EDITORIAL

Two for one? CAR-T therapy for lymphoma benefits concurrent autoimmune disorders

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In the manuscript by Dr. Wang et al., authors present population level data for patients with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) treated with CD19 directed CAR-T who concurrently suffer from rheumatic autoimmune disorders (autoID group) [1]. Their objectives were to analyze outcomes after CAR-T therapy and evaluate the impact of CAR-T therapy on rheumatologic diseases. Chimeric antigen receptor (CAR) T cells are a novel gene-engineered cellular immunotherapy where a synthetic T cell receptor is expressed to redirect the T cell to a desired target. Several B cell targeting CD19 CAR T cell products have led to durable remissions of B cell leukemias and lymphomas and data from numerous studies have established the ability of these products to yield long-term remissions and deeply deplete B cells [2–4]. Notably, the pivotal clinical trials which led to FDA approval of CAR-T therapy for B-cell lymphoma have excluded subjects with history of autoimmune disorders and patients on immunosuppressive medications and corticosteroids.

In manuscript by Wang et al., autoID group included heterogenous disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren syndrome, polymyositis rheumatica (PMR), ankylotic spondylitis (AS) and psoriasis; all with variable disease severity. Outcomes after CAR-T therapy were compared between autoID CAR-T cohort of 58 patients and R/R DLBCL CAR-T recipients without autoimmune disease using propensity score 1:1 matching. This manuscript presents important novel findings and is remarkable for a couple of reasons.

According to the National Institutes of Health, up to 23.5 million Americans (more than 7% of the population) and 5–10% of the population in Europe are affected by autoimmune disorders and the prevalence is rising globally particularly in Asia and in Hispanics [5]. Immunologic imbalance in T and B cells, disease severity and immunosupressive therapy increase the risk for developing B-cell lymphoma; in a meta-analysis from 2005, the incidence rate was 2.5–18 -fold higher compared to healthy population although in current era, use of biological therapy and rituximab potentially lowered the risk [6]. Some of these patients develop R/R DLBCL for which CD19-CAR-T represents the only potentially curative therapy.

Importantly, the autologous CAR-T therapy in patients with concurrent autoRD and R/R DLBCL appears to be feasible, well tolerated and effective in this population with deeply disarranged immune system. While the feasibility of CAR-T manufacturing in this population has been established, it is unclear if any patients remained on steroids and immunosuppressives during apheresis potentially affecting the quality of T cells. More experience and data is needed to inform on possible CAR-T engineering failure rate in this populations. Immune effector associated events such as cytokine release syndrome (CRS) were not excessive and neurotoxicity and macrophage activation syndrome were not observed. Treatment mortality, time to next treatment and survival was similar in the two cohorts. While retrospective, limited by cohorts size and detail (no grades for adverse events, no response data or time to progression), this analysis provides meaningful evidence that CAR-T therapy can be safely applied to patients with concurrent autoRD and DLBCL with similar disease control without increased risk of mortality and morbidity.

Secondly, authors report limited data on changes in autoRD course, serum inflammatory and serologic factors and the use of prednisone and disease modifying agents to treat autoRD after CAR-T therapy. Generally, systemic immunosuppressive therapy usually leads to long-term disease control but complete, sustained remissions are rare and relapses are frequent, requiring long-term maintenance immunotherapy [7]. B cells play a central role in the pathogenesis, based upon responsiveness to B cell depletion by CD20-targetting antibody-based therapy such as rituximab [8]; however, repeated infusions are needed, and responses are typically transient due to the incomplete depletion of B cells in secondary lymphoid tissues.

The findings from this analysis suggest improved control of the autoimmune disorders after lymphodepleting chemotherapy followed by CD19 directed CAR-T therapy as evidenced by significant drop in inflammatory markers soon after CAR-T infusion. Contribution of cyclophosphamide and fludarabine on early changes in lymphocyte function also needs to be considered but this effect is transient for several weeks. Patients seem to have a significantly less need for steroids and immunosuppressive agents in post CAR-T period and improved disease control long-term compared to baseline. Notably some patients never resumed their disease modifying agents suggesting the potential for sustained disease remission.

The study lacks detail on dose and duration of immunosuppression, the description of clinical flares, repopulation with naïve B cells and patient reported outcomes data.

Nevertheless, this analysis represents a notable research effort to use large population level data for uncover the impact of novel CART therapy on rheumatologic disorders. This topic recently gained significant traction.

In recent Nature Medicine paper, Mackensen et al. report the use of CAR T cells to treat severe SLE in five patients [9]. CD19-CAR T cell therapy with a 4-1BB co-stimulatory domain following lymphodepletion with fludarabine and cyclophosphamide induced a clinical remission in five out of five patients with severe, refractory SLE. The safety data demonstrated low risk of CRS and no events of neurotoxicity. Remarkably, despite the B cells repopulation after 2–5 months after CAR T infusion, all 5 patients remained in remission with no detectable autoantibodies following repopulation. The first reported use of CD19-targeting CAR T-cell therapy in a patient with severe, treatment refractory systemic sclerosis (SSc) described a dramatic improvement in heart, joint, and skin manifestations, along with seroconversion,

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highlighting the potential effectiveness of this therapy for SSc [10]. While follow-up is in these reports is relatively short (up to 17 months), the findings raised grounded optimism and the prospect of prospective clinical trial testing safety and efficacy of CAR19 -T cell therapy for some autoimmune rheumatologic conditions.

Few words of caution are needed at this time. B-cell depletion is an effective therapeutic strategy for auto-immune disorders, yet most patients who are treated with CAR-T therapy recover B-cells (usually after 6–12 months) and with effective immunoglobulin production. The follow-up of these studies is relatively short and long-term control is yet to be determined.

Generalizability of the CD19-targeted CAR T cell approach to other autoimmune diseases is unclear as this approach requires that the disease is driven by B cell activation and plasmablast generation rather than on long-lived plasma cells, which are usually CD19 negative.

Nevetheless, it appears that CAR-T benefit extends its therapeutic reach to autoimmune diseases and this data support the conduct of prospective clinical trials using CD19-CAR-T therapy for various autoRD. CAR-T can a potential to be a new revolutionary tool to change the lives for millions of people with autoimmune disorders. In addition, patients with concurrent autoRD and DLBCL should not be denied CAR-T therapy if it is clinically indicated.

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VB wrote the manuscript, PHN reviewed and revised the manuscript.

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ADDITIONAL INFORMATION

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