Impact of rosiglitazone meta-analysis on use of glucose-lowering medications

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A meta-analysis by Nissen and Wolski, published in late May 2007, showed that rosiglitazone increased the myocardial infarction (MI) rate compared to placebo or to other glucose-lowering medications [1]. The FDA issued a related safety alert on the same day the article was published [2]. On June 1, health professionals in Canada were sent a letter issued by GlaxoSmithKline and reviewed by Health Canada highlighting these harmful effects [3]. Recently published findings have indicated that use of rosiglitazone has declined sharply since the release of the Nissen and Wolski findings [4-6]. An analysis in Ontario seniors found that new use of rosiglitazone dropped abruptly following the meta-analysis [4], while a drug utilization study in a private insurance plan setting concluded that prevalent use of rosiglitazone among members fell by close to half from May 20 to Dec 7, 2007 [5]. The latter study also concluded that the percentage of rosiglitazone users with an elevated risk for a cardiovascular event declined during the same period. These studies provided evidence that the meta-analysis affected the use of thiazolidinediones (TZDs) but, importantly, did not analyze patterns of switching from rosiglitazone to other drugs or focus on the wider impacts on prevalent use of other glucose-lowering medications. Our study examined the wider impacts of the Nissen and Wolski meta-analysis including effects on patterns of prevalent and new use of glucose-lowering medications, cessation of TZDs, and switching from rosiglitazone to other medications. We also analyzed predictors of initiation and cessation of rosiglitazone, including micro- and macrovascular comorbidities. Our study focused on drug utilization in the Canadian province of British Columbia. TZDs were covered by the provincial drug plan as third-line therapies under a prior authorization process as of November 7, 2005, for rosiglitazone (Avandia) and pioglitazone (Actos) and as of August 2, 2007, for rosiglitazone-metformin (Avandamet) [7-8]. Prior to these coverage policies, TZDs were available but not covered by the public drug plan. In this paper, we

describe the impact of the meta-analysis on glucose-lowering drug utilization and provide an analysis of factors influencing rosiglitazone utilization over time.

Methods

Study population

We used linked data from provincial administrative health databases for prescription drugs (PharmaNet), physician services (Medical Services Plan or MSP), and hospitalizations (Discharge Abstracts Database). PharmaNet contains records of all dispensings at community pharmacies in British Columbia (BC), and rates of underreporting and misclassification would be expected to be minimal [9]. Similarly, physician services and hospitalizations data would be expected to be reliable based on studies comparing patient charts with administrative data in Canada [10-11]. Our study included BC residents of any age (approximately 4.3 million in 2007). We restricted the sample to those who were registered under MSP to ensure exclusion of non-residents. In our analysis of predictors of rosiglitazone initiation and cessation, we further limited our sample to those registered in the provincial income-based prescription drug plan (Fair PharmaCare) to ensure we had detailed data on income on all study subjects. The study covered a 36-month period from December 2004 to November 2007, including 29 months prior to the publication of the Nissen and Wolski meta-analysis of rosiglitazone, a transition month during which study was published online and six months afterwards. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Definitions of treatment cessation, initiation and switching

Patients with one or more days' supply of a drug falling within a given month were considered to be 'prevalent users' of a drug. Patients were defined as 'stoppers' for a given

month if their current days' supply of a drug was set to expire during that month and they did not fill another prescription for the same drug within 90 days of the end of their current days' supply [9, 12-14]. Patients were defined as 'starters' if they were dispensed a drug in the current month but had not been dispensed that drug in the previous 365 days. Patients were considered 'switchers' if they were dispensed a new glucose-lowering therapy within 30 days of stopping rosiglitazone or Avandamet [12-14].

Interrupted time series analysis

Monthly rates for prevalence of treatment, treatment initiation, treatment cessation, and treatment switching were calculated for each month during the 36-month study period. For each outcome, monthly rates were defined as the number of patients per 100,000 patients registered for medical coverage in MSP (for prevalent use or initiation) or patients per 100 users of a medication (for switching and cessation).

An interrupted time series linear regression model [15-16] was used to test for changes in these monthly rates for rosiglitazone, Avandamet, pioglitazone, all TZDs, insulin, metformin, sulfonylureas, acarbose and repaglinide. The models included an intercept, a linear trend variable, a binary indicator for the 'transition' month when the meta-analysis was published online (May 2007), level and trend variables for the period after the meta-analysis (June – November 2007), level and trend variables to indicate the period after the TZD prior authorization policy was introduced (November 2005 – November 2007), and monthly indicators to control for seasonal variation. Based on trends in prevalent use prior to the Nissen and Wolski meta-analysis, this model was also used to estimate the 'predicted' number of prevalent users of each glucose-lowering drug in the absence of the meta-analysis for comparison to observed prevalence figures for November 2007. We tested regression models for autocorrelation and

assumed autocorrelated covariance structures with 1-month lag periods in cases where a Durbin-Watson test indicated autocorrelated data.

Analysis of predictors of rosiglitazone initiation and cessation

Thirty-six monthly cohorts were created for both the rosiglitazone initiation and cessation analyses. Patients were included in a monthly cohort for the initiation analysis if they had received a diagnosis for diabetes at a physician visit in the 12 months prior to the current month (an ICD-9 code of '250' [17] or a complex care code [18] created by the BC ministry of health services specifying a diagnosis including diabetes). To be included in a monthly cohort for the cessation analysis, a patient must have been dispensed a rosiglitazone or Avandamet prescription for which the days' supply would end during the current month in the absence of a renewal.

We tested factors hypothesized to predict initiation or cessation of rosiglitazone or Avandamet using logistic regression [9, 13]. The method of generalized estimating equations (GEEs) was used to adjust for correlations within subjects across repeated observations [19-22]. The GEEs assumed a binomial distribution of the dependent variable and an autoregressive (AR1) correlation structure. Two regressions were used, one for the starters analysis and one for the stoppers analysis.

The GEEs included a term for a linear time trend, binary indicators for a transition period (May 2007) and the period following the meta-analysis, and a binary indicator for the period of BC Pharmacare coverage for TZDs. Patient characteristics were included as binary indicators for sex, age category, income level, Romano co-morbidity score level, presence of comorbidities (macrovascular or microvascular comorbidities or hypertension), and insulin dependence (defined as >= 2 insulin prescriptions in the previous 6 months). Romano comorbidity scores were included to adjust for confounding from comorbidities [9, 23], excluding diabetes (a

diagnosis assumed to be shared by all persons in the initiation and cessation analyses). Binary indicators for the presence of macrovascular comorbidities, microvascular comorbidities and hypertension were also included, based on whether a patient had received a diagnosis in one of these categories during a physician or hospital visit in the previous 365 days. Table 1 lists the relevant complex care, ICD-9 and ICD-10 codes [24].

For the macrovascular, microvascular and hypertension co-morbidity variables, we also created interaction terms with the indicator variable for the period following the meta-analysis to test whether those factors were effect modifiers during that period based on the new safety information. From these interaction terms, odds ratios and confidence intervals were calculated to represent the impact of the meta-analyis in the absence and presence of each of these comorbidities and to represent the impact of these comorbidities before and after the meta-analysis.

Results

Impact on utilization trends for glucose-lowering medications

Monthly trends in the number of prevalent users of TZDs are shown in Figure 1. The number of prevalent rosiglitazone and Avandamet users declined following the publication of the Nissen and Wolski meta-analysis, and this coincided with a more modest increase in the number of pioglitazone users, leading to an overall steady decline in TZD prevalence. The introduction of public coverage for rosiglitazone and pioglitazone under a prior authorization policy, in November 2005, modestly increased overall TZD utilization, although it had a negative impact on the use of Avandamet (which was not publicly covered until August 2007). A comparison of predicted and observed utilization for November 2007 (Table 2) showed that rosiglitazone use

had fallen by 40 percent (95% CI, 39 to 42%) as compared to the predicted level of use. At the same time, the observed number of users exceeded predicted use for pioglitazone, insulin, sulfonylureas, acarbose and repaglinide.

The results of the interrupted time series analysis evaluating the influence of the meta-analyis on drug utilization are reported in Table 3, including changes to levels and monthly trends of prevalence, treatment cessation, treatment switching and treatment initiation. The level of treatment cessation increased for rosiglitazone and Avandamet, but did not show a statistically signficant change for pioglitazone. Switching from rosiglitazone or Avandamet to other glucose-lowering drugs increased only slightly for pioglitazone (1.2%; 95% CI, 1.1 to 1.4%) and even less for other medications (and not at all for repaglinide). Levels of treatment initiation decreased for rosiglitazone and Avandamet and increased for pioglitazone, insulin, metformin, sulfonylureas and acarbose.

Predictors of rosiglitazone initiation and cessation

Characteristics of patients included in our analysis of predictors of rosiglitazone initiation and cessation are summarized in Table 4. Results of the predictors analysis are presented in Table 5. Following the meta-analysis in 2007, patients were 75% less likely to initiate rosiglitazone or Avandamet (OR=0.25; 95% CI, 0.21-0.29) and more than three times more likely to stop (OR=3.29; 95% CI, 3.01-3.61). The introduction of public coverage for rosiglitazone (under prior authorization), patient age, income level, Romano comorbidity score and insulin dependence also affected initiation and cessation.

The presence of macrovascular comorbidities was an effect modifier that strengthened both the negative impact of the meta-analysis on the level of rosiglitazone initiation (OR=0.18; 95% CI, 0.14-0.24) and the positive impact on cessation (OR=3.96; 95% CI, 3.48-4.49).

Similarly, the presence of macrovasular comorbidities was a borderline insignificant predictor of rosiglitazone initiation following the publication of the meta-analysis (OR=0.78; 95% CI, 0.59-1.02) and was a stronger predictor of treatment cessation following the meta-analysis (OR=1.36; 95% CI, 1.24-1.48). The presence of microvascular comorbidities appeared to be a weaker predictor of rosiglitazone initiation following the meta-analysis as compared to the earlier period (OR=1.31; 95% CI, 1.02 – 1.69). Also, hypertension became a significant predictor of rosiglitazone cessation following the meta-analysis (OR=1.10; 95% CI, 1.02 – 1.18).

Discussion

Publication of Nissen and Wolski's meta-analysis led to a decline in rosiglitazone utilization and a corresponding rise in monthly prevalence of other glucose-lowering drugs including pioglitazone, insulin, and sulfonylureas. The prevalence of meformin did not show a statistically significant change, perhaps because some patients who were taking metformin and rosiglitazone stopped both medications or because some patients had failed on metformin (a common first-line therapy) prior to initiating rosiglitazone. In our analysis of predictors of rosiglitazone initiation and cessation, we found that macrovascular comorbidities had a greater impact on decisions not to initiate or to stop rosiglitazone therapy following the meta-analysis.

While the decline in new and prevalent use of rosiglitazone and rise in pioglitazone use documented in our study is consistent with previous studies examining the impact of the Nissen and Wolski meta-analysis [4-6], we believe our study is the first to link the meta-analysis to an increase in prevalent use of insulin and sulfonylureas. These changes in utilization appeared to be related more to an increase in initiation of pioglitazone and other glucose-lowering drugs rather than to switching from rosiglitazone or Avandamet, which increased only slightly. This shift may have also been related to patients 'switching back' to drugs they had used at some time in the

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previous 365 days, although our analysis would not have counted them as 'new users' or 'switchers' in that case. These results differed from a study of Ontario people over age 65 (which found no increased initiation of metformin, insulin or glibenclamide) [4], perhaps because the population for our study included patients of all ages.

The number of pioglitazone users rose only modestly while rosiglizazone use steadily declined. This suggests that the increased risk of MI was not sufficiently interpreted as a class effect to reduce the use of pioglitazone, but pioglitazone was not embraced as a less harmful alternative. The rise in the number of users was greater in absolute numbers for sulfonylureas and insulin as compared to pioglitazone (in November 2007, six months after the Nissen and Wolski meta-analysis). An earlier utilization study which found that the percentage of rosiglitazone users at increased CV risk declined in the latter half of 2007 is consistent with our findings [5]. Based on our analysis of rosiglitazone initiation and cessation, we can add that macrovascular comorbidities appeared to have a stronger influence on both starting and stopping decisions for rosiglitazone following the publication of the Nissen and Wolski meta-analysis.

Other safety information may have contributed to the decline in overall TZD utilization or more specifically to caution in pioglitazone use, including warnings in Canada and the US about fracture risk in early 2007 [25-28], FDA boxed warnings related to heart failure in August 2007 [29], and a Health Canada endorsed advisory about rosiglitazone and cardiac safety in November 2007 [30]. A limitation of our study was that it was not possible to separately measure the impacts of each warning. In our analysis of predictors of rosiglitazone initiation and cessation, the influence of macrovascular comorbidities on rosiglitazone utilization may be due in part to an increase in concerns about CHF rather than only a response to the findings of Nissen and Wolski. However, we can infer from the rise in the number of pioglitazone users that the

decline in rosiglitazone use primarily resulted from the publication of the meta-analysis and related regulatory warnings and publicity.

Our study found that concerns regarding cardiovascular harm raised in the Nissen and Wolski meta-analysis of rosiglitazone in May 2007 resulted in a decline in prevalence of rosiglitazone and a shift toward greater use of pioglitazone and other glucose-lowering drugs including insulin and sulfonylureas. Utilization of rosiglitazone therapy was influenced by multiple factors, including demographic characteristics and health indicators. Our results provide evidence that macrovascular comorbidities played a greater role in decisions to start or stop rosiglitazone therapy as a result of the rosiglitazone meta-analysis. While other warnings about the safety of TZDs were issued in 2007, the Nissen and Wolski findings appeared to be more influential, and this may relate to broader coverage in the lay and professional media [4-6] or to the perceived severity of MI risk in comparison to other safety concerns.

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