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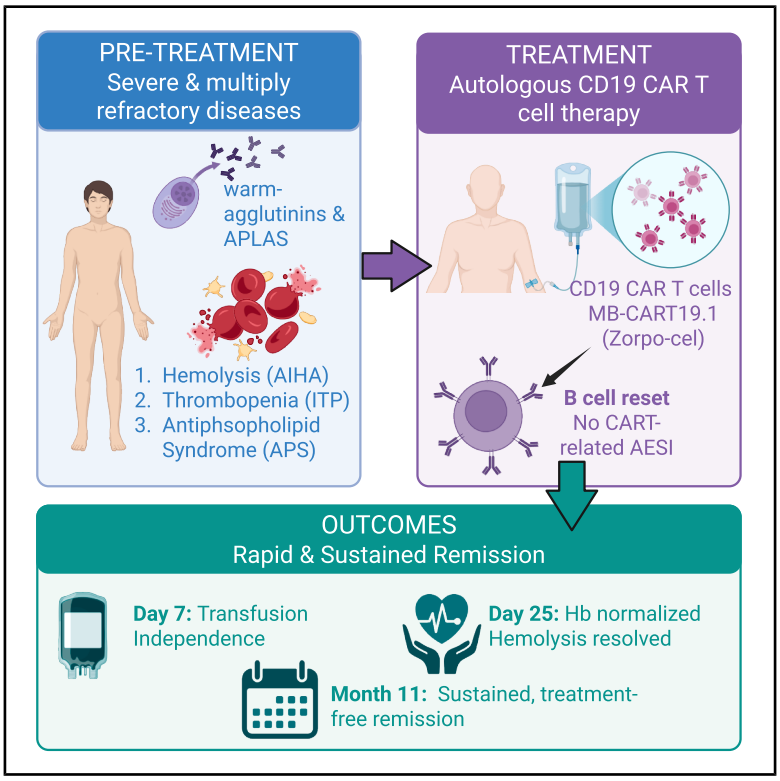
Case Report

CD19 CAR-T therapy induces remission in refractory autoimmune hemolytic anemia with ITP and antiphospholipid syndrome

Graphical abstract



Highlights

- CD19 CAR-T cells, but not rituximab, achieve a deep reset of circulating B cells
- CD19 CAR-T cells resolve three distinct autoimmune diseases in one patient

Authors

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In brief

This single-patient case report expands the indications in which CD19 CAR-T cell therapy demonstrates unprecedented clinical efficacy, achieving sustained, treatment-free remission. Following B cell abrogation, AIHA is stopped, antiphospholipid antibodies are abrogated, and an underlying ITP is stabilized without any CAR-typical side effects.

Translation to Patients

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Case Report

CD19 CAR-T therapy induces remission in refractory autoimmune hemolytic anemia with ITP and antiphospholipid syndrome

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CONTEXT AND SIGNIFICANCE Growing evidence supports the ability of CD19-directed CAR-T cell therapy to highly efficaciously reset dysregulated B cells in autoantibody-driven autoimmune diseases. However, data on refractory AIHA or antiphospholipid syndrome are very limited. Here, we present a patient with severe, treatment-refractory AIHA with coexisting ITP and APLAS who received CD19-directed CAR-T cell therapy on the basis of compassionate use. AIHA was transfusion independent from day 7 and hemoglobin normalized within 25 days. No cytokine release syndrome or neurotoxicity occurred. The pathologically elevated antiphospholipid antibodies normalized, and ITP stabilized without any additional therapy. This case demonstrates rapid, durable remission of severe, refractory cold-agglutinin AIHA with simultaneous improvement in coexisting APLAS and ITP on a highly favorable toxicity profile. This case supports further clinical validation of the concept.

SUMMARY

Background: Autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and antiphospholipid antibody syndrome (APLAS) are B cell-driven autoimmune diseases defined by pathogenic autoantibodies. CD19-directed chimeric antigen receptor (CAR)-T cells have recently demonstrated the ability to reset dysregulated B cells and induce long-lasting remission in refractory systemic autoimmune diseases. Evidence for efficacy in severe, treatment-refractory AIHA, however, is limited.

Methods: We report the clinical course of a 47-year-old woman with life-threatening cold- and warm-agglutinin AIHA refractory to nine prior treatment lines, accompanied by ITP and APLAS. In an uncontrolled flare, she received a fludarabine/cyclophosphamide-containing lymphodepletion followed by autologous CD19-directed, 4-1BB-costimulated CAR-T cells (zorpocabtagene-autoleucel [Zorpo-cel], 1×10^6/kg) on the basis of compassionate use. Treatment efficacy and safety were assessed over an 11-month follow-up period.

Findings: Zorpo-cel showed a rapid and sustained B cell depletion. Transfusion independence was achieved by day 7, with hemoglobin normalization by day 25, including resolution of hemolysis markers. Cold-agglutinin titers decreased, and previously elevated antiphospholipid antibodies normalized without recurrence throughout 11 months of follow-up. ITP stabilized. No cytokine release syndrome or neurotoxicity occurred.

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Mild transaminase elevation and thrombocytopenia were observed, most likely correlating with pre-existing severe iron overload due to erythrocyte transfusions.

Conclusion: This case demonstrates that CD19-directed CAR-T cell therapy can induce rapid, durable remission of severe, refractory cold-agglutinin AIHA and simultaneously improve coexisting APLAS and ITP on a favorable toxicity profile. However, more data from controlled clinical trials are needed for final conclusions.

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INTRODUCTION

Loss of self-tolerance and B cell dysregulation are key events in B cell-driven autoimmune diseases (AIDs) characterized by pathognomonic autoantibodies.[1] Resetting these dysregulated B cells by CD19-directed chimeric antigen receptor T (CAR-T) cells achieved lasting, drug-free remissions in refractory systemic lupus erythematosus or systemic sclerosis.[2] Hematologic AIDs with disease-driving autoantibodies include autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and coagulopathies, including antiphospholipid antibody syndrome (APLAS).

Therapy-refractory AIHA is a life-threatening condition resulting in hyperbilirubinemia and transfusion dependency with consecutive iron overload, organ damage, and significant impairment of quality of life. Management of AIHA that failed all standard therapies remains challenging. The B cell-depleting antibody rituximab showed clinical activity in two randomized trials, but approximately one-third of patients are refractory.[3,4] Because CAR-T cell therapy achieves a deeper depletion and a more efficient reset of B cells than rituximab,[2,5,6] we hypothesized that CAR-T cell therapy would achieve more durable remission in refractory AIHA and may also be effective against co-occurring AIDs.

RESULTS

Patient characteristics

A 47-year-old White female with severe, treatment-refractory AIHA with active cold and previously detectable warm agglutinins was first diagnosed in 2014 and had been refractory to nine different therapy lines, including steroids, rituximab thrice, high-dose intravenous immunoglobulins (IVIGs), azathioprine, bortezomib, hydroxychloroquine, cyclophosphamide, ciclosporin A, and mycophenolate mofetil (Figure 1A). Already at first diagnosis and several times thereafter, other B cell-driven AIDs, including systemic lupus erythematosus, have been ruled out serologically and clinically. In 2015, an APLAS was diagnosed, which led to repeated thromboembolic events and permanent therapeutic anticoagulation. In 2019, the patient developed ITP. Following the international consensus meeting definition, the patient's AIHA was severe because they remained transfusion dependent despite ongoing therapy.[7] In an uncontrolled flare, lymphodepletion with fludarabine (25 mg/m^2, d-5 to d-3) and cyclophosphamide (1,000 mg/m^2, d-5) was followed by a single infusion of 1×10^6 zorpocabtagene-autoleucel (Zorpocel; MB-CART19.1) per kg body weight on the basis of a compassionate use ("Individueller Heilversuch," §223,228 and 229 StGB). Zorpo-cel is a 4-1BB-costimulated CAR-T cell locally produced at the treatment center from an autologous leukapheresis product on the Miltenyi Prodigy platform.

Treatment course

Despite treatment with IVIGs and steroids, AIHA persisted at hemoglobin levels of 6.1 g/dL and LDH of 750 U/L, and it remained transfusion dependent, with an average of one red blood cell (RBC) concentrate per day (Figure 1B). In life-threatening AIHA and with a lack of further effective therapeutic options, we offered the patient a CD19-directed CAR-T cell therapy. Infused bridging therapy with another steroid pulse and a single dose of CD20-directed antibody rituximab 5 weeks before CAR-T cell infusion was ineffective, as AIHA worsened, and the patient required more transfusions of up to three daily RBC concentrates. Therefore, treatment with IVIGs and steroids was repeated and achieved stabilization of the AIHA with, on average, one daily transfusion of erythrocyte concentrates. Of note, the combination of IVIGs and steroids led to a transient increase in platelets (Figure 1C).

One week before leukapheresis, prednisolone was tapered to 10 mg/day. The leukapheresis product was generated and used to successfully manufacture Zorpo-cel with a transduction efficiency of 23.6%, a CD4/CD8 ratio of 2.2, and a slightly lower-than-average total yield of CAR+ T cells of 440 million.[8] After apheresis, LDH increased again, suggesting yet another flare of AIHA, and 1 mg/kg prednisolone plus IVIGs was repeated from day −11 to −9. Then, all immunosuppressants were stopped except for prednisolone, which had been tapered to 10 mg/day. At the start of lymphodepletion (day −5), hemoglobin levels were at 7.6 g/dL, LDH was 1,073 U/L, bilirubin was 3.1 mg/dL, and platelets were 102/nL (Figures 1B–1D). Circulating B cells could still be detected (Figure 1E). After lymphodepletion (day −2), prednisolone was discontinued, and maintenance therapy with hydrocortisone (50 mg/day) was initiated.

One million CAR-T cells per kg bodyweight were infused on day 0, which expanded to a maximal peak of 10.5 CAR+ T cells/μL on day 9 as determined by flow cytometry (Figure 1E).[9] Circulating B cells were rapidly depleted. As previously described, only with the disappearance of CAR-T cells from circulation did B cells recur at day 322. While rituximab did not achieve a B cell reset, the B cell phenotype of recurrence after CAR-T was 98% naive and thus showed expected reset (Figure 1F). The last RBC concentrate was transfused on day 7 (Figure 1B). Hemoglobin levels steadily increased from day 9 (hemoglobin of 7.4 g/dL), with the first reported normal value of 13.0 g/dL from day 25.

Bilirubin peaked at 13 mg/dL on day −28 during an AIHA flare, decreased after CAR-T cell infusion, and reached normal values

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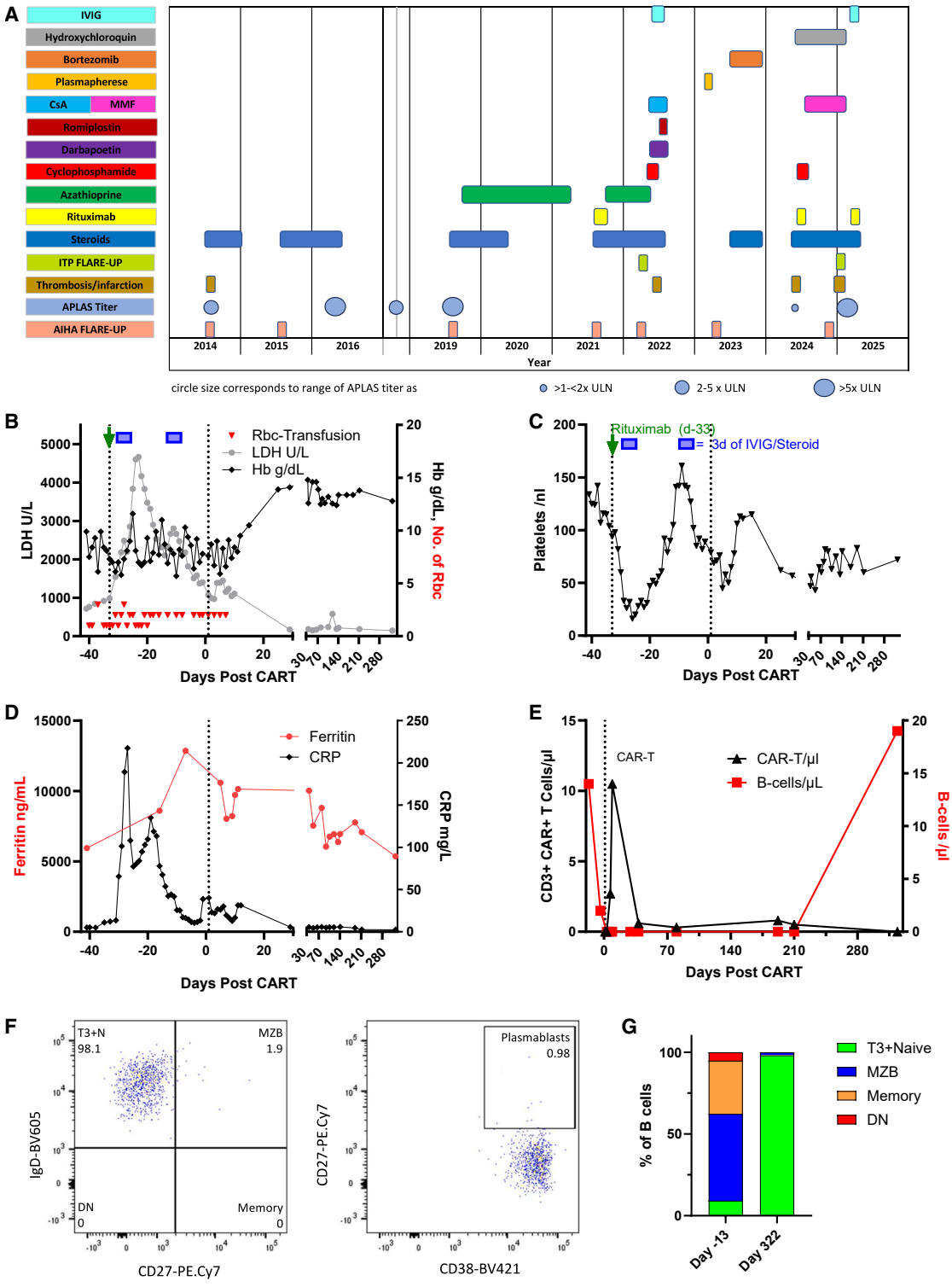

Figure 1. Treatment course including therapies and blood values

(A) Therapy course of AIHA and ITP from initial diagnosis until CAR-T cell infusion, including thromboembolic complications and documented elevated APLA titers relative to the upper limit of norm (ULN) as indicated.

(B) Changes in LDH and hemoglobin (Hb) over time and red blood cell transfusions post-CAR -T cell therapy.

(C) Course of thrombocytes after CAR-T cell infusion.

(legend continued on next page)

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by day 29. LDH decreased from a maximum of 4,601 U/L on day −24 to normal values on day 29 (Figure 1B). Haptoglobin remained low but was detectable from day 65. CRP peaked on day −27 with 217 mg/L and normalized on day 29. Ferritin peaked at day −7 with 12,857 ng/mL and slowly decreased after CAR-T cell administration (Figure 1D). Iron chelation therapy was initiated on day 12. Because it was not effective, weekly phlebotomy was added and maintained up to date, leading to a slow decrease in ferritin to 5,358 ng/mL. Due to fatigue after the procedure, the patient refused more frequent phlebotomy. Platelets were lowest on day −25, increased during CAR-T administration, and gradually increased from day 65 to 70/nL at the last visit (normal from 140/nL; Figure 1C). The cold-agglutinin titer, which was at very high levels pre-CAR-T administration, decreased gradually over time to very low levels at the last visit (Figure 2A). Warm agglutinins were found at low levels only on day 6 as an auto-anti-e. The auto-anti-e was no longer detected from day 28. APLAs were measured from frozen serum samples at the indicated time points (Figure 2B). Anti-cardiolipin IgG and IgM and anti-glycoprotein IgG antibodies were detectable at baseline and were in line with the APLAS diagnosis. The APLAs gradually decreased and have remained negative since. After discharge at day 10, the patient experienced a rapid and remarkable increase in physical strength and has been able to carry out normal everyday activity. Anticoagulation was maintained following CAR-T cell therapy, reduced to a semi-therapeutic dose, and subsequently stopped at day 320. There was no clinical evidence for subsequent thromboembolic events.

No cytokine release syndrome (CRS) and no immune effector cell-associated neurotoxicity syndrome (ICANS), according to the American Society for Transplantation and Cellular Therapy (ASTCT), occurred after CAR-T cell infusion.[10] Total leukocytes decreased following lymphodepletion and quickly recovered to normal values (Figure 2C). Maximal lymphocytopenia was of grade 4 and improved to grade 3 at the last follow-up. No clinically apparent infection has occurred after CAR-T cell therapy. As the only non-heme adverse event, transaminases, dominantly ALAT, rose from day −15 with a first peak shortly after lymphodepletion—possibly due to drug-induced liver injury—and a second peak from day 38. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) was ruled out clinically. All screening tests in the second peak, including viral or autoimmune hepatitis, remained negative, leaving drug-induced toxicity or toxicity due to iron overload as the most probable cause. Transaminases have decreased continuously since.

DISCUSSION

This case shows for the first time that Zorpo-cel (previously MB-CART19.1) is active in severe and refractory cold-agglutinin AIHA, achieving partial remission within 7 days and complete remission within 25 days of infusion. Over an as-of-today 11-month follow-up, the patient has remained blood-transfusion independent. Cold agglutinins were greatly reduced following CAR-T cell therapy, APLA normalized, and ITP remained stable at marginally higher values than baseline but without the need for additional ITP-directed therapies. During the observation period following CAR-T cell therapy, APLA levels did not increase again, suggesting that the deep B cell reset has prevented its resurgence. Thus, three distinct AIDs in one patient responded to CAR-T cell therapy. While recovery of ITP, disappearance of APLA, and efficacy in AIHA individually have been described following CAR-T,[11–13] we are the first to achieve treatment-free remission in a complex case of three distinct AIDs by a single infusion of CD19 CAR-T cells.

In our patient, CAR-T cells were active despite the previous failure of rituximab. This is in accordance with findings where only CAR-T cells, but not other B cell-depleting agents, eradicated B cells from lymph nodes or from colon mucosa and achieved sustained clinical remission.[5,14] Moreover, phase 3 trials testing rituximab in AIHA showed refractoriness in 1/3 of patients, and responders frequently relapsed over time, suggesting that CAR-T cells may be superior to other B cell-targeting agents, as shown in several AIDs.[3,4] It is unlikely that the observed efficacy was partially due to the delayed effects of rituximab pretreatment, given the lack of B cell reset before CAR-T, but it cannot formally be ruled out. The role of lymphodepletion in AID remains controversial. Supporting the need for CAR-T cells to achieve lasting responses, lymphodepletion alone was clinically inactive against myositis if CAR-T cells did not expand.[15]

Consistent with the favorable toxicity profiles of Zorpo-cel in patients with AID, no ICANS or CRS occurred.[2,8] Importantly, we find lasting bone marrow (BM) and liver toxicity in this patient. BM toxicity, as shown by leukocytes <2/μL (grade 3), granulocytes <1/μL (grade 3), and lymphocytes at 0.5/μL (grade 2) at the last visit, may be explained by more than one cause, including BM-toxic therapies before CAR-T, immune effector cell-associated hematotoxicity, immune-dysregulation, or iron overload. In line with this, liver toxicity may similarly be due to iron overload or drug toxicity. While unlikely and previously not reported, local immune effector cell-associated toxicity syndrome (LICATS) found in patients with AID after CAR-T cell therapy could also explain the toxicities.[16] To prevent iron overload and toxicity of previous treatments, one would argue in favor of earlier intervention with a more effective B cell-depleting treatment.

Limitations of the study

Limitations of the paper are the single-case character of the report, which prevents a more generalizable statement. This includes statements regarding gender, ethnicity, or age. Further, the follow-up is still short.

Final remark

Despite these limitations, this case adds to the evidence supporting a favorable toxicity profile of Zorpo-cel in this patient

(D) Ferritin and CRP levels before and after CAR-T cell therapy
(E) Development of $CD3^+$ CAR-T cell count and B cells after CAR-T cell infusion.
(F) B cell phenotype at day 322 gated for living, CD45+/CD19+/CD20+/Lin− single cells.
(G) Comparison of B cells pre- (day −13) and post- (day 322) CAR-T cell therapy, gated as depicted in (F).

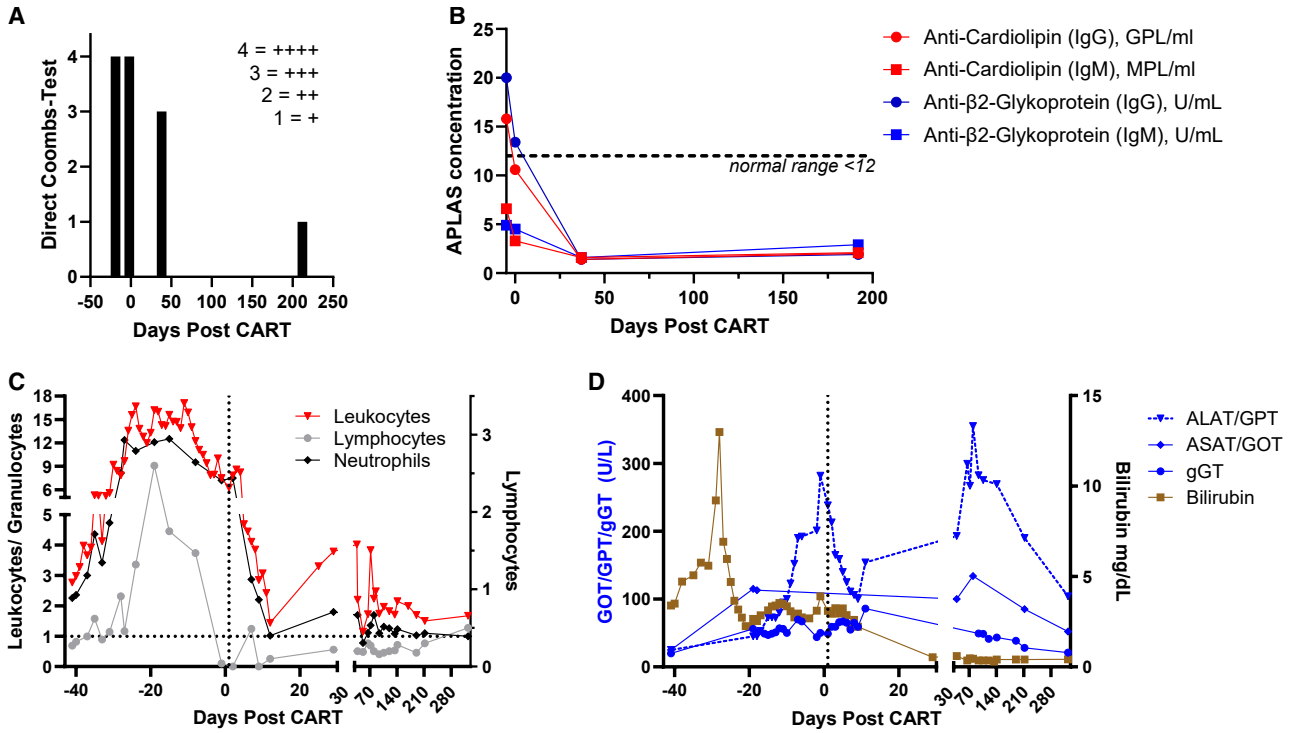

Figure 2. CAR-T cells normalize autoantibodies and show little toxicity

(A) Results of direct Coombs test are very highly positive (++++), highly positive (+++), or low positive (+). Shown are individual clinical measurements done from fresh blood within a maximum of 4 h after blood draw.

(B) APLAs were measured from frozen serum samples at the indicated time points. Cutoff for normal range of anti-cardiolipin IgG and anti-β2-glykoprotein IgG and IgM: <12 U/mL and for anti-cardiolipin IgM: <6 U/mL.

(C) Course of leukocytes, neutrophil granulocytes, and lymphocytes before and after CAR-T cell infusion.

(D) Changes in values of GOT, GPT, gamma-GT, and bilirubin in relation to CAR-T cell infusion.

with a highly complex AID and suggests that Zorpo-cel could be a valuable option for patients with severe, refractory AIHA. However, more data from controlled clinical trials are needed for final conclusions.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Prof. Dr. Fabian Müller (fabian.mueller@uk-erlangen.de).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All data reported in this paper are available from the lead contact upon reasonable request. This study did not generate custom code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

I.K.K. and F.M. had unrestricted access to all data and performed the descriptive analysis. I.K.K., S.Kharboutli., L.H., H.P., J.S., I.V., A.G., S.A., B.S., S.Krause., K.G., M.v.B., C.R., A.M., and F.M. treated the patient; S.Kretschmann. and M.A. produced the CAR-T cells; S.V., J.K.S., J.S., H.P., T.H., and F.M. performed, analyzed, and interpreted the experiments; and A.M. and F.M. designed the concept of the patient case and provided funding. All authors reviewed and approved the manuscript.

DECLARATION OF INTERESTS

S.V. has received research support from BMS. L.H. has received travel support from BeOne and Amgen. J.K.S. has received travel support from BeOne, AbbVie, Novartis, and Sobi. T.H. has received honoraria from Gilead, GSK, AbbVie, MSD, Janssen, AstraZeneca, More Media gmbh, Baxalta, and Theratechnologies. S.K. has received honoraria for lectures from Eickeler and travel support from Jazz, Alexion, and AbbVie. M.v.B. has received research support from Johnson & Johnson and has consulted for Kite/Gilead, Novartis, and BMS. A.M. has received research support from Miltenyi Biotechnology and Kyverna; has consulted for Cellgene, Century Therapeutics, Kite/Gilead,

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Miltenyi Biotechnology, and Novartis; and has received speaker's honoraria from Cellgene, Kite/Gilead, Miltenyi Biotechnology, and Novartis. F.M. has received research support from AstraZeneca, BMS, Kite/Gilead, and Miltenyi Bioscience; has consulted for AstraZeneca, ArgoBio, BMS, CRISPR Therapeutic, EcoR1, Incyte, Janssen, Kite/Gilead, Miltenyi Bioscience, Novartis, and Sobi; and has received speaker's honoraria from AbbVie, AstraZeneca, Beigene, BMS, Incyte, Janssen, Kite/Gilead, Miltenyi Bioscience, MSD, Novartis, Pfizer, Sobi, and Takeda.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Flow Cytometry Antibodies		
Anti-CD19.CAR FMC63, format PE, clone REA1297	Miltenyi	130-127-342; AB_3664309
Anti-CD14, format PerCP, clone MϕP9	BD	345786; AB_2868812
Anti-CD8, format BV510, clone SK1	Biolegend	344732; AB_2564624
Anti-CD4, format BUV395, clone SK3	BD	563550; AB_2738273
Anti-CD3, format BUV737, clone UCHT1	BD	564307; AB_2744390
Anti-7-AAD, format PerCP	BD	559925; AB_2869266
Anti-CD19, format FITC, clone HIB19	Biolegend	302206; AB_314236
Anti-CD20, format APC, clone 2H7	Biolegend	302310; AB_314258
Anti-CD27, format PE-Cy7, clone M-T271	Biolegend	356412; AB_2562258
Anti-CD45, format APC-Cy7, clone 2D1	BD	560178; AB_1645479
Anti-CD3, format PerCP, clone UCHT1	Biolegend	300428; AB_893298
Anti-CD38, format BV421, clone HIT2	Biolegend	303526; AB_10983072
Anti-IgD, format BV605, clone IA6-2	Biolegend	348232; AB_2563337

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This case report describes a single, female patient diagnosed with refractory AIHA, ITP and APLAS treated with CD19-targeted chimeric antigen receptor (CAR) T-cells MB-CART19.1 (Zorpo-cel) at the University Hospital of Erlangen, between February and March 2025 on basis of a compassionate use.

Patient age at treatment was 47 years. Clinical characteristics, prior treatments, and disease course are described in detail in the main text.

Sex and gender were recorded as part of routine clinical data collection. This study reports on a single patient, and therefore no comparisons based on sex, gender, or race/ethnicity were performed.

Ethical approval/consent

The intervention was conducted as an individual therapeutic attempt outside of a formal clinical trial protocol. Underlying ethics proposal #336-19 and amendment thereof was approved by the local ethics committee. For treatment, research, and publication, the patient provided written informed consent according to the CARE guiedleines for case reports and in accordance with the principles of the Declaration of Helsinki.

METHOD DETAILS

CAR-T-cell therapy

The patient received CD19-directed CAR-T-cell therapy (zorpocabtagene-autoleucel (Zorpo-cel, MB-CART19.1) following institutional standard protocols. Zorpo-cel is a 4-1BB co-stimulated CAR-T-cell locally produced at the treatment center from an autologous leukapheresis product on the Miltenyi prodigy platform. Lymphodepleting chemotherapy consisted of fludarabine (25 mg/m^2, d-5 to −3) and cyclophosphamide (1000 mg/m^2, d-5). The CAR-T-cell dose administered was [1 × 10^6 CAR T-cells/kg].

Sample collection

Peripheral blood samples were collected longitudinally at predefined time points before and after CAR T cell infusion as part of routine clinical monitoring.

Peripheral blood mononuclear cells (PBMCs) were isolated using density gradient centrifugation, analyzed immediately, and remaining material cryopreserved for subsequent analyses.

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Flow cytometry

Immunophenotyping was performed using multiparameter flow cytometry on a LSRFortessa (BD Bioscience) following standard protocols. For all measurements, cells were first gated for single cells (SSC-H and SSC-A) and for viable lymphocytes based on FSC and SSC characteristics, followed by identification of specific immune cell subsets using below outlined antibody mixtures. Data were analyzed using FlowJo software (version 10.9, BD Biosciences).

Total CAR-T cell and leukocyte subset counts were quantified using TrueCount technology and individual subsets were determined by flow cytometry using the antibodies listed in the key resource table.

Direct Coombs test

Agglutinins were measured per direct Coombs tests and results interpreted according to laboratory standards on a 5-tier scale from very high to absent.

ELISA

The APLAs were measured using a commercial ELISA kit (Tecan, IBL International GmbH, Hamburg Germany).

Laboratory measurements

Routine laboratory parameters including leukocyte count, lymphocyte subsets, and relevant disease biomarkers were measured at the clinical laboratory of University hospital of Erlangen using accredited diagnostic assays.

AIHA response criteria

Response of AIHA was assessed according to the international consensus criteria based on transfusion frequency, level of hemoglobin, LDH, bilirubin, and level of haptoglobin.[7] Response of the ITP was determined by platelet counts.

QUANTIFICATION AND STATISTICAL ANALYSIS

Due to the single-patient design of this study, no inferential statistical analyses were performed.

Clinical and immunological parameters were analyzed descriptively. Longitudinal changes over time were visualized graphically using GraphPad Prism (version 10.2, GraphPad Software, San Diego, CA, USA), Powerpoint and Excel.

Immune cell populations and clinical biomarkers were plotted as absolute counts or percentages over time to assess temporal dynamics following CAR T cell therapy.