Individualizing treatment of type 2 diabetes

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Type 2 diabetes (T2DM) is a heterogeneous disorder. It affects the young, middle aged and elderly. Some patients with T2DM are obese and some are lean. A category of individuals in these groups posses a cluster of cardio-vascular risk factors named as metabolic syndrome comprising dyslipidemia, high blood pressure and central obesity. All these features highlight the heterogeneity and different phenotypes of T2DM.

Hyperglycemia is the main therapeutic target in the management of T2DM. Over many decades, a number of oral hypoglycemic agents (OHA) have been introduced to control hyperglycemia in this disorder. Professional organizations formulated guidelines to use OHAs in T2DM. Most of these guidelines stipulate a vertical approach in selecting and adding OHAs. With the availability of more OHAs and better understanding of the heterogeneity of diabetes, there is a paradigm shift in the guidelines in the management of hyperglycemia in diabetes. The most recently advocated approach endorses an individualized treatment based on the age, impact of weight gain or necessity of weight loss, target glycemic control, risk of hypoglycemia, cost and patient safety in selecting the most appropriate OHA for a given patient with T2DM. This article aims to address some clinically relevant issues related to the individualized therapy in T2DM.

Metformin as the first line OHA

Metformin is one of the oldest of the OHAs to be used to control hyperglycaemia in T2DM. The findings of the United Kingdom Prospective Diabetes Study (UKPDS) revealed that it is effective in reducing mortality when used in obese patients with T2DM over sulphonylureas (1). This observation lead to recommendation of metformin as the first choice of OHA for the newly diagnosed, obese subjects with T2DM when dietary modifications alone fail to maintain the desired glycemic control. A subsequent meta-analysis revealed relative efficacy of metformin therapy over other OHAs to reduce mortality even among the non-obese patients with T2DM (2). Currently metformin is the first choice OHA for newly diagnosed subjects with T2DM either obese or non-obese.

Weight loss, gastrointestinal effects such as anorexia, nausea and diarrhea are the commonly reported adverse effects of metformin. Most newly diagnosed patients with T2DM experience loss of several kilograms in weight at the time of the diagnosis and often it is the reason for self-screening for diabetes by them. Commencing metformin for a newly diagnosed lean patient with T2DM is often faced with poor patient acceptance and adherence due to further loss of weight. Still the most evidenced based approach in initiating OHA in a patient with T2DM is to start metformin. If tolerance issues are of concern, it can be withheld and an alternative OHA can be started.

The most appropriate agent after failure of metformin monotherapy

Type 2 diabetes is a progressive disease. Although metformin is used as the first-line therapy, most, if not all patients require additional agents to achieve the recommended glycemic control with increasing duration of the disease. According to data from the National Health and Nutrition Survey in the United States, the most common oral medications used to treat diabetes after metformin monotherapy changed from sulfonylureas in 1999 to 2000 to glitazones in 2003 to 2004 (3). Introduction of incretin based therapies namely glucagon like peptide (GLP) analogues and dipeptidyl peptidase- 4 (DPP- 4) inhibitors during the past few years to treat hyperglycemia in T2DM has posed many challenges to this practice.

A recent meta-analysis using PubMed and the Cochrane central register written in English through December 2011 including 39 randomized controlled trials involving 17,860 patients with T2DM on different regimens of hypoglycemic therapy has posed new challenges to the current practice (4). According to their findings, GLP analogues resulted in greater decrease in A1c levels compared with sulfonylureas (-0.20%; 95% confidence interval [CI], -0.34% to -0.04%), glinides (-0.31%; 95% CI, -0.61% to -0.02%), glitazones (-0.20%; 95% CI, -0.38% to -0.00%), α-glucosidase inhibitors (-0.36%; 95% CI, -0.64% to -0.07%), and dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors; -0.32%; 95% CI, -0.47 to -0.17%), and resulted in A1c levels comparable to basal insulin and biphasic insulin.

The authors found that sulfonylureas, glinides, basal insulin, and biphasic insulin treatments were associated with an increased risk for hypoglycemia compared with placebo. Patients receiving sulfonylureas, glinides,

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glitazones, basal insulin, and biphasic insulin gained weight, and patients receiving α-glucosidase inhibitors and GLP analogues lost weight.

These findings and their apparent therapeutic efficacy and safety have promoted incretins as the potential agents after metformin mono therapy and some professional bodies have included them as the second line therapy in their therapeutic algorithms to control hyperglycemia in T2DM. The main drawback of GLP analogues however is that, like insulin it needs to be given as subcutaneous injections (either daily or extended release preparations once weekly). Not many patients with T2DM would willingly switch over to an injectable preparation when other oral therapies are available to control hyperglycemia. As a substantial proportion of patients with T2DM in the South East Asian region are lean, they would not benefit from weight reducing effects of GLP analogues.

The oral form of incretin, DPP-4 inhibitors or gliptins does not have the same potential to reduce HbA1C as GLP analogues. A recent study revealed an increased incidence of heart failure related hospital admissions among patients treated with saxagliptin therapy and as expected saxagliptin had no effect on the cardiovascular mortality (5). However findings of this single trial alone is not adequate to disregard the value of DPP-4 inhibitors. Therefore, recommendation of either form of incretins, injectable or oral, as the most appropriate agent to treat T2DM after metformin mono therapy should await results of the ongoing long term studies. With available evidence, the preferential use of GLP -1 analogue should be limited to selected patients with T2DM in whom weight loss and risk of hypoglycemia are major concerns. Similarly, until evidence on favorable long cardiovascular outcomes is available, gliptins can only be used as alternatives, not as preferred therapy to currently widely used OHAs such as sulphonylureas and glitazones. The 2012 position statement by the American College of Clinical Endocrinologists (ACCE) on the choice of hypoglycemic therapy has endorsed gliptins only as an alternative agent after metformin therapy in their therapeutic algorithm (6).

Place of glitazones amidst safety concerns

Glitazones (thiazolidinediones) have been in use as an OHA for more than a decade. But they have caused considerable controversy since they were introduced into the management of patients with T2DM. Until recently, there were two glitazones licensed for use in the treatment of type 2 diabetes: rosiglitazone and pioglitazone. But rosiglitazone has been withdrawn from the market in 2011 because of concerns about cardiovascular safety, mainly heart failure. But recent reports indicate that rosiglitazone may be reintroduced with safety precautions in those with incipient heart failure. Although there is no evidence to show similar cardiovascular adverse effects of pioglitazone, several reports on its association with fluid retention, fractures and bladder cancer have initiated a debate on its risks vs benefits as a therapeutic agent in T2DM.

Recently, *British Medical Journal* published a retrospective cohort study including 600 general practices in the United Kingdom among 115, 727 individuals with type 2 diabetes who were newly treated with oral hypoglycaemic agents between January 1988 and December 2009 (7). It was revealed that use of pioglitazone was associated with an increased rate of bladder cancer (rate ratio 1.83, 95% confidence interval 1.10 to 3.05). The rate increased as a function of duration of use, with the highest rate observed in patients exposed for more than 24 months (hazard ratio (HR) -1.99, CI -1.14 to 3.45) and in those with a cumulative dosage greater than 28 000 mg (HR -2.54, CI - 1.05 to 6.14).

The US Food and Drug Administration issued a warning on use of the drug. It is contraindicated in patients with symptomatic heart failure and advised to be used with caution in women with high risk for fractures. France and Germany had already suspended its use.

Although there are few concerns with safety, as an OHA, pioglitazone has a special place in management of patients with T2DM in the local setting. Its insulin sensiting effect is useful in treating patients with severe insulin resistance (IR) especially the category of patients with non-alcoholic fatty liver (NAFLD) and polycystic ovary syndrome (PCOS), both common accompaniments of T2DM. As the third or fourth OHA for those taking maximal doses of metformin and sulphonyluria with or without alpha glucosidae inhibitors, it delays the initiation of insulin for a considerable period. This property of pioglitazone avoids the need for insulin injections which majority of patients fail to adhere to long term. ADOPT (A Diabetes Outcome Progression Trial) demonstrated that initial monotherapy with glitazone provided superior durability of glycemic control compared with metformin and glibenclamide in patients with recently diagnosed type 2 diabetes (8).

These positive features of pioglitazone useful in managing patients in the local setting are too good to be overlooked in taking the decision to stop glitazones in patients who maintain satisfactory glycemic control. Therefore, in the absence of risk factors for bladder cancer, pioglitazone can be continued with caution in a selected category of patients with T2DM without heart failure or high risk for bone fractures.

Therapeutic options for OHA failure

The progressive nature of T2DM necessitates regular dose escalation and addition of newer OHAs to maintain optimal glycemic control with increasing duration of the

disease. But in most patients, optimal glycemic control cannot be maintained even with maximal doses of all the available and tolerable oral agents 5-10 years after the diagnosis of T2DM. This stage is called OHA failure in T2DM. Until recently initiation of insulin was the only option available to control hyperglycemia in these patients. Availability of GLP analogues has provided another therapeutic option to manage OHA failure. However presence of some residual beta cells is necessary for the function of GLP analogues. Both insulin and GLP analogues need to be administered as subcutaneous injections, the notable advantage of GLP analogues over insulin includes the lack of hypoglycemic risk and associated weight loss. Recently introduced basal insulin has a comparatively lesser risk of hypoglycemia than previous insulin regimens, but weight gain is a considerable concern when insulin of any type is commenced in already overweight or obese patients with OHA failure.

Clinicians should take many factors in to consideration before initiating either insulin or GLP analogues especially for the elderly patients with OHA failure. Evidence from clinical trials (ACCORD, VADIT) reveals that attempts to intensify glycemic control in elderly and those with pre-existing cardiac disease are associated with an increased risk of death (9,10). Basal insulin and GLP analogues are costly and their cost effectiveness should be given a thought when commencing in the poor resource setting. Most elderly patients find it difficult to use daily, self-injectable preparations and the long-term adherence of such therapy is doubtful. Because of all these concerns, professional associations have recently laid down less stringent glycemic targets for elderly patients with diabetes.

For younger patients with OHA failure, choice of either type of injection (insulin or GLP analogues) should be decided based on individual needs. Beta cell preserving effects of GLP analogues may be useful for younger patients if administered early in the disease. The obese would also benefit from weight losing property of GLP analogues. Insulin would be less costly and more appropriate for lean patients with OHA failure as it would cause some gain in weight and self-satisfaction for those with severe emaciation. When once daily injection and appropriate combinations of OHAs fail to achieve the recommended glycemic target, switching over to a more frequent insulin regimen should be considered.

In conclusion, clinicians should give due consideration to individual factors in different patients with T2DM when choosing the most appropriate agent to manage hyperglycemia while adhering as much as possible to the evidence based guidelines. Strict adherence to guidelines alone may sometimes cause more harm to an individual patient.

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