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Clinical Immunologic Interventions for the Treatment of Type 1 Diabetes

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ABSTRACT

Replacement insulin therapy has been the mainstay of T1D treatment ever since its introduction into clinical care over 100 years ago. Despite advances in delivery methods, insulin remains a challenging medication. It is therefore not surprising that most people with T1DM do not achieve optimal glycaemic control and remain at risk of complications. The recent introduction of Teplizumab as the first immunotherapy for T1D has ushered in an exciting era where the focus is shifted from metabolic replacement therapy with insulin to proactive disease-modifying treatments that prevent the loss of insulin secretory capacity. At least eight other clinical immunologic interventions have shown phase 2 trial efficacy in preserving beta cell function in T1D. To translate these findings to patient benefit many changes are required. These include improvements in endpoints and trial design to accelerate drug development, changing the attitude of healthcare professionals towards novel strategies and the development of effective screening programmes to identify affected individuals in early-stage disease. This will enable increasingly appropriate selection of immunomodulators tailored to an individual's response with an ultimate goal of "insulin free T1D".

1. INTRODUCTION

Type 1 diabetes mellitus (T1D) is caused by autoimmune-mediated destruction of the pancreatic β -cells. The disease starts long before a clinical diagnosis is made and progresses to dependence on exogenous insulin with absolute or near-absolute insulin deficiency¹⁻⁴. Replacement insulin therapy has been the mainstay of T1D treatment ever since the introduction of insulin into clinical care over 100 years ago⁵⁻⁸. The discovery of insulin was undoubtedly a breakthrough as it meant that T1D ceased to be a fatal disease, but it converted T1D into a chronic disease. Despite significant advances in delivery methods, insulin remains arguably the single most complex and challenging medication in current medical practice. Achieving optimal glycaemic control with insulin while avoiding hypoglycaemia is estimated to involve up to 20 or more therapeutic decisions daily including dose adjustments dependent not only on repeated blood glucose measurements but also carbohydrate counting, and alterations for physical activity, stress and intercurrent illness. It is therefore not surprising that most people with T1DM (>70%) do not achieve optimal glycaemic with this approach⁹⁻¹⁷ and remain at risk of long-term complications, while at the same time frequently reporting high levels of “diabetes distress”¹⁸. This persisting unmet need in T1D management justifies efforts to develop clinical immunologic interventions in T1D that can modify the disease course and reduce, delay or prevent the need for insulin.

2. THE CHALLENGES OF DEVELOPING DISEASE MODIFYING THERAPIES FOR T1D

2.1. Insulin therapy: a blessing and a curse

It is a striking observation that there are currently no approved disease-modifying therapies for new-onset clinical T1D whereas other common autoimmune diseases

such as psoriasis, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease have adopted disease modifying strategies more quickly with between 8 and 30 therapies already licensed. The availability of insulin as a replacement therapy although clearly “a blessing”, might also be considered a “curse” in this context, contributing to the delay in the development clinical immunologic intervention therapies in T1D in three ways.

Firstly, the availability of insulin reduces the clinical urgency and apparent priority of developing alternative approaches as well as setting a high bar for safety. Secondly, insulin confounds the use of clinical endpoints in drug development. In cell-mediated autoimmune diseases in general we do not have a robust biomarker of the pharmacodynamics of the disease process itself and rely on clinical endpoints to guide drug development. Examples of clinical endpoints currently used in drug development include skin lesion counts (PASI score) in psoriasis, joint pain and inflammation scores (e.g. DAS 28, Clinical Disease Activity Index) in rheumatoid arthritis, MRI lesion count, annualized relapse rate (ARR) and disability Expanded Disability Status Scale (EDSS) in multiple sclerosis and bowel symptoms scores (or tissue biopsies) in ulcerative colitis or Crohn’s disease. Unfortunately, comparable clinical endpoints for T1D such as average glucose levels, HbA1c and hypoglycemia rates are not reflections only of the loss of beta cell function but can also change as a result of alterations in adherence to insulin therapy, representing an additional challenge to drug development in T1D. This key issue is discussed in more detail in the next section. Thirdly, unlike most other autoimmune disease, T1D is clinical silent until a late stage, when an estimated 80% of the beta-cells have been destroyed. As a result, the “window” for intervention in clinical disease is short (around 1-5 years) before there is little clinically significant residual beta-cell function, and the population immediately available for clinical trials

– individuals with new-onset disease – represents only around 2% of all patients with T1D. This extended “clinically silent” phase is similar to the situation in, for example, renal disease in which clinical symptoms are also a late manifestation but the relatively low cost of replacement therapy with insulin as compared to renal replacement therapy is an further (financial) disincentive for drug development in T1D. An additional challenge which does not relate to the availability of insulin is that the disease is most active and rapidly progressive in children, especially under 5 years of age¹⁹. Regulatory authorities require proof of likelihood of benefit as well as safety in adults before testing in children, especially very young children, adding extra time to drug development.

2.2. Outcome assessments, clinical and surrogate endpoints in new-onset (Stage 3) T1D

The clinically relevant outcomes recognized by regulatory authorities such as the FDA for drug approvals in diabetes include long-term complications (e.g. nephropathy, retinopathy, cardiovascular disease, premature death) and acute complications (e.g. hypoglycaemia, diabetic ketoacidosis). In view of the very long time required to develop such long-term complications, surrogate measures of glycemic control which have been validated to be associated with these outcomes are also accepted, notably HbA1c. In the context of disease-modifying therapies for T1D, these endpoints are problematic as they can also be modified by improvements in insulin therapy independent of beta-cell preservation and this is particularly relevant with the advent of highly effective hybrid closed loop (artificial pancreas) insulin delivery systems²⁰.

The most relevant endpoint for disease-modifying therapies in established (Stage 3) T1D currently is a measure of beta-cell function, notably standard meal-stimulated insulin C-peptide production, which uses a combination of glucose and amino-acids

as a stimulus. This endpoint is generally expressed as a time normalised area under the curve (AUC) of C-peptide in a 2 or 4 hour mixed meal tolerance test (MMTT) referred to as the C-peptide AUC. C-peptide AUC declines in a broadly linear fashion in the first year after clinical diagnosis of T1D and is not affected by changes in insulin therapy ^{21,22}. Until recently, however, C-peptide levels were not accepted by the FDA or EMA as outcomes for drug approval as they do not directly impact on how a patient “feels, functions or survives” but rather indirectly via glucose levels. A strong case that C-peptide levels nonetheless should represent a surrogate outcome marker for drug approval has been made by the T1D community following the collection of extensive data correlating C-peptide levels to clinical endpoints and the situation is changing^{23,24}. Nonetheless, trials of at least 6-12 months with 40-70 participants with very recent onset clinical disease (typically recruited within 6-12 weeks of diagnosis) are required for early phase studies to determine optimal dosing and provide the first evidence of efficacy. All too often it is discovered late in a trial that the dose or target groups of patients were inappropriate, leading to unmet endpoints ²⁵⁻²⁷. This can easily translate into the clinic leading to the danger that certain immunotherapy agents could be administered to the patient for months without clear evidence of its efficacy in that particular individual who may be a non-responder.

2.3. *Additional challenges of outcome assessment in early (Stage 1 or Stage 2) T1D.*

While the use of AUC C-peptide represents a very valuable surrogate marker for drug development in late stage clinical disease (Stage 3 T1D), it is of less value in the early stages of the disease (Stage 1 and Stage 2) before insulin is required and indeed may show a paradoxical increase in Stage 2²⁸. This is likely due to two factors: firstly, the early change in beta-cell function comprises a delay in insulin release with reduction

in the early/first phase of secretion and a compensatory increase in the delayed secretion so that the overall AUC C-peptide changes little. Secondly, as beta-cell function declines, the glucose rise during an oral glucose tolerance test is greater and this represents a more powerful stimulus to insulin release²⁹. As a result, to date, the outcome of intervention studies in Stage 1 or Stage 2 has been progression to the next metabolic stage³⁰⁻³². Unfortunately, this is slow requiring a minimum of 2 years of follow-up in Stage 2 and longer in Stage 1. There is therefore much interest in surrogate markers of early change in beta-cell function. Markers that take into account the glucose rise during challenge testing as well as the C-peptide increase seem to perform better especially in Stage 2 (e.g. index 60³³). For Stage 1, markers that can capture changes in first phase insulin secretion (which occurs within 15 mins of stimulation) are most valuable (e.g. the intravenous glucose tolerance test or modelling of glucose, C-peptide and insulin with additional early sampling time points in the oral glucose tolerance test)^{29,34,35}. The role of continuous glucose monitoring (CGM) as a marker of disease progression is currently being assessed but without linkage to C-peptide levels may not have greater discriminatory power³⁶. The pros and cons of different metabolic outcome markers is summarised in Table 1.

Alternative markers of beta-cell function have been explored, including levels of beta-cell prohormones and exocrine enzymes. Proinsulin to C-peptide ratio (PI:C) shows some promise for this purpose as stressed beta-cells tend to release more proinsulin³⁷ and PI:C increases as individuals approach Stage 3³⁸. Interestingly and consistent with maintenance of insulin production in early stages of the disease, a high PI:C ratio was linked to increases in absolute proinsulin rather than decreased C-peptide values in Stage 2. In contrast, elevations of PI:C at the time of T1D diagnosis are more strongly linked to reductions in C-peptide³⁹.

2.4 The challenge of demonstrating longevity of effect

To date, almost all disease modifying therapies that appear to show promise in T1D appear to decline in their effect over time²³. In some cases this may be because treatment was only given for a limited time period and ongoing or repeated therapy is indicated (e.g. with golimumab or verapamil), in some the effects declined despite repeated therapy (e.g. abatacept⁴⁰) and in others repeated therapy is either not possible (e.g. teplizumab and ATG) and/or carries a risk of increased immunosuppressive risk (e.g. rituximab, alefacept). For disease modifying therapies to be cost-effective and substantially improve quality of life and reduce the risk of long-term complications, the disease process needs to be halted together or at least substantially slowed for 5-10 years or more while still maintaining a favourable balance of benefit to risk ratio. This has been achieved in other autoimmune diseases with ongoing therapy. However, demonstrating this in T1D will require long-term ambitious projects spanning 5 or more years of continued follow-up and/or the use of combination therapies or changes in therapy to maintain benefit over time. This represents an additional challenge to the profitability of drug development programmes that will need to be overcome for example by conditional regulatory approval with agreed post-marketing study programmes of long-term follow-up.

3 IMMUNOTHERAPY APPROACHES

Although effective in preserving beta cell function^{41,42}, generalised immunosuppression of the kind used in transplantation is not suitable for diabetes immunotherapy because of its adverse high-risk profile. Selective immunosuppression targeting specific cell subsets and cytokines represents a more favourable approach. Therapies that have demonstrated favourable effects so far in clinical trials listed in

Table 2 with mechanisms of action shown in Figure 1⁴³. Note that for all these agents other than teplizumab, only data from small trials (phase 2) is available and maybe subject to error⁴⁴.

The introduction of Teplizumab into the clinical management of T1D in 2022 opened a new and exciting era and represents a paradigm change in the approach of treating T1D. Administration as a daily infusion over 2 weeks to people in Stage 2 T1D delayed the need for insulin by almost 3 years^{30,45}. However, whilst the plethora of immunotherapy targets already in clinical practice for other diseases opens numerous options, there are dilemmas for T1D: what are the right targets, timings and doses for successful immunomodulation?

3.1. “Broad target” immunomodulators

Immunotherapies that initially showed success in preserving beta-cell function have broader targets (Table 2). This is the case with targeting T-cells (anti-CD3, anti-thymocyte globulin (ATG)), B-cell deletion (anti CD20) and reduction of circulating central and effector memory CD8 cells (Alefcept). Teplizumab is an Fc-nonbinding monoclonal antibody targeting T-cells through the T cell receptor (TCR) component CD3³⁰ (this approach is discussed in more detail in Chapters XXX/YYY). Low dose ATG is an immunomodulatory agent that reduces CD4+ T effector cells, thus increasing memory CD4+ cells whilst maintaining naïve CD8+ cells and most importantly having no significant effect on the T-regulatory cell compartment⁴⁶ in comparison to high dose regimens⁴⁷. A recent study suggests that ATG induces an exhaustion phenotype in CD4+ T-cells in responders⁴⁸. Rituximab addresses the autoimmunity in T1D from a different angle i.e. by modulating the antigen presentation function of B-cells through targeting their CD20 molecule⁴⁹. Alefcept binds CD2, which is expressed most prominently on CD4+ and CD8+ effector memory T-cells,

primarily responsible for autoimmune attack in T1D. It elicits a depletion of CD4+ and CD8+ central memory and effector memory T-cells, whilst preserving T-regulatory cells⁵⁰. Each of these immunotherapies have so far shown positive results by delaying C-peptide loss by 8.2-15.9 months in new onset T1D^{51,52}.

The drawback with “broad target immunomodulators” is a higher level of immunosuppression and, in earlier cell depleting therapies, problems with infusion reactions and cytokine release⁵. Selective immunosuppression may therefore be a preferable choice in the long term. An exception to this may be treatments targeting an increase in regulatory T cells – these have yet to confirm benefit but are discussed in more detail in **Chapter XXXX (Bluestone)**.

3.2. “Precision” immunomodulators

The ultimate goal is “precision” immunomodulation, which aims to target the specific pathway thought to be responsible for autoimmune attack in T1D, minimising the degree of generalised immunosuppression and resulting in significant improvements in safety and tolerance. However, translating this approach to the clinic will require a better understanding of the effect of “precision immunomodulators” on the underlying immune mechanisms in T1D as well as rate-limiting elements of the autoimmune process.

One example is Abatacept, a soluble CTLA-4 molecule fused with human IgG1. It increases CTLA4 function and inhibits co-stimulation essential for T-cell activation. Studies of Abatacept in people with new onset T1D^{53,54} and, recently, in individuals at risk of developing this disease³¹ showed a modest effect on preservation of beta-cell function. A potential explanation for this limited impact is that Abatacept treatment has a drawback: as well as targeting the T- effector cells that cause disease, it also decreases homeostasis of T-regulatory cells.

The precision required for the right choice of immunomodulation also extends to determining the right dose of the agent, which may not necessarily translate from one autoimmune disease to another. This is very well reflected with treatment with low dose Interleukin-2 (IL-2). The standard regimen includes a 5-day induction phase with 1 million units/day followed by maintenance dose of 1 million units every two weeks. This was proven to be effective in studies on a number of autoimmune diseases⁵⁵. However, such doses did not show benefit in T1D (data not published, Klatzmann study may be available at the time of publishing). On the contrary, a lower dose of 0.2 million units/m² of body surface of IL-2 twice weekly in another study in T1D was more effective in preserving beta-cell function (not published, Todd study may be available at the time of publishing). This discrepancy can perhaps be explained if the ultra-low dose allows stimulation solely of T-regulatory cells through their high-affinity IL2 receptor⁵⁶, but has no effect of effector T-cells. Additional “unexpected” effects, which may be favourable or unfavourable, need also to be taken into account in dose finding such as increases in regulatory B cells⁵⁷, CD56^{bright} NK cells, and MAIT cells⁵⁸. Similar critical dosing issues have been observed with other therapies such anti-CD3²⁵ and ATG⁴⁶.

Selective targeting of the proinflammatory cytokine TNF with Golimumab has proven to be effective in people with newly diagnosed T1D. At the end of the trial, mixed-meal-stimulated mean C-peptide level reduced by 18% in the Golimumab group and 51% in control⁵⁹. Only <50% of individuals reached the definition of remission (defined as an insulin dose-adjusted glycated haemoglobin level score of ≤ 9). The effect appeared to be sustained in some people 1 year after treatment cessation⁶⁰ and is consistent with earlier findings with Etanercept⁶¹.

Another “precision” immunomodulator is Ustekinumab, a monoclonal antibody that binds the shared p40 subunit of the IL-12 and IL-23 cytokines⁶². These two cytokines play a key role in the development of T-helper 1 cells (interferon gamma secreting) and T-helper 17 (IL-17 secreting) T-cells, respectively⁶³. Although delayed, Ustekinumab’s effect on beta-cell function in children and adolescents with newly diagnosed T1D (ref when published) was evident (mixed-meal-stimulated mean C-peptide level in Ustekinumab was 0.49 nmol/mol/L and 0.42 nmol/mol/L in control at the end of the treatments period). The effect was to some extent comparable to some “broad” immunomodulation with the advantage of targeting only a pathogenic subset of Th17 T-cells through low-risk IL-12/IL-23 inhibition without significant effect on the rest of the T-cell populations, but with resulting benefit on beta-cell function.

An interesting example in the group of precision immunomodulators is anti-IL21 monoclonal antibody that seemed to be effective in preserving endogenous insulin production only when used in combination with GLP-1 receptor agonist Liraglutide in recent onset T1D. Compared with placebo (ratio to baseline 0.61, 39% decrease), the decrease in MMTT-stimulated C-peptide concentration from baseline to week 54 was significantly smaller with combination treatment (0.90, 10% decrease), which was not seen with anti-IL-21 alone or Liraglutide alone⁶⁴.

Antigen-based therapies are perhaps the cleanest approach to immunomodulation in T1D, but so far, they have not been proven sufficiently effective to translate to clinical practice. They are discussed in detail in Chapter 15 (Autoantigen-specific immunotherapies for prevention and treatment - Mark Peakman & Pere Santamaria)

3.3 Targeting beta cell-immune systems interactions

An alternative approach to improving precision is to target beta cell immune cell interactions. This is discussed in more details in Chapters 8, 21-22. Three agents

believed to act via this pathway, at least in part, have shown efficacy in clinical trials (see Table 2). The newest addition to this category is Baricitinib inhibiting the JAK-STAT signalling pathway, which is downstream of type I and type II cytokine receptors. In this way Baricitinib blocks the action of pro-inflammatory cytokines that play an important role in the autoimmune destruction of beta-cells⁶⁵. In a recent study in people with newly diagnosed T1D showed, Baricitinib maintained endogenous insulin production over 12 months at baseline levels, as opposed to placebo where loss was demonstrated⁶⁶.

4 TIMING AND CHOICE OF IMMUNOMODULATION

Teplizumab opened the door for introducing immunotherapy for T1D into clinical practice, but we now need to keep this door wide open to allow introduction of more agents. It is unlikely that immunotherapy for T1D will simply involve one off “curative” treatment, as this has not been achieved in other autoimmune diseases. Instead, the approach will consist of the careful monitoring of autoimmune responses and repetitive interventions (either simultaneous or sequential). To achieve this, we need reliable immunological markers of efficacy to guide quick and efficient clinical trials that will lead to the translation to the clinic, despite all the limitations and difficulties in finding the right agent discussed above. Advanced trial designs may help in this regard (see next section).

Whatever is the choice of immunomodulation, the earlier we intervene the more beta-cell function can be preserved. Although intervening in Stage 3 can still lead to some beta-cell preservation and metabolic improvement²³, the greatest clinical benefit comes with prevention of the need for insulin therapy for many years. This approach requires individuals in Stage 1 and Stage 2 T1D to be identified through family studies

or population-based screening programmes. These programmes have been trialed in the research arena where they addressed the issues of appropriate age for screening, follow-up of antibody positive individuals and optimal target population⁶⁷. Unfortunately, restricting screening to individuals with a family history of T1D although convenient will miss the majority of people in the early stages of T1D as ~90% of those who will present with new T1D do not have a positive family history^{68,69}. Therefore, to identify the most individuals who would benefit from therapies to prevent T1D, those without a positive family history must also be identified. Data from public health screening in Bavaria indicates that the rate of multiple islet antibody positivity in children not known to have diabetes is 0.3%⁷⁰.

The optimal choice of immunomodulation will probably also depend on the stage of the disease and intensity of the autoimmune process that defines the rate of beta-cell loss. This is very different in different people⁷¹. The group at the University of Exeter has described two distinct patterns of insulinitis occurring in patients with recent-onset T1D, which they refer to as different “endotypes” (discussed in more detail in ?? Chapter 5). Patients diagnosed before age 7 display insulinitis with a high CD20+ cell infiltrate, whilst people diagnosed after the age of 13 have a histologically less aggressive disease with a lower frequency of CD20+ cells⁷². It remains to be established, whether the latter group is a histological equivalent of the clinically recognised cohort of “slow progressors” who develop symptomatic disease late in life and decline slowly in insulin production^{73,74}. This suggests that some individuals may need only low-grade immunomodulation or none at all. On the other hand, those most in need of immunomodulation are the ones that will rapidly progress to near total insulin deficiency. A number of clinical and laboratory tools are available to help us identify those individuals. Age of diagnosis is one of the most striking determinants of

rapid progression, with younger children progressing faster through stages of diabetes⁴⁴. Genetics, defined by the Genetic Risk Score, plays an important role in determining risk⁷⁵ and possibly also the rate of progression to T1D⁷⁶⁻⁷⁸. Taking this into account, we can postulate that the diagnosis of T1D in or shortly before Stage 3 (when limited amount of rapidly declining beta-cell function is available¹), or in younger children (irrespective of the T1D stage as they are likely to lose beta-cell function rapidly) warrants the choice of “broad” immunomodulators to cover multiple potential pathways. Treatments such as Teplizumab, that recently showed promising results even in Stage 3 T1D⁷⁹, would be suitable for this purpose. At this stage, when there is a race with time to preserve the little of beta-cell function remaining, it is reasonable to also to consider more aggressive simultaneous combinations of different agents. The choice of combinations will need to be based on a deep understanding of the pathophysiology on T1D to combine agents with complimentary activity. For instance, this can be achieved by targeting different immune cell subsets to achieve a balance between effector T-cells and regulatory T-cells or targeting different mechanistic pathways. In TN25, for example, rituximab-pvvr alone (targeting B cells) will be compared with rituximab plus abatacept (targeting B cells and T cell activation – NCT03929601). An alternative approach is to combine a broad immunomodulator such as Teplizumab with Verapamil (a calcium channel blocker) that seems to preserve β -cell function in new onset T1D⁸⁰ by reducing beta-cell stress through reduction in chromogranin A⁸¹. In this way, the beta-cell is protected from stress whilst the immunomodulator addresses the autoimmune attack. Additional combinations with verapamil involving other immunotherapy agents such as ATG and Golimumab are being tested (<https://doi.org/10.1186/ISRCTN45965456>). Note that testing of combinations potentially requires large studies if placebo arms are also included and

advanced trial designs to increase efficiency of use of trial subjects should be considered – see below ⁸².

The excellent safety profile of “precision” immunomodulators, with little evidence of generalised immunosuppression, makes them attractive therapeutic candidates for earlier stages of T1D before clinical hyperglycaemia when significant residual beta-cell function allows certain flexibility. These stages require a careful balance between high safety profile agents (as they are given to a well individual) and highly efficient agents (to prevent further beta-cell loss and insulin dependency). Agents that meet some of these criteria, certainly with their safety profile, were previously discussed (Golimumab and Ustekinumab).

It is also reasonable to expect that some individuals will demonstrate an “escape” phenomenon from one agent, which will warrant a strategy with combination of agents or a change to a different agent with broader target, eliciting more substantive immunosuppression. This will be the approach if the disease progresses, and the affected individual is approaching Stage 3 T1D.

5. ADVANCED TRIAL DESIGNS

The small numbers/difficulty in finding subjects for trials of disease-modifying agents in T1D coupled with the relatively long delay to clinical endpoints, support the use of advanced trial designs such as platform, adaptive and/or SMART (Sequential Multiple Assignment Randomised Trials) trials to accelerate progress as used in oncology and COVID-19⁸³⁻⁸⁵. Platform trials increase efficiency by including multiple interventions into a standard protocol with shared controls. Adaptive trials allow treatment arms to be dropped or new treatments introduced into a platform trial part way through the study following pre-specified interim analysis criteria. SMART trials allow subjects who

are failing in a treatment arm to be re-randomised to alternative therapies without having to recruit new subjects⁸⁶. These designs are efficient in time and recruitment requirements. They generate a signal to decide which treatments or combinations of treatments to take forward but definitive studies such as placebo-controlled randomised trials or appropriately powered factorial designed trials of combinations are required for confirmation⁸². The T1D Plus trial combining verapamil with multiple immune modulatory against in Stage 3 T1D represents an example of a platform rial design in T1D disease modification (<https://doi.org/10.1186/ISRCTN45965456>).

6. CONCLUSION

T1D is entering an exciting arena where the focus is shifted from metabolic replacement therapy with insulin to proactive disease-modifying treatments that prevent the loss of insulin secretory capacity . To achieve this goal many changes will need to be implemented. These include changing the attitude of healthcare professionals towards novel treatment strategies, the development of effective screening programmes to identify affected individuals in early stage disease, improvements in endpoints/biomarkers and trial design to accelerate drug development and enable increasingly appropriate selection of immunomodulators tailored to an individual's needs and response (see figure 1). To achieve this and accelerate progress, pharmaceutical partners both from discovery/biotech and large pharma need to be engaged along with the voice of patients, families and clinicians emphasising the value of moving towards “insulin free T1D”.

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Table 1. Comparison of strengths and weaknesses of biomarkers/endpoints at different stages of T1D. Suggested best markers are highlighted in green.

	Stage 1	Stage 2	Stage 3
HbA1c	Not applicable	Possible, not yet validated	• Possible, • confounded by insulin therapy • larger numbers required
CGM	Not applicable	Possible, not yet validated	• Possible, • confounded by insulin therapy • larger numbers required
Insulin dose/kg	Not applicable	Not applicable	• Possible • ? clinical importance • Confounded by intensity of glucose control
Hypoglycaemia	Not applicable	Not applicable	• confounded by insulin therapy • Few events in early disease • Large numbers required
AUC C-peptide	Not very sensitive	Confounded by glucose rise	Reliable, unconfounded. Represents indirect (surrogate) clinical endpoint
Index -60	? untested	Valuable	Valuable – less reliable than AUC C-peptide
First phase insulin release	• Sensitive • More invasive	• ? sensitive • More invasive	Not applicable (first phase lost)
Advanced secretion and insulin sensitivity modelling	• Under development	• May not be better than index-60	Not applicable

Table 2. Summary of clinical interventions that have shown efficacy in clinical trials of preservation of beta cell function in T1D. See text for references.

Agent	Likely mechanism of action
Teplizumab/Otelixizumab (anti-CD3)	Induction of an exhausted state in activated T cells
Alefacept (anti-CD2)	Depletion of T effector memory cells
Low dose anti-thymocyte globulin	Relative depletion of effector T cells versus T regulator cells
Rituximab (anti-CD20)	Depletion of B cells
Abatacept (CTLA4-Ig)	Impaired T cell activation
Golimumab/Etanercept (anti-TNF)	Blockade of TNF mediated beta cell stress
Imatinib (tyrosine kinase inhibitor)	Reduced beta cell stress, increased insulin sensitivity
Anti-IL-21 (in combination with liraglutide)	Reduced trafficking of CD8 T cells to the pancreas, reduced T follicular helper cell function
Verapamil	Reduced beta cell stress via the TXNIP pathway
Baricitinib (JAK 1/2 kinase inhibition)	Reduced MHC class I expression in beta cells and CD8 T cell activation

Figure: Different sites of action of clinical interventions to preserve beta cell function
(reproduced with permission from Tatovic D, Narendran P, Dayan CM. A perspective on treating type 1 diabetes mellitus before insulin is needed. Nat Rev Endocrinol. 2023 Jun;19(6):361-370)

Fig 3

