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EDITORIAL



# Pharmacotherapy for Gastrointestinal Angiodysplasia: is it effective?

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## 1. Introduction

Gastrointestinal (GI) angioectasias, or angiodysplasias (ADs), are vascular malformations that have endothelial lining which may be friable [1,2]. These anomalies can be found along the whole of the GI tract [2], often at multiple sites, and account for 7–10% of the cases of GI bleeding [3]. Clinically, their presentation is heterogeneous with iron-deficiency anemia being one of the most common presentations, but also melena, rectal bleeding, or aspecific GI symptoms, depending on the location and extension within the GI tract, number, and size of lesions [1,4]. Whilst the majority of bleeding episodes resolve spontaneously, the rebleeding rate can be up to 43% [5]. Older age (>50 years old), valvular heart disease, anticoagulants, and/or concomitant antiplatelets therapy, and renal failure [2] are factors commonly associated with increased risk of bleeding from ADs.

The treatment paradigm of angioectasia includes supportive therapy, comprising iron supplementation (oral or intravenous) and/or blood transfusion based on the severity of anemia [1,2]. Endoscopic ablation using argon plasma coagulation (APC) is indicated in cases of marked anemia despite supportive therapy. In a minority of cases, who may present with hemodynamic compromise, radiological embolization, or surgery [1,2].

The management of GI-ADs can be challenging [1,2]. Notably, between 57% and 80% of ADs are situated in the small intestine [2] usually not reachable by means of traditional bidirectional endoscopy [2]. Furthermore, up to 60% of patients who undergo endoscopic treatment for GI-ADs, can experience rebleeding within 1-year post-treatment [6]. And, as previously mentioned, patients with comorbidity have a higher risk of having ADs but also recurrent bleeding episodes. This results in multiple hospitalizations and endoscopies, use of healthcare resources, costs and with a negative impact on the patient's quality of life. In these settings, the option of a medical-pharmacological treatment is particularly appealing in the comorbid patient groups [1,2].

In this article, we review the most recent literature on the pharmacological treatment options available for GI-ADs.

## 2. Pathophysiology of GI AD

Although the pathophysiology of GI-ADs is not well understood, development of ADs has been attributed to the mechanical and the angiogenic theories [6]. According to the former, ADs form due to the obstruction of submucosal veins caused by increased pressure within the bowel wall, leading to hypoxia [5]. Consequently, ADs are more frequently found in the right colon rather than the left hemicolon. The angiogenic theory is based on the fact that the hypoxic stimulus, often related to patients comorbidity, triggers increased vascular endothelial growth factor (VEGF) release and stimulating neovascularisation and further ADs formation [1,4]. Notably, patients with ADs often exhibit elevated levels of plasma VEGF expression [5,6], which significantly decrease in responders to VEGF inhibitors therapy such as thalidomide [7].

## 3. Pharmacological management options

There have been several pharmacotherapy agents that have been tried for GI AD's including somatostatin analogues (SSAs), thalidomide, estrogen derivatives, tranexamic acid and bevacizumab.

The most studied therapies are thalidomide and SSAs. In Table 1 are summarized the therapeutic options for GI-ADs.

### 3.1. Somatostatin analogues

Somatostatin, a cyclic peptide naturally secreted by D-cells within the gastrointestinal mucosa, primarily inhibits gastric acid, bile, and pancreatic secretion. SSAs, namely Octreotide and Lanreotide, act as down-regulators of VEGF, thereby reducing angiogenesis and AD-associated bleeding. Additionally, SSAs are believed to decrease duodenal and splanchnic blood flow, increase vascular resistance, and enhance platelet aggregation [1].

Long-acting SSAs are preferred over native somatostatin due to their significantly longer half-life. Native somatostatin has a half-life of 1–3 minutes due to rapid enzymatic digestion by peptidases in the plasma and liver, whereas Octreotide has an estimated half-life of 1.7–1.9 hours, and Lanreotide 2.5

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Table 1. Summary of the pharmacological options for gastrointestinal angiodysplasias.

| Medication | | Recommended Dose | Mechanism of action | Adverse Events |
|---|---|---|---|---|
| Somatostatin Analogues | Lanreotide<br>Octreotide LAR | SC, 60–120 mg every 4–6-week<br>IM, 20–90 mg every 4–6-week<br>IM, 10–40 mg monthly | Decreases duodenal and splanchnic flow through vasoconstriction, increase platelet aggregation, reduces the nutrient and oxygen supply required for angiogenesis. Several growth factors are inhibited, including VEGF. | Very Common (>10%)<br>• Diarrhoea<br>• Gallstones<br>Common (1–10%)<br>• Hypoglycaemia<br>• Thyroid disorders/dysfunction<br>• Flatulence<br>• Abdominal pain<br>• Nausea and Vomit<br>• Headaches<br>• Injection site reactions<br>• Fatigue |
| Thalidomide | | Oral, 50–300 mg daily for 4–6 months | Inhibitor of VEGF, β-fibroblast growth factor and suppressor of tumor-necrosis factor. | Very Common (>10%) and Common (1–10%)<br>• Fatigue and somnolence<br>• Constipation<br>• Neutropenia, Thrombocytopenia<br>• Embolism and thromboembolism<br>• Peripheral edema<br>• Peripheral neuropathy (>6 months of treatment)<br>• Teratogenic |

Abbreviations: SC, sub-cutaneous; IM, intra-muscular; GI-ADs, gastrointestinal-angiodysplasias; RCT, randomized-controlled trial; Hb, hemoglobin; VEGF, vascular endothelial growth factor; SSA, somatostatin analogues; LAR, long-acting release.

hours [8]. SSAs have emerged as a potential means to prevent mid/long-term rebleeding in GI-ADs, with several studies demonstrating their efficacy [1,9]. Specifically, monthly administration of SSAs intramuscularly, has led to a significant reduction in the transfusion requirements and bleeding episodes in patients with refractory or recurrent bleeding [8]. These findings were confirmed by an individual patient data meta-analysis [3] on 212 patients from 11 studies, which demonstrated a significant reduction in blood transfusion requirements from a mean value of 12.8 to 2.3 units with SSAs administration. Notably, 51% of the patients did not require any transfusions during the study period, and 83% reduced their transfusion requirements by at least 50% [3]. Sub-analysis showed that SSAs were the most effective in patients with GI-ADs-related small bowel bleeding [10], and that Octreotide was more effective to Lanreotide [3]. However, many of the studies included were heterogenous in terms of cohort size, inclusion criteria, study design, SSAs type and route of administration.

Further evidence in support of SSAs efficacy comes from a recently published large multicentre RCT comparing Octreotide-LAR (long-acting release) 40 mg every 28 days with standard of care in patients with GI-ADs-related transfusion-dependent anemia [10], with about half of them having ADs at multiple sites and 87% with small bowel ADs. Patients receiving Octreotide had significantly lower transfusion requirements (11.0 units vs 21.2 units), with 61% achieving at least a 50% reduction in the transfusions compared to baseline, compared to only 19% in the standard of care group [10].

[9] Adverse events (AEs) of SSA are, reported in 25–65% of patients, and are mostly described as mild; they include diarrhea, gallstones, injection site reactions, and glucose intolerance [10]. Serious (AEs) necessitating therapy discontinuation, such as thrombocytopenia, renal impairment, heart failure and poor glycemic control, occurred in only 5–6% of the patients [10].

### 3.2. Thalidomide

Thalidomide is an inhibitor of angiogenesis through VEGF and β-fibroblast growth factor while also suppressing tumor-necrosis factor [7]. In GI-ADs treatment, it is administered orally in daily doses (50–300 mg), for a duration spanning from 1 to 6 months, most commonly 4 months, as it has been shown to have a lasting effect also after discontinuation [11]. Over the past two decades, numerous studies, including RCTs, have highlighted its beneficial effects on GI-ADs. Thalidomide, when used as either second line [7] or third-line treatment [12], after endoscopy and/or SSAs, was shown to be more effective compared to standard support therapy in reducing the transfusion requirement as well as increasing the mean hemoglobin levels. Notably, a large, multicentre, double-blind RCT [11] investigated the efficacy of thalidomide in reducing bleeding in a large cohort of patients with known GI-ADs. A total of 150 patients were randomly allocated into three groups receiving 100 mg or 50 mg thalidomide daily or placebo for 120 days [11]. At 1-year follow-up, 68.6%, 52% and 16% of the patients had a reduction in the number of bleeding episodes of at least 50% when receiving 100 mg thalidomide, 50 mg thalidomide and placebo, respectively [11].

AEs were frequently reported in patients receiving thalidomide in this study, ranging from 68.6% to 55.1% based on the dose (100 mg and 50 mg respectively), with 3% of patients discontinuing therapy due to AEs [11]. Consistent with previous studies [7], most AEs were mild-moderate, and included fatigue, constipation, dizziness, and peripheral edema. However, prolonged treatment with higher doses and in older patients has been associated with neutropenia, sinus bradycardia, deep vein thrombosis (1–3%) as well as neurological AEs such as sensorimotor length-dependent axonal neuropathy (severe form in 3–5%), somnolence, hearing loss, ataxia, and tremors in a significant proportion of patients [13].

### 3.3. Other therapies

Hormonal therapy has been proposed to reduce the GI-AD bleeding rate by contributing to hemostasis and decreasing fibrinolysis [1]. However, after some first promising studies, its efficacy in preventing GI-ADs bleeding was opposed in a 2001 study, which showed no differences compared to placebo [14].

There has been minimal investigation of the use of tranexamic acid (TXA) in the treatment of GI-ADs. However, the worldwide multicentre HALT-IT trial showed that TXA did not significantly reduce the risk of rebleeding or death from GI bleeding within 28 days of initial presentation [15].

Recently, Bevacizumab, a monoclonal antibody against VEGF, has been investigated as possible treatment. First used in patients with hereditary hemorrhagic telangiectasia (HHT), Bevacizumab reduced transfusion dependency in these patients [16]. In a study by Albitar *et al* [16], 21 patients with bleeding GI-ADs were administered IV Bevacizumab. After 6 and 12 months of treatment, the median transfusion requirements reduced significantly [16]. However, although effective, it has been associated with a 5.4% rate of bowel perforation [1] and a higher risk of thromboembolic events.

## 4. Expert opinion

Based on the available literature, both SSAs and thalidomide are effective in reducing bleeding episodes and transfusion requirements associated to GI-ADs bleeding. However, there are no head-to-head comparison studies, and there is a lack of international consensus or guidelines on the management of this complex group of patients.

The current evidence supports their use in clinical practice for the treatment of recurrent and/or refractory GI-ADs related bleeding. A personalized treatment approach should be advocated, where the patient history, clinical presentation, and endoscopic assessment (including traditional bidirectional endoscopy, capsule endoscopy and enteroscopy) help to guide the use of these pharmacological therapies either adjunctively with endoscopy or with standard supportive care alone. The role of combination therapy in GI-ADs has been explored by Chetcuti et al. in a retrospective cohort study showing that patients managed combining SSAs and endoscopic intervention had significantly higher hemoglobin levels (11 g/L vs 3.2 g/L) and significantly lower mean numbers of bleeding episodes compared to those receiving endoscopic therapy alone [17]. However, SSAs are costly (estimated cost for a monthly dose of Octreotride is between 614 and 1026 €) [9], hence careful consideration is required rather than widespread use.

The clinical and cost implications have been compared between SSA with endoscopic ablation, endoscopy alone and with conservative management with iron and blood products. In the study by Tai et al. [9], the bleeding episodes reduced in the combination group compared to the other arms, suggesting that there is additional clinical benefit to this premorbid group with a comparable cost. In this study [9], when used in combination, the use of SSA is cost neutral as there was no significant difference in the cost of managing small bowel ADs with standard treatment (supportive and endoscopy on demand) compared to combination therapy at 1 year follow-up.

The patients with the combination group were noted to be older with a higher Charlson Comorbidity Index (CCI) [9]. The repeated attendances to hospital negatively impacts on the quality of life of these already premorbid patients. Hence arguably the use of SSA also confers a holistic benefit to this group of patients.

A 2015 study on the cost-effectiveness of SSAs as treatment of GI-ADs-related bleeding, found that the cost of the management of patients dropped by 61.5% due to a reduction in the number of hospital admissions, endoscopies, and blood transfusions [18]. Conversely, the study by Gutierrez et al. [4] based on their clinical experience on 35 patients, suggests the benefit given by the reduction in transfusions and hospitalization does not compensate for the cost of SSAs.

In terms of safety, both treatments are associated with frequent, mostly mild AEs (see Table 1) and exhibit similar discontinuation rates. However, SSAs appear to have a better safety profile than thalidomide, especially in the longer-term, and therefore should be preferred for chronic treatment in older and premorbid patient. Indeed, one major concern regarding prolonged thalidomide use is the common (3–7%) development of severe forms of neurological, hematological and thromboembolic-vascular complications [13]. This poses a particular challenge in the older people and premorbid patients who may already have existing risk factors for cardiovascular and thromboembolic events. Thalidomide also has teratogenic effects and should be avoided in patients of childbearing age [13].

Such AEs have a significant on patients' quality of life, compliance or continuation of therapy and possible additional costs associated with their management [10,11,13]. However, there are no published studies that have directly compared the clinical and cost-effective impact of thalidomide and SSA directly.

Future research should focus on identifying noninvasive markers to predict a clinical response to treatment to better tailor patients' management. Studies comparing the cost-benefit and effectiveness of these two pharmacological treatments are needed with adequate cohort size, follow-up and including patient quality of life assessments. This would be immensely useful to guide clinicians to the most appropriate and individualized therapy for their patient cohorts.

## List of abbreviations

| | |
|---|---|
| ADs | Angiodysplasias |
| AEs | Adverse events |
| APC | Argon plasma coagulation |
| GI | Gastrointestinal |
| HHT | Hereditary hemorrhagic telangiectasia |
| LAR | Long-acting release |
| RCT | Randomized-controlled trial |
| SSAs | Somatostatin analogues |
| TXA | Tranexamic acid |
| VEGF | Vascular endothelial growth factor |

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