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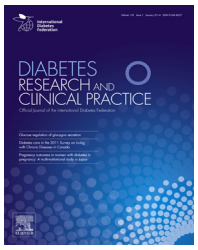

Implementing an optimized glucose-lowering strategy with a novel once daily modified release gliclazide formulation

Lawrence A. Leiter [a,*], *Marina V. Shestakova* [b], *Natalya P. Trubitsyna* [b], *Milivoj Piletič* [c], *Ilhan Satman* [d]

[a] *Divisions of Endocrinology & Metabolism, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada*
[b] *Institute of Diabetes Mellitus, Endocrinology Research Centre and M.I. Sechenov First Moscow State Medical University, Moscow, Russian Federation*
[c] *General Hospital, Novo Mesto, Novo Mesto, Slovenia*
[d] *Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey*

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ABSTRACT

Aim: The 6-months titration profile of a new scored gliclazide modified release (MR) formulation (MR 60 mg) was explored in individuals with type 2 diabetes.
Methods: This international study enrolled 7170 individuals, age ≥35 years with HbA1c ≥7.5% (59 mmol/mol) and not on insulin. Participants were started on 30–120 mg gliclazide MR 60 mg once daily as a first line (FIRST), add-on (ADD) or switch from a previous oral antihyperglycemic treatment strategy (SWITCH). Uptitration was capped at 120 mg.
Results: Women comprised 58.5% of the cohort. Mean baseline age was 58.9 years, body mass index 30.1 kg/m^2 and diabetes duration 5.1 years. Mean baseline HbA1c for the FIRST (n = 2023), ADD (n = 3136) and SWITCH (n = 1834) groups was 8.9% (74 mmol/mol), 8.8% (73 mmol/mol) and 8.8% (73 mmol/mol), respectively. Probability of reaching optimal dose at months 1, 2, 3 and 6 was 15%, 39%, 59% and 92%, respectively. Mean HbA1c changes from baseline to month 6 were FIRST: −1.98%, ADD: −1.74% and SWITCH: −1.61% (all $p < 0.01$). Overall, 65.3% achieved HbA1c ≤7.0% (53 mmol/mol); average duration for achieving glucose control was 80.1 days. Mean weight loss ranged from −1.45 to −1.27 kg. Severe hypoglycemia was experienced by 0.06% of participants. Most (95.5%) indicated a greater likelihood of adherence with the gliclazide MR 60 mg regime relative to their previous therapy.
Conclusions: In this large, real world study, progressive uptitration with gliclazide MR 60 mg once daily appears to be efficacious and safe in individuals with suboptimal glycemic control at various stages of the diabetes continuum.

* *Corresponding author.* Tel.: +1 416 867 7441; fax: +1 416 867 3696.
E-mail address: leiterl@smh.ca (L.A. Leiter).
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1. Introduction

Patients with type 2 diabetes who effectively achieve glycemic control early on in the course of the disease tend to benefit from a reduction in long-term microvascular and macrovascular complications [1]. Translating this evidence into everyday clinical practice has, however, proven to be challenging [2–4]. Worldwide, metformin is well entrenched as the cornerstone of glucose lowering therapy [5–8]. In contrast, there is less concordance on how to manage dysglycemia when metformin yields suboptimal response or is contraindicated [5–9].

Although the emerging antihyperglycemic agents are associated with less weight gain and a lower likelihood of triggering hypoglycemic episodes than some of the traditional glucose lowering pharmacotherapies [10], sulfonylureas remain the preferred second-line agent by many patients and physicians. Notably, however, many guidelines now discourage the use of glyburide because of the increased risk for weight gain and hypoglycemia.

Gliclazide is a second generation sulfonylurea that is often favoured over other members in the class [9] due to its lesser propensity to cause weight gain and hypoglycemia. Further, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study as well as observational and meta-analysis data suggest it has a relatively safer cardiovascular profile [11–17]. A modified release (MR) formulation of gliclazide, used either as mono- or combination therapy, was previously reported in an open extension study to appreciably and safely provide glycemic control over 2 years [18]. Subsequently, the ADVANCE trial revealed that intensive glucose control with gliclazide MR to progressively achieve a hemoglobin A1c (HbA1c) of 6.5% (48 mmol/mol) or less was associated with a significant 10% risk reduction of combined macrovascular and microvascular events [15,16].

Inasmuch as medication adherence is a lynchpin in achieving glycemic control, a new and convenient scored once daily gliclazide MR formulation (MR 60 mg) has been developed to reduce medication nonadherence. The primary goal of the ObsErvationAl Study to analYse titration of Diamicron MR 60 mg in daily clinical practice in a large population with uncontrolled type 2 diabetes (EASYDia) study was to explore the temporal titration profile of the new gliclazide MR formulation when used either as a first- or second-line prescription in individuals with inadequately controlled type 2 diabetes.

2. Methods

2.1. Study conduct and population

EASYDia was a 6-month long, international, multicentre, non-comparative, open-label observational study (ISRCTN00943368) conducted in accordance with the standards and principles of the Declaration of Helsinki. Ethics approval was site specific and obtained prior to study initiation. All participants provided written informed consent at or before the baseline visit.

Between July 2011 and February 2014, individuals aged ≥35 years with type 2 diabetes, HbA1c ≥7.5% (59 mmol/mol) and not on insulin were screened at 596 sites located in 8 countries (Armenia, Georgia, Lebanon, Malaysia, Russia, Slovenia, Switzerland and Turkey). Those who were pregnant or breast feeding, with hypersensitivity to sulfonylureas, severe hepatic or renal failure (creatinine clearance <30 mL/min), contraindication to gliclazide, an uncontrolled and clinically significant disease or known malignancy, a high probability of nonadherence to study treatment or follow-up or being treated with miconazole were excluded.

At the baseline visit, participants were prescribed 30 to 120 mg once daily (QD) of the gliclazide MR 60 mg formulation as a first line (FIRST; newly diagnosed and/or pharmacotherapy naïve), add-on (ADD) or switch from a previous oral antihyperglycemic treatment strategy (SWITCH). At months 1, 2 and 3, gliclazide MR 60 mg dosing was uptitrated (maximum 120 mg) based on fasting plasma glucose (FPG). Dosing and uptitration at baseline and at each subsequent visit was at the discretion of the investigator. Add-on of another oral antihyperglycemic agent was permitted if glycemic control remained sub-optimal despite gliclazide 120 mg QD. Target HbA1c was personalized and the close out visit took place at month 6.

2.2. Data collection

Physical assessments were conducted at baseline and month 6. The following were captured on case report forms at all visits: FPG, HbA1c (optional at month 3 visit), medical information, and occurrences as well as severity and resolution of adverse and serious adverse events. Severe hypoglycemic episodes were defined as those associated with transient central nervous system dysfunction without other apparent cause, in which the individual was unable to treat him/herself and required assistance from another party. Participants were counseled, if deemed necessary, on appropriate lifestyle interventions during each visit.

The primary evaluation criterion was the time between first gliclazide MR 60 mg intake and first occurrence of optimal glycemia control (typically HbA1c <7% [53 mmol/mol]). Prespecified secondary evaluation criteria included the average daily dose of gliclazide MR 60 mg at month 6; temporal gliclazide MR 60 mg doses and dose escalation; differences in FPG, HbA1c, percentage of participants with an HbA1c ≤6.5% (48 mmol/mol) and ≤7.0% (53 mmol/mol), and weight between baseline and study end; compliance as assessed through a qualitative questionnaire addressed to the investigators; and frequencies of severe hypoglycemia and adverse events.

2.3. Statistical analyses

Demographic data and other baseline characteristics are reported for the included set (IS). Temporal changes in weight and body mass index (BMI) are reported for the safety set (SS). All other pre-specified end points are reported for the full analysis set (FAS).

Data, presented as means or mean ± standard deviation (SD), were stratified according to pre-defined criteria for analysis. Intra-group changes for HbA1c and FPG between

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