SHORT COMMENT FOR THE LANCET DIABETES & ENDOCRINOLOGY

SGLT-2 inhibitor or DPP-4 inhibitor : A dilemma in the management of type 2 diabetes

A.J. SCHEEN

Division of Diabetes, Nutrition and Metabolic Disorders and Clinical Pharmacology Unit, Department of Medicine, CHU Sart Tilman, Liège, Belgium

Address for correspondence:

Professor André J. SCHEEN
Department of Medicine
CHU Sart Tilman (B35)
B-4000 Liège
Belgium
Tel : 32-4-3667238
Fax : 32-4-3667068
Email : andre.scheen@chu.ulg.ac.be

Management of hyperglycaemia in type 2 diabetes (T2DM) remains challenging despite increasing pharmacological opportunities[1]. The old drug metformin remains the first-line therapy in all guidelines. However, a significant number of patients cannot tolerate the biguanide because of gastrointestinal adverse events or may have contraindications to its use. Which drug to be prescribed to those patients or to those not well controlled with metformin monotherapy is still controversial. Advantages and disadvantages of specific glucose-lowering drugs for each patient should be considered[1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) offer some advantages over classical sulphonylureas (no weight gain, no hypoglycaemia), but are more expensive[2]. A new class of glucose-lowering therapies is emerging with the recent launch of two inhibitors of sodium-glucose cotransporters type 2 (SGLT-2) (dapagliflozin and canagliflozin), and the expected commercialisation of a third one, empagliflozin, in a near future. These agents

are unique in that they increase glucose excretion, independent of insulin secretion, by inhibiting the renal reabsorption of glucose, inducing glucosuria[3].

SGLT-2 inhibitors improve glucose control, compared with placebo, in T2DM patients treated with diet alone, metformin, metformin plus sulfonylurea or insulin[3]. Of potential interest, this positive effect occurs without inducing hypoglycaemia and, because of the specific mechanism of action, is accompanied by weight loss and a reduction in systolic blood pressure [3]. The large placebo-controlled 24-week study by Roden and colleagues[4] confirms these favourable effects with empagliflozin 10 and 25 mg compared to placebo in patients treated with diet alone, and reproduces results of a previous smaller and shorter trial[5]. Adverse events are those expected from this new pharmacological class, with a slightly increased incidence of genital and benign urinary infections[3].

Thus, SGLT-2 inhibitors exert more favourable effects than placebo in 12 to 52-week trials, with an acceptable safety profile. However, the most clinically relevant issue to position these new compounds in the increasing armaterium of glucose-lowering medications is to compare the efficacy/safety profile of SGLT-2 inhibitors with that of other available oral agents. Unfortunately, indirect comparisons may be misleading and head-to-head trials in T2DM are scarce[6]. They showed that SGLT-2 inhibitors produce similar glucose-lowering effects as metformin and sulphonylureas, with a slightly greater weight loss compared with metformin and a weight reduction (instead of a weight gain) and less hypoglycaemia compared with sulphonylureas[3]. In most trials comparing a SGLT-2 inhibitor with a DPP-4 inhibitor (including Roden's study)[4], the active comparator was used in an exploratory analysis only (open-label) whereas the true double-blind comparison was made versus placebo. Therefore, results should be analyzed with caution as statistical comparisons were not prespecified.

Roden' study was the only trial comparing a SGLT-2 with a gliptin in drug-naive patients[4] while two other studies compared empagliflozin[7] or canagliflozin[8] with sitagliptin in metformin-treated patients, and one (about canagliflozin) in patients already receiving a dual therapy metformin-sulphonylurea[9]. Compared with sitagliptin 100 mg, all clinical trials performed with empagliflozin or canagliflozin (no such comparative trial available with dapagliflozin) showed a similar (or slightly) greater reduction in HbA1c, a greater fall in fasting plasma glucose, a significant weight loss of 2 to 3 kg (versus weight neutrality with sitagliptin) and a reduction in systolic blood pressure (especially with the higher dose of the SGLT-2 inhibitor) (Table 1). Both pharmacological approaches do not expose to a higher incidence of hypoglycaemia compared to placebo, confirming previous studies[2, 3]. In general,

the subjective tolerance profile was slightly better with DPP-4 inhibitors than with SGLT-2 inhibitors. No comparative study concerned patients with renal impairment[10], a population that may show reduced efficacy of SGLT-2 inhibitors[3], in contrast to what has been reported with gliptins[2].

Most of these trials were rather short-term (12-24 weeks) so that it is difficult to conclude on the long-term efficacy of each compound. Durability of the glucose-lowering effect is a crucial issue because T2DM is an evolving disease and progressive metabolic deterioration is commonly observed with all available glucose-lowering agents. Gliptins seem more favourable compared to sulphonylureas in this regard, although some escape was also noticed after 6-12 months[2]. The longer 52-week trial comparing head-to-head canagliflozin with sitagliptin demonstrates almost similar HbA1c reduction after 12 weeks, but a significantly greater reduction with canagliflozin after 52 weeks (table 1); available data thus suggest a better durability with the SGLT-2 inhibitor[9], a finding confirmed in an open-label extension study of two phase 2 trials[5, 7] for 78 weeks with empagliflozin[11]. Longer durability with SGLT-2, if confirmed, might be explained by the insulin-independent glucose-lowering effect and by the slight sustained weight reduction.

Presently, it is difficult to choose between a SGLT-2 inhibitor and a DPP-4 inhibitor to manage hyperglycaemia in T2DM, each pharmacological class presenting some advantages and disadvantages. The clinical results of the large, long-term, prospective placebo-controlled trials with cardiovascular outcomes, currently carried out with DPP-4 inhibitors or SGLT-2 inhibitors, would probably greatly help clinician's decision in the future.

Conflict of interest statement : A.J. Scheen has received lecture/advisor fees from AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, NovoNordisk and Sanofi-Aventis.

SGLT-2 inhibitor	Reference	Duration weeks	Treatment	n	Δ HbA_{1c} %	Δ FPG mmol/l	Δ BW kg	Δ SBP mmHg
Empagliflozin								
- Diet-treated	Roden et al 2013[4]	24	Placebo	228	+0.08	+0.65	-0.33	-0.3
			Empa 10mg	224	-0.66	-1.08	-2.26	-2.9
			Empa 25 mg	224	-0.78	-1.36	-2.48	-3.7
			Sita 100 mg	223	-0.66	-0.38	+0.18	+0.5
- Metformin-treated	Rosenstock et al 2013[7]	12	Placebo	71	+0.15	+0.28	-1.2	-2.2
			Empa 10mg	71	-0.56	-1.22	-2.7	-4.4
			Empa 25 mg	70	-0.55	-1.50	-2.6	-8.5
			Sita 100 mg	71	-0.45	-0.72	-0.8	-1.8
Canagliflozin								
- Metformin-treated	Rosenstock et al 2012[8]	12	Placebo	65	-0.22	+0.20	-0.9	-1.3
			Cana 100 mg	64	-0.76	-1.40	-2.3	+1.0
			Cana 300 mg	64	-0.92	-1.40	-3.0	-4.9
			Sita 100 mg	65	-0.74	-0.70	-0.5	-0.8
- Metformin + SU-treated	Schernthaner et al 2013[9]	52	Can 300 mg	377	-1.03	-1.70	-2.3	-5.1
			Sita 100 mg	378	-0.66	-0.30	+0.1	+0.9

Table 1 : Head-to-head trials of ≥ 12 weeks duration comparing a SGLT-2 inhibitor and a DPP-4 inhibitor (sitagliptin used as exploratory comparator) in T2DM patients treated with diet alone, metformin monotherapy or metformin plus a sulphonylurea. Placebo was used as reference in all these studies except the only trial assessing triple therapy[9].

Δ : change versus baseline. FPG : fasting plasma glucose. BW : body weight. SBP : systolic blood pressure. Empa : empagliflozin. Cana : canagliflozin. Sita : sitagliptin. SU : sulphonylurea.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012; **55**(6): 1577-96.
2. Scheen AJ. A review of gliptins in 2011. Expert Opin Pharmacother. 2012; **13**(1): 81-99.
3. Riser Taylor S, Harris KB. The clinical efficacy and safety of sodium glucose cotransporter-2 inhibitors in adults with type 2 diabetes mellitus. Pharmacotherapy. 2013; Jun 6. doi: 10.1002/phar.1303. [Epub ahead of print].
4. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a randomised, 24-week, double-blind, placebo-controlled, parallel group, trial with sitagliptin as active comparator. Lancet Diabetes Endocrinol. 2013; In press.
5. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes Obes Metab. 2013; **15**(8): 721-8.
6. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab. 2012; **38**(2): 89-101.
7. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013 ; Aug 1. doi: 10.1111/dom.12185. [Epub ahead of print].
8. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012; **35**(6): 1232-8.
9. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care. 2013; Apr 5. [Epub ahead of print].
10. Scheen AJ. Pharmacokinetic considerations for the treatment of diabetes in patients with chronic kidney disease. Expert Opin Drug Metab Toxicol. 2013; **9**(5): 529-50.
11. Woerle HJ, Ferrannini E, Berk A, Manun'ebo M, Pinnetti S, Broedl UC. Safety and efficacy of empagliflozin as monotherapy or add-on to metformin in a 78-week open-label extension study in patients with type 2 diabetes. Diabetes. 2012; **61**(Supplement): [Abstract 49-LB].