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Empagliflozin (Jardiance®), A New SGLT2 Inhibitor to Treat Type 2 Diabetes: Third Time's A Charm?

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The worldwide prevalence of diabetes has increased at an unprecedented rate. According to the Centers for Disease Control and Prevention, more than 29 million Americans, or 9.3% of the United States population has this disease.[1] The prevalence of type 2 diabetes mellitus (T2DM) has more than tripled in the past 30 years.[2] If current trends continue, an alarming 1 in 3 American adults could have diabetes by 2050.[3] Additionally, in 2012, diabetes cost the U.S. healthcare system an estimated $245 billion, a 41% increase from 2007 estimates.[4] This substantial economic burden will likely continue to increase concurrent with the expected increase in the disease prevalence. These staggering projections are due, in part, to an aging population, increasing number of high-risk minorities, and the continuing obesity epidemic.

Despite the numerous therapy options currently available for patients, adequate glycemic control is still a challenge for most. Additionally, undesirable side effects limit the use of many current treatments. For example, 63% of metformin-treated patients experience GI problems, while hypoglycemia events occur in up to 20% of sulfonylurea-treated patients.[5] These side effects can reduce treatment adherence, putting patients at risk for increased HbA1c and accompanying diabetic complications.

The kidney's role in the pathophysiology of diabetes involving regulating plasma glucose levels has long been underutilized as a focus of drug therapy in diabetes. This gap has recently been filled with the development of sodium glucose co-transporter 2 SGLT2 inhibitors. The first drugs approved from this novel drug class include canagliflozin (Invokana®; Janssen Pharmaceuticals, Inc.) and dapagliflozin (Farxiga®; AstraZeneca and Bristol-Myers Squibb Company). On August 1, 2014, empagliflozin (Jardiance ®; Boehringer Ingelheim Pharmaceuticals, Inc.'s) was granted an FDA-approved indication to improve glycemic control in adults with type 2 diabetes as an addition to diet and exercise.[6] The purpose of this review is to detail the pharmacology and pharmacokinetics of this latest addition to the SGLT2 inhibitor drug class, evaluate the clinical evidence leading to its approval, and to compare and contrast the currently available SGLT2 inhibitors.

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Regulation of blood glucose can be influenced significantly by kidney function, specifically by renal glucose uptake, renal gluconeogenesis and tubular glucose reabsorption. In a healthy adult, an estimated 180 grams of glucose is filtered by the glomeruli, with the majority reabsorbed from the glomerular filtrate and returned to the bloodstream.[7] This action is mediated in part by SGLTs located in the luminal surface of epithelium in the proximal convoluted tubule. Specifically, SGLT2, a high-capacity, low-affinity transporter uniquely expressed in the kidney, is responsible for the majority (90%) of glucose reabsorption from glomerular filtrate.[7]

In individuals with T2DM, renal glucose handling is increased and this reabsorption process contributes to elevated serum glucose levels. In part, this increased reabsorption appears to be due to an up-regulation of SGLT2 that has been observed in renal cells extracted from patients with T2DM, leading to increased glucose transport compared to healthy individuals.[8] The threshold for glucose excretion in the urine is changed and therefore, glucosuria does not occur until serum glucose levels are higher than the levels at which a normal individual excretes glucose into urine. By inhibiting SGLT2 transporters, glucose reabsorption is suppressed and urinary glucose excretion is increased, reducing serum glucose concentrations. The SGLT2 inhibitors, including empagliflozin, function independently of insulin.

The various pharmacokinetic characteristics of empagliflozin are summarized in Table 1. No major metabolites have been detected in human plasma following empagliflozin administration.[9]

Drug Interactions

Co-administration of diuretics can result in increased urine volume and frequency of voids, potentially exacerbating volume depletion and symptomatic hypotension. Concomitant use of insulin or insulin secretagogues with empagliflozin may increase the risk of hypoglycemia; the insulin dose may need to be decreased with increased frequency of blood glucose monitoring.[9]

Clinical Trials

Empagliflozin has been studied both as stand-alone therapy and in combination with metformin, pioglitazone, sulfonylureas, and insulin.[10-16] Studies evaluating the safety and efficacy of empagliflozin in diabetic patients with mild-to-moderate renal impairment were also conducted.[17] The studies enrolled patients aged 18 years or older with a body mass index (BMI) ≤45 kg/m^2. The

TABLE 1 | Pharmacokinetics characteristics of empagliflozin.[9]

Characteristic	Empagliflozin
Absorption	
T_{max}	1.5 hours
Effect of food	Following high-fat and high-calorie meal: AUC reduced by ~16% and C_{max} reduced by ~37%
Distribution	
V_d	73.8 L
Protein Binding	86.2%
Metabolism	Glucuronidation by uridine 5'-diphospho-glucuronosyltransferases (UGTs): UGT2B7, UGT1A3, UGT1A8, UGT1A9
Elimination	
Half-life	12.4 hours
Fecal (%)	41.2%
Renal (%)	54.4%
Clearance	10.6 L/hour

C_{max} = maximum concentration; **T_{max} =** time to maximum concentration; **UGT =** uridine 5'-diphospho-glucuronosyltransferases; **V_d =** volume of distribution.

primary endpoint in all studies was the change from baseline in HbA1c with secondary endpoints including change from baseline in body weight, fasting plasma glucose (FPG) and systolic blood pressure. Selected clinical trials are listed in TABLE 2.

Monotherapy

To evaluate the efficacy and safety of empagliflozin as monotherapy, a randomized, double-blind, placebo-controlled study of 12 weeks' duration was conducted with a total of 408 patients.[10] Eligible subjects were adults of a median age of 58 years with treatment-naïve diabetes or were receiving 1 antidiabetic medication and underwent a 4-week washout period. Enrolled subjects were randomly assigned to one of four treatment groups: empagliflozin 5 mg daily, empagliflozin 10 mg daily, empagliflozin 25 mg daily, or matching placebo. At week 12, results with all empagliflozin treatments showed statistically significant reductions from baseline in HbA1C, FPG, and body weight (TABLE 2).

Combination Therapy

Empagliflozin was studied in combination therapy with metformin,[12,16] metformin plus sulfonylura,[13] pioglitazone with or without metformin,[14] and insulin.[15] Empagliflozin demonstrated a greater reduction in HbA1c, FPG and body weight compared to matching placebo (TABLE 2). Reductions in systolic and diastolic blood pressure were also observed with empagliflozin treatment compared to placebo.

TABLE 2 | Selected clinical trials of empagliflozin.[10-16]

Study	Design	Arms	ΔHbA1c(%)	ΔFPG (mg/dl)	ΔWt (kg)
Monotherapy vs. PBO (Ferrannini, et al; 2013[10])	12 weeks; R, DB, PC; n=408	PBO	+0.1	+0.04	-0.75
		EMP 5 mg	-0.4	-1.29	-1.81
		EMP 10 mg	-0.5	-1.61	-2.33
		EMP 25 mg	-0.6	-1.72	-2.03
Monotherapy vs. PBO vs. SITA (Roden, et al; 2013[11])	24 weeks; R, DB, PC; n=762	PBO	+0.08	+11.7	-0.33
		EMP 10 mg	-0.66	-19.5	-2.26
		EMP 25 mg	-0.78	-25.5	-2.48
		SITA 100 mg	-0.66	-6.8	+0.18
Add-on with MET (Häring, et al; 2013[12])	24 weeks; R, DB, PC; n=637	PBO + MET	-0.13	+6.38	-0.45
		EMP 10 mg + MET	-0.70	-20.04	-2.08
		EMP 25 mg + MET	-0.77	-22.28	-2.46
Add-on with MET + SU (Häring, et al; 2013[13])	24 weeks; R, DB, PC; n=666	PBO + MET + SU	-0.17	+5.52	-0.39
		EMP 10 mg +MET + SU	-0.82	-23.3	-2.16
		EMP 25 mg +MET + SU	-0.77	-23.27	-2.39
Add-on with PIO ± MET (Kovacs, et al; 2014[14])	24 weeks; R, DB, PC; n=498	PBO + PIO ± MET	-0.11	+6.47	+0.34
		EMP 10 mg + PIO ± MET	-0.59	-17.0	-1.62
		EMP 25 mg + PIO ± MET	-0.72	-21.99	-1.47
Add-on with insulin (Rosenstock, et al; 2013[15])	78 weeks; R, DB, PC; n=494	PBO + insulin	-0.01	+3.0	+0.7
		EMP 10 mg + insulin	-0.57	-10.0	-2.2
		EMP 25 mg + insulin	-0.71	-15.0	-2.0
Add-on with MET vs. GLI + MET (Ridderstråle, et al; 2014[16])	104 weeks; R, DB, AC; n=1545	EMP 25 mg + MET	-0.66	-15.3	-3.0
		GLI + MET	-0.55	-3.1	+1.0

PBO = placebo; **EMP =** empagliflozin; **SITA =** sitagliptin; **SU =** sulfonylurea; **PIO =** pioglitazone; **GLI =** glimepiride; **R =** randomized; **DB =** double-blind; **PC =** placebo-controlled; **AC =** active-controlled; **FPG =** fasting plasma glucose.

Table 3 | Adverse reactions reported in ≥2% of patients treated with empagliflozin and more frequently with empagliflozin than placebo in pooled monotherapy or combination therapy trials.[9]

Adverse Effect	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Female genital mycotic infections	1.5%	5.4%	6.4%
Upper respiratory tract infection	3.8%	3.1%	4.0%
Increased urination	1.0%	3.4%	3.2%
Dyslipidemia	3.4%	3.9%	2.9%
Arthralgia	2.2%	2.4%	2.3%
Male genital mycotic infections	0.4%	3.1%	1.6%
Nausea	1.4%	2.3%	1.1%

Renal Impairment

To evaluate the safety and efficacy of empagliflozin in patients with renal impairment, 741 patients were categorized into three groups: mild renal impairment (eGFR of 60 to 90 mL/min/1.73 m^2), moderate renal impairment (eGFR of 30 to 60 mL/min/1.73 m^2), and severe renal impairment (eGFR of 15 to 30 mL/min/1.73 m^2).[17] Participants with mild renal impairment were randomly assigned to empagliflozin 10 mg daily, empagliflozin 25 mg daily, or matching placebo for 52 weeks. In the moderate and severe renal impairment groups, patients received empagliflozin 25 mg daily or matching placebo for 52 weeks. In the mild renal impairment group, change in HbA1c from baseline at week 52 was -0.57% with empagliflozin 10 mg and -0.6% with empagliflozin 25 mg, compared to +0.06% with placebo. In the moderate renal impairment group, change in HbA1c was -0.32% with empagliflozin 25 mg and +0.12% with placebo. In patients with severe renal impairment, HbA1c was not reduced.[17]

Adverse Events

In Phase III clinical trials of empagliflozin,[10-17] female genital infections and urinary tract infections were the most common adverse reactions observed due to the pharmacological induction of glycosuria.[9] Table 3 summarizes pooled data from both monotherapy and combination therapy clinical trials. Genital infections were observed more frequently in female subjects; these infections included vulvovaginal mycotic infection, vulvitis, vaginal infection, candidiasis, genital infection, cervicitis, vaginitis bacterial and urogenital infection fungal.

The mechanism of action of empagliflozin (i.e., increased urinary glucose excretion) expectantly caused osmotic diuresis, resulting in adverse events including polyuria, nocturia, and pollakiuria. Volume depletion events related to reduced intravascular volume included hypotension, orthostatic hypotension, syncope, and dehydration. Increases in serum creatinine and decreases in eGFR were also observed. In pooled results from placebo-controlled studies, change from baseline in serum creatinine were +0.01 mg/dL for both empagliflozin 10 mg and 25 mg daily.[9] In regards to eGFR, a reduction of 0.60 ml/min/1.73m^2 was observed following treatment with empagliflozin 10 mg and a reduction of 1.40 ml/min/1.73m^2 followed treatment with empagliflozin 25 mg.[9]

Dosing & Administration

Empagliflozin is supplied as 10-mg and 25-mg tablets in quantities of 30 and 90 tablets per bottle. The recommended initial dose is 10 mg once daily in the morning, taken with or without food.[9] The dose may be increased to 25 mg in patients requiring additional glycemic control who have tolerated the initial dosing strength. No dose adjustments are recommended in patients with an eGFR ≥45 mL/min/1.73 m^2. Empagliflozin should not be initiated in patients with an eGFR <45 mL/min/1.73 m^2. Recommendations for empagliflozin use in special populations are summarized in Table 4.

Comparison of SGLT2 Inhibitors

Although all SGLT inhibitors are structurally similar, the compounds can differ in their selectivity profiles. Specifically, *in vitro* studies have found that empagliflozin has the highest selectivity for SGLT2 over SGLT1.[18] From a clinical standpoint, greater

Table 4 | Use of empagliflozin in special populations.[9]

Population	Recommendations
Pregnancy	• Pregnancy category C • No adequate and well-controlled studies in humans • Only use if benefits outweigh potential risk to fetus
Nursing Mothers	• Unknown if empagliflozin is excreted in human milk • Only use if benefits outweigh potential risk to infant
Pediatric Use	• Safety and efficacy have not been established
Geriatric Use	• No dosage change recommended
Renal Impairment	• Assess renal function prior to initiation of empagliflozin and periodically thereafter • GFR ≥ 45 mL/min/1.73 m^2: No dosage adjustment needed • GFR < 45 mL/min/1.73 m^2: not recommended
Hepatic Impairment	• Empagliflozin may be used

TABLE 5 | Cost comparison of SGLT2 inhibitors

SGLT2 Inhibitor	Cost
Empagliflozin (Jardiance®)	$322.11
Dapagliflozin (Farxiga®)	$333.80
Canagliflozin (Invokana®)	$333.71

Figures represent average price for 30-day supply.

selectivity for SGLT2 is desirable because selectivity towards SGLT1 can potentially lead to diarrhea and dehydration, due to its role in intestinal glucose absorption. However, whether this greater selectivity translates into a reduced adverse event profile, compared to other SGLT2 inhibitors, remains unknown.

Average 30-day drug costs are comparable within the drug class (TABLE 5). TABLE 6 summarizes the differing dosing recommendations according to renal function for the currently available SGLT2 inhibitors.

Dapagliflozin is the only SGLT2 inhibitor that observed occurrences of bladder cancer in clinical trials.[20] Four cases of bladder cancer were reported with less than one year's duration of treatment of dapagliflozin compared to zero for placebo. Incident bladder cancer has not been observed in clinical trials of other SGLT2 inhibitors.

FUTURE OF EMPAGLIFLOZIN & SGLT2 INHIBITORS

The FDA is requiring four post-marketing studies of empagliflozin assessing cardiovascular outcomes, nonclinical juvenile toxicity, pediatric pharmacokinetics and pharmacodynamics, and pediatric efficacy and safety focusing on bone health and development.[6] Additional SGLT2 inhibitors are in the pipeline: Pfizer's ertugliflozin is currently undergoing phase 3 clinical trials, while remogliflozin is still in phase 2 studies. Additional studies are investigating SGLT2 inhibitors' potential in type 1 diabetes, and even a SGLT1/SGLT2 combination inhibitor that would have effects on intestinal glucose absorption. Invokamet®, a combination of canaglifozin and metformin, is the first SGLT2 combination medication approved for the treatment of T2DM.

CONCLUSION

Empagliflozin, the third SGLT2 inhibitor approved in the United States, is indicated to improve glycemic control in adults with type 2 diabetes as an addition to diet and exercise. The recommended initial dose is 10 mg administered in the morning with or without food. Empagliflozin significantly improves glycemic control and reduces blood pressure and weight. Common adverse effects include genital infections (especially in women) and urinary tract infections. The typical starting dose is 10 mg once daily, with titration to 25 mg once daily in those not achieving adequate HbA1c reduction. To date, comparative studies of empagliflozin versus other SGLT2 inhibitors have not been performed; thus, whether clinically significant differences exist between agents in this class is not known.

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TABLE 6 | Comparison of dosing in renal impairment for SGLT2 inhibitors.[9]

SGLT2 Inhibitor	Renal Dosing Recommendations
Empagliflozin[9]	• GFR ≥45 mL/min/1.73 m^2: No dosage adjustment needed • GFR <45 mL/min/1.73 m^2: not recommended[a]
Canagliflozin[19]	• GFR 45 to 60 mL/min/1.73 m^2: max 100 mg daily • GFR ≤45 mL/min/1.73 m^2: not recommended • GFR ≤30 mL/min/1.73 m^2, end-stage renal disease, or dialysis: contraindicated
Dapagliflozin[20]	• GFR 30 to 60 mL/min/1.73 m^2: not recommended • GFR ≤30 mL/min/1.73 m^2, end-stage renal disease, or dialysis: contraindicated

[a]Empagliflozin should not be started in these patients; empagliflozin should be discontinued if eGFR is persistently <45 mL/min/1.73 m^2.

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Editor's Corner

Trimethoprim-sulfamethoxazole versus Clindamycin in SSTIs

A recent study published in the *New England Journal of Medicine* compared clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) for uncomplicated skin infections.[1]

The study included adults and children with cellulitis, abscesses larger than 5 cm in diameter (or smaller in children), or both. All abscesses underwent incision and drainage. All patients with complicating factors or fever were excluded. Three hundred sixty-nine adults and 155 children were randomly assigned to either clindamycin 300 mg thrice-daily, or TMP-SMX 160 mg-800 mg twice-daily. Pediatric doses were adjusted for body weight. The primary outcome was clinical cure 7 to 10 days after treatment ended.

At study end, the proportion of patients with clinical cure did not significantly differ between groups (80.3% in the clindamycin group vs. 77.7% in the TMP-SMX group; p=0.52). The accompanying editorial highlights several important aspects of this study.[2] First, many uncomplicated skin abscesses can be treated with incision and drainage only. Second, the high MRSA rate must be taken in context: the purulent material from patients with abscesses grew predominately *S. aureus* (73%) and of these, 83% were methicillin-resistant. Meanwhile, only 20% of patients with cellulitis-only had cultures and 11.4% of those cultures revealed MRSA. These findings would be expected as *S. aureus* and particularly MRSA is the most common pathogen in purulent skin infections.

A remaining question is whether TMP-SMX should be favored over clindamycin for treatment of purulent infections, given that in this trial, community-acquired MRSA strains showed modestly greater resistance to clindamycin than to TMP-SMX. Interestingly, no significant difference was observed between treatment arms in the subgroup of patients with purulent infections, possibly because a significant proportion of these patients would have recovered anyway following incision and drainage alone. With regard to non-purulent infections, which presumably have a higher proportion of beta-hemolytic streptococci than do purulent infections, clindamycin had a numerically higher cure rate (80.9%) than did TMP-SMX (76.4%), though this difference was not significant (p=0.32). These findings may indicate a lack of power to show statistical significance, a potential for TMP-SMX to be effective against beta-hemolytic streptococci, or it may be indicative of beta-hemolytic streptococci being an uncommon causative organism in these infections as suggested by the predominance of *S. aureus* in the relatively small number of nonpurulent cellulitis infections that were cultured.

The most recent IDSA guidelines for Skin and Soft Tissue infections[3] favor TMP-SMX and doxycycline for moderate purulent skin infections that require antibiotics, and a beta-lactam (e.g., cephalexin) or clindamycin for mild cellulitis.

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