Dapagliflozin for the Treatment of Type 2 Diabetes

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OBJECTIVE: To review the literature and describe the pharmacology, pharmacokinetics, clinical safety, and efficacy of dapagliflozin, a compound currently in Phase 3 clinical trials.

DATA SOURCES: A search of the literature was conducted via MEDLINE (1995–March 2009) and ClinicalTrials.gov using the search terms dapagliflozin, SGLT2 inhibitor, sodium-glucose co-transport inhibition, and renal glucose reabsorption inhibition. Bibliographies of identified articles were also used to identify useful references.

STUDY SELECTION AND DATA EXTRACTION: All English-language reports evaluating dapagliflozin were included in this review, including abstracts and scientific presentations.

DATA SYNTHESIS: Due to the increasing prevalence of type 2 diabetes, suboptimal management of the associated hyperglycemia, morbidity and mortality associated with the disease, and the limitations of currently available therapies, novel therapeutic strategies are needed for its treatment. Dapagliflozin represents the first selective, sodium-glucose cotransporter 2 inhibitor that functions by regulating renal glucose reabsorption. Clinical trial data are limited, but available evidence supports clinically significant reductions in fasting plasma glucose, postprandial plasma glucose, hemoglobin A_{1c}, and body weight with this agent. In addition, dapagliflozin has demonstrated excellent tolerability with safety data demonstrated in both Phase 1 and Phase 2 studies.

CONCLUSIONS: Dapagliflozin represents the first in a new class of drugs that may represent a promising new option in the treatment of type 2 diabetes. Results of ongoing Phase 3 clinical trials are necessary to demonstrate efficacy and safety of this agent across various patient populations and clinical scenarios.

KEY WORDS: dapagliflozin, SGLT2 inhibitor, sodium-glucose cotransporter inhibition.

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The prevalence of type 2 diabetes is increasing at an epidemic rate. Currently, there are an estimated 24 million people in the US with diabetes; this represents a tripling of the number of cases since 1980.[1] Coupled with these growing numbers is the increasing knowledge of the progressive nature and morbidity with which the disease is associated. Type 2 diabetes is characterized by insulin resistance, inadequate insulin secretion, progressive β cell dysfunction, dysregulation of incretin hormones, and subsequent hyperglycemia. The complications of hyperglycemia can lead to retinopathy, neuropathy, nephropathy, and cardiovascular disease.[2,3] Lifestyle and pharmacologic interventions that target a reduction in hyperglycemia have been shown to substantially reduce the risk of microvascular complications.[3-7] Unfortunately, the ability to achieve the glycemic goals established in these trials has proven to be more elusive than anticipated, with reports estimating that less than 40% of patients with diabetes in the US are at or near the American Diabetes Association (ADA) established hemoglobin A_{1c} (A1C) goal of less than 7%.[3,8-10]

The treatment of type 2 diabetes has been of much research interest over the past 3 decades and the number and types of available therapies continue to expand. Older, clinically established therapies such as metformin, sulfonylureas, and insulin remain the mainstay of therapy because of the availability of long-term safety and efficacy data.[3-5,11] Each of these classes is considered to be tier 1, well-validated, core therapies by the 2008 ADA consensus statement.[11] Of these agents,

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metformin is considered step 1 therapy and remains the only available drug that has demonstrated a reduction in macrovascular complications in obese patients with type 2 diabetes.[5,11,12] While metformin is used extensively, the use is limited in some patients by gastrointestinal adverse effects and it is contraindicated in patients with poor renal function due to an increased risk of lactic acidosis. Furthermore, the majority of patients with type 2 diabetes will require multiple medications to achieve glycemic goals.[1,13] Sulfonylureas are an effective drug class, but can cause significant hypoglycemia and contribute to weight gain. Additionally, the efficacy of sulfonylureas diminishes over time as pancreatic β cell reserves decrease. While insulin is the most effective therapeutic option, injectable therapies are perceived as undesirable by many patients and the risks of hypoglycemia and weight gain are limiting.

Second tier, less well-validated therapies include thiazolidinediones (TZDs) and exenatide.[11] TZDs have come under much scrutiny following the publication of a meta-analysis that indicated an increased risk of myocardial infarction in patients treated with rosiglitazone.[14] Although pioglitazone has demonstrated more favorable outcomes, the place in therapy of TZDs remains questionable due to an adverse effect profile that includes weight gain, fluid retention, variable lipid effects, and the potential to cause or worsen congestive heart failure.[15,16] Exenatide is one of the newer available agents and has a favorable impact on weight and a low incidence of hypoglycemia; however, it is administered as a twice-daily subcutaneous injection and has an expected A1C reduction of only 0.5–1% as monotherapy.[17] The newest class of drugs is dipeptidyl peptidase 4 (DPP-4) inhibitors. Sitagliptin is currently the only available agent in this class. DPP-4 inhibitors are weight neutral and well tolerated; however, there is modest efficacy and currently the drugs are quite expensive. Additional therapies such as the glinides, α-glucosidase inhibitors, and pramlintide are available for clinical use, but are limited by either minimal efficacy, high incidence of adverse effects, or both. Despite the growing armamentarium of agents, additional drugs are needed to aid in the achievement of glycemic goals. The ideal one would be weight-neutral, well tolerated with minimal hypoglycemia, and orally administered once daily, and would demonstrate significant reduction in A1C as well as microvascular and macrovascular complications.

AstraZeneca and Bristol-Myers Squibb have been working in collaboration to develop a new treatment for type 2 diabetes known as dapagliflozin, an investigational drug in Phase 2 studies in Japan and Phase 3 studies worldwide.[18] Dapagliflozin is a novel, selective inhibitor of sodium glucose cotransporter 2 (SGLT2) that functions independently of insulin to regulate the reabsorption of glucose in the kidney and may represent new hope in the treatment of type 2 diabetes.[18]

Data Sources and Selection

A search of the English-language literature was conducted using MEDLINE (1995–March 2009) and ClinicalTrials.gov using the search terms dapagliflozin, SGLT2 inhibitor, sodium-glucose co-transport inhibition, and renal glucose reabsorption inhibition. All complete published articles were included in this review. Additionally, references of complete articles were searched for additional sources of information. Abstracts or scientific presentations of completed studies not yet published were also included. Priority was given to human data, but some animal data were included for completeness.

Pharmacology

MECHANISM OF ACTION

The kidneys contribute greatly to the body's natural regulation of plasma glucose levels.[19] The normal process for the kidney is to reabsorb most of the plasma glucose filtered so that less than 1% of glucose is excreted in the urine.[19,20] By theory, blocking glucose reabsorption would result in increased glucose excretion and decreased plasma glucose levels. There are 2 sodium-glucose cotransporters (SGLTs), which facilitate renal reabsorption of glucose: SGLT1 and SGLT2.[19]

SGLT1 is a high-affinity, low-capacity transporter located in the small intestines and to a lesser extent in the late segment (S3) of the proximal tubule of the kidney.[19,21,22] As the body breaks down and digests food, SGLT1 absorbs glucose and galactose across the intestinal brush border.[23,24] This is supported by findings of mutations in the SGLT1 transporter linked to glucose-galactose malabsorption.[19,23] Once absorbed via SGLT1, the circulating blood glucose is filtered in the glomerulus of the kidney where it first passes SGLT2.[19-21,24] SGLT2 is a low-affinity, high-capacity transporter located in the brush-border membrane of the early segment (S1) of the proximal tubule. SGLT2 is responsible for 90% of the glucose reabsorption.[19,21,25] The remaining glucose is reabsorbed by SGLT1 in the late proximal tubule.[19,21,22,24]

O-Glucoside phlorizin was discovered over 150 years ago with observations that oral ingestion produced glycosuria by inhibiting SGLT1 and SGLT2.[26] Due to this nonselective inhibition, resulting in many gastrointestinal adverse effects, and its poor metabolic stability due to B-glucosidase–mediated cleavage, phlorizin was not a candidate drug for the treatment of diabetes.[24,27,26] This, along with the fact that mutations in the SGLT2 transporter were linked to hereditary isolated renal glucosuria, led researchers to discover the C-aryl glucoside–selective SGLT2 inhibitor now named dapagliflozin.[27,28] The C-glucoside link provided stability against the intestinal, hepatic, and renal glucosidases that rapidly hydrolyzed the *O*-glucoside bonds.[27]

Dapagliflozin is selective for SGLT2 inhibition, resulting in decreased blood glucose levels secondary to glucosuria.[27] Dapagliflozin is insulin independent; therefore, it has no effect on circulating insulin levels and there is no effect on the glucose counterregulatory mechanisms.[25,27] Dapagliflozin also results in submaximal mean glucose excretion rates less than half of the predicted filtered glucose in 24 hours, which may also explain the low incidence of hypoglycemia.[29] Patients with primary renal glucosuria from SGLT2 mutations have normal blood glucose levels, further supporting the infrequent occurrence of hypoglycemia.[28] With the renal dumping of glucose, the body also loses about 200–300 kcalories per day, resulting in weight loss.[30] Since dapagliflozin is selective for SGLT2 and does not affect the SGLT1 transporters within the small intestines, the gastrointestinal adverse effects should be minimized.[24] Dapagliflozin has somewhat of a diuretic action, thereby avoiding the fluid retention seen with other diabetes treatment options.[24,30]

Pharmacokinetics

Dapagliflozin demonstrates a 2-compartment model with first-order absorption.[31] Effects of age, sex, body weight, disease status, and creatinine clearance were tested, with no covariates identified.[31] Dapagliflozin is rapidly absorbed after oral administration, with an average time to maximum observed concentration of 1–2 hours (range 0.5–4).[32,33] The observed half-life is about 16–17 hours. Food has a modest effect on the maximum; however, there is no overall effect on the maximal rate of glucose excretion, duration of excretion, or amount of glucose excreted.[33] In vitro studies indicate that it is predominantly metabolized to another inactive metabolite by UGT1A9, part of the phase II enzyme UGT family. The renal excretion of dapagliflozin is minimal since it is highly protein bound (97%).

The C-glucoside chemical structure provides a prolonged half-life and duration of action to allow once-daily dosing,[18] which provides a sustained rate of glucosuria over 24-hour dosing intervals.[32] Glucosuria and fasting plasma glucose levels are dose related, as higher doses provide longer duration of glucose excretion, but not an increase in maximum glucose excretion rates.[29]

Clinical studies

PHASE 1 DATA

Dapagliflozin was evaluated in healthy subjects in 2 simultaneous Phase 1 studies designed to evaluate the safety profile and appropriate dosing of the drug.[33] Healthy adults between the ages of 18 and 45 years, with a body mass index (BMI) of 18–30 kg/m^2, were eligible for the study. Exclusion criteria included any evidence of organ dysfunction, elevated urinary calcium or creatinine, abnormal vital signs, recent surgery, acute or chronic illness, or any clinical lab abnormality. Women of childbearing age or those who were pregnant or breast-feeding were also excluded from the studies.

The first study was a randomized, double-blind, placebo-controlled, sequential, ascending, single-dose evaluation.[33] Sixty-four subjects were assigned randomly to receive placebo or dapagliflozin in one of the following doses: 2.5, 5, 10, 20, 50, 100, 250, or 500 mg. Subjects were administered a single oral dose of dapagliflozin or placebo after a 10-hour fast and urine samples were collected at 12-hour intervals for 120 hours. A panel of 8 randomly chosen subjects received the lowest dose of dapagliflozin (6) or matching placebo (2). If the dose was found to be well tolerated, the next higher dose was administered to a subsequent panel of 8 subjects.

Safety outcomes indicated good tolerability with a low incidence of adverse events. Ten (21%) subjects reported adverse events (AEs) in the dapagliflozin-treated group while 9 (35%) placebo-treated subjects reported AEs. Two events of mild, asymptomatic hypoglycemia were reported, one in the treatment group and one in the placebo group. There were no study withdrawals due to AEs. No clinically significant abnormalities in laboratory values or vital signs were observed, and there was no relationship observed between incidence of AEs and dose of dapagliflozin.[33]

Pharmacokinetic results support a dose-response relationship and a once-daily dosing profile. Sustained glucosuria was observed with dapagliflozin doses of 20 mg and higher and was dose-dependent with a mean of 3 g/h. As expected, serum glucose levels remained within the normal range throughout the study, despite glucosuria in these healthy subjects.[33]

In a second double-blind, randomized, placebo-controlled, sequential, ascending multiple-dose study, healthy subjects were assigned randomly to receive dapagliflozin or placebo in a 3:1 ratio. Dapagliflozin-treated subjects were administered 5 sequential escalating doses of 2.5, 10, 20, 50, or 100 mg and placebo-treated subjects received a matching oral capsule placebo. Subjects received a daily oral dose for 14 days and were evaluated for a total of 27 days.[33]

Safety data indicated favorable results for dapagliflozin, with AEs reported in only 11 (37%) dapagliflozin-treated subjects and 9 (35%) placebo-treated subjects. There were no serious AEs reported, no reports of hypoglycemia, and no study discontinuations due to AEs. No clinically meaningful changes in laboratory values or vital signs were observed.[33]

Pharmacokinetic and pharmacodynamic data indicated a dose-response relationship with dapagliflozin and a profile that would sustain glucosuria with once-daily dosing.

Doses of 20 mg and higher produced an approximate 20–30% inhibition of renal glucose reabsorption over the study period.[33]

Results from these Phase 1 studies demonstrate predictable and tolerable dose-dependent, sustained glucosuria with dapagliflozin administered at doses of 20–500 mg once daily.

PHASE 2 DATA

Two Phase 2 clinical trials evaluating dapagliflozin in patients with type 2 diabetes have been completed and published to date.[30,32] Study findings are summarized in Table 1. Komoroski et al.[32] conducted a double-blind, placebo-controlled, randomized, parallel-group, multiple-dose study of dapagliflozin in patients with type 2 diabetes. The primary objective of this study was to determine safety and tolerability of dapagliflozin with preidentified secondary outcomes of glycemic efficacy. Subjects were men and women between 18 and 70 years of age with a diagnosis of type 2 diabetes treated with metformin or diet alone (treatment naïve), A1C of 6–10%, fasting plasma glucose (FPG) less than 240 mg/dL, BMI less than 42 kg/m², and normal renal function. A total of 47 subjects (19 male, 28 female) were randomly assigned in a ratio of 1:1:1:2 to placebo or 5, 25, or 100 mg of dapagliflozin once daily for 14 days. Eighteen metformin-treated patients continued on their previous regimen throughout the study. Diet was strictly controlled to 2200 calories daily and all meals were provided.

All doses of dapagliflozin, alone or in combination with metformin, were found to be safe and well tolerated in the study. There were no serious AEs or study discontinuations due to AEs. Only 2 episodes of hypoglycemia were reported in the study and both were mild and resolved spontaneously. In addition, 2 female patients in dapagliflozin treatment arms reported mild vulvovaginal mycotic infections that resolved with treatment.[32]

A dose-dependent decrease in FPG was observed in dapagliflozin-treated subjects between baseline and day 13 with absolute, mean reductions of 18.8, 28.8, and 38.7 mg/dL in the 5-, 25-, and 100-mg groups, respectively, compared with a mean reduction of 6.4 mg/dL in the placebo group ($p < 0.05$ for each treatment group compared with placebo). Significant decreases in postoral glucose tolerance test (OGTT) glucose excursions were demonstrated in dapagliflozin-treated subjects with overall reduction at day 13 of 17.6 to 22.6% AUC ($p < 0.001$). Urinary glucose excretion increased in a dose-dependent fashion in dapagliflozin-treated subjects and showed no change in placebo-treated subjects. Urinary glucose clearance increased in all dapagliflozin-treated subjects in a dose-dependent manner with the 5-, 25-, and 100-mg doses inhibiting 20%, 41%, and 44%, respectively, of filtered glucose, respectively, from being reabsorbed on day 14 of the study. There were no changes demonstrated in serum insulin levels, serum c-peptide levels, or body weight.[32]

This is the first clinical trial to demonstrate statistically and clinically significant glycemic improvement with dapagliflozin in patients with type 2 diabetes. Although clinically meaningful reductions in FPG and OGTT glucose excursions were demonstrated along with a favorable tolerability profile in the study, there are several limitations to the data. The trial duration (14 days) was insufficient to allow for a meaningful comparison of A1C from baseline to study end. As the primary marker of glycemic control, the A1C data would be more applicable to clinical practice and an overall efficacy assessment. In addition, the short study duration also limits the ability to draw conclusions regarding long-term safety of the product.

A second Phase 2 study was conducted by List et al.[30] in drug-naïve patients with type 2 diabetes. This was a prospective, 12-week, randomized, parallel-group, double-blind, placebo-controlled study. A total of 389 subjects were randomized in equal numbers to receive once-daily dapagliflozin at doses of 2.5, 5, 10, 20, or 50 mg; metformin XR 750 mg with forced-dose titration to 1500 mg at week 2; or placebo. Enrolled subjects were between 18 and 79 years of age with A1C 7–10%, c-peptide less than 1 ng/mL, BMI 40 kg/m² or less, glomerular filtration rate (GFR) greater than 60 mL/min/1.73 m², and urine microalbumin/creatinine ratio 300 mg/g or less.

Forty-one subjects discontinued the trial, with the most common reason being withdrawal of consent (n = 12). Ten subjects discontinued the trial due to AEs with the following breakdown (1 in placebo group, 1 in 2.5-mg group, 3 in 10-mg group, 2 in 20-mg group, 2 in 50-mg group, and 1 in metformin

Table 1. Summary of Phase 2 Clinical Trial Efficacy Endpoints

Reference	Dosing	Endpoints	Results
Komoroski (2009)[31]	5 , 25, 100 mg vs placebo	FPG	↓ 19–39 mg/dL[a]
		OGTT AUC	↓ 17–23%[a]
		glucose clearance	37–81 g/day
List (2008)[30]	2.5, 5, 10, 20, 50 mg vs placebo vs metformin	A1C	↓ 0.55–0.9%[a]
		FPG	↓ 16–31 mg/dL[a]
		PPG AUC	↓ 7000–10,000 mg• min/dL[a]
		A1C <7%	↑ 23–31%[b]
		glucose clearance	52–85 g/day
		body weight	↓ 2.5–3.4%[a]

A1C = hemoglobin A_{1C}; AUC = area under the curve; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; PPG = postprandial glucose.
[a]Statistically significant vs placebo ($p < 0.05$).
[b]$p < 0.05$ for 50-mg dose only.

group). Overall, dapagliflozin was well tolerated by subjects completing the trial, with AEs reported in similar frequencies between all groups. No serious AEs or deaths were observed. Hypoglycemia was reported in 6–10% of dapagliflozin-treated patients compared with 4% for placebo and 9% for metformin. These events were not found to be dose-related in the dapagliflozin-treated patients and there were no fingerstick glucose values less than or equal to 50 mg/dL. Urinary tract infections were observed in dapagliflozin treatment groups at a rate of 5–12% with no dose relationship compared with 6% for placebo and 9% for metformin. Two percent to 7% of dapagliflozin-treated subjects reported other genitourinary infections as compared with 0% in the placebo group and 2% in the metformin group.[30]

Efficacy parameters in the study included change in A1C, FPG, postprandial glucose (PPG) AUC, proportion of patients achieving A1C less than 7%, urinary glucose excretion, and body weight. From baseline to week 12, all dapagliflozin groups demonstrated significant improvement in the primary outcome with mean reductions in A1C versus placebo of 0.55–0.9% in dapagliflozin-treated subjects ($p < 0.05$ for all dapagliflozin doses vs placebo), 0.18% in placebo subjects, and 0.73% in metformin-treated subjects. Significant reduction in FPG was demonstrated as early as week 1 of the study and was sustained through week 12, with mean reductions of 16–31 mg/dL in dapagliflozin-treated subjects compared with 6 mg/dL in placebo subjects ($p < 0.05$ for all dapagliflozin doses vs placebo) and 18 mg/dL in metformin-treated subjects. FPG reduction was dose-related and was statistically significant for all doses 5 mg and greater when compared with placebo. PPG AUC was also significantly reduced from baseline in dapagliflozin-treated groups compared with placebo with adjusted mean reductions of 7053–10149 mg•min/dL. Up to 59% of patients in the dapagliflozin treatment arms achieved A1C less than 7% compared with 32% in the placebo group and 54% in the metformin group. Urinary glucose excretion increased in all dapagliflozin-treated subjects as anticipated based on previous studies. Interestingly, total body weight was reduced in all study arms with mean percent reductions at week 12 of 2.5–3.4% in dapagliflozin arms versus 1.2% in placebo and 1.7% in the metformin group.[30]

This was the second trial to demonstrate clinically relevant improvement in glycemic parameters for patients with type 2 diabetes treated with dapagliflozin. The results of this study include significant reductions in A1C, as well as an increase in the proportion of patients achieving A1C less than 7%. These outcomes can be easily interpreted as meaningful in clinical practice. The reduction in body weight observed in this trial for dapagliflozin-treated subjects is an interesting finding and may prove to be a very important consideration as this drug entity moves forward in clinical studies and enters clinical practice. The study is also strengthened by the addition of the metformin group as this provides a useful benchmark when assessing the changes observed with dapagliflozin over the 12-week study timeframe. The data remain limited, however, in that 12 weeks is still a relatively short period of time and leaves us with an inability to draw definite conclusions regarding long- or even intermediate-term safety of the agent.

ONGOING PHASE 3 CLINICAL TRIALS

There are numerous ongoing clinical trials evaluating dapagliflozin alone and in combination with various antihyperglycemic agents.[34] These studies are summarized in Table 2.

Table 2. Ongoing Phase 3 Clinical Trials[34]

Design	Pts.	Comparators	Dapagliflozin Doses	Endpoints
R, DB, PC, parallel	inadequate control with insulin	insulin, placebo	2.5, 5, 10 mg	A1C, FPG, PPG, body weight, insulin dose
R, DB, PC	inadequate control with glimepiride	glimepiride, metformin, pioglitazone, rosiglitazone	2.5, 5, 10 mg	A1C, A1C <7%, PPG, body weight
R, DB, parallel	type 2 diabetes	dapagliflozin + metformin vs glipizide + metformin	2.5, 5, 10 mg	A1C, body weight, hypoglycemia
R, DB, PC, parallel	type 2 diabetes, inadequate control with metformin alone	dapagliflozin + metformin vs sitagliptin + metformin	10 mg	body weight, waist circumference, body fat %, BMD
R, DB, parallel	type 2 diabetes	dapagliflozin + metformin vs metformin vs dapagliflozin	5 mg	A1C, FPG, A1C <7%, body weight
R, DB, PC	type 2 diabetes, inadequate control with metformin	dapagliflozin + metformin vs metformin + placebo	2.5, 5, 10 mg	A1C, FPG, A1C <7%
R, DB, PC, parallel	type 2 diabetes, inadequate control with TZD	dapagliflozin + TZD vs placebo + TZD	5, 10 mg	A1C, body weight, PPG, FPG, waist circumference, BMI ≥27 kg/m^2, A1C <7%

A1C = hemoglobin A_{1C}; BMD = bone mineral density; BMI = body mass index; DB = double-blind; FPG = fasting plasma glucose; PC = placebo-controlled; PPG = postprandial plasma glucose; R = randomized; TZD = thiazolidinedione.

Adverse effects

Currently published studies are lacking long-term safety data.[30,32,33] Genetic mutations in SGLT2 cause isolated glycosuria, as does dapagliflozin by blocking this SGLT2 transporter. Those affected with this SGLT2 genetic mutation have normal life expectancies without long-term renal dysfunction or significant health problems, which provides optimism regarding the safety profile of dapagliflozin.[24,28,33] It has been suggested that the SGLT2 inhibition may be beneficial to the kidneys by decreasing the filtered glucose load and the sodium reabsorption.[25] Studies to date have found dapagliflozin to be safe and well tolerated.[30,32,33,35] No serious AEs have been reported and the AEs noted do not appear to be dose related. Reported AEs were most commonly gastrointestinal and occurred more frequently in patients also taking metformin.[32,33] Single- and multiple-dose studies found AEs reported in 21% and 37%, respectively, of patients taking dapagliflozin compared with 35% in placebo group.[33] Common AEs reported include constipation, diarrhea, headache, nausea, and infections.[30,32]

Hypoglycemia does not appear to be a significant factor, as previously discussed. The Phase 1 study reported 2 patients, 1 in the placebo and the other in the 20-mg dapagliflozin group, with mild asymptomatic hypoglycemia (value not defined) during the dose-escalating single-dose study.[33] One Phase 2 study found 2 episodes of hypoglycemia, defined as presence of symptoms and/or glucose less than or equal to 50 mg/dL on multiple occasions.[32] One patient on dapagliflozin 5 mg plus metformin had a blood glucose reading of 39 mg/dL on day 13, while another patient on 25 mg dapagliflozin plus metformin had a blood glucose reading of 75 mg/dL on day 14. Both episodes resolved spontaneously. The second Phase 2 study reported hypoglycemia in 6–10% of dapagliflozin-treated subjects unrelated to dose, 4% in placebo, and 9% in metformin.[30] None of the blood glucose readings fell below 50 mg/dL.

No significant change in electrolytes or renal function have been found with short-term dapagliflozin use.[30,32,35] The Phase 2 studies did not find any clinically meaningful changes in the estimated glomerular filtration rate (eGFR).[30,32] One of these studies reported no change in 24-hour urine excretion of electrolytes after 14 days, with the exception of sodium, which normalized by day 13.[32] It also found no changes in renal tubular markers such as *N*-acetyl-B-D-glucosaminidase and B_2-microglobulin, plasma electrolytes, vital signs, or electrocardiograms. Increases in urinary *N*-acetyl-glucosaminidase (NAG) and α-1-microglobulin (A1M) have been reported with no association of acute kidney injury, which may be explained by glucosuria.[35] The other Phase 2 study attributed the increased urine output, increased blood urea nitrogen (BUN) without a corresponding increase in creatinine, and increased hematocrit to the diuretic effect of dapagliflozin.[30] The urine output increased by a range of 107–470 mL above baseline. The BUN increased with the maximal increase being 2.03 ± 3.72 mg/dL (mean ± SD), which was not dose related. Other changes reported were increase in magnesium (maximal increase of 0.18 ± 0.16 mEq/L) and a decrease in uric acid (maximal decrease 1.14 ± 1.15 mg/dL).

There were some episodes of vulvovaginal and urinary tract infections observed in the dapagliflozin treatment groups, which may warrant further investigation.[30,32] Although patients with diabetes can have substantial glycosuria, it is undetermined whether this additional glucose excretion will promote bacterial growth.[25] A summary of adverse events observed in clinical trials can be found in Table 3.

Drug Interactions

There were no apparent drug interactions with metformin.[32] Dapagliflozin is unlikely to have significant drug interactions with cytochrome P450 or P-glycoprotein substrates, as it is predominantly metabolized by UGT1A9.[33] Further data regarding drug interactions will become available as multiple ongoing studies evaluating the combination of dapagliflozin with insulin, glimepiride, valsartan, simvastatin, and sitagliptin are completed.

Precautions and Contraindications

Currently published investigations have excluded pediatric, geriatric, and pregnant patients from participation; therefore, the efficacy and safety of dapagliflozin in these groups have not been established. Because available clinical trials have also excluded patients with type 2 diabetes who have comorbidities such as significant renal impairment (including macroalbuminuria) and heart disease, further investigations into these populations is warranted, especially considering the frequent occurrence of these comorbidities in patients with diabetes. Although urinary tract and genital infections were similar among dapagliflozin-treated and placebo subjects, the potential for an increase in these infections should continue to be assessed in clinical trials as the long-term safety of this compound is evaluated. Additionally, because dapagliflozin has not been studied in combination with insulin or other

Table 3. Incidence of Adverse Events in Clinical Trials

Adverse Event	Dapagliflozin, %	Placebo, %	Metformin, %
Hypoglycemia	6–10	1-4	9
Vulvovaginal mycotic infection	2–8	0	2
Urinary tract infection	5–12	6	7

insulin-dependent therapies, the potential positive and negative consequences of combination therapy should be carefully evaluated in clinical trials.

Economic Issues

As of June 23, 2009, there were no available data on the cost of dapagliflozin.

Dosage and Administration

Doses of 2.5, 5, 10, 20, and 50 mg have demonstrated efficacy in improving glycemic parameters in Phase 2 clinical trials.[30,32] Phase 3 trials are focusing on doses of up to 10 mg daily.[34] Both pharmacokinetic and clinical data support once-daily dosing of dapagliflozin.[30,32,33] Because the pharmacologic activity of the drug is insulin-independent, it would be expected that the once-daily dose can be taken without regard to food. Further clinical trials evaluating multiple dosing strategies, both as monotherapy and combination therapy, will be useful in confirming or refuting this assessment. As a highly protein-bound drug with minimal renal excretion, it will likely not be necessary to adjust the dose in renal dysfunction.[33] The effects of hepatic dysfunction on dosing are yet to be determined.

Summary

SGLT2 inhibitors represent a novel therapeutic option in the treatment of type 2 diabetes. Dapagliflozin is the first agent within this class with evidence to support clinically meaningful reductions in FPG, PPG, A1C, and body weight. Dapagliflozin appears to be very well tolerated with minimal AEs. The ability of this agent to act independent of insulin action, thereby minimizing hypoglycemia and weight gain, may prove to be a substantial benefit when compared with other available therapies. Oral once-daily dosing is also of great benefit compared with many of the other antihyperglycemic therapies available and, along with these other advantages, may help to establish a niche for this drug. Additionally, based upon the novel mechanism of action, it may prove useful in the treatment of type 1 diabetes, should clinical investigation be pursued. Further studies are warranted to demonstrate safety and efficacy of dapagliflozin in various patient populations and clinical scenarios, including its combination with other therapies used in type 2 diabetes. Furthermore, additional data are needed to establish long-term safety and efficacy of dapagliflozin and to evaluate its impact on morbidity and mortality.

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Dapagliflozina Para el Tratamiento de Diabetes Tipo 2

AM Brooks y SM Thacker

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EXTRACTO

OBJETIVO: Revisar la literatura y describir la farmacología, farmacocinética, eficacia clínica y seguridad de dapagliflozina, un fármaco que actualmente se encuentra en estudios clínicos de fase 3.

FUENTE DE DATOS: Se realizó una búsqueda de la literatura en los sistemas de información MEDLINE (1995–marzo 2009) y en ClinicalTrials.gov utilizando los términos dapagliflozina, inhibidor de SGLT2, inhibición del co-transporte de sodio-glucosa, e inhibición de la reabsorción renal de glucosa. También se revisaron las bibliografías de los artículos obtenidos para identificar referencias adicionales.

SELECCIÓN DE ESTUDIOS Y OBTENCIÓN DE LA INFORMACIÓN: Se incluyeron todos los informes publicados en el idioma inglés que evaluaban dapagliflozina, incluyendo resúmenes, y presentaciones científicas.

SINTÉSIS DE LOS DATOS: Se están evaluando nuevas estraterias terapéuticas para el tratamiento de pacientes con diabetes mellitus tipo 2 debido al aumento en la prevalencia de esta condición, el manejo subóptimo de la misma asociado con hiperglucemia, la morbilidad, y mortalidad relacionadas con diabetes y a las limitaciones de los tratamientos actualmente disponibles. Dapagliflozina es el primer inhibidor del co-transportador 2 de sodio-glucosa que actúa regulando la reabsorpción renal de glucosa. La información de estudios clínicos es limitada pero la evidencia disponible sugiere que este medicamento reduce significativamente las concentraciones plasmáticas de glucosa en ayuna, las concentraciones plasmáticas post-prandiales de glucosa, el A1c, y el peso del paciente. Además dapagliflozina ha demostrado excelente tolerabilidad con los datos obtenidos de seguridad en los estudios de fase 1 y fase 2. Los efectos adversos más comunes informados han sido estreñimiento, diarrea, dolor de cabeza, nauseas, e infecciones. Hipoglucemia aparenta no ser un problema significativo.

CONCLUSIONES: Dapagliflozina representa el primer medicamento en una nueva clase de agentes que pueden ser una opción prometedora en el tratamiento de pacientes con diabetes tipo 2. Los resultados de los estudios clínicos de fase 3 son necesarios para demostrar la eficacia y seguridad de este agente en diversas poblaciones de pacientes y escenarios clínicos.

Traducido por Mirza Martínez

Le Dapagliflozin dans le Traitement du Diabète de Type 2.

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RÉSUMÉ

OBJECTIF: Réviser la documentation scientifique et décrire la pharmacologie, les données pharmacocinétiques, l'efficacité clinique, et la sécurité du dapagliflozin, un produit actuellement en essai clinique de phase 3.

REVUE DE LITTÉRATURE: Une recherche de documentation a été réalisée via MEDLINE (1995–mars 2009) et ClinicalTrials.gov en utilisant les mots clé suivants: dapagliflozin, SGLT2 inhibitor, sodium-glucose co-transport inhibition et renal glucose re-absorption inhibition. Les bibliographies des articles identifiés ont aussi été utilisées pour identifier des références utiles.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Tous les comptes-rendus de langue anglaise évaluant le dapagliflozin ont été inclus dans cette révision, y compris les résumés et les présentations scientifiques.

RÉSUMÉ: De nouvelles stratégies thérapeutiques sont nécessaires pour le traitement du diabète de type 2 étant donné l'augmentation de la prévalence du diabète, la gestion sous optimale de l'hyperglycémie associée, la morbidité et la mortalité associée à la maladie et les limites des thérapies actuellement disponibles. Le dapagliflozin est le premier inhibiteur sélectif du co-transporteur sodium-glucose 2 lequel fonctionne en contrôlant la réabsorption rénale du glucose. Les données cliniques sont limitées mais des éléments de preuve disponibles supportent des diminutions cliniquement significatives avec cet agent des glycémies à jeun, des glycémies post prandiales, de l'A_{1c} et du poids corporel. De plus, une excellent tolérance a été démontrée tant dans les études de phase 1 que dans les études de phase 2.

CONCLUSIONS: Le dapagliflozin est le premier d'une nouvelle classe d'agents pouvant représenter une option thérapeutique prometteuse du diabète de type 2. Les résultats des études de phase 3 en cours sont nécessaires pour démontrer l'efficacité et la sécurité de cet agent chez diverses populations et dans divers scénarios cliniques.

Traduit par Marie Larouche