A Phase 1 trial of DSG3-CAART cells in mucosal-dominant pemphigus vulgaris patients: preliminary data

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Introduction

Mucosal-dominant pemphigus vulgaris is mediated by anti-desmoglein 3 (DSG3) autoantibodies (Abs) and treated with chronic, broad immunosuppressive therapies, which are not curative, require chronic administration, and may be associated with serious infections due to persistent immunosuppression. The ideal therapy would selectively eliminate pathogenic anti-DSG3-expressing B cells while sparing healthy B cells. Based on the long-lasting remission of B cell cancers achieved with chimeric antigen receptor T (CART) cells, we genetically modified autologous T cells to express chimeric autoantibody receptors comprising the DSG3 autoantigen (DSG3-CAART) to target only anti-DSG3 B cells.

Methods

In this ongoing open-label study of adults with active, anti-DSG3 Ab positive, biopsy confirmed mucosal-dominant pemphigus vulgaris inadequately managed by ≥1 standard therapy, 3 subjects were initially assigned to each cohort to receive a dose of $2x10^7$,$1x10^8$, $5x10^8$, $2.5x10^9$ or $5\text{-}7.5x10^9$ DSG3-CAART cells after discontinuing any immunosuppressives or tapering steroids. The primary endpoint is related adverse events (AEs) within 3 months of infusion. Secondary endpoints include DSG3-CAART persistence (qPCR), anti-DSG3 Ab levels (ELISA) and disease activity (PDAI Mucous Membrane score).

Results

The first 15 subjects enrolled and treated have been followed for at least 28 days post-infusion (screening characteristics in table below).

Subject Screening Characteristics						
	Cohort A1 2×10^7 (n=3)	**Cohort A2 1×10^8 (n=3)**	**Cohort A3 5×10^8 (n=3)**	**Cohort A4 2.5×10^9 (n=3)**	**Cohort A5 $5\text{-}7.5 \times 10^9$ (n=3)[1]**	**Overall (n=15)**
Age, years, median (range)	39 (32-57)	53 (50-54)	60 (47-70)	60 (56-70)	47 (34-57)	54 (32-70)
Female (%)	67%	67%	67%	67%	0%	53%
Disease duration, years, median (range)	3.4 (0.5-4.3)	4.3 (3.9-13.0)	0.7 (0.3-15.0)	3.5 (0.1-12.4)	1.4 (0.2-5.3)	3.5 (0.1-15.0)
Anti-DSG3 Ab level, U/mL, median (range)[2]	92 (51-104)	147 (86-168)	147 (63-169)	147 (114-162)	145 (143-169)	145 (51-169)
PDAI[3], median (range)	17 (5-20)	6 (6-14)	12 (2-18)	3 (1-4)	6 (4-18)	6 (1-20)
Prior use of corticosteroids (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	15 (100%)
Prior use of mycophenolate (%)	2 (67%)	3 (100%)	1 (33%)	2 (67%)	1 (33%)	9 (60%)
Prior use of rituximab (%)	3 (100%)	3 (100%)	0 (0%)	2 (67%)	1 (33%)	9 (60%)

[1] A 4th subject was dosed in Cohort A5 to generate additional data but has not been followed for ≥28 days to date; this subject developed Grade 1 CRS (related SAEs) several hours after each of the 2 infusions which resolved within 2 days. The events were not considered to be dose-limiting toxicities and did not delay study progression.
[2] Baseline (pre-infusion) values
[3] PDAI, Pemphigus Disease Area Index Mucous Membrane score

No dose-limiting toxicities or related serious AEs were observed over 3 months in Cohorts A1-A4 and over 28 days in the 3 subjects in Cohort A5. For subjects who completed at least 3 months of follow-up after infusion (Cohorts A1-A4), disease was clear or almost clear (PDAI 0-1) in 1, 2, 3, 6, and 4 subjects at screening, baseline (pre-infusion), and 1, 2, and 3 months after treatment, respectively, in the absence of immunosuppressive medications other than corticosteroids. Anti-DSG3 Ab levels at month 3 were increased, stable (+/-20%) or decreased in 3, 7, and 2 subjects, respectively. There was a dose dependent increase in DSG3-CAART persistence within 29 days with Cohort A4 approaching the lower end of range observed with CART therapy directed against CD19 in hematologic malignancies. One subject in Cohort A4 demonstrated a decrease in anti-DSG3 Ab levels at 2 and 3 months post-infusion while tapering steroids, reached PDAI=0 at 3 months, and was the only subject in the first 4 cohorts to sustain detectable DSG3-CAART persistence at 3 months. DSG3-CAART from all subjects exhibited specific in vitro lysis of anti-DSG3-expressing cells.

Discussion

The favorable DSG3-CAART safety profile along with the preliminary clinical and biological data from the first several cohorts provide rationale to evaluate additional dosing strategies.