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ADJUNCT THERAPIES IN TYPE 1 DIABETES: A REVIEW OF MECHANISMS, MANAGEMENT AND SAFETY OF NEW FORMS OF TREATMENT

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ABSTRACT

Type 1 diabetes is a chronic autoimmune disorder that could be defined as the immune-mediated destruction of insulin-producing pancreatic β-cells. The outcome of this process is complete insulin deficiency and permanent dependence on exogenous insulin therapy. Despite the innovative methods of insulin delivery systems, constant improvements in insulin formulations, and the introduction of continuous glucose monitors (CGMs), the management of blood glucose levels and keeping them within the recommended range prove to be difficult for patients, who additionally face the risk of hypoglycemic episodes and long-term complications associated with type 1 diabetes. The purpose of this review is to examine current and new emerging additional therapies used in the management of type 1 diabetes, with particular focus on adjunct non-insulin treatments, their mechanisms, effectiveness and safety profiles. This review was written using databases such as PubMed with direct attention to new forms of treatment in type 1 diabetes: pharmacological and immune-focused. The adjunct pharmacological therapies which include amylin analogue, GLP-1 receptor agonists, SGLT inhibitors and metformin have shown to be potentially beneficial for patients with type 1 diabetes, improving glycemic control, reducing insulin dose needs while facilitating weight loss. On the other hand, the immune-based therapies and therapies utilizing stem cells aim to restore the function of insulin-producing pancreatic β-cells or preserve it for as long as possible, slowing down the progression of the disease. However, the introduction of new therapies remains a concern, especially the risk of hypoglycemia or diabetic ketoacidosis (DKA). Ultimately, the new emerging therapies used in addition to insulin therapy have proven to be beneficial for the patients, but further research is needed in order to evaluate their effectiveness and ensure safety.
Methodology: The review was written based on scientific papers and articles available on PubMed and Google Scholar.

KEYWORDS

Type 1 Diabetes, Adjunct Therapies, Insulin-Producing Pancreatic β-cells, Pharmacotherapy, Immune-Based Therapies, Stem Cell Transplant, Safety Considerations

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Introduction

Type 1 Diabetes is a chronic metabolic and autoimmune disease characterized by immune-mediated destruction of insulin-producing pancreatic β-cells, leading to total insulin deficiency and lifelong dependence on exogenous insulin therapy [1]. Type 1 diabetes is more common in children and younger individuals than in adults; however, it can affect any age group. The new-onset type 1 diabetes usually presents with symptoms such as rapid and unintentional weight loss, polydipsia, polyuria, lethargy, hyperglycemia or even diabetic ketoacidosis (DKA), which can be life-threatening and in most cases requires treatment and monitoring in intensive care unit. The clinical presentation may vary individually. In adults, especially in a situation when the clinical presentation of new-onset type 1 diabetes may not be as severe as it is commonly in younger patients, it might be the cause of misdiagnosis as type 2 diabetes [2]. Type 1 diabetes is a complex condition that requires an individual and interprofessional approach for every patient with management and treatment planned accordingly [1].

Etiology

Type 1 diabetes is a result of the autoimmune, which is believed to be T cell-mediated [3], destruction of insulin-producing pancreatic β-cells, causing impairment of insulin production to complete insulin deficiency. The loss of β-cells function progresses from months to years. During this period patients stays asymptomatic. The exact etiology remains unknown, however the development of type 1 diabetes can be affected by genetic components as well as the influence of the environment [4]. There is also a connection with genetic predisposition associated with human leukocyte antigen (HLA) alleles DR and DQ [1]. Moreover,

the increased risk has been proven to be related to viral infections, dietary factors, vitamin D deficiency and perinatal conditions. According to recent studies, the environmental factors are suspected to trigger the autoimmune response, causing the destruction of β-cells in the genetically predisposed individuals. The antigens in the islet cell cytoplasm (ICA), insulin (IAA), glutamic acid decarboxylase isoform 65 (GAD65), insulinoma antigen 2/islet tyrosine phosphatase 2 (IA-2), and zinc transporter isoform 8 (ZnT8) are targeted by antibodies, which are used in confirming the diagnosis of type 1 diabetes [1]. However, the absence of the antibodies does not eliminate the possibility of type 1 diabetes diagnosis [2]. When the diagnosis remains uncertain it is recommended to measure C-peptide level [2].

Treatment and Management

Patients with type 1 diabetes require lifelong insulin replacement. As the disease has become a widely recognized issue, the rapid development of the innovative technologies and strategies have followed [2]. Regardless of improvements in overall insulin therapy, introducing new glucose monitoring technologies and insulin pumps that are able to connect with continuous glucose monitors (CGMs) creating closed loop systems, many patients still struggle to achieve target glucose levels, especially since the responsibility of managing the disease is predominantly placed on a patient [2]. The complex nature of type 1 diabetes interferes with daily activities, giving no other choice but to adapt to constantly changing situation, stressing the need of innovative treatments strategies [5].

Insulin replacement is the main form of therapy but it poses several limitations. In recent years, there has been ongoing research on adjunct therapies that may benefit patients with type 1 diabetes. Those pharmaceuticals would help them manage blood glucose levels alongside insulin therapy, providing better control and avoiding eventual health complications, as it has been established that achieving optimal glycemic control helps prevent the complications or at least minimize their severity [6]. The investigated drugs include glucagon-like peptide-1 receptor agonists (GLP-1 RA), sodium-glucose cotransporter-2 inhibitors (SGLT2i) and amylin analogue in an attempt to improve glycemic control through mechanisms independent of insulin action, such as reducing glucagon secretion, delaying gastric emptying, or increasing urinary glucose excretion. Clinical trials have demonstrated potential benefits including reductions in HbA1c levels, body weight, and insulin requirements [1]. Furthermore, there are also new emerging therapies based on immunomodulation that would be able to directly impact the immune system's response and its cells or stem cells treatments that would potentially help restore the insulin-producing pancreatic β-cells.

Insulin Therapy as a Main Form of Treatment

For a patients with type 1 diabetes insulin therapy is the current standard of care [4]. Types of insulin include basal insulin analogues (glargine, detemir, degludec) and rapid acting analogues (lispro, aspart, glulisine) or short acting (regular insulin). Overall, the choice of insulin typically depends on the patient's preferences, their clinical needs, and the healthcare provider's assessment of which option would be most beneficial. The insulin replacement therapy can be managed through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (insulin pump). The research has shown that patients who use insulin pumps present better glycemic control and lower HbA1c levels (according to CGMs data) than those who use multiple daily injections, which suggests that continuous subcutaneous insulin infusion should be considered as a preferred form of insulin therapy [7, 8].

MDI therapy includes administrating basal long-acting insulin one to two times a day and short acting or rapid acting insulin typically ten to fifteen minutes or more before meals, depending on the patient's current blood glucose level. The basal-bolus form of insulin dosing is created to replicate the physiological regimen of insulin secretion [9]. Nonetheless, it has its imperfections, since it is not only food that influences blood glucose levels. Fluctuations may also be triggered by infections, various medications, levels of daily physical activity, or even changes in temperature, among many other factors. As a result, patients may struggle to maintain their blood glucose levels within a tight range. All of those factors have to be taken into consideration when introducing new adjunct therapies that would be beneficial for patients with type 1 diabetes. As type 1 diabetes disrupts all of the systems and numerous physiological and metabolic processes, it is extremely important to ensure that patients have access to the newest technologies that could improve their quality of life and minimize the burden of managing the disease.

On the other hand, the insulin pump does not use long-acting insulin analogues, administrating constantly small doses of only short acting or rapid acting insulin and additionally the bigger boluses to cover the meals. The insulin pumps that are commercially available include tethered pumps with a separate cannula

and tubing and patch pumps with the already ingrained infusion set [10]. Due to introduction of continuous glucose monitors (CGMs) and development of new technologies there have been created insulin pumps that are able to connect to CGMs allowing automated insulin delivery; hybrid or full closed-loop system [11], which enables automatic adjustment of the amount of insulin given based on current blood glucose levels according to values provided by CGMs. However, despite the innovative technologies there is still a large percent of patients not able to achieve the recommended glycemic control and HbA1c level [12]. The closed-loop system is an algorithm-driven method of automated insulin delivery designed to reduce the psychological burden of frequent adjustments of insulin dosing, improve disease management and glycemic control, and ultimately enhance patient quality of life. [10]. It has proven to be beneficial for maintaining blood glucose levels within the target range, with the effect more pronounced in a full closed-loop system [1,11]. Those pumps often have the ability to suspend the delivery of insulin if the blood glucose level is low, some are even able to predict the episode of hypoglycemia and stop insulin delivery in advance - in a similar way responding to hyperglycemia by intensifying the insulin dosing. The closed-loop has shown the ability to reduce the frequency of episodes of hypoglycemia, making the use of the insulin pump much safer and more effective [13,15]; however, hyperglycemia has been proven to be more difficult for the algorithm to manage, which highlights the need for further research and introducing adjunct therapies [14]. It is possible for the system to work through the connection between the pump and the CGM and based on real-time blood glucose levels, individually created algorithm and daily glucose fluctuations tendencies, it can react accordingly [10]. In comparison to insulin therapy through multiple daily injections (MDI), the insulin pumps seem to provide better control of blood glucose level, reduce the risk of developing complications [16, 17], provide more flexibility, make easier to adapt managing blood glucose levels to patient's lifestyle [10].

Nowadays the continuous glucose monitor systems (CGMs) have become the part of the standard care in diabetes management [1]. They include a disposable sensor that is placed in subcutaneous tissue, measuring real-time blood glucose level in the interstitial fluid and a transmitter which communicates with the mobile device (usually patient's mobile phone) or a different form of receiver, allowing to continuously monitor blood glucose level and its fluctuations [10]. The sensor readings are rather accurate and comparable to values from the glucometer, so CGMs' displayed measurements can be used as a base for calculating the doses of insulin [10]. Moreover, the data from CGMs can be shared at the appointment with a doctor or a healthcare provider to be evaluated and discussed with a patient during the annual check-ups, making changes in insulin dosing if necessary much easier and more accurate. It has been proven to have a positive impact on blood glucose levels and providing significant improvement of overall glycemic control as well as lowering HbA1c level [18, 19]. Patients tend to feel more secure, while leading an active lifestyle without worrying about unexpected hypoglycemic incidents, as they are able to monitor the blood glucose fluctuations in real time [20]. Nevertheless, the constant monitoring of blood glucose levels can create significant psychological burden, which may lower quality of life, especially because insulin dosing requires frequent adjustments [4]. The data from CGMs can also be used alongside HbA1c (which shows the average blood glucose levels over the past three months) to determine the glycemic control more accurately and if the management of type 1 diabetes is satisfactory enough [10]. Overall, he use of CGMs undeniably tied to improvement of blood glucose levels and HbA1c levels [21].

However, insulin therapy has its limitations, with hypoglycemia being the main concern [22]. In addition, excessive dosing of insulin may cause weight gain, which is also considered as a risk factor of the complications typical for the individuals suffering from type 1 diabetes. In that case the insulin monotherapy might prove to be not enough to successfully manage blood glucose levels and stop the disease from progressing what creates continual demand for additional forms of treatment that could be used alongside insulin therapy with the benefits for the patients [22].

Pharmacology

Insulin therapy as a main form of treatment is the base of managing type 1 diabetes, however in some cases the adjunct therapies are required as an addition in order to help patients obtain better control of their blood glucose levels and improve their quality of life as much as possible. Better management of type 1 diabetes also means taking proactive approach in avoiding complications as unfortunately every major organ can be affected. They can be generally split into two categories - macrovascular complications such as stroke, coronary heart disease, peripheral vascular diseases and microvascular complications which entail neuropathy, nephropathy and retinopathy [22]. Those long-term complications are usually tied to poor management of type 1 diabetes and unstable blood glucose levels through the years [23].

Unfortunately, as type 1 diabetes is mainly diagnosed in childhood, the satisfactory management of type one diabetes tend to subside during puberty, which is tied to hormonal and physiological changes; the increase of sex steroids, the growth hormone (GH), the insulin-like growth factor (IGF-1), weight gain, resulting in the progression of insulin resistance and impaired insulin sensitivity [23, 24]. Especially when the body mass increases, as a consequence appears the need for higher doses of insulin, which has been proven to have a negative effect on overall metabolic health, elevating the risk of developing cardiovascular diseases later in life [9, 24]. It poses a need for a new therapy that would also be able to help patients regulate their body weight, as it is directly connected to the management of type 1 diabetes [9]. It highlights even more the demand for introduction of new, adjunct forms of treatment to help patients achieve the best control they possibly can and hopefully avoid or at least delay the complications. Some of the pharmaceuticals listed below are already used as an additional treatment to insulin therapy in patients with type 1 diabetes [25]. They can be divided into groups based on their characteristics and mechanisms [25].

Amylin analogue - pramlintide

Amylin is a neuroendocrine hormone that inhibits glucagon secretion and participates in reducing postprandial glucose fluctuations [26]. It reduces the fluctuations of blood glucose level post-meal by slowing down the gastric emptying, lowering food intake and inhibiting postprandial secretion of glucagon [9]. The patients suffering from type 1 diabetes happen to also have amylin deficiency, as it would be normally secreted alongside insulin by pancreas in response to food intake [27]. This results in postprandial hyperglucagonemia, leading to postprandial hyperglycemia, which is also tied to impaired secretion of amylin [28]. Amylin itself cannot be used as a form of treatment, because of its characteristics such as self-aggregation into the amyloid, so the amylin analogue - pramlintide - developed with enhanced water solubility in order to minimize the tendency to create amyloid form [27]. It can be administrated as an addition to insulin bolus given for a meal. It has been proven that pramlintide helps to stabilize postprandial blood glucose levels, at least to some extent. However, the use of pramlintide has its limitations due to unsatisfactory results and side effects, which included nausea, vomiting - those were the most common [25]. The cases of anorexia also occurred, which is associated with a reduction of appetite [9]. The most dangerous side effect was proven to be postprandial hypoglycemia [26], reported especially during the first month of taking pramlintide, as the doses were still being adjusted [25]. Nonetheless, there was noted a significant satisfaction and the improvement of HbA1c levels in trials with patients taking pramlintide [25]. In addition, it also plays a role in weight loss [9]. Overall, the research has shown that the use of pramlintide in addition to insulin doses given for a meal was beneficial for reducing HbA1c level, glycemic control and weight loss [9].

GLP-1 receptor agonists

GLP-1 (glucagon-like peptide) is a gastrointestinal hormone that is released in response to food intake. It helps regulate blood glucose levels, slow digestion, reduce body weight. GLP-1 RAs (glucagon-like peptide-1 receptor agonists) are mainly used in treatment of type 2 diabetes, while their effect in treatment of type 1 diabetes still a point of focus [26]. According to recent studies, GLP-1 RAs have been proven to have an anti-inflammatory effect, maintain better control of blood glucose levels, lower HbA1c levels, suppress the release of glucagon, slow down gastric emptying and to protect insulin-producing β-cells from destruction and to support their replication [22, 25]. They also show the ability to improve metabolic profiles when used as an adjunctive treatment to insulin therapy and reduce the risk of cardiovascular disease [12, 22]. Moreover, the research has shown that GLP-1 RAs by affecting the receptors in the brain are able to create a feeling of safety leading to weight loss, which could be beneficial for the patients, as it is an opposite impact to insulin therapy alone [22]. Furthermore, there is an evidence that even if most of the β-cells were destroyed, they are still able to respond to the treatment [25, 29]. The use of liraglutide (one of GLP-1 receptor agonists) is also related to decreased levels of C-reactive protein and of proinflammatory cytokines [26]. It also seems to improve glycemic control, resulting in reduction of daily insulin doses [3, 30]. In addition, GLP-1 RAs have shown to be more effective when used together with different forms of immunotherapy, rather than independently [26]. They also have shown to have a protective effect on kidneys and cardiovascular system [22, 26]. What is important is that GLP-1 RAs did not raise the risk of diabetic ketoacidosis and severe hypoglycemia [22]. Alas, they caused the side effects form gastrointestinal track such as nausea and vomiting and raised the risk of hypoglycemia, but occurring episodes were not severe [22, 31]. Additionally, the GLP-1 RAs can be potentially used as an adjunctive therapy to insulin pumps with closed-loop system, since they delay gastric emptying and increase satiety, so it could be beneficial for the patients safety [10].

SGLT inhibitors

Sodium-glucose cotransporters 2 inhibitors (SGLT2i) are able to help lower blood glucose levels through restricting the glucose reabsorption at the proximal tubule of the nephron in the kidney and increased elimination of glucose with urine [22]. This kind of mechanism allows for SGLT2i to lower glucose levels in a way that is independent of insulin [22]. According to recent studies, it has been proven that the form of treatment including insulin therapy with the addition of SGLT2i had a beneficial effect on patients control of blood glucose levels, HbA1c levels, metabolic profile, blood pressure, supported weight loss and also allowed to reduce insulin doses [22, 32]. All of above combined, it may indicate the lower cardiovascular risk and kidney protection factor and slowing down the progression of renal disease [33] as the SGLT2i inhibitors seem to reduce or delay the complications typical for patients with type 1 diabetes [26, 32]. SGLT2i do not participate in higher risk of hypoglycemia, however in some cases they can contribute to increased possibility of diabetic ketoacidosis (DKA), which significantly limits their usage [22]. The typical DKA usually include significant hyperglycemia, but most of the cases of diabetic ketoacidosis that occur during the use of SGLT inhibitors were presenting with moderate hyperglycemia to normoglycemia [32]. Additionally, they contribute to increased risk of urinary tract infections [34].

Metformin

Metformin is a drug predominantly used in patients with type 2 diabetes that can lower the blood glucose level mainly through decreasing hepatic glucose production. It improves insulin sensitivity by inhibiting hepatic gluconeogenesis, helps the glucose uptake in the muscles, decreases the absorption of glucose in the intestines and also lowers oxidation of fatty acids [23]. Those mechanisms may be particularly beneficial for patients with type 1 diabetes with simultaneous insulin resistance and poor glycemic control [23]. The use of metformin is associated with reduction of insulin doses, supporting weight loss, lowering the level of total cholesterol and blood pressure, having a positive impact on metabolic profile, but no significant reduction in HbA1c levels [25, 32]. Furthermore, clinical trials did not enclose findings about cardiovascular risk [25], however metformin seems to have a beneficial influence on overall cardiovascular health and preventing cardiovascular disease by improving glycemic control, metabolic profile and supporting the reduction of body weight [24]. The research suggests that metformin might help reduce the typical for diabetes complications, but it cannot fully prevent them [24]. There are also described the side effect of metformin such as gastrointestinal issues, episodes of hypoglycemia, lactic acidosis, which makes its safety questionable [23], even if metformin has a good safety profile and is rather well-tolerated among the population [24]. Especially lactic acidosis with the risk of diabetic ketoacidosis occurring at the same time and not being caught early enough [23]. Hence, it is unclear if introducing metformin as an additional form of treatment in patients with type 1 diabetes will be able to help to achieve long-term improvement [26].

Immune-Focused Therapies

Nowadays, patients with type 1 diabetes are able to receive insulin therapy through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (insulin pump) with additional pharmacotherapy but those means are focused on the management of the disease rather than curing it or preventing the destruction of insulin-producing pancreatic β-cells that leads to type 1 diabetes. However, the ongoing research has shown promise in providing an actual cure for type 1 diabetes or even preventing the destruction of the β-cells before it occurs.

Those treatments include regulatory cell therapy, stem cells transplant and overall immune-focused treatments. The focus of immunotherapy is to prevent the destruction of the β-cells or to delay the loss of their function as the research has proven the immune dysregulation and autoreactive T cells destroy β-cells [26]. The idea of treating type 1 diabetes is to eliminate the autoreactive cells that are responsible for the autoimmune response [35]. The focus on cell-directed or cytokine-directed therapies has been successful in some of autoimmune diseases [26], so ongoing research may present the possibility of improving the management of type 1 diabetes or even obtaining the cure in the future. Nowadays, the development of innovative forms of treatment is focusing on creating disease-modifying approach that would be able to prevent the progression of type 1 diabetes with hopefully reversing it altogether [36]. As the research continues and new strategies emerge, it has become one of the points of focus to modify the response of the immune system to pancreatic autoantigens. The idea of using a transfer of regulatory cells - dendric cells, regulatory T cells or mesenchymal stem cells - is known as regulatory cell therapy [35]. Moreover, there has been proven the immunomodulatory activity of hematopoietic stem cells (HSCs). This kind of treatment involves genetic engineering, immunomodulation and the enhancement of their function in order to prevent the autoimmune response that

would destroy the insulin-producing pancreatic β-cells [3]. Those cells can be transplanted into patients with satisfactory metabolic control in the short-term and medium-term and also notable insulin independence [35]. Despite the treatment being viewed as effective there is still risk of complications and potential of disease relapsing after the transplant [35]. More information is still needed, especially about the stability of transferred cells and long-term effects [35]. According to recent studies, these therapies were not able to achieve the satisfactory effect alone, despite being proven to be safe to use for the patients [3]. The potential side effects observed in clinical trials were mild to moderate with a tendency to subside on their own [37]. Additionally, despite the possibility of triggering immune response, these forms of therapy are considered overall safe, due to using patient's own stem cells [37].

Regulatory cell therapy

Regulatory T cells (Tregs) have been proven to be safe but have shown effectiveness only in the pediatric population, with better results observed in children with a short duration of type 1 diabetes, especially in patients who are still presymptomatic - generally in individuals who have retained the function of insulin-producing pancreatic β-cells [35, 38]. The aim is to create the therapy using Tregs that are individually specific to the patient's Tregs in order to avoid off-target effects [3]. However, the therapy involving Treg seems to be the most beneficial when combined with another agent. Hence the rapid development of genetic engineering the scientists are able to create so-called "armored" Tregs that are able to precisely identify the target and potentially suppress the immune response, preventing the destruction of the β-cells [39, 40]. The latest clinical trials have included the use of IL-2 and most recently the combination of Treg with rituximab (a B cell-depleting agent, widely used in hematology), which was able to achieve in some cases the delay for insulin dependance, slowing down the destruction of the β-cells and better metabolic control, what creates a seemingly promising perspective for the future therapy [35, 41]. Unfortunately, they have proven difficult to isolate from various tissues, and further research is needed to determine the most efficient methods for obtaining them [3]. The research suggests focusing on the possible combination of regulatory cell-based therapies and immunomodulatory treatments, which has the potential to be most beneficial for patients, with the aim of minimizing the need for systemic immunosuppression [3, 35]. The use of Tregs in the treatment of type 1 diabetes shows promise, but further investigation is essential to determine its long-term effectiveness [38].

Dendric cells

Dendritic cells (DCs) were among the first cell types to be tested in cell-based treatments for type 1 diabetes, as they are professional antigen-presenting cells (APCs) that direct adaptive immune responses [35]. However, there was no beneficial effect on blood glucose control, and no significant changes in C-peptide levels were observed (probably related to poor or no function of insulin-producing β-cells), despite being rather well-tolerated by patients and having a safe profile [35, 42].

Stem cell therapy

Stem cell replacement therapy is a new approach to treating type 1 diabetes that promises a potential cure. Their immune modulation capacity and multipotency is the main point of focus in the recent studies [37]. However, it still has certain imperfections, as there is some amount of immunosuppression needed for enabling the positive long-term effect and satisfactory function of the grafted stem cells in the patients [26]. Therefore, recent studies focus on reducing or even avoiding the need for additional immunosuppression in stem cell replacement therapy, so that transplanted stem cells do not trigger an immune response but instead secrete insulin in response to food intake and changes in blood glucose levels [4]. One of the newest achievements is Lantidra, which is an FDA-approved first allogenic pancreatic islet cell therapy [3]. It is approved for patients who suffer from episodes of severe hypoglycemia [3]. It includes infusing islet cells from a deceased donor into the hepatic vein in order to stimulate insulin secretion [4]. Patients with short duration period of the disease may undergo the treatment to preserve the remaining insulin-producing β-cells and their function to try to slow down or stop the destruction process, meanwhile the patients with long duration period of type 1 diabetes, whose β-cells function has already been damaged, might benefit from the islet transplantation [3]. However, nowadays this treatment is available for patients with several health complications from type 1 diabetes, as the therapy itself poses certain downsides including the need for lifelong immunosuppression, complications related to the surgery that is necessary to implant the cells and concern about long-term efficiency [3, 4]. Additionally, obtaining islet cells from deceased donors remains a concern due to the limited availability of donor pancreases [35]; therefore, recent research has focused on utilizing patients own stem cells, which may prove to be groundbreaking in curing type 1 diabetes without the need for immunosuppression [4]. In order to develop such treatment multipotent or pluripotent stem cells would have to be guided into insulin-producing pancreatic β-cells and then to protect the cells from the immune system response modify them through genetic

engineering to avoid rejection [4]. Nowadays, the stem cell therapy provides better results when combined with other adjunct therapies [37, 43].

In order to try to avoid the risks that are associated with transplantation of hematopoietic stem cells (HSCs) there have been different stem cell-based therapies studied, i.e. the use of mesenchymal stem cells (MSCs), as they can be obtained from various tissues and have shown promising results due to their immunomodulatory ability [35, 44]. They can be applied to treat graft-versus-host disease after the transplantation of HSCs and also presumably help the repair and regeneration of insulin-producing β-cells [35, 40].

Immunotherapy

There also has been research on immunomodulatory strategies with emphasize on antibodies targeting T effector cells such as the anti-CD3 antibodies teplizumab and otelixizumab [26]. Teplizumab, being the most promising one, was approved by FDA in 2022 as the first agent slowing down the progression of type 1 diabetes [3]. Immunotherapy creates an innovative approach that unlike conventional forms of treatment does not only manages the symptoms of type 1 diabetes, but also slows down progression of the disease, protects β-cells from immune response and eventually restoring insulin-producing function of the pancreas [41, 45]. Those antibodies have shown results in slowing down the destruction of insulin-producing β-cells and the delay of developing type 1 diabetes by 1,5-2 years [26], creating so-called immune blockade [3]. Additionally, they have helped to reduce doses of insulin needed to sustain satisfactory control of the blood glucose levels [25]. In clinical trials it has been proven that a short course of teplizumab is able to delay the progression of type 1 diabetes in individuals who are the relatives of patients with type 1 diabetes and are in high risk of developing the disease themselves [35]. Furthermore, there was an improvement in C-peptide levels, especially among newly diagnosed patients with type 1 diabetes which leads to the result of teplizumab being the first adjunct drug approved specifically for patients with type 1 diabetes [35]. It also was able to significantly lower HbA1c levels [15]. Although, if used in treatment of type 1 diabetes in the future the anti-CD3 antibodies would presumably involve a mix of different therapies, because they may not be able to completely ensure the control of blood glucose levels alone [25].

In clinical trials the use of low-dose anti-thymocyte globulin (ATG) has shown the ability to preserve the secretion of C-peptide and improve blood glucose levels, as well as the protection of β-cells [3]. The potential success of using ATG seems to be connected to the dose level and the age of the patients [26].

Moreover, the important role in many autoimmune diseases, type 1 diabetes alike, play tissue-resident memory T effector cells. However, alefacept, which is a T cell-depleting fusion protein and also is able to target CD2 (hence memory T effector cells), even if did not complete the trial, it was proven to be presumably beneficial in the management of type 1 diabetes and eventual future treatments [26]. Nonetheless, it was approved by FDA as a drug preventing renal allograft rejection [3]. However, it was proven that alefacept helped to preserve the β-cells; the research is still ongoing [3].

There have also been attempts to try anti-inflammatory cytokine-specific compounds that are used in rheumatology [26], but still more research is needed. The use of infliximab, adalimumab or enteracept as the antagonists of the central proinflammatory cytokine TNF-alfa have shown some improvement in the management of type one diabetes and recently also the use of golimumab has proven to be beneficial in preserving C-peptide as an effect of blocking TNF-alfa [26]. Those treatment strategies seem promising, especially the possibility of administrating the medication orally. Also, no severe side effects were observed [46].

Safety Considerations

New adjunct therapies are continually emerging and being tested to improve their effectiveness, with patient safety emphasized as the most important factor when introducing a new agent. Various drugs that are already in clinical trials raise concern about the potential side effects varying form minor inconveniences like possible nausea to even life threating ones such as episodes of severe hypoglycemia or diabetic ketoacidosis (DKA). For a drug to be approved, its benefits must clearly outweigh its risks. The new therapies in order to be introduced have to be safe, well-tolerated, commonly acceptable and available for the general population. However, the use of several of these treatments is limited by their imperfect safety profiles, potentially dangerous or inconvenient side effects, high cost, and lack of overall availability. Even one of the listed factors can turn out to be the cause for the treatment not to be approved.

Even if insulin is the main form of treatment, there are still downsides that can be pointed out. The main adverse effect is hypoglycemia. It is extremely important to closely monitor the blood glucose levels and insulin doses, making necessary adjustments for patient safety [2]. Moreover, the injectable nature of insulin might cause pain, discomfort and local inflammation, but also create the place of entry for a possible infection.

Additionally, continuous injections can cause lipohypertrophy, which is the proliferation of adipose tissue due to injections of insulin, usually presenting as a lump under skin that can be mildly painful. It is caused by using the same place to inject insulin or not rotating pump sites [2].

When introducing pharmacological agents as an additional therapy there are also some concerns that need to be highlighted.

As GLP-1 RAs are used as an adjunct treatment to insulin therapy they have shown to increase the prevalence of gastrointestinal adverse events and the risk of gastrointestinal disorders [31]. They also contributed to elevated risk of hypoglycemia; however the episodes where not severe [31]. It would be beneficial if the further research included the data from continuous glucose monitors (CGMs) in order to assess whether the occurring hypoglycemia can be successfully managed by patients suffering from type 1 diabetes, if they were to take GLP-1 RAs alongside insulin therapy [22].

Also, there are many advantages of taking pramlintide as an adjunct form of treatment in patients with type 1 diabetes, despite their side effects that include nausea, vomiting and anorexia [27]. The one that raises the question of safety of using pramlintide is the risk of hypoglycemia as the main concern [27]. However, according to the research, pramlintide does not cause hypoglycemia by itself but rather hypoglycemia may appear as a result of reduction of postprandial blood glucose level or delaying gastric emptying. With careful monitoring of blood glucose levels and appropriate guidance from the medical team, pramlintide used alongside insulin therapy is generally well tolerated and safe for patients [27].

Furthermore, the research has shown SGLT2i (sodium-glucose cotransporters 2 inhibitors) to increase the risk of urinary tract infections due to elimination of glucose with urine [34]. It is also connected to elevated risk of Acute Kidney Injury (AKI) as a result of dehydration and hyperosmolarity, caused by increased glucose and sodium elimination [34]. However, the main concern is the risk of DKA [34]. Diabetic ketoacidosis (DKA) is the state of insulin deficiency, resulting in high blood glucose level and excessive ketone production, although multiple additional factors have been shown to elevate the risk of DKA. [47, 48]. The body is using up lipids to produce energy which results in ketone accumulation [22]. Ketones can then be used as a source of energy but they acidify the blood, causing DKA [22]. Since SGLT2i are mostly used as an adjunctive treatment to insulin therapy, allowing to reduce the insulin doses (also to avoid eventual hypoglycemia), the diabetic ketoacidosis is a result of insufficient levels of insulin and ineffective mechanisms of suppressing lypogenesis and ketogenesis connected with accelerated glucagon levels as a compensatory mechanism [22]. Also, it has been proven that patients who are overweight, suffer from insulin resistance and are dehydrated while using SGLT2i as an additional therapy, have a higher risk of developing SGLT2i - associated diabetic ketoacidosis [22]. Some of the characteristics of DKA are hypovolemic shock, cardiac arrhythmias, cerebral edema and death, making DKA an extremely serious an even life-threatening side effect what, all of the patients who want to try taking SGLT2i as an adjunctive treatment, should be aware of, so they would not miss the eventual symptoms and try to prevent the dangerous complications before they appear [22].

The addition of metformin to insulin therapy shows a moderate improvement in blood glucose levels and insulin sensitivity; however, its long-term effect on glycemic control remains uncertain. Furthermore, the research has shown increase in the risk of gastrointestinal events, especially in patients with poor glycemic control, requiring high doses of insulin [49].

Most forms of immunotherapy carry a risk of long-lasting or even permanent changes to the immune system [26]. These modifications may have serious consequences for patients overall health and can reduce their ability to fight common infections by compromising immune response. Similarly, the clinical use of teplizumab is limited by several adverse effects, including cytokine-release syndrome, lymphopenia, and an increased risk of infection [4]. However, the prevalence of those side effects was low, so overall the safety profile of teplizumab is rather favorable [50].

All in all, the options of introducing innovative adjunct treatments in addition to insulin therapy should be explored as they may pose a benefit for the patients, but the eventual risk of side effects needs to be evaluated and considered in order not to outweigh the benefits of the treatment.

Conclusions

According to recent studies it is evident that insulin therapy remains the main form of treatment in type 1 diabetes, but its limitations - including injectable nature, weight gain and the risk of hypoglycemia - highlights the need for additional treatment strategies. Research into new treatment options that can be used alongside insulin therapy is crucial for patients with type 1 diabetes, as it may ease disease management, reduce the risk of complications, and improve quality of life. Type 1 diabetes is a chronic condition that requires constant monitoring of blood glucose levels, continuous calculation of insulin doses, and strict self-discipline. As a result, it can be mentally exhausting and take a significant toll on patients overall well-being. It emphasizes even more the demand for innovative approach with the use of the newest technologies that would be easy to apply in daily life and would work seamlessly, fitting into every individual lifestyle. The ultimate goal is, of course, to develop a cure that can halt the progression of the disease or even reverse type 1 diabetes entirely - whether by protecting insulin-producing pancreatic β-cells, modulating the immune response to prevent their destruction, or restoring β-cell function altogether. Unfortunately, reversing autoimmunity in type 1 diabetes remains a major challenge. However, even by aiming to preserve the β-cells function for as long as possible, the patients with type 1 diabetes can obtain better control of blood glucose levels, lower the risk of eventual complications connected with type 1 diabetes and predominantly improve overall health. Adjunct pharmacotherapies (amylin analogue - pramlintide, GLP1 receptor agonists, SGLT inhibitors, metformin) have shown to be beneficial for the patients by supporting better glycemic control, weight loss and reduction of insulin doses, but also elevate the risk of hypoglycemia or diabetic ketoacidosis (DKA). In comparison, immune-focused therapies and stem cell-based ones aim at preserving or restoring the function of insulin-producing β-cells by disese-modyfying approach. Clinical trials have shown promising results; however, many of these strategies remain in experimental stages and require further research to establish their safety and long-term effectiveness. The rapid evolution of fields such as genetics with genetic engineering and immunology with new studies and trials emerging leaves a bit of hope for creating alternative therapies that would be widely available for the population. More research is definitely still needed, but even currently, there are clinical trials taking place, testing various treatments with probable potential of becoming a successful solution to finally curing type 1 diabetes. Yet still, there are numerous stages of testing that a brand new therapy would have to go through before becoming accessible for general population. Also, the question of safety still remains. The hypothetical side effects would have to be minor, well tolerated and definitely not life-threatening. When discussing blood glucose management, the issue of hypoglycemia is particularly important. The frequency of hypoglycemic episodes should be minimized as much as possible, and ideally eliminated. Unfortunately several of the adjunct to insulin therapy pharmacological forms of treatment include hypoglycemia as the unwanted side effect. Therefore, the scientists have recently focused more on solutions that require rather the use of immunomodulatory agents or modified cells (stem cells) as a preferred form of therapy. The most promising research results have come from stem-cell replacement therapies and combinations of pharmacological approaches. Nonetheless, all protocols and regulatory requirements must be met to ensure the safety of these new emerging therapies. There should also be an emphasis on the importance of early diagnosis of type 1 diabetes, as it may help delay the destruction of insulin-producing β-cells or preserve the remaining cells' function for as long as possible. Overall, the rapid advances in genetic engineering and the growing understanding of the pharmacological mechanisms behind adjunct therapies make future developments highly encouraging. Continuous research, including large-scale clinical trials and follow-up evaluations, remains essential for progressing toward achieving a potential cure. The search for treatment options that are safe, effective, and widely accessible remains ongoing. Furthermore, one of the major concerns regarding stem-cell–based therapies is their limited availability, as cells often need to be obtained from deceased donors for transplantation. Additionally, the need for immunosuppressive therapy continues to pose significant risks. These drugs themselves have various side effects like elevated risk of serious infections (including viral, bacterial and fungal), greater risk for developing cancer (particularly skin cancer), metabolic issues, nausea, weight gain, fatigue, kidney damage and overall decline of organs function. It is yet to find a way to protect the insulin-producing pancreatic β-cells without relying on immunosuppression. The goal is to reduce the need for immunosuppressive therapy to eventually introducing forms of treatment that would be fully independent of any form of immunosuppression. Before any specific treatment would be introduced, the patient overall health must be also carefully evaluated in order not to miss any appearing complications that could be tied to the new form of treatment. Today, with numerous clinical trials, constant research and advancing diagnostic and testing methods, emerging treatment options and new adjunct therapies, developing a cure for type 1 diabetes may not be as distant as once believed.

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