Administration of Novel Allogeneic iNKT Cell Infusion (agenT-797) in Patients With Severe COVID-19 Acute Respiratory Distress Syndrome (CARDS) Receiving Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) Support

Poster # P1172

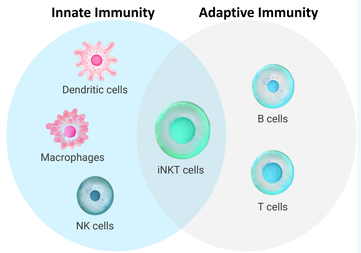
T. C. Hammond[1], M. A. Purbhoo[2], B. Yigit[2], D. Moskowitz[2], X. Michelet[2], R. Smith[2], M. Kirby[3], V. Nasonenko[3], T. Fischer[4], A. Buffa[2], W. Ortuzar[3], K. Van Besien[5], D. A. Stevens[6], R. Lee[7], M. A. Exley[2]

[1]Pulmonary, Critical Care Sleep Medicine, Saint Johns Cancer Institute, Santa Monica, CA, United States, [2]MiNK Therapeutics, Lexington, MA, United States, [3]Agenus Inc, Lexington, MA, United States, [4]Surgical Oncology, Saint John's Cancer Institute, Santa Monica, CA, United States, [5]Medicine, Weil Cornell Medical College, New York, NY, United States, [6]Oncology, Norton Cancer Center, Louisville, KY, United States, [7]Department of Cardiothoracic Surgery, Keck Hospital of USC, Los Angeles, CA, United States.

Background

- Immune system dysfunction is increasingly recognized as an important variable in survival from critical illness.
- Off the shelf immune cell therapies are emerging as potential adjunctive approaches in the treatment of a range of infectious, inflammatory and auto-immune illnesses, including COVID-19 associated Acute Respiratory Distress Syndrome (CARDS).
- agenT-797 (MiNK Therapeutics, Lexington MA) is a novel, unmodified human allogeneic invariant Natural Killer T (iNKT) cell therapy expanded *in vitro* from mononuclear cell apheresis units of healthy donors.
- agenT-797 has been trialed as a therapy in CARDS and cancer (Purbhoo et al, SITC 2022; Carneiro et al, AACR 2023).
- iNKT cells are tissue resident and demonstrate rapid homing to tissues, including the lung, liver, and kidney (Yigit et al, 2021; Purbhoo et al, 2021).
- iNKT cells play a crucial role in orchestrating the innate and humoral immune response, including against viral infections such as COVID-19 and influenza (Exley, M. et al, 2012, 2017).

Figure 1. iNKT Cell Properties



Unique Features
Respond to **lipid antigens, stress ligands, and cytokines.** Possess **invariant T cell receptor (TCR) and NK cell Receptors.**

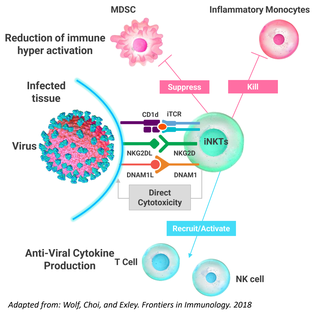
Innate and Adaptive Responses
Effector function of adaptive immune cells and **rapid activation** kinetics of innate immune cells.

Potent Activity
Amplify & accelerate immune response by interaction with a variety of effector and immunomodulatory immune cells.

Rational for agenT-797 in CARDS

- Lung hyperinflammation was characteristic of severe CARDS in alpha/delta variants of SARS-CoV-2.
- Treatment options for patients with severe CARDS were limited but high dose dexamethasone was adopted as standard of care after publication of RECOVERY 2020.
- The rationale for use of agenT-797 in CARDS was supported by the anti-viral and immunomodulatory activity of iNKT cells against influenza and hepatitis B in animal models (Exley et al, 2012).
- agenT-797 did not induce GvHD and could be used without lymphodepletion.

Figure 2. iNKT Cells in ARDS and Viral Infections



Adapted from: Wolf, Choi, and Exley. Frontiers in Immunology. 2018

Direct viral killing
Recognition of CD1d ligands in diseased tissues and activation through the invariant TCR. Recognition of stress-signals through activating NK receptors, NKG2D, DNAM1.

Recruitment of host immunity
Recruitment of host T cells and NK cells. Restoring the cytotoxic capacity, activation and production of partially exhausted T cells.

Conditioning of infection site
Kill inflammatory monocytes (protects airway epithelium). Induce maturation of immature dendritic cells. Dampen pro-inflammatory cytokines.

Patient Demographics

- Patients were enrolled in a Phase I Study of agenT-797 to treat moderate to severe ARDS in COVID-19 Patients (**NCT04582201**).
- A total of 20 patients were recruited and treated, including 4 patients on venovenous extracorporeal membrane oxygenation (VV ECMO) therapy.

Table 1. Patient Demographics of Overall Study Population

Variable	Cohort 1	Cohort 2	Cohort 3	Total
agenT-797 dose level (cells)	100 X 10^6	300 X 10^6	1000 X 10^6	
Subjects dosed (n)	3	4	13	20
Age				
Median (range)	67 (66-77)	71.5 (64-75)	62 (26-75)	66.5 (26-77)
Sex, n (%)				
Male	2 (66.7)	1 (25.0)	7 (53.8)	10 (50.0)
Female	1 (33.3)	3 (75.0)	6 (46.2)	10 (50.0)
Patient disposition, n (%)				
Early Discontinuation	0	1 (25.0)	5 (38.5)	6 (30.0)
Death	0	1 (25.0)	5 (38.5)	6 (30.0)

Table 2. Patient Demographics VV ECMO Population

Age	Race	Date of COVID-19 DX	BMI (kg/m²)	Date Received	Pre Tx SOFA	Post Tx SOFA	SOFA 72 hr	SOFA 7 days	SOFA 14 days	SOFA 30 days
49	Caucasian	10/15/21	39.64	11/19/21	6	8	13	15	Died	NA
27	Latino	11/9/21	36.14	12/3/21	7	6	6	6	3	5
54	Latino	12/22/21	27.99	1/5/22	9	5	8	8	6	4
69	Caucasian	12/26/21	23.71	1/14/22	9	5	4	3	4	9

Table 2. Four patients (male; median 51.5 years old) diagnosed CARDS on VV ECMO, treated with agenT-797 iNKT cell therapy (Cohort 3: 1000 X 10^6 cells).

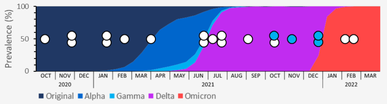


Figure 3. Date of COVID-19 DX for all patients in the context of SARS-CoV-2 strain prevalence in the USA. Patients on VV ECMO shown in blue. All patients treated in a SARS-CoV-2 variant agnostic manner.

Results

agenT-797 Demonstrates a Favorable Safety Profile in Patients on VV ECMO

Table 3. Adverse events

	Overall Study (n=20)	Patients on VV ECMO (n=4)
	n (%)	n (%)
Any AE	**20 (100.0)**	**4 (100.0)**
Any AE of grade ≥ 3	19 (95.0)	4 (100.0)
Any TRAE	**5 (25.0)**	**0 (0)**
Any TRAE of grade ≥ 3	1 (5.0)	0
Any TRAE leading to discontinuation	0	0
Any TRAE leading to dose interruption	0	0
Any TRAE leading to death	0	0

Figure 4. Serum levels of IL-1β and IL-6 in VV ECMO patients

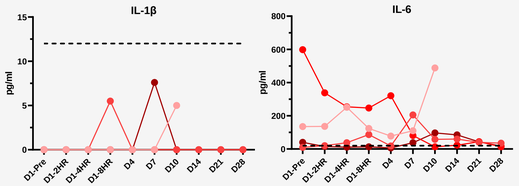
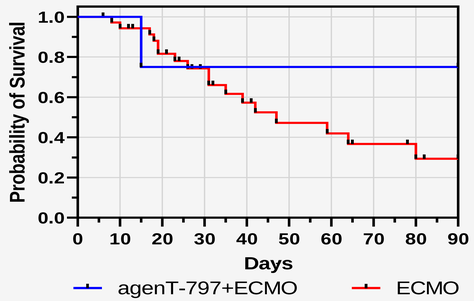


Figure 4. Serum cytokines as measured pre-infusion (D1-pre) of agenT-797, at 2-8hr post-infusion, and on subsequent visit days up to D28. Dotted line indicates upper range limit of cytokine in healthy people.

- Results from the overall study (*Purbhoo SITC 2022*) indicated that agenT-797 was well tolerated, with majority of adverse events (AEs) consistent with underlying disease. No Dose-Limiting Toxicities (DLTs) were observed, and no maximum tolerated dose (MTD) was determined. Most reported TEAEs were consistent with severe CARDS and the most frequent being anemia (n=8), fever (n=7), and acute kidney injury (n=6). One subject experienced a grade 4 TRAE of dyspnea. No TRAE were reported amongst the patients on VV ECMO (Table 3).
- Cytokine release syndrome (CRS) is a frequent post-infusion complication associated with immune cell therapies. Infusion of agenT-797 did not induce an increase in mediators (IL-1β, IL-6) of CRS, either in the overall study or in patients on VV ECMO (Figure 4). Pre-treatment levels of IL-6 were elevated in some patients on VV ECMO (as well as in the overall study) which is consistent with underlying severe CARDS.

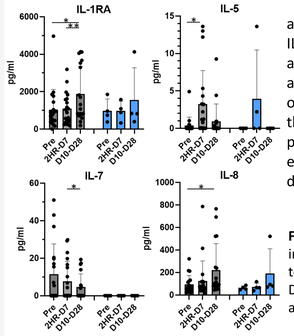
90-Day Survival of Patients on VV ECMO Treated with agenT-797 is 75%



- 90-day survival of VV ECMO patients treated with agenT-797 (n=4) was 75% compared to 30% in control data set (n=36).
- Median survival time of patients treated with agenT-797 was 119.5 days compared to 47 days in the control data set.
- In patients treated with agenT-797 there is no observed cell-therapy-associated oxygenator failure due to clogging of filters, as is seen with mesenchymal stem cell therapy in ARDS patients on ECMO. To our knowledge agenT-797 represents the first use of immune cell therapy in patients on ECMO.
- In the overall study, agenT-797 showed potential dose-dependent reduction in secondary infections, including an over 80% reduction in pneumonia at dose cohort 3 (1000 X 10^6 cells). Bacterial pneumonia in on one patient on VV ECMO cleared 12 days post-infusion of agenT-797 (patient also received concomitant antibiotics).

Figure 5. 90-day survival of patients on VV ECMO treated with agenT-797 (n=4; blue line). Control case data from patients on VV ECMO alone (n=36; red line) at the same investigator site.

Figure 6. agenT-797 Induced Anti-inflammatory Cytokines

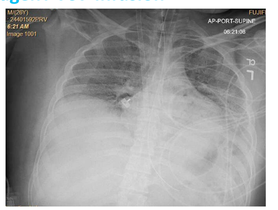


agenT-797 induced significant changes in levels of IL-5, IL-7, IL-8 and IL-1RA, highlighting the anti-inflammatory profile of agenT-797 in the overall study (grey bars; n=20) which was also mirrored in VV ECMO patients (blue bars; n=4). Levels of the pro-inflammatory cytokine IL-7 reduced over time in the overall study, but IL-7 was not detected in VV ECMO patients. IL-7 was mainly detected in the patients treated earlier during the pandemic, indicating a possible strain-dependency of the IL-7 response (Korobova et al, 2022).

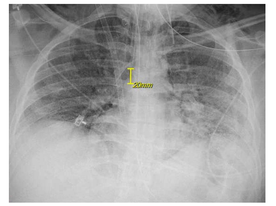
Figure 6. Serum cytokine levels shown as three timepoints: Pre-infusion (Pre), early post-infusion (average from 2hr post-infusion to day 7; 2HR-D7), and late post infusion (day 10-day 28 average; D10-D28). Significant changes: (*) 0.01<p<0.05; (**) p<0.01; data analyzed by one-way ANOVA.

Figure 7. Chest X Rays Show Improved Lung Function within 24 hours After agenT-797 Infusion

A



B



A) Pre-infusion chest X-ray (on 12/3, 0600h). **B)** Post agenT-797 infusion chest X-ray (on 12/4, 0600h) with improved lung volumes and stable parenchyma.

Conclusions

- agenT-797 demonstrates survival benefit in patients with CARDS, including those on VV ECMO (75% vs 30% survival; 119.5 vs 47d), compared to time-relevant hospital controls.
- agenT-797 was dosed to a billion cells with a favorable safety profile and induces significant anti-inflammatory changes consistent with disease modulation in respiratory distress.
- Patients with severe CARDS requiring VV ECMO rescue were dosed with a single infusion of agenT-797 up to 1 billion cells, without oxygenation failure or other significant adverse events, including cytokine release syndrome (CRS).
- These data underscore the potential of iNKT cells for the treatment of severe respiratory illness and MiNK plans to advance clinical trials of agenT-797 in this setting through externally financed programs.

References

- *Exley et al (2017). Adaptive transfer of Invariant Natural Killer T Cells as immunotherapy for advanced melanoma. Clin Can Research 23(14):3510-3519.*
- *Exley, MA (2012). NKT get the 'flu: NKT cells as (mostly) good guys in influenza; monocytic cells as double agents. J Leukoc Biol. 91(3):349-352.*
- *Carneiro et al, AACR 2023, Poster #CT275*
- *Purbhoo et al, SITC 2022, Poster #649*
- *Korobova et al (2022). Cytokine Profiling in Different SARS-CoV-2 Genetic Variants. Int. J. Mol. Sci. 23:14146*

Correspondence
Terese Hammond, M.D.

Terese.Hammond@providence.org
Providence Saint Johns Health Center, Santa Monica, CA
THammond@mednet.ucla.edu
UCLA, Los Angeles, CA