Local Injection of Bevacizumab (Avastin) and Angiolytic KTP Laser Treatment of Recurrent Respiratory Papillomatosis of the Vocal Folds: A Prospective Study

Steven M. Zeitels, MD; Anca M. Barbu, MD; Tali Landau-Zemer, MD; Gerardo Lopez-Guerra, MD; James A. Burns, MD; Aaron D. Friedman, MD; Mason W. Freeman, MD; Yuan-Di Halvorsen, PhD; Robert E. Hillman, PhD

Objectives: Photoangiolytic laser treatment of recurrent respiratory papillomatosis (RRP) is effective, but does not reliably prevent recurrence. Therefore, sublesional injections of the antiangiogenic agent bevacizumab (Avastin) were given to assess the adjunctive effect on disease recurrence. Since bevacizumab is a new therapeutic modality for RRP, there were also primary safety objectives to determine whether there was a negative impact on the voice and whether there were local or systemic complications.

Methods: A prospective open-label investigation was conducted in 20 adult patients with bilateral vocal fold RRP. The patients underwent planned 532-nm pulsed KTP laser photoangiolyis of bilateral glottal disease 4 times with an approximately 6-week interval between procedures. At each planned laser procedure, the vocal fold that on initial presentation had a greater volume of disease also underwent 4 serial sublesional bevacizumab injections (7.5 to 12.5 mg in 0.3 to 0.5 mL). A sham injection with saline solution was administered to the other vocal fold as a control. Disease resolution was compared between subjects’ vocal folds, and objective measures of vocal function (acoustic, aerodynamic), as well as patients’ self-assessments of vocal function (Voice-Related Quality of Life survey), were obtained.

Results: All 20 patients completed the study, and there were no local or systemic complications. After 4 injections, 3 of the 20 patients had no discernible disease in either vocal fold. Of the remaining 17 subjects, 16 had less disease in the bevacizumab-treated vocal fold despite starting with more disease. Only 1 of the 17 had more disease in the bevacizumab-treated vocal fold after 4 injections. Moreover, 7 of the 20 patients (35%) did not require a laser procedure in the vocal fold that had received 4 bevacizumab injections, as compared with 3 of the 20 vocal folds (15%) that were treated with laser alone. All of the vocal function measures displayed statistically significant posttreatment improvements, except for average fundamental frequency in the 3 female patients, in whom it fell below the normal range.

Conclusions: This prospective investigation provided evidence that bevacizumab injections enhanced KTP laser treatment of glottal papillomatosis without systemic or local complications. Coupling the antiangiogenesis agent bevacizumab with KTP laser photoangiolyis is conceptually synergistic and scientifically promising since the mechanisms of action are complementary.

Key Words: Avastin, bevacizumab, glottis, KTP laser, larynx, laser, papilloma, papillomatosis, recurrent respiratory papillomatosis, RRP, vocal cord, vocal fold, voice.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) has been an onmitemporal clinical problem in laryngology since the origin of the subspecialty 150 years ago.1 The mainstay of treatment through the past 2 centuries has been transoral surgical removal to restore airway and vocal function. Depending on the severity of the disease, the treatment would commonly result in permanent vocal dysfunction and, rarely, could produce airway stenosis.

Hooper noted in 1882 that “The vascularity of the growth (papillomatosis) is perhaps the most important factor in determining the rapidity of its reappearance.”2(p341) In essence, he was recognizing neoplastic angiogenesis, which would be clinically described again in 1966 by Jako and Kleinsasser3 and formally conceptualized as a watershed heuristic theory by Folkman in the 1970s.4,5

From the Departments of Surgery (Zeitels, Barbu, Landau-Zemer, Lopez-Guerra, Burns, Friedman, Hillman) and Medicine (Freeman, Halvorsen), Harvard Medical School, and the Center for Laryngeal Surgery and Voice Rehabilitation (Zeitels, Barbu, Landau-Zemer, Lopez-Guerra, Burns, Friedman, Hillman), the Translational Medicine Group, Center for Computational and Integrative Biology (Freeman, Halvorsen), and the Massachusetts General Hospital Institute of Health Professions (Hillman), Massachusetts General Hospital, Boston, Massachusetts. This work was supported in part by the Eugene B. Casey Foundation, the V Foundation, the Institute of Laryngology and Voice Restoration, and the Harvard Catalyst Program.

Correspondence: Steven M. Zeitels, MD, Center for Laryngeal Surgery and Voice Rehabilitation, Massachusetts General Hospital, One Bowdoin Square, 11th Floor, Boston, MA 02114.
Remarkably, this philosophy has been the underpinning of our treatment philosophy6-10 of RRP over the past decade. Angiolytic laser treatment of RRP comprises targeting the microvasculature of the neoplasm. It was done by means of microlaryngoscopy and general anesthesia initially, and a decade ago, an office management procedure was created that utilized topical anesthesia with a 585-nm pulsed-dye laser.7 Office-based angiolytic laser treatment of RRP was a key innovation because it obviated the need for ongoing general anesthetic interventions in a majority of adult patients with RRP. This procedure was made substantially easier by the introduction of the 532-nm pulsed KTP (potassium titanyl phosphate) laser because of its enhanced precision, reliability, and versatility.9,11,12

On the basis of the possible role of vascular endothelial growth factor (VEGF) in the neoplastic progression of RRP,13 and on the success of localized injection of bevacizumab (Avastin) for ophthalmologic neovascular growth,14 we initiated localized sublesional injection of bevacizumab as an antiangiogenesis agent to enhance angiolytic laser treatment of RRP.1 Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that binds to and inhibits the biologic activity of human VEGF. It has a molecular weight of approximately 149 kd. Bevacizumab is formulated as a clear to slightly opalescent, colorless sterile solution, and is supplied in 100-mg preservative-free single-use vials at a concentration of 25 mg/mL.

Our retrospective initial report on the off-label use of localized injection of bevacizumab involved 10 patients with laryngeal RRP. This study provided preliminary evidence that bevacizumab injections enhanced photoangiolytic laser treatment of glottal papillomatosis with associated improvements in phonatory function. From our review of the literature, this publication appears to be the first description of localized injection of a pharmacologic antiangiogenesis agent to treat a neoplasm, as distinct from treating aberrant blood vessel growth.14,15

Because of the success noted in the initial study, we embarked on a collaborative effort with the Translational Medicine Group at Massachusetts General Hospital (MGH) and initiated the prospective clinical trial reported herein. We obtained investigational new drug approval from the US Food and Drug Administration, as well as Institutional Review Board approval from MGH/ Partners Healthcare.

The primary therapeutic objective of this study was to determine whether bevacizumab treatment reduces or eliminates the need for recurrent angiolytic KTP laser photoangiolyis surgery to control the progression of RRP of the vocal folds during the treatment period. The primary safety objectives were to determine whether there was a negative impact on the voice and whether there were local or systemic complications associated with bevacizumab.

MATERIALS AND METHODS

Study Design. A phase I single-center open-label study was performed involving 20 patients in order to assess the efficacy, safety, and tolerability of bevacizumab for treating patients with bilateral vocal fold RRP. The investigation was funded from patient-based US nonprofit foundations or organizations, as well as pilot grant support from Harvard Catalyst, the federally funded Clinical and Translational Science Center grant. The study protocol, informed consent form, and relevant supporting information were reviewed and approved by the Institutional Review Board before the study was initiated. The subjects for this study were recruited from a patient population presenting to MGH Voice Center with dysphonia who received a diagnosis of RRP of the vocal folds and would normally receive KTP laser treatment. Recruitment for the study was posted on the clinical trials website (http://clinicaltrials.gov). The study was limited to patients over 18 years of age who had disease involving both the right and left vocal folds.

Subjects who enrolled in the protocol were injected with bevacizumab in one vocal fold, which was the one that retained more disease on examination before the first injection (video strobolaryngoscopy and/or microlaryngoscopy). A sham injection with saline solution was administered to the other vocal fold as a control. This therapy was administered once every 6 ± 1 weeks for 6 months; the same vocal fold selected for the initial treatment always received the bevacizumab injection. The surgeon also treated any visible RRP lesions of both vocal folds using 532-nm pulsed KTP laser photoangiolyis. At each return visit, the surgeon reviewed the strobolaryngoscopy images and compared the disease status to the disease at baseline. The subjects underwent 4 injections and were examined at approximately 6 weeks after the fourth injection, which was approximately 6 months after the first procedure.

Subject Enrollment. Study participation and enrollment were initiated from patients who were considering standard photoangiolytic KTP laser surgical treatment for bilateral vocal fold papillomatosis. The staff surgeons (S.M.Z., J.A.B., and A.D.F.) initially discussed consent for participation with each patient at an outpatient visit in the MGH Voice Center before the first surgical procedure. A patient had 24 hours from the time of the initial discussion to decide whether he or she would like to sign the con-
sent form for the first procedure. Patients could reverse their decision at any time. It was explained to all patients that their decision about study participation did not in any way affect the standard of care for their disease.

All 20 patients met the following inclusion criteria to be enrolled in this study. The patients (male or female) had dysphonia and a diagnosis of RRP of both vocal folds. They were between 18 and 60 years of age. Female subjects were surgically sterilized, postmenopausal, or using adequate contraception. (The criteria for menopause were surgical menopause [hysterectomy, oophorectomy] or age of more than 45 years with absence of menses for more than 12 months and an elevated level of serum follicle stimulating hormone, ie, more than 25 mIU/mL. Tubal ligation with menses within the past 12 months was not considered to be surgical sterilization.) The patients were willing and able to comply with the investigational nature of the study and able to communicate well with the investigators. They had the ability to comprehend and willingness to provide written informed consent in accordance with institutional and regulatory guidelines.

Patients who met any of the following criteria were excluded from the study: known sensitivity to bevacizumab; systemic treatment with bevacizumab within 4 months (approximately 6 half-lives); a hematocrit level of less than 30%; a prothrombin time or a partial thromboplastin time more than 1.2 times the upper limit of normal, or absolute platelet counts below the lower limit of normal; an absolute neutrophil count below 1,500/µL; a urine protein-to-creatinine ratio greater than 1.5 (a urine dipstick test positive for a proteinuria level of at least 3+ was not an exclusion criterion, but necessitated spot urine collections); a history of congestive heart failure, angina that remained symptomatic despite medications, myocardial infarction or a coronary artery disease-related procedure within the past 6 months (including angioplasty, stent placement, bypass graft surgery), or a prosthetic heart valve; significant uncontrolled hypertension (systolic blood pressure above 160 mm Hg and/or diastolic blood pressure above 100 mm Hg); surgery within 1 month or an unhealed surgical incision at screening; a history of thromboembolic events, gastrointestinal ulcer or bleeding, or wound dehiscence; or nursing or plans to nurse during the possibly 18-month treatment period.

Subject Evaluation. The following procedures were performed before the first treatment (baseline) and before each subsequent treatment, with the final assessment occurring approximately 6 weeks after the fourth treatment.

In terms of medical testing, we performed electrocardiography; vital signs testing including pulse, blood pressure, respiration rate, and body temperature; serum chemistry; complete blood count; physical examination; urinalysis; and pregnancy testing (female subjects of childbearing potential only).

Endoscopic imaging was also performed. Standard transnasal flexible videolaryngoscopy was performed at each visit before treatment as a basis for determining the amount of papilloma on the vocal folds. A KayPENTAX 9200-C videostroboscopic system was used to make digital recordings as the endoscope was centered on the glottis and slowly advanced and withdrawn to acquire images over a range of distances while the vocal folds were abducted during quiet breathing. Image distortion related to scope optics (barrel distortion) was measured on an optical bench and was corrected for in postprocessing with a validated Matlab-implemented algorithm. KayPENTAX system software was used to select the still image for each endoscopic assessment that showed the best exposure of the entire glottis (adducted vocal folds). The still images were saved in jpeg bitmap format, corrected for image distortion with the Matlab-implemented routine, and digitally processed to equate all of the images with respect to the size and orientation of the glottis. The cursor function in ImageJ software was then used to delineate the approximate area of the disease in square centimeters for the right and left vocal folds in each still image to assist in making comparisons based on visual judgments. For this initial report, only the imaging data from the last assessment were examined as a basis for making the simple determination about which vocal fold had the most recurrent disease after 4 treatments. This approach to the analysis actually created a bias against finding a positive treatment effect, because in each patient the vocal fold with the worst disease was injected with bevacizumab.

Noninvasive clinical voice assessment included completion of the Voice-Related Quality-of-Life survey (V-RQOL), on which 0 indicates the lowest voice-related quality of life and 100 indicates the highest voice-related quality of life,16 and objective acoustic and aerodynamic measures of vocal function. The details of the protocol for obtaining acoustic and aerodynamic measures of vocal function have previously been described.17 We focused on the same objective acoustic and aerodynamic measures that were used in an earlier pilot study of bevacizumab as an adjunct to KTP laser treatment of papilloma: 1) average fundamental frequency (F0) during reading of a standard passage (vocal pitch); 2) the noise-to-harmonics ratio during sustained vowels (voice quality); and 3) the ratio between vocal sound pres-
sure level and average subglottic air pressure during production of standard syllable strings (in decibels per centimeter of water; vocal efficiency). Group-based differences between pretreatment (baseline) and posttreatment average values for vocal function measures were assessed for statistical significance (p < 0.05) by use of simple t-tests for paired comparisons. The average values for vocal function measures were also compared to historical norms, as has been typically done in previous investigations.1 Because 11 of the 20 patients had undergone previous assessment and ongoing management for their disease at our facility before accrual for the present study (including KTP laser treatment), the decision was made to use voice data from the very first evaluation that these patients had in order to more accurately characterize their pretreatment baseline function.

Treatment Protocol. The first treatment session typically involved microlaryngoscopy and general anesthesia. Bevacizumab (7.5 to 12.5 mg) was injected into the sublesional mucosa of the vocal fold that was judged to have worse disease. The technique was described previously.1 Saline solution was injected into the other vocal fold in a comparable volume and location.

Photoangiolyis of disease was done on both vocal folds with the 532-nm KTP laser. The bevacizumab injection of the vocal fold was done either before or after the laser procedure according to nuanced individual anatomic considerations of each patient so as to most effectively deliver an accurate dose.

Three additional treatment sessions were carried out at approximately 6-week intervals. A majority of these treatments were done in the office with local topical anesthesia. At each session, bevacizumab was reinjected into the previously injected vocal fold. The KTP laser was used for photoablation of recurrent disease on either vocal fold.

RESULTS

All 20 patients who enrolled in the study completed it successfully, and none had a local or systemic complication. At the end of the treatment period, 3 of the 20 patients had no discernible disease in either vocal fold. Of the 17 remaining subjects, 16 had less disease in the bevacizumab-treated vocal fold despite starting with more disease. Only 1 of the 17 had more disease in the bevacizumab-treated vocal fold after 4 injections. This reduced appearance of disease in the bevacizumab-treated vocal fold significantly exceeds what may be expected by chance (2-tailed binomial calculation, p = 0.00027). Moreover, 7 of the 20 bevacizumab-treated vocal folds (35%) did not require laser treatment at the 6-week checkpoint subsequent to the 4 injections, as compared to 3 of the 20 saline-injected vocal folds (15%), which had less disease initially, but this difference did not achieve statistical significance ($\chi^2$ test, p = 0.114). Similarly, in the 80 bevacizumab-injected vocal folds, KTP laser treatment was required 57 times, as compared with 69 times after the 80 saline injections. Twenty-five of the 80 procedures (31%) were done by means of microlaryngoscopy and general anesthesia, and 55 of the 80 (69%) were done in the office with topical anesthesia.

The results for the comparisons between pretreatment and posttreatment vocal function measures are summarized in the Table. All of the measures displayed statistically significant posttreatment changes, which included increases in the V-RQOL rating and vocal efficiency (vocal sound pressure level divided by average subglottic air pressure), and decreases in acoustic noise levels (noise-to-harmonics ratio) and vocal pitch (F0). However, posttreatment improvements in group-based averages for vocal efficiency and acoustic noise level did not attain the normal range. For the 17 male subjects, the average F0 decreased from an abnormally high pretreatment value to within normal limits after treatment. Remarkably, the 3 female subjects displayed an average pretreatment F0 value that was within normal limits but decreased to below the normal range after treatment.

DISCUSSION

Treating RRP by coupling the antiangiogenesis...
This 49-year-old patient regularly sustained substantial recurrence of respiratory papilloma every 6 to 8 weeks before being referred. He was first patient to undergo sublesional Avastin injection. A) On presentation to us and before initiation of Avastin, he had diffuse transglottal disease, as seen on office laryngoscopy. B) Microlaryngoscopic view also demonstrates diffuse disease. C) Microlaryngoscopic view after KTP laser treatment but without Avastin injection. D) Office laryngoscopy shows extensive recurrence approximately 6 weeks after initial KTP microlaryngoscopic laser treatment. E) Office-based injection of Avastin while patient was beginning to demonstrate improvement in disease in left vocal fold. F) Office laryngoscopy at patient's most recent visit and after conclusion of investigation. Patient has been receiving office-based injections of Avastin to both true and false vocal folds (approximately 50 mg) at 8- to 10-week intervals for past 7 months. There is very limited laser use.

agent bevacizumab with KTP laser photoangiolyisis is conceptually attractive and scientifically sound, since the mechanisms of action are complementary. Observations from this prospective second investigation have provided further evidence that pharmacologic antiangiogenesis by local injection is efficacious in treating laryngeal RRP (see Figure). The investigation herein also included key safety monitoring that demonstrated a lack of local or systemic complications, which will assist clinicians who are considering initiating this promising new management strategy.

Folkman5,18,19 established that angiogenesis is a
multistep process primarily initiated through VEGF, which initiates a cascade of intracellular signal transduction pathways resulting in the formation of new vessels.\textsuperscript{20} Given the microcirculatory histology of RRP,\textsuperscript{21} there is evidence that VEGF plays an important angiogenic role in the pathogenesis of RRP.\textsuperscript{13} After sublesional injection of bevacizumab, the local soft tissue concentration is postulated to exceed the concentration required to inhibit VEGF-induced endothelial cell proliferation and neoplastic growth.

It has been well demonstrated that photoangiolytic lasers target the microcirculation of RRP and effectively involute glottal disease while preserving the superficial lamina propria of the phonatory mucosa. However, similar to all surgical interventions that remove RRP disease, this approach does not reliably prevent recurrence. Therefore, it was hypothesized that a sublesional injection of an antiangiogenic drug such as bevacizumab at the time of an angiolytic laser removal of laryngeal papillomatosis would be a clinically attractive approach that might prevent or slow disease recurrence.

Based on encouraging preliminary findings,\textsuperscript{1} the protocol herein was developed to better define the effectiveness of the adjuvant bevacizumab-laser treatment. Given the variation in surgical technique, a single-center open-label study was done to compare disease recurrence between drug-treated and non-drug-treated vocal folds longitudinally in the same patient. This contralateral control study design in the same subject minimizes confounding factors and maximizes the chance of observing differences in a relatively small patient population, particularly when the recurrence rate varies significantly from patient to patient. Given general repetitive geographic patterns of disease recurrence, injecting bevacizumab into the vocal fold with the worse disease produced a more conservative (negatively biased) test of treatment effectiveness.

The laryngeal dosage selected was based in part on the ophthalmologic experience. Ocular doses have typically been between 1.25 mg (0.05 mL) and 2.5 mg (0.1 mL). These doses were partially predicated on the desire not to have to remove vitreous fluid from the eye to accommodate the volume of drug injection. Similarly, the dose selected for vocal fold injection was based on the potential fluid expansion capacity of the phonatory mucosal compartment (Reinke's space).\textsuperscript{5,22,23} The volumes of injection proposed (0.3 to 0.5 mL) were well tolerated in all 20 subjects. The variation in subepithelial infusion volume was related to the amount of scarring present from prior procedures in the subepithelial superficial lamina propria.

The dose of 7.5 to 12.5 mg (0.3 to 0.5 mL) bevacizumab delivered locally is much less than the 5 to 10 mg/kg (300 to 600 mg for a 60-kg human) dose range approved for systemic administration for the treatment of colorectal or lung cancer. With 7.5 to 12.5 mg bevacizumab injected into a confined space in a vocal fold, the systemic exposure to the drug will be substantially less than that experienced by cancer patients treated with higher intravenous (systemic) administered dosages. Unlike in reports on intravenous cancer treatment, there were no systemic complications. This mirrors the ophthalmologic experience,\textsuperscript{24,25} as well as the substantially higher-dose (approximately 100 mg) local intranasal treatment of hereditary hemorrhagic telangiectasia.\textsuperscript{15}

The 20 patients studied herein demonstrated a wide spectrum of disease presentation, which is not surprising. We have not noted that effective surgical techniques that preserve the layered microstructure of the glottis result in a biological change in the papillomatosis-host relationship and recurrence pattern.\textsuperscript{1} This concept was reinforced by the current investigation. Both vocal folds received similar surgical treatment, yet by the end of the 6-month study period, there continued to be discernible disease in the saline-treated vocal fold in 17 of the 20 patients (85%). Given the frequency of the procedures, it is not surprising that 15% of the patients did not have discernible disease at this relatively short follow-up. However, it was remarkable that only 13 of the 20 patients (65%) had discernible RRP in the bevacizumab-treated vocal folds, which started with more disease. This is especially noteworthy because it is well accepted that laryngeal RRP generally retains repetitive geographic patterns of disease recurrence, often with consistent asymmetry of vocal fold involvement.

It was also promising to observe that of the 17 subjects who had disease after the fourth injection, 16 had less disease in the bevacizumab-treated vocal fold despite starting with more disease in that fold. Only 1 of the 17 continued to have more RRP in the bevacizumab-treated vocal fold. These observations reached statistical significance. There was also a trend toward observable resolution of the disease in the bevacizumab-treated vocal folds (7/20) as compared to the saline-injected side (3/20), although this did not reach statistical significance. This trend toward enhanced resolution might have reached statistical significance with a larger patient cohort. Alternatively stated, there is substantial evidence that the biological behavior of the RRP was altered in the localized region in which the bevacizumab was injected, because the surgical interventions were consistently applied to both vocal folds.
We expect that there will be a spectrum of responses to bevacizumab with varied patterns of recurrence commensurate with the spectrum of disease presentation. Remarkably, the opera singer whose images and history were reported in the prior publication did not participate in this study because he has been in complete remission since December 2008, when he received the last of his 5 office-based bevacizumab injections. It is likely that more-substantial angiogenic activity associated with more-aggressive neoplastic growth will be more susceptible to bevacizumab.

With regard to voice outcome, the patients displayed substantial improvement in posttreatment vocal function. This was reflected most clearly by the statistically significant increases in vocal efficiency (vocal sound pressure level divided by average subglottic air pressure) and by patients' self-assessments on the V-RQOL, accompanied by a significant decrease in the level of noise in the voice acoustic signal (noise-to-harmonics ratio). In addition, the male subjects displayed a significant post-treatment drop in vocal pitch (F0) to normal limits. However, even though the vocal efficiency and acoustic noise level improved significantly, neither of the group-based averages for these measures attained the normal range, and there was a decrease in the average vocal pitch to a slightly abnormal low value for the 3 female subjects. This is likely an effect of chronic inflammation of the superficial lamina propria similar to that seen in female smokers.

Although there was no evidence that the bevacizumab negatively affected vocal function, as has been reported with cidofovir, it is challenging to establish whether it contributed to the observed improvements in vocal function. It is extraordinarily difficult to decouple the influence of the bevacizumab and the KTP laser treatments on the observed voice improvements, because the interventions occurred simultaneously.

Despite the fact that it is difficult to prove, our observation is that a majority of the bevacizumab-treated patients developed a better voice than we would have predicted given their prior extensive surgery, associated scarring, and initial diminished pliability of the phonatory mucosal superficial lamina propria. It is likely that the papillomavirus remains in the mucosa, which is why there is a tendency for the neoplastic lesions to geographically recur in the same locations. Our impression is that the bevacizumab turns off the virally induced angiogenic switch that produces papillomatosis neoplasms but does not turn off the virally induced production of extracellular matrix proteins responsible for regenerating phonatory mucosal pliability and vocal fold vibration.

It is clear to any clinician who manages substantial numbers of RRP patients who have had large numbers of procedures (more than 50) with older technologies that a majority of the patients have remarkably stable voices despite having undergone extensive imprecise and ablative surgery. This vocal stability is not typically observed after repeated surgical treatment of other phonatory mucosal lesions. Most analogous to RRP would be patients with glottal dysplasia who have had many ablative mucosal procedures and who typically have poor voice quality. Alternatively, one can hypothetically envision how poor a patient's voice would be if he or she were to undergo 50 carbon dioxide laser procedures for a limited surgical zone of vocal fold nodules.

Our observations thus far suggest that localized laryngeal injection of an antiangiogenesis agent shows potential to improve angiolytic KTP laser treatment of RRP. It serves as an adjuvant medical management to diminish the severity and frequency of recurrence and consequently the number of ablative mucosal procedures, which poses the most significant threat to permanent voice loss. Because there is less mucosal ablation and disruption, fluctuations in vocal function are mitigated.

Until there is a systemic medical treatment for RRP, localized injections of antiangiogenesis agents provide a reasonable bridge strategy to diminish the morbidity of the disease and mitigate the impact of repeated surgical removal. An injection of bevacizumab into the superficial lamina propria of the phonatory mucosa leads to several hours of significant hoarseness due to the hydrostatic pressure in Reinke's space and is mostly resolved by the next day. Patients do not require voice rest. It is important to recognize that there will be a learning curve for surgeons to perfect subepithelial office-based Reinke's space infusions, since it is not typically in their skill-sets and deep infusion of the drug is unlikely to work. A sublesional subepithelial injection must be done, since the virus likely resides intramuscosally and a typical injection laryngoplasty is done deep to the vocal ligament.

The promising clinical findings above are noteworthy because there has been limited private-sector pharmaceutical investment in solving laryngeal papillomatosis. Recurrent respiratory papillomatosis is a classic orphan disease that has not been adopted by the pharmaceutical industry because it provides limited financial incentive for the private sector to design, produce, and market medications to treat or prevent it. Considering the enormous resources...
already invested by the pharmaceutical industry to develop antiangiogenesis agents in oncology, along with their mixed success thus far, this study suggests that a company with an effective VEGF inhibitor might consider reformulating it for specific use in RRP. Further evidence of efficacy would also provide valuable support to investigating the use of intravenous antiangiogenic agents for patients with potentially lethal airway obstruction.

CONCLUSIONS
Treating RRP by coupling the antiangiogenesis agent bevacizumab with KTP laser photoangiolyis is conceptually and scientifically synergistic, since the mechanisms of action are complementary. Observations from this second investigation have provided further evidence that pharmacologic antiangiogenesis is efficacious in treating RRP and that it appears to be relatively safe locally and systemically. Larger patient cohorts and multi-institutional studies are needed. This effort provides additional evidence that clinicians should explore new avenues for investigating local injections of antiangiogenesis pharmacologic agents as a primary or adjuvant treatment for other mucosal diseases and neoplasms of the aerodigestive and genitourinary systems, as well as skin.

REFERENCES