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Prolonged combination treatment: an efficient and safe strategy for managing SARS-CoV-2 infection inimmunocompromised patients

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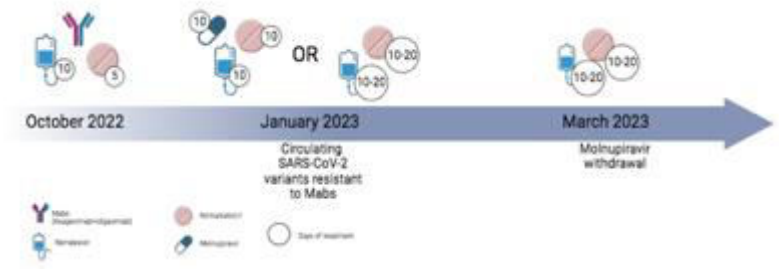
Introduction

- SARS-CoV-2 infection in immunocompromised patients can be associated with prolonged viral shedding, clinical relapses and high mortality.
- Combination treatment strategies with antivirals +/- monoclonal antibodies (Mabs) have proved efficacious but evidence is still limited.
- Prolonging antiviral treatment might improve SARS-CoV-2 clearance and outcomes.
- The aim of this study is to present safety and efficacy outcomes of combination treatment with two antivirals +/- Mabs in immunocompromised patients enrolled in an off-label protocol.

Study Design

Inclusion criteria in the off-label protocol were being immunocompromised, SARS-CoV-2 positive (RT-PCR on respiratory sample) and one of the following:

- prolonged/relapsed SARS-CoV-2
- severe COVID-19 irrespective of infection duration
- early infection in case of severe immunocompromise



Outcomes

- Virological success (negative swab within 14 days from treatment)
- Clinical success (alive, well, SARS-CoV-2 negative Day 30 and Day 100)
- Adverse events

Results

Safety

Considering 69 treatment courses, a total of 3 (4.3%) adverse events were recorded, all in Group 2 (n=2 Grade 2 bradycardia, n=1 acute kidney injury).

Results

Table 1. General characteristics and outcome measures of treated patients

	Group 1 - Late mild n=30 (47%)	Group 2 - Severe n=23 (36%)	Group 3 – Early n=11 (17%)
Age, median (IQR)	69.5(56-74.8)	73(64-79.5)	67(58.5-74.5)
Gender, female, n(%)	9(30)	8(34.7)	3(27.3)
Vaccinated	27(93.1)	19(82.6)	10(90.9)
N. vaccine doses, median (min-max)	3(1-4)	3(2-4)	3(2-6)
Underlying disease, n(%)			
NHL	18(60)	14(60.9)	3(27.3)
CLL	2(6.7)	2(8.7)	2(18.2)
AML	4(13.3)	0(0)	2(18.2)
MDS	0(0)	1(4.3)	1(9.1)
MM	3(10)	2(8.7)	1(9.1)
MF	1(3.3)	0(0)	1(9.1)
Solid tumor	0(0)	3(13)	1(9.1)
Other	2(6.7) CVID	1(4.3) liver transplant	0(0)
HSCT/CAR-T, n(%)	12(40)	3(13)	5(45.5)
SOT,n (%)	1(3.3)	1(4.3)	0
Prior early treatment, n (%)	22(73.3)	5(21.7)	0(0)
Nirmatrelvir/r	16(53.3)	3(13)	
Remdesivir	3(10)	1(4.3)	
Molnupiravir	3(10)	1(4.3)	
Prior treatment with remdesivir for moderate/severe COVID-19	0(0)	5(21.7)	
Days from early treatment to combination treatment, median(IQR)	19.5(14-40)	29(25-52)	
Treatment			
2 antivirals	26(86.7)	16(69.6)	10(90.9)
Remdesivir+Nirmatrelvir/r	26(100)	15(93.8)	10(100)
Remdesivir+Molnupiravir	0(0)	1(6.2)	0
2 antivirals+Mabs	3(10)	7(30.4)	1(9.1)
3 antivirals	1(3.3)	0	0
Treatment duration			
10 days	27(90)	15(65.2)	9(81.8)
5 days	2(6.7)	6(26.1)	1(9.1)
20 days	1(3.3)	2(8.7)	0
25 days	0	0	1(9.1)
Time from first positive swab to combination treatment, days; median (IQR)	20.5(16-40)	9(1-29)	1 (0-2)
Outcome			
Virological success Day 14, n(%)	25/29(86.2)	12/20(60)	7/11(63.6)
Days to the first negative swab, median(IQR)	7(5-9)	6(5.5-10)	9.5(6-20)
Success Day 30	26/30(86.7)	15/23 (65.2)^	10/11(90.9)
Success Day 100	18/22(81.8)°	17/23 (73.9)^	7/7(100)*°

^n=3 after second course of combination treatment
*n=1 after third course of combination treatment
°For Success Day 100, n=22 patients were evaluable in Group 1 and n=7 patients in Group 3. All Group 2 patients (n=23) were evaluable

Table 2. Univariate analysis for factors associated to virological success and clinical success at Day 30

Total, n=53	VIROLOGICAL SUCCESS, Total n=37/49*(75.5%)	p	SUCCESS DAY 30 Total n=41/53(77.3%)	p
Age, years Success vs failure, (median,IQR)	**68(56-75) vs 74(70-76)**	**0.101**	**68(57-76.5) vs 74(73-80)**	**0.050**
Gender Female vs. male, n(%)	13/17 (76.6) vs 24/32 (75)	0.909	11/17(64.7) vs 30/36(83.3)	**0.130**
N.vaccine doses Success vs failure, (median, min-max)	3(0-4) vs 3(2-4)	0.897	3(0-4) vs 3(2-4)	0.659
NHL vs other, Yes vs No (n%)	24/3 (75) vs 13/17(76.6)	0.571	27/35(77.1) vs 14/18(77.8)	0.958
Any transplant Yes vs No (n%)	13/16(81.3) vs 22/31(71)	0.444	15/17(88.2) vs 24/34(70.6)	**0.161**
COVID-19 severity Severe vs Mild (n%)	**12/20(60) vs 25/29(86.2)**	**0.036**	**15/23 (65.2) vs 26/30(86.7)**	**0.064**
Previous treatment Yes vs No (n%)	**23/26(88.5%) vs 14/23(60.9%)**	**0.025**	**24/27(88.9) vs 17/26(65.4)**	**0.041**

*total evaluable patients (patients with initial positive swab positive for SARS-CoV-2)

Conclusion

Prolonged combination treatment was safe and effective in treatment of COVID-19 in severely immunocompromised patients.

References

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2. Longo BM, Venuti F, Gaviraghi A, Lupia T, Ranzani FA, Pepe A, Ponzetta L, Vita D, Allice T, Gregorc V, et al. Sequential or Combination Treatments as Rescue Therapies in Immunocompromised Patients with Persistent SARS-CoV-2 Infection in the Omicron Era: A Case Series. Antibiotics. 2023; 12(9):1460.