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Late Cytomegalovirus Transmission and Impact of T-Depletion in Clinical Islet Transplantation

B. L. Gala-Lopez[a], P. A. Senior[a,b], A. Koh[a,b], S. M. Kashkoush[a], T. Kawahara[a], T. Kin[a], A. Humar[b,†] and A. M. J. Shapiro[a,*,†]

[a] *Clinical Islet Transplant Program, University of Alberta, Edmonton, Alberta, Canada*
[b] *Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*
**Corresponding author: A. M. James Shapiro, amjs@islet.ca*
†*Both authors have joint senior authorship.*

The epidemiology of cytomegalovirus infection (CMV) in islet transplantation (IT) is not well defined. This study defines incidence, transmission and clinical sequelae of CMV reactivation or disease in 121 patients receiving 266 islet infusions at a single institution. The donor (D)/recipient (R) serostatus was D+/R– 31.2%, D+/R+ 26.3%, D–/R+ 13.2% and D–/R– 29.3%. CMV prophylaxis with oral ganciclovir/valganciclovir was given in 68%. CMV infection occurred in 14/121 patients (11.6%); six had asymptomatic seroconversion and eight others had positive viremia (six asymptomatic and two with CMV febrile symptoms). Median peak viral loads were 1755 copies/mL (range 625–9 100 000). Risk factors for viremia included lymphocyte depletion (thymoglobulin or alemtuzumab, $p < 0.001$). Viremia was more common in D+/R+ versus D+/R– ($p = 0.12$), occurring mostly late after transplant (median 306 days). Presumed transmission from IT occurred in 8/83 of D+/R– procedures (9.6%). Of the two cases of CMV disease, one resulted from islet transmission from a CMV positive donor (D+/R–); the other was due to *de novo* exogenous infection (D–/R–). Therefore, CMV transmission presents rarely after IT and with low incidence compared to solid organ transplantation, but occurs late posttransplant. The use of lymphocyte depleting therapies is a primary risk factor.

Key words: Cytomegalovirus, immunosuppression, islet transplant, prophylaxis

Abbreviations: Alemtu, alemtuzumab; ALG, antilymphocyte globulin; ANOVA, analysis of variance; Basilix, basiliximab; cGMP, good manufacturing practice; CIT, Collaborative Islet Transplant Network; CMV, cytomegalovirus; d, days; D, donor; Dacliz, daclizumab; DM, diabetes mellitus; F, female; Immunosupp, immunosuppression; Inflix, infliximab; IT, islet transplant; M, male; MMF, mycophenolate mofetil; MTF, mammalian tissue-free; PCR, polymerase chain reaction; R, recipient; SIK, simultaneous islet-kidney transplant; SPK, simultaneous pancreas-kidney transplant; SE, standard error; TAC, tacrolimus; Thymo, thymoglobulin; Tx, transplants.

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Introduction

Solitary islet transplantation (IT) has become an accepted modality to stabilize frequent hypoglycemias or severe glycemic lability in highly selected patients with poor diabetic control, resistant to standard, intensive or insulin-pump based therapies (1,2). In IT, the epidemiology of cytomegalovirus (CMV) infection including incidence of transmission, viremia and symptomatic diseases has not been well characterized. In small case series, it has generally been reported as an infrequent occurrence, and only rarely associated with tissue-invasive disease (3,4). However, CMV is a frequent infection in solid organ transplantation, and accounts for significant morbidity and may result in organ-specific effects, such as CMV pneumonitis hepatitis, encephalitis and gastrointestinal disease (5,6). In solid organ transplantation, CMV is commonly transmitted from seropositive organ donors (Ds) to seronegative recipients (Rs), despite the use of antiviral prophylaxis (7). Many demographic and clinical factors predispose to the development of CMV disease. The most important risk factor is the D–R CMV serostatus. In the absence of prophylaxis, the incidence of CMV disease is highest (50–75%) after transplantation of an organ from a CMV-seropositive donor (D+) to a CMV-seronegative recipient (R–; 5–7). A second major risk factor is the type of immunosuppression used to prevent or treat graft rejection in solid organ transplantation. The impact of potent immunosuppressive regimen on CMV infection is well documented, especially with use of lymphocyte-depleting antibodies for induction (5,8).

Although CMV seems to be uncommon after islet-alone transplantation, few studies have examined this systematically or with sufficient numbers of transplants (Tx) for definitive interpretation. Previous reports have been case reports or small series (4,9–14). Several reasons previously postulated for decreased risk of CMV transmission and reactivation observed in IT include the small volume of tissue with low number of contaminating passenger leukocytes

transplanted, and, therefore, low-viral load transmitted, as well as corticosteroid-free immunosuppressive regimens combined with effective CMV prophylaxis (10,11).

Our goal in this study was to evaluate the epidemiology of CMV infection and disease in a large series of type 1 diabetes mellitus (DM) patients undergoing islet-alone transplantation over a period of more than 11 years at a single center at the University of Alberta. We review risk factors for viral transmission and/or reactivation, including the serological status of Ds and Rs before transplantation and the impact of different T-cell directed induction protocols.

Materials and Methods

Patients

Between March 1999 and August 2010, the clinical islet program in Edmonton has carried out 281 IT procedures in 129 patients with type 1 DM under a series of evolving induction and maintenance immunosuppressive protocols. Patients received a median of two procedures (range 1–4). Four patients were excluded from the current analysis as they were recipients of islet-after-kidney Tx (and enrolled in a National Institutes of Health [NIH] clinical consortium trial, CIT-07) and four other patients who are part of CIT-04, a trial with the NIH using belatacept induction were also excluded from this analysis, as both trials are ongoing. Thus, the study population consisted of 121 patients receiving 266 IT procedures, with a female/male ratio of 67/54. All patients underwent complete pre-Tx evaluation including CMV serology. Informed consent was obtained, and ethical approval for this study was covered under protocol 1120, approved by the health research ethics board at the University of Alberta, and by Health Canada under clinical trial agreements NCT00014911, NCT00175253, NCT00175266, NCT00434811 and NCT00468403, as registered with ClinicalTrials.gov.

Transplant procedures

Islets were prepared as previously described, using a modified Ricordi protocol (3,15–17). In brief, human deceased donor pancreata were recovered from 272 deceased donors and transported to the good manufacturing practice (cGMP) grade clinical islet isolation laboratory. Upon arrival, the pancreatic duct was cannulated and collagenase blend enzyme preparations were perfused transductally (Serva Collagenase NB1, Crescent Pharmaceuticals, Islandia, NY, USA); Liberase HI, or more recently mammalian tissue-free (MTF) enzyme, Roche Diagnostics Corporation, Indianapolis, IN, USA; Ref. 18). The pancreas was enzymatically and mechanically dissociated in a Ricordi chamber and then purified on a refrigerated Cobe 2991 centrifuge (Cobe BCT, Lakewood, CO, USA) with continuous gradient separation with Ficoll™ (Sigma-Aldrich, St. Louis, MO, USA) or more recently Biocoll separating solution™ (Biochrom AG, Cedarlane, Burlington, Ontario, Canada; Ref. 19). The majority of the islet preparations were placed in culture (median 13.0 h, range 6.4–23.0) before infusion to facilitate timing of islet infusion or as part of the immunosuppressive protocol. Patients then underwent percutaneous transhepatic portal access in the radiology department under local anesthesia and with fluroscopic and ultrasonic guidance, and islets were infused under gravity pressure from a 250-mL medium-containing intravenous islet bag (20). Portal pressure was monitored during and after infusion and at the end to minimize the risk of bleeding, the catheter tract was ablated.

Immunosuppression protocols

Induction and maintenance immunosuppressive protocols have evolved in our program over time. Initially, our practice was to induce with an interleukin-2 receptor monoclonal antibody (IL-2R mAB; daclizumab [Dacliz] 2 mg/kg intravenously at Tx and at 5 days post-Tx), combined with tacrolimus (TAC) for a target trough level of 3–6 ng/mL and sirolimus for target trough levels of 12–15 ng/mL for the first 90 days and 8–10 ng/mL thereafter (the "Edmonton Protocol" [16]). Subsequently, basiliximab (Basilix; 20 mg intravenous on day 0 and 4) has been used in place of Dacliz, with the combination of TAC (target trough level of 8–10 ng/mL) and mofetil mycophenolate (MMF; up to 2 g daily in divided dose as tolerated). Before 2003, Dacliz was given at a dose of 1 mg/kg every 2 weeks for five doses (3).

Other protocols included the use of infliximab (Inflix; 10 mg/kg) given at the time of Tx, combined with Dacliz; alternative use of Basilix (two doses of 20 mg), etanercept (50 mg weekly) or most recently potent lymphocyte depletion protocols based on alemtuzumab (Alemtu) or thymoglobulin (Thymo). Patients were stratified in the following groups according the induction protocol for analytical purposes: Thymo-based, Alemtu-based and anti IL-2R mAb group.

CMV assays and antiviral treatment

All patients and donors were assessed serologically before Tx. Serology testing for anti-CMV immunoglobulins G (IgG) and immunoglobulins M (IgM) was performed on pre-Tx serum samples using the Abbott AxSYMTM enzyme immunoassay (Abbott Laboratories Ltd., Abbott Park, IL, USA) as per manufacturer's instructions. Plasma CMV load was assessed using an in-house, real-time polymerase chain reaction (PCR) assay weekly for 3 months, every 2 weeks up to 6 months, monthly up to 12 months and then at different frequencies depending on the exposure, the use of antilymphocyte antibodies and the occurrence of seroconversion, viremia or disease. The lower limit of quantification for this assay is 500 copies/mL.

Patients received either antiviral prophylaxis or were managed using and preemptive therapy strategy depending on the D/R serostatus and the use of induction therapy (21). For D+/R– procedures, or for R+ patients who received antilymphocyte globulin (ALG) induction, antiviral prophylaxis was given as described below. For R+ patients who did not receive ALG induction, weekly CMV PCR was performed for 3 months and antiviral therapy administered for viremic patients. For prophylaxis, antiviral drugs included ganciclovir 1000 mg three times a day or since 2004, once available on the hospital/provincial formulary, valganciclovir 900 mg once a day, given orally for 3 months.

Graft function

In addition to standing graft function determination based on insulin requirement, glycemic control, hemoglobin A1C, protection from hypoglycemia, and fasting C-peptide testing, more definitive stimulated C-peptide levels were obtained at the time of mixed meal tolerance testing scheduled at intervals posttransplant (3 months for 1 year, then 6 months thereafter).

Statistical analysis

Results are expressed as means ± standard error (SE) or the median (25th–75th confidence interval range) as appropriate. Comparisons were made with a two-tailed Student's *t*-test, paired or unpaired as appropriate. For group comparisons, one-way repeated-measures analysis of variance test (ANOVA) was used and the Holm–Sidak or Dunn test used when normality tests failed. Lymphocyte count and C-peptide assays were correlated with CMV viral loads using the Pearson's test. Graft survival analysis was performed using Kaplan–Meier with log-rank test to compare differences between groups. All statistical analyses were performed using SPSS version 12.0 (Chicago, IL, USA). Significance was considered when $p < 0.05$.

Results

Patient population

Of 121 patients, 47 (38%) were seropositive for CMV before transplantation. This prevalence is significantly lower compared to one observed in D population from this study (58%, p = 0.02). There was a significantly higher prevalence of pretransplant CMV positive serology among female patients 27 of 67 (40.3%) compared to that observed in males diabetic patients (20/54, 37%, p = 0.039). All patients received a median of two Tx (range 1–4) with a mean of 170.6 days interval between the first and second procedure.

Induction protocols were mainly based on anti IL-2 treatment 176 of 266 (66.2%). Other protocols included Thymo-based treatments in 42 of 266 (15.8%) and Alemtu-based in 48 of 266 Tx (18%).

CMV transmission, reactivation or disease

CMV exposure during D/R pairing was analyzed both by first transplant and by total transplant procedures. The CMV status of the D/R pair at first transplant was: 35 of 121 D–/R– (29.0%), 39 of 121 D+/R– (32.2%), 17 of 121 D–/R+ (14.0%) and 30 of 121 D+/R+ (24.8%). When analyzing by transplant procedure (n = 266) the exposure rate showed a similar distribution: D–/R–: 29.3% (n = 78); D+/R–: 31.2% (n = 83); D–/R+: 13.2% (n = 35); and D+/R+: 26.3% (n = 70; summarized in Figure 1).

CMV prophylaxis was used in 181 of 266 (68%) Tx according to the criteria explained. For 98 procedures, patients received oral ganciclovir (54.1%) whereas for 79 of 181 (43.6%) procedures, patients received oral valganciclovir (since 2004). The median duration of prophylaxis was 90 days.

Six patients (4.9%) developed seroconversion (negative to positive) during the study period without detectable CMV DNA or clinical disease. Table 1 summarizes the characteristics of these patients. CMV viremia was detected in 8 of 121 patients (6.6%). Seven of those patients had received a D+ graft at some point (7/105, 6.7%), compared with 1 of 20 patients (5%) receiving seronegative islets (p = 0.06). However, CMV viremia occurred more commonly in D+/R+ (5/50, 10%), compared to D+/R– (3/75, 4%); although this difference was not significant (p = 0.12). Median peak viral loads in these patients were 1755 copies/mL (range 625–9 100 000).

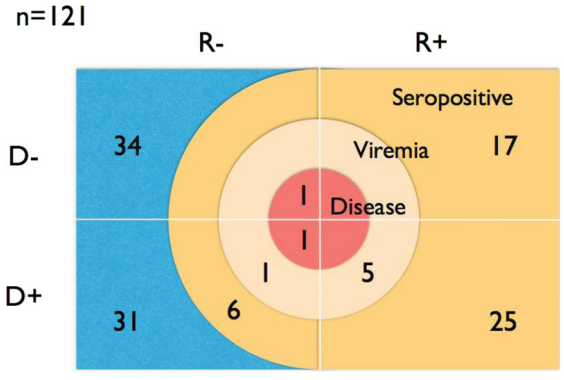

Figure 1: Summary of CMV seroconversion, viremia and disease in 121 patients undergoing islet-alone transplantation at a single institution. D = donor; R = recipient.

CMV infection occurred despite the use of prophylactic treatment, and the timing of this transmission was surprisingly late, irrespective of the type of induction therapy (median 306 days posttransplant, range 29–2340 days). Half of the patients with seroconversion received antiviral treatment and the other half did not (3/6 vs. 3/6); and in the case of patients with positive viremia, all had received viral prophylaxis.

Two patients from the total population developed clinical disease during follow-up, one in a D+/R– patient and another in a D–/R– patient from presumed exogenous exposure. Table 2 shows detailed information of the eight patients who had a positive CMV viremia during the study period, including the two patients who experienced disease. All patients with CMV infection received extended antiviral treatment with duration determined by clinical and virological response.

Three different induction therapies were compared with regard to the CMV infection and it was present in all groups. Infection presented in 5 of 42 (11.9%) of Tx induced with Thymo-based protocols, in 5 of 48 Tx treated with Alemtu-based therapy (10.4%) and in 4 of 176 (2.3%) Tx induced using anti IL-2 drugs (p = 0.05). When correlating induction treatment with occurrence of CMV viremia, a strong association is found, both in Thymo-based (4/8) and Alemtu-based groups (4/8), but not in patients receiving IL-2 induction (Figure 2, p < 0.001).

The degree of early T depletion measured by absolute lymphocyte count failed to correlate with peak CMV viremia in viremic patients (r = 0.064, p = 0.30, Figure 3). Furthermore, we analyzed the possible impact of CMV infection on long-term islet graft function assessed by loss of stimulated C-peptide over time (Figure 4). The analysis demonstrated a striking (but statistically insignificant, p = 0.15) negative impact of CMV infection upon long-term islet graft survival, with loss of stimulated C-peptide over time. Mean C-peptide survival was 115.8 months in patients with no CMV infection (n = 121) versus 84.7 months in those with CMV infection (n = 14).

Discussion

This study demonstrates a small but significant risk of CMV infection and disease in type 1 DM patients undergoing

Table 1: Summary of CMV seroconversion after islet transplant

No.	Sex	Total Txs	CMV exposure	Induction protocol	Maintenance immunosupp.	Prophylactic treatment	Time to seroconversion	Disease details
1	F	2	D+/R–	Dacliz + Inflix	TAC + SRL	Ganciclovir (117 days)	1080 days after 2nd Tx	No disease
			D+/R–	Dacliz + Inflix	TAC + MMF	Ganciclovir (138 days)		
2	F	3	D–/R–	Daclizumab	TAC + SRL	Ganciclovir (75 days)	2340 days after 3rd Tx	
			D+/R–	Daclizumab	TAC + SRL			No disease
			D+/R–	Daclizumab	TAC + SRL	–		
3	F	2	D+/R–	Alemtu + Inflix	TAC + SRL	Ganciclovir (177 days)	1290 days after 2nd Tx	No disease
			D–/R–	Alemtu + Inflix	TAC + MMF	–		
4	M	1	D+/R–	Thymo + Etanercept	TAC + SRL	Valganciclovir (98 days)	420 days after Tx	No disease
5	F	2	D–/R–	Dacliz + Inflix	TAC + SRL	Ganciclovir (110 days)	1310 days after 2nd Tx	No disease
			D+/R–	Dacliz + Inflix	TAC + SRL	Ganciclovir (92 days)		
6	F	2	D+/R–	Dacliz + Inflix	TAC + SRL	Ganciclovir (90 days)	180 days after 2nd Tx	No disease
			D–/R–	Dacliz + Inflix	TAC + SRL	–		

CMV = cytomegalovirus; Tx = transplant; M = male; F = female; D = donor; R = recipient; Dacliz = daclizumab; Inflix = infliximab; TAC = tacrolimus; SRL = sirolimus; MMF = mycophenolate mofetil; Alemtu = alemtuzumab; Thymo = thymoglobulin.

islet-alone transplantation, and that this risk is further increased in patients receiving T-depletional induction therapies. The trade-off between potent T-depletional induction with more optimal control of both allo- and autoimmunity and a small increased risk of CMV infection seems to be reasonably justified. We previously reported an absence of CMV infection where IL-2 receptor blocking antibodies were used (7,9,15). It was previously argued that the risk of transmission in IT was low because the amount of donor tissue and number of passenger leukocytes is dramatically lower than in all other solid organ Tx, resulting in an insufficient viral load to trigger transmission or disease (10,12). As such, we found only two previous reports of CMV infection in limited case series. Cure et al. from the Miami group (9) reported one seroconversion and one clinical disease in 29 patients using Edmonton-like immunosuppression protocol. Yakubovich et al. reported three patients with CMV disease after solitary IT, where T-cell depleting induction was used in 23 cases (12).

In concordance with previous studies, we have observed a lower frequency of seropositivity in patients with type 1 diabetes undergoing IT (4,11,15) than in the general population/donor population. This observation is intriguing but

Table 2: Characteristics of eight patients developing CMV viremia after islet transplant

No.	Sex	CMV status preTx	Total Txs	CMV exposure	Induction protocol	Maintenance immunosupp.	Prophylactic treatment	Onset of viremia	Peak DNA (Copies/mL)	Disease details
1	M	Positive	2	D+/R+	Thymo + Etanercept	TAC + MMF	Valganciclovir (156 d)	137 d	915	No disease
				D+/R+	Thymo + Etanercept	TAC + MMF	Aciclovir (32 d)	–	–	
2	F	Positive	2	D+/R+	Daclizumab	TAC + SRL	Ganciclovir (78 d)	–	–	No disease
				D–/R+	Thymo + Etanercept	TAC + MMF	Valganciclovir (100 d)	151 d	625	
3	F	Negative	2	D–/R–	Daclizumab	TAC + SRL	No	1951 d	9 100 000	Headaches, generalized weakness, fever. Seroconversion at time of disease
				D–/R–	Thymo	TAC + MMF	Valganciclovir (103 d)			
4	F	Positive	2	D+/R+	Alemtuzumab	TAC + MMF	Valganciclovir (186 d)	–	–	No disease
				D+/R+	Alemtuzumab	TAC + MMF		161 d	1000	
5	M	Positive	2	D+/R+	Thymo + Etanercept	TAC + SRL	Valganciclovir (95 d)	144 d	5650	No disease
				D–/R+	Basilixi + Etanercept	TAC + SRL	Valganciclovir (30 d)	–	–	
6	F	Negative	2	D–/R–	Alemtuzumab	TAC + MMF	Valganciclovir (101 d)	–	–	No disease
				D+/R–	Alemtuzumab	TAC + MMF	Valganciclovir (183 d)	193 d	1 805 000	
7	M	Negative	2	D+/R–	Alemtuzumab	TAC + MMF	Valganciclovir (114 d)			Flu-like symptoms during H1N1 epidemic. Treated with Valganciclovir + Oselta-mivir
				D–/R–	Alemtuzumab	TAC + MMF	No	709 d	1375	
8	M	Positive	2	D–/R+	Alemtuzumab	TAC + MMF	No	–	–	No disease
				D+/R+	Alemtuzumab + Etanercept	TAC + MMF	Valganciclovir (120 d)	29 d	2135	

CMV = cytomegalovirus; Tx = transplant; immunosupp, immunosuppression; M = male; F = female; D = donor; R = recipient; d = days; TAC = tacrolimus; SRL = sirolimus; MMF = mycophenolate mofetil; Thymo = thymoglobulin; Basilixi = basiliximab.

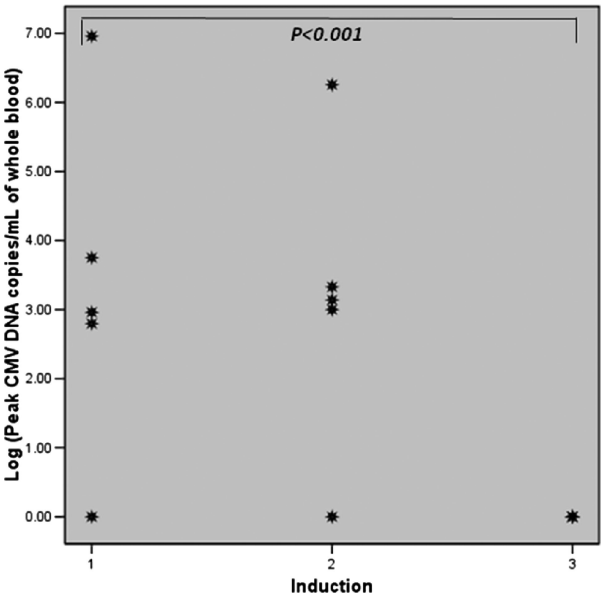

Figure 2: Peak CMV viral loads grouped by initial induction protocol. (A) Thymoglobulin group, (B) Alemtuzumab group and (C) Anti-IL-2 receptor monoclonal antibody group ($p < 0.001$ for both the thymoglobulin and alemtuzumab groups vs. anti-IL2 mAb group).

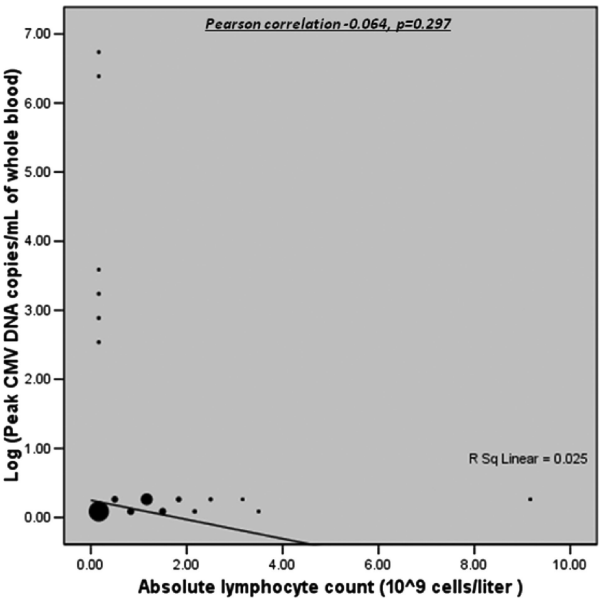

Figure 3: Absence of correlation between absolute lymphocyte count postinduction and peak CMV viral load. All patients were compared by the Pearson's test ($r = –0.064$, $p = 0.297$).

incompletely understood, and may possibly relate to a failure to generate CMV antibodies in the diabetic state, or modulation of immunological response. There is a correlation between the CMV genome and islet cell autoantibodies detected in patients with diabetes, and in a subpopulation of cases, CMV infection has been linked to the pathogenesis of type 1 diabetes (22). This phenomenon has also been reported in simultaneous pancreas–kidney and islet-kidney transplant recipients (SPK and SIK) (10,23).

In this study, we found that the highest risk of CMV infection was from D+ islets infused into R–, but that consequences were limited to seroconversion without significant viremia or clinical disease. Of the eight patients with viremia, only two developed CMV disease, one of which was likely community-acquired as both Tx were D–/R–, and the CMV disease occurred quite remotely, 6 years after the last transplant. It is likely that the T-depletional therapy contributed to the development of CMV disease in these two cases. However, the timing of late occurrence (median 305 days, with a range extending to 2340 days), well outside of the period of initial CMV prophylaxis, may reflect the heavy chronic maintenance immunosuppression given to these islet patients to suppress both allo- and autoimmune events long term.

The relationship between CMV infection and both humoral and cellular autoimmunity to islet antigens has been highlighted by several authors, and may play a role in accelerated autoimmune recurrence in whole pancreas transplantation (24,25). The loss of C-peptide secretion in IT patients following CMV infection has also been observed previously (26). In this study, we have observed a striking but statistically nonsignificant relationship between incidence of CMV infection and long-term loss of C-peptide islet graft function. Although the results do not reach statistical significance based on the limited numbers of patients with CMV infection compared to noninfection controls, the findings are concerning that CMV infection may indeed have long-term deleterious effects on islet graft function. A larger multicenter study would be better powered to define a statistical relationship based on larger numbers if CMV infections. The findings remain consistent with previous concerns that CMV infection may augment immunological responsiveness that may be sufficient to destabilize the islet allograft. Because complete loss of islet graft function is deleterious to the individual, both through return of glycemic lability and hypoglycemia and risk of broad HLA-sensitization, adequate prophylaxis to prevent CMV infection remains of considerable importance.

Finally, the use of T-cell-depleting agents has been associated with an increased risk of CMV transmission in solid organ transplant (8,27). A similar finding has been demonstrated in cynomolgus monkeys receiving IT under intensive Thymo and fludarabine-based immunosuppression (28). This clinical islet study includes a large proportion of patients (32.8%) receiving T-depletional therapy with Thymo or Alemtu. As in previous reports, lymphocyte

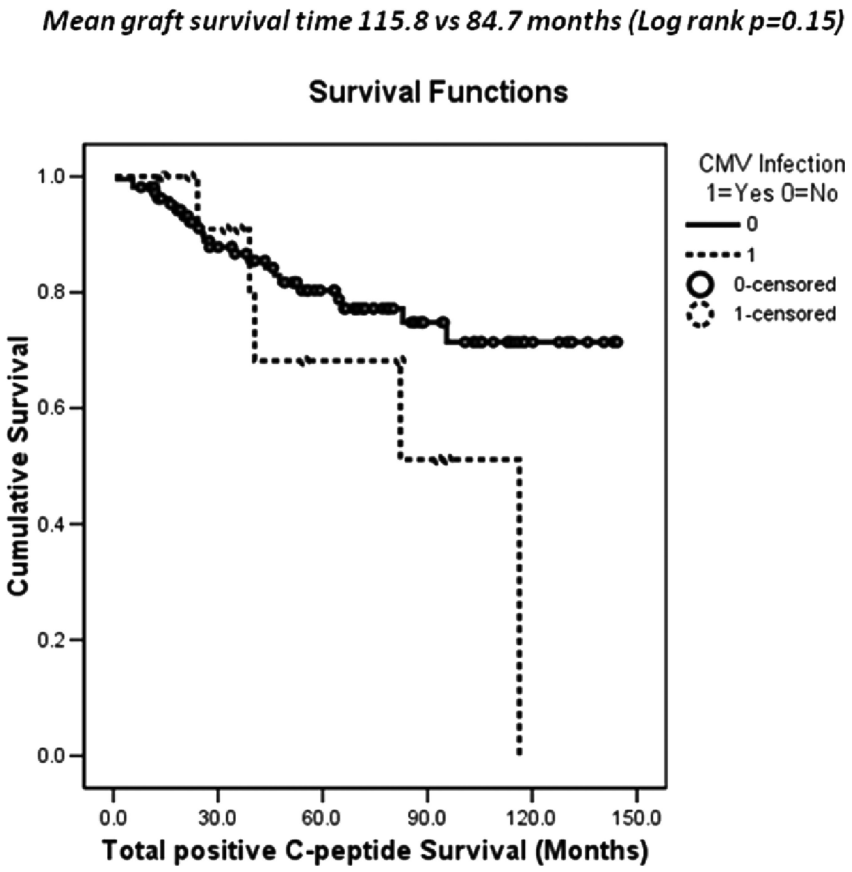

Figure 4: C-peptide Graft survival and impact of CMV infection. Kaplan–Meier graft survival for n = 121 islet-alone patients without CMV infection versus n = 14 with CMV infection (Log-rank p = 0.15, mean C-peptide survival 115.8 months with no CMV infection vs. 84.7 months with CMV infection).

depletional induction is a principle risk factor for CMV viremia. It is unclear from the current islet data whether the cases of CMV-DNAemia originated from donor transmission or reactivation despite effective CMV antiviral prophylaxis. It is clear from this study of a relatively large cohort of islet Rs that where CMV prophylaxis is given, despite seroconversion, the incidence of CMV disease is extremely rare (2/266 Tx, 0.75%). Therefore, we can conclude that effective CMV prophylaxis with valganciclovir modulates the risk of CMV disease in our T-depleted islet-alone transplant population, and thereby, helps to prevent destabilization of islet graft function. Although potent T-depletional therapies are associated with an increased risk of CMV transmission in IT, these are of minimal clinical consequence provided potent CMV prophylaxis is given routinely. This small risk is outweighed by emerging evidence that potent T-depletion results in more sustained and longer term insulin independence, with more effective control of both allo- and autoimmunity, as reflected in current data from the clinical islet transplant registry (29). A tradeoff between increased risk of mild and nondebilitating opportunistic infection and substantially increased durability of insulin-independent islet graft function is currently accepted as a reasonable and appropriate tradeoff, but it remains to be seen whether a small subset developing CMV infection in the background of T-depletion will lose graft longevity. Wherever potent T-depletional induction therapy is used in IT, effective CMV prophylaxis is strongly recommended, irrespective of D or R CMV status, along with careful clinical and laboratory follow up if the risks associated with CMV transmission are to be minimized.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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