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Alimentary Tract

Long acting release-octreotide as "rescue" therapy to control angiodysplasia bleeding: A retrospective study of 98 cases

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ABSTRACT

Background: Gastrointestinal angiodysplasias are an important cause of difficult to manage bleeding, especially in older patients.
Aim: To retrospectively evaluate the long-term efficacy of long acting release-octreotide in controlling angiodysplasia bleeding.
Methods: 98 patients with a history of bleeding due to gastrointestinal angiodysplasias lasting over 2 years were retrospectively selected among those treated from January 2000 to December 2008. All patients had received octreotide 0.1 mg tid for 28 days and, then from day 14, long acting release-octreotide 20 mg monthly, for 6 months.
Results: The mean follow-up was 78 months. In all patients mean haemoglobin levels significantly increased and the number of bleeding episodes, hospitalizations, patients requiring blood transfusions and units of transfused red cells significantly decreased, compared to the two-year observation period before starting therapy. According to outcome patients were classified as: 40 full responders (40.8%), 32 relapsers (32.6%) and 26 poor responders (26.5%). At multivariate analysis age >65 years, male sex, chronic antiplatelet therapy, chronic obstructive pulmonary disease and chronic renal failure were the only covariates independently associated with poor response to therapy.
Conclusion: Our study suggests that long acting release-octreotide could be used as rescue therapy to control bleeding due to gastrointestinal angiodysplasias in patients not suitable for endoscopic or surgical treatments.

1. Introduction

Gastrointestinal angiodysplasias (GIADs) are common and often asymptomatic lesions in elderly patients, but are sometimes responsible for difficult to manage acute or chronic bleeding, accounting for an overall mortality rate of 2% [1].

The use of somatostatin analogues in the treatment of bleeding from GIADs dates back to 1993 when Rossini et al. firstly described three patients with a history of chronic anaemia due to small bowel angiodysplasia successfully treated with octreotide [2]. The mechanisms by which octreotide might exert an anti-bleeding effect include: (1) improved platelet aggregation, (2) decreased splanchnic blood flow, (3) increased vascular resistance and (4) inhibition of neoangiogenesis [3]. Since the first report, several other studies have apparently suggested a beneficial effect of both octreotide and long acting release (LAR)-octreotide in controlling recurrent bleeding due to GIADs [4–12]. However, the nature of the studies' design, the number of patients enrolled, the heterogeneous therapeutic schedules, the short-term follow-up and the different surrogate end-points (haemoglobin or haematocrit levels, requirement for blood transfusion or iron supplementation, number of hospitalization, etc.) used to define the response to therapy may account for the poor validity of the studies that fail to supply an unequivocal evidence to recommend octreotide in the treatment of GIADs bleeding [13–15]. As a consequence the use of somatostatin analogues is not approved for the management of bleeding due to GIADs and they are currently prescribed as off-label drugs in this therapeutic setting.

The ideal should be a randomized placebo-controlled trial, but the rarity of the disease, accounting for <5% of all gastrointestinal haemorrhages [16] and ethical principles would make such a study difficult to perform.

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To provide evidence on the efficacy of LAR-octreotide in controlling the recurrent bleeding due to GIADs, we retrospectively analyzed the medical records of a cohort of patients who received this treatment with a long-term follow-up.

2. Methods

2.1. Population and study design

This was a retrospective single centre study evaluating the effects of LAR-octreotide treatment in the management of patients with GIADs.

Medical records of consecutive patients diagnosed with GIADs at the Department of Gastroenterology, Federico II University of Naples, from January 2000 to December 2008, were considered eligible for the study. The study was approved by the Ethics Committee of the Federico II University.

The inclusion criteria were: history of recurrent gastrointestinal bleeding (overt gastrointestinal bleeding or occult bleeding with a positive faecal occult blood test) lasting at least 2 years; GIADs unsuitable for endoscopic or surgical treatment because of multiple lesions, inaccessible sites, or severe co-morbidities; treatment with LAR-octreotide; and follow-up longer than 3 years. Patients were excluded if they had any of the following: cirrhotic gastropathy or portal hypertension gastropathy; severe comorbidities of cardiac (i.e., New York Heart Association class III and IV), pulmonary (i.e., Global Initiative for Chronic Obstructive Lung Disease "GOLD" scores 3 and 4), renal (i.e., Chronic Kidney Disease "CKD" stages 4 and 5), liver (i.e., Child–Pugh C cirrhosis), haematological, rheumatologic disorders, or uncontrollable diabetes mellitus; hereditary haemorrhagic diseases; systemic cancer currently undergoing chemotherapy or radiation.

To overcome the lack of a control group, that should have meant patients receiving only support therapy, we selected patients with a long history of bleeding before starting LAR-octreotide therapy, so that each patient served as his/her own control.

In all cases patients had undergone endoscopic examination including esophagogastroduodenoscopy, colonoscopy, enteroscopy or small bowel follow through, and, by 2006, video capsule endoscopy. GIADs were defined endoscopically as single or multiple flat bright red spots with round uniform or slightly irregular margins, sized 2–5 mm, or as raised and reddened areas with a distinct irregular margin, when their diameter was larger than 5 mm [17]. A bleeding or rebleeding episode was defined as any of the following: overt blood loss from the gastrointestinal tract; loss of at least 2 g/dl of haemoglobin without any other identifiable cause; ferritin concentration below 12 mg/L.

2.2. Treatment protocol

Based on the pharmacokinetic properties of LAR-octreotide, as well as to make sure of drug tolerance, the following treatment schedule had been adopted: subcutaneous injection of octreotide 0.1 mg tid for 28 days and, starting from day 14, a monthly intramuscular injection of LAR-octreotide 20 mg, for 6 months. Although not evaluated in GIAD setting, it is well known that the administration of LAR-octreotide results in an initial peak, followed by low concentrations over 1–2 weeks and thereafter by sustained octreotide plasma levels over a period of 4–6 weeks. After repeated injections at 4-week intervals, consistent and stable plasma concentrations of octreotide are obtained. In addition, subcutaneous octreotide was administered for at least 15 days before starting LAR-octreotide, to test patient's tolerance to the drug [18].

2.3. Outcome measures

According to the outcome and timing of response to therapy patients were classified as follows: "full responders": patients who, after the first cycle of therapy, did not have overt bleeding and had stable haemoglobin levels during follow-up; "relapsers": patients who, after up to three cycles of therapy, did not have overt bleeding and had stable haemoglobin levels during follow-up; "poor responders": patients who, despite continuous octreotide treatment, had overt bleeding or low haemoglobin levels that required supportive therapy during follow-up.

To assess the response to therapy we used the following indicators: haemoglobin levels, number of bleeding episodes, units of transfused red cells, iron supplementation cycles and number of hospitalizations. The analysis was carried out by comparing the last 2 years of observation period with both the first 2 years during and after therapy and the end of follow-up.

2.4. Treatment and concomitant therapies

Anticoagulant and/or anti-platelet therapy was maintained during LAR-octreotide treatment and only temporary discontinued in case of severe anaemia or overt bleeding.

Since the risk of developing gallstones and/or gallbladder sludge in patients undergoing therapy with somatostatin analogues approaches 50% [19], all patients underwent baseline and yearly ultrasound examinations and took an oral controlled-formulation of ursodeoxycholic acid, 450 mg qd.

During the treatment period, patients were followed-up monthly for the first 6 months by complete blood counts, and routine serum chemical laboratory tests, blood coagulation tests, and hepatic and renal function biochemistry tests. Concomitant therapies, such as blood transfusions and other symptomatic treatments, as well as hospitalization were recorded at each visit.

Blood transfusion was offered in the following circumstances: haemoglobin lower than 7 g/dl in otherwise healthy patients, haemoglobin lower than 10 g/dl in patients with cardiovascular co-morbidity; in case of organ failure at any haemoglobin level. Oral iron supplementation (both ferrous sulphate 200 mg bid for 3 months or ferrous gluconate 300 mg bid for 3 months) was offered to all patients if the concentration of ferritin was below 12 mg/L. If patients were intolerant to oral iron, they received intravenous iron supplementation (iron sucrose 200 mg daily for 5 days or ferric gluconate 125 mg daily for 10 days, to be repeated if necessary).

After 6 months, LAR-octreotide treatment was stopped in all cases and patients were followed-up every 3 months. In case of recurrent overt bleeding episodes or significant decrease of haemoglobin levels, patients underwent a second or third course of the scheduled therapy, and continuous treatment if bleeding did not stop after the third cycle.

2.5. Safety

Compliance to treatment was evaluated based on self-reporting by the patients during clinical visits and at 12-week intervals based on drug prescriptions.

Adverse events, including occurrence or worsening of any clinical symptoms, signs, or abnormal laboratory findings during the treatment with somatostatin analogues were recorded at any clinical visit or when patients notified them.

2.6. Statistical analysis

Continuous variables were expressed as mean ± SD. When the distribution of the variables significantly deviated from normality, they were normalized by logarithmic transformation and

log-transformed values were used in the analysis. Frequencies were calculated for categorical and reported with 95% confidence intervals (CIs). The significance of baseline differences was determined by the Chi-square test, Fisher's exact test, unpaired *t*-test, or repeated measures analysis of variance (ANOVA), as appropriate. A two-sided *p* value of less than 0.05 was used to indicate statistical significance.

Univariate analysis was performed to evaluate the independent effect of each potential risk factor on the likelihood of poor response to LAR-octreotide. Only variables that showed statistically significant difference on the outcome were included in the final logistic regression model. The reciprocal associations among the selected variables were tested by using the Pearson's Chi-square test setting the statistical significance cut-off at $p < 0.005$. The variables that showed a statistically significant association were then tested by using repeated logistic regression models and those with the highest likelihood to predict the outcome were included in the final logistic regression analysis.

To allow a comparative evaluation of the effects of the different factors on the odds ratio for re-bleeding, *Z* scores were calculated for each factor and used for the analysis. Nagelkerke R^2 was used to estimate the percent of variance in the dependent variable explained by the independent factors. The goodness-of-fit of the final model was evaluated by the Hosmer–Lemeshow test.

Finally, as a post hoc analysis, we developed a prognostic score by assigning the risk factors identified by multivariate analysis weighted points proportional to the β regression coefficient values (rounded to the nearest integer). The accuracy of the scoring system predicting the response to therapy was tested by the receiver operating characteristic (ROC) curve. The area under the ROC curve was used to measure the discriminatory ability of the prognostic indices: <0.7, no discrimination; 0.71–0.79, acceptable; 0.8–0.89, excellent; >0.9, outstanding discrimination. All statistical procedures were performed using the Statistical Package for Social Sciences (SPSS-PC version 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics and outcome

Ninety-eight out of 147 patients met the inclusion criteria and were eligible for the analysis. Demographic and clinical characteristics of the patients subdivided according to response to therapy are summarized in Table 1.

The mean follow-up was 78 months (range 36–120 months) and, in detail, it was extended up to 72 months in 86 and up to 120 months in 71 patients.

According to the outcome and timing of response to therapy patients were classified as follows: 40 full responders (41%); 32 relapsers (33%); 26 poor responders (26%). Among the 32 relapsers, 21 patients underwent 2 cycles and 11 patients 3 cycles of LAR-octreotide treatment.

Poor responders, compared to full responders and relapsers, were more frequently males ($p = 0.04$) and presented comorbidities such as ischaemic cardiac disease ($p = 0.0006$), cardiac valvular disease ($p = 0.006$), chronic obstructive pulmonary disease (COPD, $p = 0.007$) and chronic renal failure ($p = 0.03$), as well as were more frequently on concomitant antiplatelet therapy ($p = 0.002$). Regarding the onset symptom and the localization of GIADs, overt bleeding and multiple sites were significantly more frequent in the poor responder group compared to full responders and relapsers ($p = 0.004$ and $p = 0.01$, respectively).

During the two-year observation period, the mean haemoglobin level was 6.8 ± 1.7 g/dl in full responders, 7.1 ± 2.1 g/dl in relapsers and 6.7 ± 2.3 g/dl in poor responders; the percentage of patients who required blood transfusions was 63%, 66% and 69% in full responders, relapsers and poor responders, respectively. All patients required iron supplementation.

During follow-up the mean haemoglobin levels significantly increased and the number of bleeding episodes, hospitalizations, patients requiring blood transfusions and units of transfused red cells significantly decreased in all groups (Fig. 1 and Table S1).

3.2. Multivariate analysis and risk scoring system

The correlation between patient's baseline characteristics and poor response to LAR-octreotide was evaluated by a univariate model. Variables that showed statistically significant distribution on the poor response to therapy were male sex, COPD, ischaemic cardiac disease, chronic renal failure, antiplatelet therapy, overt bleeding and multiple sites of angiodysplasia. A strong association was found between sex and COPD ($p = 0.002$), sex and multiple sites of GIADs ($p < 0.0001$), ischaemic cardiac disease and antiplatelet therapy ($p < 0.0001$) and chronic renal failure and overt bleeding ($p = 0.001$). After the repeated logistic regression analyses, the final model was built by using poor response (yes/no) as dependent variable and COPD (yes/no), chronic renal failure (yes/no), use of anti-platelet drugs (yes/no) as independent factors. COPD (HR, 9.3; 95% CI 2.6–32.5; $p = 0.0001$), chronic renal failure (HR, 7.4; 95% CI 1.7–31.7; $p = 0.007$) and chronic antiplatelet therapy (HR, 5.5; 95% CI 1.8–16.8; $p = 0.003$) were all independently associated with poor response to therapy (Table 2).

By a post hoc analysis, based on the results of the multivariate analysis, we built a risk score model predictive of non-response to LAR-octreotide treatment. Each of the three prognostic variables was assigned a number of points that was proportional to its regression coefficient (Table 2). On the basis of the total risk score, we identified 3 classes of risk of non-response to therapy: low-risk (0–1 points); moderate-risk (2–3 points), and high-risk (4–6 points). The distribution of patients, subdivided according to response to therapy and risk class is shown in Fig. 2 and Table 3. Patients in high risk class were significantly more frequently poor responders to therapy ($p = 0.001$). The accuracy of the model in the prediction of response to therapy, as assessed by the ROC curve, was acceptable (AUC 0.76) (Fig. 3).

3.3. Adverse events and mortality

Common adverse gastrointestinal effects of treatment with LAR-octreotide included nausea, abdominal cramps, loose stools, mild steatorrhea and flatulence. These symptoms, which started within hours of the first subcutaneous injection, were mild and subsided spontaneously within the first few weeks of treatment. Local pain and mild erythema at the injection site were reported in few subjects ($n = 5$ and $n = 7$, respectively). One patient showed impaired glucose tolerance while no patient developed overt diabetes mellitus. Only 1 patient developed gallbladder sludge during the treatment period (see Table S2). None of the adverse events required therapy discontinuation.

During the follow-up, 27 patient deaths occurred: senescence ($n = 6$), cardiovascular events ($n = 10$), end-stage liver disease ($n = 3$), end-stage kidney disease ($n = 4$), lung cancer ($n = 2$), and prostate cancer ($n = 2$) were the causes of death.

4. Discussion

First-line treatments for GIADs, such as angiographic embolization, local endoscopic ablation, and surgical resection are largely unsuitable due to the inaccessibility or multiplicity of lesions and patients age or comorbidities [20]. Moreover these approaches, even when feasible, are not definitely effective since bleeding

Table 1
Demographic and clinical characteristics of the patients subdivided according to response to therapy.

	Overall $N=98$	Full responders $N=40$	Relapsers $N=32$	Poor responders $N=26$	p
Demographic findings					
Age (mean ± SD)	71.3 ± 9.2	71.8 ± 10	71.2 ± 7.7	70.6 ± 10.2	0.87
Male sex	59 (60%)	22 (55%)	16 (50%)	21 (81%)	0.04
Comorbidities					
Arterial hypertension	30 (31%)	10 (25%)	12 (37%)	8 (31%)	0.52
Ischaemic cardiac disease	39 (40%)	7 (17%)	16 (50%)	16 (61%)	0.0006
Heart valve disease	20 (20%)	4 (10%)	10 (31%)	6 (23%)	0.006
COPD	20 (20%)	4 (10%)	4 (12%)	12 (46%)	0.0007
Liver cirrhosis	26 (26%)	14 (35%)	6 (19%)	6 (23%)	0.27
Chronic renal failure	13 (13%)	2 (5%)	4 (12%)	7 (27%)	0.03
Diabetes	10 (10%)	5 (12%)	3 (9%)	2 (8%)	0.80
No comorbidities	15 (15%)	8 (20%)	5 (16%)	2 (8%)	0.40
Concomitant therapies					
Anti-platelet drugs	35 (36%)	8 (20%)	14 (44%)	13 (50%)	0.002
Anticoagulants	–	–	–	–	
Anti-platelets + anticoagulants	14 (14%)	6 (15%)	2 (6%)	6 (23%)	0.19
Anti-inflammatory drugs	6 (6%)	2 (5%)	2 (6%)	2 (8%)	0.90
Onset symptom					
Occult bleeding	40 (41%)	22 (55%)	14 (44%)	4 (15%)	0.004
Melena	46 (47%)	18 (45%)	14 (44%)	14 (54%)	0.71
Rectorrhage	8 (8%)	–	4 (12%)	4 (15%)	0.04
Melena + rectorrhage	4 (4%)	–	–	4 (15%)	0.003
Endoscopic techniques					
Esofagogastroduodenoscopy	98 (100%)	40 (100%)	32 (100%)	26 (100%)	
Colonoscopy	98 (100%)	40 (100%)	32 (100%)	26 (100%)	
Capsule endoscopy	86 (86%)	30 (75%)	30 (94%)	26 (100%)	0.004
Enteroscopy	14 (14%)	10 (25%)	2 (6%)	–	0.004
Site of angiodysplasia					
Stomach and duodenum	19 (19%)	12 (30%)	3 (9%)	4 (15%)	0.07
Small bowel	30 (31%)	7 (17%)	17 (53%)	6 (23%)	0.003
Colon	9 (9%)	6 (15%)	3 (9%)	–	0.11
Multiple sites	37 (38%)	12 (30%)	9 (28%)	16 (61%)	0.01

COPD: chronic obstructive pulmonary disease.
Continuous variables were expressed as mean (standard deviation) and compared by using repeated measures ANOVA; categorical variables were expressed as number and percentage and compared by Fisher's exact test.

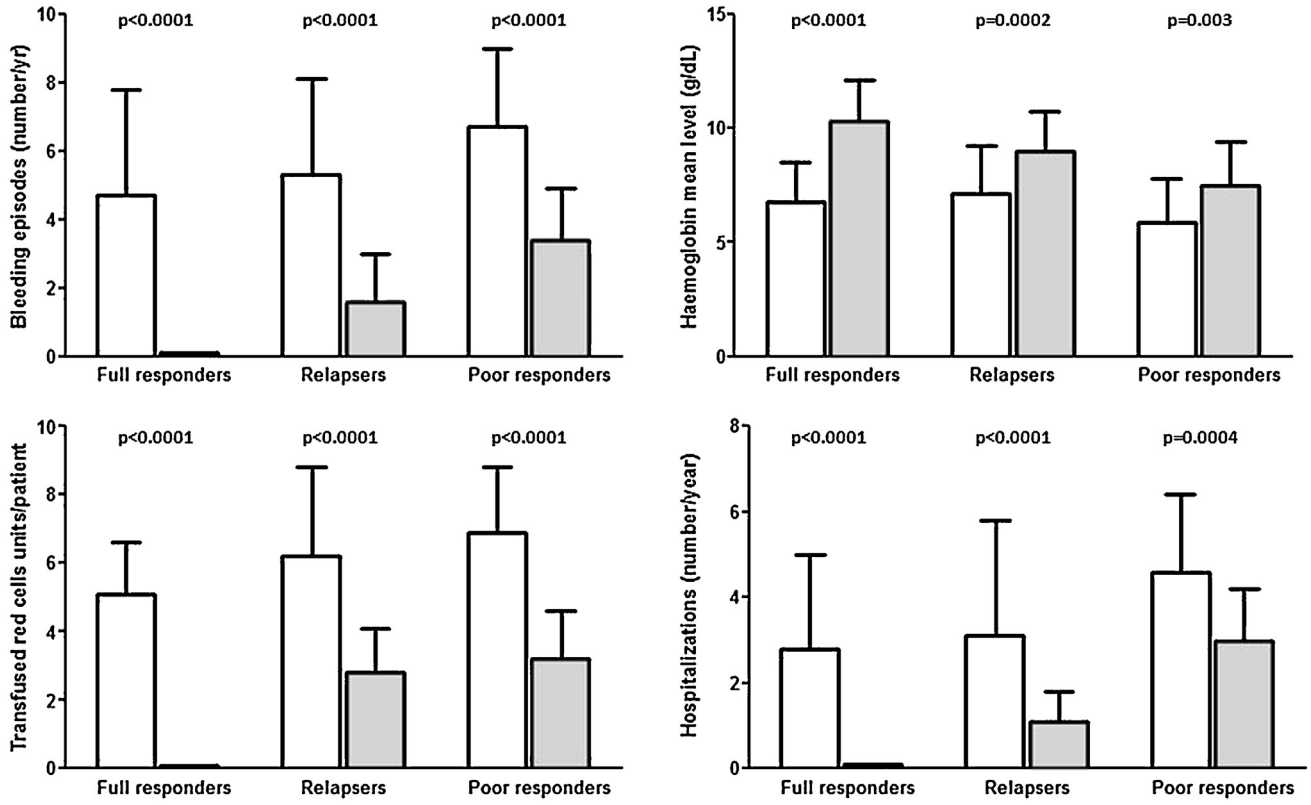

Fig. 1. Mean values of bleeding episodes, haemoglobin levels, blood transfusions and number of hospitalizations calculated taking into account all data during the last 2 years of observation before starting therapy and the first 2 years after starting therapy. Paired t test.

Table 2
Regression analysis and scoring system.

Risk factor	Prevalence	Hazard ratio (95% CI)	*p*-Value	β regression	Coefficient points[a]
Chronic obstructive pulmonary disease	20 (20)	9.3 (2.6–32.5)	0.0001	2.227	3
Chronic renal failure	13 (13)	7.4 (1.7–31.7)	0.007	2.006	2
Anti-platelet drugs	43 (44)	5.5 (1.8–16.8)	0.003	1.703	1

[a] Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 1.703 (the lowest β value, corresponding to anti-platelet drugs), multiplied by a constant (2), and rounded to the nearest integer.

Table 3
Risk score distribution in the studied population subdivided according to the response to therapy.

Risk score	Full responders *N* = 40	Relapsers *N* = 32	Poor responders *N* = 26	*p*
Low risk (0–1)	34 (85%)	24 (76%)	8 (31%)	<0.0001
Moderate risk (2–4)	6 (15%)	4 (12%)	10 (38%)	0.03
High risk (5–6)	–	4 (12%)	8 (31%)	0.001

recurs in 30–40% of the cases [21]. Therefore, an effective and safe pharmacological agent could represent an attractive option.

During the past years oestrogen–progestagens have been proposed to treat GIADs bleeding, but due to poor efficacy and serious adverse events, current evidence suggests that there is no role for hormonal therapy in this setting [22–24].

Recently, thalidomide, an anti-angiogenic agent, has been tested for the management of bleeding due to GIADs [25–28]. A recent open-label controlled study, limited to 28 patients with refractory bleeding from GIADs, reported a decrease of bleeding episodes by >50% and a significant reduction in the need for blood transfusions in the thalidomide group. However, patients with severe co-morbidities and on chronic antiplatelet treatment were excluded from the study and 71% of treated patients experienced severe side effects [29].

In our study, up to 74% of patients with bleeding due to GIADs had stable haemoglobin levels and did not require blood transfusion or hospitalization after one cycle (responders) or 3 cycles (relapsers) of LAR-octreotide. In the remaining 26 poor responders, bleeding episodes, blood transfusion requirement, iron supportive therapy and haemoglobin levels significantly improved but required continuous LAR-octreotide treatment and supportive therapy.

At multivariate analysis, COPD, chronic renal failure and antiplatelet therapy were the covariates independently associated with the poor response to LAR-octreotide treatment.

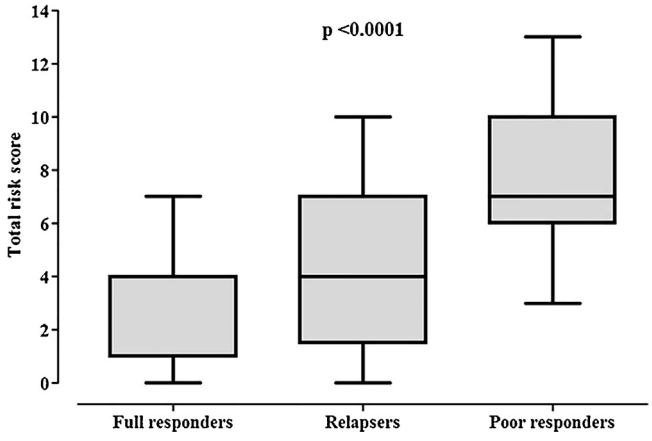

Fig. 2. Distribution of total risk score in the studied population according to the outcome of LAR-octreotide treatment. Box and whiskers represent the smallest observation (sample minimum), lower quartile, median, upper quartile and the largest observation (sample maximum). One-way ANOVA.

Chronic obstructive pulmonary disease is associated with significant comorbidity including anaemia, due to combined effect of systemic inflammation and hypercapnia/hypoxia, that in turn increase the sympathetic activity of the arterial system [30–32]. The foremost proposed hypothesis of GIAD development is that the chronic, intermittent, low-grade spasm of submucosal blood-vessels leads to gradual dilation of the venules and arteriolar capillary units feeding them. In addition long-term local low-oxygenation of the microcirculation due to COPD increases tissue Hypoxia-Inducible Factor-1α, which promotes the expression of vascular endothelial growth factor, a key mediator in the development of angiodysplasia [33]. Thus, COPD could account for the poor response to LAR-octreotide treatment observed in our patients.

Angiodysplasias account for up to 30% of gastrointestinal bleeding episodes in end-stage renal disease. The increased risk of GIAD bleeding in these patients seems to be associated with uraemia-induced platelet dysfunction on one side and the use of

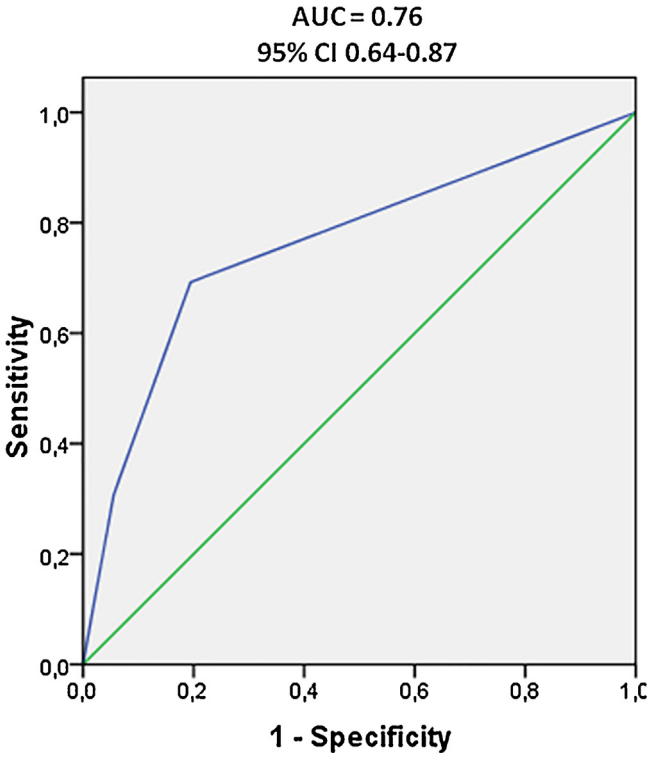

Fig. 3. Receiver-operator characteristics (ROC) curve analysis of risk score accuracy in the prediction of likelihood of poor response to LAR-octreotide treatment.

anticoagulant drugs in the dialytic stage, on the other side [34]. In our study, none of the patients included had an end-stage renal disease, implying that bleeding in such patients was independent of uraemia level or heparin use.

The use of antiplatelet drugs is increasing in the last years. Currently, about 30% of patients 60–80 years old receive chronic antiplatelet therapy for primary or secondary prophylaxis of cardiovascular events [35]. A progressively ageing population and the increasing use of antiplatelet drugs may explain the worldwide increase of bleeding due to GIADs (from 0.9 in 1996 to 2.6 in 2005) [36]. In addition, in patients with cardiovascular diseases the withdrawal of antiplatelet or anticoagulants drugs increases the risk of cardiovascular events (OR = 3.14; 95% CI 1.75–5.61) more than the risk of bleeding (RR = 1.40; 95% CI 1.07–1.83) [37,38]. Interestingly, in our study, LAR-octreotide treatment allowed to control bleeding in a substantial percentage (42%) of patients who needed to continue antiplatelet drugs.

Given the relatively large number of patients included in the analysis and the long follow-up available, as post hoc analysis, we developed a simple risk score predictive of response to LAR-octreotide treatment. This score classified patients into subgroups at low, medium, and high risk of poor response to therapy. The model showed an acceptable discrimination as assessed by ROC analysis. Indeed, patients in high risk-class were more frequently poor responders to therapy ($p = 0.001$).

We are aware that our results are biased by shortcomings inherent the retrospective nature of the study that is the non-random selection of the patients, the inaccuracy in recording data relative to the observation period before starting therapy and the lack of a standardized follow-up, as well as the absence of a real control group. However, since we selected patients with a history of bleeding lasting at least 2 years before starting therapy, each patient served as his/her own control.

The natural history of bleeding due to GIADs is known to be variable (spontaneously stopping in up to 90% of the cases and recurring in about 64% of the cases within 2 years), thus, making difficult the evaluation of the efficacy in a short-term period [39].

To the best of our knowledge, this study includes the largest number of patients with the longest follow-up after therapy published until now. In addition, the standardized therapeutic schedule (dosage and duration), the measurement of the outcome by using a combination of all available parameters and the use of multivariate methods of statistical analysis further strengthen the results of our study.

We did not perform a cost-effectiveness analysis or a quality of life assessment. However, the total costs for somatostatin analogues are approximately 8000 €/patient for a 6-month cycle of therapy, which is lower than the total costs for hospitalizations, often with unnecessary endoscopic and radiographic re-evaluation. In light of a growing attention of the medical community in controlling and streamlining public health costs, the risk score model we propose could be useful to assist clinicians in making treatment decisions.

In conclusion, the management of gastrointestinal bleeding due to GIADs remains a critical and debated issue. Our data suggest that LAR-octreotide could be used as a rescue therapy to control bleeding due to GIADs. Further prospective randomized studies are needed to evaluate the impact of LAR-octreotide in bleeding due to GIADs; ideally both the endoscopic work-up (diagnostic and therapeutic endoscopy) as well as the transfusion schedule should be balanced between the two study arms. Furthermore the risk-score should be validated in a different, prospective and possibly larger cohort of patients.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2014.04.011.

References

[1] Cappell MS, Gupta A. Changing epidemiology of gastrointestinal angiodysplasia with increasing recognition of clinically milder cases: angiodysplasia tend to produce mild chronic gastrointestinal bleeding in a study of 47 consecutive patients admitted from 1980–1989. American Journal of Gastroenterology 1992;87:201–6.

[2] Rossini FP, Arrigoni A, Pennazio M. Octreotide in the treatment of bleeding due to angiodysplasia of the small intestine. American Journal of Gastroenterology 1993;88:1424–7.

[3] Szilagyi A, Ghali MP. Pharmacological therapy of vascular malformations of the gastrointestinal tract. Canadian Journal of Gastroenterology 2006;20:171–8.

[4] Nardone G, Rocco A, Balzano T, et al. The efficacy of octreotide therapy in chronic bleeding due to vascular abnormalities of the gastrointestinal tract. Alimentary Pharmacology and Therapeutics 1999;13:1429–36.

[5] Bowers M, McNulty O, Mayne E. Octreotide in the treatment of gastrointestinal bleeding caused by angiodysplasia in two patients with von Willebrand's disease. British Journal of Haematology 2000;108:524–7.

[6] Coppola A, De Stefano V, Tufano A, et al. Long-lasting intestinal bleeding in an old patient with multiple mucosal vascular abnormalities and Glanzmann's thrombasthenia: 3-year pharmacological management. Journal of Internal Medicine 2002;252:271–5.

[7] Blich M, Fruchter O, Edelstein S, et al. Somatostatin therapy ameliorates chronic and refractory gastrointestinal bleeding caused by diffuse angiodysplasia in a patient on anticoagulation therapy. Scandinavian Journal of Gastroenterology 2003;38:801–3.

[8] Junquera F, Saperas E, Videla S, et al. Long-term efficacy of octreotide in the prevention of recurrent bleeding from gastrointestinal angiodysplasia. American Journal of Gastroenterology 2007;102:254–60.

[9] Almadi M, Ghali PM, Constantin A, et al. Recurrent obscure gastrointestinal bleeding: dilemmas and success with pharmacological therapies. Case series and review. Canadian Journal of Gastroenterology 2009;23:625–31.

[10] Scaglione G, Pietrini L, Russo F, et al. Long-acting octreotide as rescue therapy in chronic bleeding from gastrointestinal angiodysplasia. Alimentary Pharmacology and Therapeutics 2007;26:935–42.

[11] Molina Infante J, Pérez Gallardo B, Hernández Alonso M, et al. Octreotide long acting release for severe obscure gastrointestinal haemorrhage in elderly patients with serious comorbidities. Medicina Clinica 2009;133:667–70.

[12] Bon C, Aparicio T, Vincent M, et al. Long-acting somatostatin analogues decrease blood transfusion requirements in patients with refractory gastrointestinal bleeding associated with angiodysplasia. Alimentary Pharmacology and Therapeutics 2012;36:587–93.

[13] Brown C, Subramanian V, Wilcox CM, et al. Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: an overview and systematic review of prospective observational studies. Digestive Diseases and Sciences 2010;55:2129–34.

[14] Sami SS, Al-Araji SA, Ragunath K. Review article: gastrointestinal angiodysplasia – pathogenesis, diagnosis and management. Alimentary Pharmacology and Therapeutics 2014;39:15–34.

[15] Swanson E, Mahgoub A, Macdonald R, et al. Medical and endoscopic therapies for angiodysplasia and gastric antral vascular ectasia: a systematic review. Clinical Gastroenterology and Hepatology 2014;12:571–82.

[16] Rockey DC, Koch J, Cello JP, et al. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. New England Journal of Medicine 1998;339:153–9.

[17] Howard OM, Buchanan JD, Hunt RH. Angiodysplasia of the colon, experience of 26 cases. Lancet 1982;2:16–9.

[18] Gillis JC, Noble S, Goa KL. Octreotide long-acting release (LAR). A review of its pharmacological properties and therapeutic use in the management of acromegaly. Drugs 1997;53:681–99.

[19] Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. Cancer 1997;79:830–4.

[20] Gordon FH, Watkinson A, Hodgson H. Vascular malformations of the gastrointestinal tract. Best Practice and Research Clinical Gastroenterology 2001;15:41–58.

[21] Dray X, Camus M, Coelho J, et al. Treatment of gastrointestinal angiodysplasia and unmet needs. Digestive and Liver Disease 2011;43:515–22.

[22] van Cutsem E, Rutgeerts P, Vantrappen G. Treatment of bleeding gastrointestinal vascular malformations with oestrogen–progesterone. Lancet 1990;335:953–5.

[23] Barkin JS, Ross BS. Medical therapy for chronic gastrointestinal bleeding of obscure origin. American Journal of Gastroenterology 1998;93:1250–4.

[24] Junquera F, Feu F, Papo M, et al. A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. Gastroenterology 2001;121:1073–9.

[25] Kamalaporn P, Saravanan R, Cirocco M, et al. Thalidomide for the treatment of chronic gastrointestinal bleeding from angiodysplasias: a case series. European Journal of Gastroenterology and Hepatology 2009;21:1347–50.

[26] Alberto SF, Felix J, de Deus J. Thalidomide for the treatment of severe intestinal bleeding. Endoscopy 2008;40:788.
[27] Dabak V, Kuriakose P, Kamboj G, et al. A pilot study of thalidomide in recurrent GI bleeding due to angiodysplasias. Digestive Diseases and Sciences 2008;53:1632–5.
[28] Garrido Serrano A, León R, Sayago M, et al. Thalidomide treatment in cirrhotic patients with severe anemia secondary to vascular malformations. Digestive Diseases and Sciences 2012;57:1112–3.
[29] Ge ZZ, Chen HM, Gao YJ, et al. Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. Gastroenterology 2011;141:1629–37.
[30] Kierszniewska-Stepień D, Pietras T, Górski P, et al. Serum vascular endothelial growth factor and its receptor level in patients with chronic obstructive pulmonary disease. European Cytokine Network 2006;17:75–9.
[31] van Gestel AJ, Steier J. Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD). Journal of Thoracic Disease 2010;2:215–22.
[32] Portillo K, Martinez-Rivera C, Ruiz-Manzano J. Anaemia in chronic obstructive pulmonary disease. Does it really matter? International Journal of Clinical Practice 2013;67:558–65.
[33] Haja Mydin H, Murphy S, Clague H, et al. Anemia and performance status as prognostic markers in acute hypercapnic respiratory failure due to chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease 2013;8:151–7.
[34] Navab F, Masters P, Subramani R, et al. Angiodysplasia in patients with renal insufficiency. American Journal of Gastroenterology 1989;84:1297–301.
[35] Roger VL, Go AS, Lloyd-Jones DM. American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18–209.
[36] Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. The changing face of hospitalisation due to gastrointestinal bleeding and perforation. Alimentary Pharmacology and Therapeutics 2011;33:585–91.
[37] Testa L, Sheiban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. European Heart Journal 2006;27:2667–74.
[38] Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. New England Journal of Medicine 2005;352:1293–304.
[39] Richter JM, Christensen MR, Colditz GA, et al. Angiodysplasia. Natural history and efficacy of therapeutic interventions. Digestive Diseases and Sciences 1989;34:1542–6.