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Commentary

Initiating Combination Therapy in People with Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex disease with multiple pathophysiological defects: progressive deterioration of β-cell function, increased peripheral insulin resistance, and increased hepatic glucose output are the core defects. Defects in incretin axis, increased glucose reabsorption by the kidney due to upregulation of sodium-glucose co-transporter 2, and enhanced lipolysis also play important roles. Despite the introduction of a number of new classes of anti-diabetic medications over the past two decades, majority of people with T2DM fail to achieve glycaemic targets. Among others, clinical inertia remains an important contributory factor. The causes of clinical inertia are complex and multifactorial; one among them is the recommended stepwise, sequential add-on, therapeutic approach, which often leads to a delay in intensification of therapy. It is time for a paradigm shift in the management of people with newly diagnosed T2DM. Initiating combination therapy at the very outset shall not only reduce clinical inertia but also allow earlier and greater achievement of glycaemic targets in a larger number of people with newly diagnosed T2DM. Moreover, by targeting multiple pathophysiological defects, initial combination therapy has the potential to delay disease progression. It is of interest to note that a few guidelines have recognised the benefits of initial combination therapy in people with newly diagnosed T2DM, and have incorporated it in their treatment algorithms. However, information on durability, long-term side-effects, and impact of initial combination therapy on long-term micro- and macrovascular complications are currently unavailable. Moreover, compared to stepwise therapy, the initial cost of therapy is higher.

Keywords: Diabetes mellitus, type 2, new diagnosis, drug therapy, step-wise therapy, sequential therapy, combination

Introduction

Type 2 diabetes mellitus (T2DM) is a complex and progressive disease, characterized by an inexorable loss of β-cell function, partly precipitated by the toxic effects of elevated blood glucose (glucotoxicity) and free fatty acids (lipotoxicity). Early effective glycaemic control in people with newly diagnosed T2DM can ameliorate glucotoxicity and lipotoxicity, and preserve β-cell function.[1] In fact, in studies achieving tight glycaemic control in people with newly diagnosed T2DM with either intravenous/subcutaneous insulin or a combination of oral anti-hyperglycaemic agents (OHAs), there was an improvement in β-cell function, and over a quarter to half were in remission at one year.[2,3] Achievement of tight glycaemic control in the early years of the disease not only reduced the risk of microvascular complications, but also had a legacy effect that over long-term resulted in a reduction of myocardial infarction and all-cause death.[4,5] As such, every attempt should be made to achieve tight glycaemic control early in the disease, and maintain it all throughout.

Pathophysiological Defects in Type 2 Diabetes Mellitus

Harmonious interactions between insulin secretion and insulin sensitivity in target tissues maintain blood glucose in health. In people with T2DM, multiple pathophysiological defects disrupt this homeostatsis, resulting in hyperglycaemia. The core pathophysiological defects include β-cell failure, insulin resistance in muscle and fat, and increased hepatic glucose output. Defects in incretin axis, increased glucose reabsorption by the kidney due to upregulation of sodium-glucose co-transporter

2 (SGLT2), enhanced lipolysis, and central neurotransmitter dysfunction are also important in the development of T2DM.[6] No single anti-diabetic agent can target all these pathophysiological defects on its own; rather, a combination of OHAs, targeting different pathophysiological defects, is necessary to effectively manage T2DM.

What do Guidelines Suggest Regarding Initiating Combination Therapy in People with Newly Diagnosed Type 2 Diabetes Mellitus?

Many current guidelines continue to advocate stepwise therapy, with sequential addition of OHAs, for management of newly diagnosed T2DM. The 2020 American Diabetes Association (ADA) standards of care recommend comprehensive lifestyle modification along with metformin as the first line therapy for people with newly diagnosed T2DM.[7] They recommend stepwise-therapy, with sequential addition of OHAs to metformin, when metformin alone is unable to maintain glycaemic control. The 2020 ADA standards of care recommends that in people with T2DM with established atherosclerotic cardiovascular disease (ASCVD), high risk for ASCVD, heart failure or kidney disease, an SGLT2 inhibitor or a glucagon-like peptide 1 receptor agonist (GLP-1RA) should be considered as the next add-on to metformin. The choice of medication to be added sequentially in those without these co-morbidities depends on many factors including age, baseline HbA1c value, cost of treatment, risk of hypoglycaemia, body-weight, existing contraindications for a particular medication, and patient preference. Interestingly, in a departure from its earlier recommendations, the new 2019 American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD) guideline, and the 2020 ADA standards of care, recommend use of initial combination therapy in asymptomatic people with T2DM presenting with an HbA1c value 1.5%-2% above target.[8] Moreover, the 2020 ADA standards of care has taken cognizance of the results of the Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes mellitus (VERIFY) trial, noticing the more rapid attainment, and slower decline, of glycaemic control in participants receiving initial combination therapy with metformin and vildagliptin when compared with metformin alone.[9] However, they note that in the absence of generalizability of these findings to all oral agents, it should be considered only after a shared-decision making process with patients. The American Association of Clinical Endocrinologists (AACE) recommends combination therapy in asymptomatic people with T2DM when HbA1c value is greater than 7.5%.[10] Both guidelines recommend introduction of insulin in patients with newly diagnosed T2DM who are symptomatic, have evidence of catabolism, or a very high HbA1c value at diagnosis.

When to Consider Initiating Combination Therapy in People with Newly Diagnosed Type 2 Diabetes Mellitus - Our Perspective

We advocate initiating combination therapy with OHAs in all asymptomatic people with newly diagnosed T2DM irrespective of the HbA1c value at diagnosis not only to rapidly achieve target glycaemic goal to reduce on-going glucotoxicity and lipotoxicity, but also to address the other pathophysiological defects, including enhanced lipolysis. However, the initial combination regimen should not include sulphonylureas or glinides to minimize the risk of hypoglycaemia. We recommend dual combination therapy with OHAs in asymptomatic people with newly diagnosed T2DM with HbA1c value between 6.5%-7.4%, triple combination therapy with OHAs when HbA1c at diagnosis is between 7.5%-9.0%, and triple combination therapy together with a short 3-4 week period of basal insulin when HbA1c at diagnosis is greater than 9% together with a significantly elevated fasting blood glucose value (>250 mg/dL).[11] Intensive insulin therapy is treatment of choice in those who are symptomatic, show features of catabolism, or have a very high HbA1c value at diagnosis. In contrast to stepwise therapy, where one sequentially escalates therapy when HbA1c rises above target value, we recommend step-wise de-escalation of therapy as and when the person with T2DM reaches HbA1c targets.[12] We suggest stopping basal insulin in asymptomatic people with newly diagnosed T2DM with HbA1c >9% at diagnosis with elevated fasting glucose once their fasting blood glucose values are in target; similarly, we suggest de-escalation from triple to dual OHA combination therapy in asymptomatic people with newly diagnosed T2DM once their HbA1c value has dropped below 7.5%.[11] The reason for this suggested gradual de-escalation of therapy, the step-down approach, is to avoid unnecessary medication burden once the initial toxic effects of glucotoxicity and lipotoxicity on the β-cells has been rapidly reversed by initial combination therapy; moreover, this step-down approach shall reduce the cost of therapy, pill burden, and improve compliance.

Which Combinations to Consider?

There are a number of possible combinations of OHAs to choose from, and it is imperative to select a combination that is rational and individualised to the patients' needs.[12] The medications used in combination should have additive and complementary effects, and together address multiple pathophysiological defects in T2DM. In the unlikely situation where an asymptomatic person with newly diagnosed T2DM has ASCVD, is at high risk for ASCVD, has HF or renal dysfunction, the combination should include metformin and either a SGLT2-inhibitor or a GLP-1RA with proven CVD benefit. In the majority of people with newly diagnosed T2DM, who do not have any of the above co-morbidities, the choice of the combination of medications depends upon baseline and target HbA1c value, specific indications or contraindications for a particular class of OHA, impact of hypoglycaemia and weight gain, economic considerations, and patient preference. Moreover, based on baseline HbA1c value, the combination therapy regimen could include two (dual) or three (triple) classes of OHAs.

The most common dual combination used worldwide in the management of people with newly diagnosed T2DM is metformin and a sulphonylurea.[13] Metformin reduces hepatic glucose output, and sulphonylureas stimulate insulin secretion from β-cells. Apart from cost benefit and a long track record, this combination is not the ideal option for dual combination therapy; sulphonylurea causes weight gain, carries the risk of hypoglycaemia, more so in a person with newly diagnosed T2DM with a not-so-high HbA1c value, and might hasten β-cell exhaustion.[14]

The combination of metformin and a thiazolidinedione results in superior HbA1c reduction when compared to metformin monotherapy.[15] However, pioglitazone, the only thiazolidinedione available, can cause weight gain, pedal oedema, macular oedema, and increase the incidence of fractures, particularly in post-menopausal women.

A meta-analysis of eight studies comparing initial combination therapy of metformin and a dipeptidyl-peptidase 4 (DPP-4) inhibitor demonstrated superior fasting blood glucose and HbA1c reduction when compared to metformin monotherapy.[16] Moreover, the recently reported VERIFY trial confirmed not only greater but also durable glycaemic control with use of a combination of metformin and vildagliptin when compared to metformin monotherapy.[9] VERIFY was a randomised, double-blind, parallel-group trial of 5 years duration, where 2001 people with diabetes, diagnosed within 2 years prior to enrolment, were randomly assigned to either early combination therapy with metformin and vildagliptin, or metformin monotherapy and placebo. Vildagliptin was added in place of placebo in the metformin monotherapy group in case monotherapy failed to maintain HbA1c value below 7.0% over two consecutive visits, 13 weeks apart. The incidence of initial treatment failure during period 1 of the study was greater, and happened earlier in the metformin monotherapy group when compared to early combination therapy group [(62.1% vs. 43.6%) and (36.1 months vs. 62.1 months) respectively].[9]

Initial combination therapy with SGLT2 inhibitor and metformin has been very effective, with minimal hypoglycaemia and significant weight loss.[17] In a recent meta-analysis of 36 studies, initial dual therapy, including metformin plus any one of sulphonylurea, DPP-4 inhibitor, thiazolidinedione, or SGLT2 inhibitor, in newly diagnosed treatment-naïve people with T2DM, showed significant HbA1c reductions compared with initial metformin monotherapy; the combination of metformin plus sulphonylurea was associated with higher risk of hypoglycaemia.[18]

There are a number of choices for a triple drug combination for asymptomatic people with newly diagnosed T2DM with a high baseline HbA1c value at presentation. Of these, a combination of metformin, pioglitazone and an incretin-based medication (GLP-1RA or DPP-4 inhibitor) is rational and logical, as together they address five-six of the eight pathophysiological defects, with minimal side effects. People with T2DM treated with a triple drug combination of metformin 1 gm twice daily, rosiglitazone 4 mg twice daily, and liraglutide 1.2 or 1.8 mg per day showed improved β-cell function, better glycaemic control, and weight loss when compared to those on a dual drug combination of metformin and rosiglitazone.[19] In the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT) randomized controlled trial, it was noted that triple therapy, with metformin, pioglitazone and exenatide, in 134 drug-naïve people with recently diagnosed T2DM with a baseline HbA1c of 8.7%, was more effective than the standard sequential add-on therapy with metformin, sulphonylurea and then basal insulin; over a period of two years, triple combination therapy resulted in significantly greater reduction in HbA1c, 7.5 fold lower risk of hypoglycaemia, and weight loss when compared to standard sequential therapy.[20] The triple drug combination of metformin, DPP-4 inhibitor, and SGLT2 inhibitor addresses five of the eight pathophysiological defects with minimal side effects. Fixed dose combinations (FDC) of these three classes of OHAs are now available; metformin, saxagliptin, dapagliflozin and metformin, linagliptin, empagliflozin have already been approved for use by the US Food and Drug Administration.

Long-term Effects of Initial Combination Therapy in People with Newly Diagnosed Type 2 Diabetes Mellitus

When compared to stepwise therapy, initial combination therapy in drug naïve people with newly diagnosed T2DM results in earlier achievement of glycaemic goals, greater reduction in HbA1c value, targets multiple pathophysiological abnormalities, and reduces clinical inertia, all with the potential to preserve β-cell function for a longer period of time, and lead to a reduction in diabetic complications. However, the use of multiple medications at the very onset of disease might reduce patient adherence, an issue that can be addressed with the availability of more FDCs. The other disadvantage of combination therapy relates to the upfront cost of the newer OHAs, combined with lack of long-term cost-effectiveness studies. The side-effect profile of various combinations needs consideration. Although the VERIFY trial confirmed greater durability of a DPP-4 inhibitor and metformin dual combination compared to metformin monotherapy, more information on durability of various other combinations are required. Moreover, the effect of combination therapy on the long-term diabetic micro- and macrovascular complications awaits documentation.

Conclusion

Initiation of combination therapy in drug naïve people with newly diagnosed T2DM as opposed to stepwise therapy with sequential add-on of medications achieves earlier and greater reduction of HbA1c. Moreover, by targeting multiple pathophysiological defects, combination therapy has the potential to delay disease progression. The availability of many two-drug, and a few three-drug, FDCs has significantly reduced the complexity of initial combination therapy, ensuring better patient adherence. Data on the greater durability of a few two- and three-drug combinations are now available. Overall, it can be expected that early and better achievement of glycaemic goals, together with targeting of multiple pathophysiological defects, shall reduce the long-term complications of T2DM. It is heartening to see that many organisations are now beginning to accept initial combination therapy in people with newly diagnosed T2DM. The AACE recommends dual or triple combination therapy in asymptomatic people with newly diagnosed T2DM and an HbA1C value at diagnosis between 7.5%-9% or greater than 9% respectively, whereas the ADA/EASD guidelines for the first time in 2019 recommended combination therapy in asymptomatic people with newly diagnosed T2DM and a HbA1c value 1.5%-2% above target. The upfront cost of therapy is a drawback for combination therapy, and more cost effectiveness studies are required.

Declaration of conflicting interests

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