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Dapagliflozin: A Review

Morgan Long, PharmD Candidate

In the last two decades the incidence of diabetes has risen sharply among all ages, genders, and racial/ethnic groups in the United States.[1] Presently in the United States, diabetes and prediabetes affect over 26 million and 79 million people, respectively.[1] Diabetes continues to increase in prevalence throughout the world as recent estimates predict that 366 million people have diabetes with another 280 million people at high risk of developing it.[2] The vast majority of diagnosed cases, 90-95%, are type 2 diabetes.[3]

Current guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists include many types of anti-diabetes medications. These medications have mechanisms of action which range from improving insulin sensitivity to stimulating insulin secretion, exogenously providing insulin, and others. Despite the numerous and varied treatment options, the majority of patients with type 2 diabetes do not reach their therapeutic goal.[4] Many reasons exist for the suboptimal performance of current therapy including effects on comorbid conditions, hypoglycemia, gastrointestinal side effects, and the loss of efficacy over prolonged use due to the progressive nature of the disease.[5]

Achieving glycemic control is important as the disease substantially impacts quality of life. Uncontrolled diabetes is linked to complications including diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease including stroke. The United Kingdom Prospective Diabetes study demonstrated that controlling diabetes has significant impact on microvascular complications, and that for every one percent reduction in hemoglobin A1C there is a 35% reduction in the risk of these complications.[6]

Diabetes is predicted to increase in prevalence with associated complications and economic cost. A 2010 study predicted that one of every three adults in the United States could be diagnosed with diabetes by 2050.[7] In 2012, the calculated cost of diabetes in the United States was $245 billion, including lost productivity and direct medical care.[8] These costs are expected to rise with increased prevalence of the disease.[8]

On January 8, 2014 the FDA approved Farxiga® (dapagliflozin) manufactured by AstraZeneca Pharmaceuticals to improve glycemic control along with diet and exercise, in adults with type 2 diabetes. It shares a mechanism of action with canagliflozin, sodium-glucose co-transporter 2 (SGLT2) inhibition, thereby blocking reabsorption of glucose in the kidneys. This article will review the pharmacology, clinical trials, dosing, and adverse events associated with dapagliflozin.

Pharmacology

Pharmacodynamics

Sodium-glucose transporters are found throughout the body. Sodium-glucose transporter 1 (SGLT1) is the most prevalent and is the primary gastrointestinal glucose transporter but it is

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responsible for a relatively minor, 10%, amount of renal tubular glucose reabsorption. In contrast, SGLT2 is almost exclusively expressed in the renal cortex in the luminal surface of the proximal tubule and is responsible for 90% of the renal tubule glucose reabsorption.[9]

In disease free individuals, 180 grams of glucose daily enters the kidneys mostly through the glomeruli and is 90% reabsorbed in the proximal tubule. In diabetes, as plasma glucose levels rise and the rate of glucose entering the nephron reaches above 260-350 mg/min/1.73m^2 the enzymes become saturated and result in glucose in the urine.[9]

Dapagliflozin inhibits SGLT2 selectively, potently, and reversibly which results in a decreased renal reabsorption of glucose and an increased urinary glucose excretion, ultimately reducing blood glucose levels by an insulin-independent mechanism.[10] A study using dapagliflozin doses ranging from 2.5 mg to 500 mg in healthy subjects demonstrated that glucosuria is a dose dependent process.[11] The selectivity associated with dapagliflozin in vitro for SGLT2 was 1200-fold greater than for SGLT1, and the inhibition constant is 3000-fold lower for SGLT1 than SGLT2.[10]

Pharmacokinetics

The oral bioavailability of dapagliflozin is 78%.[12] While dapagliflozin can be taken without regard to meals, it is recommended to take in the morning before meals for a maximal effect on postprandial glucose levels. Under a fasting state the maximal plasma concentration occurs in 2 hours, however administration with a high fat meal can prolong time to maximal concentration by one hour.[12] In vitro studies indicate that dapagliflozin is 91% bound to plasma proteins and binding is not affected by renal or hepatic dysfunction.[10]

Dapagliflozin is primarily metabolized by O-glucuronidation by uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) enzyme to yield dapagliflozin 3-O-glucuronide, an inactive metabolite that is more water soluble than its parent drug.[10] CYP enzyme mediated metabolism is a minor component of the clearance pathway. Dapagliflozin and its metabolites are primarily eliminated by the renal system.[12]

In a study using 50 mg of radioactive dapagliflozin, 61% of the drug was converted to dapagliflozin 3-O-glucuronide, and 75% of the dose was excreted in the urine and feces with less than 2% of the urine excretion being the parent compound.[12] The terminal half-life is 12.9 hours for a single 10 mg dose.[12]

Special Populations

No dose adjustment is required for age, sex, race, or body weight.[12]

The efficacy and effectiveness of dapagliflozin is reduced in renal impairment. It is recommended that in patients with an eGFR below 60 ml/min/1.73m^2 dapagliflozin should not be initiated.[10] For patients already taking dapagliflozin if eGFR remains persistently below 60 mL/min/1.73m^2 dapagliflozin should be discontinued. Patients with moderate and severe renal impairment have a 2.04- fold and 3.03-fold higher systemic exposure to dapagliflozin than diabetics with normal renal function.[12]

Patients with moderate hepatic impairment (Child-Pugh class B) have a 12% and 36% increase in Cmax and AUC respectively, which is not clinically meaningful.[12] Patients with severe hepatic impairment (Child-pugh class C) have a 40% and 67% increase in Cmax and AUC, respectively which may be signinficant.[12] A risk and benefit analysis should be conducted before initiation of dapagliflozin in patients with severe hepatic impairment as safety and efficacy has not been specifically studied in this population.[10]

Drug-Drug Interactions

Neither dapagliflozin nor its metabolite dapagliflozin 3-O-glucuronide inhibit or induce cytochrome P450 enzymes.[12] Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucurnonide is a substrate for the organic anion transporter 3 (OAT-3).[12] Monitoring of volume status should be done when dapagliflozin is administered with a loop diuretic due to the synergistic mechanisms on volume depletion.[10]

Clinical Trials

The development of dapagliflozin has included

over 24 clinical trials to evaluate safety and efficacy. Five phase III trials studying dapagliflozin 5 mg or 10 mg were randomized, double-blinded, multicenter, and placebo-controlled. All used the same primary outcome of percent change in A1C from baseline to 24 weeks.[13-17] The trials encompassed treatment naïve patients using dapagliflozin versus placebo or active control as monotherapy. Trials also studied dapagliflozin in treatment experienced patients as add-on therapy compared to placebo or active control in patients with inadequate glycemic control already on metformin, glimepiride, pioglitazone, or a high dose insulin regimen.

The five trials included patients at least 18 years old, that had inadequate glycemic control defined as A1C 7-10% [13,14,15], ≥7 to ≤10.5[16], or ≥ 7.5 to ≤10.5.[17] All the trials except Stojerk et al. required the BMI to be ≤45 kg/m^2.[16] The mean time from diagnosis varied. Patients on monotherapy had been diagnosed ≤0.5 years, while the non-insulin combination trials averaged 5.1-7.7 years, and the patients using insulin averaged 13.1-14.2 years post-diagnosis.[10] Exclusion criteria were similar for all the trials: type 1 diabetes, severe diabetes, and impairments in liver or renal function. These and other phase III trials that used long-term primary endpoints or that used lower doses of dapagliflozin are reported in **Table 1.**[13-23]

Monotherapy

Over a 24 week study period, dapagliflozin 2.5 mg, 5 mg, and 10 mg were evaluated as add-on

Table 1 | Selected Phase III Clinical Trials of Dapagliflozin

Study	Design	Arms	N	Mean % change in A1C from baseline	A1C >7%	Change FPG (mmol/L)	Weight (%)	Hypoglycemia (%)
Ferrannini et al.[13]	24 wk R, DB, PC	1. PL 2. DAPA 2.5 mg 3. DAPA 5 mg 4. DAPA 10 mg	1. 75 2. 65 3. 64 4. 70	1. -0.23 2. -0.58 3. -0.77 4. -0.89	1. 41% 2. 44% 3. 51% 4. 32%	1. -0.2 2. -0.8 3. -1.3 4. -1.6	1. -2.2 2. -3.3 3. -3.8 4. -3.2	1. 2.7 2. 1.5 3. 0 4. 2.9
Bailey et al. [19]	24 wk R, DB, PC	1. PL 2. DAPA 1 mg 3. DAPA 2.5 mg 4. DAPA 5 mg	1. 68 2. 72 3. 74 4. 68	1. 0.02 2. -0.68 3. -0.72 4. -0.82	1. 34.6% 2. 53.6% 3. 43.4% 4. 49.1%	1. +0.23 2. -0.61 3. -1.20 4. -1.58	1. -0.96 2. -2.69 3. -2.64 4. -2.69	1. 0 2. 0 3. 1.4 4. 1.5
Bailey et al.[14]	24 wk R, DB, PC, MC	1. PL + MET 2. DAPA 2.5 mg + MET 3. DAPA 5 mg + MET 4. DAPA 10 mg + MET	1. 137 2. 137 3. 137 4. 135	1. -0.30 2. -0.67 3. -0.70 4. -0.84	1. 25.9% 2. 33% 3. 37.5% 4. 40.6%	1. -0.3 2. -1.0 3. -1.2 4. -1.3	1. -0.9 2. -2.2 3. -3.0 4. -2.9	1. 3 2. 2 3. 4 4. 4
Bailey et al.[23]	102 wk long term extension of 24 wk PC trial	1. PL + MET 2. DAPA 2.5 + MET 3. DAPA 5 mg + MET 4. DAPA 10 mg + MET	1. 137 2. 137 3. 137 4. 135	1. 0.02 2. -0.48 3. -0.58 4. -0.78	1. 15.4% 2. 20.7% 3. 26.4% 4. 31.5%	1. -0.58 2. -1.07 3. -1.47 4. -1.36	1. 1.36 2. -1.10 3. -1.70 4. -1.74	1. 5.8 2. 3.6 3. 5.1 4. 5.2
Nauck et al.[18]	52 wk R, DB, AC, MC	1. DAPA 2.5 mg titrated +MET 2. GLIP 5 mg titrated + MET	1. 406 2. 408	1. -0.52 2. -0.52	1. 27.4% 2. 32%	1. -1.24 2. -1.04	1. -3.22 2. 1.44	1. 3.5 2. 39.7

PL= placebo, DAPA=dapagliflozin, MET= metformin, GLIP=glipizide, MET XR= metformin extended release, PIO= pioglitazone, INS= insulin, SIT= sitagliptin, wk= week, A1C= hemoglobin A1C, FPG= fasting plasma glucose, GLIM= glimepride, R= randomized, DB= double blind, PC= placebo controlled, AC= active controlled, MC= multi centered NR= not reported

Table 1 Continued | Selected Phase III Clinical Trials of Dapagliflozin

Study	Design	Arm	N	Mean % change in A1C from baseline	A1C >7%	Change FPG (mmol/L)	Weight (%)	Hypoglycemia (%)
Henry et al.[20]	24 wk study 1 R, DB, PC, MC 24 wk study 2 R, DB, PC, MC	1. MET XR + PL 2. DAPA 5mg + PL 3. DAPA 5mg + MET XR 4. MET XR + PL 5. DAPA 10mg + PL 6. DAPA 10 mg + MET XR	1. 195 2. 196 3. 185 4. 203 5. 216 6. 202	1. -1.35 2. -1.19 3. -2.05 4. -1.44 5. -1.45 6. -1.98	1. 34.6% 2. 22.5% 3. 52.4% 4. 35.2% 5. 31.7% 6. 46.6%	1. -1.7 2. -2.2 3. -3.4 4. -1.9 5. -2.5 6. -3.3	1. -1.29 2. -2.61 3. -2.66 4. -1.36 5. -2.73 6. -3.33	1. 0 2. 0 3. 2.6 4. 2.9 5. 0.9 6. 3.3
Strojek et al.[16]	24 wk R, DB, PC, MC	1. PL+ GLIM 2. DAPA 2.5 mg + GLIM 3. DAPA 5 mg + GLIM 4. DAPA 10 mg + GLIM	1. 145 2. 154 3. 142 4. 151	1. -0.13 2. -0.58 3. -0.63 4. -0.82	1. 13% 2. NR 3. 30.3% 4. 31.7%	1. -0.1 2. -0.9 3. -1.2 4. -1.6	1. -0.7 2. -1.2 3. -1.6 4. -2.3	1. 4.8 2. 7.1 3. 6.9 4. 7.9
Rosenstock et al.[15]	24 wk + 24 wk extension R, DB, PC	1. PL+ PIO 2. DAPA 5 mg + PIO 3. DAPA 10 mg +PIO	1. 139 2. 141 3. 140	1. -0.42 2. -0.82 3. -0.97	NR NR NR	1. -0.3 2. -1.4 3. -1.6	1. 1.6 2. 0.1 3. -0.1	NR NR NR
Wilding et al. [17]	24 wk + 24 wk extension R, DB, PC, MC	1. PL+ INS 2. DAPA 2.5 mg + INS 3. DAPA 5 mg + INS 4. DAPA 10 mg + INS	1. 193 2. 202 3. 211 4. 194	1. -0.39 2. -0.79 3. -0.89 4. -0.96	NR NR NR NR	1. NR 2. -0.7 3. -1.1 4. -1.1	1. 0.4 2. -0.9 3. -1.0 4. -1.6	1. 51.8 2. 60.4 3. 55.7 4. 53.6
Wilding et al.[22] (Abstract)	104 wk R, DB, PC	1. PL + INS 2. DAPA 2.5 mg + INS 3. DAPA 5 mg + INS 4. DAPA 10 mg + INS	1. 197 2. 203 3. 212 4. 196	1. -0.43 2. -0.64 3. -0.82 4. -0.79	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR
Jabbour et al. [21] (Abstract)	24 wk R, DB, PC, MC	1. PL + SIT 2. DAPA 10mg + SIT 3. PL+ SIT + MET 4. DAPA 10mg+SIT+ MET	1. 111 2. 110 3. 113 4. 113	1. 0.10 2. -0.50 3. 0.0 4. -0.40	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR

therapy to diet and exercise.[13] Reduction in A1C was apparent by week 4 and was shown to be dose-dependent. Dapagliflozin 5 mg and 10 mg reduced A1C at 24 weeks compared to placebo (p<0.0001). A1C reductions with dapagliflozin 2.5 mg, 5 mg, and 10 mg ranged from -0.58 to -0.89 compared with -0.23 with placebo, leading to a higher percentage of patients achieving A1C <7% (p=0.1775, p=0.0275, p=0.0062, respectively). Fasting plasma glucose (FPG) reductions were observed at week 1 and at week 24 for dapagliflozin 5 mg and 10 mg (p<0.0001). While mean body weight decreased in the dapagliflozin 5 mg and 10 mg groups, there were no statistically significant differences compared to placebo. No statistical differences were found between cohorts dosed in the evening versus morning in A1C, FBG, or weight reduction. However, numerically greater reductions in both A1C and FPG were found in the cohort that had higher baseline A1C's (10.1-12%).[13]

Dual Therapy

Dapagliflozin was used as an add-on therapy with standard anti-diabetic agents including metformin, metformin XR, glimepride, pioglitazone, and insulin in a variety of studies.

When combined with metformin there were reductions in A1C of -0.67 (p<0.00002), -0.70 (p<0.0001), and -0.84 (p<0.0001) for dapagliflozin 2.5 mg, 5 mg, and 10 mg respectively.[14] Dapagliflozin 5 mg and 10 mg achieved A1C <7% in 37.5% and 40.6 % (p< 0.0275 and 0.0062), respectively, versus placebo of 25.9%.[14] Mean FPG levels were reduced by 0.99 (p=0.0019), 1.19 (p<0.0001), and 1.30 (p<0.0001) for dapagliflozin 2.5 mg, 5 mg and 10 mg, respectively.[14]

When combining dapagliflozin with extended release metformin titrated to 2000 mg/day, the combination achieved greater reductions in A1C over 24 weeks than monotherapy with either agent (p< 0.0001).[20] A non-inferiority trial with metformin in combination with glipizide titrated up to 20 mg or metformin in combination with dapagliflozin titrated up to 10 mg found no statistically significant difference in A1C change at one year.[18] Body weight was reduced 3.22 kg for dapagliflozin versus an increase of 1.44 kg for glipizide (p< 0.0001).[18]

Dapagliflozin added to glimepride 4 mg/day achieved reductions in mean A1C at 24 weeks for all dapagliflozin doses (p<0.0001).[16] Dapagliflozin 5 mg and 10 mg reduced FPG (p<0.0001), increased the proportion of patients achieving A1C <7% (p=0.0001 and p<0.0001, respectively), and reduced post-prandial glucose (PPG) in response to an oral glucose-tolerance test (p=0.0002 and p<0.001, respectively).[16]

Dapagliflozin 5 mg and 10 mg added to pioglitizone 30-45 mg/day achieved reductions in mean A1C at 24 weeks compared to placebo (p=0.0007 and p<0.0001, respectively).[15] This reduction was maintained during the 24 week extension study. At 24 weeks both dapagliflozin regimens were superior to placebo in reducing FPG (p<0.0001) and weight (p<0.0001). All cohorts gained weight in the 24 week extension study, but participants on dapagliflozin gained less weight than those on monotherapy with pioglitazone.[15]

Dapagliflozin 2.5 mg, 5 mg, or 10 mg daily added to a stable insulin regimen (≥30 units/day) and up to two oral anti-diabetic agents achieved greater reductions in mean A1C at 24 weeks compared to placebo. These reductions were maintained in the 24 week extension study.[17] Reductions were also seen in FPG and mean body weight. Insulin requirements were not effected by the addition of dapagliflozin, but those receiving insulin monotherapy required a progressive insulin dosage increase.[17] A 104 week study demonstrated reductions in A1C were maintained long term with the addition of dapagliflozin to insulin.[22]

Adverse Events

The most common adverse effects of dapagliflozin are listed in **Table 2** which represents data from 12 phase IIb/III trials encompassing 4684 patients.[24] The incidence of hypoglycemia, urinary tract infections (UTI), and events of genital infections are more common with dapagliflozin versus placebo.[24] Dapagliflozin can increase the rate of hypoglycemia when used in combination with other agents that cause hypoglycemia. The increase in UTI and genital infections is a mechanistic effect, as dapagliflozin increases glucose concentrations in the urine.[10] Infections were shown to respond well to common antibiotics and were

not a common reason for treatment discontinuation.[24]

Reductions in systolic/diastolic blood pressure of 4/2 mm Hg were observed for dapagliflozin versus 0.9/0.5 mmHg with placebo. There was no increase in reported orthostatic hypotension.[24] Volume depletion was reported for 0.6-1.2% of dapagliflozin treated patients versus 0.4% for placebo; minor increases in magnesium and potassium accompanied this change.[24]

Across all clinical studies, four cases of bladder cancer were reported with dapagliflozin used for less than one year compared to zero cases for placebo.[12] Currently 17,000 people are being enrolled in the DECLARE-TIMI 58 trial to access if dapagliflozin is associated with increased cardiovascular risk, liver insufficiencies, and cancers. [10]

Dosing

Dapagliflozin is available in 5 mg and 10 mg tablets for oral administration. The recommended starting dose is 5 mg once daily taken in the morning with or without food. In patients that require additional glycemic control and who are tolerating dapagliflozin 5 mg the dose can be increased to 10 mg once daily in the morning with or without food. Volume depletion should be corrected prior to initiation.

Table 2 | Safety summary: short-term double-blind placebo-controlled pool[24]

	Placebo N=1393	DAPA 2.5 mg N=814	DAPA 5 mg N=1145	DAPA 10 mg N=1193
Hypoglycemia ≥ 1 Event No. (%)	112 (8.0)	133 (16.3)	130 (11.4)	128 (10.7)
Incidence of UTI	3.7%	3.6%	5.7%	4.3%
Incidence of genital infections	0.9%	4.1%	5.7%	4.8%

DAPA= dapagliflozin, UTI= Urinary tract infections

Costs

The average monthly retail price obtained from an informal telephone survey of three different national chain pharmacies for dapagliflozin 5 mg or 10 mg was found to be $343.99 ($335.99 - $351.95) for either dose. The average cost for a year supply without insurance is $4127.88.

Summary

Dapagliflozin is the second SGLT2 inhibitor approved for use in the United States. It is indicated by the FDA along with diet and exercise to help improve glycemic control in adults with type 2 diabetes. In 24 clinical trials, it has proven to improve A1C versus placebo or was non-inferior to other anti-diabetic medications. The recommended starting dose is 5 mg daily in the morning with or without food. Dapagliflozin's mechanism of action allows for an additional oral treatment option in type 2 diabetic patients with the benefit of weight loss and a low risk for hypoglycemia. However, this same mechanism of action is responsible for the increase prevalence of UTI and genital infections.

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