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Hypogammaglobulinemia due to CAR T-cell therapy

Andrew Doan, **Michael A. Pulsipher**

Division of Hematology, Oncology, and Blood and Marrow Transplantation, Children's Hospital Los Angeles, Keck School of Medicine of USC, Los Angeles, California

Chimeric antigen receptor (CAR) T-cell therapy uses genetic engineering to express a chimeric receptor with the cytotoxic function of a T cell plus the antigen specificity of an antibody on the surface of patients' own T cells.[1] The most extensively investigated CAR T-cell therapies are specific for the CD19 antigen, which is expressed on B cells. The potent ability of anti-CD19 CAR T cells to target malignant CD19-expressing B cells also results in destruction of normal B cells, frequently producing hypogammaglobulinemia.

Hypogammaglobulinemia results in decreased antibody production, rendering patients susceptible to potentially life-threatening infections. Hypogammaglobulinemia can be managed by reconstituting the patient's immunoglobulin G (IgG) levels with intravenous (IV) or subcutaneous IgG,[2] a blood product made from pooled plasma of thousands of healthy individuals.[3] Immunoglobulin contains antibodies against a wide variety of pathogens, offering protection against opportunistic infections.

Studies have demonstrated that CAR T cells can persist for years in patients, producing long-term B-cell aplasia and hypogammaglobulinemia. Very low IgG levels can occur as early as 9 weeks after CAR T-cell infusion and persist >4 years after infusion.[4,5] As noted in Table 1, IgG replacement lowers the rates of infections in some cases and helps correct or stop ongoing infections in others. These data, plus literature describing IgG replacement in patients with congenital hypogammaglobulinemia, support routine infusion in pediatric patients with hypogammaglobulinemia after CAR T-cell therapy.[6] The ideal maintenance level of IgG after CAR T-cell infusions is undetermined, but data from patients who received rituximab (CD20-specific monoclonal antibody) show that patients with IgG levels < 400 mg/dl experienced recurrent bronchitis, sinusitis, pneumonia, and rarely, enteroviral meningoencephalitis.[2,7] Consequently, 400 mg/dl should be the lower level indicating supplementation, although higher trough levels may be needed for patients who develop recurrent infections on IV IgG replacement.

Correspondence Michael A. Pulsipher, Division of Hematology, Oncology, and Blood and Marrow Transplantation, Children's Hospital Los Angeles, Keck School of Medicine of USC, 4650W. Sunset Blvd, Mailstop #54, Los Angeles, CA 90027. mpulsipher@chla.usc.edu.

CONFLICT OF INTEREST

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When patients' IgG levels fall to 400–600 mg/dl, typically 1–3 months after infusion of CD19- and CD22-targeted CAR T cells, IgG replacement should begin and continue every 3–4 weeks as needed to maintain appropriate trough levels. Recovery of B-cell function after CAR T-cell therapy is best monitored by assessing peripheral B-cell counts. With active CAR T cells, B-cell numbers generally approach 0; if an increase is observed (especially a steady increase with serial measurements that exceed 50 μl), regular assessments should be made to determine when IgG production resumes. Once troughs > 400 mg/dl are maintained without replacement therapy, IgG can generally be discontinued.

In our practice, many patients experienced an increase in B cells to several hundred cells per microliter with little or no IgG production. Clinicians are encouraged to test IgG levels regularly to ensure that IgG is being produced, even if B-cell numbers rise and/or CAR T cells are undetectable in peripheral blood or bone marrow.

As new cellular therapies are introduced and indications for B-cell targeted therapies expand, more patients will develop hypogammaglobulinemia. Research into the best approaches and education and guidance for clinicians are imperative to ensure that patients with therapy-induced hypogammaglobulinemia have access to effective IgG replacement.

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TABLE 1

Hypogammaglobulinemia and IVIG in CAR T-cell therapy

Characteristics	Duration	Infection	Patients who received IVIG treatment (n)	Comments	Reference
Immunoglobulin below detectable limit	Weeks 9–39 after infusion	Pneumonia	1	No subsequent infections after starting IVIG	Kochenderfer et al.[5]
CD5 and CD19 cells were nearly absent 13 weeks after treatment	6 months after infusion	Not mentioned	4	None	Kochenderferet al.[8]
B-cell aplasia in all patients with response	B-cell aplasia lasted ≤2 years after infusion	Bronchitis (n = 1), acute otitis media (n = 2), *Salmonella* infection (n = 1), recurrent urinary tract infections (n = 1)	27	All patients required IVIG replacement, and no serious infectious complications were observed as a result of B-cell aplasia	Maude etal.[9]
B-cell aplasia and hypogammaglobulinemia in all patients with CR	B-cell aplasia lasted ≤4 years after infusion	Not mentioned	6	None	Porter et al.[4]

CAR, chimeric antigen receptor; CR, complete response; IVIG, intravenous immunoglobulin.