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SHORT COMMUNICATION

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Acquired hypogammaglobulinemia and pathogen-specific antibody depletion after solid organ transplantation in human immunodeficiency virus infection: A brief report

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Abstract

Hypogammaglobulinemia (HGG) frequently occurs in recipients after types of (SOT). The incidence and significance of HGG in HIV+ recipients of SOT are just being explored. We reported that 12% of the recipients in the SOT in multi-center HIV-TR (HIV-TR) Study developed moderate or severe HGG at 1 year. In LT recipients, this was associated with serious infections and death. We have now further characterized the decreased antibodies in HIV+ SOT recipients who developed HGG. We measured the levels of pathogen-specific antibodies and poly-specific self-reactive antibodies (PSA) in relation to total IgG levels from serial serum samples for 20 HIV+ SOT recipients who developed moderate to severe HGG following SOT. Serum antibody levels to measles, tetanus toxoid, and HIV-1 were determined by EIA. Levels of PSAs were determined by incubating control lymphocytes with patient serum, staining with anti-human IgG Fab-FITC, and analysis by flow cytometry. Levels of PSA were higher compared to healthy, HIV-uninfected controls at pre-transplant baseline and increased by weeks 12 and 26, but the changes were not significant. Likewise, anti-HIV antibody levels remained unchanged over time. In contrast, antibody levels against measles and tetanus were significantly reduced from baseline by week 12, and did not return to baseline, even after 2 years. For HIV patients who develop moderate to severe HGG after transplant, the reduction in IgG levels is associated with a significant decrease in pathogen-specific antibody titers, while PSA levels and anti-HIV antibodies are unchanged. This may contribute to infectious complications and other clinical endpoints.

KEYWORDS
HIV, pathogen-specific antibody, solid organ transplantation

1 | BACKGROUND

Solid organ transplantation (SOT) is a modality to treat end-organ failure, but outcomes are still suboptimal due to the incidence of infection and rejection.[1] Hypogammaglobulinemia (HGG) is a common immune deficit that occurs after all types of solid organ transplants that can significantly increase the risk of infection.[2-10] Exact definitions of moderate and severe HGG vary, but the incidence of moderate to severe HGG occurs in up to 16% and 46% of patients, respectively. Numerous studies have shown excess morbidity and mortality, including infections, in organ recipients that develop HGG. Although most studies only report on total IgG levels,

pathogen-specific antibodies are very likely important in the pathogenesis of certain infections. Solid organ transplant recipients have reduced antibody titers in response to vaccines post-transplant that are attributed to the effects of immunosuppression.[11,12] For this reason, it is recommended to complete all recommended vaccines prior to transplant, although this is not always feasible due to acute illness prior to transplantation.[13] In these ill populations, responses may also be lower than that seen for controls pre-transplant. Furthermore, even with pre-transplant vaccination, pathogen-specific antibodies can be lost, although the risk factors for this antibody loss and reverse seroconversion are unknown.[14,15]

More solid organ transplants are being performed in HIV-infected individuals with end-organ failure, particularly renal failure and liver failure, but also severe heart failure. Even less is known about pathogen-specific antibody titers after SOT, but there are reasons to believe there may be differences in humoral immune responses in HIV patients. It is important to learn about immune function post-transplant in this expanding population. Although HGG occurs relatively frequently after solid organ transplantation in patient who are not infected with HIV infection, the incidence and significance of HGG in HIV patient undergoing solid organ transplantation is just being explored. There also may be unique aspects to HGG in HIV infection as patients with HIV infection have a number of B-cell defects.[16-22] HIV-infected patients exhibit polyclonal B-cell activation and polyclonal hypergammaglobulinemia, but decreased B-cell lymphoproliferative responses to mitogens.[16-21] Much of this is due to anti-HIV antibody production as part of the host response to this chronic infection. This occurs with other chronic viral infections such as HBV and HCV as well.[19] Production of poly-specific self-reactive antibodies occurs, however, as part of the immune dysregulation observed in HIV infection.[18,19] Despite the high IgG levels, patients with HIV also exhibit loss of memory B-cell subsets, B-cell exhaustion, and aberrant B-cell phenotype.[19-21] There is also a reduced pathogen-specific antibody production, both in response to infection and vaccination.[22] Levels of antibodies to measles and tetanus are lower compared to healthy controls, associated with a reduction in memory B cells.[18] In vivo antibody responses to vaccination with polysaccharide and protein antigens are also impaired.[22]

We have previously reported that 8/79 (10.1%, cumulative 1 year Kaplan-Meier estimate 12%) of the liver transplant recipients in the multi-center HIV-TR study of HIV-infected individuals developed moderate to severe HGG as indicted by total IgG levels by 1 year.[23] There was a strong association between an IgG < 500 mg/dL and increased risk of non-opportunistic infections (non-OI) and mortality. The hazard ratio was 3.5 for non-OI infection, 95% confidence internal 1.1-10.6 (P = .03). The hazard ratio for mortality was 3.2, 95% CI 1.1-9.4 (P = .04).

The purpose of the current study was to further characterize the antibody deficiencies for the HIV-infected liver and kidney transplant recipients who developed moderate to severe HGG by examining the levels of poly-specific self-reactive antibodies (PSA), anti-HIV antibodies, and pathogen-specific antibodies to measles and tetanus. We hypothesized pathogen-specific antibody levels were reduced post-transplant in this population, and this would explain the increased risk of non-OI infections and mortality identified in our previous study. Our results showed that HGG was associated with decreases in pathogen-specific antibodies to measles and tetanus, but not with decreases in anti-HIV antibodies or PSA.

2 | METHODS

2.1 | Study design

We conducted a post hoc analysis of HGG and specific antibody titers for prospectively collected serum samples from the HIV-TR study.[24,25] Full inclusions and exclusion criteria for HIV-TR have been previously published. The study enrolled 275 subjects, 150 kidney transplant (KT), and 125 liver transplant (LT) recipients with HIV-1 infection. Induction immunosuppression with an interleukin-2-receptor blocker, thymoglobulin, or both was not required, but could be used at the discretion of the transplant team. All patients received corticosteroids and a calcineurin inhibitor, with or without mycophenolate mofetil (MMF). We proposed to examine acquired hypogammaglobulinemia in this study cohort.[23] There were 34 cases with no pre-transplant IgG level and 28 cases without a post-transplant IgG level. Two LT patients had HGG pre-transplant and were excluded from that analysis. Serial serum samples were available from 113 KT patients and 79 LT recipients (including four combined LT/KT). Serum samples were stored at −70°C until assays were performed.

2.2 | Subjects

All patients were part of the SOT in HIV: multi-site study (ClinicalTrials.gov number NCT00074386. Institutional Review Board approval of our antibody studies was granted by the University of Chicago Medicine.

Serial serum samples were collected at predefined time points (pre-transplant, week 12, week 26, week 52, and year 2) and stored for 113 KT and LT recipients (including four kidney-liver recipients) in the study. IgG levels for sequential samples had already been determined in our prior study, excluding patients who had HGG prior to transplantation. Patients were classified as having moderate HGG if they had a nadir IgG level of 350-500 ng/mL or severe HGG if nadir < 350 ng/mL. IgG levels above 500 ng/mL were considered normal or mild HGG. In addition to the data reported on the LT patients, there were 12/113 (10.6%) of KT recipients developed moderate to severe HGG (cumulative 1 year Kaplan-Meier estimate of 12%), but there were no deaths and the relative risk of infection was not statistically significant (hazard ratio 1.9, 95% CI 0.7-5.4, P = .23; unpublished data).

For those 20 HIV-infected SOT recipients (8 liver and 12 renal) who developed moderate to severe HGG following transplantation, we measured the levels of different types of antibodies in prospectively collected, serial serum samples. We looked at specific antibodies to tetanus and measles, the level of anti-HIV antibodies, and poly-specific self-reactive antibodies (PSA) in relation to total IgG

levels. We chose to look at measles since most individuals have pre-existing antibodies due to natural infection or vaccination and tetanus since most individuals have been vaccinated, and titers would not depend on recent vaccine status. Furthermore, a number of previous studies of humoral immune defects in HIV have reported on antibody titers to these pathogens.[18]

2.3 | Assays

Quantitative IgG levels were determined using the Roche IgG-s Tina-quant platform (Roche Diagnostics). Serum antibody levels to HIV, measles, and tetanus toxoid were measured using commercially available EIA kits (HIV-1,2, gp36, gp41 ELISA Kit H6008-95G, Bioassay, US Biological); measles IgG ELISA kit # 530-100-HMG; and tetanus toxoid IgG ELISA kit # 930-100-TTH, Alpha Diagnostic International;. All samples were run in duplicate.

Serum levels of poly-specific self-reactive antibodies (PSA) were determined by a previously described method[18]. Lymphocytes isolated from healthy, HIV-uninfected controls with patient serum, secondary staining with anti-human IgG Fab-FITC, and determining the reactivity as mean fluorescence intensity (MFI) by flow cytometry. The serum reactivity for the HIV-infected transplant recipients was compared to the reactivity by incubation of control lymphocytes with pooled serum from the controls. At least one control was run in parallel with each experiment. There were four healthy, HIV-uninfected controls, with no matching for age, race, sex, or other clinical characteristics.

2.4 | Statistical analysis

The difference in the various antibody levels at the different time points was analyzed by Student's *t* test for dependent samples. The difference in PSA levels for patients compared to controls was analyzed by *t* test for independent samples. To correct for repeated measures, a significance was set at $P = .125$ ($\alpha = 0.05$ divided by m, number of comparisons).

3 | RESULTS

Results of total IgG levels for the entire cohort have been reported previously.[23] Table 1 shows the clinical characteristics of the patients who developed moderate to severe HGG. Nine renal transplant recipients developed moderate HGG and three developed severe HGG. Eight liver transplant recipients, one who also had a renal transplant, developed moderate HGG. Table 2 shows the results of the serial antibody level results for this cohort of 20 patients, including total IgG levels, PSA levels, HIV antibody levels, and titers to measles and tetanus. Not all patients had samples available from every time point, but we only analyzed paired data for each time point and the N is given for each comparison.

The total IgG levels were significantly lower at all time points post-transplant, although they were trending upward by year 2. The levels of PSA were higher at the pre-transplant baseline (N = 20) as compared to the healthy, HIV-negative controls (N = 4), MFI 27.1 + 9.4 vs 12.1 + 0.66 ($P = .005$). PSA levels for the HIV-infected transplant recipients increased from pre-transplant baseline by 26% at 12 weeks and 31% by 26 weeks, but the increases were not statistically significant ($P = .10$ and .06, respectively). The levels of anti-HIV antibodies did not change from baseline over the course of the study.

In contrast, antibody levels against measles and tetanus were significantly reduced from baseline by week 12, and did not return to baseline, even after 2 years post-transplant. Not only were these decreases in specific antibodies sustained, but persisted even when total IgG was starting to recovery. At the pre-transplant baseline, three patients had equivocal levels of anti-measles antibodies (4-8 IU/mL), and in two of these patients titers turned negative (<4 IU/mL) at 12 weeks and remained negative out to 1 year. One patient remained seronegative at 2 years, while the other patient did not have a year two sample. There was another patient who had positive titer pre-transplant (>12 IU/mL) and had only equivocal levels from week 26 to year 2. All patients had protective (>0.1 IU/mL) anti-tetanus titers at the pre-transplant baseline. One patient dropped from 0.2 IU/mL to 0.1 IU/mL at week 12 and remained at this lower limit of protection through year 2.

TABLE 1 Characteristics of HIV+ transplant recipients with moderate or severe HGG

	Kidney (N = 12)	Liver (N = 8)
Age in years (median (IQR[a])	46 (42, 52)	51 (49, 54)
Male gender (N, %)	8 (67)	7 (88)
Caucasian (N, %)	7 (58)	6 (75)
HCV co-infection (N, %)	0 (0)	5 (63)
HBIG use within 1 week post-transplant (N, %)	0 (0)40	3 (38)
Donor Age in years (Median, [IQR])	40 (28, 46)	40 (26, 52)
Living donor (N, %)	7 (58)	0 (0)
Combined kidney-liver transplant (N, %)	NA	1(13)
Initial calcineurin inhibitor use (N, %)		
Cyclosporine	2 (17)	4 (50)
Tacrolimus	10 (48)	3 (38)
None	0 (0)	1 (13)
Baseline CD4+ T-cell count (cell/mm^3, media [IQR])	522 (342, 642)	331 (261, 548)
Baseline HIV RNA detectable (N, %)	(0)	2 (25)
Baseline IgG (mg/dL, median, [IQR])	1105 (847, 1293)	1110 (940, 1729)
Follow-up post-transplant in years (median [IQR])	3.1 (2.4, 4.6)	2.0 (0.8, 4.3)

[a]Interquartile range.

TABLE 2 Antibody levels in 20 HIV-infected transplant recipients with moderate or severe HGG

	Pre-Transplant (N = 20)	Week 12 (N = 17)	Week 26 (N = 17)	Week 52 (N = 15)	Year 2 (N = 10)
Total IgG mg/dL Mean ± SD (% of pre-transplant)	1242 ± 547	[a]485 ± 174 (39%)	[a]546 ± 281 (44%)	[a]576 ± 285 (46%)	[a]743 ± 314 (60%)
PSA, MFI Mean ± SD (% of baseline)	27.1 ± 9.4	34.1 ± 11.7 (126%)	35.6 ± 12.6 (131%)	32.7 ± 15.5 (121%)	29.8 ± 10.1 (110%)
HIV Ab, OD Mean ± SD	3.64 ± 0.03	3.60 ± 0.03 (99%)	3.57 ± 0.04 (98%)	3.50 ± 0.05 (96%)	3.58 ± 0.04 (98%)
Measles IU/mL Mean ± SD	95	[a]67 (70%)	71 (75%)	[a]51 (54%)	[a]52 (55%)
Tetanus IU/mL Mean ± SD	2.3 ± 1.8	[a]1.3 ± 1.2 (56%)	[a]1.8 ± 1.4 (80%)	[a]1.8 ± 1.7 (76%)	[a]1.32 (57%)

Note: Not all patients had samples available from every time point. The N for each time point is given. Reference range for the measles antibody titers is <8 is negative, 8-12 is equivocal, and >12 IU/mL is positive. The reference range for tetanus is >0.1 IU/mL is protective.
Abbreviations: IU/mL, International Units/Ml; MFI, mean fluorescence intensity for the poly-specific self-reactive antibodies (PSA); OD, optical density.
[a]Statistically significant, $P < .0125$ (.05 divided by four repeated measures).

4 | CONCLUSIONS

Our data demonstrate that HIV-infected patients who develop moderate to severe HGG after SOT have a preferential loss of pathogen-specific antibodies, while poly-specific self-reactive antibodies slightly increase at 12 weeks post-transplant (not statistically significant) then return to baseline. Levels of anti-HIV antibodies, however, remain stable post-transplant. There is a significant loss of antibodies against tetanus and measles, titers that normally are maintained for decades, even lifelong, in individuals who do not undergo solid organ transplantation. The loss of pathogen-specific antibody levels may contribute to the incidence of infection that occurs in patients who develop HGG. Our data also suggest the possibility that pathogen-specific antibodies may potentially be a more important measure to assess risk of infection than the total IgG level. This may be especially important in HIV-infected patients who have high antibody levels to HIV and self-antigens that increase total IgG levels without providing protection against infections. The lack of change in PSA and anti-HIV antibodies may be due to the fact that these are prevalent antigens to which the patient is constantly exposed rather than an invisible antigen, such as measles and tetanus, to which the host is not regularly exposed. Prior studies suggest that antiretroviral therapy preferentially improves immune response to *Candida*, cytomegalovirus, and *M tuberculosis* because of endogenous exposure to prevalent antigens, while response to invisible antigens such as tetanus and measles remain poor due to the lack of re-exposure.[26] The fact that pathogen-specific antibody levels decrease preferentially in relation to total IgG may be important in the pathogenesis of serious non-opportunistic infections and could explain our previous findings that these infections correlated with moderate to severe HGG in HIV-infected liver transplant recipients.[23]

Many studies have documented the frequency, severity, and the clinical consequences of HGG after SOT.[2-10] Measurement of IgG levels after solid organ transplantation is one type of immune monitoring that is currently recommended, although there are no specific guidelines as to when and how frequently to monitor IgG levels or other immunoglobulin levels after SOT.[27] A number of studies document poor vaccine responses post-transplant, but this depends on the particular pathogen and/or vaccine.[13] In addition to poor responses to vaccine post-transplant, there is also some limited data on the loss of pathogen antibodies after transplantation, a different, but related phenomenon. There are reports of reduced antibody levels, and even reverse seroconversion with loss of protective levels, after solid organ transplantation. Warmington and co-workers reported that loss of antibodies to measles and varicella occurred in 22.2% and 11.1% of children by 6 months after SOT (heart, kidney, and liver).[14] These antibodies usually persist for decades if not lifelong. Likewise, Rocca and co-workers documented the loss of protective antibodies to measles in 19% of 74 kidney transplanted children.[15] This suggests that pre-transplant vaccination will not eliminate all vaccine-preventable diseases. The risk factors for loss of antibodies in the post-transplant period have not been identified, although it is likely it may vary with transplant type. It is known that hemodialysis prior to renal transplantation can impair antibody responses to standard vaccinations.[28] Liver disease may also cause hypogammaglobulinemia.[29]

The exact mechanisms for reduced antibody responses and vaccine efficacy due to immunosuppression for SOT are not completely known.[12] Calcineurin inhibitors are primary agents for prevention of acute cellular rejection, but also affect T-cell-dependent humoral responses, especially against protein antigens.[30] Corticosteroids certainly can reduce antibody responses, and the effects are seen in other chronic conditions such as asthma.[31] Mycophenolate may have a greater effect on T- and B-cell function than azathioprine.[32] In our previous study, induction with Basiliximab or Daclizumab or initial therapy with MMF did not increase the risk of HGG.[23] For LT, multivariate predictors of HGG included pre-transplant MELD score, but also treated acute rejection, hazard ratio 4.5, 95% CI 1.1-19.0 ($P = .04$)[23]. For KT, thymoglobulin induction was associated with

HGG (hazard ratio 3.25, P = .04), but not treated acute rejection (hazard ratio 0.5, P = .52) (unpublished data).

Suppression of humoral immune responses to a solid organ allograft is clearly important, as antibody-mediated rejection is a major mechanism of graft loss, both acutely and chronically.[30] While hyper-acute rejection is due to preexisting donor-specific antibody (DSA) in pre-sensitized patients, chronic rejection due to de novo DSA may also occur after SOT and can lead to progressive decline in allograft function. This can occur with suboptimal compliance or inadequate immune suppression. Ideally, it would be beneficial to be able to prevent the de novo synthesis of DSA without significantly reducing production of pathogen-specific antibodies that have developed from prior infections or vaccinations.

HIV infection itself is associated with several unique humoral immune abnormalities, and HIV patients who receive an organ transplant have may not exhibit the same pattern of changes in antibody levels as HIV-negative transplant recipients. HIV infection is characterized by B-cell hyper-activation, but also poor antibody responses.[16-19] The antibodies include anti-HIV antibodies and other antibodies, including auto-antibodies, that is, poly-specific self-reactive PSA.[18,19] There is a loss of specific antibodies to a number of microbial pathogens, and there may also be a reduction in high-affinity anti-HIV antibodies, as T-cell depletion progresses.[18,19,22] In peripheral blood, a number of B-cell phenotypes are increased, including immature transitional B cells, exhausted B cells, activated mature B cells, and plasmablasts.[21] Many of these phenotypic and functional B-cell abnormalities reverse with antiretroviral therapy, including the hypergammaglobulinemia and HIV-specific and non-HIV-specific antibody responses, but again this may depend on the type of antigen, prevalent vs invisible.[26,33,34] Reversal of the loss of memory B cells and memory B-cell function, however, may not occur, at least in chronically infected individuals.[35] Earlier initiation of antiretroviral therapy my preserve humoral immune function, with higher resting memory B-cell counts and memory B cell response to HIV and non-HIV antigens.[36]

We assessed antibody levels to only two pathogens/antigens, measles and tetanus toxoid, and so we are unable to define the risk of infections with other pathogens or vaccine responses to other antigens. Furthermore, antibody levels to these two particular pathogens/antigens are known to be very long-lived after natural infection or vaccination, with persistent titers to measles often lasting a lifetime and titers to tetanus persisting for many years. In a prospective cohort study of 183 individuals in Finland, a country with no measles cases, children were vaccinated twice against measles mumps and rubella (MMR) and antibody presence checked at 20 years.[37] While 95% of individuals maintained measles antibody with two vaccinations, however, presence of mumps antibody at 20 years was only 74%, demonstrating variability of antibody persistence. In a study of diphtheria and tetanus toxoid antibody titers in 324 adult Portuguese women, only two of the women with prior vaccination were lacking antibodies, both of whom had not had vaccine booster for >30 years.[38] Based on these results, the investigators estimated that antibodies to the Td vaccine remain at a protective level for over 20 years.

Protective antibodies to other pathogens may also wane over time. The natural duration of pathogen-specific antibodies vaccination varies by individual, pathogen, vaccination type, and likely by immune system status. The level of antibody required to protect against an illness is also not well defined for most pathogens, making it difficult to determine clinical relevance of waning detectable antibody levels. It is possible that loss of antibody levels would be even greater to other pathogens or vaccine antigens where responses are known to be more short-lived, such as pneumococcus and influenza. The WHO guide to vaccinations note that while pneumococcal polysaccharide vaccines induce an initial rise in antibody levels, these levels decline in older adults to pre-vaccination levels after 4-7 years.[39,40] Many studies have shown that seasonal influenza antibodies may persist up to 4 years.[41-44]

Certainly, this small study has limitations. This is a small study looking at antibody abnormalities in only 20 patients, but these were the patients with the lowest levels of total IgG, and this was associated with clinical outcomes in the LT group. We only examined pathogen-specific antibodies to measles and tetanus. Future studies should examine titers to other pathogens and vaccine antigens as well. Further studies are needed to see if reductions in pathogen-specific antibody levels are associated with clinical endpoints. Decreases in pathogen-specific antibody levels may be a better predictor of serious non-OI infections and mortality than total IgG levels in HIV-infected solid organ transplant recipients. We did not have a comparison group of HIV-uninfected transplant recipients. It is possible that pathogen-specific antibody levels may also be lost preferentially in solid organ transplant recipients without HIV infection, and further studies in both HIV-infected and HIV-negative SOT recipients are needed. This has important implications for the risk of infection post-transplant and strategies for immunization practices pre- and post-transplant. It also is important for strategies for passive immunization, including intravenous immunoglobulin (IVIG) replacement therapy.[45-47] The future implications of HGG and loss of specific antibodies may become even greater as antibody-deleting desensitization therapies including plasmapheresis, anti-thymocyte globulin, and anti-CD20 (Rituximab) for acute antibody-mediated rejection (ABMR), and new approaches to chronic ABMR with proteasome inhibitor therapy (Bortezomib) to inhibit plasma cells, complement cascade inhibition with anti-C5 monoclonal antibodies (Eculizumab), anti-IL2-receptor MoAbs (Basiliximab, Daclizumab), and anti-IL-6-receptor therapy (Tocilizumab), and immunoglobulin G-degrading enzyme of *Strep. pyogenes* (IdeS) are utilized more frequently.[48]

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CONFLICT OF INTEREST

The authors have no associations that might pose a conflict of interest.

AUTHOR CONTRIBUTIONS

Dr Gregg, Dr Pitrak, and Dr Pursell developed the study. Randee Estes and Dr Pitrak conducted the laboratory assays. Dr, Newman aided with data analysis and manuscript preparation. All authors contributed to the manuscript and its review.

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