INTRODUCTION

Diabetes is a chronic disease that affects a large percentage of population around the world and has assumed epidemic dimensions [1,2]. The majority of these cases, approximately 90%, are of type 2 diabetes. The estimated number of diabetic patients in the world was 171.2 million (2.8%) in the year 2000 and 382 million (8.3%) in the year 2013 predicted to be 366.2 million (4.4%) by the year 2030 [3]. Of this 61.3 million patients were in India in the year 2011, and this number is expected to become close to 101.2 million in the year 2030 [4]. The prevalence of type 2 diabetes is rapidly increasing, particularly among older, overweight persons who have concomitant cardiovascular (CV) risks [5].

Type 2 Diabetes is caused by insulin resistance as well as decrease in insulin secretion [6] though there are other contributors. As the disease progresses there is a gradual but relentless decline in the beta cell function [7] necessitating gradation of the initially chosen drug with addition of more [8], eventually culminating in the use of insulin [9]. Co-administration of drugs targeting different pathophysiological processes precedes the use of insulin and if these are in the form of fixed drug combinations there is better compliance of the patient who is taking many drugs addressing other components of the disease viz: hypertension, dyslipidemia etc.; While many drug combinations most containing Metformin are approved for use, each has its own limitations and some need multiple dosing.

SGLT 2 inhibitor (SGLT2i) is a novel agent which offers the advantage of action independent of insulin and has been approved for use in Type 2 diabetes mellitus at various stages of the disease even as first line [10,11]. The article explores the issues and advantages of its combination with DPP4 inhibitor (DPP4i).

SGLT2 INHIBITOR

SGLT inhibitors block the SGLT2 protein [10-12], which plays an important role in absorption of glucose from proximal convol-
luted tubule, resulting in increased renal glucose excretion and lower blood glucose levels. These agents also increase insulin sensitivity, decrease gluconeogenesis, and improve insulin release from pancreatic beta cells by improving glucotoxicity [13,14]. However these agents are known to increase Glucagon secretion, by a mechanism as yet unknown [15].

Different types of SGLT2 Inhibitors are-

• Dapagliflozin
• Canagliflozin
• Ipragliflozin (ASP-1941), in Phase III clinical trials
• Empagliflozin (BI-10773)
• Sergliflozin etabonate, discontinued after Phase II trials
• Remogliflozin etabonate, in Phase Ib trials
• Tofogliflozin, in Phase III clinical trials
• Luseogliflozin, in Phase III clinical trials
• Ertugliflozin (PF-04971729 / MK-8835), in Phase III clinical trials

DPP4 INHIBITORS

Dipeptidyl-peptidase 4 (DPP-4) inhibitors block the action of DPP-4, an enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Incretins stimulate insulin secretion and suppress glucagon secretion in glucose dependent manner [16]. There are currently five marketed DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin and Alogliptin) approved in different regions of the world.

RATIONAL FOR COMBINING MULTIPLE MEDICATIONS

Type 2 diabetes is progressive disorder and as beta cell function decreases over time, patient needs multiple medications. For better glycemic control we have for long relied on combination of therapeutic agents that target both insulin resistance as well as defects in insulin secretion. With unraveling of additional contributors to hyperglycemia newer combinations have been added and the last one was that of Metformin and DPP-4 inhibitors. For better results the drug combination could possess one or more of the following attributes: [17-21]

• Target different pathologic process
• Synergism
• Augmentation
• Improved tolerability by minimizing/counteracting the adverse effects of the individual component

When co administered the patient has the convenience of having to take less number of pills, with better compliance and reduced potential for dosing errors.

Combination of DPP4 inhibitor and SGLT2 inhibitor may reach this IDEALISTIC GOAL.

Advantages of combination of DPP4 inhibitor and SGLT2 inhibitor include

1. SGLT2 inhibitors increase glucagon levels, by an as yet to be understood mechanism [22] and it is hypothesized that this effect has compromised the efficacy of SGLT2 inhibitors. DPP-4 inhibitors by increasing incretin levels (GLP-1 and GIP) [23-25], inhibit glucagon release; there is thus synergy in action, a much desired characteristic in any combination [26-29].

2. The HbA1c lowering of SGLT2 inhibitors is approximately 0.5%-0.8% [30] and that of DPP4 inhibitors is 0.43%-1.17% [31]. In head to head trials SGLT2 inhibitors cause better lowering of HbA1c than DPP4 inhibitors A recent study compared the effect of add-on Dapagliflozin and Saxagliptin singly or in combination in patients with background Metformin monotherapy failure. Patients on Saxagliptin alone had a HbA1c reduction of 0.9%, Dapagliflozin a reduction of 1.2% and those with the combination had a reduction of 1.5% [22,23,29-31].

As expected the impact is more when the baseline HbA1c is >8.5%.

4. This combination has another desirable trait, that of improving tolerability. The most common adverse effect of SGLT2 inhibitors is increased propensity to genital infection, which is about four times more than that occurring in the placebo group. In a study subjects receiving the combination of Saxagliptin and Dapagliflozin drugs showed no evidence of genital infection [31], this finding need to be studied further as the same was not seen when Empagliflozin was combined with Linagliptin [32].

5. There is a potential of Renal protective effect with these drugs. Several studies have shown a reduction in micro albuminuria with DPP4 inhibitors [33,34] and SGLT2 inhibitors [35-37].
6. These drugs also can be used as add-on to insulin therapy in patients with Type 1 Diabetes. DPP4 inhibitor through a possible immunomodulatory effect and the SGLT2 inhibitor through their renal action. This is being investigated, though with individual agents [38,39].

7. The other advantage is the dose does not need titrations, a bane in anti-diabetic therapy.

The other advantages offered by these medications are

1. Lack of hypoglycemia is an attribute of both the agents by virtue of their mechanism of action. SGLT2 inhibitors do not cause insulin release [40-43] and DPP-4 inhibitors release it in a glucose sensitive manner [44,45].

2. Weight loss attributable to the SGLT2 inhibitors is approximately in the range of 1-5 kgs [46,53] which is initially due to osmotic diuresis [54] and later to caloric loss with predominant reduction of (visceral) fat mass [55,56]. DPP-4 inhibitors are weight neutral [57,60].

3. Blood pressure reduction – Effects of blood pressure control especially on the micro vascular complications have amply been demonstrated by the UKPDS, ADVANCE, and other studies. Decreases in systolic (4–7 mm of Hg) and diastolic blood pressure (1–3 mm of Hg) have been observed in patients treated with SGLT2 inhibitors [46,53,54,61,62]. These decreases in blood pressure may be related to SGLT2 inhibitor–induced diuresis [63] and body weight changes. There is a blood pressure lowering data with DPP-4i as well (SBP: 2–3 mm of Hg, DBP: 1.6-1.8 mm of Hg) [28]. This would be of benefit to patients with blood pressures slightly above target.

4. Decreased levels of plasma uric acid with SGLT2 inhibitors [64,65]. The high concentration of glucose in the tubule favors the exchange of glucose for urate, resulting in increased excretion of urate in the urine [66].

So far fixed dose combination of oral anti-diabetics have always included Metformin along with one or more of the other class of drugs viz. Sulfonylureas, Thiazolidiones, α-Glucosidase inhibitors, DPP 4 inhibitors, SGLT2 inhibitors. With discovery of additional mechanisms causing hyperglycemia, there is a scope for more combination.

A combination of a SGLT2 inhibitor and a DPP4 inhibitor fulfils the criteria listed earlier. These drugs have different mechanism of action, target different pathways in the pathological process. They neither interact with each other, nor do they alter each other’s pharmacokinetic and pharmacodynamic profile [30]. While the SGLT2 inhibitors cause weight loss, the DPP4-inhibitors cause glucagon suppression overcoming the theoretical disadvantage conferred by its elevation with the use of SGLT2 inhibitors. Both intrinsically do not cause hypoglycemia and have blood pressure lowering capabilities and the risk of genital infections caused by SGLT2 inhibitors is substantially reduced when they are combined. Combinations of both these agents have synergistic effect and lead to better glycemic control.

LIMITATIONS

Both the agents have modest HbA1c lowering capabilities and would not be as potent as the Metformin - Sulphonylurea or Metformin and DPP-4i which are cheaper and/or available for a longer time. However since the combined HbA1c lowering capability is in the neighborhood of 1.5%, their addition after Metformin failure is likely to cover a vast majority of subjects without the risk of hypoglycemia.

The combination is not possible with Vildagliptin which needs to be dosed twice daily whereas the SGLT2i need a single daily dosing. Further the SGLT-2 inhibitors cannot be used across all degrees of renal insufficiency while DPP-4 inhibitors can be though some require dose modification. Combination of Linagliptin and SGLT-2 inhibitor is theoretically ideal and can be used till the GFR of 30 ml/min/1.73 m² with Canagliflozin [67] and 60 ml/min/1.73 m² with Dapagliflozin and Empagliflozin. The combination of Dapagliflozin and Saxagliptin [68] for instance can be used till GFR of 60 ml/min/1.73 m² and not beyond and while these could still be administered individually to get the best for the patient the other advantages of a fixed dose combination would be lost.

The compulsions of the manufacturer to stick to the molecules discovered/developed by them may limit the formation of the ideal formulation and the cost would be another limiting factor restricting its use. The combinations currently undergoing clinical trials include Linagliptin+Empagliflozin, Saxagliptin+Dapagliflozin, Sitagliptin+Ertugliflozin and Linagliptin+BI 38335. This only underscores the fact that the manufacturers should be willing to join hands and not tether themselves to their own molecules.

CONCLUSION

A fixed dose combination of DPP4 inhibitor and SGLT2 inhibitor could be novel addition to our armamentarium against diabetes. The combination of SGLT2 inhibition and DPP4 inhibitor is likely to emerge as an ideal combination approach for type 2 diabetes. This will offer excellent glycemic lowering efficacy with the added benefit of weight loss and low risk of hypoglycemia, with each agent targeting a different part of the pathophysiology of type 2diabetes. It would provide the best of both drugs while minimizing the adverse effects of each. Further research will help establish the role of such therapy in the future management of type 2 diabetes.
REFERENCES


