Predictors of Nonpersistence With Thiazolidinediones in Patients With Type 2 Diabetes

Julie Leblond BPharm, Danielle Pilon MD, Christian-Pierre Beaudette BSc, Pierre Maheux MD

Department of Medicine, Division of Endocrinology & Metabolism, Université de Sherbrooke, Sherbrooke, Quebec, Canada

ABSTRACT

OBJECTIVES

The objectives of this study were to evaluate persistence to thiazolidinediones (TZDs) outside the controlled environment of clinical trials, identify the determinants of persistence and compare the degree of persistence with TZDs to traditional antihyperglycemic agents (metformin and sulfonylureas).

METHODS

Data regarding persistence to 3 different oral antihyperglycemic agent categories between October 1, 2000, and July 31, 2002, were examined in a large reimbursement database obtained from the province of Quebec, Canada. A primary cohort of 18 894 patients (age 65.4±11.1 years) who had filled ≥1 prescriptions of a TZD during the study period was compared with a cohort of 25 135 patients prescribed either metformin or a sulfonylurea between January 1, 1998, and December 31, 2001, and for whom there was evidence of ≥1 filled prescription of another oral antihyperglycemic agent prior to the index date. For each patient in both cohorts, we obtained demographic, medical

Address for correspondence:
Pierre Maheux
Department of Medicine
Division of Endocrinology & Metabolism
Université de Sherbrooke
3001 12th Avenue North
Sherbrooke, Quebec
J1H 5N4 Canada
Telephone: (819) 564-5241
Fax: (819) 564-5292
E-mail: Pierre.Maheux@USherbrooke.ca

Keywords: antihyperglycemic agents, database, drug persistence, pharmacoepidemiology, thiazolidinediones

RÉSUMÉ

OBJECTIFS

Les objectifs de cette étude étaient d'évaluer la persistance des patients traités par une thiazolidinédione (TZD) en milieu non contrôlé, soit en dehors d'un essai clinique, de cerner les déterminants de la persistance et de comparer la persistance des patients traités par une TZD à celle des patients recevant des antihyperglycémiants classiques (metformine et sulfonylurée).

MÉTHODES

On a examiné une importante base de données sur les remboursements de la Régie de l'assurance-maladie du Québec, au Canada, en ce qui a trait à la persistance des patients traités par 3 antihyperglycémiants oraux différents entre le 1er octobre 2000 et le 31 juillet 2002. Une cohorte de 18 894 patients (65,4 ± 11,1 ans) qui avaient fait exécuter au moins 1 ordonnance d'une TZD pendant la période couverte par l'étude a été comparée à une cohorte de 25 135 patients ayant reçu une ordonnance de metformine ou d'une sulfonylurée entre le 1er janvier 1998 et le 31 décembre 2001 et qui, selon toute évidence, avaient fait exécuter au moins 1 ordonnance d'un autre antihyperglycémiant oral avant la date du début de l'étude. On a obtenu les données démographiques, médicales et pharmaceutiques des patients des 2 cohortes entre un an avant la date du début de l'étude et jusqu'à au moins 6 mois après cette date. Le taux de persistance cumulatif a été estimé selon la fonction de risque instantané variable avec le temps au moyen de la méthode de Kaplan-Meier et ses déterminants ont été cernés au moyen du modèle des hasards proportionnels de Cox.

RÉSULTATS

Les TZD étaient le plus souvent prescrites avec 2 autres médicaments administrés par voie orale (46,8 %) et environ 13 % des patients prenaient de l'insuline en plus de la TZD à la date du début de l'étude. La persistance des patients traités par une TZD a généralement été moindre que celle des

and pharmaceutical data for 1 year preceding the index date until at least 6 months after this date. The cumulative persistence rate with treatment was estimated using a Kaplan-Meier failure time analysis, and we identified its determinants with a Cox proportional hazards model.

RESULTS

TZDs were most often prescribed in the context of a triple oral regimen (46.8%), and ~13% of patients were taking insulin in addition to a TZD at the index date. The persistence rate to TZDs was generally lower than that with metformin over the course of the entire study period. However, persistence to TZDs was significantly higher than with sulfonylureas at 3 and 6 months ($p<0.001$). At 12 and 18 months, persistence to sulfonylureas was higher than with TZDs ($p<0.002$). The main determinants of nonpersistence with TZDs were diagnosis of congestive heart failure (CHF) or addition of a loop diuretic after the index date (relative risk [RR] 1.585, confidence interval [CI] 1.473 to 1.706), monotherapy with a TZD (RR 1.426, CI 1.342 to 1.515), use of insulin at the index date (RR 1.373, CI 1.279 to 1.475), female sex (RR 1.171, CI 1.114 to 1.231), specialist as the prescribing physician (RR 1.118, CI 1.053 to 1.188) and higher chronic disease score at index date (RR 1.052, CI 1.028 to 1.078).

CONCLUSIONS

The factors associated with nonpersistence with TZDs in this survey are consistent with the hypothesis that fluid retention and/or CHF in patients with type 2 diabetes at higher risk may diminish persistence with therapy. These considerations notwithstanding, our study shows a persistence rate to TZDs that is significantly higher than that to sulfonylureas in the first few months after their initial prescription.

patients traités par la metformine au cours de toute la durée de l'étude. Cependant, la persistance liée à la TZD était significativement supérieure à celle liée à une sulfonylurée après 3 mois et 6 mois ($p<0,001$). Après 12 mois et 18 mois, la persistance des patients traités par une sulfonylurée était supérieure à la persistance liée à une TZD ($p<0,002$). Les principaux déterminants du manque de persistance chez les patients traités par une TZD étaient le diagnostic d'insuffisance cardiaque congestive ou l'ajout d'un diurétique de l'anse après la date du début de l'étude (risque relatif [RR] de 1,585; intervalle de confiance [IC] de 1,473 à 1,706), la prise d'une TZD en monothérapie (RR de 1,426; IC de 1,342 à 1,515), la prise d'insuline à la date du début de l'étude (RR de 1,373; IC de 1,279 à 1,475), le fait d'être une femme (RR de 1,171; IC de 1,114 à 1,231), le fait d'avoir reçu l'ordonnance d'un spécialiste (RR de 1,118; IC de 1,053 à 1,188) et un score de maladie chronique plus élevé à la date du début de l'étude (RR de 1,052; IC de 1,028 à 1,078).

CONCLUSIONS

Les facteurs associés au manque de persistance des patients traités par une TZD sont compatibles avec l'hypothèse voulant que la rétention liquidienne et/ou l'insuffisance cardiaque congestive chez les patients atteints de diabète de type 2 nuit à la persistance. Sous réserve de ces considérations, notre étude montre un taux de persistance significativement plus élevé chez les patients traités par une TZD que chez ceux traités par une sulfonylurée au cours des premiers mois du traitement.

INTRODUCTION

Thiazolidinediones (TZDs) were introduced recently for the treatment of type 2 diabetes mellitus. These agents, through their agonistic effect on peroxisome proliferator-activated receptor (PPAR) -gamma, have been shown to have a significant impact on plasma glucose (PG) concentrations and overall metabolic control (1,2). Currently, they are approved in Canada for use as monotherapy or in combination with metformin or a sulfonylurea (3). In contrast to other classes of oral antihyperglycemic agents (4-6), there are no extensive data available on the persistence rate associated with this class of agent, apart from 1 study with troglitazone, a medication that has since been withdrawn from the market (5). Warnings have been issued recently about the potential for fluid retention and cardiac failure when TZDs are used concomitantly with insulin (7-9).

Assessment of how TZDs are used outside the specific confines of randomized clinical trials is an important aspect of post-marketing surveillance. To this end, we evaluated the usage pattern of TZDs in a large population of patients covered by a public drug plan and identified the factors leading to nonpersistence with this relatively new class of antihyperglycemic agents. We also compared these data with persistence measured in 2 large comparative cohorts of patients prescribed metformin or a sulfonylurea.

METHODS

Source of data

Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ), the provincial health insurance plan for the province of Quebec, Canada. This plan provides drug coverage for persons receiving social assistance, persons ≥65 years of age, and younger people without private insurance coverage ("general clientele"). Approximately 3 million individuals—~40% of the province's population—are covered by this drug plan (10). The RAMQ database includes demographic, medical and pharmaceutical data on each patient and has been used previously to examine prescribing habits

and persistence with therapy (4,11). More specifically, it provides detailed information on medical services provided in outpatient clinics and hospitals, including diagnostic and therapeutic procedures, diagnosis coded according to the International Classification of Diseases, Tenth Revision (ICD-10), and the types of institutions where medical procedures were performed. The pharmaceuticals database contains information on all dispensed prescriptions, including prescribing physician, dispensing pharmacist, drug name, dosage, formulation, quantity dispensed, date dispensed and duration of the dispensed prescription. This database was validated previously and found to be highly reliable (12).

Definition of study cohorts

Using the pharmaceutical files of the RAMQ database, we retrieved data on all patients dispensed at least 1 TZD prescription between October 1, 2000 (date when the first TZD was accepted on the restricted drug formulary of Quebec), and July 31, 2002. In the present study, the exposure to a TZD was defined as at least 1 dispensed prescription of either rosiglitazone or pioglitazone. The date of this first dispensation was defined in the present study as the index date. To be included in the study population, patients needed to have been on the Quebec drug benefit plan for at least 1 year before the index date. Patients admitted to the hospital for >30 days during the period of observation (<2% of the entire population) were also excluded because medications dispensed in the hospital are not included in the RAMQ database.

To compare persistence to TZDs with that of other commonly used oral antihyperglycemic agents (namely, metformin and sulfonylureas), we used a cohort of 25 135 patients, also obtained from RAMQ between January 1, 1998, and December 31, 2000, but selected on the basis that patients must had filled at least 1 prescription of another oral antihyperglycemic agent before the index dispensation date of either metformin or a sulfonylurea. This criterion was used with the reasonable assumption that this cohort of patients would generally have had diabetes for some time and would therefore constitute a more appropriate comparator group to patients prescribed a TZD for the first time.

Outcome definition

Nonpersistence with an oral antihyperglycemic agent was defined as the absence of any record of renewal of the dispensed prescription of an agent after a specified exposure period. A patient was considered exposed to an oral antihyperglycemic agent for the duration of the dispensed prescription (prescriptions in the public market of Quebec are dispensed for a 30-day period) plus a "permissive gap" of 30 days to allow for delays in renewal. For example, if a patient did not renew the preceding dispensation of a 30-day supply after a period of 60 days (duration of prescription plus permissive gap), he or she was considered nonpersistent to that oral antihyperglycemic agent. The length of this permissive gap, which is critical for the nonpersistence variable to be calculated (6), was determined using a sensitivity analysis in which the persistence to a TZD (primary cohort) was plotted against progressively higher permissive gap periods. Switching from one TZD to another or from one sulfonylurea to another was not considered a failure in persistence.

Covariate definition

From the database, we ascertained the presence of a priori possible determinants of persistence with treatment. Covariates such as age, sex, type of patient (≥65 years of age, welfare recipient or general clientele), use of 1 oral antihyperglycemic agent in monotherapy (for the TZD group only), prescribing physician (endocrinologist, internist or general practitioner [GP]) and chronic disease score (CDS) were measured at the index date. The CDS is defined as a global index of illness and was calculated using a method assigning scores to concomitant medications according to their usual indications in the prior year (13). The use of insulin was also assessed at the index date. Lastly, the incidence of congestive heart failure (CHF) or fluid retention was measured during the follow-up period. For the TZD cohort, evidence of CHF or fluid retention was estimated by a new dispensation of a loop diuretic alone, an angiotensin-converting enzyme inhibitor or digoxin along with a loop diuretic, or a new diagnosis of CHF (according to ICD-10 codes 428 and 429) after the index date.

Statistical analysis

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, North Carolina, United States [US]). We estimated the cumulative treatment persistence rate using a Kaplan-Meier failure time analysis with patients being censored because of the end of the observation period if they were still on treatment. This analysis was performed for the TZD, metformin and sulfonylurea subgroups. Patients who were lost to follow-up because they either moved out of the province or were no longer using RAMQ drug insurance coverage were also censored. We conducted multivariable analysis with the Cox proportional hazards model and estimated the hazard ratio (HR) with 95% confidence interval (CI) for each covariate (14).

Because we were more interested in identifying variables associated with nonpersistence than in obtaining an equation for predicting outcomes for future subjects, we built our regression models using backward selection. All clinically relevant variables were entered in the initial models; only statistically significant or the potentially explanatory covariates were kept. Variables with statistically significant associations were not removed from the final models. A Chi-square test was used to compare proportions across the 3 treatment subgroups, e.g. proportions of patients persistent to a given oral antihyperglycemic agent were compared at 3, 6, 12 and 18 months' follow-up. Data are presented as mean±standard deviation.

RESULTS

Study population

The primary study cohort included 18 894 TZD users, as previously defined. The 2 cohorts used for comparison included 15 818 patients who had been prescribed metformin and 9317 who had been prescribed a sulfonylurea for the first time. This initial dispensation of metformin or a sulfonylurea had always been done in the context of a prescription of at least 1 other antihyperglycemic agent at some point before the index date. As a result of this selection criterion, the prescription of the other antihyperglycemic agent had been done 18.7±12.5 and 15.3±12.6 months before the index date in the metformin and the sulfonylurea subgroups, respectively.

Characteristics of the 3 cohorts at the index date of dispensation are summarized in Table 1. Mean age was close to 65 years in the 3 cohorts, reflecting the fact that >60% of patients were ≥65 years of age. There was a lower proportion of patients >65 years of age in the TZD cohort compared with the metformin and the sulfonylurea subgroups ($p<0.001$, Chi-square test). The sex distribution was similar between the metformin and the sulfonylurea subgroups. A TZD had been prescribed for the first time 78.5% of the time by a GP, compared with 19.9% by an internist or an endocrinologist. However, the prescribing physician at the index dispensation was more often a specialist (internist or endocrinologist) in the TZD cohort than in the metformin or sulfonylurea subgroups of the comparator cohort ($p<0.001$, Chi-square test). To adjust for the fact that there are more GPs than specialists (internists or endocrinologists) in Quebec, we divided the number of prescriptions by the number of individual physicians in each of these categories. As of 2001, there were 7369 GPs and 542 internists and

Table 1. Patient characteristics at the index dispensation

	TZD (n=18 894)	*Metformin (n=15 818)*	*Sulfonylurea (n=9317)*
Age (years)*	65.4±11.1	66.4±11.6	63.8±12.3
Sex			
Male	10 217 (54.0)	7645 (48.3)	5054 (54.2)
Female	8677 (45.9)	8173 (51.7)	4263 (45.8)
Patient category			
≥65 years of age	12 837 (67.9)	10 974 (77.1)	5881 (71.1)
Receiving social assistance	1032 (5.5)	782 (5.5)	577 (7.0)
General clientele	5025 (26.6)	4062 (25.7)	2859 (30.7)
Prescribing physician			
Internist or endocrinologist	3762 (19.9)	1602 (10.1)	813 (8.7)
GP	14 826 (78.5)	13 794 (87.2)	8272 (88.8)
Other	306 (1.6)	422 (2.7)	232 (2.5)
Prevailing antihyperglycemic treatment at index date†			
None	3860 (20.3)	7904 (50.0)	1869 (20.1)
Oral monotherapy	5744 (30.3)	3392 (21.4)	4781 (51.3)
Oral bitherapy	8862 (46.8)	66 (0.4)	30 (0.3)
Triple oral therapy	498 (2.6)	—	—
Insulin	2448 (13.0)	146 (0.9)	50 (0.5)
Chronic disease score*	4.80±3.17	5.44±3.60	5.54±3.63
Follow-up period after index date (months)*	14.2±10.1	23.8±13.6	22.6±13.9

Data are presented as absolute numbers with percentage in parentheses, unless otherwise indicated
*Results are mean±SD
†Numbers add up to >100% as the insulin category includes patients on insulin only as well as patients who were on a combination of insulin and oral antihyperglycemic agents

GP = general practitioner
TZD = thiazolidinedione
SD = standard deviation

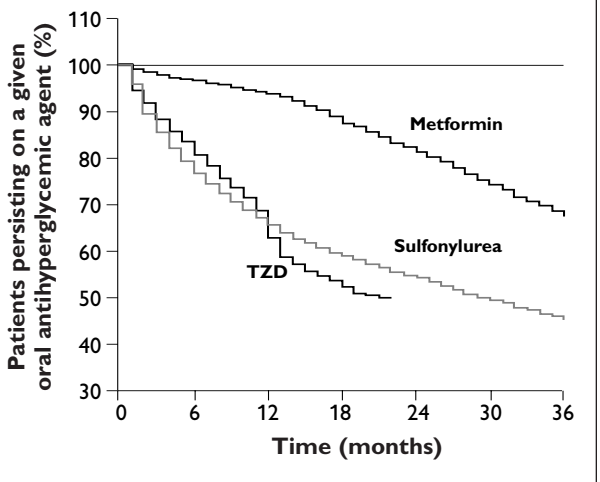
endocrinologists in the province of Quebec. This analysis produced a ratio of 7.08 TZD prescriptions per specialist prescriber compared with 1.02 for GPs.

At the index date, most patients (77.1%) were receiving a TZD prescribed on a background of either 1 (30.3%) or 2 (46.8%) oral antihyperglycemic agents; 13.0% of patients had been prescribed a TZD on a background of insulin (with or without oral agent). The average background dose of the most frequently prescribed oral agents at the time of the index dispensation of a TZD was 17.8±6.5 mg for glyburide and 1896±575 mg for metformin per day.

Persistence to TZD therapy

In the TZD cohort, the mean follow-up period was 14.2±10.1 months, with a substantial proportion of patients (39.4%) followed for ≥12 months. It should be noted that 6.1% of patients did not renew their first dispensed prescription of TZD, as defined previously. The survival curve depicting persistence to TZD therapy is shown in Figure 1. More than 60% of the population continued to renew their TZD prescription on a regular basis after 12 months. The persistence rate to TZDs, adjusted for covariates, was 80.9%, 63.1% and 52.6% at 6, 12 and 18 months, respectively. Figure 1 also illustrates the persistence rates in the comparative metformin and sulfonylurea cohorts. The mean follow-up in these 2 cohorts was longer because the observation period was longer, as previously explained. The persistence to metformin was consistently the highest of the 3 cohorts examined. Persistence to TZDs, adjusted for covariates, was significantly better than to sulfonylureas at 3 and 6 months ($p<0.001$, Chi-square test), but lower at 12 and 18 months, respectively ($p<0.002$, Chi-square test).

Figure 1. Survival curves for persistence to oral antihyperglycemic agents, adjusted for covariates



TZD (n)	18 894	12 320	6 981	2 375	–	–	–
Metformin (n)	15 818	15 169	14 645	13 639	12 234	10 722	9191
Sulfonylurea (n)	9317	5901	4179	2924	1953	1258	707

TZD = thiazolidinedione

Determinants of persistence to TZD therapy

Table 2 provides the results of a Cox proportional hazards model using persistence with the use of a TZD, metformin or a sulfonylurea as the dependent variable. In the case of TZD, 6 different covariates were associated with nonpersistence. Diagnosis of CHF or addition of a loop diuretic after the index date, use of a TZD in monotherapy, use of insulin at the index date, female sex, a specialist as the prescribing physician and higher CDS at index date were independent factors of nonpersistence to TZDs. Patient age was not associated with

Table 2. Variables associated with nonpersistence in a Cox proportional hazards model*

Variables	*Hazard ratio (95% CI)*
TZD	
Addition of a loop diuretic or CHF†	1.585 (1.473–1.706)
Use of TZD in monotherapy	1.426 (1.342–1.515)
Use of insulin at the index date	1.373 (1.279–1.475)
Female sex	1.171 (1.114–1.231)
Prescribing physician, specialist‡	1.118 (1.053–1.188)
Chronic disease score§	1.052 (1.028–1.078)
Age ≥65 years	1.000 (0.951–1.052)
Metformin	
Age ≥65 years	1.225 (1.166–1.288)
Prescribing physician, specialist‡	1.209 (1.130–1.294)
Female sex	1.095 (1.044–1.149)
Chronic disease score§	1.040 (1.033–1.047)
Sulfonylurea	
Prescribing physician, specialist‡	1.211 (1.090–1.345)
Age ≥65 years	1.096 (1.022–1.176)
Chronic disease score§	1.015 (1.005–1.025)
Female sex	1.039 (0.969–1.114)

*The outcome of interest is discontinuation of oral antihyperglycemic agent (>30 days after the duration of the last dispensation). Variables appear in descending order of hazard ratio; those that include the 1.0 ratio are listed at the end of each column
†Introduction of a loop diuretic or new diagnosis of heart failure (according to ICD-10 classification) after the index date
‡Internist or endocrinologist
§Per increment on a 3-point scale

CI = confidence interval
CHF = congestive heart failure
TZD = thiazolidinedione

nonpersistence to TZDs (HR 1.000, 95% CI 0.951-1.052). There was no colinearity between the use of insulin and CDS.

In the case of metformin or sulfonylurea, nonpersistence was mildly associated with an age ≥65 years and the fact that a specialist was the prescribing physician at the index date. Nonpersistence with metformin was also associated with female sex and CDS. The 95% CIs were, however, all close to 1.0.

A Cox proportional hazards model using "prescription of a loop diuretic after the index date" as the dependent variable was undertaken to provide more insight into the potential role of fluid retention in nonpersistence to TZDs. This analysis revealed that age, female sex and background insulin therapy were all independently associated with the new prescription of a loop diuretic (data not shown). Incidentally, 4851 individuals (or 25.7% of the total cohort) had been prescribed a loop diuretic after the index dispensation of a TZD. On average, loop diuretics were introduced 84 days after the index date.

DISCUSSION

Although our study was limited to 1 Canadian province, the fact that it included a large number of patients studied outside the controlled environment of randomized clinical trials makes this study, we believe, an important contribution to the characterization of TZDs in the real-world circumstances of daily practice. This study showed that TZDs are prescribed in Quebec mostly in triple oral therapy or with insulin, situations supported by limited clinical evidence and currently outside approved indications in Canada (3). This situation can be explained in part by the restricted access to TZDs provided by the Quebec drug formulary, which will provide reimbursement only if a patient is not adequately controlled by a combination of metformin and sulfonylurea or by a combination of metformin and insulin; if the patient is intolerant to metformin or a sulfonylurea; or if there is a contraindication to the use of either one of these less expensive medications (15). Although not assessed with precision, this result suggests that TZDs are currently being prescribed predominantly in patients in the later stages of diabetes, at a time when there is possibly either evidence of diabetes complications (such as renal failure) or secondary failure to conventional antihyperglycemic agents.

Despite the specific circumstances prevailing in the province of Quebec, the persistence rate calculated for TZDs was significantly better compared with sulfonylureas, up to ~12 months after the index date. After this time, when persistence to both agents is close to 60 to 65%, the TZD and sulfonylurea curves cross each other and the sulfonylureas show a better persistence for the remainder of the study period.

The reasons for much better persistence with metformin in patients with type 2 diabetes are not clear, as this agent is known to be associated with gastrointestinal side effects. However, the fact that metformin causes less hypoglycemia and less weight gain might theoretically explain better persistence with this medication.

A persistence rate of 63.1% at 12 months with TZDs contrasts with the only other population-based study that has looked specifically at persistence rates to this class of agent, in which persistence rates of 43.2% and 22% were reported at 12 and 24 months, respectively (5). However, it should be noted that this study concentrated on a population of patients in the US who were younger than patients in this study (60.1 years, with only 37.7% being ≥65 years of age) and covered by a health maintenance organization. In addition, that survey included a smaller number of patients treated with a TZD (n=5273) and was limited to troglitazone, a TZD that has since been withdrawn from the market because of hepatotoxicity.

We identified several factors associated with nonpersistence to TZDs, the most important being the use of insulin at the index date and the prescription of a loop diuretic or a diagnosis of CHF in the months after the first dispensation of a TZD. These 2 causes of nonpersistence are possibly related to fluid retention, a hypothesis difficult to prove definitively but substantiated by the fact that patients using insulin and TZDs are more likely to have edema (16-18); this circumstance has resulted in warnings from some health authorities (3). The fact that introduction of a loop diuretic or a new diagnosis of CHF emerged as independent variables also suggests that TZDs are possibly associated with new cases of CHF or fluid retention. In this context, it should be noted that a loop diuretic was prescribed for 25.7% of the TZD cohort on average 84 days after the index dispensation.

Women were more likely than men to be nonpersistent with TZDs. The reasons for this observation are not entirely clear, but we would like to propose a few ideas. First, it is possible women are less persistent with taking medication on a long-term basis, but we could not find any evidence in the literature to support such an assertion. Second, women might have less satisfactory responses to TZDs and might therefore be inclined to interrupt their treatment earlier. This hypothesis seems unlikely, however, because no clinical trials with TZDs have shown any such effect. Third, one should consider the possibility that women are at higher risk of developing peripheral fluid retention (19), or that their tolerance threshold to this adverse effect is lower than that of men (20). The effect of female sex on nonpersistence with TZDs was independent of the other variables included in the model, suggesting, if our hypothesis is true, that peripheral edema could be of a lower magnitude in women (i.e. not requiring the use of a loop diuretic). The significant positive association between female sex and nonpersistence to metformin suggests that women might be, in general, less tolerant of the side effects of antihyperglycemic pharmacotherapy (gastrointestinal effects in the case of metformin and peripheral edema in the case of TZDs). The fact that the HR for female sex was higher for nonpersistence to TZDs than for nonpersistence to metformin (1.171 vs. 1.068) might suggest a different intensity or acceptability of side effects in women.

Use of TZDs in monotherapy was associated with a lower than average persistence for the primary cohort, possibly relating to the fact that TZDs are less rapid in reducing PG concentrations than traditional antihyperglycemics. Finally, patients who were prescribed a TZD by a specialist (endocrinologist or internist) were less likely to be persistent with therapy. This pattern was also seen in the metformin and the sulfonylurea groups and was independent of other important variables such as CDS. Although the HRs for this variable were generally close to 1, they were statistically significant and concordant with at least 1 other paper published in the literature (21). Although specialists are individually more likely to prescribe TZDs than GPs, our data suggest that they might be less efficient in keeping their patients on them. The reasons for this observation are not clear, but could be due to the fact that they switch patients more rapidly to a different diabetes treatment modality if PG is inadequately controlled.

Lastly, 2 important points should be made regarding the present study. First, because RAMQ covers the cost of medication of only 40% of the population of Quebec, our data may not be representative of patients with type 2 diabetes covered by private health insurance companies; indeed, these patients are known to have different patterns of drug utilization (22). Second, it should be acknowledged that the HRs for nonpersistence in the metformin and sulfonylurea groups were relatively small, suggesting that, despite our multivariate approach, our models are still missing important explanatory variables for these 2 oral antihyperglycemic agents.

CONCLUSION

In conclusion, this study shows a persistence to TZDs generally comparable with persistence to sulfonylureas, when TZDs are prescribed in a restricted drug benefit program such as the one currently available in the province of Quebec. Several variables have been associated with nonpersistence to TZDs. Although hypothetical, some of these predictors of nonpersistence suggest a negative impact of water retention on the persistence rate. Therefore, in the clinic, patients with risk factors for edema should perhaps be given reinforced advice regarding the possibility that this new class of antihyperglycemic agent could result in some adverse effects.

ACKNOWLEDGEMENTS

This study was supported by an unrestricted research grant from GlaxoSmithKline Canada. Pierre Maheux and Danielle Pilon were supported by scholarships from the Fonds de la recherche en santé du Québec. The authors thank Mr. Peter Hughes for his editorial assistance.

REFERENCES

1. Goldstein BJ. Differentiating members of the thiazolidinedione class: a focus on efficacy. *Diabetes Metab Res Rev*. 2002;18 (suppl 2):S16-S22.
2. Pittas AG, Greenberg AS. Thiazolidinediones in the treatment of type 2 diabetes. *Expert Opin Pharmacother*. 2002;3:529-540.
3. Canadian Pharmacists Association. *Compendium of Pharmaceuticals and Specialties: The Canadian Drug Reference for Health Professionals*. Ottawa, ON: Canadian Pharmacists Association; 2003.
4. Catalan VS, Couture JA, LeLorier J. Predictors of persistence of use of the novel antidiabetic agent acarbose. *Arch Intern Med*. 2001;161:1106-1112.
5. Boccuzzi SJ, Wogen J, Fox J, et al. Utilization of oral hypoglycemic agents in a drug-insured U.S. population. *Diabetes Care*. 2001; 24:1411-1415.
6. Dailey G, Kim MS, Lian JF. Patient compliance and persistence with antihyperglycemic drug regimens: evaluation of a Medicaid patient population with type 2 diabetes mellitus. *Clin Ther*. 2001;23:1311-1320.
7. US Food and Drug Administration. US Food and Drug Administration web site. Modification to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labels for ACTOS and AVANDIA. Available at: http://www.fda.gov/medwatch/safety/2002/summary-actos-avandia.pdf. Accessed April 29, 2005.
8. Health Canada. Health Canada Online website. Important safety reminder for patients taking oral diabetes drugs of the glitazone class, Avandia® and Actos®. Available at: http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_132e.htm. Accessed April 29, 2005.
9. Wooltorton E. Rosiglitazone (Avandia) and pioglitazone (Actos) and heart failure. *CMAJ*. 2002;166:219.
10. Régie de l'assurance maladie du Québec. Prescription drug insurance program 2003 web site. Available at: http://www.ramq.gouv.qc.ca/en/statistiques/statistiques/assurancemedicaments 2003.shtml. Accessed April 29, 2005.
11. Grégoire J-P, Moisan J, Chabot I, et al. Appropriateness of omeprazole prescribing in Quebec's senior population. *Can J Gastroenterol*. 2000;14:676-680.
12. Tamblyn R, Lavoie G, Petrella L, et al. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol*. 1995;48:999-1009.
13. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992;45:197-203.
14. Kleinbaum DG. The Cox proportional hazards model and its characteristics. In: Dietz K, Gail M, Krickeberg K, eds. *Survival Analysis: A Self-Learning Text*. New York, NY: Springer-Verlag; 1996:83-128.
15. Régie de l'assurance maladie du Québec. Liste de médicaments assurés web site. Available at: http://www.ramq.gouv.qc.ca/fr/professionnels/listmed/lm_tdmf.shtml. Accessed April 29, 2005.
16. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc*. 2003;78:1088-1091.
17. Tang WH, Francis GS, Hoogwerf BJ, et al. Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. *J Am Coll Cardiol*. 2003; 41:1394-1398.
18. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. *Pharmacotherapy*. 2002;22:924-929.
19. Streeten DH. Idiopathic edema. Pathogenesis, clinical features, and treatment. *Endocrinol Metab Clin North Am*. 1995;24:531-547.
20. MacGregor GA, Markandu ND, Roulston JE, et al. Is "idiopathic" edema idiopathic? *Lancet*. 1979;1:397-400.
21. Pilon D, Castilloux A-M, LeLorier J. Estrogen replacement therapy: determinants of persistence with treatment. *Obstet Gynecol*. 2001;97:97-100.
22. Piette JD, Wagner TH, Potter MB, et al. Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. *Med Care*. 2004;42:102-109.