REVIEW

Emerging role of thalidomide in the treatment of gastrointestinal bleeding

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ABSTRACT

Thalidomide was initially synthesised in 1954 and marketed as a sedative and antiemetic for morning sickness. It was withdrawn in 1961 due to the realisation that it was teratogenic with over 10 000 children born with congenital abnormalities. Since then it has been used for treatment of dermatological and oncological conditions, including myeloma. In 1994, it was found to have a potent antiangiogenic effect via downregulation of vascular endothelial growth factor (VEGF). This has led to its use in gastrointestinal bleeding, as vascular abnormalities such as angiodysplasia have been found to have elevated VEGF levels. This article will review the current evidence of the use of thalidomide in bleeding associated with gastrointestinal vascular malformations, including angiodysplasia, gastric cancer and radiation-induced proctitis.

INTRODUCTION

Gastrointestinal bleeding, both upper (UGIB) and lower (LGIB), is a common condition. UGIB is responsible for 50–70 000 hospital admissions a year in the UK,¹ while LGIB accounts for approximately 25% of all GIB cases admitted to hospital.² UGIB is defined as bleeding occurring proximal to the ligament of Trietz (D3) and is potentially more serious, with 7% mortality for admissions with UGIB.² LGIB occurs distal to this, encompassing the small and large intestines and is usually self-limiting.² Non-variceal vascular malformations, such as those seen in hereditary haemorrhagic telangiectasia (HHT), angiodysplasia, gastric antral vascular ectasia (GAVE) and Dieulafoy's lesions, are an uncommon cause of bleeding, accounting for 3%–9% of small and large bowel bleeding, while the vascular abnormalities found in radiation-induced proctitis and GI malignancy are also important causes.^{1,2}

Until advances in endoscopic therapy in the early 1990s meant a switch to more interventional treatment of GI bleeding, the conventional treatment for bleeding from vascular malformations was hormonal therapy with oestrogens.³ The evidence for this was based on case reports and case series.⁴ The first randomised control trial (RCT) in 2001 showed that there was no difference between placebo and oestrogen therapy in reduction of bleeding episodes, transfusion requirements or treatment failure.⁵ This led to a further movement towards endoscopic treatment. Fortunately, acutely bleeding non-variceal vascular lesions discovered at endoscopy are rare, and as such, treatment with methods such as argon plasma coagulation (APC) of these lesions is often prophylactic at best and there is little evidence of reduction in bleeding episodes or transfusion requirements.³ Furthermore, eradication of multiple lesions and the fact that angiodysplasias recur over time, often necessitates further endoscopic procedures.⁶ More recently, interest has grown in the use of thalidomide to treat the bleeding associated with gastrointestinal vascular malformations.

Thalidomide

Thalidomide was initially developed in 1954 in Germany as a sedative prior to the availability of benzodiazepines.³ It began clinical use in 1956 as an anxiolytic but soon became recommended to treat morning sickness due to observed antiemetic effects in pregnant women.⁷ At its peak, it was marketed under at least 37 names worldwide, with 140 million tablets sold in 1960, although it never received Food and Drug Administration (FDA) approval in USA due to fears about drug safety.^{3,8} Soon after its use began, reports emerged of physical abnormalities

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in children born to mothers who had used thalidomide in pregnancy, including limb abnormalities such as phocomelia, dysmelia, amelia and bone hypoplasia and congenital internal organ abnormalities. Eventually, in 1961, thalidomide was withdrawn from the market, but by this stage over 10 000 children had been born with limb or organ abnormalities.^{3,8} Thalidomide helped pave the way for more stringent safety criteria for all drugs, but particularly in pregnancy.⁹

Despite the devastating teratogenic effects of thalidomide, the mechanisms by which it leads to birth defects are still poorly understood. The most widely supported theory was first suggested in 1994 by D'Amato *et al* and is based on the drug ability to disrupt angiogenesis by its effects on vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF).⁷ Interestingly, even the exact mechanism by which thalidomide exerts antiangiogenic effects is not fully understood; thalidomide itself is not responsible, rather species-specific hepatic metabolites are believed to be responsible.¹⁰ Other than its antiangiogenic effects, thalidomide has also been shown to have anti-inflammatory and immunomodulatory properties with effects on levels of γ -interferon, TNF α , interleukins 10 and 12 and COX-2.⁸

Despite having been withdrawn only 4 years previously, thalidomide resurfaced in 1965 when an Israeli dermatologist discovered it could be used to treat erythema nodosum leprosum (ENL), a vasculitic complication of leprosy.^{3,8} Since then thalidomide, under tight regulations, has been used in across multiple specialties including dermatology (ENL), rheumatology (variable use in joint conditions), infectious diseases (HIV-1 associated Kaposi sarcoma and proctitis) and oncology (multiple myeloma, advanced prostate cancer and Waldenstroms macroglobulinaemia).^{3,8}

Angiodysplasia, GAVE and portal hypertensive gastropathy

Angiodysplasia is thought to be one of the most common gastrointestinal vascular malformations in adults, accounting for 4%–7% of non-variceal UGIB, 35%–50% of small bowel bleeding found at capsule endoscopy and 3%–40% of lower GI haemorrhage.¹¹ They are most commonly found in the right side of the colon and small intestine and are often found in older patients and have been linked with aortic stenosis, chronic kidney disease and von Willebrand disease.¹¹ Angiodysplastic lesions are defined as abnormal, ectatic, dilated, tortuous and usually small blood vessels, which are visualised within the mucosal and submucosal layers of the gut. Histologically, they contain no or little, smooth muscle and lined by endothelium only.^{12,13} The exact pathogenesis of angiodysplasia remains unclear but increased expression of VEGF and bFGF has been demonstrated in colonic lesions.^{14,15} It has been hypothesised that local hypoxia leads to VEGF overproduction and subsequent

vessel proliferation.¹⁶ Endoscopic treatment of lesions, including APC, has been shown to be an effective treatment of actively bleeding lesions. However, there is a significant recurrence rate (34%),¹⁷ lesions are often present at multiple sites and the physical limitations of endoscopy prevent effective treatment for small bowel angiodysplasia.¹⁸ For these patients and patients unsuitable for endoscopy, it is necessary to explore pharmacological therapies. The presence of high VEGF levels within angiodysplastic lesions led to the hypothesis that thalidomide could be a potential pharmacological agent to augment angiodysplasia formation and the risk of bleeding.¹⁹

The first case report on thalidomide use for angiodysplasia bleeding refractory to conventional therapy was published in 2004¹⁶ and subsequently there have been several other case reports and case series published on the use of thalidomide in this context, including in those with bleeding diatheses.^{16,20–36} There have also been case reports of its use in patients with chronic kidney disease on haemodialysis, those with left ventricular assist devices and paediatric cases.^{31,37–40} Small bowel angiodysplastic lesions have been shown to reduce in number, size and colour intensity using video capsule endoscopy while undergoing treatment with thalidomide.²⁵ Given that the majority of publications are case reports, there is a risk of publication bias and to date there has been one published case report of treatment failure with thalidomide in angiodysplastic bleeding.⁴¹

In 2011 a RCT of 55 patients, comprising 52 with angiodysplasia and 3 with GAVE, unsuitable for, or refractory to other therapies was conducted. The patients were observed for 1 year and then randomised to receive either thalidomide 100 mg daily (n=28) or oral iron therapy 400 mg daily (n=27) for 4 months. This study demonstrated an effective response rate, defined as at least 50% decrease in bleeding episodes within 1 year, of 71.4% of patients on thalidomide compared with 3.7% of patients treated with iron. They also found decreased transfusion requirement and complete cessation of bleeding in 46.4% of patients on thalidomide compared with 0% of patients treated with iron.⁴² In addition to this, the study also noted a significant decrease in VEGF levels with thalidomide treatment, which has also been reported elsewhere.^{16,34} Response rates were not changed when the three patients with GAVE were excluded from the analysis. Unfortunately, increased adverse effects were also noted in the thalidomide group (71.4% compared with 33.3% of patients treated with iron). The most common adverse effects reported were fatigue (32%), constipation (25%) and dizziness (21%).⁴²

The same group subsequently published results of long-term efficacy of thalidomide treatment in a cohort of 80 patients, including those in the RCT, over a median follow-up of 42.6 months (12–120 months). They reported that bleeding cessation occurred in 38.5%, decreased bleeding in 32.1% and decreased

bleeding while on treatment in 9.0% and no response in 20.5%. They gave a 1-year response rate of 77%, an overall response rate of 79.5% and significantly reduced numbers of bleeding episodes, hospitalisations, blood transfusion requirements and raised haemoglobin. However, they did report a recurrence rate of 20.7% but a response rate to retreatment of 100%.⁴³ They also reported similar effectiveness and non-effectiveness between patients with comorbidities and those without. Adverse effects were observed in 60% of patients and serious adverse effects in 31.3%, although in those requiring a single course of thalidomide it was less at 26.1%.⁴³

Though the vascular lesions seen in HHT are caused by mutations within the angiogenic pathway, resulting in different lesion phenotype, elevated levels of VEGF have been found in the vascular lesions of HHT and consequently thalidomide has been suggested for its treatment. There have been encouraging results in the published cases and case series. Doses of 100–200mg/day have reduced nosebleed frequency and intensity, transfusion requirements and also produced an increased quality of life.^{44–48} There is one case report of the drug lenalidomide, a derivative of thalidomide, being used to control bleeding in a patient with HHT, who had previously been partially controlled by thalidomide. The authors concluded that lenalidomide appeared more effective, with fewer side effects, but to date this is only published use of the drug in this context.⁴⁹

Thalidomide has also been studied in the context of liver cirrhosis-associated GI non-variceal vascular malformations including portal hypertensive gastropathy (PHG) and other vascular lesions. A case series of 19 patients, given 200mg/day of thalidomide, resulted in a clinically significant increase in haemoglobin from 7g/dL pretreatment to 10g/dL after 4 months.⁵⁰ The study also noted that patient VEGF levels were decreased post-thalidomide therapy supporting the hypothesis that thalidomide suppresses angiogenesis via inhibition of VEGF. Although they did note that 42% of patients developed hepatic encephalopathy, suggesting that it should be used with caution in patients with cirrhosis. This conclusion has been called in to question, as 200mg of thalidomide is a high enough dose to potentially have sedative effects.³ There are a few case reports of the beneficial effects of thalidomide in the context of cirrhosis-related GAVE and PHG.^{51–53} Table 1 provides a summary of the available literature for the use of thalidomide in recurrent GI bleeding where thalidomide has been used and patient numbers are greater than 1.

There is a single case report of non-liver disease GAVE where thalidomide was successfully used in a patient who was unresponsive to endoscopic therapy. Within 3 months of starting thalidomide therapy they were no longer transfusion-dependent and remained transfusion-free for 9 months of follow-up.⁵⁴

Radiotherapy induced proctitis

Approximately 70% of all patients with cancer receive some form of radiation therapy. Despite improvements in the delivery of radiotherapy, there is still a high risk of radiation exposure to some part of the GI tract. The colon and rectum are particularly at risk during abdominal or pelvic radiotherapy.⁵⁵ Between 13.5% and 16% of patients undergoing radiotherapy will suffer from the complication of radiation proctitis.⁵⁶ The main mechanisms by which radiation enteropathy is suggested to occur are microvessel endothelial cell damage with increased chemotaxis and thrombogenesis in the damaged vessels.^{57,58} Animal studies have shown an increase in VEGF in cases of radiation proctitis compared with controls.⁵⁹ There have been two case reports of the use of thalidomide in patients with radiation proctitis refractory to endoscopic and aminosalicylate treatment. In both cases, patients treated with thalidomide had a decreased transfusion requirement for the duration of treatment.^{60,61} However, there was variable lasting effect post-treatment with one patient remaining transfusion independent for the duration of follow-up (3 months),⁶⁰ while the other experienced a relapse of symptoms treatment was withdrawn due to peripheral neuropathy.⁶¹

GI malignancy-related bleeding

There is limited evidence for its use in GI bleeding related to GI malignancy, mainly due to the preference for endoscopic therapy. There is one case report of thalidomide use in the treatment of bleeding from a gastric malignancy, where endoscopic therapy was deemed unlikely to be successful. The patient failed to respond to other medical therapies such as tranexamic acid, sucralfate and etamsylate. Initiation of thalidomide resulted in bleeding cessation within 4 days, although it did recur once thalidomide was withdrawn due to side effects.⁶²

Safety/tolerability

The most commonly reported adverse effects of thalidomide are sedation and peripheral neuropathy. Less common adverse effects include rash, constipation, dizziness, headache, mood changes and tremor.^{3,8,11} There have been reports of liver toxicity and even acute liver failure at higher doses, therefore the current recommendation from those experienced in its use in this context is that the dose should not exceed 100mg/day and due to the teratogenicity, although no comparison between different dosing strategies has yet been performed. Thalidomide should not be given in women of childbearing age without adequate contraception.^{3,11} There are case reports of venous thrombosis while on thalidomide;⁶³ however, these predominantly come from patients receiving the drug for malignant conditions such as myeloma, while the study into its use in GI bleeding, where there was no malignancy, reported no increased risk.⁴² Given that

Table 1 Summary of evidence for the use of thalidomide, where more than patient was in the study

Author	Year	Case report/series/RCT	N	GI condition	Inclusion criteria	Thalidomide dose; Duration	Outcomes
Ge <i>et al</i> ⁴²	2011	Open label Randomised Control Trial	55	GI angiodysplasia (n=52) GAVE (n=3)	Recurrent or refractory GI bleeding	100 mg/day versus 400 mg iron therapy per day; 4 months	Effective response rate of 71% (thalidomide) vs 4% (iron) (P<0.001) at 1 year Discontinuation in two patients
Chen <i>et al</i> ⁴³	2016	Retrospective cohort study	80	GI angiodysplasia	Recurrent or refractory GI bleeding	100 mg/day; 4 months	Response rate 79.5% Recurrence rate 21%; 100% retreatment response rate Significant reduction in bleeding and increase in haemoglobin (P<0.001) Serious adverse events 31% NB: Included patients from above RCT
Garrido <i>et al</i> ²⁸	2012	Prospective cohort study	12	GI angiodysplasia	Recurrent or refractory GI bleeding	200 mg/day; 4 months	Mean haemoglobin increased from 65g/L before treatment to 113 g/L at 2 months and 123 g/L after 4 months Discontinuation in two patients
Bauditz <i>et al</i> ¹⁶	2004	Case series	6	(1) GI angiodysplasia (n=3) (2) Crohn's disease (n=3)	Recurrent, transfusion dependent GI bleeding refractory to conventional therapy	(1) 100 mg/day; 4 months (2) 300 mg lowered to 50–100 mg/day after 6–9 months	No transfusion requirements during treatment Bleeding recurrence after stopping treatment in two patients from group 1 Bleeding stopped once thalidomide restarted.
Bauditz <i>et al</i> ²⁵	2006	Case series	3	Not described	Recurrent GI bleeding refractory to conventional therapy	100 mg/day; 3 months	No bleeding or transfusion requirement during treatment and mean follow-up of 34 months compared with 3–7 bleeding episodes and a mean number of 17 blood units in 12 months prior to treatment
Dabak <i>et al</i> ²⁶	2008	Case series	3	Not described	Recurrent, transfusion dependent GI bleeding	100–400 mg/day; Mean duration 249 days	Mean haemoglobin increased from 99g/L before treatment to 129 g/L No transfusion requirement during 6-month follow-up Discontinuation in one patient
Kamalaporn <i>et al</i> ²⁷	2009	Case series	7	GI angiodysplasia (n=3) HHT (n=3) GAVE (n=1)	Chronic GI bleeding, requiring ongoing transfusions	50–250 mg/day; 6 months	No transfusion requirement during treatment Loss of response in one patient, maintained response in second patient, third patient died from diabetic complications 4 weeks after stopping treatment Discontinuation in four patients
Bélarid <i>et al</i> ²²	2009	Case report	2	Angiodysplasia	Recurrent intestinal bleeding refractory to conventional therapy	Unknown	Improvement in transfusion requirements and bleeding episodes
de Koning <i>et al</i> ²⁴	2006	Case report	2	Angiodysplasia	Recurrent GI bleeding refractory to conventional therapy	Unknown	Cessation of bleeding and no further transfusions required

Continued

Table 1 Continued

Author	Year	Case report/series/RCT	N	GI condition	Inclusion criteria	Thalidomide dose; Duration	Outcomes
Boey <i>et al</i> ²⁹	2015	Case report	2	Angiodysplasia, von Willebrand's disease	Recurrent transfusion dependent GI bleeding, refractory to conventional therapy	50–100 mg; Ongoing treatment	Reduction in GI bleeding episodes and transfusion requirements Discontinuation in one patient
Draper <i>et al</i> ²⁹	2015	Case series	8	Angiodysplasia; Left ventricular assist devices	Recurrent GI bleeding refractory to conventional therapy	50–200 mg/day; Ongoing treatment	Reduction in number or complete cessation of GI bleeding episodes
Chan <i>et al</i> ⁴⁰	2016	Case series	4	Angiodysplasia; Left ventricular assist devices	Recurrent GI bleeding refractory to conventional therapy	25–50 mg/day; Ongoing treatment	Reduction in number of GI bleeding episodes. One patient had thalidomide stopped due to side effects, bleeding recurred and then stopped on thalidomide reintroduction at lower dose
Garrido Serrano <i>et al</i> ⁵⁰	2012	Prospective cohort study	19	Liver cirrhosis; ectasia, vascular lesions, PHG	Recurrent or refractory GI bleeding	200 mg/day; 4 months	Mean haemoglobin increased from 70 g/L before treatment to 90 g/L at 2 months and 100 g/L after 4 months Discontinuation in four patients

GAVE, gastric antral vascular ectasia; GI, gastrointestinal; HHT, hereditary haemorrhagic telangiectasia; PHG, portal hypertensive gastropathy.

Key messages

- ▶ Thalidomide is superior to iron therapy in the treatment of recurrent non-variceal vascular malformation gastrointestinal (GI) bleeding in one RCT.
- ▶ Thalidomide appears to have an acceptable safety profile.
- ▶ Hormonal therapy has been proven to be no better than placebo.
- ▶ Further RCTs are needed to prove the effectiveness of thalidomide in the treatment of recurrent non-variceal GI bleeding from vascular malformations.

the majority of patients with angiodysplasia tend to be elderly, teratogenicity is unlikely to be an important consideration in these cases.³

Many of the studies on thalidomide advocate its short term use to concerns over its side effects; however, as vascular lesions such as angiodysplasias are well documented to recur throughout the GI tract, the long term use of thalidomide could be appealing, particularly as several of the case reports and case series published report that bleeding restarted after thalidomide discontinuation, necessitating thalidomide reintroduction. This rationale is countered by fears of the effects of cumulative doses of thalidomide and the observation that repeated courses led to higher rates of adverse effects.⁴³

CONCLUSION

Thalidomide appears to offer an effective, if not risk-free, treatment option for the treatment of GI bleeding from vascular malformations, including angiodysplasia, in those in whom recurrent or obscure GI bleeding from non-variceal vascular abnormalities necessitates high numbers of admissions and blood transfusions. The evidence is limited to one RCT, several case series and case reports. This raises the possibility of publication bias and further, larger RCTs are needed to determine its efficacy as well as short-term and long-term safety.

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