Update on medical therapy for obscure gastrointestinal haemorrhage

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ABSTRACT

The development of capsule endoscopy and double-balloon enteroscopy has increased diagnostic and therapeutic rates in obscure gastrointestinal hemorrhage, where angiodysplasia of the small bowel is the most frequent cause. Nevertheless, almost 25-40% of patients who are not candidates or do not respond to endoscopic, angiographic, or surgical management may be at high risk of rebleeding, and therefore lack a clearly effective medical therapy. The utility of hormonal therapy remains unclear and is burdened by adverse effects. Subcutaneous octreotide usually controls bleeding but does not seem adequate for maintenance therapy. Non-selective beta-blockers alone or in combination with other treatments, as in the prophylaxis of portal hypertension variceal bleeding, may be helpful. Recently, octreotide LAR, a depot formulation administered once a month intramuscularly, and oral thalidomide, a powerful inhibitor of angiogenesis, have demonstrated their effectiveness and safety for long-term therapy in anecdotal case reports and deserve further investigation.


INTRODUCTION

Obscure gastrointestinal hemorrhage (OGIH) is defined as bleeding of unknown origin despite primary endoscopic studies (upper endoscopy and colonoscopy including ileal intubation). It is an uncommon clinical scenario (5% of all gastrointestinal bleeding) and can be classified into two different clinical forms: obscure-occult, as manifested by iron-deficiency anemia or positive fecal occult blood test, and obscure-overt, with recurrent passage of visible blood. The most frequent underlying lesions are small-bowel angiodysplasia as primary disease or as a gastrointestinal manifestation of several entities such as hereditary hemorrhagic telangiectasia, von Willebrand’s disease, connective tissue diseases (pseudoxanthoma elasticum, Ehlers-Danlos syndrome), radiation enteritis, end-stage renal disease, portal hypertension, valvular cardiopathies, or vasculitis. The small bowel is now fully accessible for diagnosis and therapy...
owing to the recent development of capsule endoscopy
and double-balloon enteroscopy; nevertheless, most re-
ported studies showed a diagnostic yield not greater than
75-80% at best when combining both techniques, so a
quarter of the patients lack a clear diagnosis despite ex-
haustive study (1-5). Moreover, a variable percentage of
patients with diagnosis may not be tributary to aggressive
therapeutic management due to severe comorbidity, dif-
fuse distribution of lesions, or absence of response to en-
doscopic, surgical, or angiographic therapies.

In this setting, the available medical therapy for OGIH
is limited, with questionable efficacy in some cases and
most of the times subject to empirical therapeutic trials.
The low overall prevalence of candidates for medical ther-
apy (1-2% of all gastrointestinal bleedings) is the main rea-
son why there are no longitudinal controlled studies ad-
ressing this issue, so therapy can only be guided by
means of isolated case reports or small uncontrolled series
of patients. Indications for medical therapy in OGIH, as
approved in the latest American Gastroenterology Associ-
technical review (6), are listed in table I.

Table I. Indications for medical therapy in obscure
gastrointestinal hemorrhage

| 1. Patients who are not candidates or do not respond to endosco-
| pic, surgical or angiographic therapy |
| 2. Diffuse vascular lesions in the small bowel or extended to upper |
| or lower segments |
| 3. Relative inaccessible location of lesions for endoscopic devices |
| 4. Source of bleeding unknown |

In this report we aim to show the largest number of
therapeutic options described in the literature to face the
challenge of medical therapy for patients with OGIH,
most of them elderly with comorbidity and even some-
times on antiaggregant or anticoagulant therapies, which
increases the potential risk of bleeding. These drugs have
been often used in combination schedules (7,8).

The different pharmacotherapeutic agents that have
been used to date in the literature for OIGH are listed in
table II.

| Table II. Pharmacological agents used in obscure |
gastrointestinal hemorrhage |
| 1. Estrogen-progesterone combination therapy |
| 2. Somatostatin analogs |
| Octreotide |
| Octreotide LAR |
| 3. Non selective beta blockers |
| 4. Thalidomide |
| 5. Miscellaneous (antifibrinolitics, danazol, desmopressin, recom-
| binant-activated fVIIa) |

HORMONAL THERAPY

Estrogen-progesterone combination therapy has been
the first-choice therapy for OGIH until recently. Its utility
in this clinical setting was first hypothesized because of
reports of improvement of epistaxis in patients with heredi-
tary hemorrhagic telangiectasia during pregnancy
and further relapse in the puerperium (9). Furthermore, it
proved to be effective in decreasing gastric hyperemia in
hereditary hemorrhagic telangiectasia during pregnancy
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0.05 mg and norethisterone 1-3 mg. This therapy should
be used in six-month courses with pauses to reduce the
incidence of adverse effects, mostly due to the estrogen
component (vascular thrombosis, gynecomastia and loss
of libido in men, breast tenderness and vaginal bleeding
in women). Discordant results have been shown in the
studies evaluating the effectiveness of hormonal therapy
for bleeding angiodysplasia. Van Cutsem et al. (12)
demonstrated that transfusion requirements were signifi-
cantly lower in patients on hormonal therapy in a clinical
trial of nine patients suffering from gastrointestinal vas-
cular malformations.

Nevertheless, a subsequent trial with a larger sample
size in patients with small-bowel angiodysplasia showed
no benefit from hormonal therapy compared to those re-
ceiving placebo (13). The lack of benefit from hormonal
therapy has been confirmed furthermore in the largest
placebo-controlled trial to date, in which 72 non-cirrhotic
patients bleeding from documented angiodysplasia were
included (14), with similar rates in both groups of treat-
ment failure, rebleeding and transfusion requirements.
However, this study has setbacks such as the use of low
doses of ethynil estradiol and the exclusion of patients
with vascular ectasia associated with cirrhosis and hered-
itary hemorrhagic telangiectasia (15,16), who might have
had the greatest benefit from this therapy. In light of the
these new data, hormonal therapy effectiveness remains
unclear and is further burdened by adverse effects, so
there appears to be little or no role for hormonal therapy
in patients with bleeding from angiodysplasia, except
possibly those with hereditary hemorrhagic telangiecta-
sia, von Willebrand’s disease, end-stage renal disease in
OGIH (17), and bleeding from gastric antral vascular ec-
tasia syndrome out of OGIH spectrum (18,19), where a
more solid clinical benefit has been proved, although
without improvement in the endoscopic appearance of le-
sions. Despite the low cost of hormonal therapy, recent
reports on the effectiveness of other agents with an im-
proved safety profile displaces hormonal therapy from as
first-line therapeutic option for OGIH.

SOMATOSTATIN ANALOGS

Historically octreotide has been widely used after fail-
ure of combined hormonal therapy. It is a somatostatin
Octreotide has been reported to be successful in stopping gastrointestinal bleeding from angiodysplasia in uncontrolled series and reports of isolated cases, both in acute hemorrhage (20-22) and chronic bleeding as long-term therapy (23-26), with sustained response in some cases after therapy discontinuation. The first comparative cohort study showing the benefit of long-term octreotide in preventing bleeding from angiodysplasia as compared to placebo has been recently reported (27). Octreotide markedly reduced the risk of rebleeding with a significant decrease in iron requirements when compared to placebo, but no differences were showed in terms of hemoglobin levels or transfusion requirements between both groups.

Response is immediate and the drug can be administered intravenously (50 µg per hour) or subcutaneously (50-100 µg two or three times a day). Its subcutaneous administration and its longer half-life (90-100 minutes) versus somatostatin allow its use in the outpatient setting. No significant adverse events have been reported, except mild hyperglycemia due to the inhibition of hormone secretion from the pancreas and the gastrointestinal tube. The basic disadvantage of this drug for long-term therapy is the need for parenteral administration several times a day.

**Octreotide LAR (Long Acting Release)** is a depot formulation of octreotide currently approved for acromegaly and gastrointestinal and pancreatic neuroendocrine tumors. Compared to conventional octreotide, octreotide LAR is administered intramuscularly once per month with a similar efficacy and safety profile, and does not require hospital admission, which makes it an attractive outpatient option for long-term therapy in OGIH. The effectiveness of octreotide LAR for OGIH has been described in three reports in the literature; in a series of three patients one had chronic bleeding from small-bowel angiodysplasia and the other two patients (one with von Willebrand’s disease) had severe OGIH in which the source of bleeding was not found despite exhaustive study (8,28,29). Our Unit has recently published an innovative report on octreotide LAR for severe OGIH in two anticoagulated patients with severe comorbidity and subsequent exacerbation of medical conditions (30). In one patient OGIH was idiopathic, while the other patient had diffuse small-bowel angiodysplasia. Despite a requirement for continuous anticoagulation due to a background of severe cardiovascular events, both cases required no further blood transfusions during nine months of octreotide LAR therapy. No adverse effects or drug interactions were detected. It had been used in all reports at a dose of 20 mg intramuscularly once a month, without a clear reason for not using formulations of 10 or 30 mg. The main disadvantage of this drug formulation may be its cost (from 700 to 1,100 € monthly, depending on the dose), compared to hormonal therapy and conventional octreotide. However, in very specific cases that are only tributary to conservative management it may prove to be cost-effective, particularly if one considers the economic and medical resources saved, as well as the psychological benefits for patients and families as a result of outpatient management.

Its safety profile and comfortable administration as compared to the rest of drugs listed in these report may be the most attractive potential of octreotide LAR in OGIH. Unfortunately, the appropriate dose and schedule required for long-term therapy are not known, but may be elucidated in further studies.

**NON-SELECTIVE BETA-BLOCKERS**

These drugs aim to control hemorrhage by reducing gastrointestinal blood flow due to splanchnic vasoconstriction and reduction of cardiac output. Its benefit in primary and secondary prophylaxis of variceal bleeding in portal hypertension has been demonstrated in many studies, even sometimes for portal hypertensive gastropathy and colopathy (19,20); however, its use in OGIH is anecdotal. In OGIH it has been used at conventional doses (60-80 mg per day), as monotherapy or combined with octreotide LAR for bleeding from small-bowel angiodysplasia related to hypertrophic subaortic stenosis, and in OGIH with an unknown source of bleeding (8,31).

**THALIDOMIDE**

Thalidomide is a drug with powerful immunomodulatory, anti-inflammatory and antiangiogenic effects that was withdrawn from the market in the 1960’s because of its teratogenicity; it has been recently reintroduced for the treatment of leprosy, multiple myeloma, and various tumors. In the last few years vascular endothelial growth factor (VEGF) has been identified as the key mediator for endothelial vessel formation in early phases of angiogenesis. High concentrations of VEGF result in aberrant angiogenesis with formation of angiodysplastic lesions that lack a smooth muscle cell layer and are more susceptible to rupture and bleeding. VEGF-dependent angiogenesis is inhibited by thalidomide.

Thalidomide is an innovative and promising therapeutic option for OGIH associated with angiodysplasia, and can be used in refractory cases or when other drugs or therapies are contraindicated. It is administered orally at a variable dose of 100-300 mg per day, and no significant adverse effects have been reported for OGIH, except...
transient fatigue; however, thalidomide is contraindicated in peripheral neuropathy, pregnancy, and in women with childbearing potential because of its teratogenic effects, and should be cautiously used in patients with cardiovascular or neurological disorders and hepatic or renal impairment. Owing to its immunosuppressant activity by blocking tumor necrosis factor, its use may be also discouraged in patients at risk for infection or chronic infectious disease, specially HIV patients. In all these clinical settings octreotide LAR may be safer than thalidomide for OGIH.

Thalidomide has recently demonstrated its effectiveness to control refractory bleeding from refractory bleeding portal hypertensive gastropathy and radiation-induced hemorrhagic proctitis (32,33). To date there are a few, quite recent reports on the literature about the effectiveness of thalidomide for OGIH. It was successfully used in a patient with von Willebrand’s disease and life-threatening bleeding due to small-bowel angiodysplasia refractory to other treatments such as tranexamic acid, desmopressin, octreotide, recombinant activated factor VII, and endoscopic cauterization with an argon beam laser (34). It has also been proven effective in controlling bleeding from diffuse idiopathic angiodysplastic lesions in the small bowel (35-37), chronic bleeding in Crohn’s disease and in OGIH with unknown source of bleeding (38). Recently, Bauditz et al. (39) studied the effect of thalidomide at a dose of 100 mg daily for 3 months in 3 patients with chronic bleeding from small-bowel angiodysplasia evidenced by wireless capsule endoscopy. Bleeding was controlled in all cases despite drug discontinuation for a median follow-up of 34 months. Repeat capsule endoscopy after therapy revealed a substantial reduction in lesion numbers, size, and color intensity.

Due to the fact that thalidomide inhibits angiodysplasia formation, its effect is prolonged despite therapy discontinuation. Some reports describe a control of further bleeding after a few months of thalidomide therapy, even with 1-2 years of follow-up.

**MISCELLANEOUS**

**Antifibrinolytics**

Aminocaproic acid (ACA) is a powerful inhibitor of the fibrinolytic system that blocks conversion of plasminogen to plasmin when used at low doses. There is only one isolated report in which ACA was effective in the management of epistaxis from arteriovenous malformations in two patients with hereditary hemorrhagic telangiectasia at a dose of 1.5 g twice a day, although it was not clear whether concomitant gastrointestinal bleeding was present (40).

Tranexamic acid is a synthetic lysine analog that inhibits the conversion of plasmin to fibrinogen, with less antifibrinolytic power than ACA. It has been used successfully for chronic bleeding from angiodysplasia in patients with end-stage renal failure at doses of 10-20 mg/kg every 48 hours, and it still remains unclear whether a long-term therapy or an as-needed therapy is preferable during hemorrhagic crises (41,42).

The main risk derived from the use of antifibrinolytics is thrombosis, so thrombophilia should be ruled out before prescribing them. Adverse events associated to ACA and tranexamic acid may be frequent, and the use of these drugs is not supported by randomized controlled trials, which makes antifibrinolytics a last option for OGIH. Due to their mechanism of action, antifibrinolytics may have a more important role for OGIH in patients with hematological disorders.

**Danazol**

Danazol is an anti-gonadotropin drug with weak androgenic activity that blocks pituitary secretion of FSH and LH, leading to ectopic and normal endometrial tissue atrophy. It has been widely used for endometriosis and uterine bleeding disorders. Anecdotal reports suggest a partial improvement in patients with gastrointestinal bleeding and hereditary hemorrhagic telangiectasia (43,44), although cosmetic stigmata (acne, hair loss, mild hirsutism) and uncommon but severe adverse effects (intracranial hypertension, peliosis hepatis, thrombosis, seizures) consign danazol to a secondary role in OGIH, when other therapies have failed.

**Desmopressin**

Desmopressin is a synthetic analog of the antidiuretic hormone vasopressin that lacks vasoressor activity. It increases von Willebrand’s factor and factor VIII levels, and also enhances hemostasis in patients with defective platelet function. It is indicated as a hemostatic therapy for patients with hemophilia A and von Willebrand’s disease, and can be administered intravenously, subcutaneously, or by intranasal spray. An isolated report showed a benefit of intravenous desmopressin for life-threatening gastrointestinal bleeding in a patient with hereditary hemorrhagic telangiectasia and von Willebrand’s factor deficiency, allowing elective colectomy and bleeding resolution (45).

**Recombinant activated factor VII**

Recombinant activated human factor VII is a novel drug that strongly promotes hemostasis, and is currently indicated for hemophilic A and B patients with antibody inhibitors to coagulation factors VIII or IX, congenital deficiency of factor VII, and Glanzmann’s thromboasthenia. The use of this drug has widely spread for controlling
hemorrhage, with or without hematological disorders, in massive or uncontrollable bleeding at any location. Its short half-life of 2 hours requires frequent boluses or continuous infusion to achieve hemostasis, and it can induce definite control of bleeding or be a bridge until a causal therapy can be provided. It has been mainly used in cirrhotic patients with acquired coagulation factor deficiencies, especially in variceal and non-variceal upper gastrointestinal hemorrhage related to cirrhosis or acute liver failure (46-48), although it has been used in other settings, including refractory bleeding after endoscopic sphincterotomy in patients with preexisting coagulopathy (49). Sporadic reports have shown the effectiveness of factor VIIa in patients with von Willebrand’s disease for OGIH due to small-bowel angiodysplasia or of unknown origin (50,51). Owing to its marked prothrombotic activity, secondary myocardial and cerebrovascular infarctions have been described while using factor VIIa (51,52), so particular care should be taken in patients with cardiovascular high-risk profile, and the indication should be assessed for each individual case.

**CONCLUSION**

In conclusion, combined hormonal therapy and other miscellaneous treatments (antifibrinolytics, desmopressin, danazol, recombinant activated factor VIIa) should be considered currently useful for OGIH in patients with hereditary hemorrhagic telangiectasia, von Willebrand’s disease, and end-stage renal disease. In OGIH from small-bowel angiodysplasia or of unknown origin without the above-mentioned diseases, octreotide is effective and safe, but burdened by its parenteral administration several times a day. In the future, octreotide LAR, oral thalidomide, and its potential combination with non-selective beta-blockers will probably be the pharmacologically cornerstone replacing hormonal therapy and conventional octreotide, due to its easy administration, good tolerability, and absence of major adverse effects. Further studies are needed to confirm this hypothesis and to elucidate the adequate dose and schedule needed for these novel and promising drugs.

**REFERENCES**


