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Treatment of Hereditary Hemorrhagic Telangiectasia With Submucosal and Topical Bevacizumab Therapy

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Objective/Hypothesis: Bevacizumab delivered as a submucosal and topical intranasal therapy effectively controls hereditary hemorrhagic telangiectasia (HHT)-associated epistaxis.

Study Design: Prospective institutional review board-approved study.

Methods: Between December 2009 and December 2010, 19 patients with HHT-associated epistaxis were treated with 100 mg of intranasal submucosal bevacizumab. Following treatment, patients were contacted monthly to report their epistaxis severity score (ESS) for 9 or more months after their initial treatment. If a patient had a significant increase in their ESS, they were offered treatment with 100 mg of topical bevacizumab, administered via a metered dose atomizer. All treatments were recorded.

Results: All 19 patients had a postinjection ESS documented through 9 months, whereas 17 patients had completed ESS data between months 10 and 12. Six of the 19 patients received eight additional 100 mg of topical bevacizumab treatments because they had an increase in their ESS. Results demonstrated a mean preinjection ESS of 8.12, with an ESS nadir of 2.00 reached at 2 months following submucosal injection ($P < 0.0001$). Over the following 12 months, the mean ESS steadily increased back to a maximum of 3.6 reached at 11 months following injection ($P < .0001$).

Conclusions: Intranasal submucosal bevacizumab effectively treats HHT-associated epistaxis for up to 12 months following treatment.

Key Words: Hereditary hemorrhagic telangiectasia, epistaxis, bevacizumab, Avastin, vascular endothelial growth factors.

Level of Evidence: 4

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease with affected patients developing arteriovenous malformations (AVMs) that are prone to bleeding. Population estimates vary between 1/6,000 to 18,000 across the French, Danish, and Japanese popluations.[1–3] Small AVMs lining the nasal mucosa (nasal telangiectasias) are susceptible to bleeding, with approximately 95% of HHT patients affected by age 20 years.[4] Although most patients with HHT suffer some epistaxis, a small number suffer severe epistaxis. Mild epistaxis is generally managed by nasal hygiene, avoidance of triggers (e.g., alcohol), occasional cauterization, and the application of an estrogen cream. For moderate and severe cases, epistaxis can be severe and life threatening. Patients often require blood transfusions and intravenous iron supplementation. Surgical interventions such as lasering have not been successful. Septodermoplasty is a bloody undertaking, and epistaxis ultimately relapses. The only definitive surgery is suturing the nose closed, commonly called the Young's procedure, but most consider this a rather drastic undertaking that robs patients of nasal airflow.

To make a definitive diagnosis, affected patients must meet three of the four Curaçao criteria: 1) spontaneous/recurrent epistaxis, 2) mucocutaneous telangiectasias, 3) visceral arteriovenous malformations, and 4) family history in a first-degree relative.[5] A diagnosis can alternatively be confirmed with available genetic testing. Mechanistically, HHT patients have been found to have dysfunction in the TGF-β vascular endothelial growth factor (VEGF) signaling cascade. Patients have more than a 10-fold increase in the normal serum concentration of TGF-β and more than a 15-fold increase in the VEGF serum concentration.[6] Moreover, these TGF-β and VEGF elevations have also been appreciated in the endothelial cells lining the nasal mucosa.[6] Microscopically, HHT patients have arteriovenous malformations with distal arterioles, often bypassing capillary beds and connecting directly to postcapillary venules.[7] Consequently, venules are exposed to elevated arterial pressures and are prone to dilatation and bleeding. Nasal cavity vessels are most vulnerable because they are constantly exposed to the turbulent drying airflow of respiration.

Beginning in 2006, the senior author began successfully treating HHT epistaxis with bevacizumab, a VEGF inhibitor. Our initial report was published by Simonds et al. in 2009,[8] and a safety profile was published by

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Chen et al. in 2011.[9] It was later discovered that for some milder epistaxis, topical spray was also effective.[10] Also in 2011, Karnezis and the senior author retrospectively reported on 32 successive patients presenting with recurrent HHT epistaxis.[11] Between November 2008 and May 2010, patients received 25 to 100 mg of bevacizumab applied intranasally either as a submucosal injection or as a topical spray. In many of the injected patients, the potassium titanyl phosphate (KTP) laser was used adjunctively for vessel photocoagulation. A phone interview was performed in July 2010 to assess for treatment efficacy. All 32 treated patients were contacted with pre- and post-treatment epistaxis severity scores (ESS) compared. Seventeen patients received topical bevacizumab, 10 patients received a submucosal injection, and five patients received both. In addition, 12 patients were also treated with the KTP laser at the time of their submucosal injection. In the pretreatment period the average ESS was 7.0 (standard deviation [SD] 2.1), whereas in the post-treatment group the average ESS was 2.9 (SD 1.7). This represented a significant improvement in epistaxis severity ($P < .0001$).

For the last 5 years we have been treating individuals with moderate to severe epistaxis with a 100-mg intranasal submucosal injection of bevacizumab. The 100-mg dose was chosen as bevacizumab is available in pharmacy in 100 mg/4 mL. To evaluate epistaxis fluctuations and treatment response, patients were evaluated using the ESS.[12] Introduced in 2010, the ESS offers a standardized means by which to estimate epistaxis severity.[12] The ESS stratifies patients into mild (1–4), moderate (>4–7), and severe disease (>7–10) based on answers to six nosebleed questions averaged over the prior 3 months.[12] This article reports the 1-year follow-up of patients treated with 100 mg of intranasal submucosal bevacizumab with or without topical bevacizumab using the ESS as a barometer for treatment response.

MATERIALS AND METHODS

Between December 2009 and December 2010, 19 patients were prospectively treated at the University of California San Diego (UCSD) Nasal Dysfunction Clinic for recalcitrant HHT epistaxis. At the time of initial presentation, each of the patients received a 100-mg intranasal submucosal injection of bevacizumab. Patients were taken to the operating room and received a sphenopalatine block via the greater palatine canal and then an anterior palatine block with a sublabial injection (both with 1% lidocaine with 1:100,000 epinephrine). Nasal endoscopy was then performed with active epistaxis controlled with suction bovie electrocautery. Patients were then bilaterally injected with 1% lidocaine with 1:100,000 epinephrine along the lateral nasal wall, middle/inferior turbinates, nasal floor, and bony septum. Following this injection, the patients were similarly injected with 100 mg of bevacizumab along the lateral nasal wall, middle/inferior turbinates, nasal floor, and bony septum. These injections were all made in nasal mucosa intending it to diffuse throughout the nasal cavity. Notably, attempt was made to place two-thirds of the bevacizumab injection in the anterior one-third of the nose. Finally, a fibrin sealant (Evicel) was sprayed into the nose to prevent postoperative hemorrhage. To preserve a patent airway, nasal trumpets are placed along the nasal floor after application of the fibrin sealant. These can be removed after 3 minutes but are typically removed later in the postanesthesia care unit. Following bevacizumab injection, patients were contacted monthly to document their ESS. Although the originally published ESS asked patients to evaluate their epistaxis over the last 3 months, patients were asked to estimate their epistaxis over the last 1 month for study purposes. Of note, if patients had a significant increase in their ESS, they were offered treatment with 100 mg of topical bevacizumab administered via a metered dose atomizer. All topical treatments were recorded. Statistical comparisons between the pre- and post-treatment ESS values were assessed using a paired t test.

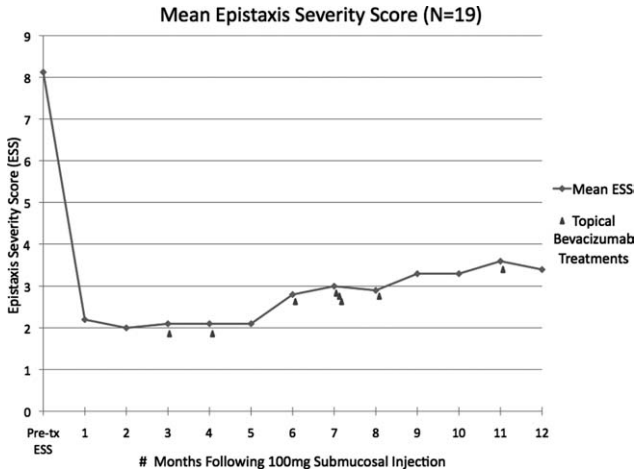

Fig. 1. Mean epistaxis severity scores (ESS) of 19 patients treated with 100 mg of submucosal intranasal bevacizumab tracked versus time in months. Six patients received eight treatments of 100 mg of bevacizumab sprayed intranasally to further control bleeding when it first began to appear. The times are indicated by the upward-pointing arrows.

RESULTS

Of the 19 treated patients, ESS data were recorded for all patients for the first 9 months following treatment, whereas data were available for 17 patients in months 10 to 12. Patients had a mean age of 60.0 years (range, 40–80 years), with 12 females and 7 males treated. Over this time period, six of the 19 patients received eight additional topical bevacizumab treatments with a 100-mg bevacizumab nasal spray. These patients were sprayed because their bleeding had increased following their submucosal injection. Topical treatments were notably given at 3, 4, 6, 7, and 11 months after their original submucosal injection.

In Figure 1, the mean ESS is documented following bevacizumab injection. The mean preinjection ESS for the 19 patients was 8.12, with an ESS nadir of 2.00 reached at 2 months following submucosal injection ($P < .0001$). Over the following 12 months, the mean ESS steadily increased back to a maximum of 3.6 reached at 11 months following injection ($P < .0001$). In Figure 2, the ESS is plotted individually for each of the 19 patients.

DISCUSSION

Bevacizumab is very effective in the treatment of HHT epistaxis. For some, it is more effective than others with the duration of control variable. Topical

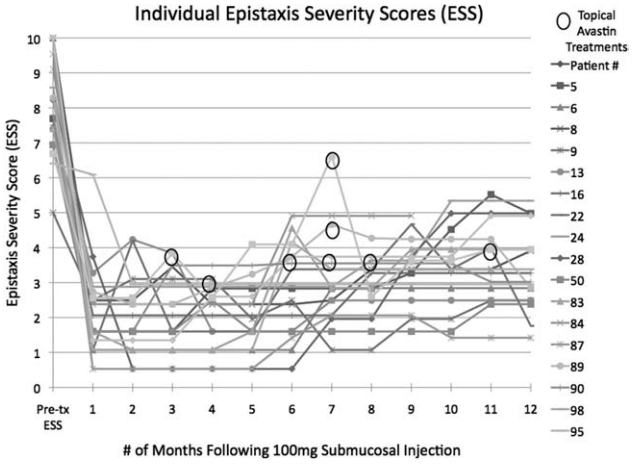

Fig. 2. Individual epistaxis severity scores (ESS) of 19 patients treated with 100 mg of submucosal intranasal bevacizumab tracked versus time in months. Supplemental 100-mg sprayings are noted with circles.

bevacizumab best treats patients with an ESS below 5 (benefit typically lasts around 3 months). More advanced disease, as measured by an ESS of 5 or greater, is initially treated with a submucosal injection followed by topical bevacizumab if bleeding recurs after an injection. This cutoff is entirely arbitrary, but so far it seems to work. Many patients persistently bleed in the first few weeks after a submucosal injection. Mechanistically, it is our impression that although VEGF inhibitors like bevacizumab can stop the development of new telangiectasias, they do not rid the mucosa of preexisting telangiectasias. Furthermore, although the natural history of nasal telangiectasias is undefined, we believe that they do turn over with some regularity. Therefore, at the time of submucosal injection it is sometimes wise to cauterize these preexisting telangiectasias because they may bleed in the initial weeks after an injection. Nonetheless, as these telangiectasias turn over, patient epistaxis will typically improve often by the 3rd postoperative week. Extensive laser surgery as previously described seemed to add little benefit, and with the injection of the bevacizumab took a long time to heal, Therefore, we discontinued routine lasering without any negative effect.[13]

During this study there were notably no complications. In addition, because bevacizumab is a very strong inhibitor of wound healing, no concomitant surgeries or laser procedures were performed at the time of injection. Although the results with the 100-mg injections have been excellent, we wondered if we could improve on our current therapy. At the UCSD Nasal Dysfunction Clinic, we have begun injecting HHT epistaxis patients with 200 mg of bevacizumab.

Ultimately, if HHT epistaxis is to be controlled with bevacizumab, patients will require repeated administrations for their recurrent disease. With such a dosing schedule, tachyphylaxis to VEGF inhibitors is a concern. In the ophthalmology literature, intravitreal VEGF tachyphylaxis has been documented in patients receiving treatment for age-related macular degeneration.[14,15] Notably, these patients indefinitely receive repeated intravitreal VEGF injections (e.g., 1.25–2.5 mg of bevacizumab) on a variable dosing schedule (typically no more frequently then every 4 weeks). Fortunately, in HHT epistaxis, tachyphylaxis has not been recognized. Whether it will, time will tell.

It is interesting that occasionally a patient will fail to respond to the submucosal injection. Repeat injection 1 month later often is successful. Is this the nature of the disease or does it represent a bad batch of bevacizumab. The answer is not known, but if a patient fails the initial injection, a repeat injection is indicated. None were required in this patient cohort.

CONCLUSION

Intranasal submucosal bevacizumab is an effective treatment for HHT epistaxis.

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