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Original Article

Effectiveness of Brand-Name and Generic Versions of Glimepiride for Diabetes Mellitus Care: Experience at a Medical Center in Taiwan

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SUMMARY

Background: We used electronic medical records (EMRs) to perform a comparative investigation of the pharmacotherapy outcomes in patients administered brand-name and generic glimepiride for treatment of diabetes mellitus.
Methods: We collected data on prescribed daily doses (PDD) and HbA1c levels of diabetes mellitus patients given metformin and glimepiride, but not pioglitazone for at least 6 months prior to October 13, 2012, after which glimepiride was replaced with generic drugs. The PDD/defined daily dose (DDD) ratio for glimepiride therapy and HbA1c levels before and after the replacement were compared.
Results: A total of 257 cases (128 males, 64.6 ± 12.0 years old) were included in the analysis. Of these, 33 (12.8%) remained unchanged in terms of antidiabetic drug dosage and/or the drugs administered, and 224 (87.2%) showed such changes after the glimepiride brand-name–generic drug switch. There was no significant difference in mean HbA1c levels measured before and after replacement. PDD/DDD ratios (3.1 ± 1.4) of glimepiride showed a significant increase in 224 cases, while PDD/DDD ratios in the aforementioned 33 cases remained 2.3 ± 1.1 before and after the medication switch.
Conclusion: Diabetic patients using generic glimepiride had similar HbA1c levels compared to patients using the brand-name drug. Nonetheless, the doses required up-titration, and the differing cost-effectiveness should be evaluated and considered. EMR analysis for brand-name–generic drug switch studies is feasible and recommended, but it is important to rigorously ensure that the study method will not introduce confounding bias before enrolling patients.

1. Introduction

The use of generic drugs is a worldwide trend aimed at reducing medical expenditure. The acceptance of and preference for generic drugs by physicians is influenced both by fact and perception.[1] Major influencing factors include prices and the marketing skill employed by companies advertising their products.[2,3] Doctors tend to choose brand-name drugs in cases of more severe illness.[1] Other issues for physicians and pharmacists to consider include the safety and efficacy of generic drugs and the sale of counterfeit drugs.[3] Studies related to a brand-name–generic drug switch are usually conducted on healthy volunteers, involve short follow-up times, and recruit small numbers.[4] The best approach for evaluation of pharmacotherapy outcomes is to perform randomized control trials (RCTs). However, RCTs are usually very expensive and require a long study period. Instead of RCTs, many countries evaluate generic drugs by means of bioequivalence tests that rely on comparisons with brand-name drugs.[5-7] However, few studies have discussed therapeutic equivalence.[7] The bioequivalence approach has two fundamental problems. First, equivalence is determined based on whether peak plasma concentration (C_{max}) in test patients is within a 90% confidence interval of reference levels. Second, most bioequivalence studies involve healthy volunteers, not patients with diseases. As a consequence, the safety and efficacy of generic drugs evaluated this way have been questioned.[8]

Some studies have demonstrated no significant difference between brand-name drugs and generic drugs.[4,9,10] Most physicians are concerned about the safety and efficacy of drugs that have a narrow therapeutic window, such as immunosuppressants, anticonvulsants, and anticoagulants.[4,8,11] Some researchers have demonstrated that among anticonvulsants, brand-name drugs have better performance, adherence, and are associated with lower medical expenditure than generic drugs.[12-15] More studies are needed to confirm safety and efficacy of generic drugs and further monitoring should be enforced when patients switch to generic drugs from brand-name drugs.[11] Treatment regimens involving antidiabetic agents for type 2 diabetes mellitus must be designed to minimize the risk of hypoglycemia and other side effects. It is crucial that the safety and efficacy of antidiabetic treatment is maintained when brand-name drugs are replaced by generic versions.

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The use of electronic medical records (EMRs) for conducting studies has become very popular in modern times.[10,14-17] EMRs, which are stored in hospitals, include not only patient demographic data but also clinical outcome data from before and after a brand-name–generic medication switch is carried out. Although these records can be used only for retrospective studies, we can evaluate pharmacotherapy outcomes of drug switching and determine the influence of the switch on disease outcomes. This approach may reduce the research costs relative to RCTs and help determine therapeutic equivalence between brand-name and generic drugs. It may also provide data that contributes to the efficient usage of drugs. We used EMRs to perform comparative study of the pharmacotherapy outcomes in patients administered brand-name and generic versions of glimepiride.

2. Patients and methods

The study protocol was approved by the Institutional Review Board (IRB) of the MacKay Memorial Hospital (IRB approval number: 15MMHIS143e). We enrolled diabetic patients prescribed both oral hypoglycemic agent and insulin (Table 1) at a medical center from April 1, 2012, to April 30, 2013. During this period, the treatment regimen included a switch from brand-name to generic medication for the antidiabetic agents glimepiride (2 mg) and pioglitazone (15 mg) (Amaryl® replaced by Glipid® on October 13, 2012, and Actos® by Anxotos® on October 29, 2012 respectively). The oral hypoglycemic agent and insulin prescription remained unchanged. To exclude the influence of the pioglitazone medication switch, patients prescribed pioglitazone were excluded from our evaluation. We screened all outpatient department patients in April 2012. Of the 96939 outpatient department patients given drugs, 918 continuously used at least metformin and glimepiride, but not pioglitazone after April 1, 2012 (6 months before October 13, 2012). These patients were included in the analysis. Patients were further excluded if any doses or medications were altered during the 6 month-period between April 1, 2012 and October 13, 2012, after which only 310 patients were left in the study. Of these, 53 patients for whom HbA1c data from before and after October 13, 2012 were unavailable were also excluded. Finally, 257 patients were included for analysis. The case management flow chart is shown in Fig. 1. The data on HbA1c from before and after the glimepiride medication switch were collected.

The defined daily doses (DDD) are used as a standard for the measurement of drug utilization and drug exposure in a population. The prescribed daily dose (PDD) is defined as the average dose prescribed to a representative sample population of patients. The World Health Organization defines the DDD of glimepiride as 2 mg.[18,19] This study used the PDD/DDD ratio to evaluate the prescribed doses of glimepiride. We collected data on age, gender, PDD, and HbA1c levels from April 2012 to April 2013.

We divided the 257 cases included in the analysis into two groups: patients who underwent changes in the administered dosage of any drug or in the number of prescribed antidiabetic agents after October 13, 2012, were categorized as Group 1, and the remaining patients as Group 2. According to the American Diabetes Association's 2017 guidelines,[20] we defined patients with HbA1c levels < 7.0% as having good diabetic control and HbA1c levels ≥ 7.0% as having unsatisfactory diabetic control

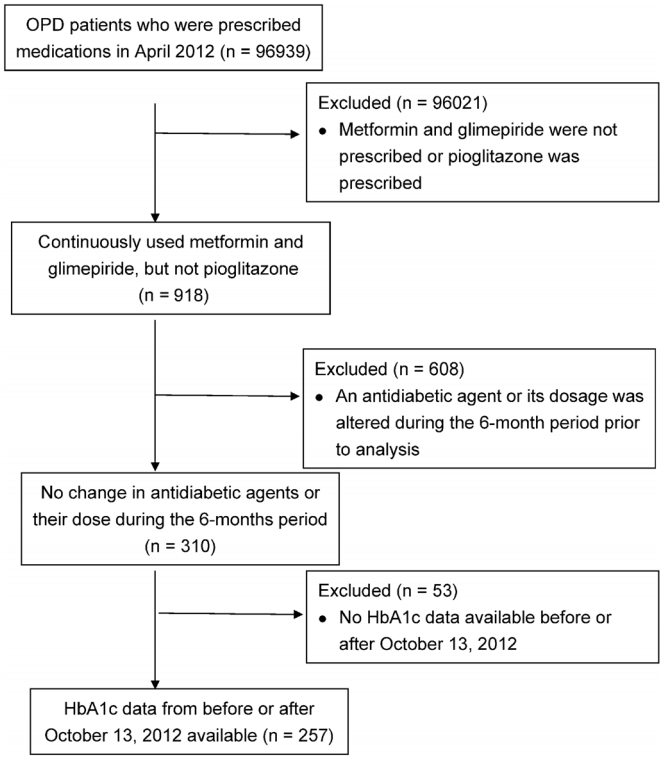

Fig. 1. Flow chart depicting the selection of patients for inclusion in our analysis.

Table 1
List of antidiabetic agents available for prescription to patients in the present study.

Pharmacologic category	Drug name	Dosage form
Biguanide	Metformin HCl 500 mg	Oral
Sulfonylureas	Glibenclamide 5 mg	Oral
Sulfonylureas	Glimepiride 2 mg	Oral
Sulfonylureas	Gliclazide MR 30 mg	Oral
Alpha-glucosidase inhibitor	Acarbose 100 mg	Oral
Meglitinide	Repaglinide	Oral
Thiazolidinediones	Pioglitazone 30 mg	Oral
Dipeptidyl peptidase-4 inhibitor	Sitagliptin 100 mg	Oral
Dipeptidyl peptidase-4 inhibitor	Saxagliptin 5 mg	Oral
Sulfonylureas & Biguanide	Glimepiride 2 mg & Metformin 500 mg	Oral
Thiazolidinediones & Biguanide	Pioglitazone 15 mg & Metformin 850 mg	Oral
Insulins	Insulin lispro 25%, Insulin lispro protamine 75% 300 IU/3 mL	Injection
Insulins	Insulin lispro 50%, Insulin lispro protamine 50% 300 IU/3 mL	Injection
Insulins	Insulin glargine 300 U/3 mL	Injection
Insulins	Insulin Aspart 300 U/3 mL	Injection
Insulins	Insulin detemir 300 U/3 mL	Injection

Pearson's chi-square test, Student's *t* test, Fisher's exact test, and the Mann–Whitney *U* method were used for data analysis. Statistical analysis was conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

3. Results

Of the 257 patients (128 males, 48.6%) included in the analysis, 224 (87.2%) experienced a change in the number of antidiabetic agents prescribed and/or administered dosage of any drug (Group 1, "Changed"), and 33 (12.8%) cases experienced no change in medication (Group 2, "Unchanged"). In Group 1 (n = 224), the doses of glimepiride were increased in 183 cases, and in the other 41 cases the doses and/or number of other antidiabetic agents were increased in addition to increase in glimepiride dosage. In no case was the number of antidiabetic agents or the administered dose reduced. There was no significant difference in gender ratio ($p = 0.854$) between the groups. The average patient age for all analyzed cases was 64.6 ± 12.0 years (mean ± SD). There was no significant difference in mean age between the two groups (65.6 ± 11.9 vs. 64.5 ± 12.1; $p = 0.600$). The average PDD/DDD ratio of glimepiride in Group 2 (2.3 ± 1.1) was higher than that in Group 1 (1.8 ± 1.1) before the switch to a generic drug ($p < 0.01$). After the replacement, the average PDD/DDD ratio for Group 2 remained unchanged (2.3 ± 1.1). However, the ratio for Group 1 (3.1 ± 1.4) significantly increased compared to the value before the switch ($p < 0.001$) and was higher than the average ratio for Group 2 ($p < 0.001$). The data are summarized in Table 2.

Before glimepiride was replaced by generic drugs, there were 143 cases of good diabetic control (HbA1c < 7.0%) and 114 cases of unsatisfactory diabetic control (HbA1c ≥ 7.0%). When we compared the ratio of patients with good diabetic control to those with unsatisfactory control for Group 1 (127 to 97) with the same ratio for Group 2 (16 to 17) before the medication switch, no significant difference was found ($p = 0.375$). The mean HbA1c level before replacement with the generic drug in all cases was 7.1% (± 1.2%). There was no significant difference in mean HbA1c levels between Group 1 (7.0% ± 1.1%) and Group 2 (7.4% ± 1.5%) before brand-name glimepiride was replaced by a generic drug ($p = 0.077$). The numbers of patients with good and unsatisfactory diabetic control were 136 and 121 respectively after brand-name glimepiride was replaced by generic drugs. There was also no significant difference between the ratio of patients with good diabetic control for Group 1 (good/unsatisfactory = 121/103) and the same ratio for Group 2 (good/unsatisfactory = 15/18) after the replacement of brand-name glimepiride with generic drugs ($p = 0.358$). The mean HbA1c level after the medication switch for all cases was 7.1% (±1.1%). There was no significant difference in this parameter between Group 1 (HbA1c 7.0% ± 1.0%) and Group 2 (HbA1c 7.5% ± 1.12%) after replacement with generic drugs ($p = 0.101$). The mean HbA1c levels as assessed using the Wilcoxon rank sum test were not significantly different before and after replacement of brand-name glimepiride with generic drugs ($p = 0.160$; Table 3).

4. Discussion

This study showed that in diabetic patients regularly receiving hypoglycemic drugs from the outpatient department, overall, the glimepiride brand-name–generic medication switch did not affect the HbA1c level, regardless of any other changes in the number or dosage of prescribed antidiabetic agents. On the other hand, the PDD/DDD ratio was altered by the medication switch in cases where

Table 2
Demographic data and PDD/DDD ratios for patients before and after the switch from brand-name to generic drugs (comparison between Changed and Unchanged groups).

	Group 1 (Changed) (n = 224)	Group 2 (Unchanged) (n = 33)	All (n = 257)	*p* value
Gender (male:female)	111:113	17:16	128:129	0.854[a]
Age	65.6 ± 11.9	64.5 ± 12.1	64.6 ± 12.0	0.600[b]
Dose of glimepiride (PDD/DDD ratio)				
Before switch to generic drug	1.8 ± 1.1	2.3 ± 1.1	1.8 ± 1.1	< 0.01[c]
After switch to generic drug	3.1 ± 1.4	2.3 ± 1.1	3.0 ± 1.4	< 0.001

[a] Pearson's chi-square test; [b] Mann–Whitney *U* test; [c] Student's *t* test.
PDD, prescribed daily dose; DDD, defined daily dose.
Group 1 (Changed): Patients who experienced changes in the administered dosage of any drug or in the number of prescribed antidiabetic agents following the glimepiride medication switch. Group 2 (Unchanged): Patients who did not experience changes in the administered dosage of any drug or in the number of prescribed antidiabetic agents following the glimepiride medication switch.

Table 3
Comparison between mean levels of HbA1c before and after replacement of brand-name with generic glimepiride in Groups 1 (Changed) and 2 (Unchanged).

	Group 1 (Changed) (n = 224)	Group 2 (Unchanged) (n = 33)	All cases (n = 257)	*p* value
Before switch to generic drug[#]				0.375[a]
HbA1c < 7.0% (good diabetic control) (n)	127	16	143	
HbA1c ≥ 7.0% (unsatisfactory diabetic control) (n)	97	17	114	
Mean HbA1c levels	7.0 ± 1.1	7.4 ± 1.5	7.1 ± 1.2	0.077[b]
After switch to generic drug[#]				0.358[a]
HbA1c < 7.0% (good diabetic control) (n)	121	15	136	
HbA1c ≥ 7.0% (unsatisfactory diabetic control) (n)	103	18	121	
Mean HbA1c levels	7.0 ± 1.0	7.5 ± 1.2	7.1 ± 1.1	0.101[b]

[a] Pearson chi-square test; [b] Mann–Whitney *U*; [c] Student's *t* test.
[#] The comparison of mean HbA1c levels before and after the switch to the generic drug. The two values were compared using the Wilcoxon rank sum test, with $p = 0.160$.

the number and/or dosage of other antidiabetic agents were altered. Since brand-name-generic drug switches are widespread in Taiwan and other countries, the novel findings of the present study have important clinical implications.

Most studies have shown that there is no significant difference in bioavailability and bioequivalence between generic and brand-name drugs.[4,6,9] Nonetheless, several studies suggest that monitoring of the brand-name–generic medication switching is necessary to understand its clinical impact.[11] We think that these data are particularly important in the case of hypoglycemic drugs because a change in drug could lead to hyper- or hypoglycemia, with the latter in particular posing significant risk to patients. Regarding the dose and number of antidiabetic agents other than glimepiride, this study found that, during the study period, although mean HbA1c levels remained stationary for both groups, the PDD/DDD ratio increased significantly following drug replacement in Group 1 (changed group), which accounted for 87.2% of all study patients, and which included patients who experienced changes in the doses and/or number of antidiabetic agents other than glimepiride. Actually, we found that the dose of glimepiride was increased by ~66.6% following the brand-name–generic drug switch (PDD/DDD ratio before the switch: 1.8 ± 1.1; after the switch: 3.1 ± 1.4). This finding raises the suspicion that the generic drug in fact possesses lower hypoglycemic potency than the brand-name drug. Nevertheless, one possible explanation for the increased dosage is that the natural course of diabetes makes a higher dose of drugs or additional drugs with other hypoglycemic mechanisms of action necessary to control blood sugar. However, when considering the question of generic drug versus brand-name drug potency, it is important to keep in mind that an increase in the number of drug tablets can adversely affect medication adherence and frustrate attempts to bring the disease under control.[21]

It is important to understand why the PDD/DDD ratio was significantly higher in Group 1 (changed group) patients after the brand-name–generic medication switch, while the HbA1c level remained minimally changed. One of the possibilities is that the patients and/or physicians in charge may regularly monitor blood sugar such that the dosage or the number of antidiabetic agents prescribed had been adjusted several weeks before HbA1c levels were checked. To clarify this issue, in the future, studies that evaluate a brand-name–generic switch of hypoglycemic drugs should collect data on blood sugar after the medication switch in addition to the measuring HbA1c levels.

To date, RCTs have been considered the best method to compare the efficacy, potency, and safety of brand-name and generic drugs.[7,9] A study on a switch from brand-name to generic drug in target patients is another method of research.[11] Unfortunately, it is the costliest approach to evaluating drug efficacy and safety. Compared to RCTs and switch studies, bioequivalence studies cost less. However, bioequivalence studies reveal only the pharmacokinetics of generic drugs in healthy volunteers. The safety and efficacy of generic drugs can be ascertained only from bioequivalence studies.[8] Some studies have used EMRs to compare the efficacy, safety, adherence, and cost of brand-name medication with generic drugs.[14,15] Our study followed the same approach but used a better design: we collected data on patients who were stable for at least 6 months and switched only one drug from brand-name to generic version. This study not only contributed new knowledge regarding brand-name drugs and generic drugs at a lower cost than RCTs and switch studies but also yielded more information about the differences between generic and brand-name drugs than can be obtained from a bioequivalence study. This may therefore be a good approach for the evaluation of pharmacotherapy outcomes in patients who undergo medication switch during treatment.

Our study has some limitations. First, we examined only the glimepiride manufactured by one pharmaceutical company. Whether the findings apply to glimepiride manufactured by other pharmaceutical companies or to other oral hypoglycemic agents remains unclear. More studies must be performed to confirm the pharmacotherapy outcomes for these other drugs. Second, during the 6-month observation period following the brand-name–generic drug switch, we did not collect data on hypoglycemic events to confirm the safety of drugs. We also did not collect patient weight data, which may have reflected self-awareness and diabetic control status of the patients during the 6-month period. Third, as mentioned before, we did not collect patient blood sugar data during the study period. These data serve as a reference for physicians when adjusting administration of hypoglycemic drugs. Finally, the data were collected from a single medical center; that is, this was not a multi-center study. The differing medical culture found in different hospitals may form a source of bias that our single-center study cannot account for. In future, longitudinal big data analysis of large-scale cohort studies will be necessary to solve these problems.

In conclusion, this study showed that diabetic patients who were administered generic glimepiride had similar HbA1c levels when compared to patients administered the brand-name drug. Nonetheless, the doses needed up-titration in case of generic drug administration, and a comparative evaluation of cost-effectiveness of the generic and brand-name medication should be considered. EMR analysis for the brand-name–generic drug switch studies is feasible and costs less than RCTs or switch studies, while also providing more clinical information about the important differences between these two versions of a drug than obtained from a bioequivalence study. The protocol used in the present study may form a good approach for the evaluation of pharmacotherapy outcomes. However, EMR analysis should be rigorously designed to avoid introducing confounding bias before enrolling patients, and is not a true replacement for prospective RCT studies.

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Author contributions

C.F. Chen, H.I. Yeh, and T.C. Hung came up with initial the concept of study. C.F. Chen, H.W. Ting, and T.C. Hung designed the experiments. C.F. Chen and C.Z. Yang conducted the experiments. C.Z. Yang and H.W. Ting analyzed the data. C.F. Chen and H.W. Ting wrote the paper. T.C. Hung and H.I. Yeh revised the paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest. The funding agency had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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