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REVIEW ARTICLE

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Recent advances in the treatment of refractory gastrointestinal angiodysplasia

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Abstract

Gastrointestinal angiodysplasia (GIA) is a common, acquired, vascular abnormality of the digestive tract, and a frequent cause of bleeding. Refractory GIA criteria usually include recurrent bleeding, transfusions and/or repeat endoscopy. Pharmacological and interventional treatments have been the subject of recent high-quality publications. This review provides an overview of the latest updates on non-endoscopic management of refractory GIA. Aortic valve replacement has shown its efficacy in Heyde syndrome and should be considered if indicated. Anti-angiogenic drugs, such as Octreotide and Thalidomide, are efficient treatments of refractory GIA-related bleeding. Somatostatin analogs should, based on efficacy and tolerance profile, be considered first. In the future, a better understanding of the physiopathology of GIA might help develop new-targeted therapies.

KEYWORDS

angiodysplasia, aortic valve replacement, bevacizumab, gastrointestinal bleeding, somatostatin analogs, thalidomide, transcatheter aortic valve implantation

INTRODUCTION

Gastrointestinal angiodysplasia (GIA) is a common, acquired, vascular abnormality of the digestive tract, and a frequent cause of bleeding.[1] It is defined as a « *clearly demarcated, bright-red, flat lesion, consisting of tortuous and clustered capillary dilatations* » surrounded by normal mucosa.[2] GIA lesions are usually multiple and can be located in all segments of the digestive tract, typically the proximal jejunum and the ascending colon.[1] The mechanisms involved in lesion development are not fully understood. Chronic ischemia is believed to lead to an increased secretion of vascular endothelial growth factors (VEGF) with subsequent upregulation of angiogenesis.[1]

GIAs are often diagnosed in the setting of occult bleeding. The typical population consists of elderly patients with associated conditions such as aortic stenosis, chronic renal, heart or liver failure, von Willebrand disease, and diabetes. Supportive therapy consisting of iron replacement therapy (IRT), red blood cell (RBC) transfusion and coagulation defect treatment are preliminary to endoscopic management.[3] While esophagogastroduodenoscopy and colonoscopy are the mainstays of both diagnosis and treatment, the management of deep small bowel (SB) lesions is usually based on a diagnostic capsule endoscopy[4] followed by a device-assisted enteroscopy for therapeutic purposes, if needed.[5] Thermocoagulation is the preferred ablation technique.[1] However, the rebleeding rate after endoscopic therapy is particularly high (35%–80% within 1–2 years).[6–8] Although there is no consensual definition of failed endoscopic treatment, refractory GIA criteria usually include recurrent bleeding, transfusions and/or repeated endoscopy. In such cases, several pharmacologic and

interventional treatments are available. They can be costly and the benefit-risk balance should be considered in these comorbid patients. However, there have been publications in recent years which have demonstrated therapeutic benefit in this challenging group of patients.

The aim of this review is to provide the clinical gastroenterologist with the latest updates on non-endoscopic management of refractory GIA. This review will not address more specific conditions such as hereditary hemorrhagic telangiectasia (HHT) or different gastrointestinal vascular conditions such as gastric antral vascular ectasia (GAVE).

PHARMACOTHERAPY

Somatostatin analogs

Somatostatin analogs (SSA) have increasingly been investigated and used in the treatment of GIA. Somatostatin, made of several peptides, is distributed not only in the growth hormone regulatory system, exocrine and endocrine glands but also in the gut. SSA is commonly used in the treatment of neuroendocrine tumors, but in the last few decades, it has been used in the context of recurrent GIA-related bleeding. However, this remains an unlicensed indication in many countries across Europe. The mode of action has been attributed to a decrease in splanchnic blood flow (by inhibiting several vasodilatory factors, including nitric oxide), increased platelet aggregation and suppression of angiogenic factors through downregulation of VEGF.[9,10] SSA are also believed to directly inhibit angiogenesis.

To date, there have been several studies, since the 90's, that have investigated its use in the context of GIA (Table 1). These drugs were initially trialed in daily doses followed by monthly long acting preparation but with small numbers, heterogeneous patient groups, inclusion criteria and study design. Some studies have combined the use of both short and long acting preparations. The three derivatives studied include Octreotide, Lanreotide and Pasireotide,[11] with the former two analogs encompassing most of the literature on SSA use in this context. Brown and colleagues[19] conducted one of the first few systematic reviews and three prospective studies involving 62 patients were included showing a clinical response to treatment of 0.76 (95% CI 0.64–0.85) and an improvement in transfusion requirement of −2.2 (95% CI −3.9 to −0.5).

Bon et al.[18] investigated its use in 15 patients who were transfusion-dependent. The majority of patients included were on antiplatelet or anticoagulant. The number of transfusions significantly decreased in the "period during" compared with the "period before" starting treatment, as did the rebleeding episodes. Holleran et al.[14] used long acting release (LAR) Octreotide in their open-label trial of 24 patients, showing a complete and partial response in 70% and 20% of patients, respectively. This was replicated in a study by Zammit and colleagues in 12 patients but using Lanreotide, demonstrating a reduction in transfusion requirement and bleeding episodes.[13] A similar theme emerged from these studies that patients included were often premorbid and with coexisting renal, cardiovascular/valvular heart disease and on anticoagulation.[13,14,18]

More recently, Goltstein et al. performed an individual patient data meta-analysis[20] on 212 patients from 11 studies, which demonstrated 83% had a good response to SSA therapy, defined as at least a 50% reduction in the number of RBC transfusions. SSA reduced the number of RBC transfusions with an Incidence Rate Ratio (IRR) of 0.18 (95% CI 0.14–0.24; $p < 0.0001$) during a median treatment duration of 12 months (IQR 6.0–12.0). An interesting observation was that GIA in the stomach fared worse compared with that in the SB and colon. Octreotide was associated with a better treatment response than Lanreotide therapy (IRR interaction 2.13 [95% CI 1.12–4.04]; p 0.02). The limitations of this analysis included the fact that the majority were cohort series, retrospective nature of several studies and only one study had randomization. Of note, some of the studies included in this meta-analysis are described in the above paragraph.

The most recent landmark study, and not included in the above meta-analysis, was a multicenter, open-label, randomized controlled trial comparing LAR Octreotide 40 mg monthly, a sufficiently high dose, with standard therapy including endoscopic Argon Plasma Coagulation

TABLE 1 Efficacy of Somatostatin analogs in angiodysplasia-related bleeding.[a]

Author (year)	Design	Total patients	Patients with decrease in blood transfusion	IRR (95% CI)
Benamouzig et al. 2018[11]	RCT	8	8	0.87 (0.26–2.93)
Frago et al. 2018[12]	CS	23	21	0.35 (0.09–0.40)
Chetcuti et al. 2017[13]	CS	8	8	0.54 (0.23–1.29)
Holleran et al. 2016[14]	CS	22	20	0.28 (0.14–0.59)
Klimova et al. 2015[15]	CS	15	12	0.12 (0.02–0.65)
Nardone et al. 2014[16]	CS	60	57	0.18 (0.11–0.28)
Salgueiro et al. 2014[17]	CS	13	11	0.30(0.15–0.57)
Bon et al. 2012[18]	CS	15	14	0.20 (0.09–0.40)

Abbreviations: CS, cohort study; IRR, Incidence rate ratio; RCT, randomized controlled trial.

[a]Based on a systematic review and meta-analysis by Goltstein et al.[20]

(APC) in patients with refractory anemia. In comparison to the standard of care group, the number of transfusions was significantly lower in the octreotide group (11.0; 95% CI, 5.5–16.5 vs. 21.2; 95% CI, 15.7–26.7 standard of care group).[21] Octreotide also reduced the annual volume of endoscopic procedures by 0.9 (95% CI, 0.3–1.5; p 0.005).

Several studies have reported adverse events with treatment of SSA (up to 20%) including diarrhea, crampy abdominal pain, injection site irritation, impaired glucose tolerance and bloating. The side effect that is noteworthy is the development of cholelithiasis, generally asymptomatic, but does require monitoring of liver function tests.[13,14,18] A pragmatic approach would be to screen patients with an ultrasound of the biliary tree before and after more than 6 months of therapy and monitoring of liver function tests and HbA1c. Only a small proportion of patients have required to discontinue therapy due to the adverse effects.[21] Furthermore, in patients with multiple comorbidities, the benefits of a reduction in transfusions from SSA often outweigh the risks of asymptomatic cholelithiasis.

Recurrent bleeding from GIA has implications on healthcare resources and negatively impacts the quality of life of the already frail patient cohort. However, SSA is cost-prohibitive compared to conservative therapy. Few studies have examined its cost impact.[15,22,23] A recent retrospective study of veterans presenting with SB bleeding concluded that the use of SSA is not cost-effective in the US where six to 12 doses of lanreotide cost between US $44,500 and $89,100.[22] Tai et al.[23] examined the clinical and cost implications of a combination therapy of SSA and endoscopic ablation, endoscopic therapy alone, and conservative management with blood transfusion and iron therapy. This retrospective study showed that the use of SSA as an adjunct to endoscopy is cost-neutral when compared to the number of bed days/transfusions etc. in the conservative arm. All these studies conferred the benefit of SSA therapy in patients with RBC transfusion-dependent anemia. Klimova et al. also analyzed the cost-effectiveness of Octreotide in a retrospective study including 19 patients. Reduction of costs of 61.5% was noted between before and after the start of treatment, suggesting a cost-effectiveness.[15] Currently, there are no studies describing different dose regimens of SSA and associated efficacy in transfusion reduction. Hence, it would be pragmatic to start with a low dose and reduced cost before intensifying the dose based on response on a case-to-case basis.

Thalidomide

Thalidomide was originally introduced as a sedative, and is notorious for causing severe birth defects. It was rediscovered in the 1990s as an immune modulator (tumor necrosis factor suppression) as well as an angiogenesis (VEGF) inhibitor. Case reports have suggested a benefit of its use in the treatment of GIA back in the early 2000s. A single center open-label, randomized controlled study including 55 patients with recurrent bleeding compared 100 mg of Thalidomide daily with placebo (oral iron supplementation). The effective response rate, defined as the proportion of patients in whom bleeding episodes had decreased by ≥ 50% in the first year of the follow-up period, was significantly higher in the Thalidomide arm (71.4% vs. 3.7%; $p < 0.001$). The number of adverse effects such as fatigue (32%), constipation (25%), lightheadedness (21%) and peripheral edema (14%) was higher in the Thalidomide group.[24] However, no validation study was published in the decade that followed.

Most recently, a multicenter, double-blinded, placebo-controlled randomized trial, including 150 patients with SB GIA, compared oral Thalidomide 100 versus 50 mg versus placebo for 4 months. Effective response, defined as a reduction >50% in the number of bleeding episodes that occurred during the year after treatment had ended, compared with the year before, was 68.6%, 51.0%, and 16.0%, respectively ($p < 0.001$). Transfusion and hospitalization requirements were also significantly lower in the Thalidomide groups. Adverse events were more frequent in the Thalidomide groups.[25] The results of the major studies published on the efficacy of Thalidomide in this setting are tabulated in Table 2. Despite these results confirming the efficacy of Thalidomide, the duration of treatment as well as optimal dosing strategy remain unclear. In addition, safety

TABLE 2 Efficacy of Thalidomide in angiodysplasia-related bleeding.

Author (year)	Design	Total patients	Efficiency (%)	Thalidomide	Follow-up (mo)
Chen et al. 2023[25]	PCS	51 versus 49 versus 50	31 (68.6) versus 25 (51) versus 8 (16)	100 mg qd versus 50 mg qd versus placebo	12
Garrido et al. 2012[26]	PCS	12	12 (100%)	200 mg qd	4
Ge et al. 2011[27]	PCS	53	20 (71.4)	100 mg qd	39
Kamalaporn et al. 2009[28]	RCS	7	3 (43)	50 mg qd increased by 50 mg/wk until 200 mg	12
Dabak et al. 2008[29]	RCS	3	2 (66)	100–400 mg qd	8
Bauditz et al. 2006[30]	RCS	3	3 (100)	100 mg qd	34
Bauditz et al. 2004[31]	RCS	6	6 (100)	300 mg qd, 50–100 mg qd after 6–9 months	33

Abbreviations: mo, months; PCS, prospective cohort study; qd, once a day; RCS, retrospective cohort study; wk, week.

concerns remain an issue. Peripheral neuropathy, for instance, is a well-known long-term dose-dependent side effect.[1] The teratogenicity of Thalidomide is also a concern in younger female patients. Finally, adherence is lower compared to that of SSA treatment (monthly injection). For these reasons, Thalidomide should be considered as a second line treatment, in the case of SSA intolerance or failure.

Bevacizumab

Intravenous Bevacizumab is a humanized anti-VEGF monoclonal antibody that specifically binds to VEGF, impeding its interaction with endothelial VEGF receptors of tremendous importance for angiogenesis induction. It is mainly used for the treatment of cancer to inhibit tumor growth and metastasis. It also finds application in vascular eye diseases like diabetic retinopathy.[32,33] It has shown some promising results in the treatment of nasal or gastrointestinal bleeding in patients with HHT[34] and GAVE.[35] The experience in the treatment of GIA is limited to case reports or small, retrospective, case series,[35,36] with favorable outcomes but likely publication bias. It is usually administered for HHT, GAVE and GIA at a lower dose than for oncologic purposes, such as 5 mg/kg every 2 weeks for induction during 2–3 months, followed by 5 mg/kg per month as maintenance for instance, with optional « top-up » infusions every other week or at higher doses in patients with partial response.[35] Despite safety concerns (such as venous thromboembolism, bowel perforation and bleeding), a recent meta-analysis in the setting of HHT did not show an increased risk of adverse events.[37] However, the low level of evidence as well as high cost place Bevacizumab as a last-resort alternative option for patients with refractory GIA.

INTERVENTIONAL TREATMENTS

Aortic valve replacement in Heyde syndrome

Heyde syndrome is the combination of GIA-related bleeding and aortic stenosis.[38] Although previous retrospective studies reported GIA in roughly 1%–10% of patients with severe aortic stenosis,[39] a recent prospective study by Yashige et al.[40] detected GIA in 94% of patients with anemia and severe aortic stenosis using capsule endoscopy. This high prevalence indicates that aortic stenosis is strongly associated with the development of GIA, justifying the focus on aortic stenosis treatment.[41]

Aortic valve replacement (AVR) is the definitive treatment for severe aortic valve stenosis.[42] Surgical aortic valve replacement (SAVR) was the only available technique before the 21st century, which limited its use in fragile patients.[42] Transcatheter aortic valve implantation (TAVI) has become the standard treatment for patients with severe aortic stenosis and an increased surgical risk. TAVI is also gaining territory over SAVR in patients with an intermediate and low surgical risk.[43] However, SAVR is still preferred in specific patient categories.[43]

Multiple retrospective studies have documented reduced GIA-related bleeding after valve repair (Table 3). Goltstein et al.[39] performed a meta-analysis including 300 patients with Heyde syndrome from 10 cohort studies, which revealed a pooled bleeding cessation rate of 73% (95% CI, 62%–81%) after valve repair. Subgroup analyses revealed significantly lower bleeding cessation rates after TAVI compared with SAVR (125/195 [64%] vs. 74/88 [82%]), attributed to paravalvular leakage, which is more common following TAVI.[53] Paravalvular leakage resulted in reduced bleeding cessation rates (RR 0.57; 95% CI 0.40–0.81).[39] Fortunately, recent advancements in next-generation TAVI valves have diminished paravalvular leakage, aligning TAVI outcomes more closely with those of SAVR.[53] Fewer bleeding episodes were reported in the first year after TAVI in patients treated with next-generation valves (1.1 vs. 1.6).[45]

AVR clearly benefits GIA-related bleeding, but the impact on GIA remains uncertain. Previous research suggests that AVR can increase large multimers of von Willebrand's factor (vWF), addressing acquired von Willebrand syndrome (AVWS) associated with shear stress around the narrowed valve.[41,54] Goltstein et al.[39] combined data from 1054 patients with AVWS from 32 studies, and observed that the majority of patients experienced AVWS recovery after valve repair (87%; 95% CI 67%–96%) (Table S1). However, AVWS resolution might not be as relevant for bleeding cessation as Yashige et al.[40] only established AVWS in 43% of patients with Heyde syndrome. More likely, AVR reduces angiogenesis similar to pharmacological treatment.[41] Yashige et al.[40] reported a significant reduction in GIA lesions from 9.0 to 4.0 following TAVI in a study of 50 patients similar to the reductions reported during Octreotide treatment.[16,55] The similarity in mechanism, compared to pharmacological treatment, could also explain the comparable effect.[21,25] However, discontinuation of anti-angiogenic treatment is followed by high rebleeding rates, whereas the benefits of AVR appear to intensify over time.[25,45] Goltstein et al.[45] reported higher bleeding cessation rates between one and 5 years after TAVI compared to the first year (53/62 [85%] vs. 37/70 [53%]). Therefore, AVR should be favored over pharmacological treatment if indicated.

PRACTICAL MANAGEMENT

Guidelines on lower gastrointestinal and SB-related bleeding focus on the management of acute bleeding and endoscopic treatment.[3,56] Second-line therapies are not covered or rely on what are now outdated studies. This review of the recent publications on non-endoscopic treatments, used to manage GIA with refractory bleeding, highlights their efficacy and confirms that they constitute a viable option. We believe that updated guidelines should now specifically address these therapeutic options.

We propose a management algorithm (Figure 1). Conservative therapy and anticoagulation/antiplatelet medication discontinuation,

TABLE 3 Efficacy of aortic valve replacement in angiodysplasia-related bleeding.

Author (year)	Design	Total patients	Cessation (%)	AVR	Follow-up
Brown et al. 2022[19]	RCS	72	56 (78)	TAVI	24 months
Godino et al. 2013[44]	RCS	6	4 (67)	TAVI	22 months
Goltstein et al. 2022[45]	RCS	70	37 (53)	TAVI	32 months
King et al. 1987[46]	RCS	14	13 (93)	SAVR	108 months
Liu et al. 2013[47]	RCS	6	6 (100)	SAVR	Unknown
McNamara et al. 1968[48]	RCS	4	3 (75)	SAVR	12 months
Rosa et al. 2021[49]	PCS	17	13 (76)	Both	24 months
Tamura et al. 2015[50]	PCS	7	7 (100)	SAVR	Unknown
Thompson et al. 2012[51]	RCS	57	45 (79)	SAVR	53 months
Waldschmidt et al. 2021[52]	RCS	47	28 (60)	TAVI	12 months

Abbreviations: AVR, Aortic valve replacement; PCS, prospective cohort study; RCS, retrospective cohort study; SAVR, Surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

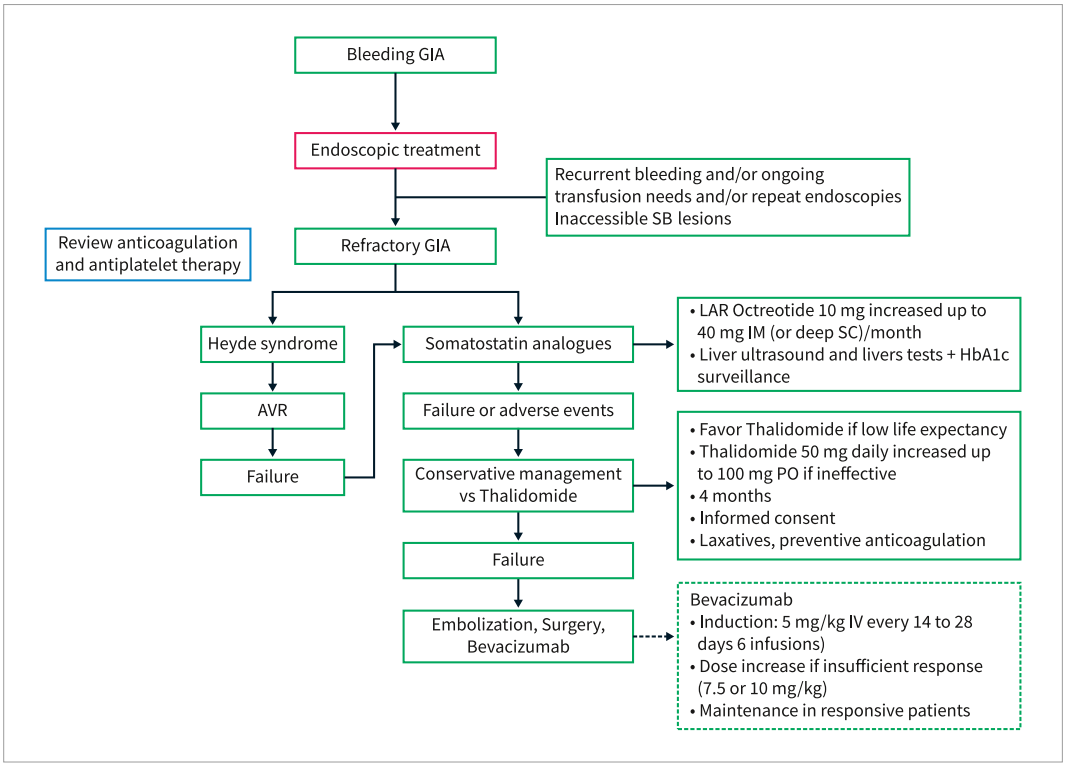

FIGURE 1 Management algorithm of refractory angiodysplasia of the digestive tract. AVR, aortic valve replacement; IM, intramuscular; IV, intravenous; LAR, Long-acting release; SC, subcutaneous; SB, small bowel.

if possible, should remain the cornerstone of the management of refractory GIA-related bleeding. There remains no consensus on the exact definition of failed endoscopic treatment. Thus, pharmacological treatment could be considered as a first-line treatment in specific cases where endoscopy is not considered to be clinically the optimal first option. This approach could be beneficial in particular in patients with SB lesions, downstream of the angle of Treitz, less accessible to endoscopic therapy. AVR should be considered in cases of aortic stenosis. Ultrasound evaluation and treatment of paravalvular leakage should be considered as it may be a cause of persistent lesions and bleeding. In other cases of refractory GIA, we suggest that SSA should be considered first based on the tolerance profile. An option would be LAR Octreotide 40 mg IM (or deep SC injection in patients with anticoagulation) on a monthly basis, with or without a 3-day 100 µg SC b.i.d. rapid acting Octreotide standard dosing to test for tolerance. Starting LAR Octreotide with lower doses may be considered as a cost-effective approach. Although we only have evidence from one randomized trial that 40 mg of LAR Octreotide is effective, a starting dose of 10 mg

which can be increased up to 40 mg could be tried based on the results of the individual patient data meta-analysis.[20] Screening for cholelithiasis by liver ultrasound before and after 6 months of therapy and monitoring of liver function tests and HbA1c should be performed, as sometimes proposed in other indications. In case of failure or discontinuation due to adverse events, Thalidomide could be considered, versus conservative management, given its safety profile. Consent should be obtained after detailed information on adverse events in all patients. Constipation is a frequent side effect that needs to be anticipated and treated. Patients and their caregivers should be warned as well of potential sleepiness during the 4 months treatment period. Preventive anticoagulation is a reasonable option because of the risk of thromboembolism. Dose-dependent axonal neuropathy occurs after 6 months of treatment in 80% of patients.[57] This explains why SSA should be prescribed over Thalidomide. Furthermore, Thalidomide would be best suited for patients who are not likely to suffer from polyneuropathy due to short life expectancy. Thalidomide could be proposed for 4 months in carefully selected patients with reasonable performance status. A 50 mg starting dose should be chosen, with a possible step-up strategy to a 100 mg if ineffective since polyneuropathy is dose effective.[25] Arguably, the evidence for using Thalidomide as second line is low and based on expert opinion. Clinicians should individualize the treatment according to the patient characteristics. Specific anti-angiogenic drugs are currently not considered a standard treatment due to limited data on their efficacy and safety. However, Bevacizumab may be considered for compassionate use if prior treatment with SSA and/or Thalidomide is inefficient. Monitoring for adverse events during treatment is imperative. Treatment should be put off in case of recent deep venous thrombosis, severe infectious disease, or severe arteriopathy. Given the lack of studies focusing on the optimal dose, initiation should be at 5 mg/kg intravenously every 14–28 days for at least six infusions. Dose increase to 7.5 or 10 mg should be considered in case of insufficient response. Maintenance therapy could be attempted in responsive patients. Doses should then be adjusted based on the patients' response and tolerance given that the long-term effectiveness is unknown (e.g., 10 mg every 2 weeks in case of frequent rebleeding or on-demand treatment with 5 mg in case of stable hemoglobin levels).

FUTURE AND PERSPECTIVES

Studies comparing SSA and Thalidomide are needed to compare efficacy and evaluate the optimal dosing and duration of treatment for Thalidomide. Lastly, a better understanding of the physiopathology of GIA will allow us to better treat our patients in the future. For instance, preliminary studies have suggested a role of angiogenic factors in the occurrence of SB GIA, such as increased expression of Angiopoietin-2. These potential serum biomarkers could help suggest the diagnosis of GIA and constitute a therapeutic target.[58–60]

It is worth mentioning that studies suggest the efficacy of pharmacological treatment, such as Bevacizumab, in terms of bleeding control in the setting of HHT.[34,61] Given the diffuse nature of this disease, the evidence from its use in HHT could be extrapolated to the management of refractory GIAs with multiple SB - located lesions. Future studies on HHT may convey interesting breakthrough therapies for the management of GIA, and vice-versa.

Biomarkers could potentially distinguish responders from non-responders. Monitoring VEGF, alongside other angiogenesis growth factors like angiopoietin-2, could facilitate response assessment.[25] In patients with symptomatic angiodysplasias, Thalidomide led to a significant decrease in VEGF levels, with responders showing a more pronounced reduction.[24] These effects on the VEGF levels remain unexplored with SSA.

CONFLICT OF INTEREST STATEMENT

Xavier Dray: Co-founder and shareholder, Augmented Endoscopy; Teaching, Sandoz; Other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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