SARS-CoV-2 serologic immune response in exogenously immunosuppressed patients

Running head: SARS-CoV-2 antibodies in immunosuppressed patients

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ABBREVIATIONS:

COVID-19: Coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ABSTRACT:

BACKGROUND: While it is presumed that immunosuppressed patients, such as solid organ transplant recipients on immunosuppression, are at greater risk from SARS-CoV-2 infection than the general population, the antibody response to infection in this patient population has not been studied.

METHODS: In this report, we follow the anti-SARS-CoV-2 antibody levels in patients with COVID-19 who are undergoing exogenous immunosuppression. Specifically, we studied the antibody response of three solid organ transplant recipient patients, three patients who take daily inhaled fluticasone, and a patient on etanercept and daily inhaled fluticasone, and compared them to five patients not on exogenous immunosuppression.

RESULTS: We found that the solid organ transplant patients on full immunosuppression are at risk of having a delayed antibody response and poor outcome. We did not find evidence that inhaled steroids nor etanercept predispose patients to delayed immune response to SARS-CoV-2.

CONCLUSION: The data presented here suggest that solid organ transplant recipients may be good candidates for early targeted intervention against SARS-CoV-2.

IMPACT STATEMENT:

This is the first reported study of antibody responses to SARS-CoV-2 infection in exogenously immunosuppressed patients. It suggests solid organ transplant patients on full immunosuppression are at risk of having a delayed antibody response and poor outcome, while it does not find evidence of such an effect with inhaled steroids nor etanercept.

INTRODUCTION:

It is presumed that patients undergoing immunosuppression therapy, such as solid organ transplant recipients, are at greater risk from coronavirus infectious disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Indeed, some preliminary reports suggest increased mortality in this patient population (1,2). Several studies have characterized the humoral response to SARS-CoV-2 in COVID-19 patients (3-6), but, to our knowledge, no reports have focused on this response in exogenously immunosuppressed patients. Here, we followed the antibody response to SARS-COV-2 in three solid organ transplant recipient patients, three patients who take daily inhaled fluticasone for asthma or chronic obstructive pulmonary disease, and a patient with rheumatoid arthritis/systemic lupus erythematosus and asthma on etanercept and daily inhaled fluticasone and compared them to responses of 5 patients not on exogenous immunosuppressive agents.

METHODS:

Patient specimens and information were utilized under the auspices of UPMC Quality Assurance for Clinical Laboratories and the University of Pittsburgh IRB #20040072. Patient samples were remnant blood specimens from standard care. ELISA-based tests for anti-SARS-CoV-2 spike protein (S1 subunit) IgA and IgG antibodies were from Euroimmun (Lubeck, Germany). These tests were used per manufacturer's instructions and processed manually. For IgG, we utilized the manufacturer's interpretation of the ratio with samples <0.8 classified as no antibody present, 0.8 - <1.1 indeterminate, and ≥1.1 containing antibodies. For IgA, we classified samples with a ratio <0.8 as no antibody present, 0.8 - < 2 indeterminate, and ≥2 containing antibodies due to the higher rates of cross-reactivity found during validation studies (7).

RESULTS:

Our goal was to investigate whether patients treated with immunosuppressive medications may have impaired SARS-CoV-2 specific immune responses when infected with this virus. Thus, we followed anti-SARS-CoV-2 specific IgA and IgG responses of several patients who were admitted to our hospital for SARS-CoV-2 infection (Figure 1). We followed antibody response as well as other clinical indications compared to day of symptom onset (Table 1).

We specifically focused on three patients who were solid organ transplant recipients and on a calcineurin inhibitor with or without the addition of an mTOR inhibitor and mycophenolate mofetil. When their antiviral antibody responses are compared with those of patients not on immunosuppression, ("control"), two of the three solid organ

transplant recipient patients exhibit a delayed antiviral immune response (Figure 1, Table 1, Patients 1-3 versus Patients 8-12). Whether Patient 3 had an apparently 'normal' antiviral immune response, or had an earlier exposure due to his residence in a group care facility with known COVID-19 patients, is unknown. The fact that his IgG extinction ratio at day 9 was >10 whereas the highest control value at this timepoint was 2.6 suggests that the latter might be true.

We also followed the antibody response of three patients who were on inhaled fluticasone for chronic obstructive pulmonary disease / asthma (Figure 1, Table 1, Patients 5-7). The antiviral antibody responses of these patients significantly overlapped with those from the control group, suggesting that inhaled glucocorticoids do not put one at significant risk of delayed humoral response during SARS-CoV-2 infection.

Additionally, we followed the antiviral antibody response of a patient with rheumatoid arthritis/systemic lupus erythematosus as well as asthma who was being treated with plaquenil, etanercept and inhaled fluticasone. This patient's antibody response may be slightly delayed, but did overlap with one of the control patients (Figure 1, Table 1, Patient 4). Thus, more studies are necessary to determine the effect of etanercept on the serologic response to SARS-CoV-2.

DISCUSSION:

Our results, while preliminary, suggest that solid organ transplantation recipients on full immunosuppression are at increased risk of experiencing a delayed antibody response

to SARS-CoV-2. We did not find evidence that inhaled steroids nor etanercept predisposes one to delayed immune response to SARS-CoV-2. Consistent with higher mortality rates previously published in the solid organ transplant patients with COVID-19 (1,2), all three transplant patients in our study passed away secondary to COVID-19 complications. While two of these patients did receive convalescent plasma, it was administered after patient seroconversion (Table 1). Convalescent plasma is a promising potential targeted treatment option for COVID-19 (8,9), particularly before more specific therapies are developed. The data presented here suggest that solid organ transplant recipients may be appropriate candidates for earlier targeted intervention because they have an increased risk of delayed immunologic response. Whether this applies to other patients undergoing exogenous immunosuppression, or patients who are otherwise immunosuppressed, is a question of great importance that remains to be answered. Even when an effective SARS-CoV-2 vaccine is available, the immunosuppressed patient population is unlikely to optimally respond to this approach. It is therefore critical that we understand the SARS-CoV-2 immune response and the potential of targeted immunotherapy to effectively treat these patients.

ACKNOWLEDGMENTS/FUNDING:

The authors would like to thank Dr. Ian Harrold and Dr. Darrell Triulzi with their assistance in determining patients' convalescent plasma status.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

Role of Sponsor: No sponsor was declared.

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Table 1. Patient Summary

Pt	Classification	Age Sex	History	Immuno-suppression	PCR (+) [a]	PCR (-) [a]	Seroconversion		Admitted [a]	Intubated [a]	CP [a]
							IgA [a]	IgG [a]			
1	SOTx + CI + mTOR inhibitor + MMF	70s M	OLTx, DM, HTN, HLD	tacrolimus, everolimus, MMF	1, 20, 28, 37, 50	-	21	21	0 - 50 (deceased)	3 - 50	23, 31, 45
2	SOTx + CI + mTOR inhibitor	60s M	SLKTx, DM	tacrolimus, everolimus	7, 27, 33	30, 32	≤ 10	15	7 - 48 (deceased)	9 - 26, 36 - 40	37
3	SOTx + CI	60s M	LRKTx, HTN	tacrolimus	2	-	≤ 9	≤ 9	2 - 17 (deceased)	- (DNR/DNI)	-
4	TNF inhibitor, aminoquinoline, and inhaled glucocorticoid	60s F	RA/SLE, asthma, HTN, DM	plaquenil, etanercept, inhaled fluticasone	6	67	≤ 13	≤ 13	11 - 23	-	-
5	Inhaled glucocorticoid	60s F	COPD/Asthma, HTN, Afib	inhaled fluticasone	3	-	10	> 10	5 - 10	-	-
6	Inhaled glucocorticoid	20s F	Asthma, HTN, OSA, HF	inhaled fluticasone	4	26	≤ 7	8	6 - 28	6 - 21	-
7	Inhaled glucocorticoid	70s F	Severe COPD, HF, HTN	inhaled fluticasone	0, 37, 45	43	8	8	0 - > 50	1 - 44	15
8	Control	30s F	Asthma	-	6	-	10	11	6 - 16	6 - 12	-
9	Control	40s M	None	-	5, 58	57, 68, 69	≤ 5	9	5 - > 70	6 - 55	-
10	Control	60s M	HTN	-	7	-	9	9	5 - 19	8 - 13	-
11	Control	60s F	HTN, CAD, HLD	-	5	-	≤ 6	9	4 - 25	6 - 19	-
12	Control	70s M	GERD	-	10, 33, 41	32, 40, 44, 45	≤ 10	14	10 - 47	15 - 26	-

[a] reported as days post symptom onset

Abbreviations: Pt patient, SOTx solid organ transplant, CI calcineurin inhibitor, CP convalescent plasma, OLTx orthotopic liver transplant, SLKTx simultaneous liver kidney transplant, LRKTx living related kidney transplant, MMF mycophenolate mofetil, DM diabetes mellitus, HTN hypertension, HLD hyperlipidemia, RA/SLE rheumatoid arthritis/systemic lupus erythematosus, Afib atrial fibrillation, COPD chronic obstructive pulmonary disease, HF heart failure, CAD coronary artery disease, GERD gastroesophageal reflux disease, DNR/DNI do not resuscitate/do not intubate, PCR polymerase chain reaction

Figure 1. Anti-SARS-CoV-2 antibody response. The levels of anti-SARS-CoV-2 IgA (top) and IgG (bottom) antibodies were measured at several time points in the patients with clinical characteristics described in Table 1. The antibody levels are reported as extinction ratios and are plotted versus days after symptom onset. Dotted horizontal lines indicate cutoff for positive antibody levels. Colored lines represent patients with differing immunosuppressive conditions (red: solid organ transplant recipients, blue: inhaled fluticasone, green: plaquenil, etanercept and inhaled fluticasone, grey: control patients).