Intranasal bevacizumab treatment on epistaxis in hereditary haemorrhagic telangiectasia: a case report

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ABSTRACT

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare, vascular, autosomal dominant disorder. The purpose of this paper is to describe the efficacy and safety of treatment with intranasal bevacizumab in HHT.

A 42-year-old woman with HHT presented with frequent episodes of epistaxis. Iron studies showed anaemia of iron deficiency from chronic blood loss. Because of the frequent epistaxis (Epistaxis Severity Score (ESS) 6.76) and varying haemoglobin levels (Hb range: 7.7–9.9g/dL) her doctors sought treatment with intranasal bevacizumab. This treatment was prescribed at the hospital pharmacy department in a laminar flow hood. 2.5 mL (25 mg) were placed in a nasal spray bottle. The recommended dosage was twice a day for two consecutive months. Nasal treatment seemed to control her epistaxis, and no adverse effects were reported. She only had a few further minor episodes of epistaxis, which were easily controlled (ESS 3.44). The haemoglobin levels evreached normal levels (Hb range: 12.8–14.1g/dL).

BACKGROUND

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare, vascular, autosomal dominant disorder. Telangiectasia and arteriovenous malformations (AVMs) of the lung, liver and central nervous system are vascular lesions present in HHT, most commonly causing epistaxis and gastrointestinal bleeding. Approximately one-third of patients have chronic anaemia, with gastrointestinal bleeding increasing with age. However, epistaxis presents as early as childhood; this symptom can be severe and life threatening; it is often the cause of chronic anaemia and can require continuous management including iron supplementation and multiple blood transfusions.¹

The prevalence of HHT is approximately 1 in 5–8000 of the population.² Diagnosis is based on the Curaçao criteria and is considered definite if at least three of the four following criteria are fulfilled: (1) spontaneous and recurrent epistaxis, (2) telangiectasia of the lips, oral cavity, fingers, nose or gastrointestinal tract, (3) AVMs of the lungs, liver and central nervous system and (4) family history in first-degree relatives. Of note, although genetic testing is available, it is not necessary for diagnosis.³

Recently, the Epistaxis Severity Score (ESS) was created as a standardised measure to estimate the degree of epistaxis. ESS is based on six questions. Four questions document epistaxis frequency, duration, intensity and need for treatment, whereas two

additional questions detail the presence of anaemia and if a patient has required a blood transfusion. Questions are variably weighted, and results are tabulated on a 0–10 scale (0=no disease, 10=severe disease). To date, the ESS has proven to be a valuable tool for recording disease progression.⁴

Pathologically, several genes have been associated with HHT including endoglin, Alk-1, and SMAD-4. Many of these genes encode proteins that function within the transforming growth factor-beta (TGF- β)–vascular endothelial growth factor (VEGF) signalling cascade.⁵ Although the mechanism is unknown, patients with HHT have elevated serum and mucosal concentrations of VEGF and TGF- β .⁶ Therefore, inhibition of angiogenic factors might be a plausible way of interfering with the disease process. Bevacizumab is a recombinant, humanised, monoclonal antibody that binds to and inhibits the biological activity of VEGF in vivo and in vitro. Bevacizumab, by binding VEGF, prevents endothelial cell proliferation and angiogenesis. To avoid the systemic adverse effects of bevacizumab, intranasal treatment with bevacizumab, by either submucosal injection or topical nasal spray, has recently been reported to be a safe alternative to intravenous injection for nosebleeds.

CASE PRESENTATION

A 42-year-old woman with HHT presented with frequent episodes of epistaxis. Other manifestations of HHT included large nasal telangiectasia, hepatic haemangioma, palpebral and upper lip telangiectasia. She had undergone gingival mucosa cauterisation 10 years ago, and it solved oral bleeding. Iron studies showed anaemia of iron deficiency from chronic blood loss.

INVESTIGATIONS

Initially, her iron deficiency anaemia was treated with oral ferropoteinsuccinylate. It was not enough; consequently, physicians replaced her treatment by intravenous iron weekly. The iron posology changed according to clinical requirements. She had received four blood transfusion in 2 years. An arterial embolisation was carried out in February 2015, and it was unsuccessful.

TREATMENT

Because of the frequent epistaxis (ESS 6.76) and varying haemoglobin levels (Hb range: 7.7–9.9g/dL) her physicians sought treatment with intranasal bevacizumab. This treatment was elaborated at the hospital pharmacy department in a laminar flow hood with Avastin 400mg/16mL phial. A

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total of 2.5 mL of undiluted bevacizumab was placed in a nasal spray bottle. Each millilitre of nasal solution contained 25 mg of bevacizumab (2.5 mg/spray). We used a plastic bottle of 10 mL for nasal spray; it was made of low-density polyethylene and polypropylene. The nasal spray was stored on fridge (2°C–8°C). Each bottle was discontinued after 21 days, and physicochemical properties will be stable during the treatment time. This stability is the result obtained of applying non-sterile solution matrix.⁷ The shelf-life for water solutions, non-oral administration is the same as the length of treatment, for a maximum of 30 days. Twice a day was the regular dosage for two consecutive months.

OUTCOME AND FOLLOW-UP

Nasal treatment seemed to control her epistaxis. She only had few minor episodes of epistaxis, which were easily controlled by herself. Treatment was well tolerated. The haemoglobin has reached normal levels (Hb range: 12.8–14.1 g/dL). The ESS has fallen to 3.44. This has allowed changing the frequency of iron treatment (monthly throughout her maintenance therapy).

DISCUSSION

Majority of patient with HHT experience epistaxis, mucocutaneous telangiectasia and a tendency to develop gastrointestinal bleeding leading to iron deficiency anaemia. Management of HHT is primarily aimed at treating the resultant iron deficiency anaemia and preventing complications of vascular lesions. Recurrent epistaxis in patients with HHT causes significant morbidity. VEGF is a key pathogenic factor that acts to increase and maintain vascular density.

Flieger *et al*⁸ reported the first case that evaluated the efficacy of intravenous bevacizumab in reducing epistaxis in a patient with HHT, while Davidson *et al*⁹ reported the first use of topical bevacizumab spray to treat recurrent epistaxis in a patient with HHT. They concluded that nasal bevacizumab might represent an exciting new option, which could possibly decrease the morbidity of current laser and surgical treatments. A topical nasal delivery system could also provide an option for earlier treatment for those patients not symptomatic enough to warrant surgical intervention.

A combination of intranasal submucosal injection of bevacizumab with targeted potassium titanyl phosphate (KTP) laser cauterization significantly decreases short-term and long-term frequency of nosebleeds and transfusions requirements.¹⁰ This study proved that treatment with KTP and bevacizumab is superior to KTP laser treatment alone in the management of HHT epistaxis. Karnezis *et al*¹¹ applied intranasal bevacizumab as a topical spray and as a submucosal injection. Both treatments improved ESS in patients affected with HHT-associated epistaxis. They suggested that the ideal treatment is to begin with a submucosal injection. This requires anaesthesia with 1% lidocaine with 1:100 000 epinephrine along nasal mucosa. Later the patients were similarly injected with 100 mg of bevacizumab and finally a fibrin sealant (Evicel) was sprayed into the nose to prevent post-operative haemorrhage. These injections were all made in nasal mucosa intending it to diffuse throughout the nasal cavity, then control the disease with repeated spraying.

The effect of bevacizumab nasal spray on epistaxis duration and frequency in HHT has been evaluated in two clinical trials.^{12–13} Dupuis-Girod *et al*¹² compared a placebo group and three groups receiving different doses of bevacizumab (25, 50 or 75 mg per treatment) administered as a nasal spray (three sprays 14 days apart for a total treatment duration of 4 weeks), resulting in total doses of 75 mg, 150 mg and 225 mg in the bevacizumab

treatment groups. In the other clinical trials,¹³ patients received twice-daily nose sprays for 12 weeks with either bevacizumab 1% (4 mg/day), estriol 0.1% (0.4 mg/day), tranexamic acid 10% (40 mg/day) or placebo (0.9% saline). No statistical difference was observed in mean duration of epistaxis after treatment in the placebo group compared with the other groups, regardless of dose group. Bevacizumab absorption varies considerably for each patient and within a single patient. Frequent nosebleeds and nasal crust are also a physical barrier to drug absorption. These factors could explain the efficacy of bevacizumab nasal in our patient; we asked her to use the nasal spray even if she is not experiencing nosebleeding. It could increase bevacizumab absorption in nasal mucosa.

Bevacizumab has been approved and effectively used for the treatment of metastatic colorectal cancer. Ophthalmologist also used it for several diseases: age-related macular degeneration, neovascular glaucoma, retinopathy of prematurity and corneal neovascularisation.^{14–15} Bevacizumab treatment for metastatic cancer has been reported to have serious side effects. These include gastrointestinal perforation, delayed wound healing, new onset hypertension and extranasal haemorrhagic events. In ophthalmology, complications are not frequent; adverse effects included blood pressure elevation, corneal abrasion, mild discomfort and uveitis. Several case series reports nasal septal perforation as a rare complication secondary to systemic bevacizumab treatment.^{16–17} Bevacizumab has also been associated with more widespread sinonasal toxicity like nasal mucosal lesions with mild epistaxis and sinonasal irritation.¹⁸ The mechanism of bevacizumab toxicity is not clearly defined and likely multifactorial. To avoid the systemic adverse effects of bevacizumab, intranasal treatment with bevacizumab, by either submucosal injection or topical nasal spray, has recently been reported to be a safe alternative to intravenous injection for nosebleeds.^{19–22}

Bevacizumab efficacy in HHT epistaxis has been demonstrated in multiple studies, but the treatment dose, administration modality and treatment frequency are not consolidated.

Patient's perspective

The treatment with intranasal bevacizumab is easy to use because of local administration. During the treatment I felt better, with fewest epistaxis. I observed changes in facial malformations. The treatment with intranasal bevacizumab is easy to use because of local administration. During the treatment I felt better, with fewest epistaxis. I observed changes in facial malformations.

Learning points

- ▶ Intranasal bevacizumab is an effective and safe treatment for severe epistaxis in patients with Osler-Weber-Rendu syndrome. This therapy reduces epistaxis severity and frequency.
- ▶ Systemic adverse effects could be avoided by using bevacizumab topically as a nasal spray.

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Competing interests None declared.

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