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Recurrent Respiratory Papillomatosis (RRP)–Time for a Reckoning?

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Objectives: Recurrent respiratory papillomatosis (RRP) is a rare disease, but one with severe morbidity and occasional mortality. The aetiological agent is human papillomavirus (HPV), and HPV types 6 and 11 account for over 90% of all cases. In the active phase of the disease, patients require multiple hospital admissions for surgical removal or ablation of these benign tumors, which are likely to obstruct the airways if left unchecked. Long-term sequelae include scarring of the vocal cords, change in voice timbre, or even muteness if a tracheostomy is required. The aim of this study was to determine if adjuvant vaccination with the quadrivalent HPV L1 vaccine (Gardasil™) would decrease numbers of surgical treatments post-vaccination.

Methods: A prospective pilot study following a cohort of 12 RRP patients, all of whom gave fully informed consent to participate. All patients had their papillomas typed and if they were found to have types 6 or 11, were vaccinated at the time of first surgical treatment in the hospital, according to the manufacturer's protocols. Patients were followed up closely with 3 or 6 month follow-up visits. Standard surgical treatments were given and were not affected by whether they participated in the study.

Results: We found a >7-fold decrease in the incidence rates of papillomatosis requiring surgical intervention from the pre-vaccination period (47.44/1000 patient-months) compared to the post-vaccination period (6.71/1000 patient-months).

Discussion: Surgical treatments for RRP are robust markers for papillomata which require treatment because of the dangers of obstruction of the airway. Despite the small size of this cohort (due to the rarity of this disease), the data suggests that adjuvant use of quadrivalent HPV L1 vaccine imparts significant benefit to this group of patients. A large multi-center randomized placebo controlled trial is required to definitively establish whether this hypothesis is true and can become the new standard of therapy.

Key Words: Recurrent laryngeal papillomatosis, HPV, vaccination, Gardasil™.

Level of Evidence: 3b

INTRODUCTION

The human papillomavirus (HPV) is the aetiological cause of several benign and malignant tumors.[1–3] Although recurrent respiratory papillomatosis (RRP) is a rare disease, there is severe morbidity and occasional mortality. The incidence of this terrible disease is low (approximately 4/100,000 live births) but this background risk rises dramatically to 1/400 in women who have detectable wart infection during pregnancy.[3] RRP can be divided into adult and juvenile forms. The adult form of RRP is thought to be from infection with HPV contracted during adulthood (most probably intimate contact) and the juvenile form of RRP is thought to be from vertical transmission from mother to child. Affected children can suffer severely when the disease is in the active phase, with multiple hospital admissions for ablative or excisional surgeries to remove the growing tumor, which can threaten the airway and cause death if untreated. The morbidity is considerable, and long-term effects include scarring of the vocal cords, delayed speech development and even muteness, if a tracheostomy has been inserted.

The aim of this pilot prospective cohort study was to examine the outcomes of vaccination of patients with RRP, in the hope that vaccination with the quadrivalent vaccine (Gardasil™, SPMSD, Lyon, France) will prevent recurrent growth of papillomata (either through prevention of new infection via antibodies, or through cross-priming from Dendritic cells (DCs) or B-cells in the generation of T-cell mediated responses against infected cells.[4–8] The rationale for this strategy is that HPV 6 and 11 are thought to cause >90% of RRP lesions.[9,10]

PATIENTS AND METHODS

This study was approved by the local research ethics committee in Bielefeld Hospital. All patients with RRP diagnosed had tissue taken for histopathology diagnosis, had HPV typing performed, and were offered the opportunity to have vaccination with the quadrivalent HPV vaccine (HPV L1 types 6, 11, 16, 18) (Gardasil™, SPMSD, Lyon, France) if they had proven HPV 6 or 11 disease. Twenty-four patients were diagnosed with RRP and offered surgical treatment with a range of different surgical

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TABLE I.
RRP Patients—Demographic and Surgical Data

Patient #	Age (years)	Gender	HPV subtypes	Pre-vacc. surgeries	Post-vacc. surgeries	Time betw. Diagnosis and vacc. (mths)	Time after Vacc. (mths) to Nov 2014
1	72	M	6	8	0	360	71
2	78	F	6	5	0	44	63
3	37	F	11	12	1	325	72
4	38	M	6	6	0	70	34
5	76	M	6	5	0	124	51
6	61	M	6	5	1	149	54
7	62	M	11	1	0	147	13
8	72	F	6	12	0	35	35
9	72	M	NA	2	1	28	25
10	27	F	6	8	0	35	21
11	56	M	6	10	0	258	4
12	56	M	16	3	0	27	4

Total no. of surgeries pre-vaccination = 76, total no. of surgeries post-vaccination = 3.

options (CO2 laser, cold steel, shaver, microdebrider). Power and sample size calculations determined that total n = 10 would be sufficient to detect partial or complete response rates of 70% between the pre-vaccine (onset to first vaccine) and post-vaccine treatment arms, with a follow-up period of at least 2–3 years.

Twelve patients accepted the chance to participate in this study and gave fully informed consent. These patients were followed up with closely and the number of surgical interventions both pre-vaccination and post-vaccination were noted. The number of surgical interventions is a robust marker of papillomatosis growth and recurrence, since surgery is first-line treatment in RRP.

GraphPad Prism™ version 7 (2016) (La Jolla, CA, USA) was used for statistical analyses. The incidence rate for surgical procedures was calculated using person-time estimation, in this case: patient-months. Analyses of pre-vaccination and post-vaccination incidence rates of surgical interventions *within* the cohort, controls for demographics such as age, gender, and other inter-patient variables. Comparison of these incidence rates were analysed using the non-parametric paired Wilcoxon Signed Rank Test. P values less than or equal to 0.05 were considered to be significant.

RESULTS

Total time in months between first diagnosed disease and first dose of vaccine = 1,602, and total time in months between first dose of vaccine to November 2014 = 447.

Therefore incidence rate of surgeries pre-vaccine = 47.44/1000 patient- months

The incidence rate of surgeries post-vaccine = 6.71/1000 patient-months

This represents a 7.07-fold reduction in incidence rate of surgeries from the post-vaccine period compared to the pre-vaccine period ($p<.0001$).

DISCUSSION

Recurrent respiratory papillomatosis is a rare but important disease with high morbidity, and occasional mortality. Treatment with surgical and ablative methods has been generally unsatisfactory, and usually requires multiple visits to hospital, general anaesthetic, and the possibility of scarring and consequent speech impediments. These effects can be devastating for the individual patient and family life.

There have been anecdotal case reports of using the off-label vaccination of patients with RRP as a therapeutic adjuvant, with clinicians desperate to find alternative effective treatments. The quadrivalent HPV L1 vaccine has been proven to provide excellent prophylaxis against infection with the 4 HPV types at the primary sites of the cervix and anus, and also some cross-protection against non-vaccine types (closely-related types).[11,12]

The high production of anti-L1 antibodies induced by the quadrivalent vaccine has been shown to be the primary mechanism of prophylaxis against infection by the 4 main HPV types. It is unclear whether this high protective antibody level is able to yield therapeutic benefits in patients already infected with the virus and with the disease. If RRP patients have an apparent "reinfection" of laryngeal mucosa from surrounding tissue following surgical removal of papillomata and that this contributes to regrowth of new papillomata, then anti-L1 antibodies could have a potential therapeutic benefit. A second possible mechanism of antiviral activity in humans against infected cells is that of the cell-mediated response (CMI) in the adaptive immune response. These are almost always predominantly viral-specific CD4+ and CD8+ T-cells. These activated T-cells can kill infected cells directly primarily via the perforin-granzyme B and Fas-Fas ligand pathways which activate apoptosis.

There are now interesting data from the large studies of female cohorts which may demonstrate an apparent therapeutic benefit in patients with prior infection. Interestingly, there are also data that seem to demonstrate an active CMI response being activated from vaccination, but it is more controversial and less clear than the antibody response,[13–16] It is known that in benign disease such as RRP, there is normal full-cycle replication of

the virus, thus exposing the immune system (both humoral and CMI) to the full spectrum of viral antigens. In this regard, we postulated that an increased stimulation of the humoral arm via vaccination would also stimulate the CMI arm of the immune response to a certain degree via the mechanisms of cross-presentation, thus yielding some therapeutic benefit against remaining infected cells that look clinically normal macroscopically.

Conversely, the use of the L1 vaccine post-exposure to HPV may just not work in any therapeutic manner, as it has already strongly demonstrated prophylactic protection against primary infection by the mechanisms described above.

We have demonstrated that in our cohort of 12 patients with RRP, there is a highly significant reduction between the number of surgeries required in the post-vaccine period, compared to the pre-vaccine period. This is direct evidence that there is either a reduction in "reinfection" of surrounding tissue following the surgery and vaccine, or an active CMI response contributing to reduced regrowth of papillomata in remaining tissue (or both) by killing virally infected cells.

The major weakness of this study is the size of the cohort (n = 12). A high n is difficult to achieve in single center studies, with a rare disease such as RRP. Furthermore, the natural biological history of RRP within individual patients and between patients is one of periods of activity (growth), quiescence (stability), and less commonly, resolution. This will undoubtedly introduce variability into any prospective study with defined study periods. Despite this, and although our cohort is small, we believe that the data are suggestive that there may be significant benefits arguing for the vaccination of currently infected RRP patients. Another prime target population for vaccination would be pregnant women with clinically obvious HPV genital disease at some time during pregnancy, as their risk of having a child with RRP is 1/400. We suggest that our data, together with other published data[17–21] support the need for a large multicenter, adequately powered, randomized, and placebo-controlled trial of vaccination in RRP patients which would definitively answer the question.

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