Improved Graft Vasculopathy Following Mycophenolate Mofetil Administration in a Child

To the Editor:

Graft vasculopathy limits survival in pediatric heart transplantation and generally leads to retransplantation, due to the technical limitations of percutaneous revascularization.1

In experimental models, rapamycin and mycophenolate mofetil (MMF) decrease intimal proliferation of graft vasculopathy. In animals, MMF is associated with a lower incidence of graft vasculopathy than azathioprine.

We describe a 5-year-old boy weighing 15 kg, with blood group O-positive, who underwent heart transplantation in August 1998 because of cardiogenic shock after chickenpox. He received OKT3 induction and maintenance therapy with cyclosporine, azathioprine and prednisone. One month post-transplantation, he presented ISHLT (International Society of Heart & Lung Transplant) Grade 3A allograft rejection. Thirteen months later, graft vasculopathy was detected by coronary angiography (Figure 1A). Azathioprine was replaced with MMF (600 mg/m² every 12 h), a statin was added and 6-monthly coronary angiographies were scheduled. The patient remained asymptomatic in subsequent outpatient follow-up visits, and showed gradual angiographic improvement (Figure 1B).

Graft vasculopathy consists of intimal hyperplasia with concentric, diffuse, gradual narrowing of the epicardial and intramyocardial arteries of the transplanted heart.2 Its 5-year incidence in children is 10%-35% (angiographic diagnosis), a figure below that of adults because of the lower long-term survival, lower use of coronary angiography and utilization of younger donors in children.3 A history of allograft rejec-

Fig. 1. A: Coronary angiogram obtained in October 1999. Right anterior oblique view. The middle third of the right coronary artery shows narrowing. B: Coronary angiogram obtained in November 2001. Right anterior oblique view. The right coronary lesion has improved significantly.
tion increases the risk. In older children, abnormal contractility on dobutamine stress echocardiography, a noninvasive method, can disclose graft vasculopathy, which would then correlate with subsequent adverse events. Intracoronary ultrasound, a technique commonly used in adults, is more sensitive for diagnosing and measuring intimal thickening. Catheters (0.96-1.17 mm diameter) can produce artifacts that make it difficult to measure and interpret the morphology of pediatric coronary lesions, probably because of luminal distention. Intracoronary ultrasound has a high negative predictive value and is more sensitive than coronary angiography, and has considerable prognostic capability. Because of their poor prognosis, patients who are symptomatic must be retransplanted. However, fewer organs from children are available, making retransplantation difficult; therefore therapeutic alternatives are sought. Balloon angioplasty in adults with proximal focal lesions is only palliative, despite initial success on angiography, and has a higher incidence of restenosis than stents. Technical problems (small coronary arteries, difficult vascular access) limit the pediatric use of this technique in focal lesions with no distal involvement, and therefore retransplantation appears to be the only effective therapy. Various drugs (rapamycin, MMF) decrease the intimal proliferation of graft vasculopathy. In experimental studies, MMF has reduced the incidence of graft vasculopathy more than azathioprine. The former drug improves endothelial and coronary microvascular dysfunction, and lowers the incidence of allograft rejection and intimal thickening. Its greater potency could lead to regression or improvement of the angiographic lesions of graft vasculopathy. Resolution of these lesions and abnormal perfusion with the use of high doses of corticoids have been reported in the early post-heart transplant stages in adults with graft vasculopathy.

Our patient received statins after the diagnosis of graft vasculopathy. In adult heart transplant recipients treated with pravastatin, the progression of intimal hyperplasia was found to be reduced. No data are yet available on pediatric graft vasculopathy, however.

We believe that the angiographic progress in our patient, in terms of both coronary improvement and remodeling, may due to the change in therapy, consisting of the introduction of MMF and a statin, which have a favorable effect on graft vasculopathy. Reports of the clinical benefits of MMF in this condition are limited to comparisons with azathioprine from the initial stages of heart transplantation, and there is no evidence that replacement with MMF would lead to angiographic improvement, as in our case.

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