Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO

HIV Drug Therapy 30 GLASGOW 2022 | HYBRID YEARS

Poster n: P258

tomaso.beringheli@unimi.it

RETROSPECTIVE STUDY COMPARING OUTCOME, SAFETY AND VIROLOGICAL CLEARANCE AT DAY 7 IN PATIENTS WITH MILD-MODERATE COVID-19 DISEASE TREATED WITH MOLNUPIRAVIR, NIRMATRELVIR/RITONAVIR AND SHORT-COURSE OF REMDESIVIR

T. Beringheli, F. Bai, V. Vitaletti, F. Molà, A. Copes, N. Gemignani, S. Pettenuzzo, D. Barbanotti, G. Mulè, R. Castoldi, B. Varisco, R. Nardo, L. Lundgren, L. Albertini, M. Augello, L. Biasioli, C. Falcinella, D. Tomasoni, T. Bini, G. Marchetti, A. d'Arminio Monforte

Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan, Italy.

BACKGROUND

- Antiviral therapies against SARS-CoV-2 (Molnupiravir-MNP, Nirmatrelvir/Ritonavir-PAX and Remdesivir-RDV) are indicated in mild-moderate outpatients within 5-7 days from symptoms onset, ≥1 risk factor for progression.
- These treatments demonstrated efficacy in randomized trials, but real-life data are lacking, especially in vaccinated patients [1, 2].
- We compared the efficacy, safety and virological clearance (VC) at day 7 (T7) post-treatment with MNP, PAX and RDV in SARS-CoV-2-infected patients at high risk (HR).

1. Najjar-Debbiny R, Gronich N, Weber G et al, Effectiveness of Paxlovid in reducing severe COVID-19 and mortality in high-risk patients, CID 2022; ciaci443.
2. Lee TC, Morris AM, Grover SA et al, Outpatient therapies for COVID-19: how do we choose?, OFID 2022; 9(3):ofac008.

MATERIAL AND METHODS

- Prospective study enrolling HR patients (BMI ≥30, chronic renal failure, immunodeficiencies, cardio- cerebrovascular, chronic pulmonary or neurological disease, age ≥65) with mild-moderate COVID-19 between Jan-Jun 2022. Patients hospitalized for COVID-19 were excluded.
- Treatments included: PAX (100mg/300mg-BID) or MNP (800mg-BID) for 5 days; RDV (200mg-IV day 1, 100mg day 2-3).
- Patients were assigned to groups depending on feasibility of the treatment (eg: possible drug interactions, availability of patients to came for iv treatment, etc.), decided by a group of 2-3 physician.
- Recovery was defined by 72 hours asymptomatic and a PCR/antigenic-negative nasopharyngeal swab.
- A nasopharyngeal swab and blood tests were performed at day 7 after treatment.
- Virological clearance (VC) at day 7 was defined as negative nasopharyngeal swab at the 7th day after treatment. We evaluate proportion of patients with VC at day 7. Factors associated with VC at T7 were investigated by uni and multivariate logistic regression analysis.
- We also calculated time to virological clearance as median days from symptoms onset to the PCR-nasopharyngeal swab
- Kruskal-Wallis and Chi-squared test were used.

RESULTS

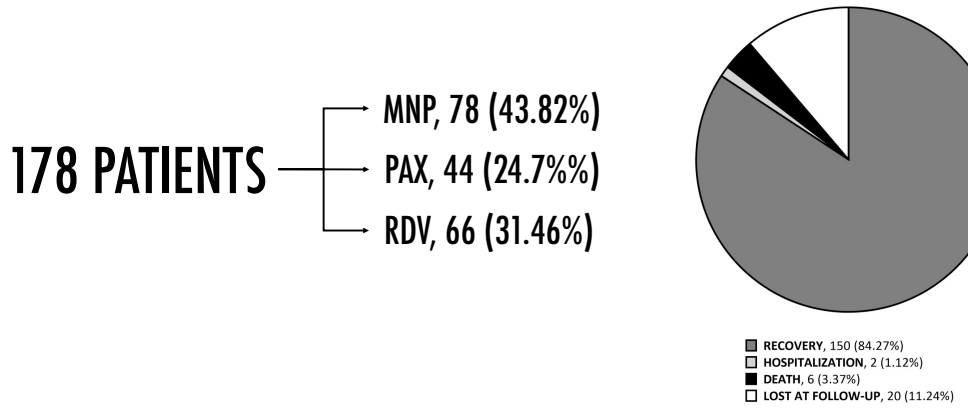
- 78/178 (43.8%) received MNP, 44/178 (24.7%) PAX and 56/178 (31.5%) RDV. *Graphic.1*
- 32 (18%) patients were either unvaccinated or incompletely vaccinated (one single dose or two doses with second dose administrated less than14 days before the infection). *Table.1*
- Patients treated with PAX were younger, presented more frequently immunodeficiency; RDV was used more in patients hospitalized for diseases other than COVID-19.
- Recovery was obtained in 70/73 (95.9%) patients with MNP, 31/32 (96.9%) PAX and 49/53 (92.5%) RDV (p = 0.59). Only 2 (1.3%) patients were hospitalized (1 MNP, 1 RDV); 6 (3.8%) died (2 MNP, 1 PAX, 3 RDV. *Graphic.2*.
- Interestingly, patients receiving PAX presented a higher proportion of VC at T7, and a shorter time to VC, compared to MNP/RDV. *Table.1* Data were confirmed after adjustment for age and immunodeficiency (Table.2; AOR 2.78 PAX vs MNP, 95% CI 0.98-7.93, p=0.055; AOR 1.42 RDV vs MNP, 95%CI 0.63-3.21, p=0.392).
- Early (<3 days from symptoms) treatment and previous vaccination did not result in higher rate of VC at T7.
- The comparison between vaccinated and unvaccinated population is shown in *Table.3*. In particular, unvaccinated patients fell ill more frequently in the period between January and February 2022 (corresponding to a wave of contagion) than the vaccinated. Furthermore, the unvaccinated more frequently experienced dyspnoea, although there is no statistical significance.
- Few mild adverse events were recorded. *Graphic.3*

Table.1 – Demographic and clinical characteristics of patients with mild COVID-19, according to anti-SARS-CoV-2 antiviral treatment

Characteristics	Study population N 178	MNP N 78 (43.8%)	PAX N 44 (24.7%)	RDV N 56 (31.5%)	p value
Age [years], median (IQR)	74 (58-82)	78 (66-84)	59 (49-78)	73 (63-83)	**<0.001**
Male sex, n (%)	100 (56.2%)	52 (67.5%)	20 (45.5%)	28 (50%)	**0.031**
COVID-19 vaccination, n (%):					
No	32 (18%)	14 (17.9%)	6 (18.8%)	12 (37.5%)	0.661
Yes (complete schedule, < 120 days)*	144 (80.9%)	64 (82.1%)	36 (25%)	44 (30.6%)	
Unknown	2 (1.1%)	0	2 (4.5%)	0	
Risk factor, n (%)					
Age > 65 years	105 (59%)	55 (70.5%)	12 (27.3%)	38 (67.9%)	**<0.001**
BMI >30	20 (11.2%)	7 (9%)	6 (13.6%)	7 (12.5%)	0.689
Cardio-vascular disease	75 (42.1%)	42 (53.8%)	8 (18.2%)	25 (44.6%)	**<0.001**
COPD or other respiratory disease	38 (21.3%)	15 (19.2%)	10 (22.7%)	13 (23.2%)	0.829
Neurological disease	11 (6.2%)	4 (5.1%)	2 (4.5%)	5 (8.9%)	0.582
Diabetes mellitus	34 (19.1%)	14 (17.9%)	5 (11.4%)	15 (26.8%)	0.141
Chronic kidney failure	10 (5.6%)	7 (9%)	0	3 (5.4%)	0.117
Cancer	12 (6.7%)	5 (6.4%)	3 (6.8%)	4 (7.1%)	0.986
Immunodeficiency	27 (15.2%)	8 (10.3%)	12 (27.3%)	7 (12.5%)	**0.034**
Calendar period, n (%):					
Jan-Feb 22	62 (34.8%)	35 (44.9%)	3 (4.8%)	24 (42.9%)	**<0.001**
Mar-Apr 22	58 (32.6%)	33 (56.9%)	17 (38.6%)	8 (14.3%)	
May-Jun 22	58 (32.6%)	10 12.8%)	24 (54.5%)	24 (42.9%)	
Treatments for COVID-19, n (%):					
Heparin	16 (9%)	3 (4%)	2 (5.6%)	11 (20.8%)	**0.004**
Corticosteroid therapy	4 (2.2%)	1 (1.3%)	1 (2.8%)	2 (3.8%)	0.671
Oxygen saturation, median (IQR)	97 (96-98)	97 (96-98)	97 (96-98)	96 (95-98)	0.180
Setting, n (%):					
Outpatient service	148 (83.1%)	75 (96.2%)	41 (93.2%)	32 (57.1%)	**<0.001**
Hospitalization for diseases other than COVID-19	30 (16.9%)	3 (3.8%)	3 (6.8%)	24 (42.9%)	
Days from symptom onset to antiviral treatment, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	2 (1-4)	0.958
Days from symptom onset to virological clearance, median (IQR)	13 (10-18)	15 (11-18)	11 (9-15)	13 (9-19)	**0.015**
Outcome, n (%):	N 158	N 73	N 32	N 53	
Recovery	150 (94.9%)	70 (95.9%)	31 (96.9%)	49 (92.5%)	0.850
Hospitalization	2 (1.3%)	1 (1.4%)	0	1 (1.9%)	
Death	6 (3.8%)	2 (2.7%)	1 (3.1%)	3 (5.7%)	
Adverse events, n (%):	N 148	N 67	N 30	N 51	
No	144 (97.3%)	66 (98.5%)	28 (93.3%)	50 (98%)	0.321
Yes	4 (2.7%)	1 (1.5%)	2 (6.7%)	1 (2%)	
Virological clearance at day 7 from symptoms onset, n (%):	N 133	N 60	N 26	N 47	
No	82 (61.7%)	42 (70%)	11 (42.3%)	29 (61.7%)	**0.053**
Yes	51 (38.3%)	18 (30%)	15 (57.7%)	18 (38.3%)	

LEGEND:
Kruskal Wallis and Chi-squared test for comparison among the three groups, as appropriate.
*Vaccination: no dose: 15, 8.4% - yes, only 1 dose: 4, 2.2% - complete cycle: 20, 11.2% - first booster dose: 136, 76.4% - second booster dose: 1, 0.6%.

Graphic.1 – Total population, group treatment, general outcomes



Graphic.2 - Outcomes for each treatment, n (%)

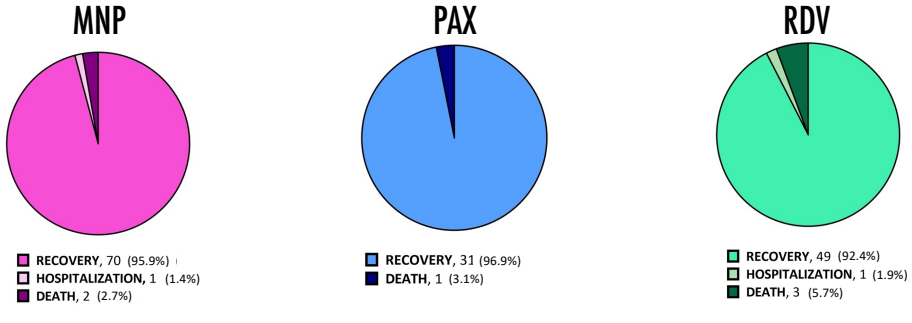


Table.2 - Treatment with Paxlovid was associated with a higher proportion of virological clearance at T7 by fitting a univariable and multivariable logistic regression

Parameters	OR	95%CI	p values	AOR	95%CI	p values
Antiviral treatment:						
Molnupiravir	1		0.059	1		0.157
Paxlovid	0.314	0.121-0.816	0.017	2.783	0.977-7.928	0.055
Remdesivir	0.690	0.308-1.547	0.368	1.425	0.633-3.206	0.392
Age, each year more	1.021	0.998-1.043	0.069	0.987	0.963-1.011	0.274
Gender,						
Female	1					
Male	1.196	0.592-2.416	0.619			
COVID-19 vaccination:						
No	1					
Yes (complete schedule, <120 days)	1.303	0.513-3.308	0.578			
Unknown						
Calendar period:						
Jan-Feb 22	1		0.032			
Mar- Apr 22	1.110	0.472-2.609	0.810			
May-Jun 22	0.364	0.150-0.883	0.025			
Risk factor for progression:						
No immunodeficiency	1			1		
Immunodeficiency	0.974	0.351-2.699	0.959	1.047	0.424-2.587	0.920
Symptoms:						
None	1					
Yes	1.730	0.437-6.846	0.435			
Setting:						
Outpatient service	1					
Hospitalization for diseases other than COVID-19	0.772	0.311-1.920	0.578			
Days from symptoms onset to antiviral treatment, each day more	0.825	0.665-1.025	0.082			

LEGEND
OR, odds ratio; AOR, adjusted odds ratio; 95%CI, 95% confidence interval. Univariable and multivariable logistic regression analysis; in the multivariable analysis the association between antiviral treatment and virological clearance at day 7th after treatment is adjusted for age and immunodeficiency.

Graphic.3 – Adverse effects for each treatment, % (black dots)

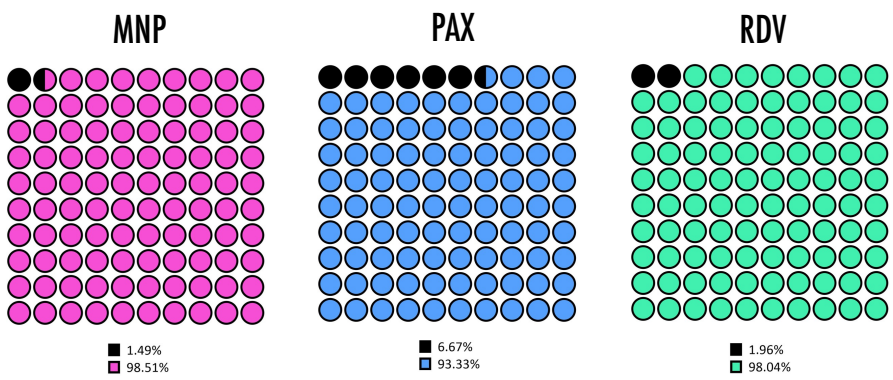


Table.3 – Comparison between patients that received complete COVID-19 vaccination schedule and unvaccinated patients

Characteristics (N 175)	Vaccinated patients N 143 (81.7%)	Unvaccinated patients N 32 (18.3%)	p value
Age [years], median (IQR)	75 (60-83)	69 (56-80)	0.292
Male sex, n (%)	82 (57.3%)	17 (53.1%)	0.663
Risk factor, n (%)			
Age > 65 years	86 (59.7%)	19 (59.4%)	1.000
BMI >30	12 (8.3%)	6 (18.8%)	**0.079**
Cardio-vascular disease	61 (42.4%)	14 (43.8%)	1.000
COPD or other respiratory disease	30 (20.8%)	8 (25%)	0.637
Neurological disease	7 (4.9%)	3 (9.4%)	0.392
Diabetes mellitus	28 (19.4%)	6 (18.8%)	0.928
Chronic kidney failure	9 (6.3%)	1 (3.1%)	0.490
Cancer	10 (6.9%)	2 (6.3%)	0.888
Immunodeficiency	24 (16.7%)	3 (9.4%)	0.301
Calendar period, n (%):			
Jan-Feb 22	46 (31.9%)	16 (50%)	**0.020**
Mar-Apr 22	54 (37.5%)	4 (12.5%)	
May-Jun 22	44 (30.6%)	12 (37.5%)	
Treatments for COVID-19, n (%):			
Heparin	12 (9%)	4 (12.9%)	0.512
Corticosteroid therapy	2 (1.5%)	2 (6.5%)	0.108
Symptoms, n (%):			
None	10 (6.9%)	4 (2.5%)	
Yes	134 (93.1%)	28 (87.5%)	0.293
Type of symptoms:			
Fever	60 (41.7%)	15 (46.9%)	0.590
Cough	74 (51.4%)	9 (28.1%)	**0.017**
Sore throat	26 (18.1%)	7 (21.9%)	0.617
Headache	13 (9%)	2 (6.3%)	0.611
Joint/muscle pain	12 (8.3%)	2 (6.3%)	0.694
Gastrointestinal disorders	2 (1.4%)	3 (9.4%)	0.014
Dyspnoea	11 (7.6%)	5 (15.6%)	0.155
Fatigue	28 (19.4%)	3 (9.4%)	0.176
Cold	20 (13.9%)	1 (3.1%)	**0.089**
Oxygen saturation >94%, median (IQR)	97 (96-98)	97 (95-98)	0.857
Setting, n (%):			
Outpatient service	122 (84.7%)	24 (75%)	0.198
Hospitalization for diseases other than COVID-19	22 (15.3%)	8 (25%)	
Days from symptom onset to antiviral treatment, median (IQR)	3 (2-4)	3 (1-4)	0.605
Days from symptom onset to virological clearance, median (IQR)	13 (10-17)	15 (10-19)	0.205
Outcome, n (%):	N 129	N 29	
Recovery	123 (95.3%)	27 (93.1%)	0.506
Hospitalization	1 (0.8%)	1 (3.4%)	
Death	5 (3.9%)	1 (3.4%)	
Adverse events, n (%):	N 67	N 30	
No	66 (98.5%)	28 (93.3%)	0.321
Yes	1 (1.5%)	2 (6.7%)	
Virological clearance at day 7 from symptoms onset, n (%):	N 109	N 24	
No	66 (60.6%)	16 (66.7%)	0.648
Yes	43 (39.4%)	8 (33.3%)	

LEGEND:
Vaccinated patients: patients who received complete vaccination schedule (first cycle and first/second booster, according to indication of Italian Ministry of Health or patients who completed the first cycle within 120 days); unvaccinated patients: patients that did not received vaccination at all or patients who received first cycle or first booster since >120 days.
Mann Whitney and Chi-squared test for comparison among the three groups, as appropriate.
Quantitative data are presented as median, interquartile range; categorical data are presented as absolute numbers, percentages.

CONCLUSIONS

- SARS-COV-2 antiviral treatments are an excellent therapeutic strategy in HR patients with mild-moderate disease.
- PAX seems characterized by a higher proportion of patients with both clinical recovery and VC as early as 7 days after treatment, nevertheless we must consider that demographic characteristics of patients were different and that patients treated with PAX were younger than whom were in the other two groups
- Taken together, these real-life data seem consistent with recent guidelines about COVID-19 therapy, that confirm the likely superiority of PAX in indirect comparisons.