Changing the course of type 1 diabetes: screening and early immunotherapy

Julie Brake, Martha K. Nicholson and Reza Zaidi

Type 1 diabetes is now recognised as a chronic, progressive autoimmune condition with a prolonged pre-symptomatic phase. The identification of diabetes-related autoantibodies, and the adoption of a three-stage classification of the condition, have enabled earlier detection and the possibility of targeted intervention before clinical onset. Immunotherapies, such as teplizumab, have demonstrated the ability to delay progression to symptomatic type 1 diabetes in high-risk individuals by preserving residual beta-cell function. Studies, including ELSA and T1DRA, are evaluating the feasibility of population-level autoantibody screening to identify people at risk. However, implementing immunotherapy within a national screening programme presents significant challenges. Early detection and modulation of the immune response show promise in shifting the paradigm from post-diagnosis treatment to prevention, but many uncertainties remain to be overcome before wide-scale adoption can begin.

Generally, the onset of type 1 diabetes appears suddenly, with the person affected presenting with distinct symptoms to a GP, walk-in centre or emergency department, often with hyperglycaemia, osmotic symptoms, ketosis or diabetic ketoacidosis (DKA).

As our knowledge of type 1 diabetes increases, so does our understanding of the complexity of the condition, its onset and its management. Over the past 40 years, the impact of the autoimmune response and subsequent destruction of insulin-secreting pancreatic beta cells has been established, as has the importance of antibody assays in its prognosis (Eisenbarth, 1986).

At diagnosis, more than 90% of individuals have one or more of the autoantibody markers of type 1 diabetes. These include autoantibodies to glutamic acid decarboxylase (GADA), insulinoma-associated autoantigen 2 (IA-2A) and zinc transporter 8 (ZnT8A) (Ziegler and Nepom, 2010).

We have moved from viewing type 1 diabetes as a sudden, acute event to a nuanced understanding of it as a chronic, progressive autoimmune process with a long pre-symptomatic phase. Can the detection of diabetes-related autoantibodies before the onset of symptoms provide an opportunity to delay the onset of insulin-requiring type 1 diabetes? And, in the future, could it help in the pursuit of a cure? To explore these opportunities, we first need to consider how type 1 diabetes progresses through its recognised stages.

Stages of type 1 diabetes

Development of type 1 diabetes autoantibodies is known to start in the months or years before the onset of symptoms (Zeigler and Nepom, 2010). In 2015, a landmark consensus statement was published by the American Diabetes Association (ADA), Breakthrough T1D (formerly JDRF) and the Endocrine Society that formally recommended a

Citation: Brake J, Nicholson MK, Zaidi R (2026) Changing the course of type 1 diabetes: screening and early immunotherapy. *Journal of Diabetes Nursing* **30**: JDN415

Article points

1. Type 1 diabetes is now understood to be a chronic, progressive autoimmune process with a significant pre-symptomatic phase.
2. Emerging immunotherapeutic strategies, most notably teplizumab, aim to delay the onset of type 1 diabetes symptoms by preserving beta-cell function.
3. Considerable practical and ethical challenges must be addressed before a national screening programme can be implemented to identify those at high risk who might benefit from immunotherapy.

Key words

- Autoantibodies
- Immunotherapy
- Population screening
- Teplizumab
- Type 1 diabetes

Authors

Julie Brake, Diabetes Nurse Consultant; Martha Nicholson, IMT3 Doctor, Diabetes and Endocrinology; Reza Zaidi, Consultant Diabetologist and National Advisor for Young Adult Diabetes (NHS England); all with the NHS University Hospitals of Liverpool Group

"Development of type 1 diabetes autoantibodies is known to start in the months or years before the onset of symptoms."

three-stage classification for the progression of type 1 diabetes (Insel et al, 2010). This framework, since adopted by Diabetes UK, recognises that type 1 diabetes starts long before clinical symptoms appear.

Stage 1: Autoimmunity+/normoglycaemia/ pre-symptomatic type 1 diabetes

This stage marks the onset of type 1 diabetes. Individuals have two or more diabetes-related autoantibodies. The immune system has begun attacking the insulin-producing beta cells, although there are no symptoms and blood glucose levels remain normal.

Stage 2: Autoimmunity+/dysglycaemia/ pre-symptomatic type 1 diabetes

As with stage 1, individuals have two or more diabetes-related autoantibodies, but now blood glucose levels have become abnormal owing to the increasing loss of beta cells. Despite this, there are still no symptoms.

For both stages 1 and 2, the lifetime risk of developing symptomatic type 1 diabetes approaches 100%.

Stage 3: Autoimmunity+/dysglycaemia/ symptomatic type 1 diabetes

This is when clinical diagnosis is typically made. Significant beta-cell loss has occurred, and individuals generally show common symptoms of type 1 diabetes – such as frequent urination, excessive thirst, weight loss and fatigue – and are at risk of DKA.

This staging classification is essential in understanding the pathogenesis of type 1 diabetes. Early diagnosis within the disease process offers the potential for intervention to preserve more beta-cell function, with the aim of improving glucose levels and reducing the long-term complications of type 1 diabetes. However, the detection of the pre-symptomatic condition relies on population-level screening, which requires careful consideration and presents many challenges (*Box 1*).

Recognising type 1 diabetes as a staged, progressive autoimmune condition reframes how the disease is studied and treated. This shift has resulted in a growing body of research exploring whether selective modulation of the immune response can alter the trajectory of beta-cell decline. The following section outlines the key immunological pathways involved and how they have informed current and emerging immunotherapeutic strategies.

Overview of immunotherapy research in type 1 diabetes

Pathogenesis and therapeutic targets

Autoimmune destruction of the insulin-producing pancreatic beta cells in type 1 diabetes leads to the gradual loss of endogenous insulin secretion and subsequent loss of glycaemic control. While exogenous insulin remains a life-saving therapy in type 1 diabetes, it does not modify the underlying immune-mediated disease process and is, therefore, a lifelong treatment rather than a cure.

The pathogenesis of type 1 diabetes involves complex interactions between multiple components of the adaptive immune system, including autoreactive CD8+ cytotoxic T lymphocytes, CD4+ T helper and regulatory T cells (Tregs), and autoantibody-producing B lymphocytes (Huang and Zhu, 2024; Biswas et al, 2025). This provides numerous potential targets for immunotherapy aimed at slowing or halting beta-cell destruction.

Biomarkers, clinical outcomes and identifying suitable candidates

Assessing the impact of immunotherapies in type 1 diabetes relies on both surrogate biomarkers for beta-cell function and clinical measures of disease progression. C-peptide, a peptide released by the cleavage of pro-insulin, is often used as a proxy measure of endogenous insulin production and, therefore, residual beta-cell function. Clinical measures such as glycated haemoglobin (HbA_{1c}) and serial blood glucose profiles reflect actual glycaemic control but do not directly measure beta-cell function. Daily insulin requirement is another measure that may be used to measure the clinical effect of immunotherapies in those with established (stage 3) type 1 diabetes (Huang and Zhu, 2024).

Long-term cohort data from the DCCT/EDIC study (Lachin et al, 2014) demonstrate that even modest preservation of C-peptide is associated with clinically meaningful improvements in outcomes, including reduced hypoglycaemia risk, lower insulin requirements and improved glycaemic control. As such, modulating disease progression via immunotherapy is particularly valuable in individuals who still retain some beta-cell function

and have not yet developed absolute insulin deficiency – that is, individuals with stage 1 or 2 type 1 diabetes.

No population-based UK screening programme currently exists to identify these people prior to symptom onset. There are, however, two ongoing studies in the UK aiming to evaluate the feasibility and acceptability of large-scale autoantibody screening for type 1 diabetes: ELSA (Early Surveillance for Autoimmune Diabetes; ELSA Study Team, 2026; Quinn et al, 2026) and T1DRA (Type 1 Diabetes Risk in Adults; T1DRA Study Team, 2026).

The therapeutic process of adjusting or regulating the immune system to achieve a desired response is known as immunomodulation. Experimental approaches for immunomodulation in type 1 diabetes include dampening T-cell activation (Herold et al, 2002; 2019), blocking T–B cell interaction (Carvalho, 2023; Sanofi, 2026), depleting B cells that are early initiators of the immune response (Pescovitz et al, 2014) and enhancing pathways that support regulatory T cells (Russell et al, 2023; Galderisi et al, 2026). The international clinical trial network TrialNet (2026), which is focused on early detection, prevention and delay of type 1 diabetes through clinical trials in at-risk and newly diagnosed individuals, is one of several research programmes actively exploring these different immunomodulatory strategies.

Current and emerging immunotherapies

To date, only one type 1 diabetes immunotherapy, the anti-CD3 monoclonal antibody teplizumab, is licensed for use in the UK by the Medicines and Healthcare products Regulatory Authority (MHRA; Electronic Medicines Compendium, 2026). Despite this, teplizumab's NICE technology appraisal is still ongoing, with guidance expected in April 2026, and its routine use in the NHS has not yet been recommended owing to insufficient evidence (NICE, 2026). In the phase 2 TrialNet teplizumab prevention study (Herold et al, 2019), a single 14-day course delayed progression to stage 3 diabetes in high-risk individuals, extending median time to diagnosis from 24.4 to 48.4 months (~59% risk reduction). Extended follow-up studies have shown persistent efficacy of the initial 2-week course, in addition to evidence of improved beta-cell function (Sims et al, 2021).

Box 1. Considerations and challenges for population-level screening and implementation of immunotherapy.

The implementation of immunotherapy for the prevention of type 1 diabetes relies on a symbiotic relationship with an established national screening programme. Currently, in the UK, screening only exists in a research capacity and not as a national scheme. As over 25% of children and young people are diagnosed while presenting with diabetic ketoacidosis (DKA), researchers have highlighted the potential benefits of early detection and subsequent immunotherapy – fewer DKA admissions, delayed need for insulin therapy and improved psychological preparation. However, numerous challenges exist and must be taken into consideration.

1. **Screening the correct population.** Targeting high-risk relatives may be insufficient, as nearly 85% of people with type 1 diabetes have no family history of the condition.
2. **Infrastructure.** The need for highly accurate autoantibody testing requires adequate laboratory capacity and the standardisation of testing and quality control across multiple NHS labs.
3. **Cost-effectiveness and health system resources.** Health policy-makers need to consider whether delaying onset of the condition justifies national spending on substantial infrastructure and drug-related costs.
4. **Ethical and psychological issues.** Families must be informed about the uncertain timelines for the onset of type 1 diabetes among those identified early. This uncertainty, and the resultant anxiety, can be compounded by limited access to psychological services in some NHS areas. Immunotherapy also involves multiple hospital visits, potential drug side effects and uncertainty regarding long-term benefits.
5. **Equity and population coverage.** Screening programmes historically risk unequal access, with under-representation of ethnic-minority populations, deprived populations and those living in rural areas.
6. **Integration into existing NHS pathways.** Implementing a national programme would require the coordinated involvement of public health, primary care and specialist services. Clear referral pathways and long-term monitoring clinics would need to be established alongside robust databases and electronic health record-tracking systems.
7. **Evidence of long-term outcomes.** Although early detection and immunotherapy show significant promise, uncertainty remains owing to limited long-term outcomes and the potential need for repeat or combination therapies.

Combination immunotherapeutic strategies targeting multiple components of the autoimmune response is a subject that has been of particular interest in recent years. The hope is that agents that demonstrate modest preservation of beta-cell function, but little clinical efficacy, may be combined to greater effect (Biswas et al, 2025). The ongoing TrialNet T1D RELAY study follows this approach, evaluating a combined regimen of rituximab (an anti-CD20 monoclonal antibody) alongside abatacept (a CTLA-4-targeting T-cell co-stimulation modulator). While both these agents have been studied individually in type 1 diabetes, and both have been found to preserve C-peptide levels to some degree, neither had a statistically

"While routine national screening is not yet widely available, the UK National Screening Committee is reviewing evidence from landmark trials to inform a potential UK-wide rollout."

significant impact on the clinical progression of type 1 diabetes alone (Pescovitz et al, 2009; 2014; Russell et al, 2023). Also within the TrialNet consortium, the JAKPOT T1D trial is assessing the Janus kinase (JAK) inhibitors abrocitinib and ritlecitinib as single-agent therapies to prevent beta-cell loss via cytokine-driven inflammation (National Institute of Diabetes and Digestive and Kidney Diseases, 2025).

The UK Type 1 Diabetes Research Consortium (UK T1D-RC) SMART study is investigating combination therapy with abatacept and interleukin-2, aiming to promote Treg cell sparing whilst simultaneously inhibiting the autoreactive T-cell co-stimulatory pathway (Tatovic, 2026; UK T1D-RC, 2026a). Additional ongoing trials include FABULINUS (Sanofi, 2026), a large multi-country phase 2 study of the CD40L antagonist frexalimab, and Beta Preserve, a phase 3 evaluation of the safety and efficacy of teplizumab (UK T1D-RC, 2026b).

Summary

The staging of type 1 diabetes and its early detection through screening could reduce the risk of complications, such as DKA, at diagnosis and provide an opportunity for treatments that could delay the progression of the condition.

Immunotherapy research has shifted type 1 diabetes treatment from managing symptoms to addressing the root cause – the immune system attacking insulin-producing beta cells. Research studies, such as ELSA and T1DRA, have identified several promising strategies, including immunotherapy, which is being explored as a treatment for early-stage type 1 diabetes.

A major milestone was the 2025 UK licensing of teplizumab, the first immunotherapy approved to delay the onset of stage 3 type 1 diabetes, by an average of 3 years, in adults and in children from 8 years of age with stage 2 type 1 diabetes.

While routine national screening is not yet widely available, the UK National Screening Committee is reviewing evidence from landmark trials to inform a potential UK-wide rollout. It is still uncertain who would deliver the screening and counsel those being screened and their families, how equitable access would be ensured and what support, outside of screening and immunotherapy, would be available. ■

Biswas S, Dhir B, Talasila S et al (2025) Immunomodulatory interventions in type 1 diabetes: a systematic review and meta-analysis revealing paradoxical dissociation between beta-cell preservation and glycemic control. *BMC Endocr Disord* **25**: 270

Carvalho T (2023) Anti-CD40L antibody frexalimab slows new brain lesions in multiple sclerosis. *Nat Med* **29**: 1882–3

Eisenbarth GS (1986) Type 1 diabetes mellitus. A chronic autoimmune disease. *N Engl J Med* **314**: 1360–8

Electronic Medicines Compendium (2026) Tzield 2 mg/2 mL concentrate for solution for infusion. Available at: https://www.medicines.org.uk/emc/product/101240/smpc#gref (accessed 12.03.26)

ELSA Study Team (2026) *The ELSA Study*. Available at: https://www.elsadiabetes.nhs.uk (accessed 23.02.26)

Galderisi A, Carr ALJ, Taylor P et al (2026) Baseline insulin secretion determines response to abatacept in stage 1 type 1 diabetes. *Diabetes* **75**: 229–40

Herold KC, Hagopian W, Auger JA et al (2002) Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* **346**: 1692–8

Herold KC, Bundy BN, Long SA et al; Type 1 Diabetes TrialNet Study Group (2019) An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* **381**: 603–13

Huang Q, Zhu J (2024) Regulatory T cell-based therapy in type 1 diabetes: Latest breakthroughs and evidence. *Int Immunopharmacol* **140**: 112724

Insel RA, Dunne JL, Atkinson MA et al (2015) Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* **38**: 1964–74

Lachin JM, McGee P, Palmer JP (2014) Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes* **63**: 739–48

National Institute of Diabetes and Digestive and Kidney Diseases (2025) *Janus kinase (JAK) inhibitors to preserve C-peptide production in new onset type 1 diabetes (T1D)*. ClinicalTrials.gov identifier: NCT05743244. Available at: https://clinicaltrials.gov/study/NCT05743244 (accessed 12.03.26)

NICE (2026) *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes* [ID6259]. NICE, London. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10981 (accessed 12.03.26)

Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H et al (2009) Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med* **361**: 2143–52

Pescovitz MD, Greenbaum CJ, Bundy B et al (2014) B-lymphocyte depletion with rituximab and B-cell function: two-year results. *Diabetes Care* **37**: 453–9

Quinn LM, Elliott J, Papanikolaou T et al (2026) Feasibility of general population screening for type 1 diabetes in the UK: the ELSA study. *Lancet Diabetes Endocrinol* **14**: 197–9

Russell WE, Bundy BN, Anderson MS et al (2023) Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. *Diabetes Care* **46**: 1005

Sanofi (2026) *FrexalimAB in preservation of endogenous insULIN Secretion compared to placebo in adUlts and adolescents on top of inSulin therapy (FABULINUS)*. ClinicalTrials.gov identifier: NCT06111586. Available at: https://clinicaltrials.gov/study/NCT06111586 (accessed 12.03.26)

Sims EK, Bundy BN, Stier K et al (2021) Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* **13**: eabc8980

T1DRA Study Team (2026) *T1DRA: Type 1 Diabetes Risk in Adults*. Available at: https://t1dra.bristol.ac.uk (accessed 23.02.26)

Tatovic D (2026) Balancing "bad" and "good" immune cells: testing a novel method for monitoring an immunosuppression strategy in people with Type 1 diabetes. *ISRCTN Registry*. Available at: https://doi.org/10.1186/ISRCTN85031369 (accessed 11.03.26)

Type 1 Diabetes TrialNet (2026) *Type 1 Diabetes TrialNet*. Available at: https://www.trialnet.org (accessed 23.02.26)

UK Type 1 Diabetes research Consortium (2026a) *SMART*. Available at: https://type1diabetesresearch.org.uk/current-research/smart (accessed 23.02.26)

UK Type 1 Diabetes research Consortium (2026b) *Beta Preserve*. Available at: https://type1diabetesresearch.org.uk/current-research/beta-preserve (accessed 23.02.26)

Ziegler AG, Nepom GT (2010) Prediction and pathogenesis in type 1 diabetes. *Immunity* **32**: 468–78