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AN INCREASED INCIDENCE OF EPSTEIN-BARR VIRUS INFECTION AND LYMPHOPROLIFERATIVE DISORDER IN YOUNG CHILDREN ON FK506 AFTER LIVER TRANSPLANTATION[1]

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The incidence of Epstein-Barr virus (EBV) infection and lymphoproliferative disorder (LPD) was determined in a pediatric liver transplant population consisting of 51 children treated with FK506 and 91 treated with cyclosporine. The incidence of symptomatic EBV infection was 21.9% (23 of 105 cases) in children <5 yr old and 10.8% (4 of 37 cases) in children 5 to 17 yr old as compared with 2.7% (9 of 323 cases) in adults ($P<0.0001$). In the under 5 yr old group on cyclosporine, the incidences of EBV infection and LPD were 9 of 68 (13.2%) and 2 of 68 children, (2.9%), respectively. In contrast, in children under 5 yr old group on FK506, the incidences of EBV infection and LPD in the FK506 group were 14 of 37 (37.8%) and 7 of 37 children (18.9%), respectively. The difference between these two groups was statistically significant ($P<0.02$). There were no cases of LPD in the 5–17 yr-old children on either cyclosporine (n=23) or FK506 (n=14). The incidence of EBV infections in the 5 to 17 yr age group, 17.4% on cyclosporine and 0% on FK506, was less than for the younger children on FK506 (37.8%). A total of 39% (9 of 23) of children under 5 yr old who had symptomatic EBV infections developed LPD, and 44% (4 of 9) with LPD died. The higher incidence of EBV infections and LPD in the younger children treated with FK506 was probably related to a greater intensity of immunosuppression for patients on FK506 than those on cyclosporine.

Following liver transplantation, Epstein-Barr virus (EBV)* infections in young children are usually primary because most children are seronegative before transplantation. However, in adults and older children, EBV infections are usually due to reactivation of the latent virus. Ho et al. estimated that 50% of pediatric transplant recipients are seronegative for EBV and two-thirds develop primary infections with EBV after transplantation (*1*). Since primary EBV infections are more likely to result in lymphoproliferative disorder (LPD), children have a greater risk than adults of developing LPD associated with their EBV infections (*1–4*).

The incidence of EBV-associated LPD in liver transplant recipients correlates well with the type and intensity of immunosuppression being used. Posttransplant LPD is most often associated with overzealous immunosuppression in the quest for the prevention or control of rejection. Monoclonal and polyclonal antilymphocytic preparations have been implicated in the etiology of EBV-induced LPD in transplant recipients (*5–7*).

A new macrolide immunosuppressant, tacrolimus (FK506), recently used in liver transplantation, has displayed similar, but more potent immunosuppressive properties when compared with cyclosporine (*8*). In both in vitro and in vivo studies, FK506 has been shown to be 10 to 100 times more potent than cyclosporine in inhibiting cell-mediated and humoral immune responses (*8*). In a large series of both adult and pediatric liver recipients, there was no difference in EBV-associated LPD between cyclosporine and FK506 therapies (*9–11*). However, there was a recent report of an increased incidence of LPD in children who were converted from cyclosporine to FK506 (*4*). This increased incidence was attributed to overimmunosuppression.

The purpose of this retrospective study was to compare the incidence of EBV infection and LPD in pediatric liver transplant recipients treated with either FK506 or cyclosporine.

MATERIALS AND METHODS

Study population. From 3/88 to 12/93 at California Pacific Medical Center, 499 liver transplants were performed, of which 346 (69.3%) were in adults and 153 (30.7%) in children (<18 years of age). In children, 142 were primary transplants while 11 (7.8%) were retransplants, and in adults 323 were primary transplants and 23 (7.1%) were retransplants. At the time of transplantation, 105 children were less than 5 yr of age and 37 were between 5 and 18 yr of age. The indications for liver transplantation in the children are shown in Figure 1.

Liver allografting was performed using conventional surgical techniques, including reduced-size liver grafts in 61 cases and living-related donor transplant in 4 cases (*12–15*). The technique for procurement consists of en-bloc removal of the intraabdominal organs, which were preserved in Wisconsin solution (*16–17*).

The standard immunosuppressive regimen included induction with (1) methylprednisolone (SoluMedrol, Upjohn, Kalamazoo, MI) i.v. initially, then conversion to oral prednisone when oral intake was begun (initial dose of 0.3–1 mg/kg/day depending on the presence or absence of coexistent infection and/or malnutrition; this was followed with a gradual taper over 7 to 10 days to 0.2 mg/kg/day), and (2) cyclosporine (Sandimmune, Sandoz, East Hanover, NJ) beginning with 2 mg/kg/day i.v. on the first or second postoperative day. Oral cyclosporine (20 mg/kg/day) was begun as soon as the child tolerated feedings and the i.v. dose of cyclosporine was gradually decreased while maintaining cyclosporine blood levels between 300 and 400 ng/ml using a whole-blood, monoclonal antibody RIA (CYCLO-Trac, Incstar, Stillwater, MN) (*18*).

For primary therapy, FK506 (Tacrolimus, Fujisawa, Deerfield, IL) beginning with 0.035 to 0.075 mg/kg/day i.v. was administered on the first or second postoperative day and the same corticosteroid induction protocol used with cyclosporine was used with FK506. Oral FK506 (0.1 to 0.2 mg/kg/day) was begun as soon as the child tolerated feedings and the i.v. dose was decreased while maintaining FK506 blood levels between 5 and 15 ng/ml using a whole-blood microparticle enzyme immunoassay (IMX, Abbott, Abbott Park, IL) or between 0.3 and 0.5 ng/ml using a heparinized plasma (separated at 37°C) enzyme-linked immunoabsorbent assay (ELISA) (*19, 20*). FK506 was used as primary therapy in 7 children while 44 were switched from cyclosporine to FK506 for refractory acute rejection in 17 cases, chronic rejection in 3 cases, hypertension in 12 children, poor absorption of cyclosporine in 9, severe hirsutism in 2, and failure to grow in 1 child.

For maintenance therapy, cyclosporine was used in 68 (65%) of children who were less than 5 yr old and in 23 (62%) of the older children. FK506 was used in 37 (35%) of children who were less than 5 yr old and 14 (37%) of the older children. At 3 months posttransplant, maintenance immunosuppressive therapy included prednisone at 0.1 to 0.2 mg/kg/day given q.d. and cyclosporine at 6 to 8 mg/kg/day given b.i.d. or FK506 given at 0.2 to 1 mg/kg/day in b.i.d. divided doses. A total of 48% of children on FK506 and 4.6% on cyclosporine were weaned completely off of prednisone.

For the EBV-infected and noninfected groups and for the FK506- and cyclosporine-treated groups, the dosage per kilogram of body weight and the blood levels of FK506 and cyclosporine at 3, 6, and 12 months posttransplant, as well as the frequency of use of antilymphocytic preparations were compared.

Initial therapy with Minnesota antilymphocytic globulin (MALG) or antithymocyte globulin (ATGAM, Upjohn, Kalamazoo, MI) (10–20 mg/kg/24 hr i.v.) was used in 74.7% children on cyclosporine and 67.3% on FK506. When MALG was no longer available for use, ATGAM was used as an alternative.

OKT3 (Orthoclone OKT3, Ortho Biotech, Raritan, NJ) was used for induction immunosuppressive therapy when recipients had donor grafts with small vessels, renal failure, ABO blood type mismatch between donor graft and recipient, or rejection. OKT3 (3–5 mg/kg/day) was given for 7 to 10 days in 54% children on cyclosporine and 57% on FK506.

One or more of these monoclonal or polyclonal antilymphocytic preparations (OKT3, MALG, and ATGAM) were given to 96.6% of children on cyclosporine and 94.2% on FK506.

Azathioprine (1 mg/kg/day) was added to the maintenance therapies (prednisone and cyclosporine or FK506) in 47% of children on cyclosporine and 36.5% on FK506.

For the first 24 to 48 hr postoperatively, patients were given i.v. ampicillin (Wyeth-Ayerst, Philadelphia, PA) (100 mg/kg/day i.v.) and cefotaxime (Claforan, Hoechst-Roussel, Somerville, IL) (75 mg/kg/

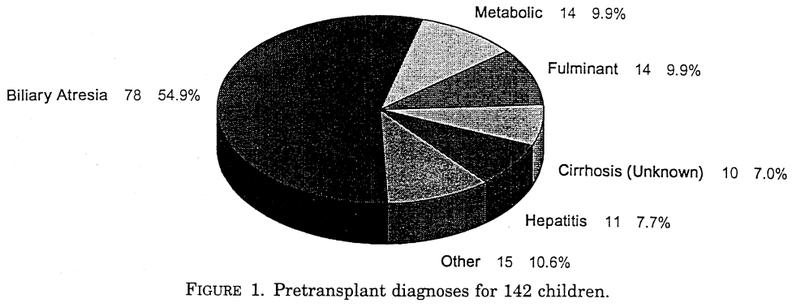

FIGURE 1. Pretransplant diagnoses for 142 children.

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* Abbreviations: EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder.

day i.v.). While hospitalized after the transplantation, children were given ganciclovir (Cytovene, Syntex Lab., Palo Alto, CA) (5 mg/kg/day i.v.) and at discharge were switched to acyclovir (Zovirax, Burroughs Wellcome, Research Triangle Park, NC) (10 mg/kg q.i.d.) for 3 months for antiviral prophylaxis. During the first two postoperative weeks, the patients were given pentamidine (Pentam, Fujisawa) (4 mg/kg i.v.) and then maintained on trimethoprim (4 mg/kg) and sulfamethoxazole (20 mg/kg) (Bactrim, Roche, Nutley, NJ or Septra, Burroughs Wellcome) taken 3 days per week indefinitely for *Pneumocystis carinii* prophylaxis.

Patients who had unexplained fever, lymphadenopathy, upper airway obstruction, rash, or unexplained diarrhea were evaluated for EBV infection (*1, 21–23*). In these patients, general virus isolation, EBV serology, antigen detection, and/or PCR were performed. EBV infection was defined as a (1) primary infection if seroconversion to all EBV markers was documented between pre- and posttransplant paired sera or (2) reactivated infection if anti-VCA IgG titer was ≥1:2560 and anti-EA/D was ≥1:20 in the presence of anti-EBNA. Reactivated EBV infection was defined by a specific titer level and not by changes in titer levels. EBV in tissue cryosections was documented by EB-associated nuclear antigen (EBNA) using anticomplement indirect immunofluorescence on needle biopsies. EBV-PCR to detect sequences for the EBNA-1 or gp220 capsid antigen was performed on DNA isolated from whole blood. LPD was defined by tissue recognition on a spectrum from atypical lymphoid hyperplasia to high-grade lymphoma. Patients who had symptomatic EBV infections were treated with ganciclovir (10–20 mg/kg/day i.v.) for 6 weeks. Immunosuppression was decreased by lowering or discontinuing FK506 or cyclosporine and lowering the prednisone dose to 0.1 mg/kg/day until rejection was evident on liver biopsy, or there was resolution of infection, or both.

Statistical analysis. Data are presented as the mean ± SD. Statistical analysis used the unpaired Student's two-tailed *t* test and chi square. A P value <0.05 was considered statistically significant.

RESULTS

The incidence of symptomatic EBV infection was 2.7% (9 of 323 patients) for adults and 19.0% (27 of 142 patients) for children ($P<0.0001$). Symptoms for the children were fewer in 27 patients, rash in 15, lymphadenopathy in 14, upper airway obstruction in 8, and diarrhea in 4. There was a mean duration of 12.8±10.4 (± SD) months, ranging from 1 to 45 months, from the date of transplant to the onset of symptomatic EBV infection.

Table 1 shows the laboratory results for the 27 patients diagnosed with EBV infection.

The indications for FK506 in the 14 children with EBV infections were refractory hypertension on cyclosporine in 6, poor absorption of cyclosporine in 3, rejection on cyclosporine in 3, and primary therapy in 2. One primary therapy patient was treated only with FK506 and corticosteroids while the other had also received ATGAM for induction. The 12 patients who were switched from cyclosporine to FK506 had this conversion within 4 weeks of their transplantation and had been on FK506 for 1 to 27 months (10±7 months) before developing EBV infection and/or LPD. Because there was a small number of children for each of the different reasons for converting children from cyclosporine to FK506, significant correlations between reasons for conversion and the risk for EBV infection and/or LPD could not be determined.

At 3, 6, and 12 months posttransplant, the doses and blood levels of cyclosporine and FK506 for the EBV-infected and noninfected children were not significantly different. There were no major changes in steroid doses except for our usual tapering protocol as noted in *Materials and Methods.* There was no significant difference in the use of azathioprine in the EBV-infected and noninfected groups on cyclosporine (46% vs. 36%) and on FK506 (29% vs. 19%).

Of the 27 EBV-infected children, all 13 cyclosporine-treated children had received one or more antilymphocytic preparations while 12 of the 14 FK506-treated children received at least one of these preparations. One or more antilymphocytic preparations were used in 96.5% of the children without EBV infections and in 92.6% of those infected with EBV. Both OKT3 and ATGAM or MALG were given to 33% of EBV-infected children as compared with 30% of the noninfected. Antilymphocytic preparations were used in the EBV-infected children for induction in all 12 of the FK506-treated children, and only for induction in 9, only for rejection in 1, and for both induction and rejection in 3 of the cyclosporine-treated children. Of the 27 children with EBV infection, 17 had been treated with OKT3 and 19 had received antilymphocytic globulin (MALG or ATGAM). For all of the cyclosporine-treated children, one or more antilymphocytic preparations (OKT3 and/or MALG or ATGAM) were given at an average of 16±13 months, ranging from 1 to 45 months, before they developed symptoms of EBV infection and/or LPD. Similarly, for 12 FK506-treated children, one or more antilymphocytic preparations were given at an average of 13±10 months ranging from 2 to 27 months before they developed symptoms of EBV infection and/or LPD. The differences in frequencies of use of antilymphocytic preparations (OKT3 or ATGAM/MALG; OKT3 and ATGAM/MALG) in 13 EBV-infected children on cyclosporine (100%; 54%) and 14 EBV-infected children on FK506 (86%; 14%) were not significant.

Viral infections occurred more frequently in the younger children (Table 2). There was a higher incidence of symptomatic EBV infection in the <5 yr old FK506-treated children as compared with the <5 yr old cyclosporine-treated children or older children who were treated with either cyclosporine or FK506 (Table 2). However, there was no difference in incidence of other symptomatic viral infections between the FK506- and cyclosporine-treated groups. Eight of the 27 EBV-infected children and 3 of the 9 children with LPD had CMV IgM titers ≥1:20, but CMV was not isolated from urine or tissue biopsies in these cases.

Table 3 demonstrates an increased incidence ($P<0.02$) of EBV infection and LPD in children under 5 yr of age treated with FK506 compared with children of a similar age treated with cyclosporine and older children on either cyclosporine or FK506. EBV infections occurred more frequently (21.9%) in the <5 yr old age group, as compared with 10.8% in the older children. All cases of LPD occurred in the <5 yr old age group, with 39.1% of children with EBV infections in this age group developing LPD.

Of the 27 EBV-infected children, 16 have had resolution of their symptoms, 6 died, and 5 (3 on FK506; 2 on cyclosporine) have persistent symptoms of lymphadenopathy and intermittent fevers (Table 1). Because of the concern that FK506 may have been responsible for the EBV infection, 6 children were switched from FK506 to cyclosporine. All 6 children had resolution of their symptoms within 4 weeks of this change. Four children remain on FK506, with 1 having resolution of symptoms and 3 having chronic symptoms. All children on cyclosporine have remained on this drug, with 9 having resolution of symptoms and 2 having chronic symptoms. Of the 6 deaths in EBV-infected patients, 4 (2 on cyclosporine; 2 on FK506) died from LPD and 2 died from noninfectious causes (liver failure from chronic rejection and cardiac arrhythmia). Of the 4 children who died with LPD, 1 on cyclosporine had polymorphic B cell lymphoma and 3 (2 on FK506; 1 on cyclosporine) had monomorphic B cell lymphoma. One child who had only been treated with FK506 and prednisone died from monoclonal B cell lymphoma, while the other 8 children with LPD had received antilymphocytic preparations. Of the 5 children who had resolution of the LPD, all had been taking FK506; the LPD was polyclonal, polymorphic B cell hyperplasia in 4 and polymorphic B cell lymphoma in 1. Though their tissue stained for EBNA, 2 of the 5 patients with B cell

TABLE 1. EBV/LPD diagnosis and outcome for FK506 and cyclosporine

A. FK506

No.	Age (years)	OLT-EBV (months)	EBV Ab	EBV PCR	EBV tissue (EBNA stain)	LPD type	Outcome
1	0.1	10	Seropositive	Negative	Vocal cord (prob +)	Polymorphic lymphoma	On FK506, resolved
2	0.4	14	Seronegative	Positive	Not done	—	Off FK506, resolved
3	1.0	13	Seropositive	Not done	Liver (+), tonsil (+)	Lymphoid hyperplasia	Off FK506, resolved
4	0.3	2	Seropositive	Positive	Tonsil (−), rectum (−), stomach (−)	—	Off FK506, resolved
5	0.9	4	Seronegative	Not done	Skull (+)	Monomorphic lymphoma	Expired
6	0.3	3	Seropositive	Positive	Duodenal (+)	Monomorphic lymphoma	Expired
7	0.5	3	Seropositive	Positive	Liver (−), gastric (−), duodenal (−)	Lymphoid hyperplasia	Off FK506, resolved
8	3.5	27	Seropositive	Positive	Tongue (−), tonsil (−), palate (−)	—	On FK506, chronic
9	2.0	14	Seropositive	Positive	Not done	No tissue	On FK506, chronic
10	1.2	9	Seropositive	Positive	Lymph node (+)	Lymphoid hyperplasia	On FK506, chronic
11	0.4	10	Seropositive	Positive	Nasopharyngeal (+)	Lymphoid hyperplasia	Off FK506, resolved
12	0.2	1	Seronegative	Not done	Liver (+)	—	Expired
13	4.3	unk	Seropositive	Not done	Not done	No tissue	Expired
14	1.1	16	Seronegative	Positive	Duodenal (−), liver (−), gastric (−)	—	Off FK506, resolved

B. Cyclosporine

No.	Age (years)	OLT-EBV (months)	EBV Ab	EBV PCR	EBV tissue (EBNA stain)	LPD type	Outcome
1	0.6	2	Seronegative	Not done	Liver (+)	Monomorphic lymphoma	Expired
2	11.1	37	Seropositive	Not done	Not done	No tissue	Resolved
3	8.6	3	Seropositive	Not done	Not done	No tissue	Resolved
4	2.8	12	Seropositive	Not done	Not done	—	Resolved
5	7.0	13	Seropositive	Not done	Not done	No tissue	Resolved
6	1.7	1	Seropositive	Not done	Liver (−)	Polymorphic lymphoma	Expired
7	1.5	15	Seropositive	Not done	Not done	No tissue	Resolved
8	1.2	13	Seropositive	Not done	Not done	No tissue	Resolved
9	1.3	23	Seropositive	Not done	Not done	—	Resolved
10	1.2	28	Seropositive	Not done	Not done	No tissue	Chronic
11	0.6	10	Seropositive	Not done	Not done	No tissue	Resolved
12	13.6	25	Seropositive	Not done	Not done	No tissue	Resolved
13	1.6	45	Seropositive	Positive	Not done	No tissue	Chronic

TABLE 2. Symptomatic viral infections[a] following liver transplantation

Age groups	Number of patients			Total number of patients
	EBV	CMV	Other viruses[b]	
FK506				
<5 yr	14[c]	4	4	37
5–17 yr	0	0	2	14
Cyclosporine				
<5 yr	9[c]	5	10	68
5–17 yr	4	0	0	23

[a] Tissue diagnosis.
[b] Adenovirus, rotavirus, echovirus, rhinovirus, herpes simplex virus.
[c] $P<0.02$.

TABLE 3. Incidence of EBV infections and LPD for cyclosporine and FK506 immunosuppression in the <5- and 5–17-yr-old liver transplant recipients

Drug	Age (yr)	Total number of patients	EBV infections		LPD	
			No.	%	No.	%
Cyclosporine	<5	68	9	13.2	2	2.9
FK506	<5	37	14[a]	37.8	7[a]	18.9
Cyclosporine	5–17	23	4	17.4	0	0
FK506	5–17	14	0	0	0	0

[a] $P<0.02$ compared with <5-yr-old group on cyclosporine.

lymphoma had negative EBV serology, which indicated that they had primary EBV infections.

DISCUSSION

A majority of children who develop EBV infection after liver transplantation are asymptomatic or have mild upper respiratory symptoms, lymphadenopathy, diarrhea, and/or rash; some children, however, develop the more serious complication of LPD (*1, 21–23*). Using serologic criteria alone, EBV infection was demonstrated in 57% of transplanted children in Pittsburgh and 13% of children in Dallas (*21, 22*). Similarly, we found symptomatic EBV infections in 19% of our children as compared with only 2.7% in our adults ($P<0.000001$). This increased incidence of EBV in children is due, in part, to the fact that many children are seronegative at the time of their liver transplantation (*1*). This may explain the higher incidence (21.9%) of EBV infections in our young children compared with the older children (10.8%), who were more likely to be seropositive at the time of transplantation.

Most cases of LPD in transplant patients are associated with EBV infection (*11*). In adults, LPD occurs in approximately 1.6% of solid organ transplant patients who have been treated with cyclosporine (*9*). On cyclosporine, the incidences of LPD in pediatric liver transplant recipients in two large series were 4.0% (10 of 253 children in Pittsburgh) and 2.2% (6 of 271 children in Belgium) (*1, 4*). Similar to results from Belgium, we observed a 2.2% (2 of 91 children) incidence of LPD in our children treated with cyclosporine.

In contrast to the Pittsburgh experience, both the Belgium study and our center have observed an increased incidence of LPD in children receiving FK506 (*4, 11*). Reyes et al. from Pittsburgh reported the incidence of LPD on FK506 to be 4.7%, which is similar to their cyclosporine experience (*11*). Reding et al. from Belgium reported LPD in 5 of 23 (21.7%) of children on FK506 after liver transplantation (*4*). We observed an incidence of 13.7% (7 of 51 children) with LPD in pediatric liver recipients on FK506. Since all of our cases of LPD occurred in children who were less than 5 years old, the incidence of LPD in this age group was particularly high ($P<0.02$) for FK506 at 18.9% compared with 2.9% for cyclosporine. A total of 39% (9 of 23 cases) of our <5 yr old children who had symptomatic EBV infections developed LPD and 44% (4 of 9 these) with LPD died.

The most likely explanation for the higher incidence of EBV infections and LPD in our young children on FK506 is that these children may have been relatively more immunosuppressed than the cyclosporine-treated children either prior to converting to FK506 or as a result of the greater immunosuppressive potency of the FK506 than cyclosporine. There was no significant difference in the use of polyclonal and monoclonal antilymphocytic preparations in the cyclosporine and FK506 treatment groups. Since OKT3 and/or other antilymphocytic preparations (MALG/ATGAM) were used in 95.7% of all pediatric liver recipients at our center, their use in 92.5% (25/27 cases) with EBV infections was similar to their use in those who did not have EBV infections. Although the use of these polyclonal and monoclonal antilymphocytic preparations may in part explain the high incidence of EBV infections and LPD in our series, it does not explain why the FK506-treated young-age group had a higher incidence of these complications than our other children.

The level of immunosuppression may have been greater for the FK506-treated patients compared with the cyclosporine-treated patients because (1) FK506 was frequently administered after cyclosporine was used; (2) FK506 is more potent than cyclosporine and, therefore, blood levels appropriate for adults may have been excessive for young children; and (3) a few (3 of 14 EBV-infected children) of the FK506-treated group had been on high doses of immunosuppression for refractory acute or chronic rejection before being switched to FK506. For the majority (44/51) of our patients and the Belgian patients as mentioned above, FK506 therapy was initiated following treatment with cyclosporine. This combination of therapies may have provided a greater risk of EBV infection than if FK506 had been used as the primary therapy. However, EBV infections and LPD occurred in most of our children on FK506 several (10±7 months) months after they had been converted to FK506 from cyclosporine. In addition, after transplantation the levels of immunosuppression for those who developed EBV infections and LPD were similar to those who did not have these complications. Between 3 and 12 months posttransplant there was no difference in blood levels or dosages per kilogram of body weight either for the cyclosporine and FK506 treatment groups with and without symptoms of EBV infection or for the different age groups.

In some cases of EBV infection and LPD, reduction of immunosuppressive therapy results in resolution of the infection and LPD (*24*). There has been limited experience with the use of acyclovir and ganciclovir for EBV infection and chemotherapy for LPD, such that it is unclear whether these drugs are beneficial (*25–26*). The clinical response to ganciclovir may be in part due to treatment of CMV that may also be present in some of these EBV-infected patients. Though we did not isolate CMV from tissue or urine, we found CMV IgM serology positive (titer ≥1:20) in 8 of our 27 patients with EBV infection and 3 of our 9 patients with LPD. By reducing immunosuppression and giving intravenous ganciclovir for 6 weeks, 59% (16 of 27 cases) have had resolution of their LPD and infections with EBV and CMV. In spite of this approach, 4 patients died from the LPD and 5 children have chronic EBV infections.

There is a spectrum of histopathology in LPD, including diffuse polyclonal B cell hyperplasia, polyclonal polymorphic B cell lymphoma, and monoclonal B cell lymphoma (*26–30*). Those patients who have B cell lymphoma are less likely to respond to reduction of immunosuppression and antiviral therapy than those with the more benign diffuse polyclonal polymorphic B cell hyperplasia. All 4 of our deaths (2 on cyclosporine; 2 on FK506) had B cell lymphoma. Of the 5 with LPD who survived, all received FK506; 4 had hyperplasia and only 1 had B cell lymphoma.

The high incidence of EBV infection and LPD in young children calls for a judicious dosage of FK506 and a high index of suspicion in children with upper respiratory symptoms, unexplained fevers, or lymphadenopathy. Due to the high incidence of EBV infections and LPD in young children, we suggest that (1) EBV serology be performed prior to transplantation; (2) immunosuppression, especially FK506, be decreased to the lowest amount without causing rejection; and (3) children who develop symptoms of EBV infection be assessed immediately by checking EBV antibodies, EBV PCR, and/or tissue biopsies with EBNA stain. Future studies should consider limiting exposure of young liver transplant recipients to EBV infection by screening potential donors and excluding those with EBV infections. This may be particularly important for the young liver transplant candidate who is serologically negative for EBV because of the association of LPD with primary EBV infections. Overimmunosuppression remains a major risk factor for developing EBV infections. The most likely explanation for the increased incidence of EBV infections and LPD in our young liver transplant recipients on FK506 was the potency of this drug. Future studies should determine whether lower doses (<0.1 mg/kg/day) of FK506 can be given to these young children without causing rejection, while resulting in a lower incidence of EBV infection and LPD. Early diagnosis of EBV infection and LPD and prompt reduction of immunosuppression should lead to a successful outcome in many patients. In our experience, after lowering immunosuppression and treating with ganciclovir, 59% had resolution of symptoms from EBV infection, and in 27% of the children LPD resolved.

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