Regulatory T Cell Expansion Strategy to Target Inflammation in AD: Phase I feasibility trial

Alireza Faridar[1], Abdulmunaim M Eid[1], Aaron D. Thome[1], Weihua Zhao[1], David R. Beers[1], Maria B Pascual[1], Mohammad O. Nakawah[1], Gustavo C. Roman[1], Charles S. Davis[2], Michael Grundman[3,4], Joseph C. Masdeu[1], Stanley H. Appel[1]

1 Stanley H. Appel Department of Neurology, Houston Methodist Research Institute, Houston, Texas, USA; 2 CSD Biostatistics, Inc., Oro Valley, Arizona, USA 3 Global R&D Partners, LLC, San Diego, California, USA; 4 University of California San Diego, San Diego, California, USA

BACKGROUND

Regulatory T cells (Tregs) are a subset of T cells that play a neuroprotective role by suppressing inflammation. Treg immunomodulatory mechanisms are compromised in Alzheimer's disease (AD) individuals, shifting the immune system toward pro-inflammatory status. We investigated the feasibility of low-dose IL-2 immunotherapy on restoring Tregs population and modifying inflammation in an AD clinical setting.

METHODS

Eight AD dementia (MMSE:12-25) individuals were enrolled in a proof-of-concept phase 1, open-label, feasibility study of low-dose IL-2 treatment. The presence of brain amyloid pathology was confirmed in all participants. Enrolled individuals received monthly five-day-courses of subcutaneous low-dose IL-2 for four cycles and were followed for an additional two-month post-treatment. Treg immunophenotype and functional analysis were assessed at screening and day 1 (before IL-2 treatment), and three days after the fifth dose of each treatment cycle during therapy, and then at weeks 17 and 24. Two-sided paired t-test was used to assess the statistical significance of changes in each analyte or clinical outcome at each timepoint.

RESULTS

1. Baseline characteristics of the study participants

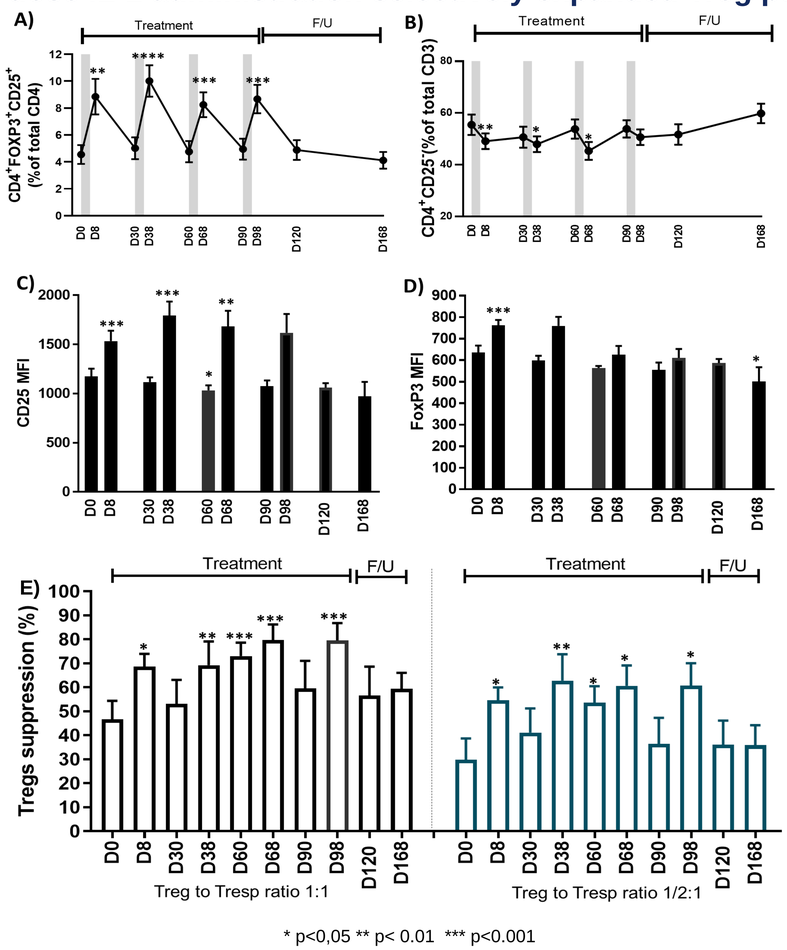
	Age	Gender	MMSE	CDR	ADAS-Cog	PIB-PET	Tau-PET	AD CSF signature	Neurodegeneration in MRI
AD1	63	F	19	5	41	+	+		+
AD2	65	F	23	4	27.66	+	+		+
AD3	69	F	16	4.5	59.66	+	N/A		+
AD4	74	M	15	7	43.66	N/A	N/A	+	+
AD5	77	M	20	5	42	N/A	N/A	+	+
AD6	75	F	23	5	30.66	+	N/A		+
AD7	70	M	12	6	42.66	+	N/A		+
AD8	72	F	24	4	34	+	N/A		+
Mean ± SD	70.6±4.8	M/F:3/5	19.0±4.3	5.1±1.0	40.1±9.9				

2. Adverse event summary

Adverse event	Number of events	Number (percentage) of Subjects affected	Related to treatment
Injection site reactions	4	3 (37.5%)	Yes
Flu like symptoms	1	1 (12.5%)	Yes
Dizziness	1	1(12.5%)	Yes
Nausea	1	1(12.5%)	Yes
Leukopenia (mild)	3	3 (37.5%)	Yes
Urinary retention	1	1(12.5%)	No
Ecchymosis	1	1(12.5%)	No
Serious adverse events	0	0	-

All adverse events were mild, and all resolved. All patients completed the four-month treatment phase as well as 2-month post-treatment follow up phase.

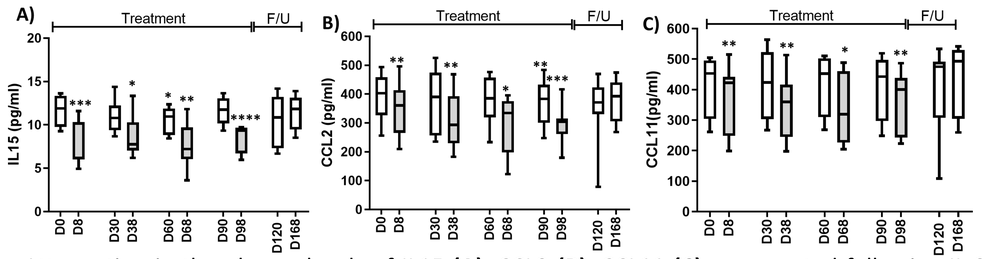
3. Low dose IL-2 administration selectively expanded Treg population



* p<0,05 ** p< 0.01 *** p<0.001

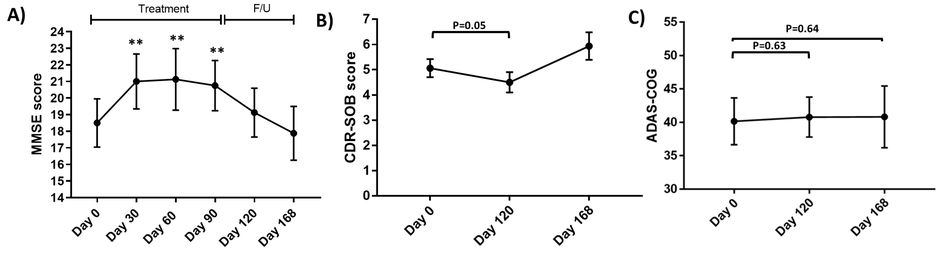
A) Percentage of Tregs was amplified following each IL-2 treatment cycle and returned to baseline before the next cycle. **B)** The percentages of CD4+CD25^{low} Tresps were decreased following IL-2 administration. **C)** CD25 MFI in Treg population was increased following IL-2 administration. **D)** FoxP3 MFI was only amplified after first IL-2 cycles administration. **E)** The suppressive function of Tregs on corresponding Tresp proliferation increased throughout the 4-month IL-2 treatment phase.

4. Low-dose IL-2 immunotherapy suppressed plasma pro-inflammatory cytokines and chemokines



Attenuation in the plasma levels of IL15 **(A)**, CCL2 **(B)**, CCL11 **(C)**, were noted following IL-2 administration.

5. Monitoring cognitive status through low dose IL-2 immunotherapy



There were improvements in MMSE scores during the low-dose IL-2 treatment phase. On days 120 and 168 at post-treatment phase, MMSE scores were comparable to the baseline level. A trend toward improvement was observed in CDR-SB on day 120 which was reversed toward baseline on day 168 . ADAS-Cog scores on days 120 and 168 of the study were comparable to the baseline levels

CONCLUSIONS

Low-dose IL-2 immunotherapy restored peripheral Treg function and ameliorated systemic pro-inflammatory mediators in AD patients. The results of this study warrant conducting a well-controlled clinical study to further evaluate the safety and efficacy of low-dose IL-2 as a potential treatment for AD.

ACKNOWLEDGEMENT

This research was supported by the Alzheimer's Association Part-The-Cloud Award. We also acknowledge the support of Coya Therapeutics.