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Intralesional Cidofovir Therapy for Laryngeal Papilloma in an Adult Cohort

Steven Bielamowicz, MD; Vicente Villagomez, MD; Sheila V. Stager, PhD; William R. Wilson, MD

Objectives: **To confirm the safety and efficacy of intralesional cidofovir in the management of laryngeal papilloma and to identify variables that correlate with number of injections needed to achieve remission.** ***Study Design:*** **An open-trial prospective evaluation of the efficacy of intralesional cidofovir in subjects with laryngeal papilloma.** ***Methods:*** **Fourteen adult subjects with biopsy-proven laryngeal papilloma were enrolled in a treatment study of intralesional cidofovir. Preprotocol disease duration ranged from 1 to 30 years with a mean duration of 7 years. Subjects received monthly injections of cidofovir with a maximum dose of 37.5 mg per injection in 6 cc saline (6.25 mg/mL). Injections were repeated until no papilloma could be visually identified during an intraoperative evaluation. After disease remission was achieved, subjects received an additional injection. All injections occurred during suspension microlaryngoscopy.** ***Results:*** **All subjects have achieved disease remission using an injection-only treatment protocol. No additional laryngeal scarring or systemic toxicity was identified. On average, 6 injections were required to achieve remission. Preprotocol disease duration and anatomical staging correlated positively with the number of injections required for disease remission.** ***Conclusions:*** **Intralesional injection of cidofovir is an excellent treatment option with limited local and systemic toxicities. The injection therapy regimen requires perseverance from both patient and surgeon. Remission of disease can be achieved in adults with laryngeal papilloma.** ***Key Words:*** **Papilloma, cidofovir, larynx, respiratory, treatment.**

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INTRODUCTION

Laryngeal papilloma develops in young children and adults with no distinct difference in the histological appearance of the disease. Respiratory papillomas are caused by infection with human papilloma virus (HPV), a DNA virus. The mechanism of acquisition and transmission of laryngeal papilloma has not been determined. Similarly, specific etiological factors that predispose adults to the development of this debilitating disease have not been defined, and the natural history of laryngeal papilloma is unpredictable. Recurrence of laryngeal papilloma after excisional therapy is common, and medical management, including interferon and indole-3-carbinol, has been disappointing. Based on the report of Snoeck et al.[1] in 1998, we obtained Institutional Review Board approval to conduct a Phase II study to further evaluate the safety and efficacy of intralesional cidofovir (Vistide, Gilead Sciences, Foster City, CA) in a cohort of adult patients. We have previously reported on three patients who completed our protocol.[2] In the current report, we present the clinical results of the first 13 subjects who completed the protocol, as well as clinical variables that correlate with numbers of injections required to achieve remission. We chose an injection-only protocol so that we could evaluate the efficacy and local adverse effects of cidofovir as treatment for laryngeal papilloma, without concerns for additional vocal fold scarring associated with lesion removal.

PATIENTS AND METHODS

Informed consent was obtained for each patient enrolled in the study. Entrance criteria included a minimum age of 18 years; biopsy-proven papilloma limited to the glottis, supraglottis, or subglottis; and no evidence of disease within the tracheobronchial tree. Initially, cidofovir was administered at a concentration of 4.17 mg/mL. No adverse reactions, including additional laryngeal scarring or systemic toxicity, were encountered after the first 32 injections, so the dose was increased to 6.25 mg/mL for all subsequent injections in hopes of minimizing the number of injections needed for disease remission. Two subjects received all injections at a concentration of 4.17 mg/mL, and eight subjects received all injections at a dose of 6.25 mg/mL. Three subjects received initial cidofovir injections at a concentration of 4.17 mg/mL and subsequent injections at a concentration of 6.25 mg/mL.

Injections occurred on a monthly basis until no visible papilloma could be identified by inspection during suspension microlaryngoscopy. Excisional treatment was not used in the current study. Injections were performed with the patient under general anesthesia in the operating room during suspension microlaryngoscopy. General endotracheal anesthesia was accomplished with either a 5.5 or a 6.0 endotracheal tube. The larynx was exposed using a Pilling Dedo laryngoscope. All lesions were treated by cidofovir infiltration into the site of each papilloma and surround-

From the Division of Otolaryngology—Head and Neck Surgery, George Washington University, Washington, DC, U.S.A.

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Send Correspondence to Steven Bielamowicz, MD, Division of Otolaryngology—Head and Neck Surgery, George Washington University, 2150 Pennsylvania Avenue Northwest, Suite 6-301, Washington, DC 20037, U.S.A. E-mail: sursxb@gwumc.edu

ing mucosa using a tuberculin syringe connected to a 27-gauge bayonet laryngeal injection needle from Xomed MicroFrance (Jacksonville, FL). Medication was injected until the lesion and surrounding mucosa blanched. Medication retention during the injection was aided by grasping each affected region of the larynx with a Bouchayer forceps before needle placement. This pinching technique stabilized the lesions, resulting in maximum retention of medication within the lesion as evidenced by minimal spillage of medication into the airway and excellent blanching of the affected regions. The maximum volume of cidofovir administered during the endoscopic procedure was 6 cc at a concentration of 6.25 mg/mL. Cidofovir is available as a 5-mL vial at a concentration of 75 mg/mL. For each injection session, 0.5 mL cidofovir was withdrawn from the vial and mixed with 6 mL injectable saline. The maximum amount of medication received by any patient during an injection was 37.5 mg. All patients were treated with cidofovir below the current U.S. Food and Drug Administration (FDA)–approved maximum dose. The drug is currently FDA approved as an intravenous infusion for cytomegalovirus (CMV) retinitis with a maximum dose of 5 mg/kg (350 mg total dose for a 70-kg subject).

A flexible or 70° rigid endoscopic laryngeal video examination was performed before each repeat injection. No patient received cidofovir if a reduction in lesion size was not observed after two consecutive procedures. All subjects were offered a terminal injection 1 month after the clinic visit in which no further papilloma was identified. Cidofovir injections were suspended after the terminal injection, and subjects were monitored for recurrent disease with video laryngeal examinations every 3 months. If lesions reappeared during subsequent clinical examinations, intralesional cidofovir was resumed on a monthly basis.

RESULTS

Thirteen patients (nine male and four female subjects) have completed the protocol at the time of writing. One subject terminated the protocol after a single injection because of fear of general anesthesia. An additional nine subjects have been recruited more recently and continue to receive cidofovir treatment in hopes of achieving remission These subjects are not included in this report. The longest remission to date is 3 years. At entrance into the study, average subject age was 48 years with an age range of 18 to 85 years. No subject was terminated from this study because of a failure of papilloma regression. All subjects achieved a clinical remission with no visibly detectable papilloma. On average, lesion remission was achieved after six injections. Eight subjects required five or fewer injections for remission. The mean volume per injection was 3.8 mL with a volume range of 0.6 to 6 mL. During each injection, the average dose injected was 22.53 mg per subject. Table I summarizes the preprotocol treatment and protocol treatment response for all subjects.

Spearman Rho rank-ordered comparisons were performed for the independent variables including anatomical and clinical papilloma staging as described by Derkay et al.,[3] preprotocol excisional treatment frequency, preprotocol duration of disease, and subject age at time of protocol entrance, with number of injections as the dependent variable. Statistically significant correlations were identified for preprotocol duration ($P = .005$) and anatomical staging ($P = .05$), whereas the remainder of the independent variables were not statistically significant. Subjects having a longer duration of disease and more extensive disease required a greater number of injections than those with shorter preprotocol disease duration or more limited disease. Gender comparisons could not be performed because of the small number of female subjects in the study.

DISCUSSION

Human papillomavirus is a DNA virus that is responsible for laryngeal papilloma. Most disease is caused by HPV types 6 and 11.[4] Laryngeal papilloma can affect adults and children and has an unpredictable natural history. No medical or surgical cure exists for

TABLE 1.
Summary Statistics for Subjects Ordered by Injections to Achieve Remission.*

Subject No.	Subject Age (y)	Gender	Anatomic Staging	Clinical Staging	Pre-protocol Duration (y)	Pre-protocol Surgical Procedures	Pre-protocol Procedures per Year (mean)	Protocol Duration (y)	Injections
1	66	Male	2	1	0.92	2	2.19	0.02	1
2	44	Male	9	1	1.08	1	0.92	0.08	2
3	71	Female	6	1	3.09	2	0.65	0.33	2
4	18	Female	9	2	5.01	1	0.20	0.30	3
5	85	Female	9	1	1.50	4	2.67	0.42	3
6	37	Male	3	1	5.00	10	2.00	0.85	4
7	28	Male	29	3	3.67	3	0.82	0.50	5
8	49	Female	6	1	26.02	40	1.54	0.63	5
9	35	Male	6	1	1.25	5	3.99	2.16	8
10	30	Male	17	2	4.00	18	4.50	1.04	9
11	38	Male	8	1	9.33	48	5.14	2.39	9
12	52	Male	12	1	10.01	12	1.20	1.05	11
13	64	Male	12	1	30.02	65	2.17	3.67	19
		Group averages	10	1.3	7.76	16	2.15	1.03	6

*Anatomic staging represents extent of disease while clinical staging represents symptoms.[3]

laryngeal papilloma. Current management includes observation, laser excision, and cold knife excision; however, treatment is frequently followed by recurrence of disease. Multiple surgical interventions can result in vocal fold scarring and voice difficulties. Although some cases of respiratory papilloma regress with time, particularly during adolescence, most patients have lifelong disease. Long-standing disease can result in malignant transformation or spread of benign disease into the tracheobronchial tree.[5,6]

The antiviral medication cidofovir has received FDA approval for treatment of CMV retinitis in human immunodeficiency virus (HIV)–positive patients. Cidofovir is a cytosine analogue and becomes incorporated into the genome of DNA viruses. Programmed cellular death occurs in epithelial cells infected by replicating papilloma viruses that incorporate cidofovir into the viral genome. However, this does not eradicate the dormant DNA virus within infected tissues. Intravenous administration of cidofovir at a maintenance dose of 5 mg/kg per week for the treatment of CMV retinitis has been associated with proteinuria, elevated creatinine, and irreversible renal failure.[7] The intralesional cidofovir dose in the present study ranges from 0.45 to 0.90 mg/kg per injection. In a previous intralesional injection study of cidofovir, renal toxicity was monitored by blood chemistry analysis and no changes were identified.[1] In this study, no systemic toxicity was identified. Although a local inflammatory response was frequently observed in our study during the 7th to 14th day period after each injection, we identified no new areas of scarring, web formation, or impaired vibration of the vocal fold mucosa.

A final concern regarding intralesional use of cidofovir is tumorigenicity. According to the minutes of the meetings from the Center for Drug Evaluations and Research from the Joint Antiviral Drugs Advisory Committee and Ophthalmologic Drugs Subcommittee (FDA) in which the drug cidofovir received approval for the use in CMV retinitis, animal studies demonstrated the development of adenocarcinomas with subcutaneous injections in female rats. However, these findings were not seen in studies on primates. During Phase I and II studies in humans, no increased incidence of tumorigenicity was identified in HIV-positive patients treated with intravenous cidofovir for CMV retinitis. In previous reports on the use of intralesional cidofovir, no new carcinomas have been identified in either adults or children.[1,2,8–10] In the study of Snoeck et al.,[1] two patients were identified with verrucous carcinoma of the larynx before treatment with cidofovir. In both subjects, their lesions resolved with cidofovir, and post-treatment biopsy specimens revealed no evidence of papilloma or carcinoma. Although the tumorigenicity of intralesional cidofovir is a potential concern, no subjects to date have developed laryngeal carcinomas after the use of intralesional cidofovir. Because of these concerns, we recommend the use of intralesional cidofovir under strict protocol and informed consent so that safety and efficacy data can be collected.

Intralesional cidofovir as an injection-only treatment has been reported for esophageal papilloma by Van Custem et al.[8] and for laryngeal papilloma by Snoeck et al.[1] In the study of Snoeck et al.,[1] cidofovir was injected within the lesions of 17 subjects with laryngeal papilloma without debulking at a concentration of 2.5 mg/mL as compared with 6.25 mg/mL in the current study. The average dose in the previous study was 17.5 mg per injection as compared with 22.5 mg in the current study. In the previous study, patients were treated every 2 weeks as compared with every 4 weeks in the current study. In the previous study, an average of seven injections resulted in disease remission as compared with six injections in the current study. The reduction in number of injections needed to achieve remission was most likely attributable to the increased concentration of medication and introduction of the pinching injection technique outlined earlier. Preprotocol duration and anatomical staging were the only variables that correlated with the number of injections required to achieve disease control. Subjects with longer duration of disease and more extensive disease required more injections for remission.

Increasing the cidofovir concentration, increasing the injection frequency, or debulking the lesions before cidofovir injection could further reduce the number of treatments required to achieve disease remission. Higher concentrations of medication would require additional study of local and systemic toxicity. In the current study, we did not debulk lesions before cidofovir injections in hopes of developing a better understanding of the efficacy and local toxicity of the drug alone in the treatment of laryngeal papilloma. A disadvantage of debulking therapy before cidofovir injection includes an increased risk of additional vocal fold scarring. However, if a reduction in numbers of treatments is identified in subjects receiving debulking therapy, the additional risk of scarring may be warranted, especially in subjects who have previously received aggressive surgical management. Pransky et al.[9,10] have reported debulking in combination with cidofovir in a series of 10 children. In their reports, the authors identified significant control of laryngeal papilloma in children with aggressive disease compared with previous treatments with excisional therapy alone. The children entering into the study of Pransky et al. were subjects who required monthly excisions to prevent airway obstruction.[10] Although not all subjects achieved remission, the frequency of recurrences diminished significantly. Cidofovir in combination with debulking therapy appeared to alter the biological behavior of the HPV infection in subjects receiving cidofovir.

CONCLUSION

Intralesional injection of cidofovir is an excellent treatment option with limited local and systemic toxicities. However, pure injection therapy requires perseverance from both patient and surgeon to achieve remission. Although this drug is effective in managing replicating HPV infections in almost all adults, the long-term remission rates for patients with respiratory papilloma are unknown. In a future report, we will characterize the long-term treatment response to intralesional cidofovir in subjects with respiratory papilloma.

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