consider octreotide if endoscopic treatment is insufficient or unfeasible.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.12.020.

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Conflicts of interest

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Data Availability

Deidentified individual participant data and a data dictionary defining each field in the set will be available upon reasonable request to Lia Goltstein and subjected to an appropriate data sharing agreement.