An eBook on Type 2 Diabetes

Chapter 2

Oral Agents for Type 2 Diabetes Mellitus

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1. Introduction

Recent advances in the pathophysiology of Type 2 Diabetes have made tremendous progress in the development of new treatment modalities for Diabetes. These new treatment regimens have allowed clinicians to tailor fit medications according to their patients' diabetes profile and phenotype.

In my review publication on pharmacologic treatment options for Type 2 Diabetes published at the Mayo Clinic Proceedings in 1996, Tan et al emphasized that only three classes of oral medications were then available for our patients namely sulfonylureas, biguanides and alpha glucosidase inhibitors [1]. Twenty years later, significant changes in the understanding of diabetes have resulted in newer and safer medications for our patients. The Ominous Octet physiology of Diabetes [2] have advanced our way of treating diabetics with monotherapy to early combination therapy using different agents acting on different mechanisms.

2. Sulfonylureas

This class of drugs has been around us for the longest. They mainly act by stimulating insulin secretion [3]. Sulfonylureas are considered potent and fast enough to lower blood sugar level and can lower the A1c by 1-2%. This is one drug that allows one to see major changes in the level of blood sugar in a short period but the major side effect of this potency is hypoglycemia. It is recommended that these agents are to be used with caution for those at risk of hypoglycemia especially among elderly and among patients with liver or renal dysfunction. Due to the risk of hypoglycemia and weight gain, it is no longer considered as the first line of treatment as recommended by the American Association of Clinical Endocrinologist (AACE)

Treatment Guidelines for 2016 [4].

The major route of elimination is renal and therefore it is contraindicated in patients with renal insufficiency. Certain sulfonylureas like glipizide and gliclazide (available only in Europe) however are excreted as inactive metabolites in the kidney and therefore are preferred in patients with mild renal insufficiency. The major advantage of sulfonylureas is the cost and is readily available in generic forms and therefore used extensively as first line agents for the treatment of diabetes in developing countries. If one prefers this drug for their patients, it is always advised that patient education and awareness of their side effects should be emphasized to guide patients on what to do if hypoglycemia occurs.

3. Biguanides

The only approved biguanide in the market is Metformin. It is known that its principal target organ is the liver and acts by regulating hepatic glucose output in both the fasting and postprandial state. It is the current first line of therapy in almost all guidelines due to its long safety record of no hypoglycemia and no weight gain [5]. Major pleiotrophic effects of this drug include remarkable cardiovascular safety [6], without increasing islet insulin secretion, and possible benefits in reducing cancer risk and improving cancer prognosis [7-8]. It is recommended as initial monotherapy or in combination with other agents and has been shown to lower A1c by 1-2%. Contraindication to the use of metformin is renal dysfunction with an estimated Glomerular Filtration Rate (eGFR) of below 30 ml/min/1.73m^2. Starting treatment with the drug in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended [9]. This drug can be used once or twice daily and comes either in the Intermediate release or Extended release form.

4. Alpha glucosidase inhibitors

Considered one of the weakest agents in the treatment of diabetes that can lower A1c by only 0.5% [10]. It's effect is mainly to lower the post prandial blood sugar. The agents act by inhibiting the cleavage of disaccharides to monosacharides on the brush border membrane of the intestinal epithelial cell. The principal side effect is increased flatulence from the undigested carbohydrate. It is not widely used worldwide.

5. Thiazolinediones

The only drug with an effect in improving peripheral insulin sensitivity and in reducing insulin resistance allowing the endogenous insulin to work more effectively. It has also been shown to help protect the cells in the pancreas, allowing them to carry on producing insulin for longer period to time. It works by binding to and modulating the activity of the nuclear transcription factors Peroxisome Proliferator Activated Receptors (PPARs) particularly PPAR

–gamma [11].

The downside in the use of these agents is the side effect of fluid retention, resulting in peripheral edema and risk of heart failure [12]. Other reported side effects of these agents include increase fracture risk [13] and some studies suggesting a small but dose and duration dependent increase in the rate of bladder cancer especially among patients taking pioglitazone but an overall reduction in the rate of other cancers like breast and colon.

6. Incretins

Incretins are peptides that are released from the gut in response to a meal [14]. They stimulate insulin production by the beta cells mainly via the substance called Glucagon-like peptide 1(GLP-1). Likewise GLP1 has been shown endogenously to stimulate glucagon production and also delays gastric emptying. The stimulation of insulin by this product has a safety net in the sense that it is abolished once glucose level approaches the hypoglycemic level. Endogenous GLP1s however are rapidly degraded by an enzyme called dipeptidyl peptidase 4 (DPP4). Oral incretin therapies are therefore developed as DPP4 inhibitors allowing levels of GLP1 in circulation longer to exert its glucose lowering effect [15].

There are now several DPP4 inhibitors in the market. Currently Linagliptin, Saxagliptin, Sitagliptin, Alogliptin and Vildagliptin are approved for use in different parts of the world. They can lower the A1c by as much as 0.7%. Due to its low risk of hypoglycemia and weight neutrality, the use of these agents has increased over the years. Except for linagliptin, DPP4 inhibitors dosing should be adjusted once the eGFR reaches 30-60 ml/min/1.73m2. Caution likewise should also be exercised for patients with history of pancreatitis [16].

7. SGLT2 inhibitors

It is now known that that kidneys play a very important role in the pathophysiology of Diabetes. Increasing levels of blood sugar result in increasing levels of glucose in the urine due to the renal threshold for glucose absorption in the kidney tubules which is 180 grams per day is being exceeded [17]. SGLT2 is a high capacity low affinity transporter of glucose and sodium located in the proximal tubule and is responsible for the absorption of 90% of glucose [18]. By inhibiting the action of these SGLT2s therefore result in the inhibition of glucose reabsorption resulting in an increase in glucose excretion by as much as 70 grams per day. This action offloads the pancreas of work and can help lower blood glucose and lose extra calories that can result in weight loss by as much as 2-3 kgs [19]. The most common adverse events include urinary tract Infection and mycotic genital infections related to glucosuria [20].

For now, there are three approved SGLT2 inhibitors in the market namely: Canagliflozin, Dapagliflozin and Empagliflozin. They can be used as monotherapy or in combination with

other agents. Caution however for very rare occurences of Euglycemic Diabetic Ketoacidosis reported in patients with diabetes who may have the following triggering factors: intercurrent illnesses, reduced food and fluid intake, reduced insulin doses and a history of alcohol intake [21].

8. Clinical practice setting

The American Diabetes Association and the American Association of Clinical Endocrinologists have updated guidelines in the use of oral agents in the treatment of Diabetes [22]. Both guidelines strongly emphasized on individualized approach based on patient characteristics, age, risk of hypoglycemia, duration of disease and presence of co-morbidities. Likewise approach to the use of different agents should be made to avoid hypoglycemia and weight gain.

Depending on the duration and onset of the disease, patients are started on monotherapy or initial combination therapy to achieve the desired A1c goals. Patients however should be included in the decision making and plan of therapy. Compliance to medications and follow-up requires physicians to practice Empathy [23]. Taking time to communicate with the patients including understanding how diabetes progress with time will give us the assurance of better long term outcome and better chances of preventing diabetes complications and disability.

9. References

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