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Safety and Potential Efficacy of Exosomes Overexpressing CD24 (EXO-CD24) for the Prevention of Clinical Deterioration in Patients with Moderate or Severe COVID-19: A Phase II, Randomized, Single-blinded Study

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ABSTRACT

Background EXO-CD24 is a novel inhaled drug of exosomes displaying CD24, a protein with anti-inflammatory properties. We evaluated the safety and potential efficacy of EXO-CD24, in a phase II, randomized, single-blinded clinical trial of EXO-CD24 in hospitalized patients with moderate or severe COVID-19, following the preliminary safety and efficacy results of a phase 1 study (ClinicalTrials.gov: NCT04747574).

Methods Two tertiary care hospitals in Athens, Greece participated. Patients received either 10^9 or 10^{10} exosome particles per dose, once per day for 5 days and were followed for 28 days. Safety and efficacy measures (including respiratory rate < 23 b/min and pulse oximetry SpO2 ≥ 94% on room air, oxygen need and levels of inflammatory biomarkers i.e. CRP, LDH, ferritin, fibrinogen and d-dimers) were compared between groups at days 3, 5 and 7. A separate analysis was conducted comparing the clinical course of treated patients with that of a control cohort (n = 70 patients) matched by propensity scoring out of a similar period hospitalized cohort (n = 202) that did not participate in the study.

Results Between June 9th and August 3rd 2021, 91 patients underwent randomization: 45 in group A and 46 in group B (109 vs. 1010 exosome particles per dose). Mean age was 49.4 (± 13.2) years and 74.4% were male. Mean time from symptom onset to randomization was 8 days. Improvement in respiratory rate and pulse oximetry was noted in 72 out of 86 (83.7%) and 55 out of 86 (64%) analyzed patients. Day 7 inflammatory indices levels dropped at least 50% from baseline admission values in 72 out of 86 (82.8%) analyzed patients (p < 0.001). No treatment-related adverse events were reported. Comparison with the propensity score matched group showed statistically significant differences in the same parameters (p ≤ 0.01 for all comparisons).

Conclusions Our results suggest safety and potential efficacy of EXO-CD24 on clinical and laboratory parameters of moderate to severe COVID-19, that deserve further investigation in a phase 3 study. (Funded by Athens Medical Society. ClinicalTrials.gov: NCT04902183, EU Clinical Trials Register EudraCT Number 2021-002184-22).

INTRODUCTION

- EXO-CD24 is a novel inhaled drug of exosomes displaying CD24, a protein with anti-inflammatory properties. Exosomes have been shown to increase stability and enhance the bioavailability of bioactive compounds.
- Phase I study showed preliminary safety and efficacy results of EXO-CD24.

METHODS

- Phase II, single-blinded, two-dose double arm randomized clinical trial (RCT) without a placebo arm to assess the dose-dependent safety and potential efficacy of EXO-CD24 in hospitalized patients with moderate or severe COVID-19 disease.
- Two tertiary care hospitals in Athens, Greece participated.
- Vaccinated individuals were excluded.
- Patients received either 10^9 (group A) or 10^{10} (group B) exosome particles per dose, once per day for 5 days in a 1:1 ratio. Patients were followed for 28 days. Any concomitant medication was allowed.
- Safety and efficacy measures (including respiratory rate < 23 b/min and pulse oximetry SpO2 ≥ 94% on room air, oxygen need and levels of inflammatory biomarkers i.e. CRP, LDH, ferritin, fibrinogen and d-dimers) were compared between groups at days 3, 5 and 7.
- Athens Medical Society in Athens, Greece, was the study sponsor.
- In a post-hoc analysis we compared treated patients with a control cohort (n = 70 patients) matched by propensity scoring out of a similar period hospitalized cohort (n = 202) that did not participate in the study.

RESULTS

- Between June 9th and August 3rd 2021, 91 patients underwent randomization: 45 in group A and 46 in group B (10^9 vs. 10^{10} exosome particles per dose).
- Mean age was 49.4 years and 74.4% were male. Most common comorbidities were obesity (43.8%), hypertension (21.3%), dyslipidemia (19.1%) and diabetes mellitus (9.0%) (Table 1).
- No treatment-related adverse events were reported.
- Improvement in respiratory rate and pulse oximetry was noted in 72 out of 86 (83.7%) and 55 out of 86 (64%) analyzed patients. Day 7 inflammatory indices levels dropped at least 50% from baseline admission values in 72 out of 86 (82.8%) analyzed patients (p < 0.001). Outcomes were similar between groups (Table 2, Figure 1).
- 51 (62.2%) patients achieved an improvement of at least 1 point in the NIAID-OS from baseline to Day 7 (Figure 2).
- Only one (1.2%) patient required invasive mechanical ventilation due to disease progression up to Day 7. One (1.1%) patient died during the 28-day follow-up.
- Significant reduction of interferon γ, interleukin (IL)-1a, IL-1b, IL-5, IL-6, IL-12, IL-13 and IL-17 were noted on Day 7 (p<0.01). IL-10 significantly increased (Figure 3).
- Post-hoc comparison with the propensity score matched control group showed statistically significant differences in rates of SpO_2 and inflammatory markers improvement on Day 7.

Table 1. Baseline characteristics

	All patients (N=89)	Group A (N=45)	Group B (N=44)	p-value
Age, years, mean (SD)	49.4 (13.2)	49.7 (14.2)	48.8 (12.3)	0.746
≤ 60, n (%)	69 (77.5)	35 (77.8)	34 (77.3)	0.954
Male sex, n (%)	66 (74.2)	33 (73.3)	33 (75.0)	0.857
BMI, kg/m², mean (SD)	30 (5.7)	29.4 (4.5)	30.4 (6.6)	0.400
≥ 30, n (%)	39 (43.8)	19 (42.2)	20 (46.7)	0.759
Comorbidities, n (%)				
Hypertension	19 (21.3)	9 (20.0)	10 (22.7)	0.754
Dyslipidemia	17 (19.1)	7 (15.6)	10 (22.7)	0.390
Diabetes	8 (9.0)	4 (8.9)	4 (9.1)	>0.999
CAD	3 (3.4)	3 (6.7)	0	0.242
Atrial fibrillation	3 (3.4)	2 (4.4)	1 (2.3)	>0.999
COPD	2 (2.2)	2 (4.4)	0	0.494
CKD	1 (1.1)	1 (2.2)	0	>0.999
Score on NIAID-OS, n (%)				
4	6 (6.7)	3 (6.7)	3 (6.8)	0.893
5	65 (73.0)	32 (71.1)	33 (75.0)	
6	18 (20.3)	10 (22.2)	8 (18.2)	
Concomitant medication, n (%)				
Antibiotics	57 (64.0)	29 (64.4)	28 (63.6)	0.726
Remdesivir	75 (84.3)	38 (84.4)	37 (84.1)	>0.999
Dexamethasone	75 (84.3)	39 (86.7)	36 (81.8)	0.560
Baricitinib	14 (15.9)	8 (18.2)	6 (13.6)	0.560
Tocilizumab	8 (9.0)	5 (11.1)	3 (6.8)	0.694
Anticoagulants				
Prophylactic	58 (66.7)	29 (65.9)	29 (67.4)	0.879
Intermediate	23 (26.4)	10 (22.7)	13 (30.2)	0.427
Therapeutic	8 (9.2)	6 (13.6)	2 (4.7)	0.147

Table 2. Efficacy outcomes

	All patients (N=86)	Group A (N=43)	Group B (N=43)	p-value
RR <23/min for at least 24 hours, on Day 7, n (%)	72 (83.7)	36 (83.7)	36 (83.7)	> 0.999
SpO2 ≥ 94% on room air for at least 24 hours, on Day 7, n (%)	55 (64.0)	25 (58.1)	30 (69.8)	0.261
Decrease by 50% in either of the inflammatory markers from baseline to Day 7, n (%)	72 (82.8)	35 (81.4)	37 (84.1)	0.739
NIAID-OS, on Day 7, n (%)				
1	5 (6.1)	2 (5.0)	3 (7.1)	
3	26 (31.7)	12 (30.0)	14 (33.3)	
4	17 (20.7)	8 (20.0)	9 (21.4)	0.975
5	21 (25.6)	11 (27.5)	10 (23.8)	
6	13 (15.9)	7 (17.5)	6 (14.4)	
Change in the NIAID-OS score from baseline to Day 7, median (IQR)	-1 (-2 – 0)	-1 (-2 – 0)	-1 (-2 – 0)	0.537
Time to improvement by at least 1 point in any of the COVID-19 clinical severity ordinal scales, median (95% CI)	6 (5.2 – 6.8)	6 (5.1 – 6.9)	4 (2.9 – 5.1)	0.462
Decrease >2 breaths/min in RR from baseline to Day 7, n (%)	34 (39.5)	14 (32.5)	20 (46.5)	0.120
Increase >2% of SpO2 values from baseline to Day 7, n (%)	28 (32.5)	14 (32.6)	14 (32.6)	0.839
Admission to discharge, days, median (95% CI)	7 (6 – 8)	7 (5.9 – 8.1)	7 (6.1 – 7.9)	0.851
ICU admission up to Day 7, n (%)	1 (1.2)	1 (2.3)	0	> 0.999
Death outcome, n (%)	1 (1.2)	1 (2.3)	0	> 0.999

Figure 1. *Mean values and change over time of absolute lymphocyte count and CRP, separately in each treatment group.*

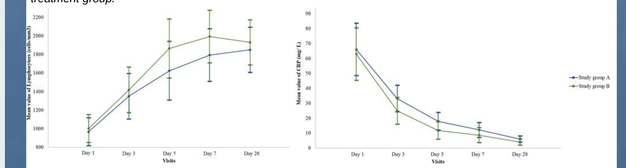


Figure 2. *Distribution of the total sample of the patients according to their responses in the 8-point NIAID- OS scale at baseline and at Day 7.*

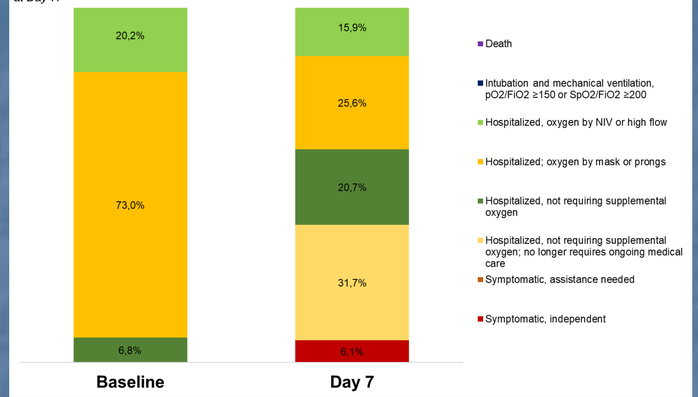
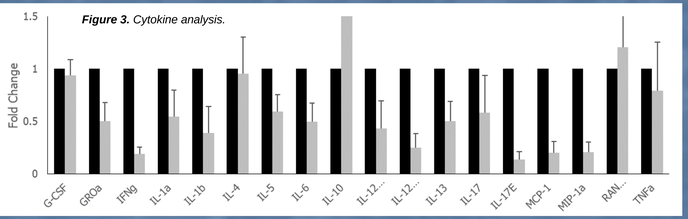


Figure 3. *Cytokine analysis.*



CONCLUSIONS

- The incidence rate of adverse events was low and none were attributed to the study medication.
- Marked improvements were noted from baseline values to Day 7 regarding respiratory signs and indices, validated COVID-19 ordinal scales and inflammatory markers.
- Cytokine analysis revealed significant reduction of the pro-inflammatory pathway and cytokines of acquired immunity, as well as significant increase of IL-10 levels likely representing activation of immune tolerance.
- Our results suggest safety and potential efficacy of EXO-CD24 on clinical and laboratory parameters of moderate to severe COVID-19.
- A phase IIb placebo-controlled RCT is currently taking place in Greece and Israel.

REFERENCES

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