Adherence to a Fixed-Dose Combination of Rosiglitazone Maleate/Metformin Hydrochloride in Subjects with Type 2 Diabetes Mellitus: A Retrospective Database Analysis

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ABSTRACT

Background: In 2002, fixed-dose combination therapy (FDCT) with rosiglitazone maleate plus metformin hydrochloride became available for the treatment of type 2 diabetes mellitus (DM-2) in subjects whose disease was uncontrolled on monotherapy with metformin or a thiazolidinedione. FDCT allows a reduced pill burden and a less complex medication regimen.

Objective: The objective of this study was to assess changes in medication adherence rates associated with oral hypoglycemic agents in subjects switching from either monotherapy or dual therapy with metformin and/or rosiglitazone to rosiglitazone-metformin FDCT.

Methods: In this retrospective database analysis, data were obtained from the pharmacy claims database of a large health benefits company. Prescription claims for subjects aged ≥18 years with DM-2 whose disease was uncontrolled on monotherapy with metformin or a thiazolidinedione were analyzed over a 12-month study period (a 6-month preindex period and a 6-month postindex period). Some subjects were receiving monotherapy with either metformin or rosiglitazone during the preindex period and remained on monotherapy throughout the postindex period (Mono/Mono cohort), switched to dual therapy with both agents (Mono/Dual cohort), or switched to FDCT (Mono/FDCT cohort). Some subjects were receiving dual therapy with metformin and rosiglitazone during the preindex period and remained on dual therapy throughout the postindex period (Dual/Dual cohort) or switched to FDCT (Dual/FDCT cohort). A medication possession ratio (MPR)—a proxy measurement of medication adherence—was calculated for each subject for each period. Changes in medication adherence were compared using a general linear model.

Results: Overall, data from the records of 16,928 subjects (8499 men, 8429 women; mean [SD] age, 58.12 [11.97] years) were included in this study. There was significantly less reduction in the MPR change for the Mono/FDCT cohort compared with the Mono/Dual cohort (–4.6% vs –12.4%; $P < 0.001$). There was significant improvement in the mean MPR change for the Dual/FDCT cohort compared with the Dual/Dual cohort (3.5% vs –1.3%; $P < 0.005$).

Conclusions: The results of this retrospective database analysis suggest that rosiglitazone-metformin FDCT yielded significant improvements in medication adherence rates compared with dual therapy regimens. (*Clin Ther.* 2004;26:2066–2075) Copyright © 2004 Excerpta Medica, Inc.

Key words: fixed-dose combination therapy, compliance, adherence, diabetes mellitus, oral antidiabetic medications, oral hypoglycemic agents.

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INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), the prevalence of diagnosed type 2 diabetes mellitus (DM-2) in the United States more than doubled between 1980 and 2002, from 5.8 million to 13.3 million.[1] The direct and indirect costs associated with this disease are estimated to total approximately US $132 billion/y.[2] In addition, the CDC estimates that of Americans born in 2000, 1 in 3 will develop DM-2.[3]

Self-care activities associated with diabetes include exercise, diet, blood glucose monitoring, and proper medication use.[4] Substantial attention has been given to enhancing self-care behaviors,[4–7] with considerable focus on medication adherence.[8–10] Evidence suggests that medication adherence decreases with the increasing complexity of diabetes therapy regimens,[11–13] which is important because of the direct relationship found between poor adherence and poor glycemic control,[14,15] and the inverse relationship found between adherence and health care service use.[16,17] Advancements in medication formulations are helping to overcome some of the limitations with multidrug regimens.

Fixed-dose combination therapy (FDCT) allows multiple medications, often with complementary mechanisms of action, to be given in a single formulation.[18] In recent years, FDCT was introduced in multiple drug classes and disease states, including DM-2.[19–22] FDCT was originally used to allow medications to work synergistically, enabling improved clinical outcomes.[18] However, due to overall reductions in regimen complexity allowed by FDCT, improvements in medication adherence have also been observed.[19,23] A study by Melikian et al[23] showed that glyburide-metformin FDCT increased subjects' medication adherence rates compared with dual therapy with the 2 agents.

FDCTs for DM-2 are available in several dosage formulations. Therefore, studies of the new FDCTs are needed to validate previous results. In 2002, an FDCT composed of rosiglitazone maleate plus metformin hydrochloride became available. It is indicated for twice-daily treatment of DM-2 in subjects whose disease is uncontrolled with metformin or rosiglitazone monotherapy or dual therapy with the 2 agents. At launch, it was available in 3 dosage formulations: rosiglitazone-metformin 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg. It has since become available in 2 additional formulations: 2 mg/1000 mg and 4 mg/1000 mg.

The objective of the present study was to assess the changes in medication adherence rates associated with switching between oral hypoglycemic agent (OHA) regimens—specifically, switching from either monotherapy or dual therapy with metformin and/or rosiglitazone to rosiglitazone-metformin FDCT using data from a population of subjects in a health benefits company database.

MATERIALS AND METHODS

Prescription claims data for this retrospective database analysis were obtained from the pharmacy claims database of a large health benefits company encompassing ~3.5 million covered members. Subjects in the database were enrolled in 1 of 4 health benefit designs: health maintenance organization (HMO), preferred-provider organization (PPO), independent plan, or Medicare risk. The privacy office and statistical department of the health benefits company reviewed and approved the limited data set used in this analysis.

Study Population

Subjects aged ≥18 years with active pharmacy benefits coverage and who had at least 1 pharmacy claim for rosiglitazone or metformin during the identification period were included in this analysis. The first study medication claim within the identification period was designated as the *index prescription*. At least 2 prescription claims for study medications in both the preindex and postindex periods were also required for study inclusion. The *index date* was defined as the first day of the postindex period. Thus, the index prescription was included as one of the postindex prescriptions. Only data from subjects who maintained continuous medication therapy during the study period were included in the analysis. *Continuous medication therapy* was defined as therapy without a lapse of >60 days between the date of days' supply expiration of any prescription fill and the subsequent claim date. Finally, only data from subjects who maintained continuous plan enrollment during the duration of the study period were included. Data from subjects <18 years of age or those with nontraditional pharmacy benefits (eg, a generic-only plan that would limit their ability to obtain the study medications) were excluded.

Subjects were stratified into 1 of 5 therapy cohorts based on study medication use (**Table I**), as follows: monotherapy with either rosiglitazone or metformin throughout the study period (Mono/Mono); monotherapy with either agent in the preindex period and dual therapy with both agents in the postindex period (Mono/Dual); monotherapy with either agent in the preindex period and rosiglitazone-metformin FDCT in the postindex period (Mono/FDCT); dual therapy throughout the study period (Dual/Dual); dual therapy in the preindex period and rosiglitazone-metformin FDCT in the postindex period (Dual/FDCT).

Study Period Definitions

All study data were obtained from a 22-month period from May 1, 2002, to February 29, 2004. Prescription claims for each subject were analyzed over a 12-month study period. The study period included a 6-month preindex and a 6-month postindex time period. The study's *identification period* was defined as the 10 months between November 1, 2002, and August 31, 2003. During this period, all subjects had an index date assigned to them. In subjects who did not switch to FDCT, the index date was defined as the first prescription fill date for a study medication during the identification period; in subjects who switched to FDCT, the index date was defined as the first fill date for FDCT during the identification period.

Adherence Rate Definitions

Using the prescription claims database, a medication possession ratio (MPR) was calculated for each subject in the 6-month preindex and 6-month postindex periods. The MPR is a proxy measurement of medication adherence, with a scale of 0% to 100%, in which higher values indicate higher medication adherence. Due to variations in days' supply, values >100% were possible with the MPR adherence rate calculation. Thus, all values >100% were truncated to 100% for the purpose of analysis. MPR was calculated as follows:

$$\text{MPR} = \frac{\text{Total days' supply obtained}}{\left(\begin{array}{c}\text{Date of last claim} - \text{Date of first claim} \\ + \text{Days' supply of last claim}\end{array}\right)}$$

For subjects using dual therapy, a dual therapy MPR (DTMPR) was calculated, as follows:

$$\text{DTMPR} = \frac{(\text{Total days' supply obtained})/2}{\left(\begin{array}{c}\text{Date of last claim} - \text{Date of first claim} \\ + \text{Days' supply of last claim}\end{array}\right)}$$

Statistical Analysis

The primary focus of this analysis was to compare changes in medication adherence between monotherapy, dual therapy, and FDCT regimens. Specifically, comparisons of interest included the adherence rates of subjects switching from monotherapy to dual therapy versus those switching from monotherapy to FDCT (Mono/Dual vs Mono/FDCT), and subjects remaining on dual therapy versus those switching from dual therapy to FDCT (Dual/Dual vs Dual/FDCT).

To compare changes in adherence, an equivalent form of analysis of covariance (ANCOVA) was performed using a general linear model.[24] The model's outcome variable (ie, change in adherence) was calculated for each subject, as follows:

$$\text{MPR Change} = \text{Postindex MPR} - \text{Preindex MPR}$$

Table I. Cohort descriptions, determined by drug therapy.

Cohort	Preindex Therapy	Postindex Therapy
Mono/Mono	Metformin or rosiglitazone	Metformin or rosiglitazone
Mono/Dual	Metformin or rosiglitazone	Metformin and rosiglitazone
Mono/FDCT	Metformin or rosiglitazone	Rosiglitazone/metformin
Dual/Dual	Metformin and rosiglitazone	Metformin and rosiglitazone
Dual/FDCT	Metformin and rosiglitazone	Rosiglitazone/metformin

FDCT = fixed-dose combination therapy.

Within this model, a multivariate slope test was performed to ensure equality of the slopes across strata. Adjusted least squares mean of the change in adherence was calculated for each of the cohorts of interest. Pairwise comparisons were performed using the Tukey test to determine whether differences were significant between the cohorts of interest. All hypothesis testing was performed at a significance level of 0.05.

Several factors were controlled for within the multivariate model, including age, gender, insulin use, nonstudy OHA use, total pill burden at the index date, and chronic disease score (CDS) (defined later) from the preindex period. Insulin and nonstudy OHA use were determined from the prescription claims data. Subjects were flagged if they had claims for any of these medication types. The total pill burden calculation included all oral nonstudy medications and was calculated for each study subject at the index date.

The CDS score is a metric that uses age, gender, and medication history obtained from pharmacy claims data to calculate a risk-adjustment score.[25,26] Preindex CDS scores were calculated for all study subjects. Specifically, the CDS score by Clark et al[25] was calculated, which includes 3 risk-adjustment metrics, including total costs, outpatient costs, and primary care visits.

To test for differences in demographic characteristics across the therapy cohorts, an unbalanced analysis of variance, chi-square, and *t* tests were used. All analyses for this study were conducted using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). Multivariate analyses were performed using PROC GLM (SAS Institute Inc.).[24]

RESULTS

Of 178,288 subjects with DM-2 identified using the database, data from the 16,928 who met the inclusion criteria were used in this analysis. As shown in **Table II**, the Mono/Mono cohort was the largest group, consisting of 14,291 (84.4%) subjects. Gender was evenly distributed in the overall population, with data from 8499 (50.2%) men and 8429 (49.8%) women included. The mean (SD) age was 58.12 (11.97) years (range, 19–99 years). Mean (SD) total pill burden at the index date was 4.53 (4.77) pills, with a median of 3.00 pills (range, 0–56). Of the total sample, 7956 (47.0%) had HMO coverage, 5222 (30.9%) had PPO coverage, 3722 (22.0%) had Medicare risk benefits, and 28 (0.2%) subjects had individual plan benefits. A total of 2700 (16.0%) subjects were concurrently using insulin therapy, and 10,045 (59.3%) subjects were concurrently using nonstudy OHAs.

The total study sample's predicted mean (SD) CDS total cost calculation was US $3211.81 ($1581.98). The mean (SD) predicted CDS outpatient cost was $1504.45 ($664.65), and the mean (SD) predicted number of CDS primary care visits was 3.20 (0.94) (range, 0.82–8.09 visits).

Analysis of Covariance

The overall result of the multivariate model was statistically significant ($F = 52.73$; $P < 0.001$), indicating that at least 1 of the independent variables was different from 0. Further investigation revealed that the results of 3 of 9 independent variables compared in the model were statistically significant. Specifically, the therapy cohorts variable was significant ($F = 125.75$; $P < 0.001$), indicating that a statistically significant difference in adherence change existed among the 5 study cohorts. In addition, gender and total pill burden at the index date were statistically significant variables ($F = 8.48$, $P < 0.004$; and $F = 4.61$, $P < 0.032$, respectively).

Monotherapy

Of the 15,571 subjects using a monotherapy regimen before the index date, 14,291 (91.8%) remained on monotherapy (Mono/Mono), 931 (6.0%) switched to dual therapy (Mono/Dual), and 349 (2.2%) switched to FDCT (Mono/FDCT) after the index date (**Table II**). The mean (SD) age of the monotherapy cohorts were 58.50 (12.17), 56.87 (11.31), and 54.91 (11.35) years, respectively. A significantly lower proportion of subjects had Medicare risk benefits in the Mono/Dual cohort (147 subjects [15.8%]; $P < 0.001$) and the Mono/FDCT cohort (54 subjects [15.5%]; $P < 0.003$) compared with the Mono/Mono cohort (3394 subjects [23.7%]). In addition, the proportion of subjects with nonstudy OHA use was significantly lower in the Mono/Mono cohort (8254 subjects [57.8%]; $P < 0.001$) and Mono/FDCT cohort (201 subjects [57.6%]; $P < 0.001$) compared with the Mono/Dual cohort (675 subjects [72.5%]). The CDS scores were each significantly lower for the Mono/FDCT cohort compared with the Mono/Mono

Table II. Baseline characteristics of the study population.*

Characteristic	Mono/Mono (n = 14,291)	Mono/Dual (n = 931)	Mono/FDCT (n = 349)	Dual/Dual (n = 1230)	Dual/FDCT (n = 127)	Population (N = 16,928)
Gender, no. (%)						
Male	7257 (50.8)	450 (48.3)	158 (45.3)	500 (40.7)	64 (50.4)	8429 (49.8)
Female	7034 (49.2)	481 (51.7)	191 (54.7)	730 (59.4)	63 (49.6)	8499 (50.2)
Age, y						
Mean (SD)	58.50 (12.17)	56.87 (11.31)	54.91 (11.35)	56.00 (9.72)	53.69 (10.58)	58.12 (11.97)
Median	58.00	56.00	54.00	56.00	53.00	58.00
Range	19–99	19–90	26–89	19–89	32–87	19–99
Total pill burden						
Mean (SD)	4.56 (4.84)	4.31 (4.36)	3.45 (3.27)	4.73 (4.67)	4.49 (3.61)	4.53 (4.77)
Median	3.00	3.00	2.00	4.00	3.00	3.00
Range	0–56	0–33	0–22	0–38	0–20	0–56
Insurance type, no. (%)						
HMO	6,607 (46.2)	463 (49.7)	172 (49.3)	657 (53.4)	57 (44.9)	7,956 (47.0)
PPO	4,263 (29.9)	320 (34.4)	123 (35.2)	462 (37.6)	54 (42.5)	5,222 (30.8)
Medicare	3,394 (23.7)	147 (15.8)	54 (15.5)	111 (9.0)	16 (12.6)	3,722 (22.0)
Independent	27 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	28 (0.2)
Insulin use, no. (%)						
Yes	12,049 (84.3)	762 (81.8)	289 (82.8)	1,026 (83.4)	102 (80.3)	14,228 (84.1)
No	2,242 (15.7)	169 (18.2)	60 (17.2)	204 (16.6)	25 (19.7)	2,700 (16.0)
Nonstudy OHA use, no. (%)						
Yes	8,254 (57.8)	675 (72.5)	201 (57.6)	837 (68.0)	78 (61.4)	10,045 (59.3)
No	6,037 (42.2)	256 (27.5)	148 (42.4)	393 (32.0)	49 (38.6)	6,883 (40.7)

FDCT = fixed-dose combination therapy; HMO = health maintenance organization; PPO = preferred-provider organization; OHA = oral hypoglycemic agent.
*See **Figure 1** for a description of each study cohort.

and Mono/Dual cohorts: predicted total cost, US $2870.94 versus $3232.79 ($P < 0.001$) and $2870.94 versus $3212.24 ($P < 0.002$), respectively; predicted outpatient cost, $1390.72 versus $1506.68 ($P < 0.005$) and $1390.72 versus $1533.39 ($P < 0.003$), respectively; and predicted primary care visits, 3.06 versus 3.21 visits ($P < 0.01$) and 3.06 versus 3.24 visits ($P < 0.007$), respectively.

As illustrated in **Figure 1**, the Mono/Dual cohort exhibited a slightly lower preindex MPR (0.80 [0.19]) compared with the Mono/Mono cohort (0.90 [0.13]) and the Mono/FDCT cohort (0.87 [0.15]). In comparing the differences in postindex and preindex MPRs, declines in the mean MPR changes for the Mono/Mono and Mono/FDCT cohorts were only slight (–1.5% and –4.6%, respectively), whereas a substantial decline was found in the Mono/Dual therapy cohort (–12.4%). As shown in **Figure 2**, the mean number of study medication refills increased slightly from the preindex to the postindex period in the Mono/Mono cohort (from 4.60 [1.34] to 5.47 [1.51]) and the Mono/FDCT cohort (from 4.11 [1.38] to 5.27 [1.62]) cohort, whereas a dramatic decrease from 5.74 [2.25] to 4.08 [2.82] was observed in the Mono/Dual cohort. A direct relationship between the changes in MPR and number of refills does not exist due to the wide variations in days' supply obtained per refill.

The pairwise comparisons in the multivariate analysis confirmed statistically significant between-cohort differences in change in adherence. As illustrated in **Figure 3**, the analysis revealed a statistically significant difference in mean MPR change between the Mono/Dual and the Mono/FDCT cohorts (7.8%; 95% CI, 5.3%–10.4%; $P < 0.001$).

Although a direct comparison between the Mono/Mono and Mono/FDCT cohorts requires cau-

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