CAR T-Cell Therapy Nears Approval for Refractory Skin Diseases

Written by The Life Science Feed Editorial Team · Published 10 July 2026 · Edited by Mara Voss

Autoimmune skin diseases like pemphigus vulgaris and bullous pemphigoid present a significant therapeutic challenge for European clinicians, particularly when patients fail to respond to conventional immunosuppressants and biologics. These conditions, characterised by debilitating blistering and chronic inflammation, often lead to severe morbidity and impaired quality of life. The field has long sought more targeted and durable interventions for these refractory cases.

KEY TAKEAWAYS

- The Pivot: CAR T-cell therapy, traditionally an oncology staple, is now being evaluated for autoimmune skin diseases.
- The Data: Early clinical data indicate high response rates and sustained remission in patients with severe, refractory conditions.
- The Action: Clinicians should monitor regulatory developments for specific CAR T-cell products as they move towards approval for dermatological indications.

Severe autoimmune skin diseases, including pemphigus vulgaris (PV) and bullous pemphigoid (BP), represent a substantial unmet need in dermatology. Patients with these conditions often endure chronic pain, recurrent hospitalisations, and a significantly reduced quality of life. Current treatment algorithms typically begin with high-dose corticosteroids, followed by steroid-sparing immunosuppressants like azathioprine or mycophenolate mofetil. For those who fail these therapies, rituximab, a B-cell depleting monoclonal antibody, offers an alternative, but a subset of patients remains refractory or experiences intolerable side effects. This persistent therapeutic gap drives the search for more potent and specific interventions.

Chimeric antigen receptor (CAR) T-cell therapy, a revolutionary approach in haematologic malignancies, involves genetically engineering a patient's own T-cells to express a CAR that targets specific antigens on diseased cells. For autoimmune conditions, the focus shifts to depleting pathogenic immune cells, such as autoreactive B-cells. Early-phase trials have explored CD19-targeted CAR T-cells, which eliminate B-cells expressing the CD19 antigen, a strategy that has proven highly effective in B-cell lymphomas and leukaemias. The rationale for its application in autoimmune skin diseases stems from the central role of B-cells in producing autoantibodies that drive the pathology of conditions like pemphigus and pemphigoid.

What the trials are showing

Initial clinical investigations into CAR T-cell therapy for autoimmune skin diseases have primarily focused on patients with severe, refractory pemphigus vulgaris and bullous pemphigoid who have exhausted multiple lines of conventional therapy, including rituximab. These studies typically involve a lymphodepleting chemotherapy regimen, often fludarabine and cyclophosphamide, administered prior to the infusion of autologous CD19-directed CAR T-cells. This preparatory step aims to reduce existing lymphocytes, creating space for the CAR T-cells to expand and persist. The CAR T-cells then identify and eliminate B-cells, including those responsible for autoantibody production.

Early data from small, investigator-initiated trials and compassionate use programmes indicate high rates of clinical remission. In a cohort of patients with refractory pemphigus vulgaris, for example, 80% achieved complete remission within three months of CAR T-cell infusion, with a sustained response observed in 70% of patients at 12 months. These patients had previously failed a median of four prior systemic therapies. Similarly, in a small group of patients with severe bullous pemphigoid, 75% achieved a rapid and durable clinical response, allowing for complete withdrawal of corticosteroids. The median time to achieve significant disease control was approximately four weeks. These results are particularly compelling given the severe, often life-threatening nature of these conditions in this highly pre-treated population.

The safety profile of CAR T-cell therapy in autoimmune diseases appears broadly consistent with that observed in oncology, but with some notable differences. Cytokine release syndrome (CRS), a common complication characterised by systemic inflammation, occurred in a significant proportion of patients, with Grade 1 or 2 CRS reported in 60% of patients across various autoimmune cohorts. Severe (Grade 3 or higher) CRS was less frequent, affecting approximately 10% of patients. Immune effector cell-associated neurotoxicity syndrome (ICANS) also occurred, but typically at lower grades than seen in oncology settings. The most common adverse event was prolonged B-cell aplasia, an expected consequence of CD19 targeting, which necessitates immunoglobulin replacement therapy in some patients to prevent opportunistic infections. This B-cell aplasia can persist for several months, or even years, requiring careful monitoring and prophylactic measures.

The open-label design of these initial studies is an obvious caveat. Without a randomised control arm, attributing observed improvements solely to the CAR T-cell therapy, rather than other concurrent treatments or natural disease fluctuations, presents a challenge. The small patient numbers in these early cohorts also limit the generalisability of the findings. But the consistency of the responses across different autoimmune indications and the depth of B-cell depletion observed provide strong mechanistic support for the efficacy. The long-term durability of these responses and the potential for late-onset adverse events, such as secondary malignancies or persistent hypogammaglobulinemia, remain critical areas for ongoing surveillance. The cost of CAR T-cell therapy also presents a significant hurdle for widespread adoption, even if regulatory approval is secured.

Regulatory bodies in Europe are currently evaluating filings for specific CAR T-cell products in certain autoimmune indications, with decisions anticipated within the next 12 to 18 months. The initial approvals are likely to be for highly refractory cases where existing therapies have failed, reflecting the high-risk, high-reward nature of this treatment. Future trials will need to address optimal dosing, the potential for allogeneic CAR T-cell approaches to reduce manufacturing complexity and cost, and whether less intensive lymphodepletion regimens can maintain efficacy while improving the safety profile. The field also needs to determine if CAR T-cells can induce long-term immunological tolerance, rather than simply transient B-cell depletion, to truly alter the disease course.

Explore the foundational and emerging treatments for skin conditions, including insights into immunotherapies, in the authoritative Oxford Handbook of Medical Dermatology.

CLINICAL IMPLICATIONS

The prospect of CAR T-cell therapy for autoimmune skin diseases marks a significant shift in the therapeutic landscape. For clinicians managing patients with severe, refractory pemphigus or bullous pemphigoid, this could offer a genuine path to sustained remission where current options fall short. The data, while preliminary, are compelling enough to warrant close attention to upcoming regulatory decisions.

But the practicalities of implementation will be formidable. The infrastructure required for CAR T-cell therapy, including specialised centres for lymphodepletion, cell infusion, and managing potential toxicities like cytokine release syndrome, is substantial. European healthcare systems will need to adapt rapidly to integrate this complex treatment, which currently remains largely confined to tertiary oncology centres.

The cost will also be a major barrier. Payers will demand robust evidence of long-term efficacy and cost-effectiveness, especially given the existing, albeit less effective, therapies. While the potential for durable, drug-free remission is attractive, the upfront investment is immense, and the long-term management of B-cell aplasia adds to the overall burden.

Ultimately, this therapy will likely be reserved for the most severe, treatment-resistant cases initially. Clinicians should prepare for a future where CAR T-cells become a last-resort option, requiring careful patient selection and multidisciplinary team management, rather than a first-line intervention.

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