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Authors
Roll, Garrett R
Lunow-Luke, Tyler
Braun, Hillary J
et al.

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COVID-19 does not impact HLA antibody profile in a series of waitlisted renal transplant candidates

Garrett R. Roll a, Tyler Lunow-Luke a, Hillary J. Braun a, Owen Buenaventura b, Mirelle Mallari b, Peter G. Stock a, Raja Rajalingam a,⇑

⇑Corresponding author at: Immunogenetics and Transplantation Laboratory, University of California San Francisco (Laurel Heights Campus), 3333 California Street, San Francisco, CA 94118, United States.

E-mail address: Rajalingam.Raja@ucsf.edu (R. Rajalingam).

Abbreviations: HLA, human leukocyte antigen; ESRD, end-stage renal disease; COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

1. Introduction

The presence of Human Leukocyte Antigen (HLA) antibodies delays access to transplantation and is a risk factor for allograft rejection following renal transplantation. Exposure to organ transplantation, pregnancies, and blood transfusions triggers HLA antibody production. Infection and vaccination can activate the immune system, which can induce the production of new HLA antibodies or enhance the level of existing HLA antibodies, which is of particular interest to patients awaiting renal transplantation [1,2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing angiotensin-converting enzyme 2 and Transmembrane Serine Protease 2 surface proteins, and patients awaiting kidney transplantation have a 10.2–15.0% risk of mortality if infected [3,4]. SARS-CoV-2 infection activates both an innate and adaptive immune response, resulting in a profound cytokine storm [5]. Kidney transplant recipients are shown to mount an effective anti-SARS-CoV-2 adaptive immune response, including potent humoral immune activity despite chronic immunosuppression [6]. Importantly, a recent report describes the presence of HLA antibodies in the convalescent serum of male patients without any known allosensitizing events who recovered from coronavirus disease 2019 (COVID-19), suggesting that infection with this virus could result in HLA antibody development [7]. Currently, no studies directly address the question of whether or not patients infected with SARS-CoV-2 develop HLA antibodies. As a result, there is no guidance for transplant providers regarding the need to repeat HLA antibody testing prior to kidney transplantation after COVID-19 infection or vaccination.

2. Materials and methods

2.1. Waitlisted renal transplant candidates

This is a single-center retrospective review of a prospectively maintained database of renal transplant candidates, performed with the approval of our institutional IRB (IRB Number: 20-31396). We routinely perform quarterly HLA antibody testing of all waitlisted patients approaching the top of the deceased donor
waiting list and use the virtual crossmatch as the final pretransplant crossmatch in the vast majority of deceased donor kidney transplants (currently >90%) [8]. Eighteen patients near the top of our waiting list were known to have contracted and recovered from COVID-19, one of whom also received a single dose of the COVID vaccine prior to repeating HLA testing.

2.2. SARS-CoV-2 RNA testing

Nasopharyngeal or oropharyngeal samples were collected using swabs immediately placed in a standard viral transport medium. Viral RNA was extracted from 400 μL of respiratory samples and eluted in 50 μL of elution buffer. Detection of SARS-CoV-2 RNA was performed by an adapted previously described real-time RT-PCR assay targeting regions of the virus nucleocapsid (N) gene and also targeting the human RNase P gene for sample quality control [9]. All 18 transplant candidates included in this study were positive for SARS-CoV-2 RNA testing.

2.3. HLA antibody testing

The HLA class I and class II antibodies were measured using the Luminex-based single antigen bead assay as previously described (One Lambda Inc., Canoga Park, CA) [8]. Serum samples are pre-treated with dithiothreitol (DTT) to prevent aggregation of high titer antibodies (termed prozone effect) and to increase the sensitivity of antibody detection. Moreover, we have re-tested pre- and post-COVID sera obtained from the highly sensitized patients with a CRPA value of >80% to confirm that no HLA antibody specificity was missed due to inhibitory effects commonly observed in sera of high cPRA patients. Based on the recommendation by Tambur et al. and baseline neat mean fluorescence intensity (MFI) values of four patients, we chose 1:16 dilution (with Phosphate buffered saline) for all >80% CPRA sera samples [10]. Antibody specificity is determined based on the known amino acid homologies and cross-reactivity patterns among core HLA allotypes. The MFI is used as an arbitrary unit of antibody quantity. If multiple beads have allelic variants of the same antigen (e.g., HLA-A*68:01, *68:02, *68:03) with similar MFI values, then the average MFI of all reactive beads is used to quantify HLA-A68 antibody MFI.

LABXpress Pipettor (One Lambda), a high throughput liquid handling system to aspirate and dispense precise volumes into test wells of a 96-well reaction plate, is used to minimize inter-assay variations. We compared the HLA antibody results before and after COVID-19 for each patient to assess HLA antibody formation.

3. Results

The patient characteristics are presented in Table 1. The average age was 51.5 years old at the time of COVID-19 diagnosis, and one patient was on immunosuppression (Prednisone 5 mg daily). Most patients were male (72%, n = 13). The majority of the patients (72%, n = 13) were Hispanic; 4 were Asians, and 1 was African American. Fourteen patients were unsensitized, and four were highly sensitized (2 with 100% CPRA, 1 with 98% CPRA, and 1 with 98% CPRA). Ten of the eighteen patients with a history of SARS-CoV-2 infection required hospitalization due to COVID-19, and the average length of hospital stay was 5.4 days. One patient required mechanical ventilation in the intensive care unit. Routine quarterly single antigen testing has been repeated an average of 53.2 days after the diagnosis of infection.

Table 1 depicts the pre-COVID and post-COVID single antigen test results for four highly sensitized patients. The HLA antibody specificities and MFI remain unchanged in post-COVID samples compared to respective pre-COVID samples. The cPRA was
Table 2
Specificity and mean fluorescence intensity (MFI) of HLA antibodies in four highly sensitized patients with a CPRA value of over 80%.

| Pt-1: CPRA 100% | Pt-2: CPRA 100% | Pt-3: CPRA 98% | Pt-4: CPRA 89% |
|-----------------|-----------------|----------------|----------------|
| **Specificity** | **Neat Serum**  | **1:16 dilution** | **Neat Serum**  | **1:16 dilution** | **Neat Serum**  | **1:16 dilution** | **Neat Serum**  | **1:16 dilution** |
| (CPRA)          | (11/2020)       | (02/2021)      | (05/2019)       | (06/2020)      | (05/2019)       | (06/2020)      | (05/2019)       | (06/2020)      |
| **Cw15**        | 19,716          | 16,588         | 4328            | 4028           | 22,595          | 17,049         | 4049            | 4302           |
| **A33**         | 19,331          | 19,482         | 9228            | 6981           | 21,315          | 19,231         | 3864            | 3928           |
| **A31**         | 18,810          | 18,431         | 9925            | 7620           | 20,743          | 18,742         | 3609            | 3714           |
| **A29**         | 18,736          | 18,325         | 11,083          | 8587           | 20,712          | 18,240         | 3676            | 3822           |
| **A80**         | 18,627          | 18,045         | 14,259          | 11,264         | 18,927          | 17,109         | 7142            | 7207           |
| **A11**         | 18,221          | 17,215         | 11,058          | 8744           | 18,287          | 17,375         | 8617            | 3585           |
| **A36**         | 18,102          | 17,861         | 8398            | 6371           | 20,167          | 19,306         | 3107            | 3306           |
| **Cw5**         | 17,944          | 14,683         | 3019            | 2696           | 20,153          | 19,140         | 3205            | 3363           |
| **A32**         | 17,870          | 17,574         | 8643            | 6428           | 20,146          | 18,367         | 3470            | 3620           |
| **A3**          | 17,782          | 17,310         | 4733            | 4104           | 20,014          | 19,258         | 3266            | 3329           |
| **A74**         | 17,633          | 16,939         | 13,014          | 11,234         | 19,939          | 18,528         | 3137            | 3270           |
| **Cw2**         | 17,035          | 14,063         | 4379            | 4086           | 19,918          | 18,592         | 3530            | 3770           |
| **B62**         | 16,767          | 13,962         | 1911            | 1714           | 19,501          | 18,930         | 2925            | 3185           |
| **B50**         | 15,885          | 12,845         | 1667            | 1408           | 19,873          | 19,212         | 2984            | 3137           |
| **B49**         | 15,694          | 13,364         | 1801            | 1526           | 19,611          | 18,611         | 3021            | 3258           |
| **A30**         | 14,547          | 14,617         | 4771            | 3566           | 19,481          | 18,707         | 3088            | 3351           |
| **B63**         | 14,456          | 12,696         | 1776            | 1278           | 19,257          | 17,661         | 2774            | 2968           |
| **B57**         | 13,854          | 11,939         | 1835            | 1674           | 18,736          | 18,499         | 3031            | 3184           |
| **Cw18**        | 13,731          | 10,585         | 1664            | 1319           | 18,582          | 18,730         | 2776            | 2858           |
| **B56**         | 12,892          | 10,058         | 1021            | 1065           | 18,115          | 18,460         | 2652            | 2685           |
| **B76**         | 12,651          | 11,897         | "              | "              | 17,573          | 17,866         | 2570            | 2569           |
| **B7**          | 12,622          | 9148           | 1136            | "              | 17,468          | 17,317         | 2360            | 2579           |
| **B77**         | 12,345          | 10,003         | 1055            | "              | 17,375          | 17,506         | 2562            | 2652           |
| **B75**         | 11,531          | 9007           | 1254            | 1145           | 17,127          | 17,139         | 2454            | 2550           |
| **Cw6**         | 11,525          | 9237           | "              | "              | 15,352          | 15,214         | 1967            | 1997           |
| **A1**          | 11,497          | 9506           | "              | "              | 14,949          | 15,621         | 1857            | 2029           |
| **A34**         | 11,434          | 11,550         | 3523            | 2684           | 12,004          | 11,548         | 1331            | 1431           |
| **B71**         | 10,570          | 8263           | "              | "              | 11,946          | 11,054         | 1199            | 1383           |
| **B45**         | 8789            | 8262           | 1488            | "              | 10,821          | 10,388         | 1159            | 1209           |
| **B46**         | 8441            | 6162           | "              | "              | 10,159          | 10,500         | 1014            | 1085           |
| **Cw17**        | 7603            | 5065           | "              | "              | 9504            | 9677           | "              | 1058           |
| **B44**         | 7086            | 8036           | 1195            | "              | 9115            | 8313           | 1035            | 1141           |
| **B41**         | 6086            | 4199           | "              | "              | 7976            | 7471           | "              | "              |
| **B13**         | 5560            | 4666           | "              | "              | 6271            | 6346           | "              | "              |
| **B60**         | 5199            | 3538           | "              | "              | 5839            | 6066           | "              | "              |
| **A43**         | 5560            | 5085           | "              | "              | 5227            | 5060           | "              | "              |
| **B61**         | 5464            | 3664           | "              | "              | 4825            | 5062           | "              | "              |
| **A66**         | 5324            | 5204           | "              | "              | 4143            | 4422           | "              | "              |
| **A26**         | 5249            | 4883           | 1211            | "              | 2935            | 1935           | "              | "              |
| **Cw4**         | 4650            | 3153           | "              | "              | 2831            | 1831           | "              | "              |
| **B47**         | 4387            | 3034           | "              | "              | 2776            | 1776           | "              | "              |

(continued on next page)
Table 2 (continued)

| Specificity | Pt-1: CPRA 100% | Pt-2: CPRA 100% | Pt-3: CPRA 98% | Pt-4: CPRA 89% |
|-------------|-----------------|-----------------|----------------|----------------|
|             | Neat Serum 1:16 dilution | Neat Serum 1:16 dilution | Neat Serum 1:16 dilution | Neat Serum 1:16 dilution |
| Specificity | Pre-COVID (11/2020) | Post-COVID (02/2021) | Pre-COVID (05/2019) | Post-COVID (06/2020) |
|             | Pre-COVID (05/2020) | Post-COVID (06/2020) | Pre-COVID (06/2020) | Post-COVID (07/2019) |
|             | Pre-COVID (09/2020) | Post-COVID (10/2020) | Pre-COVID (09/2020) | Post-COVID (12/2019) |
|             | Pre-COVID (12/2020) | Post-COVID (01/2021) | Pre-COVID (12/2020) | Post-COVID (12/2020) |
| **A2**      | 4038             | 3924             | 18,912          | 16,021          |
| **BS1**     | 2940             | 1951             | 17,077          | 15,581          |
| **B35**     | 2217             | 1321             | 8,650           | 7,907           |
| **DQ5**     | 21,490           | 21,079           | 10,545          | 9,452           |
| **DQ6**     | 20,189           | 21,090           | 9,841           | 8,881           |
| **DRS2**    | 18,731           | 17,740           | 8,926           | 7,890           |
| **DR18**    | 15,979           | 12,031           | 8,650           | 7,907           |
| **DR16**    | 15,639           | 12,122           | 8,150           | 7,405           |
| **DR17**    | 14,801           | 12,724           | 7,049           | 6,216           |
| **DR13**    | 13,826           | 10,789           | 6,010           | 5,778           |
| **DR7**     | 12,802           | 10,877           | 5,806           | 4,570           |
| **DR11**    | 12,530           | 9,320            | 5,541           | 4,563           |
| **DR14**    | 12,496           | 9,050            | 5,300           | 4,953           |
| **DQ9**     | 12,183           | 9,986            | 4,257           | 3,044           |
| **DR12**    | 8,084            | 5,500            | 3,594           | 2,326           |
| **DR8**     | 7,147            | 5,216            | 3,390           | 2,600           |
| **DR7**     | 2,116            | 1,104            | 1,288           | 988             |
| **DR9**     | 1,890            | 1,167            | 3,186           | 2,206           |
| **DP6**     | 2,688            | 2,417            | 2,374           | 1,326           |
| **DP5**     | 2,770            | 1,506            | 2,688           | 1,988           |
| **DP9**     | 2,734            | 1,326            | 2,699           | 2,015           |
| **DP15**    | 2,375            | 1,843            | 2,228           | 1,066           |
| **DQ4**     | 2,216            | 1,870            | 2,207           | 1,502           |
| **DP1**     | 2,063            | 1,844            | 2,063           | 1,844           |
| **DP5**     | 2,060            | 1,418            | 2,060           | 1,418           |

* <1000 MFI (negative).
unchanged in all patients, and there was no perceptible increase in the risk of rejection based on the HLA antibody profiles of the patients before and after COVID-19 infection. Moreover, re-testing of pre- and post-COVID sera obtained from four highly sensitized patients with a CPRA value of over 80% with 1:16 dilutions confirmed that no HLA antibody specificity was missed due to inhibitory effects commonly observed in sera of high cPRA patients (Table 2).

4. Discussion

Knowledge about the immune response in patients that recover from COVID-19 is evolving, but it is clear the virus can induce a relatively unique immune dysregulation [11]. Cytomegalovirus, influenza virus, herpes virus, and varicella virus infection have been shown to result in HLA antibody development through T-cell cross-reactivity [12–14], termed heterologous immunity. Notably, male patients without any known sensitizing events donating convalescent serum after COVID-19 infection were found to have HLA antibodies [7]. Therefore, it is essential for transplant providers to consider the possibility of the existence of either de novo HLA antibodies or increased MFI of existing antibodies after recovery from infection with COVID-19 in patients awaiting kidney transplantation.

Patients nearing the top of the waiting list undergo expensive quarterly monitoring for HLA antibodies to permit moving forward with transplant using a virtual crossmatch as the final pretransplant crossmatch. HLA antibody testing is time-consuming and therefore is usually not possible after an organ offer is received, and many centers are moving away from physical crossmatching for a majority of patients. There is no consensus to date about whether or not patients who have recovered from COVID-19 infection need repeat HLA antibody testing prior to moving forward with kidney transplantation if they receive an organ offer prior to the next quarterly single antigen testing. A larger body of published literature suggests that viral infection does not cause HLA antibody development [15–18] compared to the evidence viral infection can cause HLA antibodies [7,12–14]. Understandably, many transplant centers elect to perform a physical crossmatch at the time of transplant in a waitlisted patient who has recovered from COVID, increasing cost and potentially decreasing access to transplant.

Based on this series of patients with end-stage renal failure awaiting a kidney transplant, we found no evidence of HLA antibody development resulting from COVID-19 infection. It is interesting to note that patients with COVID-19 display a complex immune dysregulation characterized by lymphopenia and down-regulation of HLA class II molecules, which could form defective antigen-presentation and thus impaired alloantibody response [11,19]. Additionally, the above-mentioned report by Juskewitch et al. [7] certainly deserves further investigation. One additional patient not described in Table 1 received both doses of the COVID-19 vaccine and then underwent deceased donor kidney transplantation. Similar to the patients described in Table 1, this additional patient who received both doses of vaccine did not have any HLA antibodies. The impact of mRNA vaccinations on sensitization will need to be determined, but our one patient that was vaccinated remained unsensitized.

The weakness of this study is the size of the series of patients. Despite the size of this study, we feel it is important to share these results because a final conclusion about this issue will not be possible until an extensive series of patients is available. This will likely take a multi-institutional effort. Therefore, in the intervening months to years, transplant providers will continue to be pressured to perform real-time risk-benefit decisions about patients at the time of organ offer. This series is the first step in assisting providers who are currently considering organ offers for patients that have recovered from COVID-19 without time for a physical crossmatch.

In summary, transplant providers need to continue to be vigilant about the possibility of HLA antibody development in patients infected with COVID-19. This series of patients has not identified de novo HLA antibodies or the presence of a memory response in highly sensitized patients awaiting kidney transplant undergoing serial single antigen testing after infection. Our institutional plan is to continue to treat COVID-19 infection as we do other infections in this population. Therefore, we do not delay transplant to perform a physical crossmatch or repeat single antigen testing after COVID-19 infection or vaccination with the goal of reducing barriers to transplantation, but other opinions are valid. We will continue to monitor the development of HLA antibodies following vaccination and COVID-19 infection to validate our current strategy. We look forward to a more comprehensive understanding of the immune response to COVID-19 infection and vaccination in patients awaiting transplant.

5. Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by Human Immunology.

6. Financial disclosure

The authors declare that no financial support was received to perform this study.

Author contributions

Garrett R. Roll: Participated in research design, performance of the research, writing of the paper.

Tyler Lunow-Luke: Participated in performance of the research.

Hillary J. Braun: Participated in performance of the research.

Owen Buenaventura: Performed HLA antibody testing.

Mirelle Mallari: Collected and managed the data.

Peter G. Stock: Participated in performance of the research, editing of the paper.

Raja Rajalingam: Participated in research design, performance of the research, writing of the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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