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Commentary

Thalidomide in gastrointestinal angiodysplasia: translating systematic evidence into clinical practice

Junaid Khan, MD[1,*], Daniel K Daniels, MD[2]

[1]Department of Internal Medicine, TidalHealth Peninsula Regional, MD, USA

[2]Department of Gastroenterology & Hepatology, TidalHealth Peninsula Regional, MD, USA

*Author for correspondence:
Email: Junaid.khan@tidalhealth.org

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Introduction

Gastrointestinal (GI) angiodysplasia represents one of the most vexing diagnostic and therapeutic challenges in clinical gastroenterology. These arteriovenous malformations, predominantly affecting the cecum, right colon, and small bowel, are the most common vascular lesions of the GI tract and account for a disproportionately large share of obscure GI bleeding, particularly in elderly patients [1]. Despite their clinical significance, the management landscape remains fragmented, with no FDA-approved pharmacological therapy and limited long-term efficacy data for available interventions.

GI Angiodysplasia (GIA) is responsible for almost 5% cases of all GI bleeding. The common risk factors associated with the development of angiodysplasia include older age (>60 years of age), chronic kidney disease, liver cirrhosis, aortic stenosis, and diabetes [2]. Their high recurrence rate significantly impacts the quality of life, as evidence has shown that up to 20% of patients experience rebleeding within 30 days of discharge, leading to increased medical costs [3].

This commentary expands on several dimensions of the review that merit deeper discussion: integration of important new 2024–2025 developments which includes the OCEAN trial establishing octreotide's role, pomalidomide's emergence as a next-generation immunomodulatory option, and early signals for sirolimus as an mTOR-targeted approach, and the roadmap for future clinical trials.

New Evidence: The Evolving Pharmacotherapy Landscape (2024–2025)

Since the literature search cutoff of the reviewed systematic review (February 2024), several important developments have reshaped the pharmacotherapy landscape for GI angiodysplasia, offering important context for positioning thalidomide.

The OCEAN Trial and Octreotide's Consolidation

The OCEAN trial is a multicenter randomized controlled trial comparing Octreotide 40 mg monthly against standard care, including endoscopic argon plasma coagulation, and deserves recognition as the study that arguably did most to consolidate somatostatin analogs as the preferred pharmacological first-line option for refractory GIA. This multicenter, open-label randomized controlled trial (RCT) from 17 Dutch hospitals enrolled 62 patients with transfusion-dependent angiodysplasia-related anemia and randomized them to long-acting release (LAR) octreotide 40 mg intramuscularly every 28 days versus standard of care, including endoscopic therapy. The results were unambiguous: octreotide significantly reduced mean transfusion units by 10.2 (95% CI 2.4–18.1; p=0.012) and reduced annual endoscopic procedures by 0.9 (95% CI 0.3–1.5). This trial suggests that octreotide can be considered if rebleeding occurs after argon plasma coagulation (APC), bleeding persists after endoscopic treatment, or endoscopic treatment is contraindicated [4]. A concurrent

review published in the *United European Gastroenterology Journal* synthesized these developments and concluded that somatostatin analogs should be considered first-line pharmacotherapy, given their efficacy and more favorable tolerability profile compared to thalidomide, which represents a significant shift in consensus thinking [5]. The OCEAN trial fundamentally positions octreotide as a preferred first-line pharmacological choice, with thalidomide occupying a clearer role as second-line therapy for patients who fail or cannot tolerate somatostatin analogs.

Pomalidomide: A Next-Generation Immunomodulatory Option

Pomalidomide, a third-generation immunomodulatory imide drug (IMiD) structurally related to thalidomide, has emerged as a therapeutic candidate for vascular malformation-related bleeding. The landmark PATH-HHT trial, published in the *New England Journal of Medicine* (September 2024), demonstrated that pomalidomide significantly reduced epistaxis severity scores in patients with hereditary hemorrhagic telangiectasia (HHT) in a multicenter, double-blind, placebo-controlled design.

The subsequent PATH-HHT ATLAS longitudinal study [6] evaluated long-term outcomes in patients who continued pomalidomide after the main trial. While pomalidomide demonstrated sustained effectiveness for epistaxis, its impact on gastrointestinal bleeding in HHT was less consistent, with the study noting that GI bleeding outcomes were more variable and may require higher or longer treatment durations. This is mechanistically plausible: pomalidomide shares thalidomide's anti-VEGF (vascular endothelial growth factor) and immunomodulatory properties with potentially reduced peripheral neuropathy risk, though its thromboembolic profile in the HHT population remains an active safety concern requiring surveillance [6]. Whether pomalidomide could supplant thalidomide in the treatment of sporadic GI angiodysplasia outside the HHT context remains an important and unanswered research question.

Sirolimus: A Novel mTOR-Targeted Approach

A further emerging development is the early-stage investigation of sirolimus, an mTOR inhibitor, for the treatment of GI angiodysplasia-related bleeding [7]. A 2025 publication in the *World Journal of Gastroenterology* reported a self-controlled study of 11 patients with GI angiodysplasia treated with oral sirolimus (initial dose of 0.8 mg/m² daily, with trough levels of 5–10 ng/mL) [7]. The average number of bleeding episodes was significantly reduced at both 3 and 6 months, hemoglobin levels improved, and transfusion requirements decreased, with only mild adverse effects that resolved without treatment discontinuation.

While thalidomide primarily targets the VEGF pathway, sirolimus inhibits mTOR, potentially acting through broader mechanisms including suppression of cell proliferation and vascular inflammation. This mechanistic distinction could be particularly relevant in patients where VEGF-targeted therapy has failed. However, the evidence base for sirolimus remains very limited to a single small, uncontrolled series without a comparator arm. Multi-center trials with adequate power are urgently needed before sirolimus can be considered even as a rescue option. Notably, mTOR inhibitors have also been associated with vascular ectasia in certain transplant contexts, highlighting that their role in GI angiodysplasia requires careful investigation.

Bevacizumab: A Last-Resort Option

Bevacizumab is a humanized anti-VEGF monoclonal antibody that blocks VEGF from binding to its endothelial receptors, thereby suppressing angiogenesis. Best known as an oncological agent, it has also shown promise in vascular conditions, including diabetic retinopathy, HHT, and gastric antral vascular ectasia (GAVE) [5].

Its track record in GIA, specifically, however, remains thin. The available evidence consists almost entirely of case reports and small retrospective series, a body of literature that, while reporting favorable outcomes, is subject to obvious publication bias. When used in GIA, it is typically administered at sub-oncological doses: 5 mg/kg every two weeks as induction over two months, followed by maintenance dosing, with the option of dose escalation or top-up infusions in partial responders [2,8].

Safety concerns are real, which include venous thromboembolism, bowel perforation, and paradoxical bleeding, all recognized risks — though a recent meta-analysis in the HHT setting did not demonstrate a significantly elevated adverse event rate. For the frail, comorbid patients who typically present with refractory GIA, that reassurance only goes so far [9].

Ultimately, bevacizumab's place in the treatment algorithm is defined as much by what we do not know as by what we do. The evidence base is insufficient to support routine use, and the cost is considerable. It remains, at present, a compassionate-use option for patients who have failed both somatostatin analogs and thalidomide. It is a last resort in a field that still badly needs better options at every tier of its treatment ladder.

Patient Selection and a Proposed Treatment Algorithm

Integrating the evidence from the focal systematic review with post-2024 developments, a rational treatment algorithm for the pharmacotherapy of refractory GI angiodysplasia is now beginning to emerge. For patients with transfusion-dependent, endoscopy-refractory angiodysplasia, octreotide LAR should be considered first-line pharmacotherapy. Thalidomide represents an evidence-based second-line choice supported by two positive RCTs for patients who fail or cannot tolerate somatostatin analogs [1], provided there is no pre-existing peripheral neuropathy and appropriate risk evaluation and mitigation strategy (REMS) enrollment is completed.

Anticoagulant use, particularly warfarin, identified as the strongest independent predictor of hemorrhage in GI angiodysplasia, should be systematically documented and, where clinically feasible, addressed as part of bleeding risk management prior to initiating pharmacotherapy [1]. The focal review's acknowledgment that inconsistent anticoagulant reporting limits inter-study comparability underscores the need for standardized covariate reporting in future trials.

Future Research Directions

The synthesis of the Khan *et al.* review and the 2024–2025 evidence landscape identifies several urgent research priorities [1]. First, head-to-head comparative trials of thalidomide versus octreotide LAR in patients with refractory GI angiodysplasia are now feasible and scientifically justified. Such a trial would directly inform clinical decision-making regarding the sequencing and substitution of these two agents. Second, dose-optimization studies of thalidomide, particularly evaluating whether 50 mg can achieve

durable responses with reduced neuropathy risk compared to 100 mg, should be pursued as prospective dose finding trials [10].

Third, biomarker-stratified studies that incorporate VEGF levels and endothelial activation markers could identify patient subgroups most likely to respond to thalidomide, supporting a precision medicine approach. Fourth, standardization of outcome definitions through consensus among gastroenterological societies is a prerequisite for meaningful cross-study comparison and meta-analysis. A validated, disease-specific bleeding severity score for GI angiodysplasia would be a transformative tool. Fifth, prospective neuropathy surveillance studies that mirror oncology methodologies (e.g., serial nerve conduction assessments) should be embedded in all future thalidomide trials.

Conclusion

The management of refractory GIA is improving. The OCEAN trial has placed octreotide on firmer evidential ground [4]. The RCT by Chen *et al.* [10] has established thalidomide as an evidence-based second-line option with well-characterized toxicity constraints. Pomalidomide, sirolimus, and bevacizumab offer distinct alternatives, though each requires prospective validation. For a patient population that is typically elderly, frail, and has multiple comorbidities, the convergence of RCT data and emerging pharmacological agents offers genuine cause for optimism, and this progress must be matched by a commitment to well-designed, adequately powered trials.

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