

PIASTRINE: ALTERAZIONI QUALITATIVE O QUANTITATIVE

THALIDOMIDE FOR RECURRENT GASTROINTESTINAL BLEEDING IN RARE BLEEDING DISORDERS AND VENOUS MALFORMATIONS: A MONOCENTRIC EXPERIENCE

M. De Siati^{1,2}, F.G. Perretta^{1,2}, F. Ricci^{1,2}, A. Ferretti¹, M. Comand^{1,2}, S. Sorrentino¹, L. D’Innocenzo^{1,2}, D. Feliciani², B. Funaro², M.E. Riccioni³, A. Gasbarrini^{2,4}, E. De Candia^{1,2}

¹UOSD Malattie Emorragiche e Trombotiche, Fondazione Policlinico Agostino Gemelli IRCCS, Roma 00168, Italy; ²Department of Translational Medicine and Surgery, Catholic University of the Sacred Heart, Roma, Italy; ³Digestive Endoscopy Unit, Fondazione Policlinico Universitario Agostino Gemelli, IR-CCS, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli, Roma 00168, Italy; ⁴Department of Medical and Surgical Sciences, Digestive Disease Center, University Policlinic Agostino Gemelli Foundation IRCCS, Roma, Italy

Background and Aims. Recurrent gastrointestinal (GI) bleeding due to angiodysplasia or venous malformations represents a major therapeutic challenge, particularly in patients with underlying congenital or acquired bleeding disorders. Endoscopic and haemostatic treatments often achieve only transient benefit, while long-term pharmacologic options remain limited. Thalidomide, an anti-angiogenic agent, has shown efficacy in refractory gastrointestinal angiodysplasia in randomized controlled trials and meta-analyses; however, these studies were conducted in patients without systemic bleeding disorders. Consequently, real-world data on the use of thalidomide in ultra-rare bleeding disorders associated with angiodysplasias remain scarce. To evaluate the efficacy, safety, and clinical patterns of response to thalidomide in a monocentric cohort of patients with recurrent GI bleeding associated with rare bleeding disorders and angiodysplasias or vascular malformations.

Methods. We retrospectively analysed seven patients treated with oral thalidomide (50-150 mg/day) for recurrent GI bleeding unresponsive or only partially responsive to endoscopic therapy and standard haemostatic approaches. Diagnoses included acquired von Willebrand disease (AVWD), type 2B von Willebrand disease (vWD), Glanzmann thrombasthenia (GT), and Blue Rubber Bleb Nevus Syndrome (BRBNS). All patients had documented GI bleeding from angiodysplasias or from multiple venous malformations located mainly in the submucosa of the gastrointestinal tract (BRBNS). Outcomes included haemoglobin (Hb) stability, transfusion requirements, hospitalizations, recurrence of overt bleeding, treatment adherence, and adverse events.

Results. Five patients achieved sustained clinical benefit, with marked reduction of GI bleeding relapses, stabilization or improvement of Hb levels, and discontinuation or de-escalation of transfusions, IVIg, octreotide, and/or vWF/FVIII concentrate support (fig. 1). Dose-response and adherence emerged as key determinants of efficacy, particularly in type 2B vWD and one AVWD patient. The BRBNS patient achieved complete bleeding control with low-dose thalidomide (50 mg/day) (fig. 2). A type 2B vWD patient with refractory jejunal angiodysplasia-related bleeding achieved sustained bleeding control with thalidomide 50 mg/day, with no need for further transfusions and hospitalizations discontinuation of octreotide, and reduction of vWF/FVIII concentrate

support over approximately 5-6 months of follow-up. Conversely, the GT patient experienced only a transient improvement, followed by recurrent bleeding and significant toxicity, limiting long-term treatment (Fig 2). Adverse events included dose-dependent peripheral neuropathy, mild paresthesias, fatigue, constipation, and one case of suspected bone marrow suppression, in line with previously reported safety profiles.

Conclusions. In this small monocentric cohort, thalidomide provided meaningful and, in several cases, sustained control of recurrent GI bleeding in AVWD, type 2B vWD, and BRBNS, whereas efficacy was transitory in GT. These findings extend randomized trial evidence to ultra-rare bleeding conditions and support the use of thalidomide as a second-line, symptom-targeted option in carefully selected patients with bleeding disorders and recurrent GIBs, provided that toxicity is closely monitored and adherence maintained. Larger real-world studies are needed to better define optimal dosing, treatment duration, and long-term safety.

Diagnosis	Treatment's length	Before Thalidomide		During Thalidomide	
		pRBC units transfused	Mean haemoglobin (g/dL)	pRBC units transfused	Mean haemoglobin (g/dL)
Case #1	AVWD	30 months	5	11.8	Periodic IVIg infusions IVIg supplementation Transcatheter arterial embolization
Case #2	AVWD	24 months	4	9.7	Agonist plasma coagulation IVIg supplementation
Case #3	AVWD	24 months	10	11.6	Periodic IVIg infusions Octreotide supplementation Agonist plasma coagulation Endoscopic treatment Cyclosporine
Case #4	vWD 2B	22 months	8	6.7	Eltrombopag Agonist plasma coagulation Endovascular embolization Endoscopic treatment
Case #5	GT	24 months	> 1/week	7.9	Endovascular embolization Octreotide Agonist plasma coagulation Endoscopic treatment Transcatheter arterial embolization
Case #6	BRBNS	11 months	2	7.7	Schleatherapy Endovascular embolization Lamivudine
Case #7	vWD 2B	6 months	2	8	Endoscopic, sclerotherapy Octreotide Plasma-derived vWF/FVIII concentrate prophylaxis Transcatheter arterial embolization

Figure 1: Clinical outcomes before and during thalidomide therapy in seven patients with recurrent gastrointestinal bleeding associated with rare bleeding disorders and gastrointestinal vascular lesions. The table shows transfusion requirements, mean haemoglobin levels, and concomitant therapies before and during treatment, highlighting reduced transfusion needs, improved haemoglobin stability in most patients, and de-escalation of supportive therapies in responders.

Patient	Diagnosis	Treatment's length	Thalidomide's dose	Response	Side effects
Case #1	AVWD	30 months	50 mg/die	Complete response	None
Case #2	AVWD	24 months	from 50 mg/48h to 50 mg/die	Complete response	Paresthesias
Case #3	AVWD	24 months	from 50 mg/48h to 50 mg/die	Complete response/dose-dependent	Lower limb pain
Case #4	vWD 2B	22 months	from 50 mg/die to 100 mg/die	Partial response limited to first 18 months	None
Case #5	GT	24 months	from 50 mg/die to 100 mg/die	Partial response limited to first 6 months	Mental confusion Walking instability Paresthesias Neutropenia
Case #6	BRBNS	11 months	50 mg/die	Complete response	None
Case #7	vWD 2B	6 months	50 mg/die	Complete response	Paresthesias Fatigue

Figure 2: Summary of thalidomide dosing, treatment duration, clinical response, and adverse events in six patients, showing sustained benefit in most disorders except GT, and variable toxicity profiles.