New Microbiologica, 44, 3, 184-186, 2021, ISSN 1121-7138

SHORT COMMUNICATION

Kidney transplant rejection rate in screened patients for anti-SARS-CoV-2 antibodies, during COVID-19 pandemic in Northern Italy

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SUMMARY

Coronavirus is a high-risk pathogen for kidney transplant recipients receiving immunosuppressive therapy; Coronavirus disease 2019 (COVID-19) is an infection causing severe acute respiratory syndrome (SARS-CoV_2), and progressive withdrawal of immunosuppressive drugs has been suggested in transplanted patients. At IRCCS San Matteo Hospital in Pavia, Northern Italy, during the pandemic we performed a screening and all transplanted patients were evaluated for IgG anti SARS-CoV-2; 12 of 201 kidney transplant recipients (6%) screened for IgG anti SARS-CoV-2 (s) developed kidney transplant rejection; 10 (83%) were negative and 2 (17%) resulted positive for SARS-CoV-2 IgG, while among 189 patients without rejection, 162 (86%) resulted negative and 27 (14%) positive (P=0.69). COVID 19 course may be more severe in kidney transplant recipients but it does not significantly increase risk of kidney rejection.

Received June 30, 2021 *Accepted* October 21, 2021

Kidney transplant patients may be at high risk of developing severe COVID-19 (Hui *et al*., 2020; Akalin *et al*., 2020; Banerjee et al.2020) as a consequence of immunosuppressive therapy (Mayer *et al*. 1997). COVID-19 induces variable clinical courses in normal hosts but seems to progress more rapidly in immunocompromised hosts, with greater rates of intensive care unit admissions and death. Therefore, an expert consensus document has suggested a progressive withdrawal of immunosuppression depending on the severity of the disease (Maggiore *et al*., 2020). However, one unresolved issue about COVID-19 is the influence of immunosuppressive therapy minimization on disease course, in particular rejection incidence. At IRCCS San Matteo Hospital in Pavia, Northern Italy, a zone considered at high risk during the COVID-19 pandemic (Cavagna *et al*., 2020; Piccinini *et al*., 2020), between June and December 2020 we screened 201 kidney transplant recipients for IgG anti SARS-CoV-2 and identified 29 positive patients (14%), 24 of whom (86%) were also positive for anti-SARS-CoV-2 nucleic capsid protein (NCP). Serum samples were tested for detection of IgG antibody to SARS-CoV-2 spike (S) and NCP protein by ELISA assay (Euroimmun, Luebeck, Germany), according to the manufacturer's instructions. The semi-quantitative (IgG) results were expressed as a ratio with respect to an internal calibrator: a ratio <0.8 was considered negative, ≥1.1 was considered positive and intermediate results were considered borderline. The samples were also available at multiple time-points outside the period considered in this study.

More than one IgG anti SARS-CoV-2 and NCP protein by ELISA assay was performed for each patients to rule out the possibility of a false negative or positive antibody test, until resolution of symptoms, if present, and the negativization of nasopharyngeal swab. The test is not configured as a criterion for minimizing immunosuppressive therapy in asymptomatic cases.

The most common symptoms reported by patients were fever in 48%, cough in 24%, asthenia, diarrhea, headache and dyspnea in 17%. 9 patients (31%) were

Key words:
IgG anti SARS-CoV-2; Kidney; transplant rejection; immunosuppressive therapy

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Table 1

Pt	*Sex*	*Age*	*Time since transplant (yr)*	*Therapy*	*Symptoms*	*IgG anti SARS-CoV-2 (s)*	*IgG anti SARS-CoV-2 (NCP)*	*Admission for COVID-19*	*Outcomes*	*Kidney Rejection*	*HLA match*	*DSA*	*Source of donor*
1	M	59	7	CyA/ ster	fever / cough / diarrhea / nausea / phlegm / asthenia / dyspnoea	7,3	4,5	outpatient	alive	acute cellular rejection	1	Neg	deceased donor
2	M	62	5	CyA/mmf	asymptomatic	<0,8	<0,8	outpatient	alive	chronic rejection	3	Neg	deceased donor
3	M	29	7	tac/ever	asymptomatic	<0,8	<0,8	outpatient	alive	acute cellular rejection	3	Neg	living donor
4	M	56	3	tac/ever/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute cellular rejection	2	Neg	deceased donor
5	F	49	3	CyA/mmf/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute cellular rejection	3	Neg	deceased donor
6	F	49	5	CyA/mmf/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute humoral rejection	2	Pos	deceased donor
7	M	42	9	tac/mmf	asymptomatic	<0,8	<0,8	outpatient	alive	chronic rejection	4	Pos	deceased donor
8	F	39	0,6	tac/mmf/ster	fever/cough	<0,8	<0,8	outpatient	alive	acute cellular rejection	3	Neg	deceased donor
9	M	51	4	tac/ster	fever / conjunctivitis / diarrhea / dyspnoea	7,8	4,7	hospitalized	alive	chronic rejection	3	Neg	deceased donor
10	M	23	1	tac /mmf/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute cellular reject	3	Neg	deceased donor
11	M	55	1	ever/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute cellular reject	2	Neg	deceased donor
12	M	52	0,1	tac/mmf/ster	asymptomatic	<0,8	<0,8	outpatient	alive	acute humoral reject	3	Neg	deceased donor

Legend

CyA	Cyclosporine A
mmf	Mycopenolate mofetil
Tac	Tacrolimus
ever	everolimus
ster	steroids
yr	years
Pt	patient

asymptomatic, 4 patients (14%) developed pneumonia, 2 (8%) died of sepsis. 22 (75%) of 29 patients were hospitalized, 7 (25%) were monitored at home. Of the 12 patients with kidney transplant rejection, only two (17%) were positive for anti-SARS-CoV-2 IgG and had the most common symptoms reported for the other patients who did not develop kidney rejection. One patient had an acute rejection, the other one a chronic rejection (*Table 1*); acute cellular rejection is an impediment to long-term allograft survival (Ingulli, 2010). In our study kidney rejection was not correlated with symptoms.

We minimized the immunosuppressive therapy depending on the severity of COVID-19 disease. In particular, mycophenolate mofetil was stopped until resolution of symptoms and the negativization of nasopharyngeal swab (Sanders et al, 2020) (*Table 1*). Also, mTOR inhibitors were stopped depending on degree of lymphopenia (Libetta *et al*., 2015), and steroid was administered at high doses as recommended for the treatment of severe-moderate COVID-19. In particular, 4 (33%) of 12 patients were receiving cyclosporine/mycophenolate mofetil/steroids, 2 (16%) were receiving tacrolimus/mycophenolate mofetil/steroids, 2 (16%) were receiving tacrolimus/everolimus/steroids, and only one (8%) tacrolimus/mycophenolate mofetil.

Our results show that 12 of 201 patients (6%) developed kidney transplant rejection, 10 of 12 patients (83%) were negative for IgG anti SARS-CoV-2 (s) and 2 resulted positive (17%), while 162 (86%) of 189 recipients without rejection resulted negative for IgG anti SARS-CoV-2 (s) and 27 positive (14%). There was no significant association between rejection and IgG anti SARS-CoV-2 positivity (P=0,69).

Kidney biopsy revealed acute rejection in 9 patients (75%) and chronic kidney rejection (25%) in 3 patients (Table 1). The source of graft was deceased donor (91%) for 11 patients and living donor for one (9%); donor-specific alloantibodies (DSA) were absent in 10 patients (83%) and present in 2 (16%). Donor's recipient HLA matching is described in *Table 1*.

Median age of kidney transplant recipients with rejection was 48 years (range 29-62). 72% of recipients were male and 27% were female. The clinical course was favorable and the patients with acute kidney rejection fully recovered renal function.

Several studies (Akalin *et al*,, 2020; Fahad *et al*., 2020; Toapanta *et al*., 2021) reported that kidney transplant recipients infected with coronavirus have a significant risk of graft loss and death.

On the contrary, we found that an immunosuppressive minimization strategy in kidney transplant recipients with COVID-19 appears safe. Although the sample size of our study is low, this observation suggests that SARS-CoV-2 infection is not a major trigger of allo-reaction in kidney transplant recipients, while on the other hand it might contribute to immune suppression, including alloimmune response.

In conclusion, although renal transplant patients are a more vulnerable population for COVID 19 disease due to chronic immunosuppression (Kalluri *et al*., 2012; Phanish *et al*., 2020), our results show that SARS-CoV-2 infection is not correlated to rejection despite immunosuppressive therapy minimization.

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