Emerging Therapies for Type 2 Diabetes

Abstract

Type 2 diabetes is a common medical condition associated with many comorbidities. Tight glycemic control is associated with improved clinical outcomes. Traditional therapies such as metformin or sulfonylureas are prescribed for management of hyperglycemia, and new therapies for the treatment of type 2 diabetes have been developed that are associated with additional clinical benefits. Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have emerged as antihyperglycemic therapies associated improved renal and cardiovascular outcomes in individuals with type 2 diabetes. Dipeptidyl peptidase-4 inhibitors are an additional class of antihyperglycemic medications that may be useful in select individuals. Oral semaglutide, a glucagon-like peptide-1 receptor agonist, may improve ease of administration of this class of medication. The decision of which additional antihyperglycemic therapy to add to an individual's current treatment regimen is increasingly based on underlying comorbidities and risk profile.

Introduction

Type 2 diabetes is a common medical condition that affects 34.2 million people in the United States, and 88 million people currently have prediabetes.[1] Studies have identified the positive clinical outcomes of glycemic control on microvascular complications caused by diabetes such as neuropathy, retinopathy, and nephropathy.[2,3] Tight glycemic control has become the standard of care for management of type 2 diabetes.[4] Recently, new therapies have been developed for the management of type 2 diabetes, which show benefit for macrovascular complications such as cardiovascular and cerebrovascular disease.[5] Although treatment of diabetes typically starts with traditional therapies, the addition of newer antihyperglycemic medications may improve outcomes in diabetes and its associated comorbidities.[6] This article will review traditional antihyperglycemic medications, review recent advancements in pharmacotherapy for type 2 diabetes, and address emerging issues in the treatment of type 2 diabetes.

Traditional Medications

Metformin

Metformin remains a first-line medication in the treatment of type 2 diabetes due to its effectiveness, affordability, and favorable side effect profile.[6] Metformin is a biguanide that lowers blood glucose level by increasing peripheral insulin sensitivity and decreasing hepatic glucose output.[7] Gastrointestinal side effects are most widely reported with metformin use, but metformin is not commonly associated with hypoglycemia when used as monotherapy and is generally well tolerated.[6] Metformin requires renal dosing adjustments. It should not be prescribed if estimated glomerular filtration rate is less than 30 mL/min out of concern for

development of severe lactic acidosis.[8-10] Metformin is used as monotherapy or in combination with other agents.[6]

Sulfonylureas

Sulfonylureas such as glyburide, glipizide, glimepiride, and gliclazide are oral therapies that lower blood glucose level by stimulating insulin secretion in pancreatic beta cells.[6] They are efficacious, affordable, and widely available.[11] However, sulfonylureas are associated with increased hypoglycemic episodes and weight gain, which may limit their tolerability in some individuals.[11] They are a common choice for antihyperglycemic therapy due to affordability, although the risk of hypoglycemia must be considered with administration of this class of medication.[6]

Thiazolidinediones

The thiazolidinediones, pioglitazone and rosiglitazone are oral medications that increase insulin sensitivity.[6] Thiazolidinediones are prescribed as monotherapy or as part of combination therapy and have high glucose level lowering efficacy.[12,13] This benefit is somewhat offset by safety concerns regarding worsening of congestive heart failure and fluid retention, as well as increased fracture risk in women.[14, 15]

Insulin

Insulin is often prescribed for treatment of type 2 diabetes because of its high efficacy in lowering glucose level in patients who do not achieve control of blood glucose levels with other antihyperglycemic agents.[6] However, insulin increases the risk of hypoglycemic episodes and has not shown the reduced mortality or reduced development of cardiovascular disease that has been seen with other antihyperglycemic agents.[16] Insulin use is limited by the need for subcutaneous injection and difficulties with appropriate use.[6]

Newer Antihyperglycemic Medications

Several newer therapies targeting specific pathways have been developed. The administration of these newer antihyperglycemic medications is associated with reduced all-cause mortality, specifically for glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[5]

Glucagon-Like Peptide-1 Receptor Agonists

The GLP-1 receptor agonists resemble GLP-1, a hormone released from the gut after oral glucose intake that stimulates insulin release from the pancreas in a glucose-dependent manner.[17] Administration of GLP-1 receptor agonists not only results in insulin release but is also associated with early satiety and decreased appetite.[18] Currently prescribed GLP-1 receptor agonists require subcutaneous injection, but an oral formulation of the GLP-1 receptor agonist semaglutide has recently been developed.[6, 19]

The GLP-1 receptor agonists can be categorized by their duration of action. The short-acting GLP-1 receptor agonists liraglutide, lixisenatide, and short-acting formulated exenatide are advantageous because they have a stronger association with delayed gastric emptying and earlier satiety than long-acting GLP-1 receptor agonists. They have a greater effect on postprandial plasma glucose levels than long-acting GLP-1 agonists. The long-acting GLP-1 receptor agonists exenatide (weekly formulation), albiglutide, dulaglutide, and semaglutide are associated with a stronger effect on 24-hour plasma glucose levels and fasting plasma glucose levels than the short-acting GLP-1 receptor agonists.[20]

The GLP-1 receptor agonists have several benefits. Meta-analysis has found that the GLP-1 receptor agonists reduce hemoglobin A_{1c} levels by 1.1% to 1.6%.[21] Certain GLP-1 receptor agonists, specifically liraglutide, semaglutide, and dulaglutide, are associated with improved cardiovascular outcomes. Clinical trials have demonstrated that death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was reduced with administration of these medications when compared with placebo.[22-24] There is benefit of GLP-1 receptor agonist administration for glycemic control and evidence of reduced cardiovascular disease, particularly for dulaglutide.[25]

When administered alone, GLP-1 receptor agonists are associated with a small increase in risk of hypoglycemia, but less than insulin or sulfonylureas.[26] Typical side effects include nausea, vomiting, and diarrhea, which usually subside over time.[6] In a trial involving semaglutide, there was an increase in retinopathy of diabetes, which requires further investigation.[23] Overall, GLP-1 receptor agonists are well tolerated.[6]

Recently, an oral formulation of the GLP-1 receptor agonist semaglutide was approved after a series of clinical trials demonstrated increased antihyperglycemic efficacy of the oral formulation compared with placebo, similar efficacy to an injectable GLP-1 receptor agonist for glycemic control, and no increase in negative cardiovascular outcomes with oral semaglutide use.[19, 27, 28] This oral formulation increased the ease of use of GLP-1 receptor agonists and had a similar safety profile as the injectable GLP-1 receptor agonists. This may lead to earlier use of GLP-1 receptor agonists for the treatment of type 2 diabetes.[29]

In summary, GLP-1 receptor agonists are effective options to add to an individual's antihyperglycemic regimen and have an added benefit in of reducing the risk of cardiovascular disease. Side effects are generally tolerable. Currently, GLP-1 receptor agonists require

subcutaneous injection; however, oral semaglutide will likely make administration of these medications more practical.

Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce the degradation of hormones involved in glucose regulation, including GLP-1. This results in glucose-dependent insulin secretion stimulated by GLP-1 and other hormones.[18] The DPP-4 inhibitors can be used alone or in combination with other agents, particularly metformin.[6] They have been shown in a meta-analysis to reduce hemoglobin A_{1c} levels from 0.6% to 1.1%.[21]

The DPP-4 inhibitors are generally not associated with severe hypoglycemia but may potentiate the hypoglycemic effects of other antihyperglycemic medications when used as combination therapy, particularly with sulfonylureas.[30,31] When compared with metformin and GLP-1 receptor agonists, DPP-4 inhibitors had fewer gastrointestinal side effects.[32] The DPP-4 inhibitors have been associated with an increased risk of pancreatitis and severe musculoskeletal complications.[33, 34]

The safety of DPP-4 inhibitors with respect to cardiac disease is unclear, specifically in regard to heart failure. A trial of linagliptin compared with glimepiride showed linagliptin to be noninferior to glimepiride in terms of preventing major cardiovascular complications,[35] and a recent trial of linagliptin compared with placebo in patients with high risk for cardiovascular disease demonstrated no increased risk of major cardiac outcomes with linagliptin.[36] However, the DPP-4 inhibitor saxagliptin did demonstrate an association with increased hospitalization for heart failure.[37] In addition, a meta-analysis has provided some evidence (considered weak by study authors) of association of DPP-4 use with hospitalization for heart failure.[38] Saxagliptin should be avoided in individuals with heart failure,[39] though DPP-4 inhibitors are generally well tolerated and are a reasonable treatment option for appropriate individuals.[6]

Sodium-Glucose Cotransporter-2 Inhibitors

The SGLT2 inhibitors are a relatively new class of antihyperglycemic medication that control glucose level independent of insulin and have benefits related to cardiovascular and renal disease.[6] Located almost exclusively in the proximal tubule of nephrons, SGLT2 is a cell membrane transporter that actively reabsorbs 90% of the glucose filtered in the kidney.[40] The SGLT2 inhibitors increase renal secretion of glucose and remove glucose from the entire system instead of sequestering it in the intercellular space like most other antihyperglycemic medications.[41]

The SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin have many benefits in individuals with diabetes. They reduce hemoglobin A_{1c} level by 0.69% (95% CI 0.62% to 0.75%) and have a modest effect in reducing weight and blood pressure.[42] Empagliflozin and canagliflozin have been shown to be associated with a reduction in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke when compared with placebo in large

clinical trials.[43, 44] Similarly, various meta-analyses have demonstrated a reduction in cardiac complications with SGLT2 inhibitors, including in patients with chronic kidney disease. [45-47] The administration of SGLT2 inhibitors is associated with a slowed progression of renal disease, although monitoring of creatinine level is needed out of concern for acute kidney injury associated with SLGT2 inhibitors, and the administration of SGLT2 inhibitors is not recommended below an estimated glomerular filtration rate of 30 mL/min.[6, 48]

Recently, a large double-blind trial of individuals with type 2 diabetes and chronic kidney disease comparing canagliflozin with placebo demonstrated a significant reduction in a composite primary outcome of development of end-stage renal disease, doubling of creatinine level, or death from renal or cardiovascular disease (hazard ratio [HR] 0.70; 95% CI 0.59 to 0.82; $P < .001$).[49] Additionally, a recent trial demonstrated a significant reduction in major cardiac events (HR 0.80; 95% CI 0.67 to 0.95; $P = .01$) and a significant reduction in hospitalization due to heart failure (HR 0.61; 95% CI 0.47 to 0.80; $P < .001$) in individuals given canagliflozin compared with those given placebos.[49] While a previous trial had demonstrated an increased risk for amputation associated with canagliflozin administration,[44] this recent trial did not demonstrate the same increased amputation risk, although patients at high risk for amputation were excluded.[49] The SGLT2 inhibitors shown to have cardiorenal benefits are now recommended in individuals with type 2 diabetes and chronic kidney disease, atheroschlerotic heart disease, or heart failure to prevent negative heart failure and cardiovascular outcomes, although care must be taken in individuals at risk for amputation.[25]

The use of SGLT2 inhibitors is associated with a low risk of hypoglycemia.[41, 42] The most commonly reported side effects are mycotic genital infections, orthostatic hypotension, dehydration, and increased urination due to the mechanism of increasing glucose in urine.[6, 41, 42] The SGLT2 inhibitors have many benefits, although some individuals have difficulty with long-term compliance due to side effects.[6]

In summary, SGLT2 inhibitors have efficacy for lowering blood glucose level and have an added benefit of reduction in negative cardiovascular and renal outcomes. They have a high potential for benefit when added to an individual's antihyperglycemic regimen though side effects may result in difficulty with compliance.

Emerging Concepts in Type 2 Diabetes Treatment

Given the recent advancements in pharmacotherapy for type 2 diabetes and the option to add either an SLGT2 inhibitor or a GLP-1 receptor agonist to an individual's current antihyperglycemic therapy, deciding which therapy to add requires additional clarification. A recent meta-analysis of randomized trials may help guide this decision.[50] A total of 764 trials involving 421 346 individuals showed that both SGLT2 inhibitors and GLP-1 receptor agonists lowered all-cause mortality, cardiovascular complication rate, and the rate of kidney failure.[50] Compared with GLP-1 receptor agonists, SGLT2 inhibitors reduced the rate of hospitalization from heart failure and heart failure mortality though SGLT2 inhibitors had a higher rate of mycotic genital infections.[50] In contrast, GLP-1 receptor agonists reduced stroke risk when

compared with SGLT2 inhibitors, although GLP-1 receptor agonists had a higher rate of gastrointestinal side effects.[50] The decision of which of these therapeutics to add to antihyperglycemic treatment regimens may need to be based on the individual's risk profiles and side effect tolerability.[50,51]

Discussion

There have been considerable advances in pharmacologic therapy for the treatment of type 2 diabetes. Deciding which medications to prescribe for management of type 2 diabetes is becoming increasingly complex. Guidelines have made recommendations for the medical management of diabetes, and shared decision making with patients is necessary. Metformin remains the recommended initial therapy for most individuals with type 2 diabetes.[6] Generally, a step-wise initiation of additional antihyperglycemic medications is recommended; however, a recent trial showed a significant reduction in treatment failure with the combined administration of metformin and the DPP-4 inhibitor vildagliptin compared with metformin alone (HR 0.51; 95% CI 0.45-0.58; *P* <0.001).[6, 52] Shared decision making is recommended regarding initial treatment with combination medications or monotherapy with metformin.[51]

The decision for prescription of additional medications if initial therapy is ineffective is based on multiple factors. The SGLT2 inhibitors provide benefits for individuals with diabetes who are at risk of cardiovascular complications, heart failure, or renal complications.[51] If therapy with an injectable agent is needed, GLP-1 receptor agonist prescription is generally preferred to insulin; however, insulin therapy is recommended in individuals with extreme symptomatic hyperglycemia.[6] Providers must consider cost, accessibility, and side effect profile when adding additional medications to their current regimens.[6]

Further research is needed regarding emerging type 2 diabetes management, specifically the role of combined therapy with GLP-1 receptor agonists and SGLT2 inhibitors. The role of oral semaglutide in the treatment of type 2 diabetes remains to be established in guidelines.

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