Emerging drugs for the treatment of type 1 diabetes mellitus: a review of phase 2 clinical trials

Thinzar Min & Stephen C Bain

Abstract

Introduction: Despite therapeutic advances in the field of diabetes management since the discovery of insulin 100 years ago, there are still unmet clinical needs for people with T1DM.

Area cover: Genetic testing and islet autoantibodies testing allow researchers to design prevention studies. This review will discuss the emerging therapy for prevention of T1DM, disease modification therapy in early course of T1DM and therapies and technologies for established T1DM. We will focus on phase 2 clinical trials with promising results, thus avoiding the exhausted list of every new therapy for T1DM.

Expert opinions: Teplizumab has demonstrated potential as a preventative agent for individuals at risk prior to the onset of overt dysglycaemia. However, these agents are not without side effects and there are uncertainties on long-term safety. Technology advances have led a substantial influence on quality of life of people suffering from T1DM. There remains variation in uptake of new technologies across the globe. Novel insulins (ultralong acting), oral insulin, inhaled insulin attempt to narrow the gap of unmet needs. Islet cell transplant is another exciting field and stem cell therapy might have potential to provide unlimited supply of islet cells.

Key words: Immunotherapy; insulin pump; oral insulin; Type 1 diabetes; therapy for type 1 diabetes; ultra-long-acting insulin.

1. Background

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in children and young people. It is characterised by hyperglycaemia due to insulin deficiency following destruction of pancreatic beta cells. The incidence and prevalence of T1DM is increasing worldwide, accounting for 9.5% of people with diabetes with an incidence rate of 15 per 100,000 people[1]. In the United Kingdom (UK), about 8% of people with diabetes have T1DM and the prevalence is highest in people aged 35-60 years of age [2]. In the United States, 80% of newly diagnosed diabetes patients under 19 years have T1DM[3]. There is geographical vacation in the incidence of T1DM, Finland and Sardinia recording the highest incidence while China has the lowest[4]. The age of presentation of T1DM has a bimodal distribution, peaking in the early childhood (age 6 months to 5 years) and again during puberty[5]. Although it commonly presents in children and young people, it can present in adult life[6]. In the region with higher prevalence of T1DM, the incidence among children and young adult was comparable in individual aged 40-100 years (37.8 per 100,000 persons per year and 34.0/100,000/year, respectively)[7]. There is no gender difference in the overall incidence of T1DM[7].

Both genetic factors and environmental risk factors play a role in the development of T1DM. Individuals who have a close relative with T1DM have a significantly increased lifetime risk of developing T1DM. While the lifetime risk of developing T1DM in individuals without any family history is 0.4%[4] , the risk in in those with a first degree relative with T1DM is approximately 5%[8, 9]. While genetic factors increase the susceptibility, exposure to environmental factors such as viral infection[9] and dietary factors , is thought to trigger the autoimmune reaction leading to destruction of insulin secreting pancreatic beta cells[4].

The pathogenesis of T1DM has a long latent phase[10]. The process of autoimmune destruction of beta cells in the islets of Langerhans is thought to be initiated by environmental triggers in genetically susceptible individuals. This process usually takes months or years during which the individual remains asymptomatic and euglycaemic. Symptoms of hyperglycaemia only develop once sufficient pancreatic beta cells (estimated 90%) are destroyed, although impaired glucose tolerance may predate the onset of overt diabetes. Therefore, it is suggested that genetic markers of T1DM are detectable from birth, autoimmune markers after the onset of autoimmune process and metabolic markers once enough beta cell destruction occurs[10, 11]. Stages of T1DM as per the International Society for Paediatric and Adolescent Diabetes (ISPAD) guideline are shown in Table-1[10]:

The most common clinical presentation of T1DM is hyperglycaemia without acidosis and ketosis. Classical presentation includes osmotic symptoms such as polyuria, nocturia and polydipsia, and weight loss. Other common symptoms include blurred vision and vaginal candidiasis[4]. Diabetic ketoacidosis is the second most common clinical presentation, accounting for up to 58% of newly diagnosed T1DM[12, 13] in paediatric populations. A small percentage of patients are diagnosed before the onset of clinical symptoms of hyperglycaemia and the diagnosis is often made by a family member or through the screening studies[14].

It is well established that poor glycaemic control leads to long-term microvascular complications such as retinopathy, nephropathy, neuropathy and cardiovascular disease including myocardial infarction, heart failure and atrial fibrillation[15]. Furthermore, people with T1DM have an increased risk of premature death compared with the general population[16, 17].

2. Medical Needs

There is unequivocal evidence on the impact of intensive glycaemic control on chronic metabolic decompensation and mortality [18, 19]. Despite this conclusive evidence for the benefits of optimal glycaemic control, a considerable proportion of patients with T1DM are not able to achieve the recommended target HbA1c of 7%[20]. According to the National Diabetes Audit (NDA) (2020-2021), only 22% of patients with T1DM in England achieved Hba1c <7% and 34.8% achieved HbA1c <7.5%[21]. In a Brazilian study, only 13.2% of patients with T1DM achieved the HbA1c target[22] and in an Italian study, only 14.7% had a HbA1c <7%[23]. In the T1D Exchange study, recommended HbA1c goal of < 7.5% for youth was achieved by 17% and the goal of < 7% for adults achieved by only 21%[24].

Several potential barriers to intensive glycaemic control have been identified and hypoglycaemia is considered as a major obstacle. Hypoglycaemia is more common in patients with long duration of diabetes and those with impaired hypoglycaemia awareness[25]. Recent advances in blood glucose monitoring system enable the reduction in hypoglycaemia occurrence[26]. However, there is a geographical variation in the uptake and availability of the real time blood glucose monitoring systems[27].In addition, fear of hypoglycaemia remains a major challenge in the clinical management of people with T1DM, affecting quality of life as well as glucose control[28, 29]. Weight gain is another potential adverse effect of intensive insulin therapy, and it occurs when insulin doses are matched for nutritional intake and when glycosuria is eliminated[30]. Other potential barriers include the desire to avoid multiple daily injections and frequent self-monitoring of glucose, misconceptions about insulin treatment, reluctance to the adoption of newer technologies, therapeutic inertia[28] and factors related to patient's lifestyle, education and their environment[31]

3. Existing Treatment

Exogenous insulin therapy remains the only treatment option for the vast majority of people with T1DM. Different insulin preparations and delivery systems have been developed since the discovery of insulin in 1921. The goal of insulin therapy is to mimic the physiological insulin profile in order to maintain blood glucose concentrations within the normal range. The most commonly used insulin delivery is multiple daily injections (MDI), which include a basal insulin (administered either once or twice daily) and prandial bolus insulin administered before each meal[32]. The choice of basal and prandial insulins depends on patient preference, lifestyle, and cost. Available basal insulin preparations include analogue insulins (degludec, glargine U-100 and U-300, detemir) and human (Neutral Protamine Hagedorn [NPH]). Insulin degludec and glargine U-300, and U-100 are administered once daily whilst insulin detemir and NPH are usually administered twice daily. It is generally accepted that analogue insulins are associated with less hypoglycaemia compared to human insulin. Studies demonstrated that long-acting insulin (glargine or detemir) were associated with a modest glycaemic efficacy, less weight gain and lower risk of severe hypoglycaemia and nocturnal hypoglycaemia, compared with NPH insulin[33]. Insulin degludec was shown to have similar efficacy with less nocturnal hypoglycaemia but no significant difference in severe hypoglycaemia occurrence when compared to insulin glargine[34]. Prandial insulin preparations include rapid-acting insulin (lispro, aspart, glulisine) and short-acting insulin (regular) and these need to be administered 20-30 minutes before meal. In addition, two ultra-rapid-acting insulin: FIasp and Lyumjev are now available for clinical use. The advantage of these ultra-rapid-acting insulin are convenience for patients regarding timing of pre-meal administration and less hypoglycaemia as these can be administered just before or even immediately after meals. Despite all these advances in insulin preparations, patients are still required to manage and coordinate their diet and lifestyle with insulin administration and blood glucose monitoring.

Flash glucose monitoring and continuous glucose monitoring (CGM) systems are becoming more widely available and have a positive impact on quality of life, hypoglycaemia reduction and HbA1c reduction[32]. However, there are barriers to CGM in people with T1DM: cost[35], wear discomfort and psychosocial factors[36].

Inhaled insulin has been developed as an alternative to the subcutaneous route. The first inhaled insulin (Exubera) was available for a short period of time and discontinued from the market in 2007 due to poor acceptability by patients and clinicians[37]. Then in June 2014, Afrezza [recombinant regular human insulin] inhalation powder was approved by the FDA to use as a prandial insulin in adults with diabetes who do not smoke nor have any chronic lung diseases. It is available as prefilled cartridge and delivered through a hand-held, pocket-size, breath-powered inhalation device. The glycaemic efficacy of inhaled insulin is generally less than that of subcutaneous insulin. Cough is the most common side effect associated with inhaled insulin therapy. Other limitations include the need to monitor pulmonary function, selective eligibility criteria and uncertainty regarding long-term pulmonary toxicity[38].

Insulin pumps deliver insulin continuously throughout 24 hours via subcutaneous infusion. There is a geographical and age variation in the uptake of insulin pump[39, 40]. While 63% of people with T1DM used an insulin pump in the USA in 2018[24], insulin pump used in England and Wales was between 9 to 21 % [41]. Insulin pumps can be used alone or in combination with a continuous glucose monitoring system, a combination known as sensor augmented insulin pump therapy. The hybrid closed loop system is a more advanced insulin delivery system, which can suspend basal insulin infusion when blood glucose levels approach a threshold value so as to prevent hypoglycaemia. Patients are still required to determine and

administer bolus insulin doses for each meal or food intake . The advantages of insulin pumps include fewer injections, less time in hypoglycaemia, more time in range and improvement in glycaemic control[42]. The main safety concern of insulin pump therapy is pump failure (sensor failure) which can lead to DKA if patients are not diligent enough to detect symptoms of hyperglycaemia with ketosis. In addition, substantial education and support for patients is needed; this involves considerable diligence regarding self-management including blood glucose monitoring, carbohydrate counting, and application of 'sick-day' rules for all people with T1DM using an insulin pump[42].

Adjunctive therapies, approved for the management of T1DM are the amylin analogue (pramlintide), a sodium glucose co-transporter-2 (SGLT-2) inhibitor (dapagliflozin) and a dual SGLT-1 and -2 inhibitor (sotagliflozin). Pramlintide is approved by the Food and Drug Administration (FDA) as an adjunct therapy in combination with insulin[43]. Pramlintide affects blood glucose levels by slowing gastric emptying, promoting satiety, and suppressing glucagon secretion[44]. Studies have demonstrated that pramlintide reduces HbA1c by 0.3% with a lower insulin requirement and is associated with modest weight loss[45, 46]. Pramlintide is administered subcutaneously with each meal and hence the potential clinical benefit is offset by the inconvenience of taking more injections. The common side effects include GI symptoms such as nausea and vomiting. In addition, there are no long-term data on safety and cardiovascular outcomes.

Following the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 diabetes (DEPICT) trials[48, 49], dapagliflozin was approved by the European Medicines Agency (EMA)[50] in February 2019 as an option for treating T1DM in adults with a BMI at least 27kg/m^2, when insulin alone does not achieve adequate glycaemic control. The National

Institute for Health and Care Excellence (NICE) also set out several prerequisites such as completion of a structured education programme and specialist prescription. The potential benefits of dapagliflozin are offset by the potential serious adverse effect of DKA[48] and hence the FDA does not approve use of dapagliflozin for patients with T1DM[51]. Following Astra Zeneca's decision to remove the T1DM indication for dapagliflozin, the EMA recently published the withdrawal of recommendation for dapagliflozin in T1DM[52]. Sotagliflozin is a dual SGLT-1 and SGLT-2 inhibitor, approved in the Europe for use in T1DM. Sotagliflozin produces a greater reduction in HbA1c (mean difference in HbA1c -0.46%), weight (-2.98kg), systolic blood pressure (-3.5mmHg) and mean daily bolus insulin dose (-2.8 unit per day) compared with placebo ($p<0.002$ for all comparison) in selected people with T1DM who have no history of severe hypoglycaemia or DKA. However, the rate of DKA was higher in the sotagliflozin group (3% versus 0.6%), as was the frequency of dehydration and genital infections[53].

The goals of pancreas and islet transplantation are to allow independence from exogenous insulin, slow progression of diabetes complications and improve quality of life. Simultaneous pancreas and kidney transplant (SPK) is commonly performed for people with diabetes and end-stage kidney disease. Pancreas after kidney (PAK) transplant and pancreas-transplant alone (PTA) are less commonly performed procedures[54]. Survival rates for any form of pancreas transplantation range from 96-99% at 1 year, 89-91% at 5 years and 70-80% at 10 years post-operation[54]. Earlier graft failure rate was approximately 8-9.4% and 5-year pancreas graft survival rate for SPK, PAK and PTA were 73%, 65% and 53% respectively[55]. Islet transplantation is considered minimally invasive and associated with less surgical morbidity. However, a higher rate of insulin independence was observed with pancreas transplant (85% versus 50%) with islet transplant at 1 year and (53-73% versus 20-30%) at 5

years[56]. Of note, the recipients of islet transplants still had some endogenous beta cell function as evidenced by detectable serum C-peptide at the time of graft failure [57]. Both pancreas and islet transplantation require lifelong immunosuppression to prevent graft rejection and hence the adverse effects of immunosuppressive therapy must be considered when transplantation is offered to people with T1DM, particularly those without end stage renal disease.

4. Current research goals

Current research goals in the management of T1DM can be divided according to the stage of diabetes. In the early phases (Stage 1 and Stage 2), therapeutic interventions are aimed to prevent or delay the onset of clinical diabetes. For those with elevated risk, the goal is to prevent the onset of diabetes. For those with a new diagnosis of clinical diabetes, the research goals are aimed at disease modification therapies which preserve beta cell function and enhance beta cell survival. For those with established T1DM, current research goals are to develop adjunctive therapies and precision insulin formulations, and insulin delivery systems which can mimic physiological insulin secretion profile.

5. Scientific rationale

Preservation of beta cells in the early stage of disease process is associated with better glycaemic control and lower incidence of hypoglycaemia with favourable long-term outcome [58] and reduced occurrence of DKA[59]. Earlier research therefore focused on preserving beta cell survival by using immunomodulators in those with recent onset T1DM (tertiary prevention). Disease modifying immunotherapies, some of which have been used in other

autoimmune conditions, have been tried and tested. The long latent phase of T1DM provides a window of opportunity to regulate the immune system in the early phases of T1DM before overt hyperglycaemia. Screening studies have enabled the identification of high-risk individuals[60] and hence paving a path to primary and secondary prevention studies with the aim to prevent or delay the onset of clinical diabetes. Primary prevention studies are conducted before the development of autoimmunity and secondary prevention studies are aimed at individuals with positive islet autoantibodies Since primary prevention studies include individuals without any evidence of autoimmunity nor dysglycaemia, interventions must have an extremely safe profile. Primary prevention interventions could potentially be based on dietary modification or vaccination. Secondary prevention interventions include benign therapies (such as nicotinamide and antigen-based therapy) and immune therapy (such as teplizumab).

Once the clinical diagnosis of diabetes is established, insulin forms the mainstay treatment option for most people with T1DM. Despite the development of modern insulins and advances of insulin delivery system and technologies in glucose monitoring, insulin administration is largely parenteral (i.e., subcutaneous injections or subcutaneous infusion) and patients are required to do multiple injections. The search for ultra-long-acting insulin and oral insulin formulations has continued and would narrow the gap of unmet clinical needs such as psychological distress associated with needle phobia. With the advances in technologies, sensor-augmented insulin pumps which regulate basal insulin infusion rate in accordance with blood glucose concentrations have been made available in the market. The next phase of these advances is leading to the development of fully automated insulin delivery device (or artificial pancreas).

Islet transplantation using a steroid free Edmonton Protocol demonstrated insulin independence in some subjects [61] and is considered for patients with disabling severe hypoglycaemia and hypoglycaemia unawareness. One of the major challenges of islet transplant is harvesting the islets from the deceased donors. Stem cell derived islet transplant would overcome this challenge and be able to provide unlimited supply of uncontaminated islets.

6. Competitive environment: a review of drugs and therapeutic options in phase 2 developments

In this section, we aim to include a comprehensive list of emerging treatment options for various stages of type 1 diabetes. Publications were identified through searches of Medline, PubMed and Google Scholar for articles published. Search terms included “type 1 diabetes”, “antigen-based therapy for type 1 diabetes”, “immunotherapy for type 1 diabetes”, “teplizumab”, “otelixibumab”, rituximab, imatinib, abatacept, alfefacetp, ustekinumab, anti-thymocyte globulin, interleukin 21 antibody, liraglutide, verapamil, novel insulins, artificial pancreas, islet transplant. We reviewed drugs that were tried and tested in phase 2 development with promising results or those which progressed to phase 3 development. For consideration, studies had to be published in English. Relevant publications from before were reviewed by authors.

6.1 Antigen-based therapy

Allergy studies demonstrated that immunological tolerance can be achieved by the administration of antigen[62]. It was hypothesised that administration of a diabetes autoantigen in high-risk individuals can reduce the incidence of islet autoantibodies and diabetes[63]. Mucosal administration of antigen (oral or intranasal) is the preferred route in order to create a protective immunity rather than a destructive immunity. Since insulin is considered as the most

beta cell specific antigen, several studies have attempted to modify the course of type 1 diabetes by using various routes of insulin. The Diabetes Prevention Trial-Type 1 (DPT-1) study group investigated the use of injected or parenteral insulin in participants with a projected 5-year risk of ~50%[64], and oral insulin in participants with a projected 5-year risk of 25-50%[65]. The Belgian Diabetes Registry explored the use of pre-meal parenteral insulin in individuals with positive autoantibodies and normal glucose tolerance[66]. The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study evaluated the use of intranasal insulin in newborns without family history but with high-risk HLA-DQB1 alleles[67]. All of the above-mentioned studies did not demonstrate any benefit of antigen-based therapy using insulin.

Glutamic acid decarboxylase (GAD) is another antigen-based therapy evaluated in prevention studies. The Diabetes Prevention- Immune Tolerance (DIAPREV-IT) study, assessing the use of GAD vaccine in children who had positive GAD antibodies and at least one additional autoantibody and not yet clinical diabetes failed to demonstrate delaying the diabetes progression[68].

6.2 Immunotherapy

Several immunotherapies have been tested in patients with T1DM, targeting T-lymphocytes, B-lymphocytes, and cytokines with the aim of halting the immune destruction of pancreatic beta cells. These include monoclonal antibodies against the T-cell CD3 receptor (teplizumab and otelixizumab); a monoclonal antibody against the B-cell CD20 receptor (rituximab); inhibitors of T-lymphocyte activation (abatacept, alefacept); a tyrosine kinase inhibitor (imatinb); an anti-interleukin (IL) antibody (anti-IL-21); and a monoclonal antibody against IL-12 and IL-23 (ustekinumab). Some have shown promising results whiles others not.

Amongst them, teplizumab holds a promising potential, particularly in delaying the onset of clinical diagnosis of T1DM.

6.2.1Anti-CD3 monoclonal antibody

6.2.1.1 Teplizumab

Teplizumab, a humanised Fc receptor non-binding anti-CD3 monoclonal antibody, modifies CD8+ T-lymphocytes, which are thought to be important effector cells that destroy pancreatic beta cells. It was suggested in a pre-clinical trial that an anti-CD3 monoclonal antibody needs an active immune response[69], therefore, initial studies of teplizumab were conducted in people with recent onset T1DM [70-73]. These studies demonstrated that teplizumab delayed the loss of beta cell function up to 7 years after the clinical diagnosis of T1DM but had no impact on the total insulin requirement or HbA1c reduction. In a randomised placebo-controlled trial by Herold et al, teplizumab was assessed in 58 participants with T1DM of 4-12-month duration, the primary outcome being C-peptide response to a mixed meal tolerance test (MMTT) after 1 year. C-peptide levels were 17.7% higher in the teplizumab group (after correcting for baseline HbA1c) compared to the placebo group (0.44 vs 0.38: difference, 0.049 nmol/L, p=0.009). A greater proportion of the placebo group lost a detectable C-peptide response at 12 months (p=0.03). The teplizumab group required less exogenous insulin but there were no differences in the end-of-trial HbA1c between the two groups. Teplizumab was well tolerated with rash, lymphopenia and nausea being the most common adverse effects [72].

Following the promising results of teplizumab phase 2 studies, ‘Protégé’, a phase 3 randomised controlled trial (RCT), which examined the efficacy and safety of teplizumab at 1 year and 2 years in recently diagnosed T1DM patients (n=513) was conducted. In this study, three intravenous (IV) dosing regimens of teplizumab (14-day full dose; 14-day low dose; 6-day full

dose) were given at baseline and at 6 months. After 1-year follow-up, teplizumab did not achieve the primary composite endpoint (insulin requirement <0.5 units/kg/day and HbA1c <6.5%). However, an exploratory analysis showed a significant improvement in the area under the curve (AUC) of mean C-peptide concentration during a 4-hour MMTT in the 14-day full dose treated group[71]. A 2-year report from this study confirmed that the 14-day full dose teplizumab reduced the loss of AUC C-peptide at 2 years versus placebo (p=0.027). However, there was no significant change in HbA1c from baseline in all groups. In a subset analysis, individuals with the duration of diabetes ≤6 weeks had the largest treatment difference versus placebo. The other baseline characteristics favoured positive outcome were U.S. residents, individuals with C-peptide mean AUC >0.2 nmol/L, those with HbA1c <7.5% (58 mmol/mol) and insulin use <0.4 units/kg/day, and 8–17 years of age[70]. Of note, participants from India had higher baseline HbA1c and higher insulin requirement compared to those from USA. This observation suggested that baseline metabolic and immunological characteristics influenced the outcome of study and may help to identify a subgroup with robust response to immune therapy in future studies. With regards to safety and tolerability, no differences in adverse events nor serious adverse events among groups were observed at 2 years. Increased frequency of lymphopenia was observed in teplizumab groups but no apparent differences in the incidence of infections (viral infection) were noted. The most common infection was upper respiratory infection (16.3% of placebo vs. 15.5% of 14-day full-dose patients). Rash or cytokine related adverse events were not observed after two years of treatment[70].

Following these promising results, a phase 2 RCT was designed to investigate the effect of teplizumab on delaying the onset of clinical diabetes in individuals at risk of T1DM, defined as presence of two or more diabetes-related autoantibodies and evidence of dysglycaemia (i.e., Stage 2 of T1DM). A total of 76 participants were randomly assigned to a single 14-day course

of teplizumab or placebo and followed-up for progression of clinical T1DM every 6 months using oral glucose tolerance tests. The median time to diagnosis of T1DM was 48.4 months in the teplizumab group compared to 24.4 months in the placebo group. The incidence of diabetes was 43% in treatment group and 72% in the placebo group (hazard ratio 0.41, 95% CI 0.22-0.78, p=0.006) and the annualized rates of diagnosis of T1DM were 14.9% in the teplizumab group and 35.9% in the placebo group[74]. In the extended follow-up study, the median time to diagnosis were 59.6 months in teplizumab group and 27.1 months in the placebo group (HR=0.457, p=0.01)[75]. In July 2021,the FDA did not approve the use of teplizumab for prevention of T1DM but granted 'Breakthrough Therapy Designation', citing that more data on its pharmacokinetics are required. Similarly the EMA granted 'PRIME (Priority medicines) designation [76]. It is anticipated that the phase 3 PROTECT study will provide additional data; this is a phase 3 RCT to investigate the efficacy and safety of teplizumab (a single daily infusion for 12 days at baseline and 6 months) in children and adolescents (aged 8-17 years) with recently diagnosed T1DM (within 6 weeks)[77]. In November 2022, the FDA approved teplizumab for prevention of stage 3 T1DM in adults and children ages 8 years and above who currently have stage 2 T1DM (FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes | FDA).

6.2.1.2 Otelixizumab

Otelixizumab is another anti CD-3 monoclonal antibody which has been assessed in clinical trials. It is a chimeric antibody with partial/reduced binding capacity to complement or Fc receptor, minimising the risk of cytokine reaction [78]. Otelixizumab downregulates pathogenic T-cells and upregulates regulatory T-cells, hence influencing the autoimmune process responsible for the development of T1DM. In a phase 2 trial by the Belgian Diabetes Registry, which included 80 patients with recent-onset T1DM, otelixizumab was administered

for six consecutive days. For those patients receiving a total dose of 48-64 mg, there was a reduction in insulin requirement and improvement in beta cell function. Indeed, residual beta cell function was 80% higher in the otelixizumab treated group than placebo at 36 months and this correlated with higher residual beta cell function at baseline and treatment at a younger age[79]. One of the adverse effects of otelixizumab was reactivation of Epstein Bar virus (EBV) infection. Low dose otelixizumab (a total dose of 3.1mg) was used in the Durable Response Therapy Evaluation for Early or New-Onset Type 1 Diabetes (DEFEND-1) in order to minimise the risk of EBV reactivation. The DEFEND-1 was a phase 3 RCT to examine the efficacy and safety of otelixizumab in patients with new-onset T1DM[80]. The primary endpoint was change in AUC of C-peptide after a 2-hour MMTT at 12 months and secondary endpoints were changes in HbA1c, insulin requirement and glucose variability. At 12 months, both primary and secondary endpoints were not achieved, suggesting lack of efficacy of low dose otelixizumab. As a result, the DEFEND-2 trial which focused on an adolescent population (aged 12-17) was terminated early (DEFEND-2)[81]. It was concluded that a total dose of 3.1mg otelixizumab was not efficacious in preserving beta cell function in adolescent and adults at high risk of T1DM. Further studies may be able to identify a therapeutic dose window with minimal adverse effects.

6.2.2 Rituximab

Rituximab is an anti-CD20 monoclonal antibody, targeting B-lymphocytes. Rituximab is licenced for treatment of B-lymphocyte lymphoma[82] and selective depletion of B-lymphocytes with rituximab may slow down beta cell loss[83]. In a study by the Diabetes TrialNet Anti-CD20 Study group, rituximab (Rituxan, Genentech and Biogen Idec) infusion at week 0, 1, 2, and 3 after T1DM diagnosis was shown to delay decline of beta cell function at 12 and 24 months[84]. At one year, the mean AUC for C-peptide response to a 2-hr MMTT

was 0.56 pmol/mL compared with 0.47 pmol/mL in the placebo group (p=0.03). The rituximab group also had lower levels of HbA1c over the 12-month period (6.76±1.24% vs. 7.00±1.30%, P<0.001) and required lower doses of insulin (0.39±0.22 Unit/kg vs. 0.48±0.23 Unit/kg, P<0.001). The rituximab group had a higher incidence of adverse reactions during first infusion (93% with rituximab vs 23% with placebo). These reactions were reduced in subsequent infusions and no increase in infection or neutropenia with rituximab was observed.

6.2.3 Imatinib

Imatinib is a tyrosine kinase inhibitor, used as a therapeutic option for chronic leukaemia[85]. Imatinib is thought to have an influence on both immunological and metabolic pathways, hence potentially altering the immune development of T1DM. In pre-clinical studies, imatinib was shown to prevent diabetes and induce diabetes remission in non-obese diabetes mice[86]. The phase 2 RCT investigating the efficacy and safety of imatinib in patients with recent-onset T1DM, aged 18-45 years (n=67) was recently published, suggesting a positive impact of imatinib on beta-cell function for up to 12 months[87]. In this study, imatinib mesylate (Gleevec, Novartis), administered orally as four 100mg tablets per day for 26 weeks resulted in higher 2-hour C-peptide AUC in response to a 4-hour MMTT at 12 months compared to the placebo (0.583 nmol/L vs 0.489 noml/L), however, this effect was not maintained at 24 months. Reduction in insulin dose was also observed at 3 months and 6 months in the imatinib group compared to the placebo. Increased frequency of adverse events was noted in the imatinib group compared to placebo, but most events were mild to moderate severity. Infection and infestation (27% vs 18%), gastrointestinal adverse events (13% vs 0%) were more common in the imatinib group.

6.2.4 Abatacept

Abatacept, a cytotoxic T-lymphocyte protein 4-immunoglobulin (CTLA4-Ig), selectively binds to CD80/86 blocking the interaction with CD28. This prevents the early phases of T-lymphocyte activation, proliferation, and survival and potentially inhibits the B-cell immunological response [88]. Abatacept has been used for the treatment of other autoimmune conditions, such as psoriatic arthritis and rheumatoid arthritis[89]. In a study by the Type 1 Diabetes TrialNet Abatacept Study Group, abatacept (CTLA4-Ig, Orencia, Bristol-Myers Squibb) infusion was given on days 1, 14, 28, and then every 28 days (total 27 doses over 2 years). A total of 112 participants with recently diagnosed T1DM (age 6-36 years) were randomly assigned to abatacept or a placebo infusion[90]. Abatacept achieved the primary outcome of mean AUC C-peptide response to MMTT: adjusted C-peptide AUC was 59% higher at 2 years with abatacept (0·378 pmol/ml) vs placebo (0·238 pmol/ml) (p=0·0029). Abatacept was associated with an estimated 9.6-month delay in decline of beta cell function throughout the study. The abatacept group also had significantly lower HbA1c throughout the study than the placebo group (p=0.002). At 24 months, 34 (47.2%) abatacept treated participants had HbA1c <7%, compared to 8 (25.8%) with placebo. No increase in infections nor neutropenia were observed. Overall, the incidence of adverse events was low, and a few clinically non- significant infusion-related adverse events were noted.

Of note, there is an ongoing prevention study of abatacept in at risk individuals of both paediatric and adult population. The inclusion criteria are participant in Trial Net Natural History/Pathway to Prevention Study, aged between 1-45 years at the time of enrolment and age ≥ 6 at time of randomization in this trial[91].

6.2.5 Alefacept

Alefacept is a recombinant fusion protein that binds CD2 and targets CD4 and CD8 effector memory T cells. Alefacept is used to treat moderate-to-severe plaque psoriasis[92]. Alefacept was found to prevent beta cell decline in a phase 2 multi-centre study of 49 participants. In this study, alefacept (Amevive, Astellas) administered as two 12-week courses of 15mg/week, separated by a 12-week pause) produced a significantly greater C-peptide response at 24 months (15 months after the last dose of alefacept). Insulin requirements were lower ($P = 0.002$) and rates of major hypoglycaemic events were reduced by approximately 50% ($P < 0.001$) in the alefacept group compared with placebo at 24 months. There was no apparent between-group difference in glycaemic control or adverse events[93].

6.2.7 Golimumab

Golimumab (Simponi) is a human monoclonal antibody specific for tumour necrosis factor-alpha that has been approved for the treatment of rheumatoid arthritis, ulcerative colitis and other autoimmune conditions in paediatric and adult settings. In this phase 2 study, 84 children and young adults were randomly assigned to receive either golimumab (56 participants) or placebo (28 participants)[94]. C-peptide levels were higher and insulin use was lower with golimumab than placebo. A greater proportion of participant (43%) in the golimumab group achieved a partial remission response defined as an insulin dose adjusted HbA1c score compared to 7% of those in the placebo group. The safety profile of golimumab was comparable to the placebo. There was no difference in frequency of hypoglycaemia events, any injection-site reaction. Any infection events were higher in the golimumab group (71% vs 61%) but no serious infection was reported in both groups.

6.2.8 CXCR1/2 inhibitor

In the pre-clinical studies, the IL-8 receptors CXCR1/CXCR2 blockade was associated with preserving beta cells and ameliorating hyperglycaemia in NOD mice[95]. Ladarixin, an inhibitor or CXCR1/2 chemokine receptors was assessed in 76 adult patients (aged 18-46 years) with newly diagnosed T1DM[96]. The primary endpoint was change in the AUC for C-peptide response to mixed meal tolerance at 13 weeks from baseline. Secondary endpoints were HbA1c, daily insulin requirement, severe hypoglycaemia, proportion of participants achieving HbA1c <7% without severe hypoglycaemia and maintaining a residual beta cell function at 13 weeks, 26 weeks and 52 weeks. Apart from the transient metabolic benefit at 26 weeks (proportion of participants achieving Hba1c <7% without severe hypoglycaemia was greater in the ladarixin group (81% vs 54%, p=0.024), ladarixin did not achieve the primary endpoint and secondary endpoints. Of note, CXCR1/CXCR2 blockade did not demonstrate any beneficial outcome on islet inflammation-mediated damage in patients with pancreatic islet transplant[97].

6.2.9 Ustekinumab

Ustekinumab is a fully human monoclonal antibody against IL-12 and IL-23 inhibiting the action of IL-12 and IL-23 in inducing pathogenic T-cell subsets[98]. It is licenced in the UK for the treatment of psoriasis in children and adults and psoriatic arthritis and Crohn's disease in adults. There are two ongoing phase 2 clinical trials investigating the efficacy of ustekinumab (Stelara, Janssen-Cilag) in preserving beta cell function as compared to placebo. The USTEK1D is a phase 2 randomised, double-blind placebo-controlled study in children with recent onset T1DM (age 12 to 18 years) [99] and UST1D2 is a phase2/3 trial involving adults with recent onset T1DM (18-25 years)[100]. The primary endpoint is to compare beta-cell function by measuring AUC of stimulated C-peptide during a MMTT at 1 year between ustekinumab and placebo. These studies are expected to complete in 2025.

6.3 Combination therapy

Since the pathogenesis of T1DM involves several immune pathways, combination therapy has been proposed as a potential strategy to develop a safe (minimisation of adverse effects of immunomodulation) and practical regime in order to preserve C-peptide secretion [101].

6.3.1 Anti-thymocyte globulin and granulocyte-colony stimulating factor

Anti-thymocyte globulin (ATG), [Thymoglobulin, Sanofi], is licenced for prophylaxis and treatment of acute rejection in patients receiving a kidney transplant. ATG depletes T-cells through apoptosis, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. ATG has been one of the immunomodulatory drugs tested in T1DM in an attempt to preserve beta-cell survival. The START study, which used high-dose ATG (6.5mg/kg) alone did not demonstrate any C-peptide preservation in humans with T1DM[102]. Pre-clinical studies had suggested that a combination of low dose anti-thymocyte globulin and granulocyte-colony stimulating factor (GCSF) could achieve diabetes reversal in NOD mice[103]. The Type 1 Diabetes TrialNet Study group conducted a three-arm, randomised, double-blind, placebo-controlled trial in 89 people with T1DM: low dose ATG/GCSF group (n-29); low dose ATG alone (n=29) and placebo (n=31). At one year, the mean AUC C-peptide was significantly higher in subjects treated ATG alone (0.646 nmol/L) versus placebo (0.406 nmol/L) (P = 0.0003) but not in those treated with ATG/GCSF (0.528 nmol/L) versus placebo (P = 0.031). However, significant reductions in HbA1c at one year were observed in both the ATG and ATG/GCSF groups[104]. The two-year follow-up had similar findings (higher C-peptide concentration with ATG monotherapy and lower HbA1c in both ATG monotherapy and ATG/GCSF combination therapy, suggesting a benefit of low dose ATG in preserving beta cell

function up to 2 years[105]. The number of immune reactions was higher in the treatment groups but no significant differences in infection , neoplasm, or lymphatic cancers were observed when comparing ATG/GCSF or ATG only versus placebo. The 5-year report of this study, which followed 25 participants, showed no statistically significant differences in the mean AUC C-peptide between those who received ATG/GCSF versus placebo (P = 0.41). In their modelling analysis, ATG/GCSF responders achieved nearly unchanged HbA_{1c} over 5 years, but the study did not have suffient power for comparisons against non-responders or placebo due to small numbers[106]. Of note, the ongoing STOP-T1D study investigates a low dose ATG in delaying or preventing T1DM in individual aged 12-35 years with a 50% risk of clinical diagnosis of T1DM within 2 years.

6.4.3 Anti-interleukin-21 and liraglutide

In another phase 2 trial, combination therapy of anti-IL-21 antibody which has low-grade immune-modifying property and liraglutide which prevents beta cell apoptosis was examined in participants with recent onset T1DM (n=308). Participants were randomly assigned to either anti-IL-21 plus liraglutide, anti-IL-21, liraglutide or placebo. At 54 weeks, the stimulated C-peptide levels were significantly higher with the combination therapy but not with anti-IL-21 or liraglutide alone compared with placebo. All treatment groups achieved a greater reduction in HbA1c compared to placebo who also required a higher insulin dose. No significant difference in rate of hypoglycaemia nor DKA were observed[107].

6.4 Adjunct therapy

6.4.1 Glucagon like peptide-1 receptor agonist

Glucagon like peptide-1 receptor agonists (GLP-1RA) are an established glucose-lowering therapy for type 2 diabetes (T2DM), exhibiting a favourable cardiovascular outcome and

weight loss. GLP-1 is thought to ameliorate beta cell stress and prevent apoptosis in in-vitro studies [108]. In addition, GLP-1 has insulinotropic and glucagonostatic effect, and delays gastric emptying time[109]. All of these properties of GLP-1 may be of benefit in people with T1DM. Several GLP-1RAs (exenatide[110, 111], liraglutide[112-114], albiglutide[115]) have been tested as an adjunct therapy to insulin. Exenatide (high dose and once weekly extended released exenatide) and albiglutide did not produce any significant changes in HbA1c. On the other hand, liraglutide (Victoza, Novo Nordisk) produced a mixed effect. ADJUNCT ONE, a 52-week, phase 3, double-blind, treat-to-target trial with 1398 participants[113] and ADJUNCT TWO, a 26-week phase 3, RCT with 835 participants[114], investigated the efficacy and safety of three liraglutide doses (0.6mg, 1.2mg or 1.8mg) against placebo in adult T1DM. In both studies, liraglutide 1.2mg and 1.8mg produced a significant reduction in HbA1c (0.23-0.54%) compared to placebo. Most of the HbA1c benefit was observed in the first 3 months, after which the levels gradually increased back to baseline by the end of studies. The liraglutide treatment groups had a higher incidence of symptomatic hypoglycaemia and hyperglycaemia with DKA. The Lira-1 trial investigating the efficacy and safety of liraglutide in people with T1DM and overweight (n=100), did not observe any significant change in HbA1c from baseline (between-group difference -0.2%, p=0.18). However, there were reductions in bolus insulin requirement (difference -5.8 units, p=0.02), body weight (difference -6.8kg, p=0.01) and number of hypoglycaemia events[112]. There are currently no plans to licence liraglutide for the treatment of T1DM.

6.4.4 Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4) increase GLP-1 concentrations and are used for glucose-lowering in the management of T2DM. Since the GLP-1RA might have a role in the

pancreatic beta cell preservation [108], it was hypothesised that DPP-4 inhibitors might have beneficial effect in T1DM. Sitagliptin was found to reduce insulin requirements when used in patients with newly diagnosed T1DM[116]. While animal studies demonstrated that a combination GLP-1 and gastrin increased beta cell mass and restored euglycaemia[117], human studies failed to produce a similar finding. In the study by Griffin et al, combination therapy with sitagliptin and lansoprazole (which increases gastrin concentration) did not achieve C-peptide preservation at 12 months[118].

6.4.5 Verapamil

Verapamil is an anti-hypertensive medication, which has been widely used for over 30 years. Verapamil downregulates thioredoxin-interacting protein (TXNIP) and overexpression of TXNIP induces beta cell apoptosis. Some retrospective studies suggested that verapamil was associated with reduced risk of developing T2DM[119]. In a pilot study of 32 participants diagnosed with T1DM within 3 months, verapamil use was associated with greater C-peptide concentration at 3 months and 12 months when compared to placebo[120]. In addition, insulin requirements in the verapamil group were only increased by 27% as compared to 70% in the placebo group. No clinically significant adverse events were observed, confirming its safety profile in younger, normotensive patients. A phase 2 trial investigating the effect of verapamil on the preservation of beta cell function in recently diagnosed T1DM, [Verapamil SR in Adults with Type 1 Diabetes (Ver-A-T1D)] is ongoing and expected to enrol 138 participants and complete by 2023. The study has a cross-over design and a duration of approximately 24 months, with 12 months treatment phase and 12 month follow-up[121].

7. Therapy for established T1DM

Therapies for the management of established T1DM aim to improve glycaemic control, minimise the risk of hypoglycaemia, improve quality of life and delay diabetes related complications.

7.1 Ultra-long-acting insulin

Since insulin remains the only therapy option for T1DM, the development of novel insulin preparations which allow flexibility and reduce the burden of injection has continued. Ultra-short-acting insulins such as Fiasp (insulin aspart) and Lyumjev (insulin lispro) are available for clinical use and can be injected immediately with meals, rather than 20-30 minutes beforehand. Ultra-long-acting insulins which allow for once weekly injection are being developed and tested in phase 2 and phase 3 trials. Insulin icodec (Novo Nordisk), a novel insulin with 1 week half-life, which allows once weekly dosing is found to have a comparative efficacy and safety profile to daily insulin glargine in people with T2DM[122, 123]. In the phase 2, 26-weeks RCT, the efficacy and safety of insulin icodec versus insulin glargine U100 was investigated in insulin naive patients with inadequately controlled T2DM. At 26 weeks, the mean HbA1c change from baseline was -1.33% and -1.15% in the icodec group and the glargine group, respectively. There was no between-group difference in insulin related adverse events between two groups[122]. Another phase 2 study investigating the efficacy of insulin icodec in patients with insulin treated T2DM also demonstrated that insulin icodec (first dose loading dose) achieved greater time-in-range as compared to insulin glargine. Rates of hypoglycaemia were comparable between insulin icodec and insulin glargine[123]. Following these findings, a phase 3 clinical trial investigating once weekly insulin in patients with T1DM (ONWARDS-6) is ongoing with publications anticipated in 2023.

Another ultra-long-acting once weekly insulin, Basal Insulin Fc (BIF: LY3209590) developed by Eli Lilly has shown a comparable efficacy and safety against insulin degludec in a 32-week phase 2 clinical trial involving 399 people with T2DM previously treated with a basal insulin[124]. The study included three treatment arms: BIF with fasting glucose targets ≤140mg/dL (BIF-A1); BIF with fasting glucose targets ≤120mg/dL (BIF-A2); and insulin degludec with fasting glucose targets ≤100mg/dL. At 32 weeks, BIF achieved similar glycaemic control as compared to insulin degludec despite higher fasting glucose targets and numerically lower time in hypoglycaemia. The percentage of time in range was similar for the 3 treatment groups. A clinical trial of Basal Insulin Fc in people with T1DM started enrolment in 2022.

7.2 Oral insulin

The search for alternative route of insulin administration began following the discovery of insulin in 1922 but few developments have reached to phase 1 and 2 clinical trials. Amongst them, ORMD-0801 (oral insulin) has the potential to achieve clinical use. ORMD-0810 demonstrated glucose lowering efficacy when used in conjunction with standard insulin therapy in people with T1DM. In the pilot study with 8 participants with T1DM, ORMD-0801 was associated with a significant 24.4% reduction in the frequency of glucose readings > 200 mg/dL and a significant mean 16.6% decrease in glucose AUC[125]. In a recently published study ORMD-0810 was given for 28 days in 188 patients with T2DM after a 2-week wash-out of other medications. Treatment with ORMD-0801 was associated with a greater time-in-range without increasing the risk of hypoglycaemia[126]. In a phase 2 clinical trial to investigate the efficacy and safety of ORMD-0801 (developed by Oramed Pharmaceuticals Inc.), 373 participants with T2DM were given ORMD-0801 in different regimens across a dose range for

up to 12 weeks or placebo. The primary outcome was mean change in HbA1c from baseline to 12 weeks. In the intention-to-treat analysis, a reduction in HbA1c up to -0.95% was observed with ORMD-0801[127]. With these promising findings of phase 2 trials, Oramed has initiated two phase 3 trials of oral insulin ORMD-0801: ORA-D-013-1[128] and ORA-D-013-2[129] in patients with inadequately controlled T2DM.

7.3 Artificial pancreas

Insulin pumps currently mimic the most physiological delivery of insulin during a 24-hour period. Despite recent technological advances, insulin pumps available for clinical use are not fully automated yet, requiring users' input on carbohydrate counting. The iLet bionic pancreas (Beta Bionic, Inc.) is a novel fully automated delivery insulin system in conjunction with CGM and the only input required to initiate the pump is patient's body weight. The iLet can be used in insulin-only configuration or bihormonal configuration delivering both insulin and glucagon. In a random-order cross-over study, 43 participants with T1DM were assigned to bihormonal bionic pancreas and subsequent comparator (conventional or sensor-augmented pump therapy) or vice visa. The bihormonal bionic pancreas demonstrated superior glycaemic control without the need for carbohydrate counting when compared to comparator[130]. In 2019, the FDA granted breakthrough device designation to the iLet Bionic pancreas system[131] and the Insulin-Only Bionic Pancreas Pivotal Trial: Testing the iLet in Adults and Children With Type 1 Diabetes was initiated in March 2020 and is expected to complete in January 2022. I think this is now published:

Kruger D, Kass A, Lonier J, Pettus J, Raskin P, Salam M, Trikudanathan S, Zhou K, Russell SJ, Damiano ER, El-Khatib FH, Ruedy KJ, Balliro C, Li Z, Marak MC, Calhoun P, Beck RW. A Multicenter Randomized Trial Evaluating the Insulin-Only Configuration of the Bionic

Pancreas in Adults with Type 1 Diabetes. Diabetes Technol Ther. 2022 Oct;24(10):697-711. doi: 10.1089/dia.2022.0200. PMID: 36173236; PMCID: PMC9634987.

Messer LH, Buckingham BA, Cogen F, Daniels M, Forlenza G, Jafri RZ, Mauras N, Muir A, Wadwa RP, White PC, Russell SJ, Damiano ER, El-Khatib FH, Ruedy KJ, Balliro CA, Li Z, Marak MC, Calhoun P, Beck RW. Positive Impact of the Bionic Pancreas on Diabetes Control in Youth 6-17 Years Old with Type 1 Diabetes: A Multicenter Randomized Trial. Diabetes Technol Ther. 2022 Oct;24(10):712-725. doi: 10.1089/dia.2022.0201.pub. PMID: 36173237; PMCID: PMC9529304.

This Pivotal trial aimed to include 440 participants with T1DM and compare efficacy and safety endpoints using the insulin-only configuration of the iLet Bionic Pancreas (BP) System versus Usual Care (UC) during a 13-week study period[132].

7.4 Stem cell derived islet transplant

Allogenic islet transplantation has been a treatment option for people with T1DM who have disabling severe hypoglycaemia and/or who have end-stage renal disease needing renal transplant. Islet cell transplantation is considered minimally invasive but still carries the risk from immunosuppression. Donor availability is the main limiting factor in allogenic islet transplant from cadaveric samples as two or three donor pancreases are typically required for one islet transplant. Stem cell derived islet cells potentially could be a renewable, uncontaminated, and unlimited supply of islet cells for transplantation. Pre-clinical studies have demonstrated that cells differentiated from human pluripotent stem cells (hPSC) display insulin secretory properties similar to human islets[133, 134]. Phase 1 and phase 2 trials investigating the efficacy and safety of hPSC derived islets are underway (NCT02239354, NCT03163511, and NCT02939118). In the initial report from Henry et al, VC-01, stem cell

derived islet cells encapsulated in a device, was safe and tolerated with minimal adverse events related to the surgical insertion. In addition, the delivery device provided protection against the host immune system with no evidence of immune rejection despite participants not being on immunosuppressive medications[135].

8. Potential development issues

Disease modifying agents targeting the autoimmune destruction process of pancreatic beta cells are mostly immunomodulatory drugs and hence adverse reactions related to immune dysfunction or immune suppression are inevitable. Re-activation of viral infection, in particular, has been a major concern. Suitable dose selection to produce the desired effect of preservation of beta cell damage with minimal risk of immune suppression is a major challenge for most of the emerging drugs. Furthermore, patient selection is paramount. It is not uncommon for people with newly diagnosed T1DM to achieve a partial remission known as the ‘honeymoon period’ without any immune mediated therapy. Certain risk factors affecting ‘honeymoon frequency and duration’ have been identified[136]. These include younger age (<5 years at the time of diagnosis), DKA as a presenting feature and long duration of symptoms[137]. Regarding precision insulin therapy and insulin delivery system, a significant breakthrough has been achieved and a fully automated artificial pancreas system is on the horizon. However, these new technologies to deliver insulin are not easily accessible in some part of the world due to high cost. Stem cell derived islet transplant holds a new future for islet cell replacement therapy, but these studies are in their infancy.

9. Conclusions

T1DM is a lifelong disease affecting day-to-day life of the person affected and imparts significant comorbidities and premature mortality. The aetiopathogenesis of T1DM is complex and results from an interplay of genetic susceptibility, environmental triggers leading to autoimmune destruction of pancreatic beta cells. Initially research focused on the disease modification aspect by immunomodulation therapies (most of them are used in other autoimmune disease such as rheumatoid arthritis, psoriasis, and Crohn's disease) in order to halt the process of beta cell destruction in people with recent clinical diagnosis of T1DM. A few potential drugs have been progressed to phase 3 clinical trial, but none have been yet approved for clinical use. Disease modifying therapy in high-risk individuals (without symptoms of hyperglycaemia) have demonstrated the potential to prevent or delay the onset of clinical diabetes. Teplizumab is the forerunner and has been approved by FDA and granted priority status by EMA. Once-weekly insulins and oral insulins could also be a game changer for some people with T1DM, reducing the burden associated with multiple daily insulin injections. A fully automated insulin delivery system (Bionic pancreas) has shown the potential to mimic physiological insulin profile but will remain an expensive option, even if successful.

10. Expert Opinion

Over the last three decades, great efforts have been made to develop therapies to reverse type 1 diabetes. However, there are no approved medications to date to halt autoimmune destruction of beta cells after a clinical diagnosis of T1DM and the goal of achieving cure for T1DM remains elusive. Disease modifying agents which are widely used in other autoimmune diseases have been tried and tested in the people with recently diagnosed T1DM with the aim of preservation of beta cell function. These include teplizumab, rituximab, imatinib, abatacept, alefacept, thymoglobulin and ustekinumab. Phase 2 trials of these immunomodulators showed

evidence of therapeutic efficacy (preservation of endogenous insulin secretion) in people with recent onset T1DM but only a few progressed to phase 3 studies. Phase 3 trial of ustekinumab in adult with T1DM is underway and expected to complete in 2025. Other immunomodulators, anti-CD3 monoclonal antibodies: teplizumab and otelixizumab achieved primary end points of preservation of C-peptide concentration in phase 2 trials. However, phase 3 trials of these agents did not achieve significant change in primary and secondary endpoints (insulin requirement <0/5 units/kg/day and HbA1c <6.5%, C-peptide response to MMTT). Of note, the 2-year report of the Protégé trial demonstrated therapeutic efficacy of teplizumab in preservation of C-peptide response. In line with this, teplizumab showed evidence of beta cell preservation in individuals with elevated risk of T1DM, delaying the onset of clinical diabetes by approximately 2 years. Teplizumab has become the first agent approved for use in high-risk individuals to delay the onset of clinical diagnosis of T1DM. Of note, immunomodulating agents are not without side effects and immune suppression, risk of infection, immune related reactions, risk of re-activation of viral infection are common adverse effects. Since most of these studies had a follow-up period of 12 to 24 months, there is limited evidence on long-term efficacy or safety of these immunomodulation therapies. Another point to consider is the 'honeymoon period' in people with recently diagnosed T1DM. The frequency and duration of honeymoon period varies; one Italian study reported that more than 80% of children with T1DM achieved a partial remission and this lasted more than 12 months in approximately 40% of patients. The mean duration of remission was 11.7 +/- 8.9 months, irrespective of sex, duration of the symptomatic period preceding T1DM diagnosis, parental education, presence of DKA, HbA1c and duration of hospital stay[136]. There was a significant difference in beta-cell residual function in those who experienced a honeymoon period and in those who experienced no remission. These observations are important to consider when designing immunotherapy for newly diagnosed T1DM patients. In addition, the majority of studies

included both paediatric and adult population of T1DM and the long-term consequences of immunomodulation in paediatric population is another point to consider for both clinicians and prospective patients and their parents. Another important challenge is the cost of these medications and resources required to initiate and closely monitor these therapies.

Attempts have also been made to develop therapies for primary and secondary prevention of T1DM. However, primary, and secondary prevention studies rely on effective case identification. Current strategy for primary prevention study requires genetic screening and intervention at birth. These interventions therefore must be extremely safe as these are directed to individuals (infants) without any sign of autoimmunity nor metabolic impairments. Dietary interventions such as Cow milk, vitamin D have been tested but the effectiveness of these interventions remain inconclusive. Screening strategy for secondary prevention study include follow-up of a birth cohort with high genetic risk until the development of autoimmunity or screening for autoimmunity in high-risk individuals (with family history of T1DM in first degree relatives). Antigen-based therapy using parenteral/ oral/ nasal insulin as a sensitising agent in individual with elevated risk failed to achieve primary outcome. The lack of efficacy of these studies could be explained by the age of participants; the median age of participants in these trials were 8 to 10 years. The ongoing GPPAD-POInT-Study was therefore designed to include children in their early life (aged from 4 months to 7 months). Amongst immunomodulatory therapy for secondary prevention, teplizumab has demonstrated a promising efficacy. However, there are challenges regarding its clinical use in wider population Screening and case finding (which is associated with cost, increased demand for clinician time, increased demand for laboratory facility etc.) would be one of the potential barriers and the lack of long-term safety outcomes being another barrier.

Future care of established T1DM would include precision insulin therapy, non-injectable insulin formulations and fully automated insulin pumps. Phase 3 clinical trials of once weekly analogue insulins as well as oral insulin capsule are currently ongoing and their availability for clinical use are on the horizon. Once weekly ultra-long-acting insulin would reduce the burden associated with MDI therapy while an oral insulin capsule would bring a significant impact for those with needle phobia. Fully automated insulin pump therapy is also in development and iLet Bionic insulin pump (artificial pancreas) has received breakthrough device status. Artificial pancreas has potential to maintain tight glycaemic control without the expanse of hypoglycaemia. In summary, T1DM has proved to be more resistant to therapeutic intervention either conventional or experimental approach, whether the therapeutic goal is disease prevention or reversal. Results of ongoing phase 3 clinical trials of teplizumab and ustekinumab are eagerly awaited. Regarding therapy for established diabetes, substantial advances have been made in modern insulin therapy and technologies using continuous blood glucose monitoring and insulin pump to create artificial pancreas.

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