The Successful Management of Respiratory Complications With Long-Term, Low-Dose Macrolide Administration in Pediatric Heart Transplant Recipients

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Summary

We report three pediatric heart transplant (HTx) patients whose respiratory symptoms were successfully controlled with long-term, low-dose macrolide administration (clarithromycin: CAM; approximately 2.5 mg/kg bid). The first case was an 18-year-old boy who underwent HTx at the age of three for dilated cardiomyopathy (DCM). Beginning at age 5, he had repeated fevers and respiratory symptoms. He was diagnosed with chronic sinusitis at age 11 and sinobronchial syndrome with mild bronchiectasis at age 14. Administration of long-term, low-dose CAM and otolaryngeal topical therapy led to significant improvement of his symptoms. The second case was a 7-year-old boy who underwent HTx for DCM at age one. Starting at age 4, he had repeated fevers and cough due to atelectasis and pneumonia. As antibiotics and respiratory physical therapy proved ineffective, he received long-term, low-dose CAM, resulting in successful control of his atelectasis and recurrent pneumonia. The third case was a 13-year-old boy who underwent HTx at age 6 for DCM. He had chronic sinusitis starting at age 7, and was diagnosed with obstructive sleep apnea syndrome at age 10. Adenotonsillectomy and continuous positive airway pressure support therapy were indicated. At age 13, long-term, low-dose CAM administration was started following mycoplasma infection. In all three cases, the levels of calcineurin inhibitors (cyclosporine and tacrolimus) and everolimus were kept in the optimal range with careful drug monitoring. Long-term, low-dose macrolide administration effectively prevents and treats respiratory complications in pediatric HTx patients as long as attention is paid to potential drug interactions. (Int Heart J 2014; 55: 560-563)

Key words: Respiratory symptoms, Adenotonsillectomy, Continuous positive airway pressure support therapy, Calcineurin inhibitors

Chronic respiratory complications significantly affect quality of life of pediatric heart transplant (HTx) patients. The potential benefits of macrolides related to immunoregulatory and anti-inflammatory function make them interesting candidates for research. We report 3 patients whose respiratory symptoms were successfully controlled with long-term, low-dose macrolide administration.

Case Reports

A summary of the cases is presented in the Table. The first case was an 18-year-old boy who underwent heart transplantation at age 3 for dilated cardiomyopathy (DCM). Since the age of 5, he had repeated fever and respiratory symptoms such as cough with expectoration, rhinorrhea and nasal obstruction. Because he had an episode of monomorphic T-cell post-transplant lymphoproliferative disorder (PTLD) at age 10, his post-transplant immunosuppressive regimen was changed from cyclosporine to everolimus. Chemotherapy was administered and PTLD-affected sites in the ileum were resected. Immunoglobulin replacement therapy was also initiated. No relapse of PTLD was observed; however, he was diagnosed with chronic sinusitis at age 11 and recurrent lower respiratory infections continued. Computed tomography scan of his chest showed multiple nodular consolidations, irregular peribronchial thickening, and mild bronchiectasis in the bilateral lower lobes. Sinobronchial syndrome with mild bronchiectasis was diagnosed at age 14, and he received everolimus at this time. Upon initiation of long-term, low-dose clarithromycin (CAM) therapy (100 mg bid, ie, 5.7 mg/kg/day), daily everolimus dosing was reduced by 50%, from 2.0 mg to 1.0 mg, and was then gradually adjusted to 0.75 mg to reach the optimal everolimus trough level of 8 ng/mL. Everolimus dose adjustment took 17 days. No symptoms of rejection or over-immunosuppression were observed during this period. Echocardiography revealed normal cardiac function, and renal function and serum electrolytes were in normal range. Administration of CAM and otolaryngeal topical therapy resulted in significant improvement of symptoms and chest CT findings (Figure).

The second case was a 7-year-old boy who underwent HTx for DCM when he was one year old. At age 4 he was di-
Diagnosed with suspected PTLD and treated with anti-CD20 antibody (rituximab) and immunoglobulin. Around the same time, he had repeated fevers and respiratory symptoms such as cough with expectoration. Chest X-rays showed atelectasis and pneumonia repeatedly. As antibiotics and respiratory physical therapy were ineffective, he was started on long-term, low-dose CAM (40 mg bid, ie, 5.0 mg/kg/day). He was already being treated with tacrolimus, and this was continued without modification (1.0 mg/day). Although fine adjustment was needed, there was little change in drug concentration and the tacrolimus trough level remained in optimal range. No symptoms of rejection or over-immunosuppression were observed during this period. Echocardiography revealed normal cardiac function. Renal function and serum electrolytes were also in normal ranges. Since CAM initiation, his atelectasis and recurrent lower respiratory tract infections have been well-controlled.

The third case was a 13-year-old boy who underwent HTx at age 6 for DCM. Since age 7, he had repeated fever and respiratory symptoms such as cough with expectoration, rhinorrhea, and nasal obstruction. Chronic sinusitis was observed at age 7. He was also affected by acute tonsillitis repeatedly and sleep disordered breathing such as snoring and obstructive apnea developed. He was diagnosed with obstructive sleep ap-
Adenotonsillectomy was performed and continuous positive airway pressure support therapy was initiated. Following mycoplasma infection at age 13, long-term, low-dose CAM (75 mg bid, ie, 4.5 mg/kg/day) therapy was started. He was receiving cyclosporine at this time. Upon CAM initiation, the daily cyclosporine dosage was reduced by 83.4% (from 150 to 125 mg) and it took 7 days to obtain optimal cyclosporine blood levels. No symptoms of rejection or over-immunosuppression were observed during this period. Echocardiography revealed normal cardiac function, and renal function and serum electrolytes were also normal. Clinical symptoms due to chronic sinusitis improved significantly after CAM administration.

**DISCUSSION**

The first macrolide antibiotic, erythromycin, was introduced into clinical practice in 1952. The mechanism of action of the macrolides is obstruction of protein synthesis by binding to bacterial 50S ribosomal subunits. This pharmacological effect is mainly bacteriostatic, although the drug is bactericidal at higher concentrations. In addition to their antibacterial effects, macrolides were recently found to significantly improve the prognosis of diffuse panbronchiolitis (DPB) upon long-term, low-dose administration. Since this discovery, the potential benefit of 14-membered ring macrolides (eg, erythromycin and clarithromycin) related to immunoregulatory and anti-inflammatory function has become an interesting research topic. In addition to DPB, long-term macrolide treatment has been found to benefit chronic inflammatory airway diseases, particularly cystic fibrosis, chronic obstructive pulmonary disease, and obliterative bronchiolitis. Obliterative bronchiolitis is a form of chronic allograft dysfunction in lung transplant recipients and has been reported to be a condition in which macrolide therapy may be indicated.

Although the efficacy and adverse effects of macrolides for chronic respiratory disease in children requires further evaluation in prospective studies, we anticipate that long-term, low-dose macrolides may be beneficial in treating respiratory complications in pediatric HTx recipients when administered in addition to conventional therapeutic options such as expectorants, other antimicrobial agents, immunoglobulins, and chest physiotherapy. In pediatric HTx recipients, the respiratory tract is the most common site of infection. Non-infectious chronic respiratory complications also occur and affect patients’ quality of life. The individual in our first case was diagnosed with sinusobronchial syndrome with mild bronchiectasis. Sinobronchial syndrome is a condition characterized by chronic parenal sinusitis and simultaneous chronic pulmonary infection. Although the efficacy of long-term macrolide treatment of sinobronchial syndrome or non-cystic fibrosis bronchiectasis is less well established, our first case showed significant improvement in sinobronchial syndrome with mild bronchiectasis after CAM administration. In all 3 cases, other antimicrobials such as faropenem sodium were given prior to CAM administration but were not effective. Because neither severe onset of infection nor worsening course of signs or symptoms was observed, surgical treatment of sinusitis was avoided.

Increased susceptibility to infections in transplant recipients is primarily related to long-term immunosuppressive therapy. Gennery and colleagues reported that children who had undergone HTx and received immunosuppressive therapy at young ages (less than 4 years) failed to show an antibody response to polysaccharide antigen, even later in childhood. Although not demonstrated in our cases, immunosuppressive therapy may strongly influence the process of immune system maturation in the background.

PTLD is one of the major post-transplant complications related to immunosuppressive therapy. In our first and second cases, PTLD was diagnosed based on gastrointestinal symptoms. Each case of PTLD was proven to be associated with EBV infection. As a general rule, although respiratory symptoms may be associated with PTLD, we concluded that there was little relationship between respiratory symptoms and PTLD in these two cases.

Previous studies have described the occurrence of sleep disordered breathing (SDB) in HTx recipients. Adenotonsillar hypertrophy occurred in the third case and may have been responsible for his SDB symptoms. Because SDB is undoubtedly associated with cardiovascular morbidity in adults and also surely in childhood, its successful treatment in pediatric HTx recipients is thought to be indispensable for improving cardiovascular outcomes. Adenotonsillectomy is still the best initial treatment, although residual SDB after surgery may be more common than previously believed. For patients with residual SDB despite adenotonsillectomy, continuous positive airway pressure (CPAP) is indicated. Our third case underwent adenotonsillectomy twice, and experienced significant symptomatic improvement after receiving nasal-CPAP after the second procedure.

Our third case also underwent splenectomy for his hereditary spherocytosis. The function of the spleen is to filter and phagocytize bacteria in the bloodstream and to produce antibodies. The lack of splenic function can lead to fulminant, potentially life-threatening infection. Indeed, overwhelming post-splenectomy infection (OPSI) is associated with high morbidity and mortality. Although our third case had not experienced severe infections such as sepsis or meningitis, it was thought that splenectomy contributed to his increased susceptibility to infections overall.

At the time macrolide administration was begun, our first, second, and third cases were receiving everolimus, tacrolimus, and cyclosporine, respectively, as post-HTx regimens. Both everolimus and the calcineurin inhibitors (cyclosporine and tacrolimus) are metabolized by CYP3A4, as is clarithromycin. The addition of clarithromycin inhibits the metabolism of these immunosuppressants, and their blood levels are known to increase. In addition, clarithromycin, cyclosporine, tacrolimus, and everolimus are all substrates for P-glycoprotein. Since there might be other still undefined individual variations in drug metabolism, it is critical to monitor immunosuppressant blood levels and adjust dosages accordingly. In all three cases, immunosuppressant levels reached their optimal range following frequent blood measurements.

In our experience, it is difficult to detect whether CAM administration exerts its effects independently or in combination with other therapeutic options. Because the precise mechanism by which macrolides develop their benefits remains a challenge, it is also still unclear when the medication can be administered but were not effective. Because neither severe onset of infection nor worsening course of signs or symptoms was observed, surgical treatment of sinusitis was avoided.

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safely discontinued. Moreover, the prescribing of macrolides for long-term treatment could lead to the development of microbial resistance. While some issues remain in clinical practice, our experience suggests that the administration of a long-term, low-dose macrolide effectively prevents and treats the respiratory complications of pediatric HTx recipients. Implementation of this therapy requires that clinicians consider the effects of drug interactions and monitor blood levels of immunosuppressants.

REFERENCES


