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POOLED ANALYSIS OF RANDOMIZED TRIALS COMPARING DRUG EFFICACY FOR EARLY COVID-19 DURING OMICRON WAVES

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BACKGROUND

Antivirals and monoclonal antibodies are largely used for early treatment of COVID-19 in high-risk people, based on data from randomized trials (RCTs) among unvaccinated people before the omicron era. No evidence from RCTs is available on the comparison of clinical efficacy of currently available treatments. We present a pooled analysis of two RCTs conducted in Italy during omicron waves.

METHODS

MANTICO (EudraCT 2021-002612-31) and MONET (EudraCT 2021-004188-28) are two multicentric, open-label, phase 4 RCTs supported by the Italian Drug Agency.

Non-hospitalized patients (pts) with early COVID-19 (≤5 days after symptoms onset) and >=1 risk factor were randomized 1:1:1 to receive 500 mg of intravenous sotrovimab (SOT) or 600 mg of intramuscular tixagevimab/cilgavimab (T/C) or oral 5-days course of nirmatrelvir/ritonavir (N/r) 300/100 mg BID.

Primary outcome was COVID-19-related hospitalization or death within 29 days after randomization. Fisher's exact test for pooled data and incidence of failure was reported as overall and by arm with respective 95% CI. Exact logistic regression models were implemented to estimate differences between arms and to adjust for residual confounding (age, sex, and variables with imbalance >=5%).

Secondary outcome analysis on the variation of symptom prevalence over time across the arms by fitting hierarchical mixed multivariate regressions.

A: Main characteristics of study population by arms.

Patients' characteristic		ARM					
		Nirm/rit		Tixa/cilg		Sotrovimab	
		N	%	N	%	N	%
Age >65	no	160	48,19%	178	54,43%	155	46,69%
	yes	172	51,81%	149	45,57%	177	53,31%
Sex	female	159	47,89%	180	55,05%	170	51,20%
	male	173	52,11%	147	44,95%	162	48,80%
Time between symptoms and randomization	≤2 day	139	41,87%	117	35,78%	132	39,76%
	3 days	121	36,45%	134	40,98%	131	39,46%
	4-5 days	72	21,69%	76	23,24%	69	20,78%
BMI	<30	276	83,13%	268	81,96%	269	81,02%
	>30	56	16,87%	59	18,04%	63	18,98%
Diabetes	no	284	85,54%	288	88,07%	274	82,53%
	yes	48	14,46%	39	11,93%	58	17,47%
Cardiovascular disease	no	183	55,12%	172	52,60%	160	48,19%
	yes	149	44,88%	155	47,40%	172	51,81%
COPD*	no	281	84,64%	263	80,43%	286	86,14%
	yes	51	15,36%	64	19,57%	46	13,86%
Liver disease	no	327	98,49%	321	98,17%	328	98,80%
	yes	5	1,51%	6	1,83%	4	1,20%
Renal impairment	no	313	94,28%	315	96,33%	316	95,18%
	yes	19	5,72%	12	3,67%	16	4,82%
Immunocompromised status	no	270	81,33%	278	85,02%	282	84,94%
	yes	62	18,67%	49	14,98%	50	15,06%
Neurological diease	no	315	94,88%	302	92,35%	319	96,08%
	yes	17	5,12%	25	7,65%	13	3,92%
Vaccinated**	no	21	6,33%	29	8,87%	23	6,93%
	yes	311	93,67%	298	91,13%	309	93,07%
Overall		332	100,00%	327	100,00%	332	100,00%

**chronic obstructive pulmonary diseases; ** who received at least the primary cycle*

This RCT pooled analysis in the omicron era showed that ***Nirmatrelvir/ritonavir was superior to Tixagevimab/Cilgavimab in reducing COVID-19 hospital admission or death.*** *The study is inconclusive for other comparisons.*

RESULTS

991 pts (SOT=332, T/C=327, N/r=332) enrolled from Mar 2022 to Feb 2023. Vaccinated people were 93%. Diabetes, lung, and cardiovascular diseases reported an imbalance between 5% and 10% (TAB A).

Among the 8/991 hospitalizations observed, one resulted in death. ***The overall estimate of failure was 0.81% (95%CI; 0.35-1.58%).*** Incidence across the arm varied from 0% (0.00-1.10) for N/r, to 0.60% (0.07-2.16) for SOT and 1.83% (0.68-3.95%) for T/C (p=0.015 by Fisher test for pooled data).

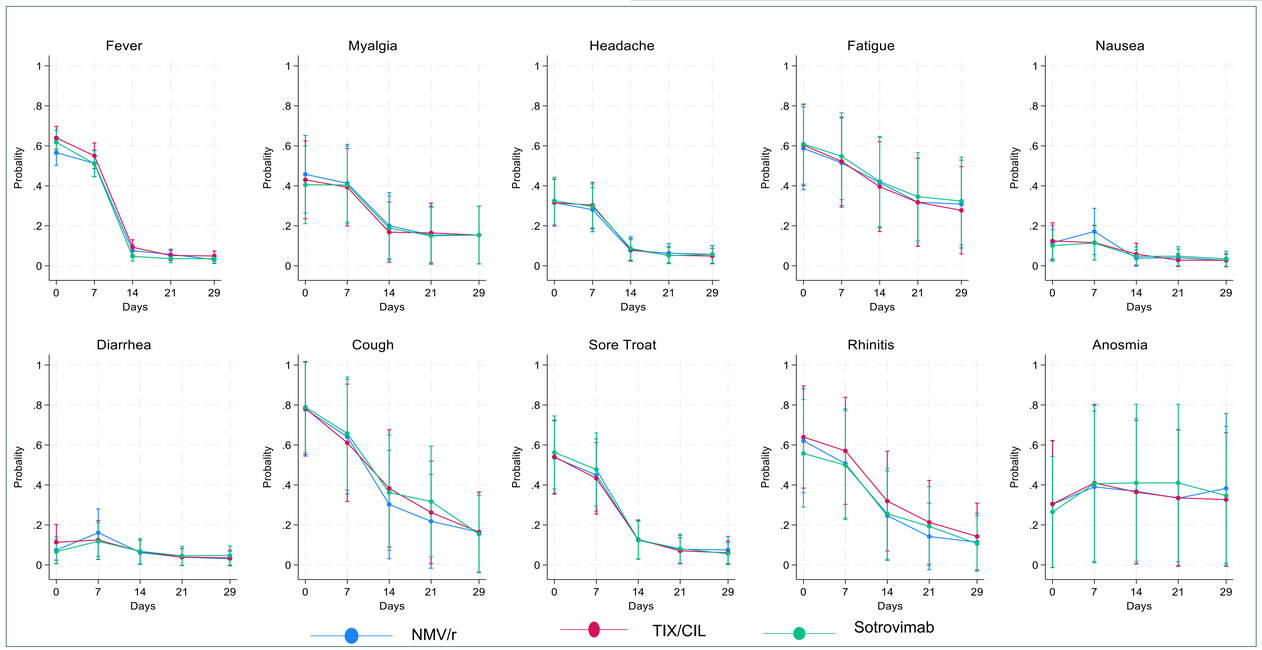
The adjusted model showed evidence for an increased risk of failure in T/C arm compared with N/r arm (OR 8.41; 95%CI 1.21-inf. p=0.015) but not for other comparisons (TAB B).

No difference was detected in symptom prevalence over time between arms, with some symptoms persisting in more than 15% of pts on day 29 (Fig C).

B: Pair-wise comparison by unadjusted and adjusted regression models.

Correction	Arm	Pair-wise comparison											
		Nirm/rit				Tixa/cilg				Sotrovimab			
		OR	95% CI		P	OR	95% CI		P	OR	95% CI		P
Unadjusted	Nirm/rit	base	-	-	-	**0,12**	**0,00**	**0,83**	**0,015**	0,41	0,00	5,32	0,499
	Tixa/cilg	**8,41**	**1,21**	**inf.**	**0,015**	base	-	-	-	3,08	0,55	31,41	0,174
	Sotrovimab	2,42	0,19	inf.	0,499	0,32	0,03	1,83	0,174	base	-	-	-
Age & sex	Nirm/rit	base	-	-	-	**0,11**	**0,00**	**0,78**	**0,012**	0,43	0,00	5,53	0,499
	Tixa/cilg	**8,97**	**1,28**	**inf.**	**0,012**	base	-	-	-	3,42	0,60	35,09	0,156
	Sotrovimab	2,33	0,18	inf.	0,499	0,29	0,03	1,67	0,156	base	-	-	-
Age & sex & CV diseases	Nirm/rit	base	-	-	-	**0,11**	**0,00**	**0,78**	**0,012**	0,43	0,00	5,49	0,499
	Tixa/cilg	**9,03**	**1,29**	**inf.**	**0,012**	base	-	-	-	3,42	0,60	35,07	0,156
	Sotrovimab	2,35	0,18	**inf.**	0,499	0,29	0,03	1,66	0,156	base	-	-	-
Age & sex & Diabetes	Nirm/rit	base	-	-	-	**0,11**	**0,00**	**0,79**	**0,013**	0,43	0,00	5,50	0,499
	Tixa/cilg	**8,88**	**1,26**	**inf.**	**0,013**	base	-	-	-	3,37	0,59	34,68	0,158
	Sotrovimab	2,34	0,18	inf.	0,499	0,30	0,03	1,70	0,158	base	-	-	-
Age & sex & COPD	Nirm/rit	base	-	-	-	**0,12**	**0,00**	**0,86**	**0,029**	0,41	0,00	5,26	0,247
	Tixa/cilg	**8,24**	**1,17**	**inf.**	**0,029**	base	-	-	-	2,99	0,51	30,99	0,278
	Sotrovimab	2,45	0,19	inf.	0,247	0,34	0,03	1,94	0,278	base	-	-	-
Age & sex & Time	Nirm/rit	base	-	-	-	**0,11**	**0,00**	**0,78**	**0,012**	0,43	0,00	5,49	0,499
	Tixa/cilg	**8,94**	**1,27**	**inf.**	**0,012**	1,00				3,39	0,60	34,68	0,158
	Sotrovimab	2,35	0,18	inf.	0,499	0,30	0,03	1,68	0,158	base	-	-	-

C: Symptoms prevalence over time by arms.



CONCLUSIONS

This RCT pooled analysis in the omicron era showed that N/r was superior to T/C in reducing hospital admission or death. Given the low number of events, the study is inconclusive with regard to the other comparisons.

The study provides no evidence for a difference in symptom prevalence over time across the arms.

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