



USING CAR-T THERAPY IN CNS AUTOIMMUNE DISEASES CAN CAUSE CYTOKINE STORMS AND POSSIBLE DEATH

TO THE EDITOR:

Chimeric Antigen Receptor T cell (CAR-T) therapy is a system in which T lymphocyte activation against target cells can trigger severe inflammation, including a cytokine storm (1). CAR-T cells recognize target cell antigen through the CAR's scFv domain. The CAR receptor has an antigen-recognition transmembrane domain and the intracellular signaling domains CD3 ζ + CD28, or CD137 (4-1BB), which is a protein belonging to the tumor necrosis factor (TNF) receptor family (2). When the CAR recognizes the target antigen, a cascade is activated, starting from the CAR, inducing CD3 ζ , Lck/ZAP70, LAT/SLP-76, Ca²⁺/calcineurin, and NFAT (3). The CD28, PI3K, and mTOR pathways, as well as NF- κ B, are also activated. These reactions lead to the release of inflammatory mediators that can cause a cytokine storm, that can also lead to death. The most responsible cytokines for activating the inflammatory network are interleukin (IL)-1, TNF, interferon-gamma (IFN- γ), IL-2 (which induces IL-1), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (4).

Chemokines are a functional subclass of cytokines that also participate in inflammation. They create signals that cause immune cells to migrate towards the inflammatory site, further fuelling the local and systemic inflammatory response (5).

CAR-T cells are emerging as an experimental approach in the treatment of both cancer and autoimmune diseases of the central nervous system, especially when autoimmunity is due to B cell dysfunction. In autoimmune diseases, CAR-T cells are not used to cells as they do with cancer but are used to prevent abnormal B cells from producing autoantibodies. B cells and plasma cells express the CD19 receptor, which CAR-T cells target through B cell recognition (6). CAR-T cells eliminate these autoimmune B cells, promoting replacement with non-autoreactive B cells.

Blocking inflammatory cytokines with anti-inflammatory cytokines or anti-receptor cytokines such as IL-1RA, monoclonal antibodies, or corticosteroids has become an important experimental therapeutic target (5). Additionally, the use of tocilizumab, an antibody directed against the IL-6 receptor, can reduce the inflammatory cascade.

The application of CAR-T cells to autoimmune neurological diseases such as autoimmune encephalitis, multiple sclerosis, and myasthenia gravis, amongst others, is a very active field of research and holds great promise for therapy. However, the severe inflammatory effect of CAR-T treatment, which can lead to a cytokine storm, must be resolved before these engineered cells are used for therapies.

Pio Conti*

Postgraduate Medical School, University "Gabriele d'Annunzio" of Chieti/Pescara, Chieti, Italy.

*Correspondence to:

Prof. Pio Conti,
Postgraduate Medical School,
University "Gabriele d'Annunzio" of Chieti/Pescara,
Chieti, Italy.
e-mail: pioconti@yahoo.it

Conflict of interest

The author declares that they have no conflict of interest.

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