Clinical Update on 10 Children Treated With Intralesional Cidofovir Injections for Severe Recurrent Respiratory Papillomatosis

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Objectives: To continue assessment of the benefits and risks of intralesional administration of cidofovir, an acyclic nucleoside phosphonate, for treating severe recurrent respiratory papillomatosis (RRP) in pediatric patients, and to discuss guidelines for larger prospective multi-institutional studies of the use of cidofovir.

Design: Prospective case series.

Setting: Tertiary care children’s hospital.

Patients: A total of 10 patients with severe RRP (defined as requiring debulking procedures to maintain airway patency at least once a month) underwent intralesional cidofovir therapy. The original 5 patients have received more than 1 year of follow-up since their last cidofovir injection, and 5 subsequent patients have been treated with a revised injection protocol.

Intervention: Microsuspension laryngoscopy with intralesional injection of cidofovir after repetitive carbon dioxide laser treatments and mechanical debulking of papillomas.

Main Outcome Measures: Papilloma stage at the time of serial laryngoscopies. Histologic examination of biopsy specimens of laryngeal tissue obtained 1 year or more after last cidofovir injection.

Results: There was evidence of marked improvement in the 4 of the 5 new patients enrolled under the revised injection protocol, continuation of a disease-free state in 1 of the original 5 patients, and sustained improvement in 4 of the 5 original patients, resulting in a significantly reduced interval of intervention.

Conclusions: Intralesional cidofovir therapy continues to show benefit in the treatment of severe RRP in pediatric patients. Safety profiles have not been fully established, but current histologic data are reassuring.


Recurrence Respiratory papillomatosis (RRP) continues to be a problematic disease in regard to maintaining an adequate airway and preserving voice quality. Children with aggressive RRP, necessitating frequent surgical procedures, are at higher risk of airway compromise from their disease and iatrogenic morbidity from their treatment. In 1996, the use of intralesional injections of cidofovir, an acyclic nucleoside phosphonate, was initiated at our institution to treat children with severe RRP. The favorable clinical response to intralesional cidofovir injections in 5 children was described in a previous report by Pransky et al.1 To date, there are no long-term data concerning the efficacy of cidofovir in treating RRP or its potential complications. Herein, we report the extended clinical response to cidofovir of the original 5 patients and the current response to cidofovir of 5 new patients, in whom a revised protocol was used, all 10 of whom had severe RRP, requiring debulking at least once a month. We also describe the histopathologic findings in biopsy specimens of laryngeal tissue obtained more than 1 year after the patients underwent repeated cidofovir injections and propose guidelines for future studies of the use of cidofovir.

Recurrent respiratory papillomatosis is the most common benign neoplasm of the larynx in children. This disease can be devastating, often requiring multiple surgical procedures and adjuvant therapy. Long-term airway compromise and complications can result from RRP and its treatment.2-3 Van Cutsem et al4 and Snoeck et al5,6 initially reported the successful use of cidofovir for laryngeal papillomatosis in 1995, 1996, and 1998. In 1999, Pransky et al7 reported the initial response of 5 children with severe RRP, requiring surgical intervention every 4 weeks, to the intralesional injections of cidofovir (1-[(S)-3-hydroxy-2-(phosphonomethoxy)-propyl]cytosine), an acyclic nucleoside phosphonate with broad activity against members of the DNA virus family.7,8 Cidofovir is presently approved by the Food and Drug Administration for use in the treatment of cytomega-
PATIENTS AND METHODS

ORIGINAL PATIENTS

After receiving treatment with intralesional cidofovir, our original 5 patients were clinically followed up. They underwent periodic office nasopharyngolaryngoscopy (NPL) and were brought to the operating room for formal suspension microlaryngoscopy on an “as-needed” basis. Spontaneous ventilation with a micro-suspension laryngoscope (Benjamin; Karl Storz Endoscopy-America Inc, Culver City, Calif) was used to perform the procedures. Biopsy specimens were obtained using cupped forceps, and any residual papilloma was treated with a carbon dioxide (CO\textsubscript{2}) laser.

Papilloma severity was graded using a format published by Derkay et al.\textsuperscript{10} This system grades papillomas by subsite and severity at each subsite on a 4-point scale (0 indicates none; 1, minimal; 2, moderate; and 3, severe). The total gives a general severity score. The results were recorded and photodocumented at each procedure. None of the original 5 patients received further treatment with cidofovir or other adjuvant medications.

NEW PATIENTS

Five children who required operative treatment of RRP at 1-month intervals or less were offered intralesional cidofovir therapy. Several of these children had undergone a trial of adjuvant therapies, without success. Human papillomavirus (HPV) typing was performed on all children prior to cidofovir injections. The parents were informed of the off-label use of cidofovir and of its potential complications. The cidofovir was prepared as a 5-mg/1-mL solution and administered intratrasionally in amounts ranging from 2 to 4 mL. Each patient received 4 injections at 2-week intervals. The operative technique was the same as described for the original 5 patients, other than the concentration of cidofovir. The cidofovir was injected using a laryngeal needle (Leurlock, Straight 8598B; Karl Storz Endoscopy-America Inc.). Papillomas were debulked with forceps and/or CO\textsubscript{2} laser prior to injection. All the children were discharged home on the day of surgery. No systemic steroids were given. A complete blood cell count, chemistry panel, and liver function tests were performed before the first injection and repeated every 4 weeks during therapy. The severity of each child’s papillomatosis was recorded and photodocumented at each surgery as described for the original 5 patients.

RESULTS

Table 1 lists the injection and follow-up data of the 5 original patients. All 5 continue to show marked improvement compared with their original status. None have evidence of adverse effects from treatment with cidofovir.

Patient 1 was the first of our patients to be treated with cidofovir. Before he began cidofovir therapy, he needed operative treatment for RRP every 2 weeks. At the time of this writing, it was 19 months since his last cidofovir treatment, and he has undergone only 1 operative procedure for removal of a small focus of papilloma in the right infraglottic region 14 months after his last injection. A biopsy specimen showed squamous papilloma with mild koilocytic atypia, and a biopsy specimen of a currently disease-free portion of laryngeal mucosa showed nonspecific chronic inflammation. There was no evidence of carcinoma. He is presently disease free on office NPL.

Patient 2 had the best response to cidofovir of the original 5 patients, and this trend has continued to the present time. Before she began cidofovir therapy, she required operative intervention for papillomatosis every 3 weeks. She has undergone 3 endoscopies since finishing her treatment course with cidofovir 18 months ago and has shown no evidence of papillomatosis. A biopsy specimen of her laryngeal mucosa showed squamous metaplasia, spongiosis, and focal koilocytic atypia, with no evidence of malignancy.

Patient 3 has been followed up for 19 months since his last cidofovir injection. Before he began cidofovir therapy, he was undergoing operative treatment every 2 to 4 weeks. He has undergone 3 endoscopies since the treatment was discontinued. The first endoscopy was performed 9 months after his last injection, at which time he was found to have mild papillomatosis in 3 subsites, with a severity score of 4. Three months later, he was found to have a similar presentation, with a severity score of 3. His last procedure revealed minimal papillomatosis, with a severity score of 2. He was treated with a CO\textsubscript{2} laser at each endoscopy. Biopsy specimens showed squamous papilloma with koilocytic atypia and no evidence of malignancy. He is presently disease free on office NPL.

Patient 4 improved during treatment with cidofovir but did not have a dramatic response. After receiving 11 injections in San Diego, Calif, he relocated to Houston, Tex. In Texas, he did not receive cidofovir initially, and his papillomatosis became more severe. Treatment with systemic interferon alfa-2a and cidofovir injections was then initiated, with dramatic response. It has now been 19 months since the patient’s last treatment with cidofovir and interferon, and he has undergone 2 interval endoscopies, with the findings of minimal disease and severity scores of 3 and 0, respectively. Presently, he has no active lesions. No biopsy specimens were obtained after his treatment with cidofovir.

Patient 5 received 8 cidofovir injections over a 3½-month period before moving to the Philippines 22 months ago. He periodically returns to San Diego for evaluation. He has undergone 2 endoscopies since his last cidofovir injection and was found to have very mild disease, with 3 small areas of papilloma, and was treated with the CO\textsubscript{2} laser. His biopsy specimen showed laryngeal papilloma, with no evidence of malignancy.

All 5 original patients were periodically screened for systemic sequelae with blood chemistry profiles and complete blood cell counts. No adverse effects were noted.

\textsuperscript{9}lovirus retinitis in patients with acquired immunodeficiency syndrome.
The subjective voice quality of each patient showed marked improvement.

NEW PATIENTS

Table 2 provides the relevant information for each of the 5 new patients, including their treatment and typing of their papilloma prior to their first cidofovir injection. Table 3 lists their responses to cidofovir therapy and their current status.

Patient 6, a 6-year-old Asian girl, was diagnosed as having RRP at the age of 4 years. She had massive papillomatosis and required laser laryngoscopy every 3 to 5 weeks. She underwent 11 endoscopies before receiving cidofovir injections, and her average severity score was 15.4. Treatment with indole-3-carbinol was initiated, with no improvement. Her HPV type was 11. At her first cidofovir injection, her severity score was 16. Her severity score at her second injection improved to 2. She continued to show improvement and had severity scores of 5 and 2 at her last 2 treatments. She was followed up clinically, with office NPL, for some time and underwent laser laryngoscopy 17 weeks after her last injection for very mild disease, with a severity score of 4. Office NPL, which was performed 10 months after the patient completed treatment, showed no clinical evidence of papillomas. During 5 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens showed continued evidence of benign squamous papillomas with mild cytologic atypia and koilocytotic change.

Patient 7, a 6-year-old Hispanic boy, recently moved to San Diego from Texas. He had been treated in Texas for RRP with multiple laser endoscopies and systemic interferon therapy. He was undergoing operative procedures every 4 weeks, with worsening disease, and needed 2 emergent debulking procedures for airway distress. His HPV type was 11. Before he began cidofovir therapy, his average severity score was 15. He was followed up clinically, with office NPL, for some time and underwent laser laryngoscopy 17 weeks after his last injection for very mild disease, with a severity score of 4. Office NPL, which was performed 10 months after the patient completed treatment, showed no clinical evidence of papillomas. During 5 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens showed continued evidence of benign squamous papillomas with mild cytologic atypia and koilocytotic change.

Table 1. Follow-up Data From the Original 5 Patients

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>HPV Type</th>
<th>No. of Procedures Before Cidofovir Injections</th>
<th>Routine Laser Interval for 6 mo Before Cidofovir Injections, d</th>
<th>No. of Cidofovir Injections</th>
<th>Period of Injections, mo</th>
<th>Time of Follow-up From Last Injection, mo</th>
<th>No. of Procedures Needed After Cidofovir Injections</th>
<th>Biopsy Results</th>
<th>Present Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M 6/11</td>
<td></td>
<td>33</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>19</td>
<td>1</td>
<td>No evidence of carcinoma</td>
<td>Disease free</td>
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<tr>
<td>2/F 6/11</td>
<td></td>
<td>18</td>
<td>7-21</td>
<td>15</td>
<td>8</td>
<td>18</td>
<td>3</td>
<td>No evidence of carcinoma</td>
<td>Disease free</td>
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<tr>
<td>3/M 11</td>
<td></td>
<td>12</td>
<td>14-28</td>
<td>13</td>
<td>7½</td>
<td>19</td>
<td>3</td>
<td>No evidence of carcinoma</td>
<td>Disease free</td>
</tr>
<tr>
<td>4/M 11</td>
<td></td>
<td>20</td>
<td>28</td>
<td>18</td>
<td>13½</td>
<td>19</td>
<td>2</td>
<td>No biopsy</td>
<td>Disease free</td>
</tr>
<tr>
<td>5/M 6</td>
<td></td>
<td>12</td>
<td>28-42</td>
<td>8</td>
<td>3¾</td>
<td>22</td>
<td>2</td>
<td>No evidence of carcinoma</td>
<td>Minimal disease</td>
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Table 2. Patient Data for the 5 New Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>HPV Type</th>
<th>No. of Procedures Before Cidofovir Injections</th>
<th>Procedure Interval for 6 mo Before Cidofovir Injections, wk</th>
<th>Average Severity Score Before Cidofovir Injections</th>
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<tr>
<td>6/F/6</td>
<td>11</td>
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<td>3-5</td>
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<td>2-6</td>
<td>20.5</td>
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<tr>
<td>9/M/6</td>
<td>6/11</td>
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<td>2-6</td>
<td>20</td>
</tr>
<tr>
<td>10/M/6</td>
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<td>24</td>
<td>4</td>
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</table>

Table 3. Follow-up Data for the 5 New Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Severity Score at First Injection</th>
<th>Severity Score at Second Injection</th>
<th>Severity Score at Third Injection</th>
<th>Severity Score at Fourth Injection</th>
<th>Interval to First Follow-up Procedure, wk/Severity Score</th>
<th>Interval to Second Follow-up Procedure, wk/Severity Score</th>
<th>Present Status</th>
</tr>
</thead>
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<tr>
<td>6</td>
<td>16</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>17/4</td>
<td>None</td>
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</tr>
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<td>19</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2½/1</td>
<td>8/8</td>
<td>Mild disease</td>
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<tr>
<td>8</td>
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<td>17</td>
<td>8</td>
<td>2</td>
<td>2/3</td>
<td>10/7</td>
<td>Mild disease</td>
</tr>
<tr>
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<td>3</td>
<td>1</td>
<td>1</td>
<td>8/8</td>
<td>7/8</td>
<td>Moderate disease</td>
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<tr>
<td>10</td>
<td>27</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>9½/19</td>
<td>5/28</td>
<td>Severe papillomatosis</td>
</tr>
</tbody>
</table>

*See “Original Patients” subsection in “Patients and Methods” section for explanation of severity scores.
to respond well, with severity scores of 5 and 2 at injections 3 and 4, respectively. His first follow-up endoscopy 2.5 weeks after his fourth, and final, cidofovir injection revealed a small focus of papilloma. Laryngoscopy performed 12 months after the final injection showed minimal disease, with a severity score of 3. During 9 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens revealed continued evidence of benign laryngeal papillomatosis with focal koilocytosis.

Patient 8, a 10-year-old Hispanic boy, was diagnosed as having RRP at the age of 8 years. His HPV type was 6/11, and he underwent 17 laryngoscopies before cidofovir therapy was initiated. In the 6 months before he began cidofovir therapy, his disease worsened, requiring laser laryngoscopy every 2 to 6 weeks, with an average severity score of 20.5. At his first cidofovir treatment, his severity score was 20 and he had diffuse disease. At his second injection, he continued to have diffuse disease, with a severity score of 17. He then began to show improvement and had severity scores of 8 and 2 at his third and fourth injections, respectively. At a follow-up laryngoscopy 2 weeks after his last injection, his severity score was 3. His second follow-up laryngoscopy was 10 weeks later, and he had minimal disease, with a severity score of 6. Laryngoscopy performed 6 months after his final cidofovir injection showed moderate clinical disease, with a severity score of 7. During 8 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens revealed squamous papillomas with mild koilocytic atypia.

Patient 9, a 6-year-old black boy, was first diagnosed as having RRP at 2 years of age. He was treated with laser endoscopy in San Diego and Washington State. He was also treated with interferon while living in Washington, without significant improvement. We performed 17 endoscopies on this patient in addition to those performed in Washington. His HPV was type 6/11. His disease process worsened in the few months before cidofovir therapy was initiated, requiring laser endoscopy every 2 to 4 weeks, with severity scores averaging 20. His larynx was graded as having a severity score of 16 at his first injection. At the time of his second injection, he was markedly improved, with a severity score of 3. He had a severity score of 1 at each of his last 2 injections. Laryngoscopy performed 15 months after the final cidofovir injection showed minimal clinical disease, with a severity score of 4. During 3 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens revealed minimal koilocytic atypia.

Patient 10, an 8-year-old Hispanic boy, was first diagnosed as having RRP at the age of 15 months. He was treated with laser endoscopy 24 times before he was referred to us because of worsening of his disease. Operative intervention was needed every 3 to 4 weeks. His HPV type was 11, and his severity score at his first cidofovir treatment was 27. His average severity score was 26 for the 6 months prior to his first treatment. He did not receive adjuvant medication. He responded well to his treatment, with severity scores of 2, 6, and 6 at each subsequent injection. After his fourth, and final, cidofovir injection, he was followed up clinically for 9.5 weeks.

He then underwent formal endoscopy, which revealed severe papillomatosis, with a severity score of 19. He was treated with the CO2 laser and was examined in the operating room 5 weeks later, where his disease was found to have worsened, with a severity score of 28. He underwent a second series of 4 cidofovir injections because of the continued aggressive nature of his disease. Laryngoscopy performed 5 months after the final cidofovir injection in the second series showed no evidence of clinical disease. During 13 months of histologic follow-up, the histologic profile of the patient’s laryngeal biopsy specimens revealed continued evidence of benign laryngeal papillomatosis with mild koilocytic atypia and acute and chronic inflammation.

No patient who underwent cidofovir treatment and follow-up showed evidence of dysplastic or malignant transformation. All 5 new patients were followed up with serial complete blood cell counts and blood chemistry profiles, including liver function tests. No adverse drug effects were seen. None of the patients experienced airway compromise as a result of their injections.

The original 5 patients who received cidofovir injections have done extremely well. Four of the 5 presently have no evidence of papillomatosis, and 1 has minimal disease. This is especially notable given how severe their RRP disease was at the initiation of cidofovir therapy. They have improved from needing at least monthly surgical intervention to only requiring rare operative intervention.

This excellent response has made a profound impact on these children and their families. Our follow-up period on these patients now ranges from 18 to 22 months, with no evidence of any rebound effect. They all remain healthy and show no clinical or laboratory evidence of any adverse effects from their treatment with cidofovir.

Because of concerns of laryngeal carcinoma arising in patients who had previously been treated with cidofovir, we obtained biopsy specimens of the laryngeal mucosa in 4 of the original patients more than 1 year after their last cidofovir injection. They all had evidence of chronic inflammation, but no evidence of malignancy. Grossly, laryngeal papillomatosis is characterized by exophytic, warty, friable, tan to white growths. The usual histologic findings of laryngeal papillomatosis include exophytic papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores. Little or no keratin production is noted, and stromal invasion is not observed. Cytologic atypia, especially koilocytic atypia, is often present. Dysplasia, carcinoma in situ, or overt squamous cell carcinoma suggests that there may be infection with an oncogenic HPV DNA type or squamous cell carcinoma arising in papillomatosis, or that the lesion may in fact represent a primary exophytic squamous cell carcinoma.

We also contacted the Armed Forces Institute of Pathology (AFIP) in Washington, DC, where the original biopsy specimens obtained by Snoeck et al were reviewed. The AFIP reports that 2 of the original biopsy specimens (which were obtained before treatment with
cidofovir) were actually not papillomatosis, but carcinoma. The pathologists at AFIP were not given patient data with the slides they reviewed, so they cannot say whether these data relate to the patients in question (C. Adair, MD, oral communication, March 1999).

With these concerns in mind, we modified our injection protocol in our new patients in an attempt to determine the ideal injection protocol, one that would reduce the exposure to cidofovir, yet provide a substantial and prolonged response. Each patient received 4 injections of cidofovir, given at 2-week intervals at the concentration of 5 mg/1 mL.

The initial response to cidofovir of all 5 new patients was as impressive as that of the original 5 patients. All 5 new patients showed a remarkable reduction in their severity scores during their injection period. After their injections, a variable response to the treatment was seen. Patient 6 has continued to do very well and has needed only 1 endoscopy, 17 weeks after her last injection, for minimal disease. Since that time, she has remained free of gross lesions on office NPL and has an excellent voice. Patient 7 has required 2 endoscopies since completing his injection cycle and continues to have several small foci of papilloma; however, his need for operative procedures has been reduced and his disease is mild compared with his pretreatment status. Patient 8 has followed a course very similar to that of Patient 7, other than having a delayed response to treatment. He has also needed only 2 endoscopies since completing his cidofovir regimen. He presently has mild disease and is able to wait 10 weeks between his 2 procedures. At his last endoscopy, his severity score was 7, compared with his average score of 20.5 before treatment. Also, before he began cidofovir therapy, he required debulking procedures every 2 weeks. Patient 9 responded rapidly to treatment and has required operative treatment every 8 weeks for moderate disease since his last injection. His average severity score at 2- to 6-week intervals was 20; the findings at the 2 procedures after treatment showed a decrease in his severity score to 8. He has effectively doubled his treatment interval and halved the extent of his disease. Patient 10, who had the most severe disease of all our new patients, responded quickly to cidofovir therapy and maintained this response throughout his injection cycle. Unfortunately, he quickly returned to his pretreatment status of severe papilloma after completing the series of 4 injections. He showed a significant response to a second series of 4 injections, becoming clinically free of disease.

None of our new patients received adjuvant therapy during their injection cycle or after their injections. They all underwent periodic screening with complete blood cell counts and blood chemistry profiles, with no evidence of adverse effects from their exposure to cidofovir.

In comparison to the original 5 patients, the second group does not appear to be responding as well to treatment with respect to long-term control of their RRP. Patient 10 did show a dramatic response to a second series of 4 injections of cidofovir. This may indicate that some patients need a more prolonged treatment course with cidofovir, as was the case with our original 5 patients and in the original report of Snoeck et al. Nevertheless, all 10 of our patients did show a significant and often dramatic ini-

tial response to the treatment, indicating that cidofovir does inhibit the growth of HPV lesions.

In an effort to explain the differential response to therapy, several possible explanations come to mind. The most obvious is the duration of treatment. However, the question as to the role of other adjuvant therapies, such as indole-3-carbinol, in conjunction with cidofovir injections is important. For example, patient 6, who had the best and most prolonged response, had been treated with indole-3-carbinol before beginning cidofovir therapy. Another factor is the ability of the individual patient to mount an adequate immune response to HPV once the tumor burden is decreased. This response is what may provide these patients with long-term control of their disease and could account for the variability of the success seen in our patients.

In our small series of patients with severe RRP, we have found that cidofovir therapy is an effective and beneficial treatment. At the present time, it appears to be quite safe in children with proven HPV 6/11 disease. More thorough investigation is needed to determine the optimal dose and duration of cidofovir therapy. A broad-based, multi-institutional study will be necessary to generate a sufficient patient population with severe RRP disease to answer these questions. Increasing the size of the treatment group would add statistical strength to future studies and allow trials of adjuvant therapies. Because of the lack of statistical data with regard to the safety of cidofovir, we would suggest that only children with severe RRP, needing operative treatment on a monthly basis, should be included in future protocols.

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