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Abstract: Some centers prefer CMV-IVIG over IVIG for the prophylaxis of EBV-related PTLD in solid organ transplant patients. Our objective was to compare the relative dose-related EBV ELISA antibody concentrations and cost of standard IVIG and CMV-IVIG. The concentration of EBV IgG to VCA was analyzed via ELISA in four lots of IVIG and four lots of CMV-IVIG. Relative EBV ELISA antibody concentrations and cost were compared assuming an IVIG dose of 0.5 gm/kg and CMV-IVIG dose of 0.15 gm/kg in a 50-kg patient. The price of IVIG was \$70/gm and CMV-IVIG \$430/gm. IVIG contains the same EBV antibody concentrations (20 790 ELISA antibody units/mL) than CMV-IVIG (17 430 ELISA antibody units/mL, $p > 0.2$) in the four lots of each product sampled. When factoring in the dosing scheme for a 50-kg patient, IVIG contains two times more EBV antibody than CMV-IVIG. Yet, CMV-IVIG is 1.8 times more expensive than IVIG (\$3225 vs. \$1750). In the four lots of each product sampled, IVIG contains more EBV antibodies and costs less than CMV-IVIG when factoring in the dosing scheme. Studies are needed to determine whether there is clinical efficacy of immunoglobulin products for EBV-related PTLD prophylaxis.

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EBV is an important viral pathogen in solid organ transplant recipients (1). In the transplant population, EBV can cause an array of clinical syndromes including PTLD. PTLD has an incidence of 1.7% to 20% in solid organ transplants depending on the type of organ transplanted, the age of the patient, and the pretransplant EBV serostatus of the donor and recipient (1–3).

Given the high morbidity and mortality of PTLD, preventative strategies including minimizing immunosuppression, antivirals, and IVIG products have been used (2).

Some centers that use immunoglobulins for PTLD prophylaxis prefer CMV-IVIG, which is derived from pooled adult human plasma selected for high titers of antibody for CMV, instead of standard IVIG (4, 5). Our objective was to compare the relative dose-related EBV antibody concentrations and cost of standard IVIG and CMV-IVIG.

Materials and methods

ELISA antibody concentrations

We measured the concentration of EBV IgG to VCA in four lots of standard IVIG (Privigen, CSL Behring, King of Prussia, PA, USA) and four lots of CMV-IVIG (Cytogam, CSL Behring) via the EBV VCA IgG ELISA II (Wampole Laboratories, Princeton, NJ, USA) on the DSX automated ELISA system. As a control, we measured the concentration of CMV antibodies in the two immunoglobulin products via the CMV IgG ELISA (Wampole Laboratories) on the DSX automated ELISA system.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence antibody; IVIG, intravenous immunoglobulin; PTLD, post-transplant lymphoproliferative disorder; VCA, viral capsid antigen.

Two-fold dilutions of the standard IVIG and CMV-IVIG samples were carried out, and all lots were run at least in duplicate. The final EBV and CMV antibody concentrations were determined as the geometric mean between the highest positive and clear negative ELISA value. A *t*-test was performed to compare the mean EBV and CMV antibody concentrations in the standard IVIG and CMV-IVIG.

Indirect IFA assay

IFA was performed on some of the standard IVIG and CMV-IVIG lots because it is considered the gold standard for EBV serologic studies (6). Two of the lots of standard IVIG (Privigen, CSL Behring) and two of the lots of CMV-IVIG (Cytogam, CSL Behring) were tested for EBV VCA IgG antibodies by IFA at Focus Laboratories (Cypress, CA, USA).

Comparison of EBV antibody concentrations and cost

We compared EBV ELISA antibody concentrations and cost assuming an IVIG dose of 0.5 gm/kg and CMV-IVIG dose of 0.15 gm/kg in a 50-kg patient (7). We also compared CMV ELISA antibody concentrations assuming the same dosing scheme. We calculated the cost of standard IVIG and CMV-IVIG in a 50-kg patient assuming that the price of IVIG is \$70/gm and CMV-IVIG \$430/gm.

Results

Standard IVIG contains the same EBV VCA antibody concentrations than CMV-IVIG in the four lots of each product tested (20 790 ELISA antibody units/mL vs. 17 430 ELISA antibody units/mL, $p > 0.2$) (Table 1). CMV-IVIG contains 3.3 times the CMV ELISA antibody units than standard IVIG in the four lots of each product tested (63 840 ELISA antibody units/mL vs. 19 110 ELISA antibody units/mL, $p < 0.01$).

Consistent with the ELISA results, the EBV VCA antibody concentrations were the same in the standard IVIG and CMV-IVIG lots that were tested by IFA.

Assuming a 50-kg patient and standardized immunoglobulin doses of 0.5 gm/kg of standard IVIG and 0.15 gm/kg of CMV-IVIG, IVIG contains two times more EBV antibody than

CMV-IVIG (Table 2). Yet, CMV-IVIG is 1.8 times more expensive than IVIG (\$3225 vs. \$1750). Using the same dosing scheme, CMV-IVIG contains two times the CMV antibody compared with standard IVIG.

A 1 gm/kg dose of standard IVIG contains the same amount of CMV ELISA antibody units compared with 0.15 gm/kg CMV-IVIG though is minimally more expensive (\$3500 vs. \$3225, respectively).

Discussion

Although CMV-IVIG is preferred by some centers for EBV-related PTLD prophylaxis in solid organ transplant patients, our data indicate that standard IVIG contains two times more EBV antibodies in the four lots of each product sampled and costs less when factoring in the dosing scheme (Table 2).

Previous animal and human studies have assessed the clinical benefit of immunoglobulins for the prevention of EBV-related disease including PTLD (4, 5, 8–11). The use of immunoglobulin for the prevention of PTLD in solid organ transplant recipients has not shown clear benefit in human studies (4, 5, 8). One multicenter study of pediatric liver transplant patients randomized patients to receive placebo or CMV-IVIG (4). CMV-IVIG was used because unpublished, industry data showed 10- to 100-fold greater EBV antibody titers in this product compared with standard IVIG (4). There was a non-significant trend toward lower EBV-related PTLD after two yr in the CMV-IVIG compared with the placebo group (PTLD-free rate 91% vs. 84%, respectively). Another multicenter study randomized their adult and pediatric solid organ transplant patients who were donor EBV serodiscordant to ganciclovir/placebo or ganciclovir/CMV-IVIG (5). CMV-IVIG was used because there was little lot-to-lot variability in the amount of anti-EBV antibodies (5). Although the study was not powered to detect a difference in PTLD incidence, the three cases of PTLD were in the ganciclovir/CMV-IVIG group.

Table 1. Relative EBV and CMV ELISA antibody concentration of IVIG and CMV-IVIG*

	IVIG	CMV-IVIG	p value
EBV ELISA concentration (antibody units/mL, range)	20 790 (19 110–26 880)	17 430 (13 440–19 110)	>0.2
CMV ELISA concentration (antibody units/mL, range)	19 110 (19 110)	63 840 (53 760–76 020)	<0.01

*The reported antibody concentrations are the geometric mean.

Table 2. EBV and CMV ELISA antibody units and cost of IVIG and CMV-IVIG using standardized doses* in a 50-kg patient

	IVIG	CMV-IVIG
EBV	5 197 500 antibody units	2 614 500 antibody units
CMV	4 777 500 antibody units	9 576 000 antibody units
Cost†	\$1750	\$3225

*Standard doses – IVIG 0.50 gm/kg and CMV-IVIG 0.15 gm/kg.

†Cost – assumes standard doses in a 50-kg patient.

Multiple factors could impact the results of prior studies evaluating the efficacy of immunoglobulins for PTLD prophylaxis including small sample sizes and the preferential use of CMV-IVIG for prophylaxis. Our data suggest that standard IVIG may be better suited for future PTLD prevention studies given that, in the lots sampled in this study, this product contains more EBV antibodies than the CMV-IVIG when factoring in the dosing scheme. Additional studies are needed to determine whether there is clinical efficacy of immunoglobulins, the relative efficacy and the specific components that may be beneficial in the two immunoglobulin products, and the most appropriate dosing regimen for EBV-related PTLD prophylaxis.

An important limitation of our study is that only one commercial brand of IVIG was used. Additionally, the EBV antibody levels were only measured in four lots each of IVIG and CMV-IVIG. However, the consistency in EBV antibody levels across the four lots of each product is reassuring. Future PTLD prophylaxis studies should account for possible variability in EBV antibody concentrations by immunoglobulin manufacturer and possibly by lot. The cost comparison between standard IVIG and CMV-IVIG was based on one dose of each product. The cost differential of standard IVIG and CMV-IVIG would likely be larger if the multiple dose regimens used in some studies were incorporated (4, 5).

Our data suggest that in the four lots of each product sampled, standard IVIG contains two times more EBV antibodies than CMV-IVIG when used at standard dosing and is less expensive. Although the benefit of immunoglobulins for PTLD prevention is unclear, when used, standard IVIG should be used preferentially over CMV-IVIG. More studies are needed to determine whether there is clinical efficacy of immunoglobulins for PTLD prophylaxis.

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Authors' contributions

JC performed concept/design. LR, OG, and JC carried out data analysis/interpretation. LR drafted the article. LR, OG, and JC carried out the critical revision of the article. LR, OG, and JC approved the article. OG performed data collection and sample.

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