

How many oral antidiabetic drugs before insulin?

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ABSTRACT

Worsening of glycemic control in type 2 Diabetes mellitus occur on account of declining beta cell function. This calls for up titration of the chosen drug, addition of another agent with complementary action and eventually insulin usually after 2 or three OADs. Introduction of insulin has many issues which include parenteral route of administration, cost and enhancement of hypoglycemic tendency. We propose the addition of another OAD in lieu of insulin in whom glycemic control can be achieved equally well without insulin

Key words: Diabetes, insulin, oral antidiabetic drugs

INTRODUCTION

A 50-year-old male patient with Type 2 diabetes mellitus of 7 years duration was referred to our clinic with fasting and postprandial blood sugars of 104 and 200 mg/dl respectively and an HbA1c of 7.4%. His current medications included metformin 1000 mg BD, glimepiride 2 mg BD, and sitagliptin 100 mg OD. Despite adequate lifestyle modifications he was overweight with body mass index of 28 kg/m² and was concerned about his weight. What are the options for him?

Type 2 diabetes mellitus is characterized by progressive beta-cell failure, and eventually, most of the patients require insulin initiation after failure to achieve adequate control despite maximum possible or tolerated dual or triple therapy with oral anti-diabetic drugs (OADs). ADA 2016^[1] statement recommends shifting the patient to insulin therapy if HbA1c goal is not achieved with a maximum of three OADs. However, with the availability of newer OADs, some with beta cell independent action, the universality of this dictum can be challenged.

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Negative perception and noncompliance are significant issues with insulin treatment. A significant number of patients report insulin omission and nonadherence to prescribed doses. Even treating physicians are hesitant to initiate insulin. This is particularly evident when despite dual or triple OAD therapy HbA1c is only marginally above target level yet well within the efficacy target of remaining oral agents. The risk of hypoglycemia and weight gain with insulin always exists in the background. Insulin needs proper storage, particularly during travel and extremes of temperature. In such a scenario, the addition of another oral agent in lieu of insulin is an attractive alternative.

The ominous octet model proposed by DeFronzo suggests that effective treatment of Type 2 diabetes requires combinations of drugs to correct the multiple pathophysiological defects.^[2] The availability of newer classes of OADs has widened the scope and possibility of such a treatment plan. These drugs act by different and often complementary mechanisms, addressing different pathophysiological processes that perpetuate hyperglycemia. Among the oral agents, only glitazones and sulphonylurea (SU) produce weight gain and later also cause hypoglycemia. Other agents do not produce

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hypoglycemia and are either weight neutral or may even cause weight loss. Importantly, agents such as metformin, alpha-glucosidase inhibitors (AGI), and sodium glucose cotransport inhibitors (SGLT2-i) act independently of insulin secretion. Although each drug has its own efficacy ceiling, they can be combined for greater HbA1c reduction. The HbA1c reduction thus achieved may not necessarily equate to the sum of their individual HbA1c lowering capacities.

Cardiovascular effects of the OADs are a matter of concern. However, results of recent cardiovascular safety trials are encouraging, with most trials indicating either cardiovascular neutrality or benefit. The recent EMPA-REG OUTCOME³¹ trial has shown lowering of primary composite cardiovascular outcomes and heart failure.

It remains an undisputed fact that insulin is the treatment of choice in symptomatic patients, in patients with very poor glycemic control (HbA1c >9%) and the presence of comorbidities such as advanced renal and hepatic failure. However in other cases, the addition of another OAD can be an alternative, especially when the drug has the likelihood of helping the patient to achieve HbA1c target.

The combination of OAD regimens without SUs and glitazones offers glycemic control without hypoglycemia and weight gain. The patient can be on metformin, DPP-4i, SGLT2-i, AGIs; although the order in which these agents are introduced after metformin can vary. The addition of SUs to this regimen would cause as much harm as insulin in terms of hypoglycemia and weight gain. The addition of glitazones to this regimen promises glycemic control without hypoglycemia while causing weight gain.

The management of Type 2 diabetes mellitus is multifaceted, incorporating management of blood pressure, lipid derangements, weight gain in addition to glycemic control. Although guidelines recommend tight glucose control to reduce the risk of microvascular complications, this should not come at the cost of hypoglycemia and weight gain. The choice of treatment regimens for add-on therapy should be evaluated in light of current HbA1c levels and the risk of hypoglycemia. Individualization of therapy with respect to cost, patient preference, and adverse effect profile of medications

should be given adequate importance along with glycemic control.

Limitations of multiple oral anti-diabetic drugs

Adding another agent increases the pill burden and may significantly increase the cost of treatment especially with newer agents. Drug interactions and additive adverse effects may limit the use of multiple OADs. Lack of clinical studies and guidelines also hinder many from prescribing multiple agents.

Coming back to our case, the therapeutic options were discussed with the patient with respect to the risks and benefits of adding another OAD (AGIs, pioglitazone or SGLT2-i) versus insulin initiation. He opted for SGLT2-i, and at a follow-up of 3 months later, his HbA1c was 6.9% with fasting and postprandial values of 97 and 138 mg/dL, respectively. In addition, a weight loss of 1.9 kg was documented.

CONCLUSION

In clinical practice, the timing of insulin initiation after OAD is a matter of conjecture and physician preference especially in cases where HbA1c targets can be equally met with OADs. The ADA Standards of Diabetes Care 2016 mandate that if HbA1c target is not achieved after approximately 3 months of triple therapy move to injectables (either GLP-1 RA or insulin). Whether the addition of more drugs can be considered in lieu of insulin in select patient populations who fail to achieve glycemic targets with current OADs needs to be evaluated in terms of safety, efficacy, and cost-effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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