Reducing B cells with CAR T cells is effective treatment of experimental lupus

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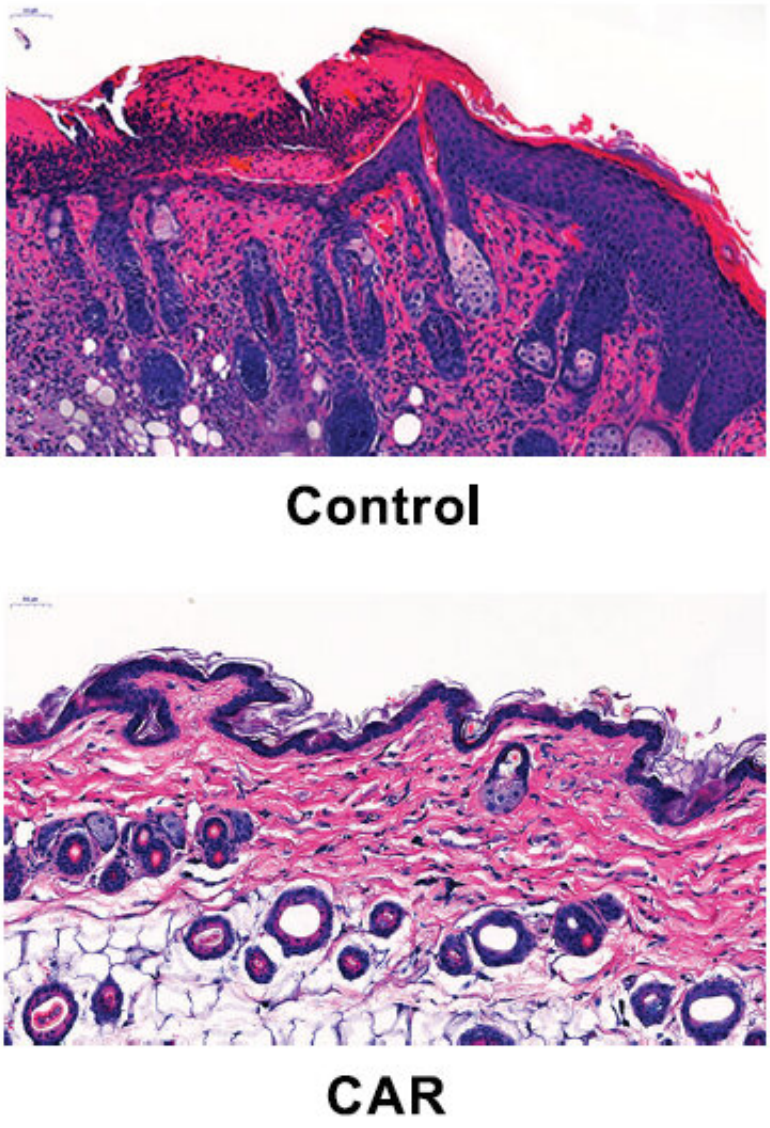

CD-19-targeting CAR-T cells restored proper skin structure and reduced inflammation in mouse models of lupus (bottom). Credit: R. Kansal et al.,

Depleting the number of harmful B cells with a novel immunotherapy that employs modified T cells may offer an effective strategy to treat lupus, according to a new study funded by the Lupus Research Alliance. These findings offer a renewed optimism for the elimination of B cells to provide a therapeutic option in lupus and pave the way for clinical research to test this new approach.

B cells are a critical component of the immune system and play an important role in lupus including the production of auto-antibodies which can lead to inflammation and organ damage. B cells can also directly activate other cells of the immune system—T cells—and can secrete molecules, cytokines, that worsen the inflammatory immune response leading to disease flares. Given the central role and wide range of effects of B cells on lupus, it is not surprising that this cell type has been the subject of intense research in lupus for decades.

Depleting the number of B cells has been one tantalizing approach that was tested in systemic lupus and lupus nephritis with rituximab: a humanized monoclonal antibody approved to treat blood cancers as well as several autoimmune diseases including rheumatoid arthritis and Pemphigus Vulgaris. Rituximab was not approved for lupus because the Phase 3 trials testing its use in lupus patients did not reach statistical significance. Yet the agent is still used off-label because it helps some lupus patients.

Marko Radic, Ph.D., of the University of Tennessee Health Science Center, Memphis, TN, and colleagues developed a novel approach to achieve B cell depletion in lupus. Specifically, the team created a new type of T cells by inserting into their DNA a genetic code for a chimeric

molecule—the result of merging parts of three (entirely) different immune molecules to create a unique entity that does not exist naturally. The modified T cells recognize the CD19 molecule found on almost all B cells. When given to mice with lupus, these modified T cells, called chimeric antigen receptor (CAR) T cells, significantly lessened/improved disease symptoms and progression. Also, the lifespan of the animals treated with the special CAR T cells was significantly longer than the control-treated animals. In addition, the treatment lessened several manifestations of lupus including elevated protein in the urine, skin inflammation, and levels of proteins in the blood associated with chronic inflammation. The CAR T cells continued to be effective for up to a year.

CAR T cells have been extensively tested and recently approved as a treatment for cancer; their potential beyond oncology is gaining momentum with studies in pemphigus vulgaris and now lupus with Dr. Radic's publication.

Dr. Radic's studies demonstrate the potential of CAR T cell therapy in lupus and other autoimmune diseases. However, extending these animal model studies to human trials needs to proceed with caution, as this therapy carries potential risks that must be carefully evaluated. Radic and colleagues report their findings this week in *Science Translational Medicine*.

"These are exciting results," Kenneth M. Farber, President and CEO of the Lupus Research Alliance commented. "When we awarded Dr. Radic the Novel Research Grant in 2014, using CAR T cells was just showing promise in cancer, and our scientific advisors recognized the potential of this extremely innovative approach for lupus. It has proven transformative for cancer patients, and we hope clinical research can demonstrate safety and effectiveness of CAR T cells in improving the lives of people with lupus."

More information: R. Kansal el al., "Sustained B cell depletion by CD19-targeted CAR T cells is a highly effective treatment for murine lupus," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aav1648

Provided by Lupus Research Alliance