EVIDENCE-BASED GI
AN ACG PUBLICATION

Stemming the Tide: Is Long-Acting Octreotide Injection Better Than Standard of Care for Angiodysplasia-Related GI Bleeding?

Philip N. Okafor, MD, MPH

Senior Associate Consultant, Department of Gastroenterology, Mayo Clinic, Jacksonville, Florida

Philip N. Okafor, MD, MPH
Associate Editor

This summary reviews reviews Goltstein L, Grooteman KV, Bernts LH et al. Standard of care versus octreotide in angiodysplasia-related bleeding: a multicenter randomized control trial. Gastroenterology 2024;155: 690-703.

Correspondence to Philip N. Okafor, MD, MPH, Associate Editor. Email: EBGI@gi.org

Keywords: GI hemmorrhage, small bowel bleeding, angiectasia

STRUCTURED ABSTRACT

Question: Does 40 mg octreotide long-acting release injected intramuscularly every 28 days reduce transfusion requirements compared to standard of care in patients with recurrent bleeding from gastrointestinal (GI) angiodysplasia?

Design: Randomized, open-label, multicenter, parallel-group, superiority study conducted between September 2015 and April 2021.

Setting: Seventeen hospitals (15 peripheral and 2 academic medical centers) in the Netherlands.

Patients: Adults with transfusion-dependent anemia due to endoscopically

confirmed angiodysplasias who had received at least 1 endoscopic treatment and at least 4 transfusion units (parenteral iron or red blood cell transfusions) in the preceding year.

Intervention: Participants received 2 intramuscular long-acting octreotide intramuscular [IM] injections of 20 mg (40 mg in total) every 28 days for 52 weeks versus standard of care, which was defined as oral iron supplementation.

Patients in both groups could receive endoscopic therapy with argon-plasma coagulation (APC) of angiodysplasias, discontinuation of antithrombotics, and tranexamic acid. If standard of care was deemed inadequate in this open-label study, then patients could be switched to octreotide, but this was considered a protocol violation.

Red blood cell (RBC) transfusion was performed per the following thresholds: individuals with severe co-morbidities and hemoglobin (hgb) <9.5g/dl; individuals with symptomatic anemia and fewer co-morbidities and hgb <8 g/dl; and healthy individuals with asymptomatic anemia with hgb <6.5g/dl.

Outcomes: The primary outcome was the mean difference in blood and parenteral iron requirements (units) between the intervention and standard-of-care group. Blood requirement was defined as red blood cell transfusions per 500 cc or packed cells, while iron requirements were defined as intravenous iron infusions per 500 mg. Secondary outcomes included the proportion of participants in both groups that experienced ≥ 50% (good response) and 100% (full response) reduction in the number of transfusion units received during the study year compared to the baseline. Other secondary outcomes included serum hemoglobin and ferritin levels.

Data Analysis: Analyses were performed based on both intention-to-treat and per-protocol. Analyses of covariance were used to compare the number of transfusion units, endoscopy procedures, bleeding episodes, healthcare utilization, fatigue levels, and quality of life.

Funding: The trial was funded by Novartis between 2015 and 2019, and then by the Netherlands Organization for Health Research and Development between 2019 and 2022.

Results: Sixty-two patients were randomized: 52% male; mean age-72 years old; location of angiodysplasia-small intestine (87%), colon (48%), stomach (27%);

and concurrent antiplatelet or anticoagulant use was approximately 80% in both groups. No patients withdrew from the study but 7 died before study completion.

During the 52-week treatment period, octreotide-treated patients received a mean adjusted number of transfusion requirements of 11 vs 21.2 in the standard of care group (difference of 10.2, 95% 2.4-18.1, *P*=0.01) (Table 1). A good treatment response, defined as ≥50% reduction in transfusion requirements, was observed in 61% of patients in the octreotide group vs 19% of patients in the standard of care group. A full response, defined as 100% reduction in transfusion requirements, was observed in 19% of the octreotide group vs 3% in the standard-of-care group. Mean endoscopy utilization was also lower in the octreotide group (0.3 vs 1.2, adjusted difference of 0.9; 95% confidence interval [CI] 0.3-1.5), as were the number of bleeding episodes (adjusted difference 3.2; 95% CI, -0.2 to 6.6). Octreotide-related adverse events (AEs) included pain at the site of administration, diarrhea, abdominal pain, and glucose intolerance. Serious AEs were reported in 2 patients on octreotide including acute cholangitis and symptomatic hypoglycemia.

	Octreotide (n=31)	Standard of Care (n=31)	Difference
Transfusion units	11.0 (5.5–16.5)	21.2 (15.7–26.7)	10.2 (2.4–18.1) *P=0.12
RBC transfusion	8.2 (3.2–13.2)	16.8 (11.8–21.8)	8.6 (1.4–15.7)
IV iron transfusions	2.8 (1.3–4.3)	4.6 (3.1–6.0)	1.8 (0.3–3.9)
Transfusion decrease ≥50%	19/31 (61)	6/31 (19)	13/31 (42)
Transfusion decrease 100%	5/19 (26)	1/6 (17)	
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)

Table 1: Octreotide vs standard of care (outcomes of intention-to-treat analysis).

IV, intravenous; RBC, red blood cells.

COMMENTARY

Why Is This Important?

In the last year, the therapeutic landscape for angiodysplasia-related GI bleeding has been met with new level 1 evidence from international randomized trials that medical therapies including thalidomide.[1,2] and octreotide improve outcomes. In this multicenter trial from the Netherlands Goltstein et al, provide the best evidence so far that the somatostatin analog, octreotide, at a dose of 40 mg administered every 28 days reduces transfusion requirements compared to the standard of care.

Somatostatin analogs are believed to reduce angiodysplasia-related GI bleeding by decreasing blood flow to the splanchnic vasculature in the GI tract. Prior studies on somatostatin analogs have mostly been small and observational in design.[3] Endoscopic therapies, hitherto regarded as the mainstay of treatment, are associated with high rebleeding rates. Chen et al, in a recent study, showed that thalidomide reduced the risk of recurrent bleeding at doses of 50 mg and 100 mg after treatment for 4 months, compared with placebo.[2] While the antiangiogenic effects of thalidomide led to a reduction in rebleeding risk, they also reported side effects such as constipation, limb numbness, and dizziness in 71% of patients which could potentially impact its use in the real world.[2] Concerns about axonal neuropathy with long-term thalidomide use also exist.[4] Importantly, in the United States, thalidomide may not be as widely available for prescription. Due to its widespread use, octreotide may be easier to obtain and its availability in long-acting depot formulation may increase patient compliance. Importantly, in this study, patients on antithrombotic therapy, including antiplatelets and anticoagulation monotherapy, were included.

Key Study Findings

Octreotide treatment was associated with a significant reduction in the number of transfusion requirements by 10.2 (95% CI: 2.4-18.1, P=0.01) among patients with angiodysplasia-related GI bleeding. This benefit was obvious as early as the first month of treatment and persisted for the duration of the study.

In addition, patients in the octreotide group were more likely to achieve a full treatment response with complete resolution of need for transfusion. Severe adverse events were seen in 2 patients receiving octreotide, and the study drug was discontinued in 1 of these patients.

Caution

From a study design perspective, one limitation of the trial was the lack of blinding. As such, the investigators and patients were aware of the treatment. In addition, the study used a relatively high dose of octreotide of 40mg IM, which the investigators allude could explain higher dose-related AEs compared to

prior studies. High-dose continuous octreotide infusion has also been associated with cardiac arrhythmia, but this has not been reported among patients with intermittent dosing which was used in this study. Race and ethnicity data were also not reported which may limit secondary generalizability.

My Practice

In my clinical practice, we offer deep enteroscopy to patients with angiodysplasia-related GI bleeding. Despite the availability of this endoscopic resource, we still see a significant number of readmissions especially among the subgroup of patients on anticoagulation and/or antiplatelet therapy. The study by Golstein et al offers promise that these patients have lower transfusion requirements with octreotide use which is practice changing. Octreotide offers an option that can be easily prescribed using a monthly depot formulation with side effects that are mostly self-limiting, which increases medication adherence and compliance. Based on the recommendations of the investigators, I will probably use octreotide IM at the higher dose for recurrent bleeding after argon plasma coagulation, or when endoscopy is contraindicated. For practitioners that don't have access to double-balloon enteroscopy, they may consider this first-line therapy after confirming small intestinal arteriovenous malformations by capsule endoscopy if patients require recurrent RBC transfusions, especially if the patient is using antithrombotic agents that can't be discontinued. I'd reserve thalidomide for patients who fail octreotide therapy since it's harder to access and is associated with more adverse events.

For Future Research

We now have 2 adequately powered clinical trials supporting the benefits of thalidomide and octreotide for angiodysplasia-related GI bleeding.[1,2] Future studies could consider head-to-head comparisons of thalidomide and octreotide, including efficacy in reducing angiodysplasia-related GI bleeding and side effect profiles. More research is needed on the efficacy of lower octreotide doses and the feasibility of combination with thalidomide.

Conflict of Interest

Dr. Okafor reports no conflicts of interest.

Note: One of the authors of the published article are active on social media. Tag them to discuss their work and this EBGI summary.

@joostphdrenth

Joost PH Drenth

REFERENCES

1. Okafor P. Overt evidence for the efficacy and safety of thalidomide in gi bleeding from small intestinal angiodysplasia. Evidence-Based GI Dec 13 2023. https://gi.org/journals-publications/okafor_December2023/
2. Chen H, Wu S, Tang M, et al. Thalidomide for recurrent bleeding due to small-intestinal angiodysplasia.

N Engl J Med 2023;**389** (18):1649-1659.
3. Bon C, Aparicio T, Vincent M, et al. Long-acting somatostatin analogues decrease blood transfusion requirements in patients with refractory gastrointestinal bleeding associated with angiodysplasia. Aliment Pharmacol Ther, 2012**;36**(6):587-93.
4. Chaudhry V, Cornblath DR, Corse A, et al. Thalidomide-induced neuropathy. Neurology, 2002;**59**(12):1872-5.