Clinical Trial of Photodynamic Therapy With Meso-Tetra (Hydroxyphenyl) Chlorin for Respiratory Papillomatosis

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Objective: To determine the efficacy of photodynamic therapy (PDT) with meso-tetra (hydroxyphenyl) chlorin (m-THPC) photosensitizer for recurrent respiratory papillomatosis.

Design: Parallel-arm, randomized trial of patients requiring surgery at least 3 times yearly with single PDT 6 or 18 months after enrollment and 12-month follow-up. Disease extent was scored and papillomas were removed during direct endoscopy every 3 months after enrollment.

Setting: Tertiary medical centers.

Patients: Of 23 patients aged 4 to 60 years enrolled in the study, 15 patients, plus 2 in the late group without PDT owing to airway risk, completed the study. Six patients withdrew voluntarily after PDT.

Intervention: Intravenous administration of m-THPC 6 days before direct endoscopic PDT with 80 to 100 J of light for adults and 60 to 80 J for children.

Main Outcome Measures: Difference in severity scores between the early and late groups and between pre- and post-PDT scores for all patients. Secondary measures were the associations between baseline characteristics and response and changes in immune response and the prevalence of latent viral DNA.

Results: There were significant differences between groups, with marked improvement in laryngeal disease across time after PDT \((P = .006)\). Five of 15 patients were in remission 12 to 15 months after treatment, but there was recurrence of disease after 3 to 5 years. Tracheal disease was not responsive to PDT. No change occurred in the prevalence of latent human papillomavirus DNA. The immune response to virus improved with clinical response.

Conclusions: Use of m-THPC PDT reduces the severity of laryngeal papillomas, possibly through an improved immune response. Failure to maintain remission with time suggests that this is not an optimal treatment.


RECURRENT RESPIRATORY PAPILLOMATOSIS (RRP) is a potentially life-threatening disease with a clinical course marked by multiple recurrences. Human papillomavirus (HPV) types 6 and 11, which cause RRP, exist as latent infections in morphologically normal tissue of the airway and are believed to be the source of recurrent disease. To achieve cure, therapy must either eliminate latent infection or prevent its activation. The HPV is a commensal organism in humans, with widespread latent infection usually suppressed by the host immune system. Results of recent studies suggest that the immune response to HPV proteins is altered in patients with RRP.

Numerous treatment modalities have been tried for RRP, with limited success in preventing recurrent disease. Current experimental treatments include adjuvant indole-3-carbinol, intralesional mumps vaccine, and cidofovir injections. These therapies seem to be effective in a subset of patients, but not all patients respond, and the mechanisms for the intralesional therapies are not known. Direct laryngoscopy with mechanical or carbon dioxide (CO2) laser surgery is still the most common method of treatment today and the only approved treatment for RRP.

Photodynamic therapy (PDT) was originally developed for the diagnosis and treatment of cancer. Using a rabbit model, Shikowitz et al were the first to demonstrate the effect of PDT on papillomavirus-induced lesions. Previous clinical trials evaluated the efficacy of PDT with the photosensitizer dihematoporphyrin-ether on RRP. Dihematoporphyrin-ether PDT induced a 50% decrease in the
The primary objective of this trial is to test the hypothesis that a single adjunct treatment with m-THPC PDT reduces the frequency of recurrent disease compared with surgery alone. Secondary objectives are to determine whether m-THPC PDT reduced the prevalence of latent laryngeal HPV infection or altered the immune response to HPV protein.

STUDY METHODS

STUDY DESIGN

The design of this multicenter, parallel-arm, randomized, controlled study is shown in Figure 1. Disease extent was scored and papillomas were removed during direct endoscopy using a CO₂ laser or microdebrider every 3 months for the duration of the study, with intermediate procedures performed if necessary to maintain an airway. Five months after enrollment, patients were randomized to 1 of 2 treatment groups. One group received PDT at 6 months, and the second was treated by surgery for 12 additional months before PDT, with the delayed group serving as a control group in addition to the control period before PDT for each patient. A random numbers table was used to generate random assignments to treatment groups at Long Island Jewish Medical Center, and the randomizations were transmitted to the surgeon by the nurse clinician either personally or by telephone; the randomization ratio was 1:1. Patients and physicians were not masked to treatment group. All patients were followed up with scheduled endoscopies every 3 months for at least 12 months after PDT. A biopsy sample from clinically normal tissue was collected 9 to 12 months after PDT for analysis of HPV DNA persistence. Blood samples were collected at multiple times after PDT from a subset of patients treated at Long Island Jewish Medical Center to measure host immune response to HPV protein.

PARTICIPANTS

Patients older than 2 years with multiple papilloma recurrences requiring surgical removal 3 or more times per year or tracheobronchial involvement were eligible for enrollment. Patients were recruited from the practices of the investigators and by referral from other otolaryngologists between January 1, 1996, and December 31, 2002. Evaluations were performed before and after PDT at any of the participating sites, but each patient was followed at a single site. Data were analyzed at Long Island Jewish Medical Center and Montefiore Medical Center. All patients or guardians signed informed consent forms before enrollment. The study was approved by the institutional review board of the Institute for Medical Research and had Food and Drug Administration approval to use m-THPC (Foscarnet, Scotia Pharmaceuticals Ltd, Stirling, Scotland) as an investigational new drug.

INTERVENTION

At enrollment, patients underwent chest radiography, a complete blood cell count with a differential count, liver function tests, and urine analysis, followed by direct laryngoscopy with bronchoscopy if indicated, was performed using jet ventilation as previously described. At enrollment, patients received 0.15 mg/kg of body weight of m-THPC intravenously as an outpatient. Just before PDT, blood samples were collected to determine plasma drug levels, as previously described. Infusion of m-THPC and PDT were performed at Long Island Jewish Medical Center. At PDT, endoscopic laryngoscopy, and bronchoscopy if indicated, was performed using jet ventilation as previously described. Activating light at 652 nm was delivered by a diode laser (Ophir Optronics, Inc, Wilmington, Mass) with a 400-µm-diameter quartz fiber with a 1.5- to 3.0-cm cylindrical diffuser tip. The light dose ranged from 80 to 100 J for adults and 60 to 80 J for children, depending on the concentration of drug in the plasma at the time of PDT. Total activation time varied from 200 to 330 seconds, with the patient apneic to reduce any movement of the centrally located fiber. The jet ventilation needle was withdrawn into the scope to avoid any shadow effect, which could decrease the effectiveness of the therapy.

MONITORING AND EVALUATION

At each endoscopy, before and after PDT, the extent of disease was scored and photodocumented on videotape by each treating physician as previously described elsewhere. At each endoscopy, before and after PDT, the extent of disease was scored and photodocumented on videotape by each treating physician as previously described elsewhere. Assessing the number of disease sites, the surface area involved, and the extent of lumen obstruction. Rate of papilloma growth within the interval (severity score) was calculated as the total papilloma score divided by the number of days since the last surgical removal. For patients who required intermediate procedures between the scheduled endoscopies, scores for each subinterval were summed and then divided by the total number of days in the scheduled interval.

STATISTICAL ANALYSIS

An initial power analysis determined that for a 2-tailed test with a type 1 error of 0.05, 28 patients would be required in each group to demonstrate a 50% difference in the growth rate across time with 90% power. We could not recruit the desired number of patients, but the effect of PDT was greater than 50% (see the “Results” section), permitting determination of statistical significance. There were several reasons for the limited enrollment: the study design required that some patients wait 18 months after enrollment before receiving PDT, concerns about...
photosensitivity restricted enrollment during those months that would have resulted in PDT during the summer, and the absence of an immediate response caused many patients and physicians to conclude that the treatment was not effective.

Analysis was performed using a statistical software program (SAS version 8.2; SAS Institute Inc, Cary, NC). Hierarchical linear models, which do not generate means and standard deviations, were used to determine the significance of differences across time between the 2 treatment groups (early vs late PDT, considered to be the concurrent control during the first 9 months after randomization). The units of analyses were the participants’ “average scores per day” (referred to subsequently as “scores”) and the percentage change from randomization relative to the score obtained at the initial surgery. This model was optimal because it allowed for missing observations at various times. For a particular assessment date, time was computed as the number of days from the date of entry (first surgery) to that assessment date. Covariance structures for several models (random effects, compound symmetry, autoregressive, unstructured, and regression) were examined for data from the entire period, and the model that yielded the smallest magnitude of the Akaike Information Criterion was cited as the best model. Additional models were derived for selected periods (ie, for the first 9 months after the early group was treated with PDT, or longer) to best isolate periods in which differences between groups were significant. In addition, data from the time at which the individual received treatment through follow-up were pooled for all treated patients, with the assessment at which treatment was initiated considered the baseline among these treated patients. Hierarchical linear models were derived to determine the significance of trends over time. Analysis of response was performed according to the intention-to-treat principle. Treatment × time interactions for models comparing treatment effects and time for the pooled treated group were considered significant at P<.05. Associations between baseline characteristics and changes in scores and between groups were assessed using Spearman rank correlations, Wilcoxon rank sum and Kruskal-Wallis tests, and Fisher exact tests.

DNA ANALYSIS

DNA samples were extracted from biopsy samples and analyzed for latent HPV by polymerase chain reaction amplification, followed by Southern blotting for confirmation as previously described.2 Standard precautions to prevent polymerase chain reaction contamination were used. As a positive control, 25 fg of cloned HPV DNA was mixed with 50 ng of HPV-negative human tonsil DNA and amplified and analyzed at the same time as the biopsy DNA sample in each experiment. Amplification without the addition of tissue DNA served as a negative control for each assay. Clinically normal sites were biopsied using separate instruments that were not used on any active control for each assay. Clinically normal sites were biopsied using separate instruments that were not used on any active control for each assay.

EVALUATION OF HOST IMMUNE RESPONSE

Expression of interferon γ (IFN-γ) and interleukin 10 (IL-10) messenger RNA cytokines by peripheral blood mononuclear cells was measured after exposure to HPV-11 E6 protein as described elsewhere.2 Briefly, peripheral blood mononuclear cells were incubated for 4 hours in recombiant E6 protein ranging from 50 to 0.2 ng/mL in 2-fold dilutions, and expression of IL-6 and IFN-γ messenger RNAs was determined. Cytokine-specific dose-response curves were generated for each patient’s peripheral blood mononuclear cells. The threshold of each dose-response curve was defined as the minimal concentration of viral protein required to increase the messenger RNA level greater than 2 SD above the mean, untreated baseline level. Thresholds were in the linear range for the detection of product.

RESULTS

PATIENTS

Twenty-three patients were initially enrolled in the study. Five patients withdrew after PDT when there was no immediate improvement and enrolled in other experimental treatments, and 1 relocated and was not followed up for the full 12 months. Fifteen patients received PDT followed by at least 1 year of scheduled evaluations. Two patients in the late PDT group withdrew after completion of the control period but before PDT, 1 owing to concerns about airway obstruction and 1 who had a spontaneous remission at the time of scheduled PDT. There were 12 patients in the early group and 5 in the late group available for analysis. Participant flow through the study is shown in Figure 1. Patient demographics and disease characteristics are given in Table 1. The ages of the patients at enrollment ranged from 4 to 60 years. At the time of PDT, there were 3 patients aged 4 to 9 years, 3 aged 10 to 20 years, 6 aged 21 to 40 years, and 5 aged 41 to 60 years. One adult had juvenile-onset disease, and the remaining 3 had adult-onset disease. Of 5 patients with tracheal involvement, 1 underwent a tracheotomy before referral to Long Island Jewish Medical Center, and 1 had no laryngeal disease. Table 2 gives the treatment variables for patients in the 2 groups (n=3 for the late group because 2 patients were not treated). There was no significant difference in the light dose for the 2 groups. However, plasma levels of photosensitizer at time of PDT varied widely among patients (mean, 88 ng/mL; median, 91 ng/mL; range, 30-135 ng/mL [0.44 × 10−6M to 198.4 × 10−6M]), although all had received comparable doses based on body weight. This variation was consistent with an earlier preclinical study17 that showed marked variation in drug clearance between individual animals.

Table 1. Baseline Characteristics of the Patient Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early Group (n = 12)</th>
<th>Late Group (n = 5)</th>
<th>Total (N = 17)</th>
<th>P Value for Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>10 (83)</td>
<td>3 (60)</td>
<td>13 (76)</td>
<td>.54</td>
</tr>
<tr>
<td>F</td>
<td>2 (17)</td>
<td>2 (40)</td>
<td>4 (24)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>White</td>
<td>10 (83)</td>
<td>5 (100)</td>
<td>15 (88)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Adult</td>
<td>7 (58)</td>
<td>3 (60)</td>
<td>10 (59)</td>
<td></td>
</tr>
<tr>
<td>Juvenile</td>
<td>5 (42)</td>
<td>2 (40)</td>
<td>7 (41)</td>
<td></td>
</tr>
<tr>
<td>Disease sites</td>
<td></td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Larynx</td>
<td>8 (67)</td>
<td>4 (80)</td>
<td>12 (71)</td>
<td></td>
</tr>
<tr>
<td>Larynx and trachea</td>
<td>3 (25)</td>
<td>1 (20)</td>
<td>4 (23)</td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (6)</td>
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</tr>
</tbody>
</table>
The most common adverse effect of PDT is skin photosensitivity, which is seen in all patients. Photosensitivity in the patients treated in this study required elimination of all sun and bright light exposure for 2 to 4 weeks. One patient disregarded instructions to avoid the sun and experienced erythema and swelling that lasted for several days. One patient, a young child with severe disease, experienced substantial swelling of the airway within a few hours of PDT that required intubation for several days to maintain an airway, prolonged hospitalization, and eventually a tracheotomy. Based on that event, the participating physicians recommended not performing PDT on the patient in the late group who had very extensive disease and a narrowed airway.

**CLINICAL RESPONSE TO PDT**

The primary goal of the study was to determine whether there is a reduction in severity of disease after PDT, as measured by the rate of papilloma regrowth. Figure 2 shows the median relative severity scores of laryngeal papillomas in the 2 groups of patients during the 18 months after enrollment, normalized to the severity score at study entry. There was increased variation for patients in the early treatment group 3 months after enrollment, reflecting increased severity in 2 patients and decreased severity in 1 patient. Most patients in both groups showed a modest relative decrease in disease severity during the 3- and 6-month pre-PDT evaluations, which continued at the 9-month evaluation in the control group. The decrease could reflect the effects of surgery at regular, relatively frequent intervals because other researchers have suggested that frequent removal of recurrent papillomas can modify the course of disease. Five patients had a worsening of disease severity after PDT that lasted for 3 to 5 months, whereas most patients had no change in disease severity during that period. In the worst case, 1 patient had a 7-fold increase in the rate of papilloma growth. However, there was a marked decrease in relative severity 6 to 9 months after treatment, with 5 (45%) of 11 patients in the early treatment group free of laryngeal disease. One of these was the patient with the worst exacerbation after PDT. Of patients who did not achieve remission by 15 months after PDT, 4 of 11 showed improvement of 40% to 50% compared with entry severity, and 2 showed no improvement (<25% change). The 12th patient in the early group had tracheal disease only and is not included in Figure 2. The remissions lasted for 3 to 5 years. Since then, 4 patients we have continued to follow have had small areas of recurrent papilloma that were easily treated using a CO₂ laser (data not shown).

The first statistical analysis compared the early PDT-treated group with the concurrent control regarding fol-

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**Table 2. Treatment Variables for the Patient Groups**

<table>
<thead>
<tr>
<th>Treatment Variable</th>
<th>Early Group (n = 12)</th>
<th>Late Group (n = 3)</th>
<th>Total (N = 15)</th>
<th>P Value for Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light dose, J</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>4 (33)</td>
<td>0</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>5 (42)</td>
<td>3 (100)</td>
<td>8 (53)</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>3 (25)</td>
<td>0</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Plasma drug level, ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤91*</td>
<td>8 (67)</td>
<td>0</td>
<td>8 (53)</td>
<td></td>
</tr>
<tr>
<td>&gt;91</td>
<td>4 (33)</td>
<td>3 (100)</td>
<td>7 (47)</td>
<td></td>
</tr>
</tbody>
</table>

*1.34 × 10⁻⁴M.

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**Figure 2. Response to photodynamic therapy (PDT).** Median severity scores at each 3-month interval relative to scores at initial direct endoscopy are shown for the early group, which received PDT 6 months after enrollment (A), and the control group (ie, the late group), which received PDT 18 months after enrollment (B). Error bars represent range; diagonal hash marks, a break in the linear scale of the y-axis.
low-up points (before treatment for the late group) for laryngeal and tracheal scores. Percentage of change from baseline (randomization) was not performed because some scores were zero (undefined) at baseline. Instead, the score obtained at the initial assessment was used to derive the percentage of change. For analyses using data from all points, models for which treatment group and time were considered fixed effects and subject was considered random yielded lower Akaike Information Criterion values than other models for the same outcomes. Table 3 provides statistics for the analyses involving laryngeal and tracheal scores using 0, 3, and 6 months (randomization) and subsequent points until the late group was treated. The resulting Akaike Information Criterion values and corresponding \( P \) values for the analyses indicate that group \( \times \) time interactions were statistically significant for laryngeal but not for tracheal models.

The significant interaction found for laryngeal scores likely indicates that there were differences between the groups during the times preceding randomization. There were too few degrees of freedom to analyze the difference between the groups regarding the times starting from the time of randomization. In addition, for tracheal scores, it seems that the 2 groups were significantly different throughout the assessment period \( (P = .01) \), indicating that randomization likely did not result in balanced groups. Regarding the analysis of differences in the percentage change scores (Table 3), differences between the early and late treatment groups seemed to increase later in the course of treatment. In contrast, median scores seemed to converge.

The final analyses were performed on the pooled treated cohorts (Table 3). There was a significant reduction from the initial evaluation in laryngeal score among those treated 6 months after the initial evaluation, with laryngeal values for the 12 months after PDT being significantly different from the 3 values preceding PDT (laryngeal Akaike Information Criterion percentage change, 1227.5; median scores, from 0.102 at entry to 0.04), and a significant reduction in disease \( (P = .007) \). For tracheal disease, the percentage change was not significant \( (P = .16) \), with median scores of 0.099 at entry and 0.111 at 12 months. The trend for change in disease severity before PDT for the delayed treatment (control) group was not significant \( (P = .44) \). We then asked whether response was associated with other variables, including plasma levels at the time of PDT. There was no association between demographic or treatment variables and response to PDT (Table 4).

**EFFECTS ON PAPILLOMAVIRUS PERSISTENCE**

We questioned whether the reduction in disease 1 year after PDT reflected a loss of latent HPV from the respiratory tissues in those patients. The prevalence of latent infection in the biopsy samples \( (n=20) \) was 41%, comparable with our recent study\(^2\) of viral latency in patients treated with CO\(_2\) laser ablation, in which 44% were comparable with our recent study\(^2\) of viral latency in patients treated with CO\(_2\) laser ablation, in which 44% were positive. This is a typical finding, suggesting that latent infection is “patchy” but widespread. The amount of HPV DNA in the biopsy samples varied but was generally in the range of 0.1 to 1.0 copy per cell compared with amplification of cloned HPV DNA. Remission was not due to elimination of latent HPV infection.

**CHANGE IN HOST IMMUNE RESPONSE AFTER PDT**

Patients with RRP do not mount an effective immune response to HPV proteins,\(^3\) with a correlation between the amount of HPV E6 protein required to induce response...
and disease severity. We asked whether PDT altered immune response to E6, and whether this could explain the pattern of delayed response. Figure 3 shows the concentration of E6 required to induce IL-10 and IFN-γ messenger RNA expression by peripheral blood mononuclear cells from 3 patients compared with disease severity at the time of each analysis. Interferon γ is important in the control of viral infections, whereas IL-10 is immunosuppressive. The amount of E6 required to induce IFN-γ and IL-10 expression by the 3 patients decreased when disease severity improved after PDT and increased when patients showed worsening of their disease. Two patients (Figure 3A and B) required comparable concentrations of E6 to induce IL-10 and IFN-γ, whereas the third patient (Figure 3C) required different amounts of E6 to induce the 2 cytokines. Increased amounts of E6 were required by this patient to induce IFN-γ when his severity score significantly worsened 3 months after PDT, and again 13 months after PDT, possibly predicting future worsening of disease. We did not assess the patient’s subsequent disease severity to determine whether this was true.

**COMMENT**

The concept of using a photosensitive dye activated by light to destroy tumor cells has a long history. We applied it to the treatment of benign papillomavirus-induced lesions, using hematoporphyrin derivative and dihematoporphyrin-ether photosensitizers in preclinical and clinical studies and m-THPC in preclinical studies. This article describes the effects of m-THPC PDT on RRP.

Several conclusions can be drawn from the study. First, most patients responded to treatment, but the response was delayed, with an initial transient increase in disease severity in many patients. The small sample size provided limited power for assessment of responses between the PDT arm and its concurrent control, and the effect observed in the pooled treated groups may have been due to natural reduction in severity of disease across time. However, we would not have expected the marked median improvement seen 12 months after treatment (Figure 2). Second, patients who were followed up after completing the study had small recurrences 3 to 5 years later, but the rate of recurrence was reduced compared with their original pattern. Third, clinical improvement did not reflect elimination of latent viral DNA, consistent with previous studies of dihematoporphyrin-ether PDT, explaining the recurrence of disease after several years of remission in this study. Instead, our results suggest that PDT altered the host immune response to viral proteins. This mechanism is consistent with findings from a previous study indicating that PDT induced cytotoxic T cells in mice with subcutaneous tumors and with the recent suggestion that the effects of PDT on the immune response to cancer are mediated by an in situ “vaccination” mediated by local release of tumor antigens by necrosis.

In contrast to laser or mechanical surgical removal, PDT induces slow necrotic destruction of papilloma tissue. Thus, released HPV proteins would be more likely to mediate tumor cell death than to allow tumor cells to escape immune surveillance. The delayed response to PDT may be due, in part, to the slow process of tumor cell death by PDT. The central role of the host immune response to viral proteins is consistent with previous studies showing that virus-specific cytotoxic T cells are present in patients with high-grade RRP.

**Figure 3.** Relationship between immune response and disease severity after photodynamic therapy (PDT). Results of multiple assays across time for the threshold of human papillomavirus E6 protein required for the induction of 2 cytokines that regulate immune response are shown for 3 patients (A, B, and C). Interferon γ (IFN-γ) is a positive regulator, and interleukin 10 (IL-10) is immunosuppressive. Bars indicate the disease severity score at each assay time; transposition marks, a break in the linear scale of the x-axis.
to interact with antigen-presenting cells, for example, Langerhans cells, which present the antigens to T cells in regional lymph nodes. A rapid increase in the amount of HPV proteins in the absence of concomitant matura-
tion of presenting cells could cause a shift in HPV-
specific immune responses from low HPV protein level T-cell ignorance/tolerance to high HPV protein level T-
cell suppression/anergy,23 resulting in temporary wors-
ening of disease. With time, in the context of more ma-
tured presenting cell function, immune response would 
increase and disease would improve. However, when re-
mission was achieved it was not permanent, suggesting 
that PDT effects on the immune system are insufficient 
to maintain improved T-cell responses to HPV.

A previous study5 showed that patients with severe RRP express relatively more IL-10 than IFN-γ when chal-
enged with E6 protein. Genetic polymorphisms associ-
ated with immune response genes are important in pre-
dicting disease severity and predisposition to RRP.14,23 Therefore, genetic factors are likely to be important in generating competent HPV-specific immunity, and they may play a major role in determining the long-term ef-
fects of PDT for RRP.

In conclusion, PDT with m-THPC showed signific-
ant efficacy in the treatment of RRP, probably reflect-
ing improvement in the immune response by indirectly 
imunizing the patient to HPV proteins. However, the 
effects were not permanent, possibly owing to a rela-
tively short-term immune improvement.

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REFERENCES

1. Steinberg BM, Topp W, Schneider PS, Abramson AL. Laryngeal papillomavirus 
2. Abramson AL, Nouri M, Mulloloo V, Fisch G, Steinberg BM. Latent human pap-
   72:473-477.
   papillomatosis: altered CDS(+)-t-cell subsets and T1/T2 cytokine imbalance. 
5. DeVoti JA, Steinberg BM, Rosenthal DW, et al. Failure of gamma interferon but 
   not interleukin-10 expression in response to human papillomavirus type 11E6 pro-
6. Healy BB, Gelber RD, Trowbridge AL, Grundfast KM, Ruben RJ, Price KN. Treat-
   ment of recurrent respiratory papillomatosis with human leukocyte interferon. 
   rent respiratory papillomatosis: results of a randomized study in twelve colla-
9. Rosen CA, Bryson PC. Indole-3-carbinol for recurrent respiratory papillomato-
10. Pashley NR. Can mumps vaccine induce remission in recurrent respiratory 
11. Pransky SM, Magit AE, Kearns DB, Kang DR, Duncan NO. Intralusalional cidofovir 
   for recurrent respiratory papillomatosis in children. Arch Otolaryngol Head Neck 
12. Shikowitz MJ, Steinberg BM, Abramson AL. Hematoporphyrin derivative ther-
   112:42-46.
13. Abramson AL, Shikowitz MJ, Mulloloo VM, Steinberg BM, Amelia CA, Rothstein 
   HR. Clinical effects of photodynamic therapy on recurrent laryngeal papillomas. 
14. Abramson AL, Shikowitz MJ, Mulloloo VM, Steinberg BM, Hyman RB. Variable 
   light dose effect on photodynamic therapy of laryngeal papillomas. Arch Otol-
   therapy for respiratory papillomatosis: immediate and long-term results. 
16. Ronn AM, Nouri M, Lofgren LA, et al. Human tissue levels and plasma pharma-
   (hydroxyphenyl) chlorin in multiple species: clinical implications for photody-
18. Lofgren LA, Ronn AM, Abramson AL, et al. Photodynamic therapy using m-tetra 
   1994;120:1355-1362.
22. van Duijnhoven FH, Aalbers RI, Rovers JP, Terstra OT, Kuppen PJ. The immu-
   nological consequences of photodynamic treatment of cancer, a literature review. 
   Immunobiology. 2003;207:105-113.
   E6, and disease severity in patients with recurrent respiratory papillomatosis. 
25. Vambutas A, Bonagura VR, Reed EF, et al. Polymorphism of transporter asso-
   ciated with antigen presentation 1 as a potential determinant for severity of dis-
   ease in recurrent respiratory papillomatosis caused by human papillomavirus types 