Deep B and Plasma Cell Depletion in Pemphigus and Other Autoantibody-Mediated Diseases

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SUMMARY OF KEY RESEARCH FINDINGS

Pemphigus is a group of autoimmune bullous diseases driven by pathogenic autoantibodies against desmogleins. Currently, the treatment of choice for moderate-to-severe disease is B cell depletion with rituximab (RTX), an anti-cluster of differentiation (CD)20 antibody, in combination with corticosteroids.[1] After a single cycle, only about one-third of patients reach complete, drug-free remission at 12 months.[2] Autoreactive B cell clones may persist for years despite anti-CD20 therapy,[3] and long-lived plasma cells, which lack CD20, remain unaffected. The same two limitations define refractory autoantibody-mediated disease far beyond the skin, in haematology, gastroenterology, rheumatology, neurology, nephrology, and other disciplines.

The authors recently reported successful treatment of two patients with RTX-refractory pemphigus, one foliaceus and one vulgaris, with teclistamab, a bispecific antibody engaging CD3 on T cells and B cell maturation antigen (BCMA), expressed on B cells and plasma cells.[4,5] Teclistamab was administered off-label in a subcutaneous step-up scheme (0.06, 0.3, and 1.5 mg/kg on Days 1, 3, and 5), followed by a single maintenance dose (1.5 mg/kg). Circulating B cells were rapidly depleted, and serum free light chains, a surrogate marker for the plasma cell compartment, disappeared completely within 3 weeks. Desmoglein antibodies seroconverted within 8 weeks, and both patients reached a Pemphigus Disease Area Index (PDAI) activity subscore of 0 within weeks. Adverse events were manageable, comprising Grade 1 cytokine release syndrome (CRS) in both patients, upper respiratory tract infections, transient hypogammaglobulinaemia requiring Ig substitution, and 1 day of Grade 3 neutropenia in one patient. After 17 and 21 weeks of B cell aplasia, B cells returned with a naïve phenotype consistent with *de novo* reconstitution, and free light chains and Igs reappeared around Weeks 32 and 36. Despite reconstitution of both compartments, desmoglein antibodies did not re-emerge, indicating a reset of the B and plasma cell compartment. Both patients have remained disease- and treatment-free for more than 1 year. These cases indicate that deep B and plasma cell depletion with an off-the-shelf T cell engager can induce treatment-free remission in RTX-refractory pemphigus.

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WHAT CHALLENGE DOES THIS ADDRESS?

Patients who fail RTX have few evidence-based options, and prolonged immunosuppression carries cumulative morbidity. Most anti-CD20 antibodies rely on relatively weak effector mechanisms and cannot reach the CD20-negative plasma cell compartment residing in bone marrow and inflamed skin; in lymphoid tissue they reduce but rarely deplete B cells, and plasma cells persist.[6] Teclistamab addresses both limitations simultaneously. Direct killing via T cell engagement is considerably more potent than antibody-dependent phagocytosis or complement activation, and BCMA extends depletion into the plasma cell compartment. The complete free light chain depletion is the most direct clinical evidence in pemphigus that the reservoir supplying pathogenic autoantibodies can be emptied, although bone marrow and lesional plasma cells were not sampled.

The same principle is now being established across specialties. BCMA-directed T cell engagers, first reported in rheumatology,[7,8] have been used to induce remission in refractory connective tissue disease,[9] myasthenia gravis,[10] immune-mediated neuropathy,[11] and immune thrombocytopenia,[12] and, combined with obinutuzumab, cleared anti-human leukocyte antigen (HLA) antibodies and enabled kidney transplantation in a patient sensitised for 2 decades,[13] extending deep depletion to other medical fields beyond autoimmunity.[14] In the RESET-PV study, CD19-directed CAR-T cells without lymphodepletion improved disease activity in all four patients with pemphigus vulgaris, but reduced autoantibodies in only two, despite adequate cell expansion,[15] which supports plasma cell targeting as a critical variable in pemphigus.

RELEVANCE TO EUROPEAN PRACTICE

T cell engagers are off-the-shelf therapies and require no apheresis, no individualised manufacturing, and no lymphodepleting conditioning. Teclistamab is already licensed in Europe for multiple myeloma, meaning supply chains, dosing protocols, and CRS management pathways exist in most tertiary centres. The practical model is interdisciplinary, with medical specialties like dermatology, nephrology, neurology, or rheumatology selecting and following the patient while an experienced core team supervises administration and toxicity. Patient selection must be equally disciplined, and use will initially be confined to centres experienced in both the underlying disease and CRS management until these limitations are overcome.

WHAT ARE THE NEXT STEPS?

The obvious limitation is sample size. Two patients cannot establish efficacy, and prospective trials with defined inclusion criteria and standardised endpoints are needed. Whether a single course suffices, or whether re-treatment or anti-CD20 maintenance to block B cell redifferentiation is required as autoreactive clones re-emerge,[9] can only be answered with long-term follow-up. Several mechanistic questions remain open. Whether the naïve reconstitution phenotype reliably predicts durable tolerance; how BCMA-directed engagement compares with CD19-directed engagers, dual targeting, cell therapies, and *in vivo* CAR-T cells;[16] and which dose and schedule are minimally sufficient[17] warrant systematic study in a shared effort across specialties.

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