Safety of mycophenolate in covid-19 infection: A case series

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Abstract

Background: The pandemic of Covid-19 infection has affected all countries in the world. Kidney transplant recipients show higher mortality due to Covid-19 infection than general population. Cytokine storm is an important cause of mortality. Antiviral and immunosuppressive agents are used in the treatment of Covid-19 infection. In patients who are on Mycophenolate for other indications, it is promptly discontinued after development of Covid-19 infection. We studied a series of 14 patients in whom Mycophenolate was continued during Covid-19 infection.

Aim: To see whether Mycophenolate administration was safe in Covid-19 infection.

Materials and Methods: We studied records of 14 cases, 7 kidney transplant recipients and 7 patients with glomerular diseases, in whom Mycophenolate was continued along with standard of care during Covid-19 infection.

Results: 4 renal transplant recipients had 30% to 75% lung involvement on high resolution tomography of the chest while 3 patients with glomerular diseases had 30% (1 patient) and 50% (2 patients) lung involvement because of Covid-19 infection. All patients recovered completely within 2 weeks. There was no worsening of renal function and drop in blood cell counts. Mycophenolate was well tolerated, and no adverse effects were noted.

Conclusions: Mycophenolate administration is safe during Covid-19 infection. Mycophenolate, an Inosine Monophosphate Dehydrogenase (IMPDH) inhibitor, decreases guanosine synthesis, the basis of its antiviral and immunosuppressive effects. It could be an effective immunosuppressive agent in Covid-19 infection. Its antiviral effects would be helpful in decreasing the mortality. It is likely to be useful in different strains other viral pandemics in future.

Keywords: Covid-19, Cytokine storm, Mortality, Mycophenolate.

Introduction

The pandemic of the Covid-19 infection has affected the population of almost all the countries in the world. As per the worldometer website, 147,164,515 people have been infected by the Covid-19 (SARS CoV 2) and 3,115,020 people have died worldwide (overall mortality rate 2.11%) till the date of writing this report.[1] The aberrant immune response resulting in the cytokine storm is an important cause of morbidity and mortality in Covid-19 infection.[2,3] This also necessitates the need for administration of immunosuppressive agents along with antiviral drugs in the management of Covid-19 infection.

Though immunosuppression is an important component of treatment of Covid-19 infection, kidney transplant recipients have been shown to have significantly higher mortality compared to those who are not on immunosuppressive medications.[4] Early reports of outcomes of Covid-19 infection were published in Kidney International. In one series of 7 kidney transplant recipients, 5 patients were managed as inpatients, one patient died, and one had Acute Kidney Injury (AKI).[5]

In another series of 20 kidney transplant recipients, 87% patients developed radiological progression of lung involvement with 73% requiring escalation of Oxygen supplementation therapy. Six patients developed AKI and one patient required hemodialysis. Five patients died after a median period of 15 days.[6]

A recent multicentre study in India revealed that the mortality due to Covid 19 infection in the kidney transplant recipients was five times higher compared to the normal population (29 out of 250 renal transplant recipients with Covid 19 infection died over 6 months period).[7]

The treatment of Covid 19 infection involves nasal Oxygen supplementation and respiratory support (with non-invasive and invasive ventilation), if required, and pharmacotherapy. Different pharmacological agents have been used with variable success in different parts of the world. These include antiviral agents like Lopinavir, Ritonavir,[8] Favipiravir[9] and Remdesivir,[10] immunosuppressive agents like Methylprednisolone[11] and monoclonal anti-Interleukin 6 antibodies (Tocilizumab)[12] and supplements of Vitamin C and Zinc. Agents like Ivermectin[13] and Colchicine[14] etc. have been used in the treatment by some centres with variable success.

In patients who are already on the drug Mycophenolate [Mycophenolate Mofetil (MMF) or Mycophenolate Sodium (MPS)], for indications like kidney transplant, lupus nephritis, proliferative glomerular diseases etc, Mycophenolate is promptly stopped after the diagnosis of Covid-19 infection as standard of practice.[3-6] This also increases the risk of allograft dysfunction due to acute rejection in transplant recipients and relapse of the original glomerular disease in those with glomerular diseases.

Here we present a case series of 14 patients, 7 kidney transplant recipients and 7 patients with glomerular diseases, who were already on Mycophenolate at the time of diagnosis of Covid-19 infection. As there was shortage of hospital beds and travel restrictions due to the Covid-19 pandemic, patients were managed at different clinics and hospitals wherever appointments were available. The investigations and the

treatment were done as per the discretion of the treating physicians. In all these patients Mycophenolate was not stopped by the treating physicians and was continued along with the standard of care for Covid-19 infection.

Materials and Methods

This retrospective study was done in city in western Maharashtra, India.

Mycophenolate was continued by the treating physicians in fourteen patients, who were already taking the drug, after the diagnosis of Covid-19 infection. Out of these fourteen, seven patients were kidney transplant recipients and seven were patients with glomerular disease. These patients received other treatment for Covid-19 infection as per the discretion of the treating physician.

Data were collected retrospectively from the medical records to assess the impact of Mycophenolate on the outcomes of these patients during Covid-19 infection.

Results

In this report, we describe the outcomes of 7 renal transplant recipients and 7 patients with glomerular diseases who were on Mycophenolate when they developed Covid 19 infection.

None of these patients were vaccinated against Covid-19 infection as vaccine was not available in India when these patients developed Covid-19 infection.

The demographics, co-morbidities, medicines, and outcomes of kidney transplant recipients are presented in Table 1.

In kidney transplant recipients, other immunosuppressive agents (Tacrolimus or Sirolimus and steroids) were continued. Oral prednisolone was discontinued, and injectable Methylprednisolone was started in patients who required in-patient treatment. Patients treated on out-patient basis continued to receive oral prednisolone.

Five out of seven kidney transplant recipients had normal allograft function while two patients had mild allograft dysfunction at the time of diagnosis of Covid-19 infection. Out of 7 kidney transplant recipients, 4 patients were hospitalized for the treatment while 3 patients were treated on out-patient basis. Out of four in-patients, three patients underwent High Resolution Computed Tomography (HRCT) of thorax. Four patients had 30%, 50%, 60% and 75% lung involvement on HRCT thorax. All four in-patients received injection Methylprednisolone while 3 of them also received injection Remdesivir. Two patients required Oxygen supplementation by prongs for 2 days and one patient required High Flow Nasal Oxygen (HFNO) for 2 days before she could be rapidly weaned off to room air in 3 days. None of these patients developed acute allograft dysfunction or drop in blood cell counts during Covid-19 infection. Despite the co-morbidities shown in the table 1, the mortality in the kidney transplant recipients was zero percent. Not a single patient required the support of non-invasive or invasive ventilation. All patients got cured in 8 to 10 days without any worsening from their baseline symptoms and clinical parameters. Patients did not report any post Covid weakness and were able to resume their normal activities in 10-12 days after the diagnosis of the Covid-19 infection.

The demographics, co-morbidities, medicines, and outcomes of patients with glomerular diseases are presented in Table 2.

In the glomerular disease cohort, 5 out of 7 patients were treated as in-patients at different centres. Two patients were treated as out-patients. All 5 in-patients were investigated and treated as per the discretion of their treating physician. However, Mycophenolate was continued in all the 7 patients throughout the course of Covid-19 infection. Two in-patients and two out-patients also had chronic kidney disease. Three patients underwent HRCT thorax out of which two patients had 50% lung involvement while one patient had 30% lung involvement. All 5 patients required Oxygen supplementation by nasal prongs for 3-4 days. All patients recovered completely. None of these patients developed drop in blood cell counts, renal dysfunction or required non-invasive or invasive ventilatory support during Covid-19 infection. Patients did not report any post Covid weakness and were able to resume their normal activities within 8-14 days from the onset of symptoms.

Table 1: Data of Kidney Transplant Recipients and Covid-19 Infection

Patient ID	1	2	3	4	5	6	7
Age	27	54	33	29	15	27	48
Gender	M	M	F	M	M	M	M
Date of Kidney Transplant	11-04-2019	05-05-2019	03-08-2016	10-09-2020	03-12-2013	09-09-2010	25-11-2019
Covid-19 Test	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR
Month of Covid-19 Diagnosis	August 2020	October 2020	February 2021	April 2021	August 2020	October 2020	April 2021
Inpatient / Outpatient	Inpatient	Inpatient	Inpatient	Inpatient	Outpatient	Outpatient	Outpatient
Hospital stay	10 days	5 days	10 days	5 days	Not applicable	Not applicable	Not applicable
Oxygen requirement on admission	8L by mask	4L by mask	High Flow Nasal Oxygen	4L by mask	NIL	NIL	NIL
Comorbidities	Diabetes mellitus Hypertension Seizure disorder Hyperuricemia	Diabetes mellitus Hypertension History of pulmonary tuberculosis	Hypertension	Diabetes mellitus Hypertension	Anemia Hyperuricemia	Hypertension Hyperuricemia	Diabetes mellitus Hypertension
MMF*/MPS** Dose (per day)	MPS 720mg	MPS 720mg	MPS 720mg	MPS 720mg	MMF 1000mg	MPS 1080mg	MPS 720mg

Hemoglobin (g%)	12.4	13.2	12.4	13.2	11.3	12.7	12.9
Total Leucocyte Count (per cmm)	4400	7900	6600	8600	7600	8700	3100
Platelet Count (per cmm)	295000	177000	163000	135000	294000	274000	161000
Creatinine (mg%)	1.40	0.90	1.30	1.72	0.90	1.80	1.89
HRCT Thorax	50% lung involvement	30% lung involvement	70% lung involvement	60% lung involvement	Not done	Not done	Not done
Concomitant medications	Sirolimus 2mg/day Deflazacort 6mg/day Febuxostat 20mg/day Vitamin supplements	Sirolimus 2mg/day Prednisolone7.5mg/day Calcitriol 0.25mcg/day Vitamin supplements	Tacrolimus 2mg/day Prednisolone 10mg/day Calcitriol 0.25mcg/day Vitamin supplements	Sirolimus 2mg/day Prednisolone 10mg/day Calcitriol 0.25mcg/day Vitamin supplements	Tacrolimus 2mg/day Prednisolone 2.5mg/day Calcitriol 0.5mcg/day Febuxostat 20mg/day Vitamin supplements	Tacrolimus 1mg/day Prednisolone 10mg/day Calcitriol 0.25mcg/day Febuxostat 40mg/day Vitamin supplements	Sirolimus 2mg/day Deflazacort 6mg/day Calcitriol 0.25mcg/day Vitamin supplements
ACEI^ / ARB^^	NIL	NIL	NIL	NIL	NIL	NIL	NIL
Medicines to treat Covid-19	Methylprednisolone Remdesivir Zinc supplement Vitamin C	Methylprednisolone Remdesivir Zinc supplement Vitamin C	Methylprednisolone Remdesivir Zinc supplement Vitamin C	Methylprednisolone Zinc supplement Vitamin C	Zinc supplement Vitamin C	Zinc supplement Vitamin C	Zinc supplement Vitamin C
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered
MMF* - Mycophenolate Mofetil; MPS** - Mycophenolate Sodium; ACEI^ - Angiotensin Converting Enzyme Inhibitors; ARB^^ - Angiotensin Receptor Blockers							

Table 2: Data of Patients with Glomerular Diseases and Covid-19 Infection

Patient ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age	61	55	40	43	48	36	62
Gender	F	M	M	F	F	M	M
Glomerular Disease	Mesangioproliferative Glomerulonephritis	HIV associated Nephropathy	IgA Nephropathy	Lupus Nephritis	Membranous Nephropathy	Mesangioproliferative Glomerulonephrits	Sarcoidosis
Covid-19 Test	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR
Month of Covid-19 Diagnosis	July 2020	August 2020	September 2020	October 2020	November 2020	July 2020	July 2020
Inpatient / Outpatient	Inpatient	Inpatient	Inpatient	Inpatient	Inpatient	Outpatient	Outpatient
Hospital stay	10 days		24 days	11 days	18 days	Not applicable	Not applicable
O2 requirement on admission	4L by mask	6L by mask	High Flow Nasal Oxygen (HFNO)	8L by mask	6L	NIL	NIL
Comorbidities	Hypertension Hypothyroidism Hyperuricemia	HIV infection Hypertension Hyperuricemia Chronic kidney disease	Hypotension Hypothyroidism Hyperuricemia	Systemic Lupus Erythematosus, Anemia Chronic kidney disease Hypertension Hyperuricemia	Hypertension Hyperuricemia	Hypertension Chronic kidney disease	Hypertension Sarcoidosis Chronic kidney disease Ischemic heart disease Hyperuricemia
MMF/MPS Dose (per day)	MMF 1500mg	MPS 1080mg	MPS 360mg	MPS 360mg	MPS 360mg	MMF 500mg	MPS 720mg
Hemoglobin (g%)	12.6	13.2	11.6	7.8	11.6	15.9	14.2
Total Leucocyte Count (per cmm)	10100	9800	19900	11900	15600	5600	5800
Platelet Count (per cmm)	183000	124000	343000	102000	283000	239000	172000
Creatinine (mg%)	0.74	2.5	1.53	5.8	1.0	1.65	3.55
HRCT Thorax	Not done	30% lung involvement	40% lung involvement	30% lung involvement	Not done	Not done	Not done
Concomitant medications	Prednisolone 20mg/day Thyroxine 100mcg/day Febuxostat 20mg/day Hydroxychloroquine 200mg/day	Prednisolone 5mg/day Calcitriol 0.25mcg/day Febuxostat 40mg/day Darbepoietin 40mcg/week Vitamin supplements Antiretroviral drugs	Thyroxine 50mcg/day Olmesartan 10mg/day Calcitriol 0.25mcg/day Vitamin supplements	Prednisolone 10mg/day Thyroxine 50mcg/day Febuxostat 40mg/day Hydroxychloroquine 200mg/day Calcitriol 0.25mcg/day Darbepoietin 40mcg/week Vitamin supplements	Prednisolone 7.5mg/day Olmesartan 40mg/day Enalapril 10mg/day Calcitriol 0.25mcg/day	Enalapril 2.5mg/day Calcitriol 0.25mcg/day Vitamin supplements	Prednisolone 10mg/day Febuxostat 80mg/day Vitamin supplements

	Olmesartan 60mg/day Calcitriol 0.25mcg/day Vitamin supplements						
ACEI / ARB	Olmesartan 60mg/day	NIL	Olmesartan 10mg/day	NIL	Olmesartan 40mg/day Enalapril 10mg/day	Enalapril 2.5mg/day	NIL
Medicines to treat Covid-19	Methylprednisolone	Methylprednisolone Remdesivir	Methylprednisolone Remdesivir Enoxaparin	Methylprednisolone Enoxaparin Zinc supplement Vitamin C	Methylprednisolone Zinc supplement Vitamin C	Zinc supplement Vitamin C	Zinc supplement Vitamin C
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered
MMF* - Mycophenolate Mofetil; MPS** - Mycophenolate Sodium; ACEI^ - Angiotensin Converting Enzyme Inhibitors; ARB^^ - Angiotensin Receptor Blockers							

Discussion

It has been observed that the mortality due to Covid-19 infection in patients on immunosuppression is higher than the otherwise normal population. The current standard of practice involves immediate discontinuation of Mycophenolate, because of the fear of worsening of infection, in the patients who are already taking it as immunosuppressive agent for various indications. The studies have shown that the mortality due to Covid-19 infection is significantly higher in transplant recipients compared to general population.[4-7] In our case series, we observed that the patients had good outcomes with zero percent mortality and complete recovery despite continuation of Mycophenolate during Covid-19 infection. Contrary to the current belief, based on our observations, it appears to be safe to continue Mycophenolate during Covid-19 infection. In our opinion, stopping Mycophenolate after developing Covid-19 infection would not be a good strategy. The higher mortality after stopping Mycophenolate could be possibly related to the rebound response by the immune cells which needs to be studied further.

Mycophenolic acid (MPA) is a fermentation product of Penicillium bravicompactum and related fungi. Mycophenolate is a prodrug of MPA which increases the oral bioavailability of the drug.

Mycophenolate inhibits the enzyme IMPDH thereby reducing guanosine synthesis. Guanosine being an essential nucleotide in the synthesis of RNA and DNA, its deficiency inhibits the multiplication of the viruses and the proliferation of the lymphocytes.[15-17] This mechanism of action explains the anti-viral effects of Mycophenolate reported in the previous studies involving other viral infections.

There are two isoforms of IMPDH. Type I isoform is found in all non-lymphocytic cells while type II isoform is expressed preferentially in the T and the B lymphocytes. Mycophenolate preferentially inhibits the type II isoform of the IMPDH enzyme. Therefore, it inhibits the proliferation of the T and the B lymphocytes without affecting other normal cells of the body.[18]

In previous studies, Mycophenolate has been shown to be effective in inhibiting Dengue virus (DV) replication. In their study, Diamond MS et al showed that Mycophenolate effectively blocked DV infection, decreasing the percentage of infected cells by 99% and the levels of secreted virus by up to a millionfold.[19] Takhampuriya R et al showed that Mycophenolate along with Ribavirin led to a dramatic reduction of the intracellular viral replicase activity. Guanosine reversed this inhibition suggesting that one mode of antiviral action was by inhibition of IMPDH enzyme resulting in the depletion of Guanosine Triphosphate (GTP) pool.[20]

Mycophenolate has also been shown to have antiviral action in other viral infections including Coxsackie B3 virus (21), West Nile virus,[22] Yellow fever virus[23] and Human Immunodeficiency Virus (HIV).[24]

Inhibition of proliferation of the lymphocytes could also help in containing the exaggerated immune response which is the reason of the cytokine storm. The cytokine storm is known to cause increased morbidity and mortality necessitating the use of immunosuppressive medications like methylprednisolone, dexamethasone, and tocilizumab.

Mycophenolate is also known to have antifibrotic actions.[25] The antifibrotic actions of mycophenolate would also be useful in preventing post-covid complications like lung and myocardial fibrosis which are responsible for long term morbidity and even mortality in patients after recovery from Covid-19 infection. In our case series, no patient developed any post covid signs of respiratory insufficiency suggestive of lung fibrosis, thrombotic complications, generalised weakness, or cardiac arrhythmias.

The safety and adverse effect profile of Mycophenolate is very well known because of its availability since more than 20 years and the vast experience of using this drug in transplantation and autoimmune diseases worldwide. The literature search did not reveal any study that has directly assessed the safety and efficacy of Mycophenolate in Covid-19 infection.

Our observations are in agreement with the available literature about effect of Mycophenolate in other viral infections. The limitations of this case series are that we were not able to get all the necessary investigations done to assess the severity of infection and the extent of pulmonary involvement because of the issues of availability of the facility, logistic issues due to nationwide lockdown and the affordability of the patients. Based on our results, we feel that there is a need to conduct a prospective study to assess the efficacy of mycophenolate in general population with Covid-19 infection. We have initiated an open label prospective study [CTRI/2021/01/030477 (Registered on: 14/01/2021)] to assess the effect of low dose mycophenolate on the course

of Covid-19 infection in general population and the results appear to be very promising (unpublished data).

Learning Points

Mycophenolate can reduce or limit the severity of Covid-19 infection. It can reduce the organ damage and the post Covid fibrosis. It is likely to reduce morbidity and mortality in patients with Covid-19 infection. The mechanism of action being host oriented, it is likely to be useful in different strains of Covid-19 virus and in any viral pandemic in the future.

Conclusions

We conclude that in patients who are already on Mycophenolate for some other indication, it is safe to continue Mycophenolate as an immunosuppressant. It should not be stopped after developing Covid-19 infection. Mycophenolate also appears to be efficacious in limiting the viral replication of the Covid-19 virus as well as the intensity of the immune response thus preventing severe tissue damage. Mycophenolate, if used in general population with Covid-19 infection, is likely to reduce morbidity, mortality, cost of the treatment, need for hospitalization, length of stay in the intensive care unit (ICU) and the hospital and thus the burden over the healthcare system in Covid-19 infection. It is also likely to reduce post-covid fibrotic complications and thus improve the quality of life. Thus, it appears to be a safe and useful drug in the treatment of Covid-19 infection in the general population.

The unique mechanism of antiviral action of Mycophenolate is not specific to any virus so it is likely to prove efficacious not only in different Covid-19 strains but also in any other viral pandemics in future. The likelihood of development of viral resistance to this drug also appear less because of its host specific action. These are additional advantages of Mycophenolate during viral pandemics. Prospective studies will certainly help in establishing the role of this drug in Covid-19 pandemic.

Abbreviations

AKI – Acute Kidney Injury, MMF – Mycophenolate Mofetil, MPS – Mycophenolate Sodium, IMPDH – Inosine, Monophosphate Dehydrogenase Inhibitor, RNA – Ribonucleic acid, DNA – De-oxyribonucleic acid, HRCT – High Resolution Computed Tomography, MPA – Mycophenolic Acid, DV - Dengue Virus, GTP – Guanosine Triphosphate, HIV – Human immunodeficiency Virus, ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers.

Conflict of Interest

The authors declare that there is no conflict of interests

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None.

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