

Use of 532-nm Pulsed Potassium Titanyl Phosphate Laser and Adjuvant Intralesional Bevacizumab for Aggressive Respiratory Papillomatosis in Children

Initial Experience

Stephen Maturo, MD; Christopher J. Hartnick, MD, MS, EPI

Objective: To describe the initial pediatric experience with intralesional bevacizumab (Avastin) treatment for children with severe, recurrent respiratory papilloma (RRP).

Design: Retrospective medical chart review.

Setting: Tertiary care multidisciplinary aerodigestive center.

Patients: Three children, aged 3 to 6 years, with severe RRP requiring more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to adjuvant treatment with intralesional bevacizumab.

Intervention: All 3 children were treated as follows: surgical debridement with a microdebrider, pulsed potassium titanyl phosphate laser treatments, and adjuvant intralesional injections with bevacizumab (1.25 mg total).

Main Outcome Measures: Time interval between operative interventions, Derkay severity scale for RRP, and pediatric voice-related quality of life (PVRQOL) scores.

Results: All 3 children demonstrated increased time between operative interventions. Two children had a substantial decrease in their Derkay score and improved PVRQOL scores. One child, although time between operative interventions improved, did not have any change in Derkay score and required further adjuvant therapy.

Conclusions: Injectable bevacizumab appears to show some efficacy in prolonging the time between treatments and therefore reducing the number of treatments per year in children with severe RRP. However, before any meaningful conclusions can be drawn, further studies must be conducted in the form of head-to-head trials looking specifically at the issues of time between treatment intervals, efficacy of one adjunct over another, vocal outcomes, and whether several adjunctive treatments confer advantage over 1 treatment. In-depth and careful informed consent is mandatory for these studies so that parents are aware of the risks and benefits (known and unknown) before such individualized decisions are made.

Arch Otolaryngol Head Neck Surg. 2010;136(6):561-565

RECURRENT RESPIRATORY PAPILLOMATOSIS (RRP) is the most common benign neoplasm of the larynx in children.¹ It most commonly presents with hoarseness, stridor being the second most common presentation. It is most commonly caused by human papillomavirus (HPV) types 6 and 11, although HPV-16 and HPV-18 can also be associated, and these types raise concern about possible malignant transformation.²⁻⁴ Reports estimate the incidence of RRP in the United States at 4.3 per 100 000 children and 1.8 per 100 000 adults.^{5,6}

Although it is a benign disease, RRP can recur often and cause frank airway obstruction; moreover, there is the concern about malignant conversion. According to

the National Registry of Children with RRP,⁷ which includes patients of 22 pediatric otolaryngology practices, children with RRP undergo an average of 19.7 procedures or an average of 4.4 procedures per year, equivalent to more than 10 000 surgical procedures annually for children with RRP in the United States. The frequency of these procedures and the severity of the symptoms substantially impact the quality of life of children and their families⁸ and are associated with considerable economic cost, estimated at \$150 million annually.⁶ In addition, the effects of multiple anesthetic administrations on the developing child are of growing concern, in terms of behavior changes and possible learning delays.^{9,10} Age at onset appears to predict severity of illness in

Author Affiliations:
Department of Otolaryngology,
Massachusetts Eye and Ear
Infirmary, Boston.

children with RRP; diagnosis before vs after age 3 years is associated with 3.6 times greater likelihood of needing more than 4 surgical procedures per year and almost 2 times greater likelihood of having 2 or more anatomic sites affected.⁶

There is no “cure” for RRP, and no single treatment has been consistently effective in eradicating RRP. The current standard of care is surgical therapy with a goal of complete removal of papillomas and preservation of normal structures. Surgical techniques may consist of cold knife endolaryngeal incision with or without phonosurgical techniques,¹¹⁻¹³ excision with the microdebrider¹⁴⁻¹⁶ or with the carbon dioxide laser,¹² treatment with photodynamic therapy,^{17,18} the flashed pumped-dye laser,¹⁹ the 585-nm pulsed-dye laser,²⁰⁻²³ the 532-nm pulsed potassium titanyl phosphate (KTP) laser,²⁴ or a combination of these techniques.

In approximately 20% of cases, some form of adjuvant therapy may be needed in addition to standard surgical treatment.¹ Examples of adjuvant therapies include oral indole-3-carbinol treatment,^{25,26} artemisinin (Robert Bastian, MD, personal communication), or intralesional injections of cidofovir²⁷⁻²⁹ or the mumps vaccine.³⁰ The most widely accepted indications for adjuvant therapy are a need for more than 4 surgical procedures per year, rapid regrowth of papillomas with airway compromise, or distal multisite spread of disease.¹ Because animal studies have demonstrated a high level of carcinogenic effects for cidofovir,³¹ and there have been case reports of progressive dysplasia in patients with RRP who received cidofovir,³² the RRP Task Force³³ has published guidelines for clinicians interested in using cidofovir to treat RRP.³³ Extensive pretreatment counseling with the patient’s family is absolutely necessary before embarking on this treatment regimen. Furthermore, there is a small but significant subpopulation of children with refractory and aggressive RRP despite multiple surgical debridements and treatments with adjuvant medications such as cidofovir.

Bevacizumab (Avastin; Genentech, San Francisco, California) is a human monoclonal antibody that binds to and neutralizes the biologic activities of vascular endothelial growth factor (VEGF) isoforms, preventing them from interacting with their receptors. The rationale for using bevacizumab to treat children with aggressive RRP stems from basic research that has found VEGF receptors in laryngeal papilloma specimens taken from affected children³⁴ as well as the recent experience of Zeitels et al³⁵ in using bevacizumab to treat adults with RRP. There was much patient enthusiasm generated over the RRP Foundation’s patient-focused Web site (<http://www.rpf.org/>) following the report by Zeitels et al,³⁵ and many families inquired about possible application of this treatment to children. Herein, we report the use of intralesional bevacizumab in the treatment of 3 children with aggressive RRP.

METHODS

Three children aged 3 to 6 years were deemed suitable candidates for this pilot study; medical chart review was approved by the institutional review board. No other child with RRP

treated at our institution underwent bevacizumab injection prior to these 3 children. Two of the 3 children had aggressive RRP, defined as requiring more than 4 operative treatments in 1 year for airway symptoms and not responsive to 3 cidofovir injections. There had been lengthy discussions with the families about possible adjuvant therapies. One of the 3 patients came from abroad and had 22 surgical treatments the year before. The mother refused Cidofovir treatment.

The families were each provided literature on bevacizumab and given special informed consent forms disclosing that this was an off-label use of bevacizumab and listing of the possible risks and benefits. This informed consent form had been reviewed by the pharmacists at the Massachusetts Eye and Ear Infirmary. After reading these documents, the families chose between continuation of standard surgical therapy or initiation of bevacizumab adjuvant therapy. The parents had to sign both the expanded bevacizumab consent form and a standard consent form before the bevacizumab could be used to treat the children.

Standard surgical therapy (as defined by C.J.H.) consists of a combination of microdebrider therapy of bulky diseased tissue followed by pulsed KTP laser treatment of papilloma immediately adjacent to the anterior commissure, true vocal folds, or within the ventricles. Use of the pulsed KTP laser has been the standard laser therapy for at least 2 years with approximately 20 children treated (C.J.H.). Advantages of treatment with the pulsed KTP laser include increased selective photoangiolytic, which helps preserve the important layered structures of the vocal cords.²⁴ This has helped treat papillomas in sensitive areas such as the anterior portion of the vocal cord, thus preventing vocal cord scarring and web formation.²²

Our technique for adjuvant injection of bevacizumab included suspension microlaryngoscopy with first gross debulking of the papilloma with a microdebrider and then application of pulse KTP laser to sessile areas and sensitive areas such as the anterior vocal cords and interarytenoid region. Afterwards, we used a laryngeal needle to inject a total of 1.0 mL of bevacizumab (1.25 mg/mL) into the areas most affected by the papilloma. The first treatment for these 3 children occurred in April 2009.

RESULTS

The results were obtained after the institutional review board of the Massachusetts Eye and Ear Infirmary approved a retrospective medical chart review of the children’s records (**Table**).

PATIENT 1

A 3-year-old boy with RRP of 1 year’s duration (HPV-6) had undergone 12 microdebrider procedures with 7 injections of cidofovir at an outside institution. Six weeks after the last cidofovir injection, he was again symptomatic, and the mother signed our special informed consent for bevacizumab injections following microdebrider debulking and pulse KTP procedure. The child’s Derkey severity grade for RRP at the time of this treatment was 21. Seven weeks later, the patient presented to an outside institution where he was urgently brought to the operating room for microdebrider removal of papilloma (no records available for calculation of Derkey score). Within a week of this procedure, the patient returned to our operating room for a second bevacizumab injection. Postoperatively, he did well. At follow-up 3

Table. Selected Patient Characteristics Before and After Bevacizumab Adjuvant Treatment

Patient Sex/Age, y (Bevacizumab Injections, No.)	SPPM During the Year Before the Study, No.	SPPM After Initial Treatment, No. ^a	Pretreatment Derkay Score	Posttreatment Derkay Score	Pretreatment PVRQOL	Posttreatment PVRQOL ^b
M/3 (3)	1.00	0.75	21	6	Not measured	Not measured
M/6 (3)	2.00	1.00	21	23	5.0	67.5
F/5 (1)	0.66	0.00	13	NA ^c	45.0	75.0

Abbreviations: NA, not applicable; PVRQOL, pediatric voice-related quality of life score; SPPM, mean surgical procedures per month.

^aImprovement occurred in all patients after bevacizumab injection.

^bParental proxy PVRQOL improved.

^cPatient did not require return to operating room, and so no measurement was taken.

weeks later, only minimal microdebriding was needed, and his Derkay score was 6. At that time, a third bevacizumab injection was administered. Four weeks later, the mother reported good voice and no stridor.

PATIENT 2

A 6-year-old boy presented with recurrent stridor after having been treated 22 times in the previous year in Africa for RRP and respiratory distress. His mother noted that she planned to return to Africa after the next 6 months. After a detailed conversation involving the risks and benefits of each adjuvant therapy, she opted not to pursue cidofovir therapy and requested that her son receive debulking therapy followed by pulsed KTP laser treatment of the anterior commissure, true vocal fold, and ventricular RRP followed by local injection of bevacizumab.

At the time of the child's initial treatment at Massachusetts Eye and Ear Infirmary, he was markedly stridorous and nearly aphonic with bulky RRP obstructing 90% of the airway and involving the regions of the true vocal folds, anterior commissure, and ventricles. The child's Derkay severity grade for RRP at the time of this treatment was 21. The mother assessed his voice by completing the PVRQOL, and his score at this initial visit was a 5 (0-100). Analysis of biopsy specimens confirmed RRP (HPV-6).

Postoperatively, the patient did well. He was observed for several hours and then discharged. At a scheduled follow-up evaluation 6 weeks later (4 weeks beyond the time he would typically have re-presented with stridor requiring treatment), he had almost completely obstructing papilloma (unchanged Derkay score) that was again treated with microdebrider, pulsed KTP laser, and a second bevacizumab injection. Four weeks later, the patient had similar findings. Although the injections seemed to be spacing out the intervals between surgery, we did not give a third bevacizumab injection. Adjunctive therapies were again discussed with the patient's mother, and she agreed to cidofovir injection. Over the next 8 weeks, the patient received 2 cidofovir injections and at last report, the patient had gone 6 weeks without needing treatment.

PATIENT 3

A 5-year-old girl with RRP (HPV-6) of 2 years' duration had undergone procedures to improve her airway. Her 3 treatments prior to bevacizumab treatment were approximately 4 weeks apart and involved microdebrider debulking, pulse KTP laser treatment, and 3 injections of cidofovir.

Three weeks after the last cidofovir injection, she was again symptomatic, and her grandmother, who was her legal guardian, signed our informed consent form for bevacizumab injections following the debulking procedure. The child's Derkay severity grade for RRP at the time of this treatment was 13, and her grandmother assessed her voice by PVRQOL score at this initial visit as 45 (0-100). Six months after the injection, the girl remained symptom free and did not require further operative intervention. Her grandmother completed the parent proxy PVRQOL measure at the 3-month postoperative follow-up and assessed her voice score at 75.

COMMENT

Treatment of aggressive pediatric RRP remains a difficult problem. The central tenet of "do no harm" finds specific direction in the challenge to open a child's airway while interfering to the least extent possible with the child's subsequent ability to speak, eat, and drink (without aspirating). Specific to the treatment of children with RRP (unlike in the treatment of adults for whom office-based procedures without general anesthesia are possible) there is also the recently reported behavioral and cognitive risks inherent in the use of multiple anesthetics.^{9,10} Given that the necessity to breathe trumps all other issues, and that there is still no effective medical treatment for RRP, the goals of any surgery are to open the airway and to extend the interval to further surgical intervention for the longest time possible. This is the primary reason that surgeons consider adjuvant therapies like cidofovir injections to treat children with aggressive disease.

Although the goal of such adjuvant therapy is laudable, enthusiasm over such treatment must be tempered by the knowledge that there remains a paucity of randomized trials comparing head-to-head efficacy of different surgical strategies and different adjuvant therapies. Such comparative studies are limited by the relative scarcity of patients. Single-institution studies struggle to achieve adequate sample sizes, and multi-institutional studies pose challenges arising from different indications for surgery between institutions and different surgical options available at the various centers and regions across the country. For example, angiolytic lasers are relatively new and not yet proven in randomized controlled studies, so many institutions have not acquired them. For specific adjuvants such as cidofovir, there is growing single-arm experience across several centers,²⁷⁻²⁹ and recently

a systematic review documented efficacy,³⁶ but there are certainly cases of RRP for which such adjuvant therapy is only marginally helpful at best. Parents of children with aggressive RRP are in search of other treatment regimens that are safe and offer some benefit.

Bevacizumab is a human monoclonal antibody that binds to and neutralizes the biologic activities of VEGF isoforms and prevents them from interacting with their receptors.³⁷ It received US Food and Drug Administration approval for intravenous treatment of metastatic colorectal carcinoma in 1994. Bevacizumab has been used in its injectable form to treat ocular conditions such as diabetic retinopathy and wet macular degeneration. Intravenous bevacizumab administration has adverse effects that include bleeding, blood clotting, high blood pressure, hypothyroidism, and others.³⁷ Intraocular injections of bevacizumab at a dose 100 to 400 times lower than the intravenous dose has not been shown to have adverse effects, although very small amounts of bevacizumab have been detected in the serum of rabbits after intravitreal injection of 1.25 mg.³⁸⁻⁴⁰

The rationale for using bevacizumab to treat children with aggressive RRP stems from basic research that has found VEGF receptors in laryngeal papilloma specimens taken from affected children³⁴ as well as the recent experience of Zeitels et al³⁵ in using bevacizumab to treat adults with RRP. Although the initial doses of bevacizumab used to treat adults ranged from 5 to 7 mg,³⁵ given that this was the initial pediatric experience, we decided to use a total dose of 1.25 mg, which had been safely used in pediatric ophthalmology (Avery et al³⁹ and personal communication, Antonio Capone, MD).³⁹ Our institutional pharmacy prepared bevacizumab in a formulation such that the total dose administered was 1.25 mg.

Before we administered bevacizumab, we spoke at length with the patients' parents. Written materials were provided for them, describing bevacizumab and the other adjuvant therapies available. The following were highlighted in these discussions and written materials: (1) the proposed treatment was an off-label use of bevacizumab; (2) little data of any kind and no long-term data existed to document treatment effect in children with RRP; and (3) a range of adverse effects was possible, although unlikely. Reported adverse effects of intravenous bevacizumab treatment include bleeding, blood clotting, high blood pressure, and hypothyroidism, and others.³⁷ No adverse effects have been noted from ocular intralesional injections of bevacizumab at a dose of 1.25 mg. We also discussed the possibilities of voice abnormalities, vocal cord scarring, and the risk of malignant degeneration with injection of any adjuvant therapy. The parents were given a background in the pediatric ophthalmologic literature describing the use of injectable bevacizumab and a summary of the early bevacizumab treatments described by Zeitels et al³⁵ in adult patients with RRP. Parents who wished to proceed with treatment then signed both a traditional consent form and a special informed consent particular to the off-label use of bevacizumab.

All 3 children treated with bevacizumab had HPV-6 RRP. It remains unclear whether bevacizumab would exert a similar affect on RRP in children with HPV-11. None of the 3 patients was treated with antireflux measures be-

cause none had symptoms of gastroesophageal or laryngopharyngeal reflux. Finally, it also must be noted that, as with all laryngeal injectables, possible adverse effects must be considered with the use of bevacizumab, namely vocal cord scarring, inflammatory response, and development of acute airway obstruction. This has not been seen in the 3 patients described herein, but it is clearly a possibility and will have to be followed closely in further studies.

In our small series, injectable bevacizumab seemed to show some efficacy in prolonging the time between treatments and therefore reducing the number of treatments per year needed by children with severe RRP. Patient 3 had excellent success in that she did not require any treatment procedures at 6-month follow-up from the last injection. Patient 1 had moderate success in that the interval of his last follow-up evaluation represented the longest interval in the last 12 months without a surgical procedure. Although patient 2 also showed increased time intervals between procedures, the papilloma continued to grow substantially, and this patient required additional adjunctive measures that have now extended the intervals between treatments even further.

While it is true that children with RRP often experience some degree of spontaneous improvement or resolution over time,⁴¹ the 3 children in the present study experienced newly aggressive disease, so it is unlikely (although possible) that the findings seen were due to spontaneous regression alone. We are currently considering bevacizumab therapy as adjunctive treatment for children who have had at least 4 surgical procedures for respiratory distress from RRP in the preceding year and whose disease has not responded to at least 3 cidofovir injections over the following year or whose families refuse to consider cidofovir as first-line adjunctive therapy. It remains unclear whether bevacizumab should be injected 1 time alone or over multiple administrations. However, under the same protocol we use in our practice to administer cidofovir, all patients must demonstrate biopsy-proven RRP (repeated biopsies are performed roughly yearly) to qualify for adjuvant bevacizumab treatment. In these cases, we offer as many as 3 injections at intervals (dictated by symptom severity) followed by reevaluation.

Clearly, before any meaningful conclusions can be drawn, further studies must be conducted in the form of head-to-head trials looking specifically at the issues of time between treatment intervals, efficacy of one adjunct over another, vocal outcomes, and whether several adjunctive treatments confer advantage over 1 treatment. In-depth and careful informed consent is mandatory for these studies so that parents are aware of the risks and benefits (known and unknown) before such individualized decisions are made.

Submitted for Publication: July 15, 2009; final revision received December 4, 2009; accepted December 19, 2009.
Correspondence: Christopher J. Hartnick, MD, MS, EPI, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3914 (Christopher_hartnick@meei.harvard.edu).

Author Contributions: Dr Hartnick had full access to all the data in the study and takes responsibility for the in-

tegrity of the data and the accuracy of the data analysis. *Study concept and design:* Hartnick. *Acquisition of data:* Maturo and Hartnick. *Analysis and interpretation of data:* Maturo and Hartnick. *Drafting of the manuscript:* Maturo and Hartnick. *Critical revision of the manuscript for important intellectual content:* Maturo and Hartnick. *Statistical analysis:* Maturo and Hartnick. *Administrative, technical, and material support:* Maturo and Hartnick. *Study supervision:* Hartnick.

Financial Disclosure: None reported.

REFERENCES

- Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope*. 2008;118(7):1236-1247.
- Mounts P, Kashima H. Association of human papillomavirus subtype and clinical course in respiratory papillomatosis. *Laryngoscope*. 1984;94(1):28-33.
- Mounts P, Shah KV. Respiratory papillomatosis: etiologic relation to genital tract papillomaviruses. *Prog Med Virol*. 1984;29:90-114.
- Silverberg MJ, Thorsen P, Lindeberg H, Ahdieh-Grant L, Shah KV. Clinical course of recurrent respiratory papillomatosis in Danish children. *Arch Otolaryngol Head Neck Surg*. 2004;130(6):711-716.
- Armstrong LR, Derkay CS, Reeves WC; RRP Task Force. Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg*. 1999;125(7):743-748.
- Derkay CS. Task force on recurrent respiratory papillomas: a preliminary report. *Arch Otolaryngol Head Neck Surg*. 1995;121(12):1386-1391.
- Reeves WC, Ruparella SS, Swanson KI, Derkay CS, Marcus A, Unger ER. National registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg*. 2003;129(9):976-982.
- Lindman JP, Lewis LS, Accortt N, Wiatrak BJ. Use of the Pediatric Quality of Life Inventory to assess the health-related quality of life in children with recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2005;114(7):499-503.
- Kalkman CJ, Peelen L, Moons KG, et al. Behavior and development in children and age at the time of first anesthetic exposure. *Anesthesiology*. 2009;110(4):805-812.
- Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology*. 2009;110(4):796-804.
- Dean C, Sataloff RT, Hawkshaw M. Recurrent vocal fold papilloma: resection using cold instruments. *Ear Nose Throat J*. 1998;77(11):882-884.
- Sawchuk WS, Weber PJ, Lowy DR, Dzubow LM. Infectious papillomavirus in the vapor of warts treated with carbon dioxide laser or electrocoagulation: detection and protection. *J Am Acad Dermatol*. 1989;21(1):41-49.
- Zeitels SM, Sataloff RT. Phonomicrosurgical resection of glottal papillomatosis. *J Voice*. 1999;13(1):123-127.
- El-Bitar MA, Zalzal GH. Powered instrumentation in the treatment of recurrent respiratory papillomatosis: an alternative to the carbon dioxide laser. *Arch Otolaryngol Head Neck Surg*. 2002;128(4):425-428.
- Pasquale K, Wiatrak B, Woolley A, Lewis L. Microdebrider versus CO2 laser removal of recurrent respiratory papillomas: a prospective analysis. *Laryngoscope*. 2003;113(1):139-143.
- Patel N, Rowe M, Tunkel D. Treatment of recurrent respiratory papillomatosis in children with the microdebrider. *Ann Otol Rhinol Laryngol*. 2003;112(1):7-10.
- Shikowitz MJ, Abramson AL, Freeman K, Steinberg BM, Nouri M. Efficacy of DHE photodynamic therapy for respiratory papillomatosis: immediate and long-term results. *Laryngoscope*. 1998;108(7):962-967.
- Shikowitz MJ, Abramson AL, Steinberg BM, et al. Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg*. 2005;131(2):99-105.
- Bower CM, Waner M, Flock S, Schaeffer R. Flash pump dye laser treatment of laryngeal papillomas. *Ann Otol Rhinol Laryngol*. 1998;107(12):1001-1005.
- Franco RA Jr, Zeitels SM, Farinelli WA, Anderson RR. 585-nm pulsed dye laser treatment of glottal papillomatosis. *Ann Otol Rhinol Laryngol*. 2002;111(6):486-492.
- Franco RA Jr, Zeitels SM, Farinelli WA, Faquin W, Anderson RR. 585-nm pulsed dye laser treatment of glottal dysplasia. *Ann Otol Rhinol Laryngol*. 2003;112(9 Pt 1):751-758.
- Hartnick CJ, Boseley ME, Franco RA Jr, Cunningham MJ, Pransky S. Efficacy of treating children with anterior commissure and true vocal fold respiratory papilloma with the 585-nm pulsed-dye laser. *Arch Otolaryngol Head Neck Surg*. 2007;133(2):127-130.
- McMillan K, Shapshay SM, McGilligan JA, Wang Z, Rebeiz EE. A 585-nanometer pulsed dye laser treatment of laryngeal papillomas: preliminary report. *Laryngoscope*. 1998;108(7):968-972.
- Zeitels SM, Akst LM, Burns JA, Hillman RE, Broadhurst MS, Anderson RR. Office-based 532-nm pulsed KTP laser treatment of glottal papillomatosis and dysplasia. *Ann Otol Rhinol Laryngol*. 2006;115(9):679-685.
- Rosen CA, Bryson PC. Indole-3-carbinol for recurrent respiratory papillomatosis: long-term results. *J Voice*. 2004;18(2):248-253.
- Rosen CA, Woodson GE, Thompson JW, Hengesteg AP, Bradlow HL. Preliminary results of the use of indole-3-carbinol for recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg*. 1998;118(6):810-815.
- Pransky SM, Brewster DF, Magit AE, Kearns DB. Clinical update on 10 children treated with intralesional cidofovir injections for severe recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg*. 2000;126(10):1239-1243.
- Pransky SM, Magit AE, Kearns DB, Kang DR, Duncan NO. Intralesional cidofovir for recurrent respiratory papillomatosis in children. *Arch Otolaryngol Head Neck Surg*. 1999;125(10):1143-1148.
- Snoeck R, Wellens W, Desloovere C, et al. Treatment of severe laryngeal papillomatosis with intralesional injections of cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine]. *J Med Virol*. 1998;54(3):219-225.
- Pashley NR. Can mumps vaccine induce remission in recurrent respiratory papilloma? *Arch Otolaryngol Head Neck Surg*. 2002;128(7):783-786.
- Lott DG, Krakovitz PR. Squamous cell carcinoma associated with intralesional injection of cidofovir for recurrent respiratory papillomatosis. *Laryngoscope*. 2009;119(3):567-570.
- Wemer RD, Lee JH, Hoffman HT, Robinson RA, Smith RJ. Case of progressive dysplasia concomitant with intralesional cidofovir administration for recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2005;114(11):836-839.
- Derkay C; Multi-Disciplinary Task Force on Recurrent Respiratory Papillomas. Cidofovir for recurrent respiratory papillomatosis (RRP): a re-assessment of risks. *Int J Pediatr Otorhinolaryngol*. 2005;69(11):1465-1467.
- Rahbar R, Vargas SO, Folkman J, et al. Role of vascular endothelial growth factor-A in recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2005;114(4):289-295.
- Zeitels SM, Lopez-Guerra G, Burns JA, Lutch M, Friedman AM, Hillman RE. Microlaryngoscopic and office-based injection of bevacizumab (Avastin) to enhance 532-nm pulsed KTP laser treatment of glottal papillomatosis. *Ann Otol Rhinol Laryngol Suppl*. 2009;201:1-13.
- Chadha NK, James AL. Antiviral agents for the treatment of recurrent respiratory papillomatosis: a systematic review of the English-language literature. *Otolaryngol Head Neck Surg*. 2007;136(6):863-869.
- Ribatti D. The discovery of antiangiogenic molecules: a historical review. *Curr Pharm Des*. 2009;15(4):345-352.
- Bakri SJ, Snyder MR, Reid JM, Pulido JS, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology*. 2007;114(5):855-859.
- Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology*. 2006;113(10):1695.e1-1695.e15.
- Duch S, Buchacra O, Milla E, Andreu D, Tellez J. Intracameral bevacizumab (Avastin) for neovascular glaucoma: a pilot study in 6 patients. *J Glaucoma*. 2009;18(2):140-143.
- Hawkes M, Campisi P, Zafar R, et al. Time course of juvenile onset recurrent respiratory papillomatosis caused by human papillomavirus. *Pediatr Infect Dis J*. 2008;27(2):149-154.