Initial Combination with Linagliptin and Metformin in Newly Diagnosed Type 2 Diabetes and Severe Hyperglycemia

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ABSTRACT

Making appropriate treatment decisions for patients newly diagnosed with type 2 diabetes mellitus (T2DM) and severe hyperglycemia (glycated hemoglobin [HbA1c] >10% or fasting plasma glucose ≥250 mg/dL) presents a formidable challenge to primary care physicians. Extreme defects in insulin secretion make it unlikely that these patients will achieve glycemic targets with metformin monotherapy. Additionally, uncontrolled hyperglycemia is associated with an increased risk of short-term acute complications, such as hyperosmolar coma, and long-term complications affecting the micro- and macrovasculature. Thus, severely hyperglycemic patients require prompt, intensive treatment to re-establish glycemic control. Current guidelines indicate that either initial insulin therapy or initial combination therapy with metformin plus non-insulin drug(s) are the treatments of choice for these challenging-to-treat patients. This mini-review examines the clinical evidence supporting these two treatment options, with particular reference to the findings of a phase 3 study of treatment with an initial combination of metformin plus the dipeptidyl peptidase-4 inhibitor, linagliptin. Intensive insulin therapy can induce sustained euglycemia and improve beta-cell function in newly diagnosed patients. However, insulin use is associated with an increased risk of adverse events, such as hypoglycemia and weight gain. These potentially serious side effects cause concern among patients and physicians, and are a major barrier to initiating and maintaining adherence to insulin treatment. In the phase 3 study, open-label treatment of severely hyperglycemic patients (HbA1c ≥11.0%) with linagliptin plus metformin resulted in a mean change in HbA1c of −3.7% ± 1.7%. This combination therapy was generally well tolerated with most adverse events being of mild or moderate intensity; asymptomatic hypoglycemia was reported by
just 1 of 66 (1.5%) patients. These findings provide evidence in support of linagliptin plus metformin as a well-tolerated and effective treatment alternative to insulin for new-onset patients with T2DM and severe hyperglycemia.

**Keywords:** Dipeptidyl peptidase-4 inhibitor; Initial combination therapy; Initial insulin therapy; Linagliptin; Metformin; Severe hyperglycemia; Type 2 diabetes

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder of glucose homeostasis, characterized by a range of pathophysiological defects spanning multiple organ systems [1]. The core pathophysiology of T2DM include impaired insulin secretion from pancreatic beta-cells; muscle, liver, and adipose tissue insulin resistance; hypersecretion of glucagon by pancreatic alpha-cells, promoting hepatic glucose production; and decreased sensitivity of pancreatic beta-cells to the incretin hormones, glucagon-like peptide (GLP)-1 and glucose-dependent insulinoctropic polypeptide [1]. The resultant increases in both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels are symptomatic of the progressive failure of beta-cell function that defines the natural history of T2DM. Recently, the clinical management of T2DM has grown increasingly complex with the arrival of a number of novel glucose-lowering drugs [2–4]. The difficulties of identifying the optimal treatment strategy for each individual patient is reflected in the numerous guidelines and treatment algorithms that have been published by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD), the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), and other organizations during this period [5–10]. However, not much has been written on the particular problems associated with the management of patients newly diagnosed with T2DM and severe hyperglycemia (glycated hemoglobin [HbA1c] >10.0% or FPG ≥250 mg/dL) [7]. In this mini-review, the use of initial insulin therapy is compared with the initial combination of metformin and the dipeptidyl peptidase (DPP)-4 inhibitor, linagliptin, in the treatment of this challenging-to-treat patient population. Linagliptin is regarded as being unique in the DPP-4 inhibitor class because it is eliminated primarily via the enterohepatic system, as noted in a recent position statement from the ADA/EASD [10], thus negating the need for dose adjustment in any patients with T2DM, even those patients with renal or hepatic impairment. The use of linagliptin for the treatment of T2DM has been reviewed recently [11].

## METHODS

A nonsystematic PubMed literature search was conducted to identify relevant, peer-reviewed clinical articles published between 1980 and May 2012 relating to the initial treatment of severe hyperglycemia in patients newly diagnosed with T2DM. Search terms included “type 2 diabetes,” “type 2 diabetic,” “insulin,” “insulin therapy,” “insulin treatment,” and “newly diagnosed” (in the title and/or abstract fields). Initial searches yielded approximately 150 citations. Case studies and editorials were excluded. Primary manuscripts, clinical practice guidelines, and review articles were reviewed, and an assessment of their clinical relevance was performed. Key references reporting initial combination therapy with metformin plus another non-insulin drug were obtained.