Comparison of Adherence to Glimepiride/Metformin Sustained Release Once-daily Versus Glimepiride/Metformin Immediate Release BID Fixed-combination Therapy Using the Medication Event Monitoring System in Patients With Type 2 Diabetes

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ABSTRACT

Purpose: The purpose of this study was to compare the adherence of the glimepiride/metformin sustained release (GM-SR) once-daily fixed-dose combination and glimepiride/metformin immediate release (GM-IR) BID fixed-dose combination in type 2 diabetes therapies.

Methods: An open-label, randomized, multicenter, parallel-group study was conducted at 11 hospitals in the Republic of Korea. A total of 168 patients with type 2 diabetes treated with >4 mg of glimepiride and 1000 mg of metformin by using free or fixed-dose combination therapy for at least 2 weeks were enrolled. Patients were randomized to receive GM-SR 4/1000 mg once-daily or GM-IR 2/500 mg BID for 24 weeks. Adherence was compared by using the Medication Event Monitoring System (MEMS).

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Findings: A significant difference in adherence was observed between the 2 groups. Overall adherence, defined by the number of container openings divided by the number of prescribed doses, was 91.7% in the GM-SR group and 88.6% in the GM-IR group ($P < 0.001$). The percentage of treatment days with the correct number of doses taken was 85.3% in the GM-SR group and 75.1% in the GM-IR group ($P < 0.001$). The percentage of missed doses was 11.7% in the GM-SR group and 15.3% in the GM-IR group ($P < 0.001$). The percentage of doses taken in the correct time window and therapeutic coverage were higher in the GM-SR group ($P < 0.001$). There was no significant difference in glycosylated hemoglobin changes or number of adverse events between the 2 groups. A total of 168 patients randomized to receive GM-SR once daily (86 patients) or GM-IR twice daily (82 patients). Mean Age were 57.8 ± 9.6 years old. Male : female ratio was 47.6 : 52.4 %. Body mass index were 66.3 ± 12.0 kg/m2, Diabetes duration were 10.5 ± 6.6 years.

Implications: This study showed that patient adherence with GM-SR once daily was significantly better than with GM-IR BID. ClinicalTrials.gov identifier: NCT01620489. (*Clin Ther.* ▮▮▮▮;▮:▮▮▮–▮▮▮)

Key words: fixed dose combination, MEMS, sulfonylurea, glimepiride.

INTRODUCTION

The prevalence of diabetes is increasing worldwide due to an aging society, obesity, and lack of exercise; the burden on society is increasing due to medical costs, complications, disability, and death.[1] In the Republic of Korea, the prevalence of diabetes was 0.5% in the 1960s but rose to 7.2% in 1990 and 13.7% by 2013–2014.[2]

Although the target goal of glycosylated hemoglobin (HbA_{1c}) for managing hyperglycemia has increased, many patients with type 2 diabetes still do not reach that target.[3,4] The proportions of patients with diabetes meeting an HbA_{1c} goal of $<6.5\%$ and $<7\%$ were 27% and 45.6%, respectively, in the Republic of Korea.[4] One of the most important problems in treatment is patient nonadherence. In type 2 diabetes, taking various medications is one of the factors that can decrease adherence. Due to the progressive nature of type 2 diabetes, many patients require multiple antihyperglycemic agents. Along with comorbidity and complications, patients with type 2 diabetes require more medications; in 1 study, these patients were prescribed a mean of 8.4 (3.0) medications per day.[5]

Adherence is commonly overlooked in clinical practice, although it is an essential part of treating chronic diseases. In a retrospective observation study, Rozenfeld et al[6] reported that for each 10% decrease in drug adherence, a 0.1% decrease in HbA_{1c} level was observed. The adherence rate for oral antidiabetic agents ranged from 65% to 85%. Guillausseau et al[7] reported in a prospective observation study that patients were less likely to adhere to treatment as the frequency of dosing increased from once daily to 3 or 4 times per day, and treatment efficacy exhibited an inverse correlation with dosing frequency. In one randomized controlled trial (the UMPIRE [Use of a Multidrug Pill In Reducing Cardiovascular Events] trial), fixed-dose combinations for aspirin, statins, and hypertension medication improved adherence and clinical outcomes (blood pressure and LDL-C).[8]

Current American Diabetes Association and Korean Diabetes Association guidelines recommend sulfonylurea as a second-line agent after metformin.[9,10] Sulfonylurea is the most widely used second-line agent after metformin and is widely used in combination with insulin in the Republic of Korea.[11] The glimepiride/metformin immediate release (GM-IR) 2/500 mg tablet is a fixed-dose combination product widely used BID in the clinical setting. Recently, a glimepiride/metformin sustained release (GM-SR) 2/500 mg fixed-dose tablet was developed.[12] Metformin is sustained release and glimepiride is immediate release in this fixed-dose tablet. GM-SR can be administered once daily and is designed to enhance drug adherence.

Although direct observation of therapy is the most accurate way to measure adherence, it is impractical. Although measuring drug levels and drug byproducts with a blood test may be objective, conditions such as "white-coat adherence," in which patients only show good adherence for 5 days before visiting the hospital, may create false information, and performing laboratory tests may be inconvenient. Therefore, indirect methods such as patient self-reported adherence, the pill count method, and rate of prescription refill are commonly used. Such methods are objective and