Novel Autologous Dendritic Cell Therapy AVT001 for Type 1 Diabetes

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INTRODUCTION

Studies in several animal models and of humans with type 1 diabetes (T1D) have suggested that Qa-1/HLA-E restricted CD8+ T regulatory cells (Tregs) are important in maintaining self-tolerance and a defect thereof playing a key role in T1D pathogenesis.[1] To evaluate the safety and efficacy of targeting this pathway in T1D we undertook a first in human, phase 1/2 study of AVT001, an investigational autologous dendritic cell-based vaccine designed to address this immunologic mechanism. ClinicalTrials.gov number, NCT03895996

MATERIALS & METHODS

Participants: Individuals studied (n=25) were 16 years and older, within 1 year of clinical diagnosis of T1D, and with an ex-vivo correctable defect in the function of HLA-E-restricted CD8+ T regs. Participants were randomly assigned in a 2:1 ratio to receive AVT001 or placebo.

Treatment: Participants, independent of treatment assignment, underwent leukapheresis to obtain primary monocytes. AVT001 was an individualized preparation of autologous immature dendritic cells (DCs), derived by culture from the subject's adherent primary monocytes with GM-CSF and IL-4 for 6 days, and loaded passively with the synthetic oligopeptide (QMRPVSRVL) from Hsp60 signal peptide.[2] Treatment (n=16) or matched placebo (n=9) was given monthly via intravenous infusion of approximately 10 million CD11c+ DCs per dose, for three doses.

Endpoints and Assessments: The primary analysis was performed after the last subject completed the Month 5 study visit (Day 150). The primary objective was to determine the safety and tolerability profile of AVT001. The secondary endpoints included assessment of the HLA-E-restricted CD8+ T cell regulatory activity ("potency assay"). Using a mixed model of repeated measures, changes from baseline in the area under the curve (AUC) of stimulated C-peptide over the first 4 hours of a mixed meal tolerance test (MMTT), changes from baseline in HbA1c, and change from baseline in total daily insulin dose (U/kg) were analyzed.

Table 1. **Key Characteristics of Participants at Baseline**

Characteristic	AVT001 (n=16)	Placebo (n=9)
Male sex – no. (%)	10 (62.5)	7 (77.8)
Age, Years Mean (SD)	26.5 (9.00)	26.2 (6.24)
Race – no (%)		
White	13 (81.2)	9 (100)
African American	1 (6.3)	0 (0)
Native American	1 (6.3)	0 (0)
More than one race	1 (6.3)	0 (0)
Body weight, kg Mean (SD)	69.5 (11.89)	76.7 (14.25)
Body Mass index, kg/m^2 (SD)	23.0 (3.33)	25.2 (3.05)
Months from T1D diagnosis	7.9 (2.66)	8.8 (1.9)
HbA1c	6.04 (0.732)	5.66 (0.673)
Daily Insulin (U/kg)	0.36 (0.190)	0.37 (0.235)
C-peptide AUC nmol/L	0.53 (0.090)	0.61 (0.059)
C-peptide Fasting nmol/L	0.23 (0.197)	0.22 (0.115)
C-peptide Peak nmol/L	0.73 (0.504)	0.84 (0.245)
Autoantibodies Number (%) Positive		
GAD65 (>20 DK units/mL)	15 (93.8)	8 (88.9)
IA-2 (>5 DK units/mL)	13 (81.3)	5 (55.6)
ZnT8 (> 0.020 Index)	11 (68.8)	2 (22.2)

RESULTS

Table 2. **Adverse Events (AEs) Day 1 to Day 150**

	AVT001 (n=16)	Placebo (n=9)	All (n=25)
Any AE*	12 (75.0)	7 (77.8)	19 (76.0)
Related AE†	6 (37.5)	6 (66.7)	12 (48.0)
Serious AE	0 (0)	0 (0)	0 (0)
AE Causing Discontinuation	0 (0)	0 (0)	0 (0)
AE by Maximum Grade			
All AEs			
Grade 1	5 (31.2)	5 (55.6)	10 (40.0)
Grade 2	7 (43.8)	1 (11.1)	8 (32.0)
Grade 3	0 (0)	1 (11.1)	1 (4.0)
Related AEs			
Grade 1	3 (18.8)	5 (55.6)	8 (32.0)
Grade 2	3 (18.8)	0 (0)	3 (12.0)
Grade 3	0 (0)	1 (11.1)	1 (4.0)

*No AEs greater than grade 3 reported. †Attributed as possible, probable, definitely related.

Figure 1. **HLA-E Restricted CD8+ Treg Function, Assessed by Potency Assay**

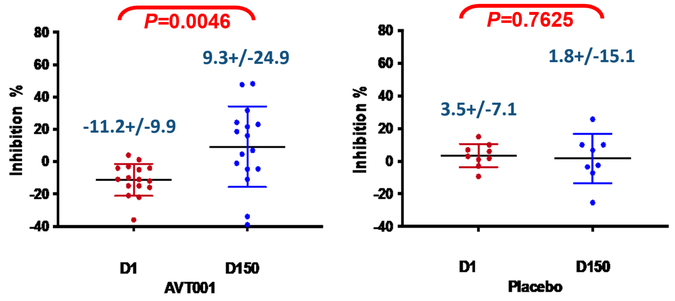


Figure 2. **C-Peptide AUC at Baseline and D150.**
A. AVT001 treated. B. Placebo. C. Change from Baseline.

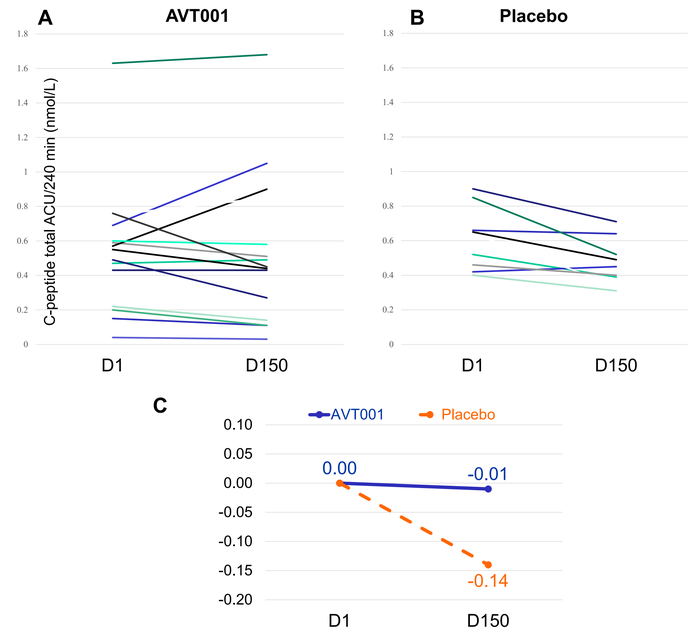
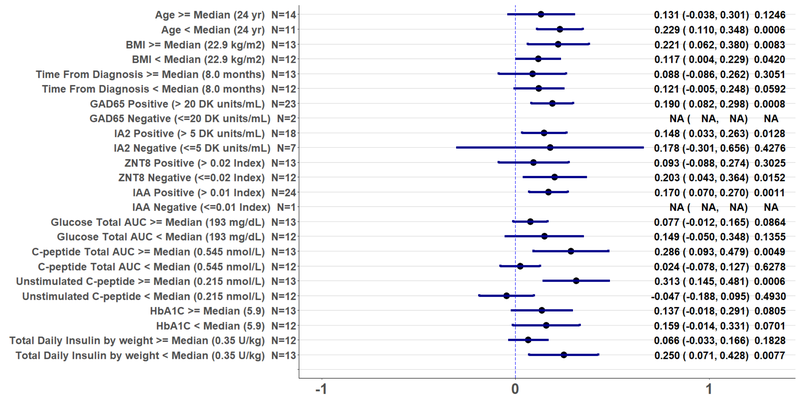


Table 3. **Summary of Findings.**

Parameter	Baseline		Day 150			
	AVT001 n=16	Placebo n=9	AVT001 n=16	Placebo n=9	Treatment effect (AVT001 vs Placebo)	p-value
HbA1c (%)	6.04 (0.73)	5.66 (0.67)	6.15 (0.85)	5.82 (0.84)		
CFB*			0.006	0.263	-0.257	0.2534
Daily Insulin (U/kg)	0.36 (0.19)	0.37 (0.24)	0.38† (0.26)	0.42 (0.26)		
CFB*			0.048	0.055	-0.007	0.8575
C-Peptide AUC (nmol/L)	0.531 (0.363)	0.611 (0.178)	0.518 (0.430)	0.472 (0.134)		
CFB*			0.006	-0.166	0.172	<0.0001

Data presented as mean (SD). CFB = change from baseline.
*Estimated using Mixed-effect Model for Repeated Measurements (MMRM).
†Missing daily insulin data in one subject at day 150 (n=15).

Figure 3. **Subgroup Analysis of C-peptide AUC Treatment Effect**



CONCLUSIONS

AVT001 treatment was safe and well tolerated with evidence of significant preservation of endogenous insulin secretion at day 150. Despite preservation of C-peptide, there was not a significant difference in HbA1c or insulin utilization from baseline between the groups. More robust treatment effect was associated with younger age, lower baseline insulin requirement, higher fasting C-peptide, and higher C-peptide AUC at baseline. Correction of HLA-E restricted CD8+ Treg dysfunction provides direct mechanistic support for this approach. These results are the first clinical evidence that a DC-based vaccine targeting HLA-E restricted CD8+ Tregs can delay progression of T1D in people.

REFERENCES

1. H. Jiang, S.M. Canfield, M.P. Gallagher, H.H. Jiang, Y. Jiang, Z. Zheng, L. Chess. HLA-E-restricted regulatory CD8(+) T cells are involved in development and control of human autoimmune type 1 diabetes. J Clin Invest. 2010. PMID: 20877010.
2. W. Chen, L. Zhang, EB. Liang, Y. Saenger, J. Li, L. Chess, H. Jiang. Perceiving the avidity of T cell activation can be translated into peripheral T cell regulation. Proc Natl Acad Sci U S A. 2007. PMID: 18077361

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