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Current and Future Management of Recurrent Respiratory Papillomatosis

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Objectives: Recurrent respiratory papillomatosis (RRP) is a chronic disease of the respiratory tract that occurs in both children and adults. It is caused by the human papillomavirus (HPV), in particular low-risk HPV6 and HPV11, and aggressiveness varies among patients. RRP remains a chronic disease that is difficult to manage. This review provides perspectives on current and future management of RRP.

Results: The current standard of care is surgical excision, with adjuvant therapies as needed. Surgical management of RRP has evolved with the introduction of microdebriders and photoangiolytic lasers; the latter can now be used in the office setting. Numerous adjuvant pharmacologic therapies have been utilized with some success. Also, exciting preliminary data show that HPV vaccines may prolong the time to recurrence in the RRP population. There is also optimism that wide-spread HPV vaccination could reduce RRP incidence indirectly by preventing vertical HPV transmission to newborns.

Conclusion: To date, the biology of RRP is not well understood, although it has been noted to become more aggressive in the setting of immune suppression. Additional research is needed to better understand immune system dysfunction in RRP such that immunomodulatory approaches may be developed for RRP management.

Key Words: Recurrent respiratory papillomatosis (RRP), human papillomavirus (HPV), laryngeal papillomatosis, microdebrider, vaccine.

Level of Evidence: 4

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a rare disease caused by low-risk human papillomavirus (HPV) types 6 and 11; it is characterized by recurrent exophytic papillomas of the epithelial mucosa in the respiratory tract (Fig. 1).[1,2] Based on the age of patients, RRP is characterized as juvenile-onset or adult-onset. Patients presenting with this disease before 12 years of age are diagnosed with juvenile-onset recurrent respiratory papillomatosis (JO-RRP), while patients presenting after 12 years of age are diagnosed with adult–onset recurrent respiratory papillomatosis (AO-RRP).[3] Derkay et al. estimated an incidence rate of 4.3 per 100,000 in JO-RRP and 1.8 per 100,000 in AO-RRP.[4] However, prevalence of RRP is variable and depends on several factors, including geographic location, age of onset, and socioeconomic condition (Table I). JO-RRP occurs via vertical transmission during pregnancy or is acquired at birth from an HPV-infected mother; it has a more aggressive clinical course.[5,6] Acquisition of AO-RRP is not well studied. A report showed that AO-RRP risk is associated with the number of sexual partners; however, this finding was not confirmed in a subsequent study.[7,8]

Literature estimates that 5% of the population carries HPV DNA in the larynx, yet only a small percentage develop RRP.[9] So, why do some HPV-infected individuals not develop RRP? It is hypothesized that RRP is a multigene disease that polarizes innate and adaptive immune responses to tolerate HPV6/11 infection and predisposes certain individuals to develop RRP. Studies have shown that early HPV proteins, driven predominately by HPV E6, alter the innate immune response and skew adaptive immunity to a T_H2-like phenotype.[10–16] In addition, certain HLA alleles as well as the absence of specific innate immune receptors may also predispose an individual to RRP development and contribute to disease severity.[17,18] There is also evidence that, of the low-risk subtypes, HPV11 is associated with a more aggressive clinical course than HPV6, but more research is necessary to understand the differences between these viral proteins.[19] Furthermore, a 2% malignant degeneration incidence has been observed in RRP patients.[20] Spontaneous degeneration may be due to the fact that low-risk HPVs can drive gene expression in papilloma similar to that characteristically found in some malignancies.[13]

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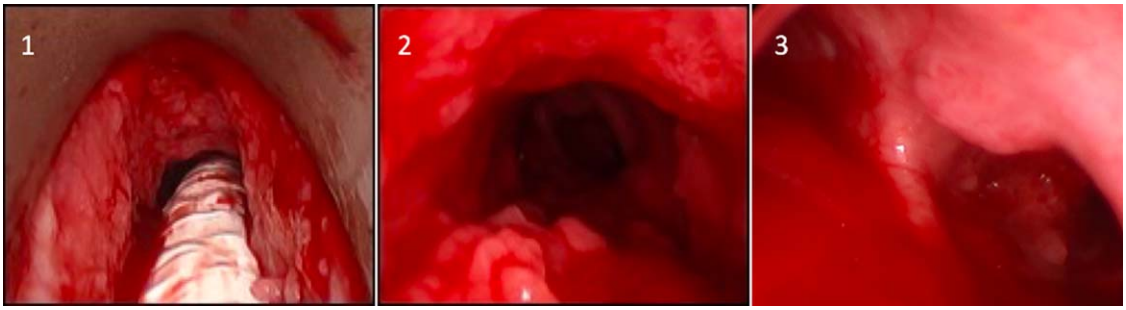

Fig. 1. Single patient with tracheal and right mainstem bronchial involvement. This indicates more severe RRP with distal spread. **1.** Subglottic papilloma. **2.** Distal tracheal papilloma. **3.** Two sites of papilloma growth: at the anterior tracheal wall just proximal to carina and just distal to the carina at the right proximal mainstem bronchus.
RRP = Recurrent respiratory papillomatosis.

Currently, there is no cure for the disease, and treatment is primarily focused on maintaining airway patency and voice quality. Patients often require multiple surgeries in a short amount of time and occasionally adjuvant therapy when surgery is unable to control the disease, making RRP an expensive disease to treat. It has been reported that the average number of surgeries in the first five years of diagnosis is 5.1 per year, dropping to 0.1 per year after 15 years.[5,21] Chesson et al. estimated that the lifetime cost per case of RRP is $198,500, not including drug treatment, with tracheotomy care accounting for approximately 5% of this estimate and the remainder from surgical costs.[22]

Traditional management of RRP has been surgical excision in the operating room (OR) under general anesthesia, primarily with potassium-titanyl-phosphate (KTP) lasers or microdebriders, with some surgeons also using CO_2 lasers or cold steel instruments. The advent of the flexible fiber delivery system has made in-office laser procedures possible, which can save time and health-care expense and be more convenient for patients.[23,24] RRP remains a difficult disease to manage; this review provides perspectives on current and future means of RRP management.

COUNSELING RRP PATIENTS

HPV is classified as a sexually-transmitted virus; however, RRP is not. Newly diagnosed AO-RRP patients often have many questions regarding disease acquisition, course, and transmission, making it important to provide a framework for discussion between the patient and the health-care provider. In children, vertical transmission from an HPV-positive mother is presumed to occur in the birth canal and not from caregivers or siblings via horizontal transmission.[25,26] A maternal history of genital papilloma is the leading risk factor for JO-RRP, and there is conflicting evidence whether birth by caesarian section is protective against RRP incidence in newborns.[25,27,28] In addition, there is evidence for horizontal transmission of HPV in children with a history of suspected sexual abuse.[29] HPV6 and HPV11 are the most common causes of genital papilloma, spreading by direct contact in areas of friction and mucosal disruption.[30] Thus, one possible mode of HPV infection related to AO-RRP is orogenital spread of HPV.[31,32] HPV6 and HPV11 were reported to be present in the oral cavity of less than 0.5% of the non-RRP population between 14 and 69 years of age.[33] On the other hand, 26 of 27 (96%) RRP patients were found to have concurrent oral cavity HPV. Moreover, 67% of long-term sexual partners of HPV-positive RRP patients had oral cavity HPV present.[34] However, data is conflicting regarding correlation of RRP risk with number of sexual partners, and health-care providers are not obligated to disclose HPV status with a patient's sexual partner(s). It should be noted that the disclosure of anogenital HPV could result in anxiety and negatively impact interpersonal relationships.[35] In general, health-care providers should convey the up-to-date literature regarding HPV to RRP patients; however, this discussion needs to proceed in a careful and sensitive manner.

SURGICAL MANAGEMENT OF RRP

The current standard of care for the management of RRP is surgical excision. Objectives of surgery are to preserve adequate voice quality and airway patency.[36] Complete eradication is not necessarily the goal, as HPV is believed to remain dormant in laryngeal epithelial cells whether active papilloma is visible or not. More extensive excision of papilloma from sites that are not contributing to airway or voice-related goals has not been shown to reduce recurrence rates.[37] In fact, aggressive resection may be counter-productive, in that injury to the mucosal surface has been associated with increased expression of HPV in nearby HPV-infected cells.[38] Aggressive resection is also contraindicated in the setting of disease involving the anterior or posterior commissure; these sites often require staged or sub-total removal of the papilloma. This measured surgical approach preserves function by preventing webbing and scarring at the anterior commissure to limit dysphonia and at the posterior commissure to limit airway obstruction. Interestingly, a retrospective study of 29 patients found that the most common sites of recurrence were the anterior commissure, subglottis, and epiglottis, and that these subsites tended to be closely correlated with submucosal glandular density. In this study, recurrence rates at these subsites were controlled by en bloc

TABLE I.
Summary of Epidemiological Data in Reviewed Studies.

Study	Study Years	Study Design	Incidence Rate	Prevalence Rate	Conclusion
Lindeberg and Elbrond[107]	1965–1984	Retrospective study of 231 patients first presenting with RRP between the years 1965 and 1984	Overall: 3.84 per 100,000; JO-RRP: 3.62 per 100,000; AO-RRP: 3.94 per 100,000	N/A	The incidence rate in the Danish subpopulation remained constant between 1969 and 1984; the low incidence from 1965–1968 could be real or due to selection bias
Derkay[4]	1993–1994	315 otolaryngologists completed the survey	JO-RRP: 4.3 per 100,000; AO-RRP: 1.8 per 100,000	N/A	A registry of patients with current RRP would benefit future research protocols and help the long-term follow-up of patients
Armstrong et al.[108]	1996	101 physicians in Atlanta and 139 physicians from Seattle participated	JO-RRP: 1.11 per 100,000 in Atlanta and 0.36 per 100,000 in Seattle	JO-RRP: 2.59 per 100,000 in Atlanta and 1.69 per 100,000 in Seattle	Data represents a crude estimate of the national incidence and prevalence rates
Armstrong et al.[109]	1997–1998	20 tertiary care pediatric otolaryngology centers surveyed	N/A	N/A	Children diagnosed before the age of 3 were more likely to have severe RRP than those diagnosed after the age of 3
Reeves et al.[5]	1996–2002	22 tertiary care pediatric otolaryngology centers surveyed	N/A	N/A	Young age was the most important determinant of disease severity
Campisi et al.[110]	1994–2007	Multicenter	JO-RRP: 0.24 per 100,000 children aged 14 years and younger	JO-RRP: 1.11 per 100,000 children aged 14 years and younger	Successfully developed Canadian national database for JO-RRP

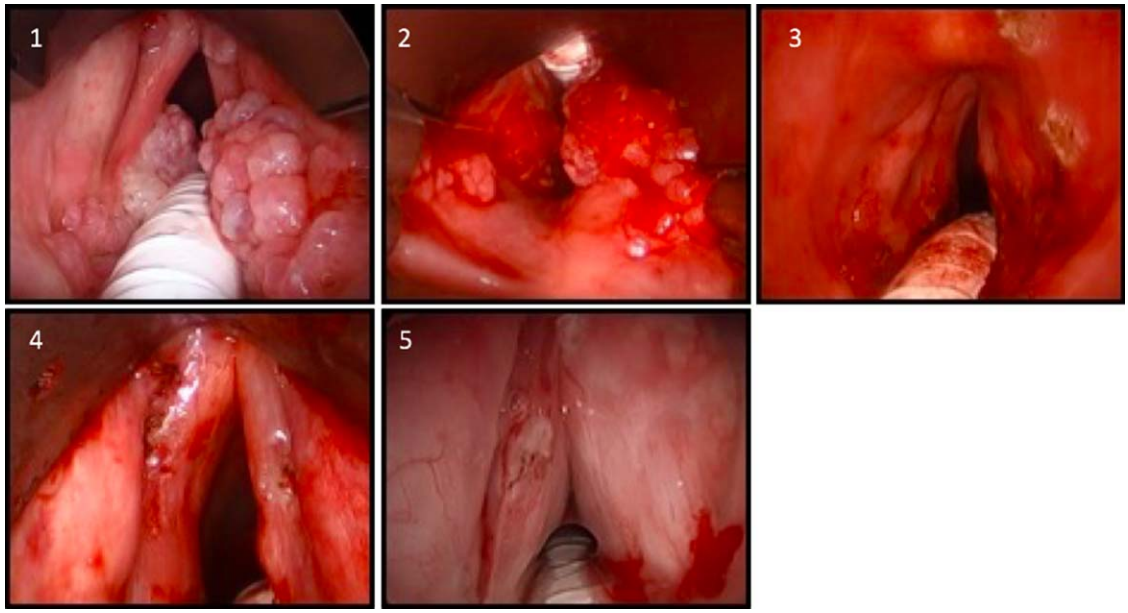

Fig. 2. Images 1–4 are from a single patient. **1.** Appearance of papilloma with supraglottic and vocal fold involvement. **2.** Appearance during debridement. **3.** Appearance post-KTP laser treatment. **4.** Magnified view of vocal folds post-KTP laser treatment. **5.** Appearance after cidofovir injection into vocal folds (separate patient).
KTP = potassium-titanyl-phosphate; RRP = Recurrent respiratory papillomatosis.

excision that included underlying submucosal glands and scar tissue from previous procedures.[36] In patients with very aggressive disease, an additional goal is to prevent distal spread of papilloma to the lower respiratory tract.[37,39] Tracheotomies are usually reserved for patients with aggressive disease that has the potential to occlude the airway, as studies have shown that a tracheostomy provides an additional site for rapid colonization and distal spread of RRP. If tracheotomy is unavoidable, decannulation is advised as soon as the disease is controlled and patency of the airways is maintained.[40,41]

Surgical instruments have evolved in the management of RRP from non-powered laryngeal instruments to lasers, and more recently to microdebriders (Fig. 2).[42–46] Different types of lasers and cold instruments can be used separately or in combination, and both cold instruments and lasers can offer excellent surgical outcomes. In comparison to lasers, an increase in complication rate and a decrease in voice quality have been reported for cold instruments; however, these differences may be highly dependent on the surgeons' technical skills.[47]

Lasers

Laser surgery offers several advantages and disadvantages in the removal of laryngeal papillomas. Lasers have better hemostatic properties and longer working distances than cold instruments.[48] However, laser procedures require more personnel to ensure efficacy and safety and have greater installation and maintenance costs.[48] Mechanically, it is important that repeated laser energy is not delivered to the same location because it could result in deep tissue injury. For this reason, the shortest possible pulse and lowest possible power that will effectively accomplish the procedure is recommended.[24] Other safety concerns of lasers include tracheal injuries, tracheoesophageal fistula formation, and airway tract burns.[24,49] Determining whether or not laser surgery is the best option should be based on the surgeon's experience and skill, anatomical location of the lesion, and the patient's anatomy.[50]

There are two broad categories of lasers that differ in their selectivity: cutting/ablating lasers, such as 10,600-nm CO_2 and 2,013-nm Thulium lasers, which target water, and photoangiolytic lasers, such as 585-nm pulsed-dye (PDL) and 532-nm potassium-titanyl-phosphate (KTP) lasers, which target hemoglobin.[24] The first laser utilized in managing RRP was the CO_2 laser. Multiple surveys report that CO_2 lasers are more widely used than photoangiolytic lasers, although KTP lasers are gaining popularity.[40,42,51] The CO_2 laser's cutting ability, along with its ability to cauterize, have made it a popular tool.[24,52] Conversely, photoangiolytic lasers precisely target hemoglobin within the microcirculation of the highly vascularized papillomatous tissue and may have better hemostatic effects than the CO_2 laser.[50] Photoangiolytic lasers have also shown better preservation of surrounding normal tissue.[24,53] However, one group did report in 2004 that CO_2 lasers are less likely to cause deep tissue damage than photoangiolytic lasers.[54]

Comparing the two different photoangiolytic lasers, hemoglobin absorbs the KTP laser wavelength more strongly than the PDL wavelength, resulting in greater coagulation and less adjacent tissue damage.[55] Thus, KTP lasers are more widely used than PDLs for the removal of papillomas. Kuet et al. investigated the effectiveness of both KTP and PDL photoangiolytic surgery in the treatment of RRP in a retrospective case series

including 68 KTP cases and 13 PDL cases, and found that both significantly improved voice-related quality of life, Derkay score, and need for operative intervention under general anesthesia at the 18-month follow-up interval.[56] The Derkay score is a staging system to classify the severity of RRP; the operating surgeon assigns a score from 0 to 3 (0 = absent, 1 = surface lesion, 2 = raised lesion, and 3 = bulky lesion) to each site in the aerodigestive tract, and these scores are added to obtain the composite severity score.[57] Early clinical data with photoangiolytic lasers in RRP have been encouraging and should be further investigated.

Microdebrider

Microdebriders have gained popularity due to the possible risks associated with the use of lasers and the speed they provide when removing bulkier lesions. Microdebriders afford the surgeon simultaneous debridement by the rapidly rotating blade and selective suctioning of the affected tissue.[49] In fact, microdebriders are often used in combination with lasers, with microdebriders first removing the bulk of the papilloma, then lasers providing hemostatic ability and more precise treatment of sessile disease. Advantages of microdebriders over lasers and cold instruments include shorter operating time and absence of thermal injury.[58]

In-Office Procedures

The advent of awake in-office laser procedures for RRP has offered an alternative to traditional OR management under general anesthesia. In general, office laser procedures are well-tolerated in adult patients who have received adequate topical anesthesia, and most patients experience minimal postoperative pain.[59,60] In many cases, patients can drive themselves to and from the appointment. Several studies have shown that both KTP and PDL lasers are safe and effective for in-office treatment of RRP.[61–65] Serious complications are very rare, with mild discomfort during the procedure being the most common complication.[62] Advantages of in-office procedures over OR management include avoidance of general anesthesia risks, reduced health-care cost, and shorter procedural times.[23,24] While office procedures decrease the number of surgeries and general anesthetics, it is not an option for every patient; those with bulky or extensive papillomas or inadequate tolerance of the scope are poor candidates. Awake procedures are also not suitable for most children with RRP.[23] Literature suggests that adult patients presenting with a new diagnosis of RRP should be treated first in the OR under general anesthesia to allow for disease evaluation and tissue biopsies; however, subsequent procedures can be done in the office depending on time and extent of disease, patient tolerance, and surgeon experience. Furthermore, if there is a significant change in growth pattern, a new biopsy is warranted in the OR.[23] A study found that patients were less likely to be managed in the office if they were diagnosed at an earlier age, had greater disease severity, or had diabetes.[66] In addition, two pilot studies showed preliminary evidence for post-excision, office-based, intralesional administration of the adjuvants bevacizumab and cidofovir improving the outcome of KTP and CO_2 laser excisions, respectively.[67,68]

ADJUVANT THERAPIES FOR RRP

Surgery is the primary treatment modality for RRP; however, approximately 20% of RRP patients require adjuvant therapy because surgery alone cannot control the disease.[42,69] A survey indicated that surgeons typically consider adjuvant therapy in patients getting surgery more than 3–4 times per year, but actual indications are not well-defined. In young professionals with high voice demands, for example, adjuvant therapy may be used sooner.[4] Current adjuvants have a range of actions including immunomodulation, disruption of HPV replication, control of inflammation, and prevention of angiogenesis; yet, due to the incurable nature of RRP, these therapies can only be considered as adjuvant to surgery. In addition, some of these therapies have only been evaluated in small group or case studies and need more powerful randomized controlled trials to sufficiently evaluate their efficacy in RRP management.

Interferon

Interferon (IFN) therapy is one of the first systemic adjuvant treatments used to manage RRP.[49] Interferons are proteins released from leukocytes in response to a variety of stimuli, including viral infection, to upregulate antigen production and activate immune cells.[70] The clinical efficacy of IFN therapy in the treatment of RRP is controversial.[70–72] One group reported that 117 of 160 (73.1%) of patients treated with adjuvant IFN-alpha-2b had complete or partial response measured by extent of recurrence.[72] Conversely, another group showed that initial growth rate reduction of papillomas from IFN-alpha treatment in the first six months post-treatment was not durable and became insignificant in the second six months post-treatment.[70] Unmodified recombinant IFN-alpha is no longer on the market and has been replaced by pegylated-IFN-alpha-2a (peg-IFN-alpha-2a). One study treated 11 AO-RRP patients with peg-IFN-alpha-2a in combination with granulocyte monocyte–colony-stimulating factor (GM-CSF) and found that 11/11 (100%) showed no relapse at 12 months' follow-up.[73] Side effects for IFN therapy include neurologic disorders, mental disturbances, thrombocytopenia, leukopenia, hair loss, and fever.[71] Despite some positive evidence for adjuvant IFN therapy, it is rarely used due to the emergence of intralesional adjuvants, such as cidofovir and bevacizumab, which have fewer local and systemic side effects.

Cidofovir

Cidofovir is a cytosine nucleotide analog that blocks the replication of DNA viruses by inhibiting viral DNA polymerase.[74] Its mechanism of action against HPV is not well understood, although it has been hypothesized that it acts by augmenting the immune system or

inducing apoptosis.[75] Intralesional administration of cidofovir has been fairly well-tolerated, with limited systemic toxicity.[76–80] Prospective trials in patients treated with intralesional cidofovir have shown marked papilloma regression as well as complete disease remission in both the JO-RRP and AO-RRP populations (Table II). A group investigated the efficacy of intralesional cidofovir following surgical excision in 16 JO-RRP patients and found a 75% complete remission rate, with stable disease to a mean of 33.6 months.[81–83] In a separate cohort by the same group, intralesional cidofovir with surgery in 19 AO-RRP patients induced an 89% complete remission rate, with stable disease to a mean of 24 months.[81,82,84] Interestingly, Broekema and Dikkers reported that 5 of 188 (2.7%) patients receiving intralesional cidofovir developed dysplasia. However, it is important to note that cidofovir is most likely not the cause of dysplasia in this cohort since the incidence of spontaneous malignant degeneration in RRP is 2–3%.[76] According to a 2013 RRP task force survey of 74 laryngeal surgeons that have used cidofovir to treat RRP, cidofovir may be initiated when surgical debulking is required every two to three months, and dosing should remain below established safe levels (3 mg/kg) and volume.[85]

Bevacizumab

Bevacizumab is a recombinant monoclonal humanized antibody that blocks angiogenesis by inhibiting the human vascular endothelial growth factor A (VEGF-A).[49] Approved by the FDA in 2004, it was the first angiogenesis inhibitor available in the US and was used as an adjuvant to chemotherapy in metastatic cancers.[86] Rahbar et al. conducted a retrospective study to determine the role of VEGF-A in the pathogenesis of RRP patients.[87] Strong expression of VEGF-A mRNA was noted in the squamous epithelium of all 12 RRP patients, and strong expression of VEGFR-1 and VEGFR-2 were noted in the endothelial cells of the papillomas' blood vessels.[87] These observations provided the rationale for assessing the use of bevacizumab in the context of RRP. Several studies have shown that bevacizumab is relatively safe and active in JO-RRP and AO-RRP (Table III). Sidell et al. treated eight JO-RRP patients by debulking the papillomas with a KTP laser, then administering intralesional bevacizumab at 14.25 mg doses at four- to six-week intervals.[88] The median Derkay scores decreased by 58% post-treatment and, moreover, the time between procedures more than doubled.[88] Another group studied the efficacy of adjunct bevacizumab with KTP laser excision on 20 adult patients with bilateral vocal fold RRP.[89] They reported that 19/20 (95%) patients had better disease control in the bevacizumab/KTP laser-treated vocal fold than on the KTP laser-only-treated vocal fold, despite selecting the vocal fold with more extensive disease to receive the bevacizumab/KTP laser treatment.[89] Consistent with these studies, other groups have reported promising results using the combination of KTP laser and bevacizumab, with minimal complications.[88,90–92]

Celecoxib

Celecoxib is a COX-2-selective non-steroidal anti-inflammatory drug used to manage pain and inflammation associated with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, painful menstruation, and other acute and chronic pain indications.[49] Overexpression of COX-2 was observed in the papillomas of RRP patients, and this increase was proposed to be a consequence of epithelial growth factor receptor (EGFR) and phosphatidylinositol 3-kinase (PI-3K) signaling.[93] In 2009, Limsukon et al. showed success in treating an RRP patient with a combination of celecoxib and erlotinib (a tyrosine kinase inhibitor) at doses of 400 mg per day and 150 mg per day, respectively.[94] This patient had several surgical procedures and received IV cidofovir, but her recurrence rate accelerated and her disease began to involve the mainstem and segmental bronchi.[94] The patient underwent a 3-month surveillance bronchoscopy following erlotinib/celecoxib therapy and surprisingly, there was no evidence of disease recurrence.[94] A randomized double-blind controlled study to determine the safety and efficacy of celecoxib in both pediatric and adult RRP patients was recently completed (NCT 00571701). The primary objective of this trial is to determine the efficacy of celecoxib response in comparison to conventional endoscopy and surgical treatment. All the patients in this study were evaluated under general anesthesia for disease severity at three-month intervals for 30 months; any papillomas present at the time of evaluation were surgically excised. Patients were randomly divided into early and delayed treatment arms. Patients in the early treatment arm received 12 months of 400 mg (adults), 200 mg (pediatric weight greater than 25 kg), or 100 mg (pediatric weight between 12 and 25 kg) of celecoxib daily, then 12 months of placebo daily. The late treatment arm received daily placebo for the first 12 months, then daily celecoxib for the second 12 months. Primary endpoint data showed that celecoxib treatment did not affect the mean percent change in papilloma growth rate at the 12-month measurement compared to baseline ($p = 0.57$). Analysis of secondary outcomes showed no reduction in papilloma growth rate when comparing age (juvenile- vs. adult-onset, $p = 1.00$), gender (male vs. female, $p > 0.3$), or HPV subtype (HPV6 vs. HPV11, $p > 0.5$).

PD-1 Inhibitor

Programmed cell death protein 1 (PD-1), which is present on the surface of leukocytes, negatively regulates the immune system when it binds to ligands PD-L1 and PD-L2 on antigen-presenting cells (APCs); PD-L1 has been shown to be highly expressed in HPV-associated head and neck squamous cell carcinoma (HNSCC).[95,96] PD-1 inhibitors, such as pembrolizumab, block the interaction between PD-1 and its ligands and have clinical efficacy in numerous advanced solid tumors, including HPV-associated HNSCC.[97] The activity against HPV-associated HNSCC has prompted investigators to initiate a Phase II clinical trial to assess the efficacy of pembrolizumab in RRP (NCT02632344). RRP

TABLE II.
Summary of Cidofovir in Reviewed Studies.

Study	Patients (*N*)	Mean No. of Injections	Mean Concentration (mg/mL)	Treatment (mo.)	Mean Follow-up (mo.)	Results	Conclusion
Snoeck et al.[80]	17 (16 AO/1 JO)	7.0	2.5	5	15	Complete remission in 14 (82.4%) patients, 13 AO and 1 JO	Treatment was well-tolerated and no immediate side effects were observed
Bielamowicz et al.[111]	14 AO	6.0	4.17-6.25	12	Up to 3 years	Complete remission in all 14 (100%) patients	Intralesional cidofovir is a good treatment option with limited local and systemic effects
Akst et al.[112]	11 JO	4, if recurred an additional 4	5, if recurred an additional 10	4, if recurred an additional 4	1	Derkay severity score decreased in all patients from a mean ± SD of 13.7 ± 6.0 to 2.1 ± 3.4	Intralesional cidofovir reduced burden of disease in children with RRP; recurrent disease may be treated with increased dosage
Lee et al.[113]	16 (12 AO/4 JO)	3.5	2.5-5	3 weeks	25.4	Complete remission in 10 (77%) patients, 8 AO and 2 JO	Found to be efficacious in treating RRP; more follow up is needed to analyze long-term effectiveness
Naiman et al. and Coulombeau et al.[81–83]	16 JO	8.9	5–7.5	2–4 weeks	33.6	Complete remission obtained in 12 (75%) patients; remission stable to a mean of 33.6 months follow-up	Surgical excision in combination with intralesional cidofovir is efficacious; relapse associated with long delay in initiating cidofovir treatment
Naiman et al. and Coulombeau et al.[81,82,84]	19 AO	4.5	5–7.5	2–4 weeks	24	Complete remission was obtained in 17 (89%) patients; remission stable to a mean of 24 months follow-up	Surgical excision in combination with intralesional cidofovir is efficacious in AO-RRP; concentration and interval between injections influenced the number of injections needed to achieve remission

AO = adult-onset; JO = juvenile-onset; RRP = Recurrent respiratory papillomatosis

TABLE III.
Summary of Bevacizumab in Reviewed Studies.

Study	Therapy Techniques	Patients (*N*)	Mean Age (yr. ± SD)	Mean Dose (mg ± SD)	Treatment Interval	Results	Conclusion
Maturo et al.[90]	Surgical debridement with microdebrider, KTP laser debulking, and intralesional bevacizumab injection	3	4.66	1.25	1–6 mo.	Derkay scores lowered significantly and PVRQOL scores improved in two patients; time between surgeries increased in all patients	Bevacizumab appears to show efficacy in increasing time between surgeries for children with severe RRP
Zietels et al.[89]	KTP laser debulking followed by bevacizumab injection into vocal folds	20	18–60	10	Once every six weeks for six months	19/20 (95%) patients showed less disease in the bevacizumab-treated vocal cord despite starting with more disease	Bevacizumab has a synergistic effect with KTP laser in RRP without systemic or local complications
Best et al.[91]	KTP laser (63/100 procedures) then intralesional bevacizumab injection	43	48 ± 14	30 ± 13	Mean 2.3 treatment sessions	No local or systemic side effects measured by physiologic data	Higher doses of bevacizumab are relatively safe in adult patients with laryngeal RRP
Rogers et al.[92]	Surgical debridement with microdebrider, KTP laser debulking, and intralesional bevacizumab injection	10	3.55	2.5	6–9 weeks	Time between surgeries increased, number of procedures per year decreased, Derkay scores decreased, and PVRQOL scores improved	Intralesional bevacizumab treatment may increase duration of time between surgical procedures; can improve voice QOL
Sidell et al.[88]	KTP laser debulking followed by intralesional bevacizumab injection	8	9.25	14.25	4–6 weeks	Median Derkay scores decreased by 58% post-treatment and time between procedures increased by a median of 2.05x	High-dose bevacizumab appears to yield positive results for pediatric patients with RRP

KTP = potassium-titanyl-phosphate; RRP = Recurrent respiratory papillomatosis; PVRQOL = pediatric voice-related quality of life; QOL = quality of life

TABLE IV.
Other Adjuvant Therapies.

Treatment	Rationale	Study Type	Treatment Type	Administration	No. of Patients	Follow-Up	Results	Conclusion
Acyclovir[114]	Antiviral drug that targets thymidine kinase expressed by herpes simplex virus-1 and Epstein-Barr virus, which are occasional concurrent and co-infections of HPV in RRP	Case series	Antiviral agent	PO	3 adults	1 year	Complete remission with no residual disease after 1 year follow-up in 2 patients	Oral acyclovir as an adjuvant to surgery may reduce recurrence in RRP; larger cohort studies are needed to assess efficacy
Ribavirin[115]	Antiviral drug that is used to treat respiratory syncytial virus pneumonia in infants and has shown some promise in treating aggressive RRP	Uncontrolled clinical trial	Antiviral agent	PO	4 (1 child; 3 adults)	4 months	2 adults achieved minimal recurrence; the other adult and child achieved increased intervals between surgeries	Ribavirin may be an effective adjuvant to laser surgery, but needs a larger controlled clinical trial to assess efficacy
Indole-3-carbinol (I3C)[116]	RRP lesions exhibit increased estrogen binding, and a study in mice showed that inhibition of estrogen metabolism with I3C reduced HPV-induced papilloma tumor formation by 75%[117]	Prospective, open label, multicenter	Dietary supplement (cruciferous vegetables)	PO	33 (9 children; 24 adults)	Mean 4.8 years	After 8 months or more of treatment, 11 (33%) patients had cessation of papilloma growth and did not require further surgery, 10 (30%) had reduced papilloma growth rate, and 12 (36%) had no evident response	There is potential for I3C as an adjuvant to surgery, but larger blinded, controlled studies need to be performed
Cis-retinoic acid[118]	In the aerodigestive tract, vitamin A deficiency has shown increased hyperkeratinization and squamous metaplasia, while excess has shown to suppress squamous differentiation and cause mucous metaplasia	Double-blind, randomized pilot	Retinoid	PO	9	18–34 months	4/6 (67%) treated patients experienced recurrence, and all experienced toxicity	Cis-retinoic acid appears ineffective as an adjuvant to surgery in RRP and further studies do not seem warranted

HPV = human papilloma virus; RRP = Recurrent respiratory papillomatosis

patients will be administered 200 mg pembrolizumab as a 30-minute IV infusion every three weeks on day 1 of each cycle, after all procedures and assessments have been completed. This is consistent with current dosing standards in treatment of recurrent or metastatic HNSCC.

HPV Vaccine

Perhaps the most exciting development in the management of RRP is prevention through HPV vaccination. The quadrivalent HPV vaccine, Gardasil, has activity against both low-risk HPV types 6 and 11 and high-risk HPV types 16 and 18.[49] Since HPV6 and HPV11 are the predominant etiologic factors for RRP, the quadrivalent vaccine has been used to manage RRP.[98] Forster et al. used the quadrivalent vaccine to treat a two-year-old boy with severe JO-RRP.[99] The boy's condition was stabilized after the third immunization and no surgery was needed for 10 months.[99] Young et al. conducted a retrospective chart review of 20 RRP patients treated with Gardasil and reported that 13/20 (65%) patients had complete remission or partial remission, with a 3.1-month increase in the time between surgical interventions.[100] Another study of 11 AO-RRP patients reported an increase in the mean time between surgical interventions from 271 to 537 days ($p = 0.03$) and a decrease in mean surgeries per year from 2.16 to 0.93 ($p = 0.02$) after quadrivalent vaccination.[101] A recent systematic review of seven studies investigated the role of quadrivalent HPV vaccination for secondary prevention of RRP. All seven case reports or cohort studies treating active RRP with quadrivalent HPV vaccination reported an increased interval between surgeries or decreased recurrence.[102] Furthermore, studies have shown that quadrivalent vaccination in RRP patients with HPV DNA-positivity and zero or low anti-HPV antibodies increased both anti-HPV6 and anti-HPV11 antibodies.[98,103,104] These case reports and small study series show encouraging results; however, multi-center randomized controlled trials are needed to fully assess the efficacy of the HPV vaccination as a therapeutic vaccine in the RRP population. Currently, the Centers for Disease Control and Prevention (CDC) recommends the new nonavalent vaccine, Gardasil-9. Current trends indicate that wide-spread vaccination of pre-adolescent females will further decrease HPV genital wart acquisition. This is expected to reduce the incidence of secondary laryngeal infections to newborns via vertical HPV transmission and, in turn, reduce JO-RRP and overall RRP incidence.[105]

Other Adjuvants

Other novel adjuvant approaches have been attempted for the management of RRP, with some clinical success (Table IV). Gefitinib, an EGFR tyrosine kinase inhibitor, was used in a life-threatening RRP case when all other treatments were exhausted. This particular case was a 14-year-old black male born with fetal alcohol syndrome. He underwent a tracheostomy at three-months-old due to extensive HPV11-associated RRP and subsequently, disease recurred with complete airway stenosis that extended to the trachea and mainstem bronchi. He was treated with IFN-alpha-2a until he developed hypertension, nephrotic syndrome, and renal failure at age eight. Attempts to control disease with surgical resection, local debulking, oral and inhaled ribavirin (antiviral), indole-3-carbinol, and PDT all failed, and he was not a candidate for cidofovir due to renal failure. After being treated surgically for a life-threatening airway obstruction, gefitinib was administered at a dosage of 250 mg twice daily for 11 months because his papillomas overexpressed EGFR and were becoming increasingly life-threatening. Debulking procedures were significantly reduced from 15 procedures per three months before gefitinib treatment to five procedures per three months during gefitinib treatment, with acceptable toxicity.[106] This exciting case report suggests that EGFR inhibitors may be offered as second-line therapy in EGFR-positive RRP.

CONCLUSION

RRP is a chronic disease that is difficult to manage due to the unpredictability of its recurrence and aggressiveness. Literature supports that low-risk HPV 6/11 enters the basal epithelium and drives local immune dysfunction, resulting in benign, exophytic papillomas. Evidence points toward the polarization of the adaptive immune system to a T_H2-like or T-reg phenotype by low-risk HPV E6, which suppresses clearance of HPV infection.[10,16] It is still unclear, however, why certain RRP patients experience a more severe disease course than others. There is evidence that frequency of certain HLA alleles as well as the absence of certain innate immune receptors may predispose people to develop RRP, and also may be linked to disease aggressiveness.[11,18] Research is building to support the notion that the papilloma microenvironment is immunocompromised, and thus, regaining T_H1 cell function may be a tractable approach to prevent persistent infection.

Currently, RRP is managed by surgical excision primarily, both in the operating room and in the office setting. Tools including the microdebrider, useful for removing bulky disease, and photoangiolytic lasers such as the KTP laser, useful for more precise targeting of pathologic tissue, are both frequently employed in surgery for RRP. The advent of the flexible laser system and good topical anesthesia techniques have allowed for office-based procedures to replace OR procedures in many RRP cases. This is an advantage for both the patient and the surgeon, as it has been shown to decrease procedural time and costs, minimize risks of anesthesia, and allow patients to take less time off work. Patient selection for in-office procedures is dependent upon a variety of factors, including extent of disease, patient tolerance, and surgeon experience.

When surgery is insufficient to control the disease course, adjuvant pharmacologic therapies are administered. IFN-alpha was the earliest treatment strategy to augment the immune system in RRP patients; however,

systemic side effects of IFN-alpha have limited its use, and adjuvant therapies have moved toward intralesional bevacizumab and cidofovir. Immunomodulatory agents, such as the anti-PD-1 antibody pembrolizumab, have shown activity against HPV-associated HNSCC, and an ongoing Phase II clinical trial has been initiated to assess the efficacy of pembrolizumab in RRP. Furthermore, HPV vaccines, including the newly developed nonavalent Gardasil-9, have shown therapeutic benefit, but randomized clinical trials are needed to evaluate the efficacy of HPV vaccines to reduce the recurrence rate of RRP. Due to the low incidence of RRP, acquiring a sufficient number of patients may be difficult for a single institutional study; thus, large, multi-center clinical trials are required to assess the efficacy of the HPV vaccines. Routine HPV vaccination in pre-adolescent children is also expected to secondarily reduce RRP incidence by decreasing the incidence of genital warts caused by HPV, thus reducing vertical transmission of HPV to newborns.

In conclusion, RRP is incurable with current treatment modalities. Adjuvant therapies are utilized when surgery cannot control disease, and the efficacy of adjuvants is limited to increasing the time interval between surgical procedures. Additional research on the interplay between low-risk HPV and the immune system is critical and may lead to the development of novel immunomodulatory approaches to better manage RRP patients.

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