Effective treatment of gastrointestinal bleeding with thalidomide - Chances and limitations

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Abstract

For more than 50 years bleeding from gastrointestinal angiodysplasias has been treated by hormonal therapy with estrogens and progestagens. After a randomized study finally demonstrated that hormones have no effect on bleeding events and transfusion requirements, therapy has switched to endoscopic coagulation. However, angiodysplasias tend to recur over months to years and endoscopy often has to be repeated for long time periods. Thalidomide, which caused severe deformities in newborn children in the 1960s, is now increasingly used after it was shown to suppress tumor necrosis factor alpha, inhibit angiogenesis and to be also effective for treatment of multiple myeloma. In 2011 thalidomide was proven to be highly effective for treatment of bleeding from gastrointestinal angiodysplasias in a randomized study. Further evidence by uncontrolled studies exists that thalidomide is also useful for treatment of bleeding in hereditary hemorrhagic telangiectasia. In spite of this data, endoscopic therapy remains the treatment of choice in many hospitals, as thalidomide is still notorious for its teratogenicity. However, patients with gastrointestinal bleeding related to angiodysplasias are generally at an age in which women have no child-bearing potential. Teratogenicity is therefore no issue for these elderly patients. Other side-effects of thalidomide like neurotoxicity may limit treatment options but can be monitored safely.

Key words: Thalidomide; Angiodysplasia; Vascular malformation; Gastrointestine; Bleeding; Therapy; Angiogenesis; Vascular endothelial growth factor

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it is still notorious for its teratogenicity. Patients with gastrointestinal bleeding related to angiodyplasias are generally old and teratogenicity is not an important issue. Other side-effects of thalidomide like neurotoxicity may limit treatment options but can be monitored safely.

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**INTRODUCTION**

In the absence of more specific therapeutic options, gastrointestinal bleeding due to vascular malformations has been treated by hormonal therapy since the 1950s. With the invention of flexible endoscopy of the digestive tract, treatment has more and more switched to endoscopic measures. Typically, different coagulation techniques are applied in these patients. However, if there are multiple lesions, endoscopy has to be performed repeatedly, as it is often not possible to extinguish all lesions and angiodyplasias tend to recur for months and years[1].

After hormonal therapy has been proven to be ineffective by a randomized study[2], endoscopy is by far the preferred treatment in most hospitals. However, as an acutely bleeding angiodyplastic lesion is only rarely present during endoscopy and therefore coagulation is generally prophylactic, efficacy of endoscopic treatment is not self-evident and has neither been proven for reduction of bleeding episodes nor transfusion requirements.

After the first report on the use of thalidomide for bleeding from gastrointestinal angiodyplasias during the Congress of the American Gastroenterological Association (AGA) in 2002[3] and several subsequent case series[4-6], a randomized study finally proved the efficacy of thalidomide in 2011[7]. Despite this breakthrough, endoscopic therapy remains the treatment of choice in many hospitals. In this review aspects of treatment of gastrointestinal vascular malformations and the potential and side-effects of thalidomide will be discussed.

**APPEARANCE AND ETIOLOGY OF GASTROINTESTINAL VASCULAR MALFORMATIONS**

Bleeding from vascular malformations occurs in different clinical settings. In addition, vascular malformations differ in appearance according to their underlying pathophysiology. Angiodysplasias, which are predominantly found in elder patients (and therefore also termed “senile angiodyplasias”) typically present with a characteristic appearance of cherry-red complex vascular tumors, which are often slightly elevated above the level of the gastrointestinal mucosa (Table 1 and Figure 1). It is speculated that local hypoxia within the gastrointestinal wall causes an overproduction of growth factors like vascular endothelial growth factor (VEGF), which results in an exaggerated vessel growth. However, occurrence of angiodyplasias is not correlated to presence of coronary heart disease, peripheral arterial disease or other ischaemic vascular diseases. Further investigations are therefore necessary to understand the pathophysiology of angiodyplasias[4].

In contrast, the underlying pathophysiology of hereditary hemorrhagic telangiectasia (HHT, Osler’s disease) is better understood than those of sporadic angiodyplasias. Pathologic vessel growth in HHT is based on different mutations within the angiogenic signaling cascade, causing a stimulation of neoangiogenesis, which also implicates overproduction of VEGF. Due to its genetic origin HHT is classified as type I (mutations within the endoglin-gene, chromosome 9[8] and type II (activin receptor-like kinase 1 mutations; chromosome 12q)[9]. However, not all mutations have been identified. Especially, no genetic alterations have been found in patients with severe hepatic manifestation of Osler’s disease[10]. Corresponding to the different pathophysiology of vessel malformation in HHT, vascular lesions are not characterized by a flat tumorous appearance like sporadic angiodyplasias but present as enlarged ectatic vessels on mucosal surfaces (Table 1 and Figure 2), which may form net-like structures and are labeled

| Type of vascular malformation | Sporadic/senile Angiodysplasia | Angiectasia in HHT/Osler’s disease | Angiectasia associated to liver disease |
|--------------------------------|---------------------------------|-----------------------------------|----------------------------------------|
| Macroscopic appearance         | Flat complex cherry-red vascular tumors | Telangiectatic vessels | Telangiectatic vessels, watermelon stomach |
| Etiology                      | Unknown (local hypoxemia?) | Several mutations | Unknown; association to liver disease and portal hypertension |
| Site of manifestation          | Colon, stomach, small bowel | Nose; gastrointestinal tract; hepatic, pulmonal, cerebral shunts | Stomach, colon, small bowel |
| Age of manifestation          | Mostly > 50 yr | Mostly teenagers, adults < 40 yr | Related to liver disease; medium aged/older adults, rarely children |

HHT: Hereditary hemorrhagic telangiectasia.
A third important group of patients, in which bleeding from gastrointestinal malformations occurs are patients with liver cirrhosis, infrequently accompanied by clinical relevant portal hypertension. These patients present with different types of vascular malformations, some with angiodysplastic lesions, some with telangiectatic vessels and others with gastric arteriovenous ectasia (GAVE)-syndrome or watermelon stomach. GAVE is characterized by multiple vascular malformations in the prepyloric antral mucosa, appearing in a chain-like or disseminated fashion (Table 1 and Figure 3). The underlying pathophysiology of liver cirrhosis-associated vascular growth and appearance of malformations is not understood in detail. However, liver cirrhosis is also accompanied by multiple well-known vascular alterations like spider naevi or palmar erythema which are useful for establishing a diagnosis. As increased plasma levels of VEGF and basic fibroblast growth factor (bFGF) have been documented in cirrhotic patients, incidence of vascular lesions may reflect an unspecific generalized activation of angiogenesis\(^1\).

Despite different macroscopic appearance and different etiologies, vascular lesions in all three groups of patient are characterized by fragility of vessels, which lack a normal wall structure with a muscular layer. This makes such vessels or vessel-like structures susceptible to rupture and results in bleeding due to their superficial location. Another consistent finding of these vascular structures are short circuits between the arterial and venous system. In all gastrointestinal vascular malformations therapeutic anticoagulation or treatment with thrombocyte aggregation inhibitors like aminosalicylic acid are known to trigger manifestation or to aggravate bleeding. As a first treatment option for bleeding patients, anticoagulant therapy or thrombocyte aggregation inhibitors should be therefore ceased, whenever possible\(^1\).

**MEDICAL AND ENDOSCOPIC THERAPY**

From the 1950s on, gastrointestinal bleeding due to vascular malformations has been treated by estrogens with especially unpleasant side effects in men. Evidence for efficacy of this treatment had come from case reports and case series but not controlled studies. However, in the absence of other agents, hormonal therapy, mainly by use of ethinylestradiol, established as a standard treatment with unproven efficacy. Until the 1990s, impressive but small case series supported this concept\(^2\). With the invention of gastrointestinal endoscopy therapy switched to interventional treatment by heat or argon beamer coagulation, however endoscopic measures remain insufficient in cases of multiple vascular malformations. In severe cases, angiography or resection of bowel segments can also be performed, however, as angiodysplasias tend to recur in other bowel segments, often without lasting effect. In 2001 Junquera et al\(^2\) published a large randomized study in which the efficacy of hormones for treatment of bleeding from gastrointestinal angiodysplasia was investigated. In this trial 72 noncirrhotic patients bleeding from gastrointestinal angiodysplasia were randomized to receive treatment with ethinylestradiol plus norethisterone or placebo for at least 1 year in double-blind conditions. Failure of treatment occurred in 39% of patients in the treatment group and 46% of patients in the placebo group.
Furthermore, no differences were found according to number of bleeding episodes and transfusion requirements\textsuperscript{[2]}. Beside hormones other agents like somatostatin analogs were also evaluated for treatment of angiodysplasias within numerous case reports and retrospective investigations\textsuperscript{[13]}. Nardone et al\textsuperscript{[14]} reported efficacy of somatostatin in 40%-72% of patients. Another study demonstrated cessation of bleeding in 77% of patients, however in the control group bleeding also stopped in 55% of patients\textsuperscript{[15]}. Such an especial high rate of spontaneous cessation of bleeding may occur. Bleeding from gastrointestinal angiodysplasias can repeat for months to years and then stop spontaneously. However, it also indicates that bleeding episodes in these patients were less frequent or severe compared to other trials. Recently, a meta-analysis came to the conclusion that somatostatin analogs are an effective therapy for bleeding from gastrointestinal angiodysplasias\textsuperscript{[16]}. Present data therefore suggest that octreotide treatment may be beneficial in preventing rebleeding from gastrointestinal angiodysplasias. However, several uncontrolled studies also had suggested efficacy of hormonal therapy. Therefore further controlled studies should be performed to confirm the interesting data on use of somatostatin analogs.

**EFFICACY OF THALIDOMIDE FOR TREATMENT OF BLEEDING VASCULAR MALFORMATIONS**

The first use of thalidomide for treatment of bleeding from gastrointestinal angiodysplasias resulted from the occasional observation that the drug proved to be highly effective in patients with severe bleeding from Crohn’s disease\textsuperscript{[17]. Although anemia in Crohn’s disease may be quite severe\textsuperscript{[18], single episodes of intestinal bleeding in active Crohn’s disease are generally rather moderate. However, a small percentage of patients suffer from acute massive bleeding episodes. In our pilot study for use of thalidomide in steroid-resistant Crohn’s disease several patients suffered from recurrent severe bleeding episodes\textsuperscript{[17]}. The observation that thalidomide dramatically improved bleeding in these cases and one patient presented with multiple prominent angiodysplastic vessels in the colon led us to the idea that the substance may be also useful for an old patient with severe recurrent bleeding from multiple angiodysplasias in the small bowel and colon which presented in our hospital shortly afterwards. Thalidomide also proved to be highly effective in this situation\textsuperscript{[19]. We therefore further evaluated the efficacy of the drug in patients with angiodysplasias choosing a relatively low dose of 100 mg/night as we had observed substantial side effects with a dose of 300 mg in our initial trial in Crohn’s disease\textsuperscript{[17]. Thalidomide proved to be effective in several further series of patients with 100 mg/d being a dose with only moderate sedative side effects\textsuperscript{[19]. These results were confirmed by several other case reports and pilot studies\textsuperscript{[4,6]. In 2011 efficacy of thalidomide for treatment of bleeding from gastrointestinal angiodysplasias was ultimately proven in a randomized study\textsuperscript{[7]. In this study 55 patients with recurrent bleeding from gastrointestinal vascular malformations (at least 6 bleeding episodes in 1 year) unresponsive to endoscopic or medical approaches received either 100 mg thalidomide (n = 28) or 400 mg iron (n = 27, controls), daily for 4 mo. Patients were observed for one year before and at least one year after treatment. Patients with liver cirrhosis were excluded from the study. The primary end point was the effective response rate, defined as the proportion of patients in whom bleeding episodes had decreased by \( \geq 50\% \) in the first year of follow-up. Rates of response in the thalidomide and control groups were 71.4% and 3.7%, respectively (\( P < 0.001 \)). All secondary end points, which were rate of cessation of bleeding, blood transfusions, overall hospitalization, and hospitalization for bleeding differed significantly different between both patient groups. Not surprisingly, 32% of thalidomide-treated patients reported fatigue. However, no severe adverse effects were observed. VEGF plasma levels were reduced by thalidomide\textsuperscript{[7]. Thalidomide was also evaluated for treatment of hereditary hemorrhagic telangiectatic. To date, at least 31 patients were treated within case studies and small patient series\textsuperscript{[20,21]. Thalidomide at a dose of 50-250 mg/d (mostly 100-200 mg) was shown to reduce frequency and intensity of nosebleeding, reduction of transfusion requirements and improvement of quality of life\textsuperscript{[21]. In an experimental model of HHT with mice heterozygous for a null mutation in the Eng gene (encoding endoglin), thalidomide treatment stimulated mural cell coverage and rescued vessel wall defects and also increased platelet-derived growth factor-B (PDGF-B) expression in endothelial cells and stimulated mural cell activation. Within the same study, biopsies of nasal epithelium taken from patients with HHT treated with thalidomide showed that similar mechanisms may be present in humans\textsuperscript{[22]. Although these clinical and experimental findings are promising, a randomized study for treatment of HHT is still missing. Thalidomide was further used for patients with cirrhosis and gastrointestinal bleeding related to vascular malformations. Two case reports and a correspondence letter reported on efficacy of thalidomide in this setting\textsuperscript{[23-25]. Garrido Serrano et al\textsuperscript{[25} employed a dose of 200 mg/d in 19 patients, finding an increase of haemoglobin levels during a 4-mo treatment. However, hepatic encephalopathy was frequently observed in these patients (42%), and was speculated to be related to thalidomide. Unfortunately, only sparse data are given and treatment or bleeding
episodes were not well documented. As 200 mg/d thalidomide presents a dose with relevant sedative side effects, the incidence of hepatic encephalopathy may also have been overestimated. Furthermore, no data are given on follow-up after end of treatment. Therefore, current information on the use of thalidomide in patients with cirrhosis is very limited and has to be interpreted with caution.

Another indication, in which thalidomide was reported to be effective, is rectal bleeding related to radiation-induced proctitis\textsuperscript{[26]}. Thalidomide was found to improve bleeding in a patient with multiple bleeding episodes. We also used thalidomide in this setting and could document reduction of bleeding episodes and rectal ectatic vessels.

**EFFECTS AND TOXICITY OF THALIDOMIDE**

Initially, thalidomide was developed in Germany in the 1950s as a sedative before benzodiazepines became available. Later on it was recommended for morning sickness due to a moderate antiemetic effect. After it had not been possible to determine an LD 50 in rat experiments, thalidomide was falsely rated to be a particularly safe drug. In spite of a missing systematic evaluation of security in humans, which was not standardly performed in the 1950s, thalidomide became obtainable without a prescription. During 5 years between the first birth of a child with phocomelia and recognition of its teratogenic effects in 1961 about 10000 children with shortened extremities and organ deformations were born, many of them in Germany, where thalidomide was the most commonly used sedative with more than 140 million tablets sold in 1960\textsuperscript{[27]}. After it had already been taken from the market, Sheskin J, an Israeli dermatologist, discovered an antiproliferative activity in erythema nodosum leprosum (ENL), a late manifestation of leprosy, which can cause severe insomnia due to leprotic neural infiltrations\textsuperscript{[28]}. Further studies confirmed its efficacy in ENL. Thalidomide is still regarded as a treatment of choice in ENL by the WHO and was approved by the NIH of the United States in 1998\textsuperscript{[27]}.

After thalidomide was also detected to suppress tumor necrosis factor, it was also successfully used for treatment of Crohn’s disease\textsuperscript{[14,29,30]}. However, thalidomide is not only an immune modulator but also an inhibitor of angiogenesis. This activity, which involves VEGF und bFGF mediated effects was discovered in 1994\textsuperscript{[31]} and may be also responsible for its teratogenicity. The exact mechanism for its antiangiogenic activity is unclear but is not caused by thalidomide itself but by species-specific hepatic metabolites. *In vitro*-studies demonstrated thalidomide-induced impaired vessel growth of explanted rat vessels or human endothelial cells only if these are co-incubated with human or canine liver microsomes, but not with rat liver microsomes\textsuperscript{[32]}. Consistent with these findings rats were shown to be highly resistant to thalidomide-mediated teratogenic effects, whereas canines and higher primates proved to be highly sensitive\textsuperscript{[33]}.

This well documented teratogenicity, although from today’s perspective not really a surprise for any drug with antiproliferative or antiangiogenic activity, is thalidomide’s great burden. In fact, the so-called Thalidomide experience in the 1960s dramatically changed perception of drugs. Before thalidomide, evaluation of drug safety wasn’t standardized as nowadays and human teratology was just developing. Interestingly, during the first half of the 20\textsuperscript{th} century the human placenta was believed to be impermeable and to act as a perfect barrier to the fetus\textsuperscript{[34]}. In this situation thalidomide entered western medicine and changed the paradigm of the human placenta, which was since then newly realized to be especially vulnerable against toxins. Thalidomide became notorious as a most toxic substance and is still handled with extreme caution in western countries, although numerous chemotherapeutic agents have a similar toxicity. Especially in Germany, where the thalidomide trial was the second largest after the Nuremberg Nazi trials, physicians are very cautious in using this drug. Governmental restrictions with observational programs and special receipts further impede its use. In the United States the System for Thalidomide Education and Prescribing Safety Programm (www.celgene.com) was initiated when thalidomide was approved. This program *i.e.* includes that women with child-bearing potential are obliged to watch a movie or pictures of children with phocomelia. Such measures have prevented the birth of malformed children, however could be applied for any chemotherapeutic agent. It is to be feared that the special attention on thalidomide’s side effects also restricts its use, an effect which also contributes to its very limited use in Crohn’s disease despite recent promising results\textsuperscript{[35]}. Furthermore, thalidomide is not patented since several decades, resulting in a lack of marketing by pharmaceutical companies.

Patients with bleeding from sporadic angiodysplasias are generally old and the overwhelming majority of women don’t have child-bearing potential, which is also true for women with liver cirrhosis-associated vascular malformations. Teratogenicity therefore is not an important issue in these cases. However, the situation is different in patients with HHT. Bleeding in HHT occurs at all ages and therefore thalidomide has to be handled very carefully in this situation. Interestingly, a relatively short treatment with thalidomide (3-4 mo) exerts a lasting effect on bleeding from sporadic angiodysplasias. In many patients clinically relevant bleeding does not recur for several years\textsuperscript{[19]}. However, a disease with a genetic basis like HHT presumably has to be treated repeatedly or for longer periods of time.
Regarding long-term treatment sedation, which is relatively mild at a nightly dose of 100 mg/d and especially neurotoxicity are the most relevant side-effects of thalidomide. Early studies reported on peripheral sensoric neuropathy in 1%-25% of patients[36], which also seems to be dose-dependent. An increased incidence of neuropathy was reported for cumulative doses > 20 g or 40 g, respectively[37]. Our own clinical investigations confirm these findings, in our patients neuropathy first occurred after 9 mo continuous treatment in a patient with Crohn’s disease. In this case, thalidomide treatment was stopped due to paresthesia. Unfortunately, severe bleeding related to Crohn’s disease occurred after cessation of thalidomide and was not controllable by steroids or immunosuppressants. Therefore, thalidomide was started again at a lower dose and was effective once more. Because of previous polyneuropathy, thalidomide was then applied at a lower dose (100 mg instead of 300 mg) and one more time proved to be effective. However, after further 20 mo treatment, paresthesia occurred again and thalidomide finally had to be terminated.

The underlying pathophysiology of neurotoxicity is not clear. As VEGFs exerts both neurotrophic and neuroprotective effects[38] and neural cells express neuropilin-1, an additional VEGF-receptor, which is implicated in axonal regeneration[39], it seems possible that neurotoxicity of thalidomide is also related to antiangiogenic effects. However, potential neurotoxicity should not be considered a general contraindication against treatment. Electromyography allows sensitive diagnosis of preexisting neuropathies and monitoring of subclinical neurotoxic effects. After dose reduction or cessation of thalidomide, neuropathy is generally reversible.

Numerous cases of venous thrombosis have been reported during treatment with thalidomide, suggesting an increased risk of thromboembolic events[40]. However, most of these reports come from patients with malignant diseases, especially multiple myeloma, which are also associated with thrombosis. On the other hand, neither in pilot trials in non-malignant diseases nor in the study of Ge et al[7] for treatment of bleeding from angiodysplasias, thromboembolic events were observed[3-5,7,16,19,22,29,30,35]. Further studies are necessary to definitely clear this question.

CONCLUSION

Thalidomide is a very valuable drug for treatment of gastrointestinal bleeding from vascular malformations. However, due to its very special history, thalidomide is treated as a highly toxic drug in western countries and is also not marketed by pharmaceutical companies, impeding widespread use. In patients with no child-bearing potential neurotoxicity is the most relevant side-effect, especially for long-term treatment.

REFERENCES

1. Gordon FH, Watkinson A, Hodgson H. Vascular malformations of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2001; 15: 41-58 [PMID: 11355900 DOI: 10.1053/bega.2000.0155]
2. Junquera F, Feu E, Papo M, Videla S, Armengol JR, Bordas JM, Saperas E, Piqué JM, Malagaldeja JR. A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. Gastroenterology 2001; 121: 1073-1079 [PMID: 11677198 DOI: 10.1053/gast.2001.28650]
3. Bauditz J, Schachschal G, Wedel S, Lochs H. Thalidomide for treatment of severe intestinal bleeding. Gastroenterology 2002; 122: A194
4. Shurafa M, Kambo G. Thalidomide for the treatment of bleeding angiodysplasias. Am J Gastroenterol 2003; 98: 221-222 [PMID: 12526972 DOI: 10.1111/j.1572-0241.2003.07201.x]
5. Bauditz J, Lochs H, Voderholzer W. Macroscopic appearance of intestinal angiodysplasias under antiangiogenic treatment with thalidomide. Endoscopy 2006; 38: 1036-1039 [PMID: 17908171 DOI: 10.1055/s-2006-944829]
6. Dahak V, Kuriakose P, Kambo G, Shurafa M. A pilot study of thalidomide in recurrent GI bleeding due to angiodysplasia. Dig Dis Sci 2008; 53: 1632-1635 [PMID: 17990111 DOI: 10.1007/s00607-006-0067-9]
7. Ge ZZ, Chen HM, Gao YJ, Liu WZ, Xu CH, Tan HH, Chen HY, Wei W, Fang JY, Xiao SD. Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. Gastroenterology 2011; 141: 1629-1637.e1-e4 [PMID: 21784047 DOI: 10.1053/j.gastro.2011.07.018]
8. McAlister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 1994; 8: 345-351 [PMID: 7894484 DOI: 10.1038/ng1294-345]
9. Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, Stenzel TT, Speer M, Pericak-Vance MA, Diamond A, Guttmacher AE, Jackson CE, Attisano L, Kucherlapati R, Porteous ME, Marchuk DA. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat Genet 1996; 13: 189-195 [PMID: 86042255 DOI: 10.1038/ng0696-189]
10. Piantanida M, Buscarini E, Dellaveccchia C, Minelli A, Rossi A, Buscarini L, Danesino C. Hereditary haemorrhagic telangiectasia with extensive liver involvement is not caused by either HHT1 or HHT2. J Med Genet 2001; 38: 10620-007-0067-z
11. van Cunen E, van de Meent S, Ruts A, Vantrappen G. Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. Lancet 1990; 335: 953-955 [PMID: 1976032 DOI: 10.1016/S0140-6736(00)01106-8]
12. Li CP, Lee FY, Hwang SJ, Lu RH, Lee WP, Chao Y, Wang SS, Chang FY, Whang-Peng J, Lee SD. Spider angiomata in patients with liver cirrhosis: role of vascular endothelial growth factor and basic fibroblast growth factor. World J Gastroenterol 2003; 9: 2832-2835 [PMID: 14669345 DOI: 10.3748/wjg.v9.i12.2832]
13. van Cunen E, Rutgeerts P, Vantrappen G. Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. Lancet 1990; 335: 953-955 [PMID: 1976032 DOI: 10.1016/S0140-6736(00)01106-8]
14. Nardone G, Compare D, Scarognato C, Rocco A. Long acting release-octreotide as “rescue” therapy to control angiodysplasia bleeding: A retrospective study of 98 cases. Dig Liver Dis 2014; 46: 688-694 [PMID: 24893688 DOI: 10.1016/jjd.2014.04.011]
15. Junquera F, Saperas E, Videla S, Feu F, Villaseca J, Armengol JR, Bordas JM, Papé JM, Malagaldeja JR. Long-term efficacy of octreotide in the prevention of recurrent bleeding from gastrointestinal angiodysplasia. Am J Gastroenterol 2007; 102: 254-260 [PMID: 17631630].
Bauditz J. Treatment of gastrointestinal bleeding with thalidomide

17311647 DOI: 10.1111/j.1572-0241.2007.01053.x

16 Jackson CS, Gerson LB. Management of gastrointestinal angiodysplastic lesions (GIADs): a systematic review and meta-analysis. *Am J Gastroenterol* 2014; 109: 474-483; quiz 484 [PMID: 24642577 DOI: 10.1038/ajg.2014.19]

17 Bauditz J, Wedel S, Lochs H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn’s disease. *Gut* 2002; 50: 196-200 [PMID: 11788559 DOI: 10.1136/gut.50.2.196]

18 Schreiber S, Howaldt S, Snoor M, Nikolaus S, Bauditz J, Gasché C, Lochs H, Raedler A. Recombinant erythropoetin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996; 334: 639-642 [PMID: 8925254 DOI: 10.1056/NEJM199603073341002]

19 Bauditz J, Schachschal G, Wedel S, Lochs H. Thalidomide for treatment of severe intestinal bleeding. *Gut* 2004; 53: 609-612 [PMID: 15016759 DOI: 10.1136/gut.2003.029710]

20 Kurstin R. Using thalidomide in a patient with epithelioid leiomyosarcoma and Osler-Weber-Rendu disease. *Onkologie* (Williston Park) 2002; 16: 21-24 [PMID: 11831608]

21 Franchini M, Frattini F, Crestani S, Bonfanti C. Novel treatments for epistaxis in hereditary hemorrhagic telangiectasia: a systematic review of the clinical experience with thalidomide. *J Thromb Thrombolysis* 2013; 36: 355-357 [PMID: 23143669 DOI: 10.1007/s11239-012-0840-5]

22 Lebrin F, Srun S, Raymond K, Martin S, van den Brink S, Freitas C, Bréant C, Mathivet T, Larivière B, Thomas JL, Arthur HM, Westermann CJ, Disch F, Mager JF, Snijder RJ, Eichmann A, Mummery CL. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. *Nat Med* 2010; 16: 420-425 [PMID: 20364125 DOI: 10.1038/nm.2131]

23 Karajeh MA, Hurlstone DP, Stephenson TJ, Ray-Chaudhuri D, Gleeson D. Refractory bleeding from portal hypertensive gastropathy: a further novel role for thalidomide therapy? *Eur J Gastroenterol Hepatol* 2006; 18: 545-548 [PMID: 16607153 DOI: 10.1097/00006532-200605000-00016]

24 Moser S, Fischer A, Karpf A, Schleicher M, Stavjanik S, Gschwantler M. Evidence that thalidomide is effective in recurrent bleeding from watermelon stomach associated with liver cirrhosis. *Endoscopy* 2014; 46 Suppl 1 UCTN: E384 [PMID: 25254589 DOI: 10.1055/s-0034-1377369]

25 Garrido Serrano A, León R, Sayago M, Márquez JL. Thalidomide treatment in cirrhotic patients with severe anemia secondary to vascular malformations. *Dig Dis Sci* 2012; 57: 1112-1113 [PMID: 22089255 DOI: 10.1007/s10620-011-1971-9]

26 Craenen ME, van Triest B, Verheijen RH, Mulder CJ. Thalidomide in refractory haemorrhagic radiation induced proctitis. *Gut* 2006; 55: 1371-1372 [PMID: 16905712 DOI: 10.1136/gut.2006.099416]

27 Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet* 2004; 363: 1802-1811 [PMID: 15172781 DOI: 10.1016/S0140-6736(04)63083-8]

28 Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther* 1965; 6: 303-306 [PMID: 14296027]

29 Ehrenreich ED, Kane SV, Cohen LB, Cohen RD, Hanauer SB. Thalidomide therapy for patients with refractory Crohn’s disease: an open-label trial. *Gastroenterology* 1999; 117: 1271-1277 [PMID: 10579967 DOI: 10.1016/S0016-5085(99)70276-3]

30 Vasilioukas EA, Kam LY, Abreu-Martin MT, Hassard PV, Papadakis KA, Yang H, Zeldis JB, Targan SR. An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn’s disease. *Gastroenterology* 1999; 117: 1278-1287 [PMID: 10579968 DOI: 10.1016/S0016-5085(99)70277-5]

31 D’Amato RJ, Lowenhoff MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; 91: 4082-4085 [PMID: 7513432 DOI: 10.1073/pnas.91.9.4082]

32 Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. *Biochem Pharmacol* 1998; 55: 1827-1834 [PMID: 9741304 DOI: 10.1016/S0006-2952(98)00006-X]

33 Gordon GB, Spielberg SP, Blake DA, Balasubramanian V. Thalidomide teratogenesis: evidence for a toxic aren oxide metabolite. *Proc Natl Acad Sci USA* 1981; 78: 2548-2549 [PMID: 6941308 DOI: 10.1073/pnas.78.4.196]

34 Dally A. Thalidomide: was the tragedy preventable? *Lancet* 1998; 351: 1197-1199 [PMID: 9643709 DOI: 10.1016/S0140-6736(97)09038-7]

35 Lazerini M, Martelloso S, Magazzù G, Pellegrino S, Lucanto MC, Barabino A, Alvi A, Arrigo S, Lionetti P, Lorusso M, Mangiantini F, Fontana M, Zuin G, Palli G, Maggiore G, Bramuzzo M, Pellegrin MC, Maschio M, Villanacci V, Mantesi S, Decorti G, De Iudicibus S, Paparazzo R, Montico M, Ventura A. Effect of thalidomide on clinical remission in children and adolescents with refractory Crohn disease: a randomized clinical trial. *JAMA* 2013; 310: 2164-2173 [PMID: 22481461 DOI: 10.1001/jama.2013.280777]

36 Ochonsky S, Verroust J, Bastuji-Garin S, Gherardi R, Revuz J. Thalidomide neuropathy incidence and clinic-electrophysiological findings in 42 patients. *Arch Dermatol* 1994; 130: 66-69 [PMID: 8285742 DOI: 10.1001/archderm.130.1.66]

37 Cavaletti G, Beronio A, Reni L, Ghiglione E, Schenone A, Brianzi C, Zara G, Cecchi D, Isardo G, Ciaramarzo P, Plassma R, Pastorelli F, Frigo M, Piatti M, Carpo M. Thalidomide sensory neurotoxicity: a clinical and neurophysiological study. *Neurology* 2004; 229: 1229-1232 [PMID: 15201988 DOI: 10.1212/WNL.62.12.2291]

38 Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, Greenberg DA. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. *J Clin Invest* 2003; 111: 1843-1851 [PMID: 12813020 DOI: 10.1172/JCI200317977]

39 Sokor S, Takashima S, Miao HQ, Neufeld G, Klagsbrun M. Neuropillin-1 is expressed by endothelial and tumor cells as an isofrom-specific receptor for vascular endothelial growth factor. *Cell* 1998; 92: 735-745 [PMID: 9529250 DOI: 10.1016/S0009-8674(00)81402-6]

40 Bennett CL, Angelotta C, Yarnold PR, Evens AM, Zonder JA, Raisch DW, Richardson P. Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 2006; 296: 2558-2560 [PMID: 17148721 DOI: 10.1001/jama.296.21.2558-c]

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