Case Report
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Use of Intravenous Immunoglobulin in Severe Covid 19 Infection - A Potential Game Changer

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Abstract

The novel Coronavirus has emerged as one of the deadliest pandemics in human history. India is facing challenges of uncontrolled proportions of new cases/death toll, highly virulent variants of Coronavirus and limited therapeutic options. The disease spectrum has mild, moderate and severe stages. Complications like SIRS, cytokine storm, ARDS and MODS are seen at severe stage and hence this stage remains a crucial target to reduce hospital stay and mortality. Immunomodulation is the cornerstone in treating hyperimmune response during severe stage. Though there are various upcoming immunomodulators, there is uncertainty about the efficacy of each. Search for the best innovative therapeutic option continues. In this context, Intravenous Immunoglobulin (IVIG) is one of the potential interventions with a unique feature of pleiotropic immunomodulating actions. In this case series, we describe two cases who were in severe stage of Covid-19 infection and didn't respond to any conventional antiviral and immunomodulators. IVIG was administered to both. It was found that there was remarkable improvement in patient's condition. Both the patients recovered clinically and were discharged from hospital. Hence, IVIG can be considered as a potential therapeutic strategy in severe Covid-19 infection.

Keywords: Immunomodulation, Immunomodulators, Severe Covid 19, IVIG

1. Introduction

The novel Coronavirus (also known as SARS-CoV-2 or COVID-19) has emerged among the list of deadliest pandemics in human history, with death tolls crossing 3.4 million worldwide. COVID-19 infection is a spectrum of disease ranging from mild, moderate and severe stages. Mild stage is characterized by acute viral phase with heavy viraemia. In severe stage there is immune dysregulation and multiorgan dysfunction (which persists after viral clearance)[1] Heavy respiratory viral load and viraemia are risk factors for severe disease. Severe stage can be subdivided into early and late. **Early stage -** SIRS and hyperimmune response causes ARDS and MODS whereas in **Late stage -** Anti-inflammatory cytokines dominate leading to a state of immune exhaustion and susceptibility to secondary infections[2].

As the disease progresses to severe stage, viral load declines to such an extent that continued deterioration in late stages is unrelated to viral replication rather due to abnormal immune response. Hence treatment of covid patient shouldn't depend on antiviral agents alone as they may not be beneficial in later stages, a combined antiviral and immunomodulatory approach needs to be implemented[1,2] Immunostimulators (Thymosin Alpha) or Immunosuppresors: Corticosteroids, HCQS, Colchicine, JAK pathway inhibitors, Anti TNF alpha, IL-6/IL-1 inhibitors, RAAS inhibitors, statins, Azithromycin, GM-CSF blockers, interferons are tried. Intravenous (**IVIG)** is one of the immunomodulatory drugs which

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has benefit of both immunosuppression and stimulation. IVIG contains all subclasses of immunoglobulin G obtained from pooled human plasma. It has shown its effects on both adaptive and innate immune system. Most important effects being regulating T-regulator and T-helper cells, inhibiting inflammatory/proinflammatory cytokines, modulating B cell functions, neutralizing complement system components[3] There is limited evidence about use of IVIG in India. We report the use of IVIG in a case series of severe covid infection.

2. Case Series

Case 1:

A 37-year female, known case of type 2 diabetes mellitus presents to hospital with complains of fever, cough with expectoration, body ache since 5 days and breathlessness since 2 days. History of primary contact present (from regular visit to a gym center). Since the start of symptoms, she initially consulted nearby hospital where she was diagnosed with Covid-19 infection on day 5, HRCT chest showed extensive pneumonitis with CT severity score of 23/25. She was given conventional treatment at nearby hospital for 6 days after which was referred to our hospital in view of worsening condition and need for critical care support. She was admitted to ICU in our hospital (day 12). Evaluation for other common causes of fever (dengue, malaria, H1N1, leptospira, rickettsia, HIV, Hepatitis, pulmonary TB) were negative. Pregnancy test was negative and cardiac evaluation was normal. Antibiotcs adviced as per stewardship to counter sepsis and ARDS. Initially started with piperacillin tazobactum (4.5gm TID, azithromycin 500mg for 5 days), later escalated to meropenem (1gm TID) and levonadifloxacin (800mg BD) as per culture and sensitivity. Standard adult dose and duration of remdesivir (100mg OD), ivermectin (12mg BD) and doxycycline (100mg BD) were administered. During the first week high dose steroids (methylprednisolone sodium succinate 40- 250mg) and 2 units convalescent plasma. During second week single dose of bevacizumab 400mg IV given. Inj enoxaparin 1mg/kg sc to target D-dimer levels within 500ng/ml. Patient condition continued to worsen. On day 14, IVIG 40 gm administered without any adverse events. Subsequent doses were tapered down to 30gm daily for 6 days under strict observation. Total duration of IVIG therapy was 7 days. On day 26, repeat COVID RT PCR was done and was reported negative. Inj voriconazole (200mg IV BD) started for oral thrush.

Case 2:

43-year male, no known co-morbidities presented to hospital with complains of fever, cough, running nose and breathlessness since 3 days. He consulted nearby hospital on day 3, diagnosed with Covid-19 (by RT-PCR) and was started on conventional treatment. After 3 days, he was referred to our hospital in view of worsening condition and need for critical care. In our hospital, patient was admitted in ICU on day 6 with high oxygen support. Evaluation for other common causes of fever (dengue, malaria, H1N1, leptospira, rickettsia, HIV, Hepatitis, pulmonary TB) were negative. Cardiac evaluation was normal. HRCT chest done at admission showed bilateral extensive patchy pneumonitis, CT severity score of 22/25. Antibiotics initiated as per stewardship to counter sepsis and ARDS. Initially started with cefoperazone+sulbactum (1.5gm BD), azithromycin 500mg OD for 5 days, later escalated to meropenem (1gm TID), Tigecycline (50mg BD), Teicoplanin (400mg OD) and Polymyxin B (5LU BD) according to culture and sensitivity. Standard adult dose and duration of remdesivir (100mg OD), ivermectin (12mg OD) were used Inj enoxaparin 40–60mg sc to target D-dimer levels <500ng/ml. Immunomodulators: high dose steroids (methylprednisolone sodium succinate 40–250mg/day). During first week, 1 unit of convalescent plasma was given. During second week single dose of bevacizumab 400mg IV was given. Patient condition continued to worsen. On day 19, IVIG 40gm IV stat administered without any adverse events. Subsequent doses were tapered down to 30gm daily for 6 days under strict observation. Total duration of IVIG therapy was 7 days. On day 27, repeat COVID RT PCR was done and was reported negative.

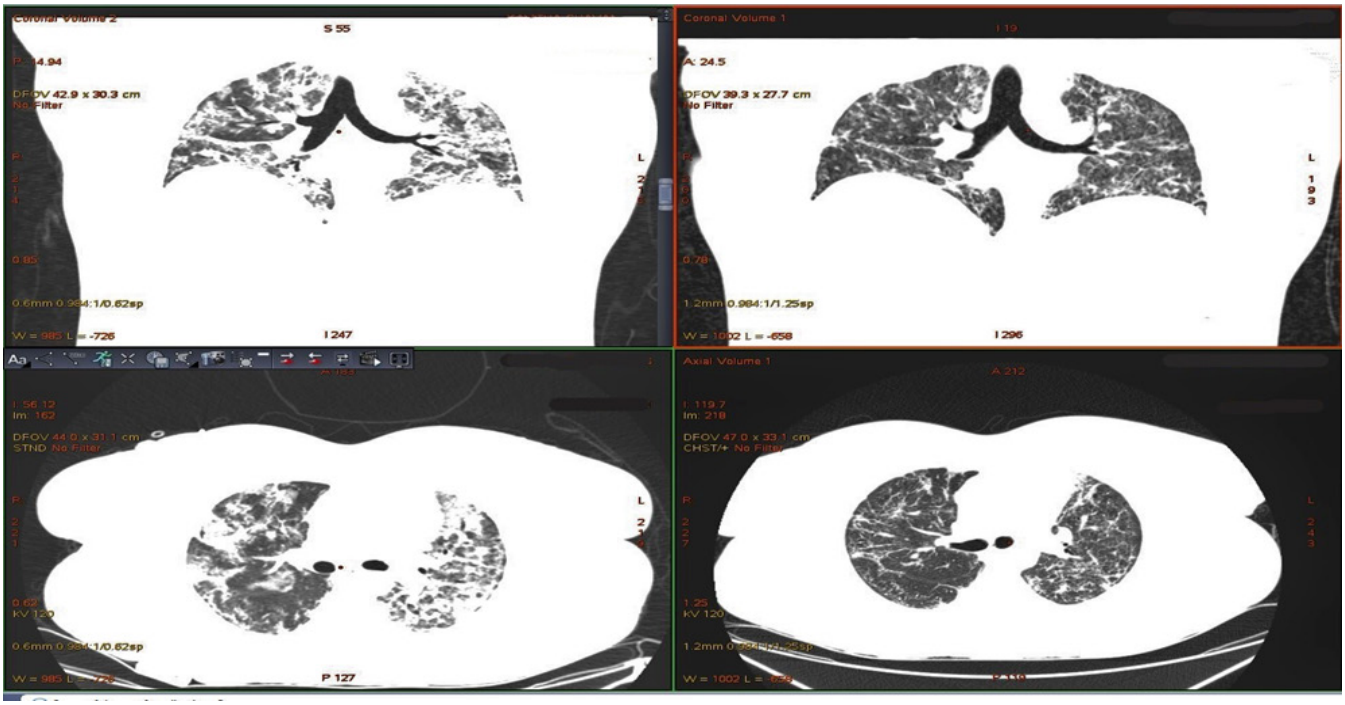
Intense clinical monitoring of vital parameters, intake and output, peripheral oxygen saturation were done. Serial blood count profile, renal function test, liver function test, inflammatory markers (CRP/IL6, LDH, ferritin) and D-dimer levels were performed as per requirement. 2D echocardiogram, chest x-ray, HRCT chest (before and after IVIG) were performed to guide the management. Respiratory support was provided with devices like Oxygen mask, NRBM mask, bipap mask, High Flow Nasal Cannula mask with appropriate oxygen

Table 1. Depicting clinical, laboratory and radiological parameters of case 1 during hospital stay (CTSS-CT severity score, NRBM: Non re breathing mask, HFNC: High flow nasal cannula)

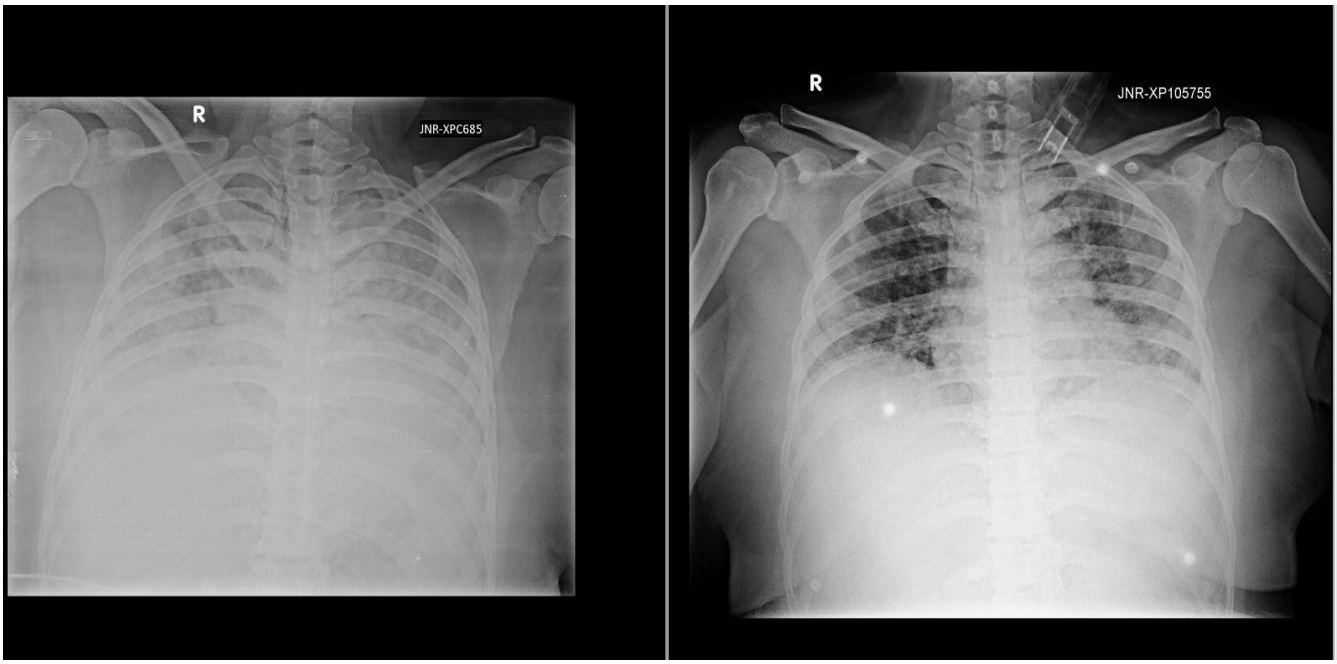
Case 1	admission			IVIG (D1)	IVIG (D2)	IVIG (D3)	IVIG (D4)	IVIG (D5)	IVIG (D6)	IVIG (D7)			Discharge
Date	**21/4 (D7)**	**1/5 (D17)**	**2/5 (D18)**	**3/5 (D19)**	**4/5 (D20)**	**5/5 (D21)**	**6/5 (D22)**	**7/5 (D23)**	**8/5 (D24)**	**9/5 (D25)**	**11/5 (D27)**	**16/5 (D32)**	**20/5 (D36)**
Temperature (degree F)	98.6	100	101	99	98.6	98.5	98.6	98.7	98.6	98.6	98.8	98.5	98.6
Heart rate (bpm)	90	110	115	105	98	95	88	80	85	78	82	72	78
Blood pressure (mm/hg)	130/90	106/60	108/62	118/70	120/70	116/76	130/70	124/78	136/80	132/76	120/70	116/60	122/66
Respiratory rate (cpm)	30	32	30	28	20	21	20	22	19	17	19	15	17
SPO2 (%)	91	86	89	89	91	93	93	92	90	94	95	93	95
TOTAL COUNT (cells/ mm3)	10350	20490	22300	20300	16560	9420	12340	6780	10340	4930	7680	9000	7070
LYMPHOCYTE (%)	12	7	4	3.8	5.5	7	9	6.6	9.1	8.5	7.9	14	16
NEUTROPHIL (%)	83	87	93	94	90	90	86	91	86	90	89	79	78
PLATELETS (lakhs/ml)	1.6	2.9	2.8	2.7	2.2	2.1	2	1.8	2	1.6	1.7		
D DIMER (ng/ ml)	650	2110	760	600	600	1344	1832	2658	2871	570		480	
IL-6 (pg/ml)	35	197	101	62	48	19	20	2.2			8.9		
CRP (mg/L)	32	157	256	150	85	62	28	17	11	8	3.3		
VENTILATION MODE	NRBM	NIV	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	NRBM	Nasal prong
Oxygen flow (L/ min)	15	N/A	60	60	60	60	50	50	50	50	40	10	2
FIO2 (%)	80	80	100	100	80	80	80	50	50	40	40	60	28
PAO2:FIO2 ratio	173	83	63	55	61	75	134	160	118	120	272	183	305
CHEST XRAY (AP view)	status quo	worse-ned	worse-ned	worse-ned	status quo	mild improve-ment	mild improve-ment	improve-ment	status quo	status quo	mild improve-ment	Improved	Improved
HRCT CHEST (CTSS)	23/25												14/25

Table 2. Depicting clinical, laboratory and radiological parameters of case 2 during hospital stay (CTSS-CT severity score, NRBM:Non re breathing mask, HFNC: High flow nasal cannula)

Case 2	admis-sion		**IVIG (D1)**	**IVIG (D2)**	**IVIG (D3)**	**IVIG (D4)**	**IVIG (D5)**	**IVIG (D6)**	**IVIG (D7)**				Discharge
DATE	27/4 (D12)	28/4 (D13)	29/4 (D14)	30/4 (D15)	1/5 (D16)	2/5 (D17)	3/5 (D18)	4/5 (D19)	5/5 (D20)	6/5 (D21)	14/5 (D29)	19/5 (D34)	21/5 (D37)
Temperature (degree F)	98.8	99	98.6	98.5	98.7	98.6	98.9	98.6	98.7	98.6	98.6	98.6	98.6
Heart rate (bpm)	125	105	98	101	90	95	92	89	82	85	79	72	78
Blood pressure (mm/hg)	140/88	118/80	126/70	120/70	136/86	122/62	110/66	130/70	116/60	122/70	128/82	110/60	124/78
Respiratory rate (cpm)	32	30	29	29	25	26	27	25	28	24	19	18	17
SPO2 (%)	86	89	89	90	89	91	90	91	92	93	95	94	95
TOTAL COUNT (cells/mm3)	11310	14490	14410	9440	10650	11860	13590	12130	10270	10540	6560	4610	7050
LYMPHOCYTE (%)	4.60%	5.2	5.1	8.3	5.5	6	4.9	7.7	10	27	32	43	34
NEUTROPHIL (%)	94.00%	92	92	88	90	90	92	86	83	66	57	45	58
PLATELETS (lakhs/ml)	2.1	2.07	2.36	2.3	2.8	2.9	3.09	3.08	2.7	2.4	1.4	2.2	3.2
D DIMER (ng/ml)	9544	8214	11760	6410	6580	5070	4030	4420	5928	4289	1470	1490	
IL-6 (pg/ml)	29				13.2	5.9	7.2	8.8		20		0.4	
CRP (mg/L)	112	85	112	28	16.9	ND	6.7	4	14	11.7	17	8	
VENTILATION MODE	NIV	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	NRBM	FACE MASK	Nasal prong
Oxygen flow (L/min)	N/A	60	60	60	60	60	60	60	60	60	6Lt	3Lt	2Lt
FIO2 (%)	100	100	100	100	100	100	100	90	90	90	40	30	28
PAO2:FIO2 ratio	49	74	65	64	66	64	61	62	110	68	195	366	339
CHEST XRAY (AP view)	worsen-ing	worse-ning	status quo	Status quo	status quo	status quo	mild worsen-ing	status quo	status quo	mild worsen-ing	improv-ing	Improv-ing	improv-ing
HRCT CHEST (CTSS)	22/25												19/25

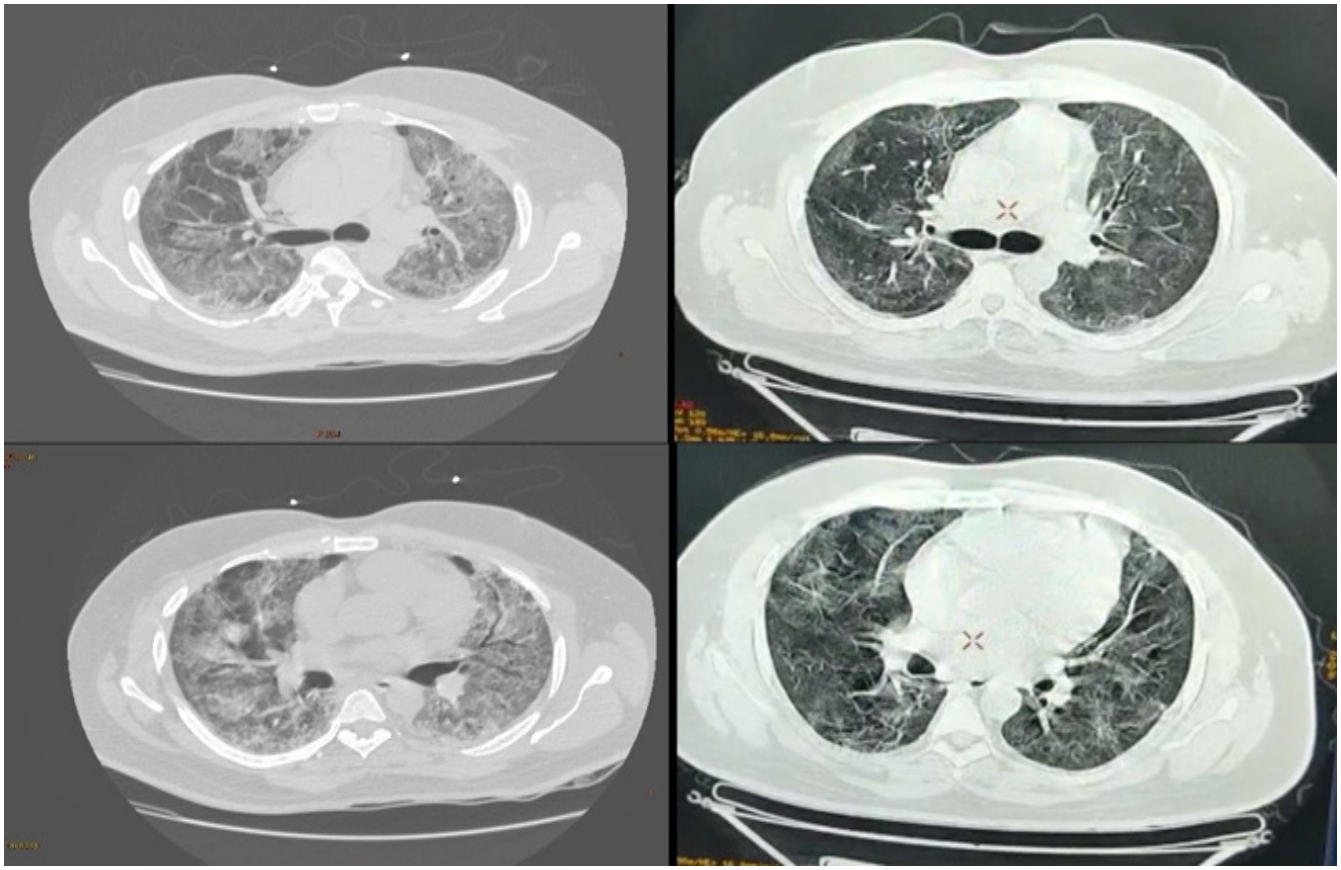


(a)



(b)

Figure 1. (A) HRCT chest, coronal (top) and axial (bottom) sections before (left) and after (right) IVIG course of case one. (B) Chest xray AP views, before(left) and after(right) IVIG course of case 1.



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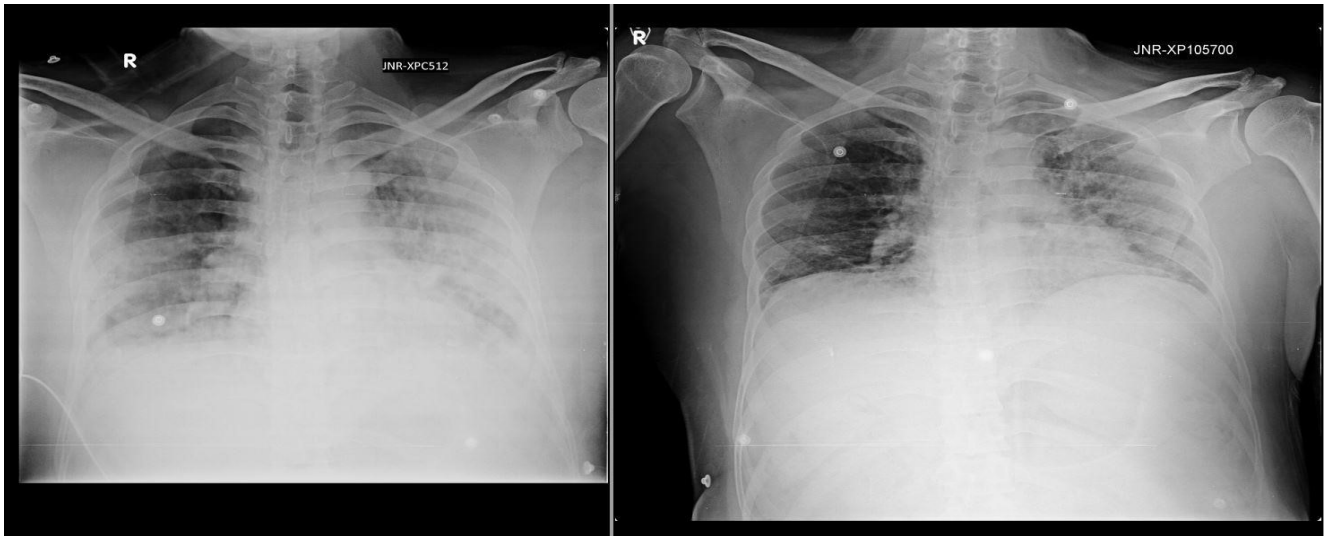

(b)

Figure 2. (A) HRCT chest, axial views, before (left) and after (right) IVIG course of case 2. (B) Chest Xray AP view before (left) and after (right) IVIG course of case 2.

flow to target oxygen saturation of 90-92%. Patient underwent regular awake proning (8hrs at night and intermittent in morning), chest and limb physiotherapy, deep breathing exercises, Incentive spirometry, Intercostal muscle training exercises. However, their condition worsened to severe stage requiring ICU admission wherein inflammatory markers were high (cytokine storm), pneumonia worsened to severe ARDS (CT severity score worsened), oxygen requirement increased from face mask to Bipap support and finally landing in high flow nasal cannula with 100% fio2. At this point, patients were decided on starting IVIG after obtaining informed consent (consent was taken from their relatives) IVIG dose: 40gm IV on day 1, 30gm from day 2 to day 7. Patients tolerated IVIG well with no adverse reactions. There was clinical improvement in both patients with simultaneous stabilization of laboratory (as shown in Tables 1 and 2) and radiological parameters (as shown in Figures 1–3). Case 1 started showing improvement 2 days after completion of IVIG. Case 2 started improving from day 4 of IVIG itself with successful avoidance of invasive ventilation. Repeat covid RT PCR test were negative (day 27 for case 1, day 26 for case 2). Patients were discharged (on day 36 for case 1, day 38 for case 2) with home oxygen requirement of 2-3lts and were asked to follow up after a week.

3. Discussion

Cytokine storm and viral evasion of immune responses play equally important role in pathogenesis and final outcome of Covid-19 infection. Severe Covid stage is further divided into two parts: Early stage of MARS-Mixed Antagonistic Response syndrome: in early severe stage wherein hyperinflammatory status leads to cytokine storm causing SIRS, ARDS, MODS/MOF and late stage of CARS-Compensatory Anti-inflammatory Response Syndrome: in late severe stage wherein anti inflammatory cytokines (like IL4, IL10) and T-reg cells dominate causing inhibition of immune cells activation,

Table 3. Mechanism of action of IVIG[10,11]

BIOLOGIC TARGET	MODE OF ACTION
T Lymphocytes	Inhibition of T cell derived IL2, IL10,TNF B and IFN Y. Antibodies against CD4 cells+HLA 1 AND 2+CCR-5, normalizing Th1:Th2 balance
B Lymphocytes	Auto reactive Antibody neutralization, inhibition of antibody production Inhibition of IL6 and TNF A production, induction of B cell apoptosis
Monocyte/ Macrophage system	IL8 production, suppress phagocytosis, surface expression of inhibitory FcYRIIB receptor (anti inflammatory) and suppress FCYRI , FCYRIII expression
Dendritic cells	Suppress IL12 production, stimulate IL10 production
Complement system	Antibodies against C1, C3a,C3b and C4,Prevent MAC formation, inhibiting C3 convertase precursors
Cytokine system	Modulate IL1,2,3,4,5,10 , TNF alpha and GM CSF, production of IL1 receptor antagonist
Non specific	Suppress platelet consumption, enhance glucocorticoid receptor binding affinity and improve its effect especially against lymphocyte activation, increased expression of PPARY for anti inflammatory effect, suppress TLR4 expression. Block cell migration by binding to ICAM-1.

immune exhaustion and susceptibility to secondary infections. Hence it is important that critically ill covid 19 patients need an appropriate immunomodulation accordingly: immunosuppression in MARS stage and immunostimulants in CARS stage[(2)] In the present series, both the cases had a disease progression starting from mild symptomatic stage on week one followed by moderate stage from week 2 to severe stage by 3rd week. Timing of immunomodulation is important. It was found that cytokine storm generally starts 5-7 days after initiation of symptoms and this is the "time window" for starting immunomodulators to have maximum benefit[4].

In the present series, antiviral therapy like remdesivir, favipiravir, azithromycin, ivermectin and doxycycline were started in first week. Case 1 was started on steroids with convalescent plasma and bevacizumab on second week. Case 2 took steroids from first week (worsening symptoms), later received convalescent plasma and bevacizumab in second week. As such, most of immunomodulation were started at appropriate time window.

IVIG is a blood product derived from pooled serum of thousands of healthy donors. Serum IgG (mainly IgG1 and IgG2) is the major component. Traces of IgA, IgM are also present[4]. Two forms are available Lyophilized (needs to be diluted with water/ saline/5% Glucose) and liquid form(0.5 OR 10% solution, ready for direct use)[11] On historical grounds, IVIG was first used to treat immunodeficiency disorders due to hypoglobulinemia. Later upon discovering its pleiotropic immunomodulating actions (on both innate and adaptive immunity), it was used to treat immune mediated diseases involving hematologic, neuromuscular, rheumatologic, ophthalmologic and dermatologic systems[4] IVIG was also used to treat infectious diseases like SARS, MERS, influenza with positive results in the past[6]. IVIG acts on all the components of immune system and exerts its beneficial effect (Table 3). IVIG has both immunosuppression and immunostimulation properties to collectively provide a beneficial outcome in severe stage covid infection. IVIG can be used in both early and late severe stage of covid infection

In our study, IVIG was considered as a last resort after exhausting all therapeutic options (antiviral+immunomodulators). IVIG was started on third week for both cases (case 1 started on day 1 , case 2 on day 19). Upon using IVIG, promising results seen in terms of patient survival including significant improvement in patient symptoms, laboratory reports and radiologically, the results were similar to those observed by other authors earlier in covid 19 infections, it also reduced the need for mechanical ventilation, duration of hospital stay[4–6]. The high cost and lack of enough evidence to propose IVIG as a standard method of treatment remains a major drawback for use of IVIG.

4. Conclusion

IVIG therapy in severe Covid-19 infection can be beneficial in terms of clinical, laboratory, radiological improvement and can act as a "game changer" by reducing mortality. In the difficult situation of acute covid crises, when all the existing modialities fail, IVIG may be of use in saving the life of the patient.

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