

Successful use of anti-CD19 CAR T-cells in severe treatment-refractory stiff-person-syndrome

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SI APPENDIX

Methods

Patient History

The female patient first presented with symptoms at the age of 59 in 2014. She reported sudden loss of leg control, leading to repeated falls. Work-up detected anti-GAD65 immunoglobulin (Ig)G both in the cerebrospinal fluid (CSF) (titer 1:10) and serum (titer 1:320). Onconeurological antibodies, including anti-glycine receptor antibodies, and a diagnostic work-up including PET-CT for malignancies, were negative. Treatment with corticosteroids and intravenous Ig (IVIg) resulted in only minor improvement of rigidity, and therefore a series of plasma exchanges was performed. Treatment with azathioprine, prednisolone, and diazepam (Figure 1a) led to disease stabilization for three years. Subsequent exacerbations were treated with a combination of plasma exchanges and immunoadsorptions. The patient's walking distance, however, decreased progressively to 500 meters and she required wheeled walker support. In 2021, an increase of serum anti-GAD65 antibody-titers (1:3200) associated with gait imbalance that restricted walking ability to a few steps, was observed. Immunotherapy was escalated to rituximab (three courses), but severe leg stiffness remained and resulted in a bed-bound state. In 2023, therapy was escalated using the proteasome inhibitor bortezomib with only transient stabilization. B-cell targeting therapeutic strategy was escalated to use of an anti-CD19 CAR T-cell approach.

Anti-CD19 CAR Construct and Evaluations

CAR T-cells were engineered using a second generation anti-CD19 CAR construct (KYV-101, Kyverna Therapeutics, Inc. CA, USA) comprising a fully human CD19 binding domain, a CD8 α hinge and transmembrane domain, a CD28 co-stimulatory domain, and a CD3 ζ activation domain (1). Clinical evaluations were performed at regular intervals following administration of KYV-101. Stiffness was assessed using the Modified Ashworth scale (MAS). Pain was assessed using the numeric rating scale (NRS, range 0-10). Fatigue was assessed using the fatigue severity scale (range 9-63). Anti-GAD65 titers were quantified using an immunofluorescence test of transfected cells (Euroimmun, Germany).

References

1. J. N. Brudno *et al.*, Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma. *Nature medicine* **26**, 270-280 (2020).

Video 1

Video documentation of a patient with treatment-refractory Stiff person syndrome, successfully treated with anti-CD19 Chimeric Antigen Receptor (CAR) T Cells. Walking two days prior, four months and 6.5 months after CAR T-cell therapy, depicting marked improvement of stiffness, gait and walking speed using a wheeled walker.