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Octreotide long-active release in the treatment of gastrointestinal bleeding due to vascular malformations: Cost-effectiveness study

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ABSTRACT

Introduction: Gastrointestinal hemorrhage due to vascular malformations has a negative impact on patients' quality of life and consumes an important quantity of resources.

Objective: Analyze the cost-effectiveness of long-active releasing octreotide (OCT-LAR) in the treatment of gastrointestinal haemorrhage secondary to vascular malformations.

Material and methods: Retrospective study, including 19 pacients that were treated with mensual injections of OCT-LAR between 2008-2013. The number of blood transfusions, hemoglobin levels, hospital admissions and possible side effects during the year before treatment and the year after the start of the treatment were assessed, and cost-effectiveness was analyzed.

Results: After the beginning of the treatment with OCT-LAR, complete response was observed in 7 patients (36.8 %), partial response in 7 patients (36.8 %) and 5 patients (26.3 %) continued to require admissions, blood transfusions and/or endoscopic treatment. We observed significant reduction in the length of admission per year (in days) before and after the start of the treatment (22.79 *versus* 2.01 days, $p < 0.0001$) as well as in the number of blood transfusions administered (11.19 *versus* 2.55 blood transfusions per year, $p = 0.002$). The mean haemoglobin levels increased from 6.9 g/dl to 10.62 g/dl ($p < 0.0001$). We observed reduction of costs of 61.5 % between the two periods (from 36,072.35 € to 13,867.57 € per patient and year, $p = 0.01$). No side effects related to treatment were described.

Conclusion: In conclusion, OCT-LAR seems to be a cost-efficient and safe pharmacological treatment of gastrointestinal haemorrhage secondary to vascular malformations, mainly in patients in whom endoscopic or surgical treatment is contraindicated.

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INTRODUCTION

Gastrointestinal haemorrhage secondary to vascular malformations represents an important clinical problem that has a major negative impact on the quality of life of patients, as it frequently requires numerous therapeutic interventions, and is therefore associated with high economical burden (1).

The natural history of vascular malformations has not been entirely understood, although some factors such as hypoxy and subsequent release of epithelial growth factors may play a role in its physiopathology and may be used as a target of future therapies (2-4).

Endoscopic interventions are the mainstay in both diagnosis and treatment of vascular malformations. The most frequently implicated therapeutic method is argon plasma coagulation; however, due to relatively high rebleeding rate some patients may require various treatment sessions (5). Repeated endoscopies may carry high risk of complications, mainly in elderly patients with important comorbidity, who represent a significant proportion of the affected population. Conservative medical treatment with octreotide and octreotide LAR has therefore been intended as a maintenance therapy with promising results in this group of patients (5-7).

The objective of the present study was to assess the long-term effect and cost-effectiveness of OCT-LAR in the treatment of gastrointestinal bleeding from vascular malformations in our centre. To our knowledge there is no other published study that evaluates the economical impact of treatment with this drug.

MATERIAL AND METHODS

Our hospital is a tertiary centre that attends the area with approximately 638,000 inhabitants. Our Department of Gastroenterology consists of three sections: Gastroenterology, hepatology and endoscopy. Patients that suffer from recurrent gastrointestinal bleeding from vascular lesions are assessed and treated in the Clinic of Gastroenterology and Endoscopy.

We performed a retrospective study, in which we included all patients with recurrent gastrointestinal bleeding secondary to vascular malformation that were treated with mensual administration of OCT-LAR between January 2008 and December 2013 in our centre, in total 24 patients when the study started.

Patients

Clinical evaluation and indication of OCT-LAR treatment in each patient was performed by a responsible consultant in the clinic. Given that the treatment is administered off-licence, a protocol was elaborated and at least two of the following criteria had to be fulfilled in order to be able to prescribe OCT-LAR:

- Recurrent gastrointestinal bleeding with necessity for blood transfusion (more than 4 transfusions per year) or frequent hospital admissions (more than 2 hospital admissions per year or more than 10 admissions to emergency department per year).
- Important comorbidity (ASA III or IV) and high risk related to performing surgical or repeated endoscopic interventions.
- At least 3 sessions of unsuccessfull endoscopic treatment, and continuous need for high transfusional requirements and/or admissions.
- Multiple lesions with difficult endoscopic access and high transfusional requirements and/or admissions.

We found 24 pacients that fulfilled at least two of the above mentioned criteria. Five of those were excluded from the study: Three because they died from different causes than digestive bleeding few months after the start of the treatment, and two because they started the treatment recently (2 and 3 months before the start of the study, respectively), which means the response to the therapy could not be correctly evaluated (Fig. 1).

In order to assess the efficiency of the treatment, we collected the variables during one year before and one year after the start of OCT-LAR , excluding the time before the diagnosis.

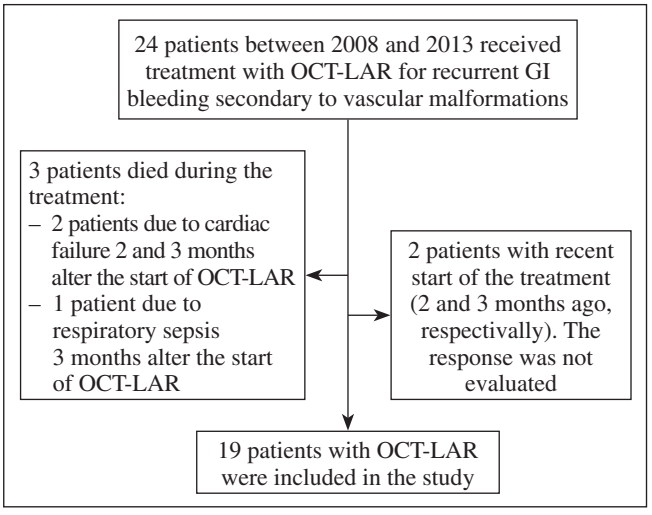

Fig. 1. Flow chart on selection of patients for the study.

Data sources

In our centre, OCT-LAR is used off-licence and data of all the patients that were given the treatment in this indication are stored in the Department of Pharmacy.

We reviewed clinical history of these patients (electronically in the hospital intranet or in written form as obtained from the archive of the hospital), including their previous medical history, relevant comorbidity, medication that interferes with blood coagulation or agregation, levels of haemoglobin, necessity of blood transfusions, administration of iron supplements orally or intravenously and its doses, administration of subcutaneous erytropoetin, number of diagnostic and therapeutic endoscopies, hospital admissions related to gastrointestinal haemorrhage and total length of admissions per year (in days).

In our hospital, the economical evaluation of health servicies is based on the system of codification of Group of Related Diagnosis (Grupo de Diagnóstico Relacionado; GDR). Each hospital admission, visit to the emergency department or ambulatory assistence receive a numeric code based on the final diagnosis according to CIE-10. Each code has an economical value asigned by health authorities of each Spanish independent community. Equally, depending on the length and number of services rendered, a unit is asigned to each of the codes, that represent the number of times that suggests how many times the codified value can be multiplied in order to reach the final value that is invoiced. In order to obtain the costs for the purpose of our study, we contacted the Department of Codification in the central hospital archive, and we collected the codes and the units of each hospital assistence of all patients using the programme HCIS. The equivalent value in euros was

calculated using the "Boletín oficial de la comunidad de Madrid 215 (BOECM 215)" issued on the 10th of September 2013 where the monetary equivalence of each code is described. In order to obtain the value of services that are not codified, such as digestive endoscopies, we asigned a mean value to the upper gastrointestinal endoscopies, colonoscopies and capsule endoscopies according to the data available in the department of costs of our hospital. The Department of Pharmacy provided us with the value of each presentation of the drug at the purchase price. The costs also include the price of all medication administered during the admissions, such as erythropoetin and intravenous iron supplements, as well as of any other treatments and investigations that were performed. In our hospital there is no day centre in which procedures such as intravenous iron administration or blood transfusions could be performed, and patients requiring these measures are usually admitted to the emergency department.

The costs included the last year before the start of the treatment and the first year afterwards. The costs related to the investigations which lead to the final diagnosis were excluded from the analysis in order not to bias the beneficial effect of the drug.

Definitions

The diagnosis of vascular malformations of the digestive tract (angiodysplasias or watermelon stomach) was established by endoscopic studies (upper GI endoscopy, colonoscopy or capsule endoscopy), associated or not with relevant imaging techniques (for example computer tomography with intravenous contrast).

Therapeutic interventions

In our centre, the treatment of vascular lesions with OCT-LAR is performed according to a protocol developed by colaboration of Department of Gastroenterology and Pharmacy, always off-licence and after excluding all other treatment possibilities due to motives that were described previously. We started with the dose of 10 mg administered monthly by intramuscular injection; the effect was reviewed at least every 3 months, and the dose was increased to 20 or 30 mg monthly (or not) according to the clinical response. In some cases we started directly with the dose of 20 mg or 30 mg monthly, based on the criteria of the prescriber. Once the treatment was started it was maintained indefinitely if the patient continued to present good response.

Measuring effectivity

After the start of the treatment, the number of blood transfusions, levels of haemoglobin, hospital admissions including the length of admission, admissions to the emergency department, necessity for endoscopic treatment and possible side effects were assessed at least once every three months. The criteria for response were defined as follows:

- *Complete response:* No further need for blood transfusions, admissions nor endoscopic treatment, with mean blood hemoglobin of at least 9.5 g/dl.
- *Partial response:* At least 50 % decrease in the necessity for blood transfusions, admissions or endoscopic treatment, with mean blood hemoglobin of at least 9.5 g/dl
- *No response:* All the patients that did not fulfill the criteria of partial or complete response.

Analysis of subgroups

We have analyzed different subgroups in our cohort, nevertheless, they were not included in the present study given the small number of patients in each subgroup, which would then limit the validity of the obtained results.

Statistical analysis

The statistical analysis was performed using SPSS programme version 21.0 (IBM SPSS Statistics, Chicago, IL). Normal distribution was evaluated using the Shapiro-Wilk test for small samples. Continuous variables were expressed as media, mediana with confidence interval of 95 % and were compared using the t-Student test if normal distribution was confirmed, and using non-parametric tests (Wilcoxon test for related samples) if the distribution was not normal. We performed comparations between the year before and after the start of the treatment. P-value inferior than 0.05 was considered statistically significative.

Ethical aspects

The data were collected according to the ethical standards our centre.

RESULTS

Finally 19 patients were included in the study, 17 men and 2 women, with mean age of 74.11 years (range 62-87, standard deviation 6.86). All patients had important comorbidity that limited the performance of exhaustive endoscopic therapy (ischemic heart disease, valvulopathy, cardiac arrhythmia like atrial fibrillation or ictus); three patients presented chronic obstructive pulmonary disease, three liver cirrhosis with portal hypertension and three chronic renal insufficiency.

As far as concomitant medication was concerned, fourteen patients were on oral anticoagulants and/or antiag-

gregants: Seven of those were receiving simultaneous anticoagulant and antiaggregant medication, five only antiaggregants and two only anticoagulants.

All 19 patients presented anemia which was difficult to control; eleven of them described overt recurrent hemorrhage in form of melena, hematochezia or rectorrhagia. Except for 1 patient with important cardiac and pulmonary comorbidity, all patients had an upper GI endoscopy and colonoscopy. Moreover, 15 patients underwent endoscopic study of small intestine with capsule endoscopy (15 cases) and/or enteroscopy (2 cases).

Endoscopic study revealed angiodysplasias in 16 patients; 3 patients with liver cirrhosis presented hypertensive gastropathy, 2 of these lesions called watermelon stomach; only 1 patient with severe comorbidity did not undergo any endoscopy. Ten patients had angiodysplasias localized in the small intestine, three in the colon and three lesions affecting simultaneously both small and large bowels. No patient presented skin involvement or previous family history of gastrointestinal hemorrhage. Fifteen patients received previous endoscopic treatment, the mean number of sessions was 2.46 (range 1-8, SD 2.02). Argon plasma coagulation was the method of choice in all cases and no relevant complications were observed. The long-time success rate, however, was quite low, as all patients presented rebleeding, after mean time of 38.4 days (range 3-96 days) after the treatment. Likewise, the treatment did not reduce the necessity for hospital admissions and/or blood transfusions. Surgical interventions were contraindicated due to age and/or associated comorbidity.

Baseline characteristics of all patients are resumed in table I.

We compared the year before the start of treatment to the year afterwards in all patients.

The mean time from the diagnosis to the start of the treatment with octreotide was of 25.42 months (range 11-48 months; SD 17.34). As for the anemia, we found significant reduction in the accumulated mean annual doses of iron supplements, counting with both oral and intravenous supplements during both periods (408.5 g per year *vs.* 203.6 g per year and patient; p = 0.002). Before starting OCT -LAR, 18 patients required treatment with iron (15 patients oral and intravenous and 3 patients oral) and afterwards, 15 patients continued to need supplements (7 patients both oral and intravenous and 8 patients oral). Similarly, we observed reduction in number of patients and the dose of darbepoetin alpha. During the first period, six patients received treatment with an accumulated dose of 396.7 mcg per year and per patient, while in the second period only half of them continued to receive darbepoetin, with an accumulated dose of 156.7 mcg per year and per patient (p = 0.013). Mean hemoglobin, mean dose of iron supplements per (both oral and intravenous), mean dose of darbepoetin alpha per year, mean length of admission in days per year and mean number of blood transfusions in the two periods are depicted in figures 2-4.

Twelve patients started treatment with the dose of 10 mcg of OCT-LAR, administered by intramuscular injection; of these, three required increase in dose to 20 mcg monthly, six patients initiated with dose of 20 mcg and one patient (number 19) directly with 30 mcg of OCT-LAR monthly. The mean duration of treatment was of 26.32 months, eleven patients received treatment during more than 24 months.

For the purposes of this study we only analyzed the year before the start of the treatment and the year afterwards. Of these 19 patients included in the analysis, 13 continued with the same initial dose during a mean time of 18.8 months (range 11-26). Six patients required adjustment of dose. In three of them the dose was increased from 10 to 20 mcg after mean time of 7.5 months (range 4.5-12 months) due to persistent anemia and necessity for blood transfusions (patients number 6, 7, and 11) and in other three patients the treatment was stopped due to lack of the effect after 17, 19, and 22 months of administration (patients 7, 16, and 18). It is interesting that all these cases were patients with liver cirrhosis with portal hypertension.

We have obtained complete response in 7 cases (36.8 %), partial response in another 7 patients (36.8 %). The rest of the patients (5/19; 26.32 %) precised the same or higher number of blood transfusions, iron and darbepoetin alpha supplements and/or endoscopic treatment and hospital admissions related to the gastrointestinal hemorrhage. All patients with complete or partial response presented angiodysplasia. Three of the five patients that did not respond to treatment had cirrhosis with lesions related to portal hypertension, associated with gastric antral vascular ectasia (GAVE) in two cases, and given the lack of response to OCT-LAR treatment, the drug was stopped in these three cases.

When we compared the subgroup of patients that were receiving anticoagulants and/or antiaggregants to those that did not, we did not find any significant differences in the necessity of readmissions or number of blood transfusions.

Before OCT-LAR was started, 13 patients underwent endoscopic therapy with mean number of 2.46 sessions per patient; of theses, only 5 required posterior endoscopic treatments, with a mean number of 1.2 sessions. All of them belonged to the group of patients with no response to treatment (patients 7, 11, 15, 16, and 18).

When we compared the three different types of response (complete, partial and none), no statistically significant differences were found as far as mean hemoglobin levels, the length of the admission in days, mean number of blood transfusions or the mean costs in the period before the start of the treatment are concerned. In the period after the start of the treatment, we found statistically significant differences between the group with complete response (CR) and the group of partial response (PR) in the number of blood transfusions (0 and 1.13; p = 0.005), the mean annual dose of iron (27.8 g and 180.6 g; p = 0.003) and length of admis-

Table I. Analytical and clinical evolution of patients before and after the first year of treatment with OCT-LAR

Before the treatment

Nr	*Symptoms*	*Hb g/dl*	*Iron g per year*	*BT per year*	*Darbepoetin mcg/year*	*Antiaggregants*	*Anticoagulants*	*Number of endoscopic treatments*
1	Anemia	10.0	175; O: 175, IV: 0	4.00	400	No	Sintrom (2.2)	0
2	Melena	7.7	168; O: 168; IV: 0	9.6	0	ASA 100	No	0
3	Anemia	6.0	245; O: 245 IV: 0	14.4	0	No	No	1
4	Anemia-FOB	7.3	0	2.5	0	ASA 100 Clopid 75	No	0
5	Anemia	8.0	488; O: 288 IV: 200	9	0	No	Sintrom (2.4)	1
6	Anemia	8.8	480; O: 288 IV: 200	0	0	No	No	2
7	Melena	7.1	580; O: 180 IV: 400	5.5	0	No	No	4
8	Anemia	6.1	568; O: 168 IV: 400	6	0	ASA 100	Sintrom (2)	1
9	Anemia	5.7	388; O: 188 IV: 200	34.5	320	ASA 100		1
10	Anemia	4.9	350; O: 150 IV: 200	60	400	Clopid 75	Sintrom (1.9)	2
11	Anemia	5.7	440; O: 240 IV: 200	4	400	Clopid 75	Sintrom (2.1)	1
12	Anemia	7.1	496; O: 96 IV: 400	11.25	0	ASA 100	Sintrom (2.5)	0
13	Anemia	5.7	640; O: 240 IV: 400	7.5	440	Clopid 75	Sintrom (1.8)	4
14	Anemia	6.0	400; O: 200 IV 200	4.8	420	ASA 100	Sintrom (2)	0
15	Melena	5.4	380; O: 180 IV: 200	12.4	0	No	Sintrom (2.2)	1
16	Melena	5.6	380; O: 180 IV: 200	5.25	0	No	No	8
17	Melena	9.0	688; O: 288 IV: 400	2	0	ASA 100	No	0
18	Rectorrhagia	7.3	568; O: 168 IV 400	15	0	No	No	3
19	Rectorrhagia	8.7	320; O120 IV: 200	5	0	ASA 100 Clopid 75	No	3

After the start of the treatment

Nr	*Symptom*	*Hb g/dl*	*Iron g/year*	*BT /year*	*Darbepoetin mcg/year*	*Antiaggregants*	*Anticoagulants*	*Number of endoscopic treatments*
1	Melenas	12.5	88	1	0	No	Sintrom (1.8)	0
2	No symptom	10	0	0	0	ASA 100	No	0
3	Hematoche-zia	11.8	88	2	0	No	No	0
4	Anemia	9.7	0	15	0	ASA 100 Clopid 75	No	0
5	No symptom	16.1	0	0	0	No	Sintrom (2.3)	0
6	No symptom	11.5	75	0	0	No	No	0
7	Melena	7.7	290	0	0	No	No	1
8	No symptom	15	180	1.3	0	ASA 100	Sintrom (1.8)	0
9	No symptom	11.8	48	0	0	ASA 100		0
10	Anemia	6.8	150	3.6	0	Clopid 75	Sintrom (2.2)	0
11	Anemia	5.7	440	4.7	0	Clopid 75	Sintrom (2.4)	1
12	Anemia	12.8	48	1.3	0	ASA 100	Sintrom (2)	0
13	No symptom	9.5	320	0	160	Clopid 75	Sintrom (1.9)	0
14	No symptom	9.6	440	6	380	ASA 100	Sintrom (2.2)	0
15	Anemia	9.5	650	5.5	0	No	Sintrom (2)	1
16	Melena	9.2	460	11	0	No	No	2
17	No symptom	11.8	24	0	0	ASA 100	No	0
18	Rectorrhagia-anemia	7	420	12	0	No	No	1
19	No symptom	11.3	134	0	0	ASA 100 Clopid 75	No	0

Hb: Hemoglobin in g/dl; BT: Blood transfusions; FOB: Fecal occult blood test (positive); ASA: Acetylsalicylic acid; clopid: Clopidogrel; Sintrom: Acenocoumarol. Hemoglobin was expressed in grams on decilitre, the dose of iron in grams received per year, the dose of darbopoetin in micrograms per year and the dose of ASA and clopidogrel in mg every 24 hours. As far as acenocoumarol is concerned, the mean INR level is expressed in parenthesis; 100 = 100 mg, 75 = 75 mg, Sintrom () = INR.

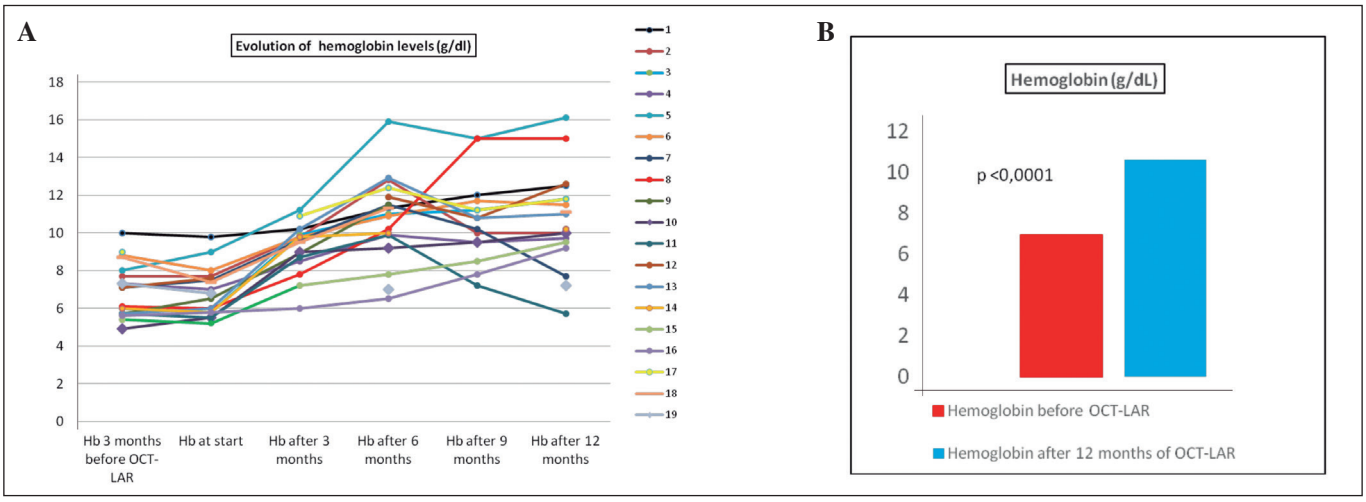

Fig. 2. A shows changes in mean haemoglobin levels measured 3 months before treatment with OCT-LAR, at start of the treatment with OCT-LAR, and after 3, 6, 9 and 12 months of treatment. B shows comparison between mean haemoglobin levels (in g/dL) before starting OCT-LAR and after 12 months of treatment, with statistically significant differences in favour of OCT-LAR (abbreviations: Hb: Hemoglobin expressed in g/dL).

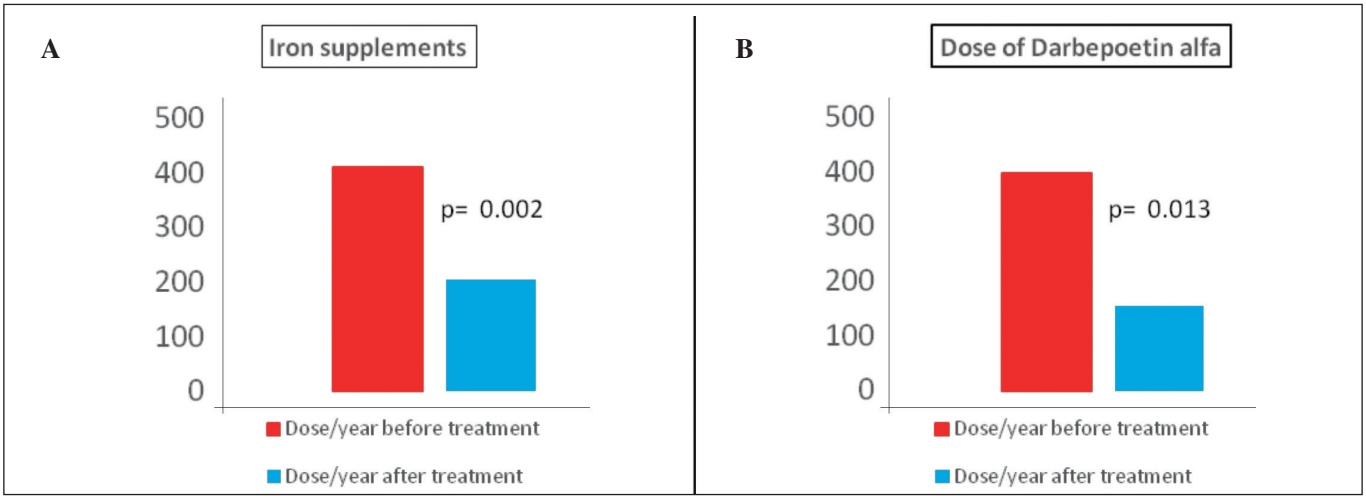

Fig. 3. Comparison of the mean accumulated dose of iron supplements before and after OCT-LAR, expressed in grams per year (A). Comparison of the mean accumulated dose of darboetin alpha before and after OCT-LAR, expressed in micrograms of pacients per year (B).

sion in days (0 and 11.8; p = 0.048). When the group with PR was compared to the group with no response (NR), statistically significant differences were found in the number of blood transfusions (1.13 and 7.8; p = 0.003), days of admission (5.4 and 11.8; p = 0.048), the mean annual dose of iron (180.6 and 480; p = 0.002) and total annual costs (11,269 € and 23,742; p = 0.002). The comparisons between the three groups are shown in figure 5.

No side effects related to the OCT-LAR treatment were observed, only one patient was diagnosed with asymptomatic colelithiasis during the treatment, altough we do not know if it was present before the start of the therapy.

The mean annual costs of the treatment before the start of OCT-LAR were of 36,072.34 € per patient (range 1,610.49 € to 122,840.50 €, SD 35,975.52 €) and in the period afterwards was of 13,867.57 € per patient (range 7,371.96 € to 36,891.64 €, SD 4,453.02 €), including the cost of the drug that in our Department of Pharmacy was of 614.33 € per dose in the presentation of 10 mg, 820.15 € per dose in the presentation of 20 mg and 1,025.97 € per dose in the presentation of 30 mg. Table II resumes the costs of the admissions to the hospital and the emergency department and the endoscopic treatments before and after the treatment.

With the previous data we calculated reduction of 61.5 % of the mean costs between the two periods (from 36,072.35 € to 13,867.57 € per patient/year, p = 0.01). The item that implies the major expense was the hospital admission that represented 95 % in the period before the start of the treatment and 88 % of the costs in the later period.

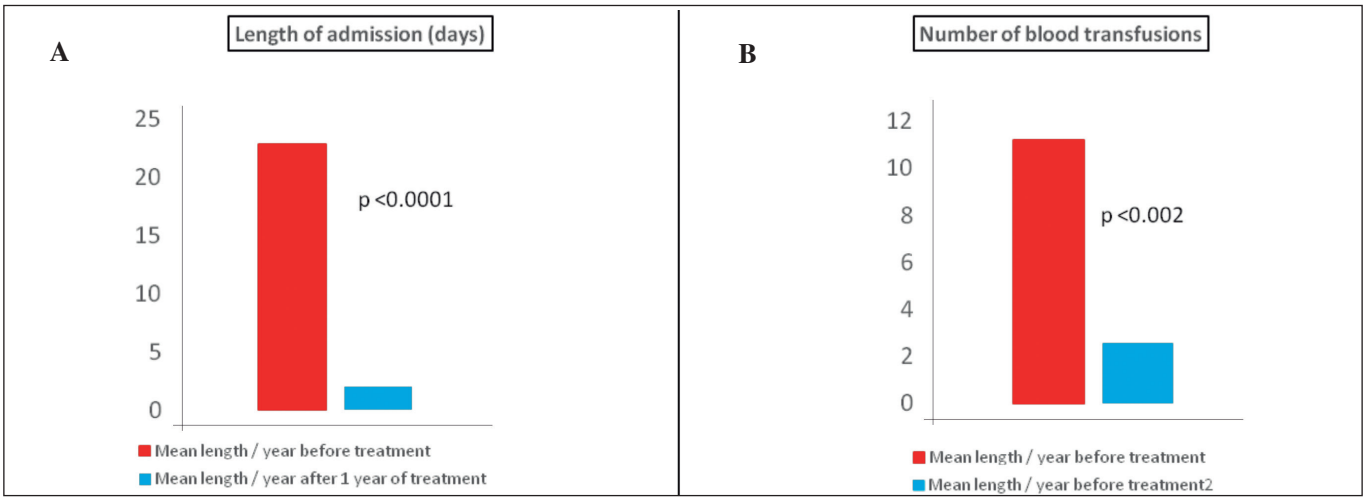

Fig. 4. Comparism of the mean admission length expressed in days per year before and after 12 months of treatment with OCT-LAR (A), and comparation of the mean number of blood transfusions administered the year before the start of the treatment and at 12 months of treatment with OCT-LAR (B).

When we analyzed the costs of treatment of each patient separately, we observed similar costs reduction in fourteen of them, while five patients maintained similar or higher costs after the start of OCT-LAR. Two of the latter presented angiodysplasia with continuous need for blood transfusions but not hospital admissions and limited initial clinical response, which required adjustment of the dose of OCT. In the other two patients had liver cirrhosis with portal hypertension, no improvement in any of the assessed items was observed, and the fifth one did not present clear clinical response, although reduction in total treatment costs was appreciated (patient 7).

DISCUSSION

Patients with chronic anemia related to gastrointestinal hemorrhage secondary to vascular lesions represent a diagnostic and therapeutic challenge for clinical gastroenterologists, as many of them suffer from relevant co morbidities that complicate the realization of invasive procedures. Moreover, the treatment of associated anemia implies major economical costs (4,6).

We have performed a retrospective single-centre study that includes all the patients that have been treated with OCT-LAR in the above explained indication. We have excluded from the analysis all the patients whose treatment was shorter than 3 months, as we considered that it was an insufficient time to be able to evaluate its long-term benefit.

We intended to establish a group of control among patients with digestive bleeding and chronic anemia during the same study period. However, in our hospital, we only start the treatment with octreotide when endoscopic treatment failed or is not feasible due to associated risks, such as relevant comorbidity. Therefore, it was impossible to find a group of control with similar baseline characteristics, in which repeated endoscopic and/or surgical treatment would be contraindicated. Nevertheless, in all cases there was a minimum of 14 weeks gap between the last endoscopic intervention and the start of the treatment; which reduces the risk of possible overvaluation of previous costs.

Similarly, another factor that could play an important role in the final results was the dose of antiaggregant or anticoagulant treatment, both of which are frequently used in this group of patients. Before the start of OCT-LAR was considered, the necessity of continuing with this medication was assessed by a cardiologist and/or neurologist in each patient; dose adjustment of treatment suspension was performed in strictly indicated cases. All these changes were performed before the period that was included in our study. There were no posterior changes in the dosage of antiaggregants or in the ranges of INR in patients treated with dicumarinics.

Our results demonstrate an acceptable efficacy in the treatment of gastrointestinal hemorrhage due to vascular lesions, with partial and complete response in 36.8 % respectively, and treatment failure rate of 26.3 %.

In the current literature there are few studies that would assess this type of treatment prospectively. Brown et al. (8) published a paper in which he analyzed three prospective studies that included a total of 62 patients with a global response rate (complete or partial) of 76 % (IC 95 % 0.64-0.85).

Junquera et al. (9) studied 32 patients that received subcutaneous octreotide at a dose of de 50 mcg twice a day during 1-2 years, and compared them to 38 patients that received placebo. In his work there were 23 % patients in which the treatment failed.

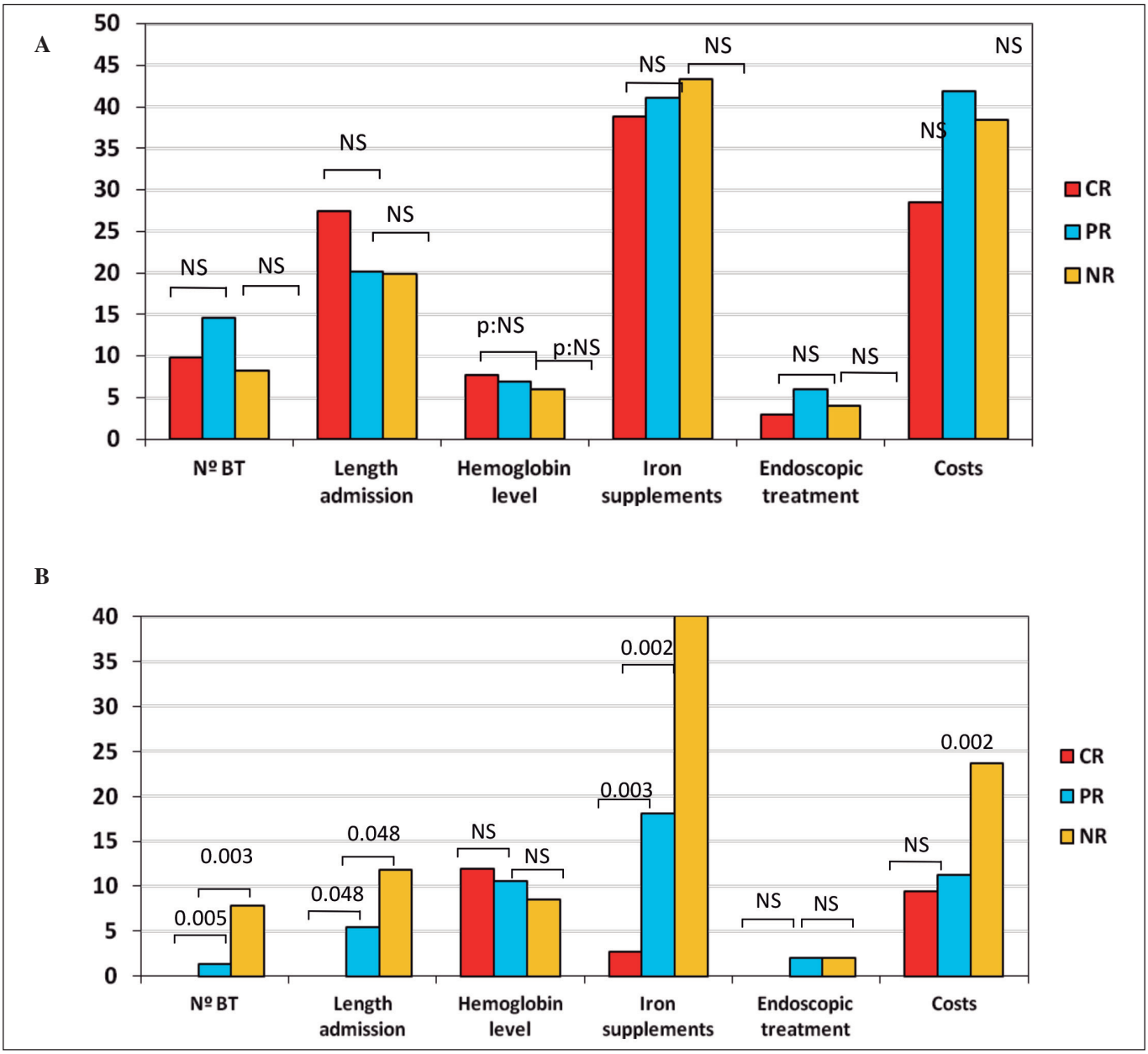

Fig. 5. Comparison of three response patterns during the year before (A) and after (B) the start of OCT-LAR. Nº BT: The mean number of blood transfusions administered. Admission: Mean admission length expressed in days. Hbg: Mean levels of haemoglobin. Iron: Mean annual dose expressed in grams. Endoscopy: Patients that underwent endoscopic treatment. Costs: Value in thousands of euros. CR: Group of complete response. PR: Group of parcial response. NR: Group of no response. NS: p-value not statistically significant (CR: Complete response; PR: Partial response; NR: No response; Nº BT: Number of blood transfusions).

More recently Nardone et al. (10) published a retrospective study, including 98 patients with digestive bleeding secondary to angiodysplasias. His results are superposable to those observed in our study, obtaining a complete response in 40.9 %, recurrence of hemorrhage in 32.6 %, and no response in 26.5 % of all cases.

A Spanish study presented by Molina et al. (11) that evaluated 11 patients with significant comorbidity and advanced age found complete response in 18 % of the patients, although significant reduction of transfusion requirements and length of hospital admissions were observed after the start of the treatment.

The optimal dose of OCT-LAR can vary and is not well-defined in the literature; most often doses between 10 and 30 micrograms monthly are used, and most studies were performed using the dose of 20 micrograms monthly. Most of our patients received 10 micrograms monthly. We do not know if higher doses would produce major clini-

Table II. Mean annual costs of treatment and investigation of the 19 patients included in the study

	Mean	*Range*	*Standard deviation*
Costs of hospital admissions before OCT-LAR	37833,8	2718,4-182660,7	43006,2
Costs of hospital admissions after OCT-LAR	4242,8	0-25567,6	6971,0
Costs of admissions to emergency before OCT-LAR	605,3	0-3000	894,7
Costs of admissions to emergency after OCT-LAR	742,1	0-6000	1443,5
Costs of endoscopios before OCT-LAR	494,7	0-2000	608,9
Costs of endoscopios after OCT-LAR	200	0-2500	569,1
Annual OCT-LAR costs	8682,7	7371,9-12311,6	1437,8
Total annual costs before OCT-LAR	36072,4	1610,5-122840,5	34417,6
Total annual costs after OCT-LAR	13867,6	7371,9-36891,6	8754,9

All the values are expressed in euros. We describe the mean number, the range and standard deviation. The costs of hospital admissions before and after the start of the treatment: Include the costs of the medication administered and investigations performed. The costs of emergency admissions before and after the start of the treatment: Costs of visits to the emergency department, including the administration of blood transfusions and intravenous iron supplements. Costs of endoscopies before and after the start of the treatment: Costs of diagnostic and therapeutic endoscopies performed before and after the start of the treatment. Annual cost octreotide: Costs of treatment of octreotide during the first year of treatment. Annual costs before and after the start of the treatment: Total costs of treatment during the two periods.

cal benefit, and we have not found any studies that would compare different doses of the medication.

The side effects described so far are usually mild (colelithiasis, nausea, vomiting, abdominal pain, diarrhea or difficult control of diabetes) (12). In our series of patients no adverse effects were observed, except for one case in which colelithiasis was incidentally diagnosed in an otherwise asymptomatic patient. Given the retrospective character of the data collecting, it is possible that some minor side effects were not registered in patients' clinical history.

At this moment, the optimal length of treatment has not been established. In most studies, OCT-LAR is maintained between 1 and 2 years, and the effect of treatment was maintained over approximately 1 year after stopping the treatment (9). In our patients, the mean treatment duration of OCT-LAR was of 26.3 months (range 6-84 months; SD 17.8). Four patients that have been receiving treatment for more than 24 months, presented an excellent tolerance, maintaining clinical response with frequent previous exacerbations, which were the motives for long treatment administration. The treatment was stopped in three patients who failed to respond. Two patients who required increase in dose of OCT-LAR due to new episode of hemorrhage, presented good response to higher dose and continue with the treatment.

In our study we concluded that treatment with OCT-LAR seems to be a reasonable and cost-effective therapeutic modality in patients with relevant comorbidities, given the significant reduction in total treatment costs resulting from decrease in number of hospital admissions and their length, decrease in admissions to emergency department, decrease in dose of iron supplements, darbopoetin and/or number of blood transfusions. To our knowledge, there is currently no similar study that would evaluate this aspect of the treatment and given high price of the drug we consider that it is essential to assess it, as it may change its use in this indication. Based on the results of the present study we consider that our criteria of the start of OCT-LAR therapy are reasonable and are in accordance with good clinical conduct.

It should be emphasized that the reduction of costs has not been observed in patients that did not require frequent blood transfusions or hospital admissions, or in case of cirrhotics with portal hypertension, although limited number of patients prevents us from making further conclusions.

Previous studies have described promising results in the treatment of EVAG in patients with cirrhosis (9,13). Nardone et al. (14) included 3 cirrhotic patients with portal hypertension and EVAG that were treated with octreotide, achieving complete response in one of them and decrease transfusion requirements during 2 years of follow-up.

Thalidomide has been used as an alternative to the treatment with OCT-LAR. The data available in the literature are limited, based on case reports or series of cases, which have also shown effectiveness in terms of reduction of in transfusional requirements (including its capacity to complete resolution of the endoscopical image of vascular lesions) (15,16). In our centre, we have indicated the administration of thalidomide in case of only one patient, in whom the drug had to be stopped due to its adverse effects.

As previously mentioned, the principal limitations of our study are the fact that it was retrospective, single-center and with small number of patients. However, our results are very similar to those in previously published studies, contributing additional information about the effectivity of the treatment.

In conclusion, OCT-LAR seems to be an efficient treatment option in patients with chronic gastrointestinal haemorrhage secondary to vascular malformations, mainly in patients with relevant comorbidity that makes other therapeutical modalities more difficult. In spite of its relatively high costs, in the present study we describe a significant decrease in total costs in patients with clinical response.

Prospective and multicentric studies are needed to confirm these results.

REFERENCES

1. Jackson CS, Gerson LB. Management of gastrointestinal angiodysplastic lesions (GIADs): A systematic review and meta-analysis. Am J Gastroenterol 2014;109:474-83.
2. Gerber HP, Condorelli F, Park J, Ferrara N. Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes. Flt-1, but not Flk-1/KDR is upregulated by hypoxia. J Biol Chem 1997;272:23659-67.
3. Marti HH, Risau W. Systemic hypoxia changes the organspecific distribution of vascular endothelial growth factor and its receptors. Proc Natl Acad Sci USA 1998;95:15809-14.
4. Junquera F, Saperas E, de Torres I, Vidal MT, Malagelada JR. Increased expression of angiogenic factors in human colonic angiodysplasia. Am J Gastroenterol 1999;94:1070-6.
5. Regula J, Wronska E, Pachlewski J. Vascular lesions of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2008;22:313-28.
6. Gunian D, Sharma V, Rana SS, Bhasin DK. Small bowell bleeding: A systematic review. Gastroenterol Rep 2014;2:1-14.
7. Junquera F, Feu F, Papo M, Videla S, Armengol JR, Bordas JM, et al. A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. Gastroenterology 2001;121:1073-9.
8. Brown C, Subramanian V, Wilcox CM, Peter S. Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: An overview and systematic review of prospective observational studies. Dig Dis Sci 2010;55:2129-34.
9. Junquera F, Saperas E, Videla S, Feu F, Vilaseca F, Armengol JR, et al. Long-Term efficacy of Octreotide in the prevention of recurrent bleeding from gastrointestinal angiodysplasia. Am J Gastroenterol 2007;102:254-60.
10. Nardone G, Compare D, Scarpignato C, Rocco A. Long acting release-octreotide as "rescue" therapy to control angiodysplasia bleeding: A retrospective study of 98 cases. Dig Liver Dis 2014;46:688-94.
11. Molina Infante J, Pérez Gallardo B, Hernández Alonso M, Mateos Rodríguez JM, Dueñas Sadornil C, Fernández Bermejo M. Octreotide long acting release for severe obscure gastrointestinal haemorrhage in elderly patients with serious comorbidities. Med Clin (Barc) 2009;133:667-70.
12. Bornschein J, Drozdov I, Malfertheiner P. Octreotide LAR: Safety and tolerability issues. Expert Opin Drug Saf 2009;8:755-68.
13. Patwardhan VR, Cardenas A. Review article: The management of portal hypertensive gastropathy and gastric antral vascular ectasia in cirrhosis. Aliment Pharmacol Ther 2014;40:354-62.
14. Nardone G, Rocco A, Balzano T, Budillon G. The efficacy of octreotide therapy in chronic bleeding due to vascular abnormalities of the gastrointestinal tract. Aliment Pharmacol Ther 1999;13:1429-36.
15. Ge ZZ, Chen HM, Gao YJ, Liu WZ, Xu CH, Tan HH, et al. Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. Gastroenterology 2011;14:1629-37.
16. Bauditz J, Lochs H. Angiogenesis and vascular malformations: Antiangiogenic drugs for treatment of gastrointestinal bleeding. World J Gastroenterol 2007;13:5979-84.