New Horizons: Emerging anti-diabetic medications

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ABSTRACT

Over the past century, since the discovery of insulin, the therapeutic offer for diabetes has grown exponentially, in particular for type 2 diabetes. However, the drugs in the diabetes pipeline are even more promising because of their impressive anti-hyperglycemic effects coupled with a remarkable weight loss.

An ideal medication for type 2 diabetes should target not only hyperglycemia but also insulin resistance and obesity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the new class of GLP1 and gastric inhibitory polypeptide (GIP) dual receptor agonists counteract two of these metabolic defects of type 2 diabetes, hyperglycemia and obesity, with stunning results that are similar to the effects of metabolic surgery.

An important role of antidiabetic medications is to reduce the risk and improve the outcome of cardiovascular diseases, including coronary artery disease and heart failure with reduced or preserved ejection fraction, as well as diabetic nephropathy, as shown by SGLT2 inhibitors.

This review summarizes the main drugs currently under development for the treatment of type 1 and type 2 diabetes highlighting their strengths and side effects.

Key words: type 2 diabetes, antidiabetic medications, incretins, GLP1 receptor agonist, gliflozin

In spite of the large number of anti-diabetes medications available, including combination therapies, the percentage of people achieving an adequate glycemic control with a glycated hemoglobin <7% remains lower than 60%. A recent analysis of the trends of diabetes treatment and risk-factor control within the National Health and Nutrition Examination Survey (NHANES) shows that the percentage of participants with HbA1c <7% was 44.0% in 1999–2002, 57.4% in 2007–2010 and 50.5% in 2015–2018 (1). A leading cause of the failure to achieve an adequate glycemic control resides in the poor medication adherence, especially in type 2 diabetes (T2D), which is as low as 60% (2). The total costs of diagnosed diabetes in US increased by 26% in 5 years, from $245 billion in 2012 to $327 billion in 2017 (3).

In the last few years, pharmaceutical industries sought to identify new pharmacological molecules with improved selectivity and specificity. For instance, targeting the principal defects of insulin action in T2D can improve patient outcomes and reduce the clinical burden of this condition.

An ideal medication for T2D should target not only hyperglycemia but also insulin resistance and obesity. Glucagon-like peptide-1 Receptor Agonists (GLP1-RAs) and the new class of GLP1 and Gastric Inhibitory Polypeptide (GIP) dual receptor agonists counteract two of these metabolic defects in T2D, hyperglycemia and obesity, with stunning results that are similar to the effects of metabolic surgery.

An important role of antidiabetic medications is to reduce the risk and improve the outcome of cardiovascular diseases, including coronary artery disease and heart failure with reduced or preserved ejection fraction, as well as diabetic nephropathy, as shown by Sodium-glucose co-transporter-2 (SGLT2) inhibitors.

Herein we define as "emerging anti-diabetic medications" those anti-diabetic medications recently approved by the Food and Drug Administration (FDA) and/or by the European Medicines Agency (EMA), or by other local regulatory agencies, such as the Japanese PMDA, or drugs in the pipeline for type 1 (T1D) or type 2 diabetes with specific and innovative pharmacologic targets.

TYPE 1 DIABETES

Oral insulin was always regarded as a mirage since it would avoid injections, which is a particularly painful and hated procedure for young patients. However, until now this aim was difficult to achieve because of the unpredictability of insulin absorption through the oral route.

Immunomodulatory strategies

Targeting T cells reduces the presence of T cells that migrate from the thyme to the endocrine pancreas, where they destroy islets.

Teplizumab - a fragment crystalline (Fc) receptor–nonbinding anti-CD3 monoclonal antibody - was used in a phase 2, randomized, placebo-controlled, double-blind trial (RCT) to verify whether the elapsed time from randomization to the clinical diagnosis of T1D could have been delayed in relatives of individuals with T1D at high risk for development of clinical disease (4). The median time to diagnosis was doubled in participants under teplizumab treatment as compared with placebo (48.4 vs. 24.4 months) and the proportion of participants with diagnosis of diabetes was reduced by about 30% (43% vs. 72%).

An ongoing Phase III trial (PROTECT RCT; ClinicalTrials.gov NCT03875729) is in the midst of evaluating the safety and efficacy of teplizumab in children and adolescents with recent onset T1D.

Alefacept is a fusion protein, which contains two Lymphocyte Function-Associated Antigen 3 (LFA-3) molecules bound to the Fc portion of immunoglobulin G1 (IgG1) (5). It binds the cell surface marker CD2 mainly expressed on CD4+ and CD8+ effector memory T cells that are responsible for the destruction of β-cells in T1D (6). In an RCT, involving 49 subjects with newly onset T1D, two 12-week courses of 15 mg/week intramuscular alefacept separated by a 12-week pause were compared with placebo. At 24-month follow-up, alefacept reduced insulin requirements (P=0.002) as well as major hypoglycemic events (P<0.001) when compared with placebo (7).

Amylin

The neuroendocrine hormone, amylin, reduces glucagon secretion improving glycemic control in T1D. Pramlintide, an injectable amylin analogue, approved in USA as an adjunct to meal-time insulin reduces post-prandial glycemic excursions (8). The modest efficacy associated with side-effects, such as nausea and hypoglycemia, precluded its extensive use in clinics.

SGLT inhibitors

Sotagliflozin and dapagliflozin have been approved in the European Union and Japan and are under scrutiny by the FDA for patients with T1D and overweight.

Sotagliflozin, belonging to the gliflozin class of antidiabetic drugs, blocks both intestinal SGLT1 and renal SGLT2 glucose carriers with consequent reduction of glucose absorption in the intestinal tract and increases renal excretion of glucose with urine, overall reducing the circulatory levels of glucose.

It was shown that 28.6% of patients in the oral sotagliflozin group, receiving 400 mg of the drug daily, met the primary endpoint of HbA1c<7.0% as compared with 15.2% (P<0.001) in the placebo group (9).

In patients with T1D and chronic diabetic nephropathy, sotagliflozin reduced the risk of the composite endpoint of cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure in

comparison with placebo (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group) (10).

Hopefully, the use of sotagliflozin as an add-on therapy to insulin can permit to obtain better glycemic control and reduce cardiovascular events in T1D. On May 3 2021, FDA approved oral dapagliflozin tablets to "reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression". However, in addition to an increase in genital mycotic infections, sotagliflozin has shown a 5–17-fold risk increase of diabetic ketoacidosis (DKA), which seems to be dose-dependent (11). A Consensus Report (12) recommends measuring ketone bodies in the presence of symptoms consistent with DKA, such as nausea or vomiting or malaise and fatigue. Blood levels of β-hydroxybutyrate higher than 0.6 mmol/l or the presences of even bland ketonuria indicate early ketosis.

GLP1-RAs

The ADJUNCT 1 and 2 trials demonstrated the efficacy of liraglutide as an adjunct to insulin in reducing the daily need of insulin injections, in improving glycemic control, and in reducing body weight in participants with T1D and overweight (13-14). However, important safety concerns are the increased risk of hypoglycemia (21.3 vs. 16.6 events/patient/year; P = 0.03) as well as of DKA (0.5 vs. 0.1 events/patient/year; P = 0.01).

TYPE 2 DIABETES

Insulin resistance in type 2 diabetes

Currently, insulin resistance is considered the primary defect in subjects with type 2 diabetes, manifesting long before hyperglycemia (15). Only when insulin secretion decreases, overt diabetes

emerges as a result of relative β-cell failure. A finding supporting this paradigm is the preserved insulin secretory capacity of the endocrine pancreas observed in the presence of T2D, particularly in subjects with associated obesity, as compared with individuals with normal insulin sensitivity (16-17). In other words, subjects with T2D and obesity have insulin hypersecretion but circulating insulin levels are unable to overcome the insulin resistance state. Moreover, the absence of the early phase of insulin secretion associated with a more pronounced compensatory second phase do not permit to individuals with T2D an adequate and quick response to rapidly increased circulating glucose levels (18).

Skeletal muscle is the major site showing impaired insulin-mediated glucose uptake and utilization with reduced glycogen formation/deposition and impaired glucose oxidation (19).

Obesity and especially visceral obesity increase cytokine secretion that alters insulin signaling thus contributing to insulin resistance (20). Moreover, the increased afflux of free fatty acids to the liver from the intra-abdominal fat compartment increases hepatic glucose production, a major player in insulin resistance (21).

Hence, drugs targeting insulin resistance and concurrently reducing body fat should represent the best therapeutic candidates for treating T2D.

Unfortunately, only two drugs target directly insulin resistance, metformin and the drug class of thiazolidinediones (TZDs). Metformin reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis and by stimulating insulin-mediated glucose uptake and glycogenesis in the skeletal muscle (22).

TZDs are ligands of the nuclear peroxisome proliferator-activated receptor gamma, which becomes activated and increases transcription of insulin-sensitive genes (23). Unfortunately, TZDs not only do not decrease body weight but rather increase it, although moderately. However, body fat distribution

changes with increased subcutaneous fat at the expense of the visceral fat which decreases with an improvement in insulin sensitivity (24).

Current ADA/EASD hyperglycemia treatment guidelines for T2D recommend using drugs that reduce body weight, such as GLP-1 RAs and SGLT2i (25). By reducing fat accumulation and obesity, in fact, they improve glycemic control.

Emerging drugs for type 2 diabetes

Since 1920 when a guanidine compound, Synthalin, was synthesized in Germany and successively commercialized, and since 1922 when insulin was first used in humans by Banting and Best, a great number of anti-diabetic medications entered the market. Over a century, the therapeutic possibilities for the management of diabetes have grown exponentially. However, the drugs in the diabetes treatment pipeline are even more promising because of their impressive anti-hyperglycemic effects coupled with remarkable weight loss.

The development of SGLT2i and GLP1-RAs has offered new tools for improving not only glycemic control but also cardiovascular and kidney outcomes in people with T2D.

New members or doses of GLP1-RAs

GLP1-RAs reduce HbA1c in ranges of 1-1.5% when added to the standard of care (26). This effect is achieved through the simultaneous stimulation of insulin secretion, the suppression of glucagon release, and the delay of gastric emptying time. Gastric emptying delay slows carbohydrate absorption but causes also gastrointestinal side effects, principally nausea, which can affect up to 30% of subjects (27).

Since the first GLP1-RA – Byetta exantide from AstraZeneca – was approved in the US in 2005, other short-acting and long-acting GLP1-RAs have been approved by both FDA and EMA, hence, are commercially available in the USA and EU.

Efpeglenatide is a modified exendin-4 molecule conjugated with an Immunoglobulin G4 at the level of the fragment crystallizable region (IgG4 Fc), which is injected once a week and, potentially, once a month, but it is not yet approved by FDA or EMA. Efpeglenatide significantly reduces cardiovascular events, occurring in 7.0% of participants assigned to Efpeglenatide and in 9.2% of those receiving placebo (hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P<0.001 for non-inferiority; P=0.007 for superiority) (28).

A double-blind phase III RCT, SUSTAIN FORTE, comparing the efficacy of 2 mg with 1 mg subcutaneous semaglutide once a week, showed the superiority of the 2 mg dose for both the glycemic control and the weight loss effect (29). In fact, HbA1c was reduced from baseline by −2.2% with semaglutide 2.0 mg and by −1.9% with semaglutide 1.0 mg with a significant (P=0.0003) estimated treatment difference of –0.23%. The body weight decrease from baseline was −6.9 kg with semaglutide 2.0 mg and −6.0 kg with semaglutide 1.0 mg (P=0.015). On March 2022, FDA granted the approval to semaglutide 2 mg sc once a week for the treatment of T2D.

Dual GLP1 and GIP Receptor Agonists

A new and very promising class of drugs is the dual GLP1 and GIP receptor agonist. SURPASS-1 (30) was a double-blind, randomized, controlled, phase 3 trial involving 478 participants with T2D and HbA1c between 7.0% and 9.5%, who were insulin-naïve and were receiving metformin alone or in concomitance to SGLT2 inhibitors. Participants were randomly assigned (1:1:1:1) to subcutaneous

administration of 5 or 10 or 15 mg tirzepatide once a week or placebo. Tirzepatide was administered following a slow dose escalation regimen with 2.5 mg dose increment every 4 weeks until reaching the maintenance dose. The primary endpoint was HbA1c mean change from baseline at 40 weeks of follow-up.

At 40 weeks, the mean HbA1c concentrations reached near-normal values of 6.08% (43 mmol/mol) with tirzepatide 5 mg, 6.06% (43 mmol/mol) with tirzepatide 10 mg, and 5.88% (41 mmol/mol) with tirzepatide 15 mg. The mean treatment difference with the control group was about −2%.

The effect of tirzepatide on weight loss was remarkable, −7.0±0.52 kg with 5 mg, −7.8±0.53 kg with 10 mg and −9.5±0.54 kg with 15 mg, with an estimated mean treatment difference versus the control group varying from −6.3 to −8.8 kg. Weight loss was dose-dependent with 13% to 27% of the participants showing 15% or greater weight loss versus none in the insulin degludec group. Gastrointestinal side effects, in particular nausea, diarrhea and vomiting, were the most frequent adverse effects reported in 12-18% of participants.

SURPASS-2 trial (31) was designed to show non-inferiority of tirzepatide at a dose of 5 mg or 10 mg or 15 mg versus semaglutide at a dose of 1 mg in regard to the change from baseline in HbA1c at 40 weeks in subjects with T2D inadequately controlled with metformin monotherapy.

Tirzepatide at doses of 5, 10 and 15 mg was found to be superior to semaglutide 1 mg used as an active comparator.

Tirzepatide 5, 10 and 15 mg reduced HbA1c by −2.01%, −2.24% and −2.30% as compared with −1.89% with semaglutide 1 mg. It is interesting to note that semaglutide 2.0 mg reduces HbA1c by

−2.2% from baseline (29), which is very close to the effect of tirzepatide. Moreover, while the effect of tirzepatide on glycemic control was more or less similar with the three doses, a clear dose response effect on weight loss was evident. In fact, the weight loss obtained was −7.6 kg, −9.3 kg and −11.2 kg with tirzepatide 5 mg, 10 mg and 15 mg respectively as compared with −5.7 kg with semaglutide 1 mg.

Although the number of adverse events was similar with tirzepatide and semaglutide, a higher number of serious adverse events was observed with the former. Mortality was observed among subjects treated with tirzepatide but not in those treated with semaglutide, although it was not imputed to the pharmacological treatment.

SURMOUNT-1 RCT, dedicated to obesity, showed −3.1% (95% CI, −4.3 to −1.9) weight loss with placebo, −15.0% (95% CI, −15.9 to −14.2) with 5-mg weekly dose of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10 mg and −20.9% (95% CI, −21.8 to −19.9) with 15 mg (P<0.001 for all comparisons with placebo) (32). Therefore, the maximal weight loss in excess to placebo was about 18% with 15 mg tirzepatide. Fifty% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants receiving tirzepatide 10 mg or 15 mg obtained a weight loss exceeding 20%.

Tirzepatide is a single linear peptide composed of 39 amino acids conjugated with a 20-carbon atom fatty dicarboxylic acid at the lysine residue at position 20. This peptide is bound to albumin in order to obtain a slow release, permitting a once-a-week subcutaneous administration. Tirzepatide has an affinity for GIP receptors close to that of the native GIP, but it binds the GLP1 receptor with about a 5-fold weaker affinity than native GLP-1. Therefore, its action on the GIP receptor is stronger than that on the GLP1 receptor.

GIP stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner, thus under hypoglycemic conditions circulating glucagon levels increase maintaining the physiological anti-hypoglycemic role of glucagon (33).

On May 13 2022, tirzepatide of Eli Lilly and Co. was approved by FDA to treat T2D with commercial name Mounjaro at doses 5, 10 and 15 mg.

Imeglimin

A new class of oral anti-hyperglycemic medications containing tetrahydrotriazine, the so-called "glimins", includes imeglimin. At the moment, imeglimin is commercialized only in Japan.
This drug amplifies glucose-stimulated insulin secretion and improves insulin sensitivity both at the level of the liver and the skeletal muscle. These effects are likely mediated by its inhibitory action on the mitochondrial oxidative phosphorylation (34).
Efficacy and safety of imeglimin was evaluated in phase 3, TIMES 1 RCT (35). 213 patients with T2D were randomized 1:1 to oral imeglimin at the dose of 1000 mg twice daily or to placebo. After 24 weeks, the estimated HbA1c treatment difference with placebo was 20.87% (95% CI 21.04 to 20.69), P<0.0001.

Serious adverse events were observed in the 3.8% of subjects in the imeglimin group and in 0.9% in the placebo group. No differences between groups in terms of incidence of gastrointestinal disorders were observed.

Its long-term efficacy is evaluated in the ongoing DIGNITY trial, Durable Effect of Imeglimin on the Glycemic Control in Patients With Type 2 Diabetes Mellitus: a Multicenter, Open-label, Randomized, Controlled Trial, ClinicalTrials.gov Identifier: NCT05366868.

Glucagon Receptor Antagonist RVT-1502

Circulating glucagon levels decrease during GLP1-RA therapy but only by ca. 10% (36, 37). It has been shown that glucagon receptor knockout mice do not develop hyperglycemia or other metabolic disorders associated with diabetes (38). Therefore, glucagon receptor antagonists are actively studied as anti-diabetic medications.

RVT-1502 is a glucagon receptors antagonist orally bioavailable that suppresses hepatic glucose production (39).

A recent phase 2 RCT evaluated the efficacy in terms of change from baseline of HbA1c levels and safety of RVT-1502 at doses of 5, 10, and 15 mg compared with placebo over 12 weeks (40).

After 12 weeks of treatment, the mean HbA1c changes relative to placebo were 20.7% (95% CI 21.1 to 20.4%; P <0.001), 20.8% (21.1 to 20.4%; P <0.001), and 21.1% (21.4 to20.7%; P <0.001) with 5, 10, and 15 mg RVT-1502, respectively.

The most frequent mild to moderate adverse events observed in 35.5% of patients receiving RVT-1502 were diarrhea, increased AST, proteinuria, and urinary tract infection and they were not dose-related; however, 36.6% of the participants under placebo had AEs.

Transient changes in liver enzymes, which however remained at the high level of normality, and mild increases in blood pressure were also observed.

Amylin

Pramlintide, an amylin analog, is approved in the US since 2005 in injectable form as an adjunct to insulin treatment in type 1 and type 2 diabetes (41). It decreases glucagon secretion, reduces gastric emptying and induces satiety (41).

Cagrilintide (42) is a long-acting amylin analogue with agonistic effects on both native amylin and calcitonin receptors. Native amylin is a hormone co-secreted with insulin that delays gastric emptying and suppresses appetite and induces satiety.

The injection of 4.5 mg of cagrilintide reduced body weight from baseline by 6% more than liraglutide 3 mg after 26 weeks of treatment (42). It reduced also HbA1c levels by 1.2±2.4 (mean±SE) %. Another more recent study showed that cagrilintide reduces 15% body weight after 20 weeks of treatment (43).

11 β -Hydroxysteroid Dehydrogenase Type 1 Inhibitors

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme catalyzing the transformation of cortisone to its active form cortisol. This NADPH-dependent enzyme is mainly expressed in the liver and adipose tissue (44).

11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) is a NAD+ dependent enzyme mainly present in the kidney, which oxidizes cortisol to inactive cortisone and, thus, counteracts the action of 11β-HSD1 (44). When 11β-HSD1 is inhibited, the hypothalamic-pituitary-adrenal axis (HPA) activates to ensure homeostasis (45).

None of the drugs (BI 187004, BI 135585, RO 5093151/RO-151, RO5027383/RO-838, ABT-384, MK-0916, AZD4017) that showed a significant preclinical effect on glucose metabolism by improving insulin sensitivity and glycemic control arrived to phase 2. The 11β-HSD1 inhibitor, AZD4017, was

the only one used in a phase II RCT with two primary outcomes: the percentage change from baseline to week 12 in liver fat fraction, and the percentage change from baseline to week 12 in the conversion of 13C cortisone to 13C cortisol. It failed the first primary outcome and succeeded only in drastically reducing the formation of cortisol in tissues (46).

Glycogen Phosphorylase Inhibitors

Glycogen phosphorylase catalyzes the breakdown of glycogen to glucose-1-phosphate at the α-1,4-glycosidic linkage in the liver and other tissues, such as skeletal muscle, to increase glucose availability and meet high energy demand.

The active form of this enzyme is the phosphorylated one obtained through the phosphorylation of serine-14 by phosphorylase kinase (47).

Together with gluconeogenesis, hepatic glycogenolysis regulates circulating levels of glucose and, therefore, it represents a good target for the treatment of diabetes. Other than competitive inhibitors binding the active site of glycogen phosphorylase, molecules that bind the purine inhibitory site (I site) of the enzyme, such as caffeine and other heteroaromatic analogues, counteract the action of glycogen phosphorylase (48).

Although promising in rodent models of diabetes, this class of anti-diabetic medications did not reach the clinical phase, mainly for the barriers of targeting the specific hepatic isoform and, thus, avoiding reduced availability of glucose in the skeletal muscle that can limit physical activity (49).

Glucokinase Activators

Glucokinase (GK) or hexokinase IV, is an enzyme covering a central metabolic role. GK promotes glucose uptake and glycogen synthesis in the liver. It phosphorylates glucose to glucose-6-phosphate, which is then oxidized in the glycolysis and produces pyruvate in the mitochondria. In pancreatic β-cells, GK increases ATP/ADP ratio closing the K^+ channel with consequent cell membrane depolarization and insulin secretion.

Heterozygous mutations in the GK gene cause maturity-onset diabetes of the young (MODY2) (50). While theoretically promising drugs, some of them, such as AZD6370, piragliatin, DS-7309, and ARRY-403 terminated their clinical development because of toxicity and low effectiveness in the long term (51).

G Protein-Coupled Receptor Agonists

FFAs activate several G protein-coupled receptors (GPCRs), which are expressed in pancreatic islets, including GPR119, GPR132, GPR84, GPR119, GPR120, GPR43 (FFAR2), GPR40 (FFAR1), and GPR41 (FFAR3) (52).

GPR119 is a G protein-coupled receptor expressed on the cell membrane of β-cells and gut endocrine cells. It stimulates insulin secretion in a glucose-dependent manner and increases intracellular cyclic AMP (cAMP) levels and incretin release, including GLP-1, GIP, and glucagon-like peptide-2 (GLP-2) (53).

Until now, no drugs belonging to this class have succeeded and entered the market.

DS-8500a enhanced insulin secretory capacity, but not insulin sensitivity (54).

GlaxoSmithKline's GSK-1292263, which completed a Phase 2 trial in May 2010, did not improve glucose control in patients with type 2 diabetes (55).

Fasiglifam is a selective GPR40 agonist that significantly reduced HbA1c and fasting glycemia as compared with placebo, but its clinical development was terminated after phase 3 RCT due to liver toxicity (56).

Protein Tyrosine Phosphatase 1B Inhibitors

Protein tyrosine phosphatase 1B (PTP1B) is a key cellular enzyme that controls cell growth and metabolism (57). Importantly, it catalyzes the removal of the phosphate group from tyrosine residues on the activated insulin receptor impairing its action and, thus, reducing insulin-mediated glucose uptake. Consequently, PTP1B inhibitors increase the phosphorylation of insulin receptor and improve glucose disposal.

Unfortunately, PTP1B inhibitors, such as Ertiprotafib, ISIS-113715 and Trodusquemine, failed in phase 2 clinical trials due to undesirable side effects and/or low selectivity (58).

Kinases

Glucokinase (GKA) is a liver enzyme that phosphorylates glucose to glucose-6-phosphate, this latter representing the hub to five major pathways, glycolysis, gluconeogenesis, glycogenesis, glycogenolysis and pentose phosphate pathway. Glucokinase activators stimulate β-cell insulin secretion and promote hepatic glycogen synthesis with subsequent reduction of hepatic glucose output (59). Preclinical animal studies demonstrate that GKAs normalize blood glucose levels, but induce severe hyperlipidemia and hypertension (60). Many GKAs entered trials, such as RRY-403, AZD1656, PSN010, which have been

however discontinued. Dorzagliatin is a novel GKA acting on both pancreatic and hepatic glucokinases, which is in phase 3 trial, while TTP399 is a compound selective for liver GKA (59) in phase 2 trial.

AMP-activated protein kinase (AMPK) is a key energy regulator. Several AMPK activators are registered in trials: two of them, PXL770 and PBI-4050, completed phase 2 trials (61).

Fructokinase (FK) is an enzyme located in the liver, the intestine, and in the kidney cortex, which catalyzes the conversion of fructose into fructose-1-phosphate. FK activation depletes the cell of phosphates with the consequent activation of AMP deaminase ending in uric acid production. Uric acid is a pro-inflammatory molecule, which can induce insulin resistance (62). The FK inhibitor, PF-06835919, is currently in phase 2 development. Tolimidone (MLR-1023) is also in phase 2. Tolimidone stimulates Lyn protein, which is a member of the Src family of intracellular membrane-associated tyrosine kinases (63, 64). Lyn tyrosine kinase phosphorylates insulin receptor substrates augmenting insulin receptor signaling (65, 66). Tolimidone enhances insulin sensitivity and its action is insulin-dependent (63).

CONCLUSIONS

Although currently, we have an ample drug choice to treat diabetes, the antidiabetic armamentarium is increasing substantially with a relevant pipeline of new medications.

Apart from oral insulin and immunomodulatory strategies in clinical development and Sotagliflozin under FDA scrutiny for type 1 diabetes, the great majority of antidiabetic drugs target type 2 diabetes. The major defect of type 2 diabetes is the presence of insulin resistance, which becomes more and more severe as body weight increases up to morbid obesity. Therefore, aside true insulin secretion failure due to β-cell exhaustion, the insulin secretion impairment observed in type 2 diabetes is often relative because higher than normal insulin levels are required to overcome reduced insulin-mediated glucose uptake. An ideal antidiabetic medication should target not only hyperglycemia but also insulin resistance and obesity. The GLP1-RA semaglutide in combinations with the long-acting amylin analog cagrilintide and the new class of GIP and GLP1 dual receptor agonists, which at the moment includes only tirzepatide, counteract two of these metabolic defects of type 2 diabetes, hyperglycemia and obesity with stunning results that are almost similar to the effects of metabolic surgery.

An important role of antidiabetic medications is to reduce the risk and improve the outcome of cardiovascular diseases, including coronary artery disease and heart failure with reduced or preserved ejection fraction, as well as diabetic nephropathy, as shown by SGLT2 inhibitors.

We are still waiting for a drug simultaneously targeting hyperglycemia, obesity and insulin resistance as the Holy Grail of T2D treatment.

However, the major challenges for an adequate treatment of people with diabetes is not the lack of effective therapies but the inequalities in the populations with diabetes. For instance, the insulin cost in the US is ca. 800% higher than in other developed countries (67). The net price of insulin increased by 252% in 2016 (68). Insurance plans with high deductible oblige the patients to pay out of their pocket before the insurance begins to pay for covered costs. Therefore, many people cannot afford buying insulin and this accounts, at least in part, for the poor adherence to anti-diabetic medications observed.

Tackling economic inequalities and/or improving the health insurance offering may help improving glycemic control in people with diabetes.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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