Expert Opinion

Rosiglitazone in Canada: experience in clinical practice

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Background: Type 2 diabetes mellitus is a growing public health concern throughout the world. In North America, most people with type 2 diabetes receive care for their diabetes from a general or family practitioner and so the performance of a new therapeutic agent is best assessed in this setting. The first of a novel new family of oral hypoglycemic agents, rosiglitazone became available in Canada in February 2000. *Objective and methods*: In this article, we discuss an observational, prospective, cohort, open-label study to assess the clinical efficacy and safety of rosiglitazone in a typical type 2 diabetes population receiving care at a family practice setting with several drug therapies and comorbidities. *Results/conclusion*: During seven and a half years of experience in our clinical practice, rosiglitazone has been shown as a safe and effective treatment for type 2 diabetics on maximal tolerated or therapeutic doses of metformin and sulfonylurea, in a family practice setting.

Keywords: clinical experience, family practice, rosiglitazone, type 2 diabetes

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1. Introduction

1.1 Background and aims

The worldwide prevalence of type 2 diabetes is increasing owing to changing lifestyles and we are aware of the coming epidemic of type 2 diabetes worldwide [1,2]. Most of the care of type 2 diabetes is given by a general or a family practitioner. The Diabetes Screening in Canada study (2001) showed that 23.5% of patients presenting in a family physician's office in Canada have type 2 diabetes and that a third of these have not been diagnosed [3]. DICE study in Canada (2005) has shown that < 50% of diabetics are treated to Canadian Diabetes Association (CDA) guideline targets of hemoglobin A1c (HbA1c) level < 7.0% [4], leading to an increase in morbidity and mortality from the microvascular and macrovascular complications of diabetes [5-8]. The ACCORD study has generated some controversy concerning HbA1c targets. The study looked at whether more aggressive treatment with a target HbA1c of < 6.5% would improve cardiovascular outcomes [9]. In fact, there were excess cardiovascular deaths in the intensively treated group. It is now generally accepted that to minimize the risk of microvascular and macrovascular complications of diabetes, glucose levels should be controlled to an HbA1c level of < 7.0%, which is equal to mean glucose of 9.5 mmol/l and this is the current guideline of the CDA [10].

Rosiglitazone, approved for use in Canada in February 2000, was one of the first of a new family of hypoglycemic agents – the thiazolidinediones (TZDs) – used in treating patients with type 2 diabetes with insulin resistance. Rosiglitazone has shown efficacy for improving glycemic control in monotherapy as well as in combination with sulfonylureas, metformin and insulin [11-14].

In this article, we discuss an observational, prospective study that was intended to assess the clinical efficacy and safety of rosiglitazone in a typical type 2 diabetes

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population receiving care at a general family practice setting with several drug therapies and comorbidities.

2. Materials and methods

2.1 Design

This was an observational, prospective, cohort, open-labeled study carried out in a family practice setting on patients not achieving glycemic control target (HbA1c < 7%) after maximal doses of metformin and sulfonylurea. The patients were seen at our three clinical practices in Ontario, Canada. The data were taken from April 2000 to September 2007.

2.2 Setting and participants

We report here on 543 patients, 289 men and 254 women, mean age 69 years, mean weight 94.5 kg (207 lbs). Average duration of diabetes at entry was 11 years, and 99% of the study participants were Caucasian.

2.3 Inclusion and exclusion criteria

Inclusion criteria: the patient must had have type 2 diabetes and be insulin resistant or on maximal therapeutic or tolerated doses of biguanide (metformin 2 g/day) and sulfonylurea (glyburide 20 mg/day or gliclazide 320 mg/day) and not achieving target glycemic control according to CDA guidelines (HbA1c > 7.0%). The maximum dose of metformin licensed in Canada is 2.5 g/day; however, clinical studies have shown that there is no proven benefit in increasing dosage to > 2 g/day, and so this dose is the maximum dose that we use. Glyburide and gliclazide are the only sulfonylureas in common use in Canada. Although tolbutamide and chlorpropamide are licenced in Canada, they are not commonly used and the CDA guidelines recommend against their use because of the long duration of action [10]. Restrictions under the public drug plans in Canada limited the addition of rosiglitazone to those patients who had failed therapy with maximum doses of sulfonylurea and metformin. Because of this, there is a bias towards those who had failed conventional treatment. The co-administration of rosiglitazone and insulin is not indicated in Canada [12]; however, it is commonly used this way as off-label and these patients were included in the study.

Exclusion criteria: patients who met the inclusion criteria, but were not started on rosiglitazone were those with contraindications as per the product monograph [15]: individuals who could become pregnant, patients with severe liver disease and those with a high risk for congestive heart failure (New York Heart Association class III–IV).

2.4 Intervention

All patients were maintained on standard therapy for comorbidities associated with type 2 diabetes and were treated to the CDA guideline targets for blood glucose, lipids, blood pressure and microalbuminuria (MAU). Subjects started on 4 mg rosiglitazone per day and if glycemic target (HbA1c < 7%) was not reached after 3 months, consideration was given to increasing to the maximal therapeutic dose of 8 mg/day. Patients were assessed at 3-month intervals for HbA1c, fasting blood glucose and average blood glucose. The average number of medications per person was 7.8 to achieve treatment goals; the average number of visits was 4.3 per year. We report on 90 months (7 years and 5 months) of clinical experience. This study is also part of our normal quality control procedures and has received no outside funding.

2.5 Outcome measures

The predefined primary outcomes were markers for blood glucose control (HbA1c, fasting glucose, average glucose). The average glucose was the mean of all of the readings in the patient's meter from the previous 14 days. Secondary outcome measures were followed in accordance with CDA guidelines and include lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), triglycerides and cholesterol:high-density lipoprotein ratio) and nephropathy (MAU, albumin;creatinin ratio). Rosiglitazone was not expected to cause an improvement or decline in lipids or kidney function; they were monitored as part of multifactorial treatment of the patient with diabetes. Muscle enzyme (CK; creatinin kinase) was also monitored because nearly every patient on rosiglitazone was also on a statin. Liver enzymes (ALT) were also followed as recommended in the initial product monograph. Finally, we observed the tolerability of rosiglitazone and compiled the reason for discontinuation in those patients who stopped rosiglitazone.

2.6 Analysis

Data were collected from a computerized patient database (Humabase) and manually entered in Microsoft Access. For each outcome measure, we analyzed the number of patients with a value in the given quarter, as well as the mean, s.d. and maximum/minimum values for all patients in that quarter. The value at that particular quarter was compared to the value at baseline and analyzed for statistical significance using a one-tailed z-test.

2.7 Results

2.7.1 Glycemia

The intention was to treat population that was comprised of 385 patients (from 543 patients at baseline, we lost to follow-up 158 patients). In the first 6 months of rosiglitazone therapy, the data showed a significant decrease in HbA1c of 1.5% ($p < 0.0001$); fasting glucose of 1.1 mmol/l ($p < 0.0001$) and average glucose of 1.9 mmol/l ($p < 0.0001$). These markers for improved glycemic control were maintained over the course of the study. **Tables 1 – 3** show the primary outcomes in the first year of rosiglitazone treatment.

Average HbA1c on entering the study was 8.4%; maximal reduction occurred at 9 months, when average HbA1c fell to 6.9% (1.5% absolute reduction) and remained stable for the 90 months of the study, suggesting that rosiglitazone may slow or halt β-cell destruction. There was an overall

Table 1. Change in HbA1c after initiation of rosiglitazone.

Quarter	Mean	Change from baseline	Standard deviation of the mean	n Value	Range
0	8.4		1.62	385	4.6 – 1.48
1	7.5	-0.81 ($p < 0.001$)	1.28	275	5.0 – 1.16
2	7.0	-1.40 ($p < 0.001$)	1.12	249	4.8 – 1.22
3	6.9	-1.50 ($p < 0.001$)	1.10	189	4.8 – 1.08
4	6.9	-1.50 ($p < 0.001$)	1.09	205	4.7 – 1.18

HbA1c: Hemoglobin A1c.

Table 2. Change in fasting glucose after initiation of rosiglitazone.

Quarter	Mean	Change from baseline	Standard deviation of the mean	n Value	Range
0	8.80		2.86	324	2.6 – 20.8
1	7.70	-1.14 ($p < 0.001$)	2.41	272	3.8 – 15.9
2	7.53	-1.27 ($p < 0.001$)	1.87	256	3.4 – 15.5
3	7.38	-1.42 ($p < 0.001$)	1.76	189	4.2 – 16.7
4	7.10	-1.70 ($p < 0.001$)	1.48	193	3.4 – 12.2

Table 3. Change in 'average' glucose after initiation of rosiglitazone.

Quarter	Mean	Change from baseline	Standard deviation of the mean	n Value	Range
0	9.20		2.59	291	4.2 – 22.5
1	8.34	-0.86 ($p < 0.001$)	2.17	256	4.3 – 16.7
2	7.69	-1.51 ($p < 0.001$)	1.87	223	3.7 – 16.0
3	7.30	-1.90 ($p < 0.001$)	1.75	197	4.4 – 15.5
4	6.90	-2.30 ($p < 0.001$)	1.69	186	3.4 – 14.9

reduction in dose and number of other hypoglycemic medications. Over 80% of subjects attained the goal of HbA1c of < 7.0% (**Figure 1**, **Table 1**).

Fasting glucose was 8.8 mmol/l (158 mg/dl) at baseline, and maximal reduction of fasting glucose was seen at about 12 weeks with average fasting glucose 7.7 mmol/l (138 mg/dl) for 1.1 mmol/l (19 mg/dl) reduction (**Figure 2**, **Table 2**).

Average glucose (from self blood glucose monitoring) was 9.2 mmol/l (165 mg/dl) at baseline and decreased to 7.3 mmol/l (131 mg/dl) at 9 months for a 1.9 mmol/l (34 mg/dl) reduction. The modest decline continued until average glucose was below 7.0 mmol/l (126 mg/dl) and remained stable thereafter (**Figure 3**, **Table 3**).

Overall, in the first 6 months of rosiglitazone therapy, the data showed a significant decrease in HbA1c of 1.5% (absolute reduction) ($p < 0.001$), fasting glucose reduction of 1.1 mmol/l (19 mg/dl) ($p < 0.001$) and an average glucose reduction of 1.9 mmol/l (34 mg/dl) ($p < 0.001$). These markers for improved glycemic control were maintained over the course of the study.

2.7.2 Lipids

Lipids were not significantly affected, although there was a trend to improve lipids with decreased total cholesterol, triglyceride and LDL. The following reached statistical significance later in the study: total cholesterol had decreased by 0.24 mmol/l at 15 months ($p = 0.014$), triglycerides had decreased by 0.45 mmol/l at 24 months ($p = 0.003$) and LDL had decreased by 0.23 mmol/l at 30 months ($p = 0.018$). These decreases were maintained throughout the remainder of the study. This improvement in lipids, however, may be owing to concomitant use of statins and other cholesterol-lowering drugs, and there was a trend to lower triglycerides (this may simply be a manifestation of improved glycemic control).

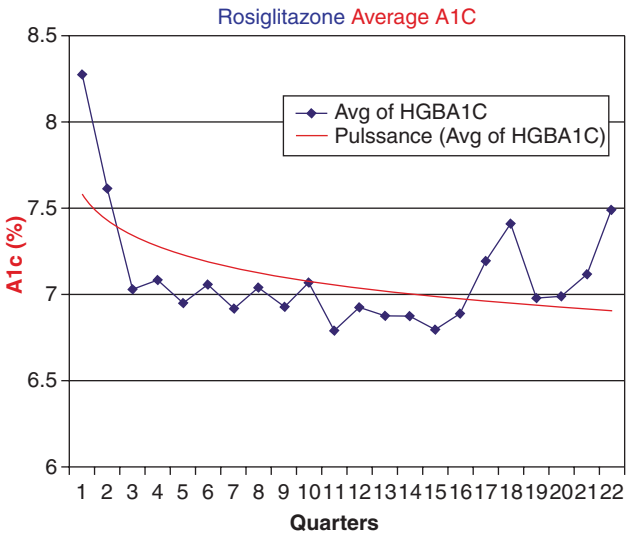

Figure 1. Mean HbA1c observed following commencement of rosiglitazone therapy.
HbA1c: Hemoglobin A1c.

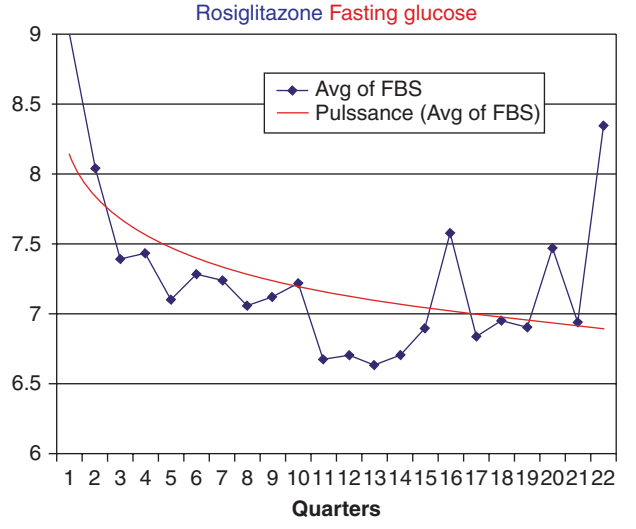

Figure 2. Fasting glucose observed following commencement of rosiglitazone therapy.

All our patients were treated to CDA guideline target lipids with statins or fibrate as appropriate (**Figure 4**).

Muscle enzyme (CK) was also monitored because nearly every patient on rosiglitazone was also on a statin. CK changes were not significant.

2.7.3 *Weight*

There was minimal weight gain (1.5 kg over 7.5 years) and we feel that this was because all subjects were extensively counseled about the potential for weight gain and fluid retention and they were advised to weigh themselves daily. Several patients did have significant weight gain (up to 5 kg) and a few (< 2%) discontinued the drug owing to weight gain or fluid retention.

2.7.4 *Liver function*

There was some improvement in ALT, which may be because of a decrease in the steatohepatitis of diabetes that is observed with TZD therapy. There were no subjects who had to discontinue rosiglitazone because of increased liver enzymes.

2.7.5 *Renal function*

Most subjects demonstrated nephropathy as manifested by MAU at baseline. There was progressive decline of MAU or albumin;creatinin ratio. Because hypertension treatment was not standardized and was carried out to achieve CDA guideline targets, the study design does not allow us to state that rosiglitazone was responsible for changes in renal function.

2.7.6 *Tolerance and safety*

Discontinuation rate was 11% (64 subjects), with the most frequent reasons for discontinuing being lack of efficacy (16), anemia (10), edema (10), congestive heart failure (16), weight gain (7), headaches (3) and nausea (2).

2.7.7 *Limitations*

There are limitations to this study. It was observational and carried out on patients in a single practice in several locations. Treatment was conducted to CDA guideline targets and individuals on rosiglitazone may have had other agents adjusted or added as needed. A total of 158 patients were lost to follow-up; although this number would be high in a controlled study, it reflects the reality of a practice in which patients were referred in consultation, but then return to their primary care practitioner for follow-up. Because this is a longitudinal study with a high number of lost-to-follow-up patients, the n-values, and thus statistical validity, decreases with time.

3. Conclusion and discussion

This observational, prospective, cohort study was undertaken to assess the efficacy of rosiglitazone in a typical type 2 diabetes population receiving care at a general family practice setting. Previous studies have shown that, compared to baseline, 6 months of treatment with rosiglitazone 4 mg monotherapy decreases HbA1c by 0.3% [11], combination therapy with a sulfonylurea decreases HbA1c by 0.9% [12], combination therapy with metformin decreases HbA1c by 0.6% [13] and combination therapy with insulin decreases HbA1c by 0.6% from baseline [14]. The treatment after 6 months with 8 mg rosiglitazone daily, when used in monotherapy, decreased HbA1c by 0.6% [11], combination therapy with metformin decreased HbA1c by 0.8% [13] and combination therapy with insulin decreased HbA1c by 1.2% from baseline [14]. These different studies have shown rosiglitazone to be efficacious in strict settings [11-14].

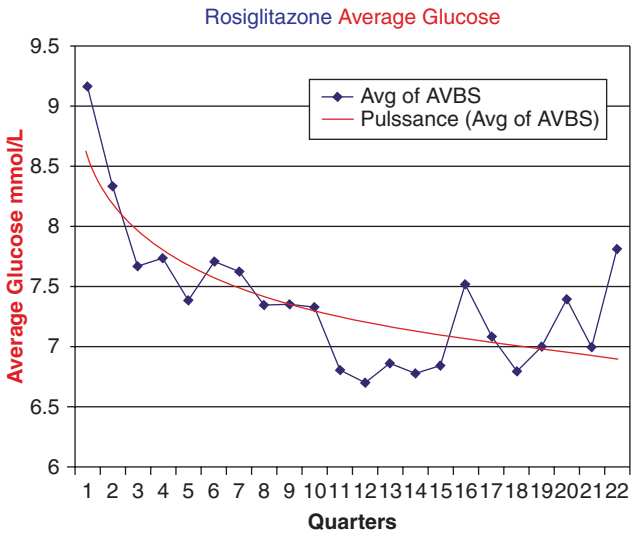

Figure 3. Average glucose observed following commencement of rosiglitazone therapy.

Our study was conducted using patients taking a variety of drugs for diabetes and other comorbidities, with the only exclusion criteria being those listed in the product monograph [15]. When evaluated in our family practice setting in which most patients received treatment, rosiglitazone still showed the ability to reduce HbA1c.

Rosiglitazone was the first TZD approved on the Canadian market. We have also studied pioglitazone in a similar cohort and results were essentially identical. Rosiglitazone proved to be an effective drug for lowering blood glucose levels in patients with type 2 diabetes and comorbidities taking a variety of medications and it is appropriate for use in a primary care setting. Although by today's standards we would be more selective about whom to treat with TZD, using it mainly in the early stages of diabetes, the degree of efficacy was nonetheless impressive with a consistent 1.5% HbA1c reduction. The failure rate of rosiglitazone was higher in people with longer duration of diabetes who had less endogenous insulin production; overall, only 11% of study subjects discontinued the medication, the most common reason being lack of efficacy. An insulin sensitizer only has therapeutic value if there is insulin production and insulin resistance. The DREAM and the ADOPT studies suggest that there is delayed progression of pancreatic dysfunction in people treated with rosiglitazone [16,17]. The PROACTIVE study suggests the same protective effect of pioglitazone, delaying significantly time to insulin [21]. We feel that the place for TZD therapy is early in the disease process although there is pancreatic function to preserve. As with all treatments, there are risks and benefits that need to be individually evaluated for each patient. The benefits of improved glycemic control and preservation of β-cell function need to be balanced against the risk of increased fluid retention, weight gain and increased fracture risk in women. Although this class of medications does have well-documented risks, these are generally manageable. Two-thirds of our patients showed significant benefit (65% reached HbA1c < 7.0% and > 80% presented > 5% improvement in HbA1c). Doses of sulfonylurea and metformin were modified during the follow-up period to maintain glycemic control. Generally speaking, there were minimal changes in metformin dose although there were decreases in sulfonylurea use. The rate of adverse events was low (5%), and there was no significant weight gain and no significant lipid changes. Dilutional anemia owing to fluid retention is a well-documented side effect of TZD use, but we have found a small proportion (3.8%) who develop severe anemia, which resolves on withdrawing of the drug [18,19]. Weight, glycemia and hemoglobin should be regularly monitored during TZD therapy. We did not see any osteopenic fractures during follow-up period, and one person died owing to myocardial infarction. Our data did not indicate a significant increase in weight; this may be owing to counseling regarding the side effects of the medication and lifestyle adjustments the patient could make to counterbalance the effects of the drug.

Rosiglitazone is an effective drug for lowering blood glucose levels when used in patients with a number of comorbidities taking a variety of medications. It had previously been shown to be effective when used in studies with rigid inclusion and exclusion criteria, utilizing therapies and treatment team approaches that are unrealistic for the average patient. Rosiglitazone is generally well tolerated, with our data consistent with previous published reports of adverse events.

4. Expert opinion

The worldwide prevalence of type 2 diabetes is increasing, owing to changing lifestyles. Most of the care of type 2 diabetes is given by primary care practitioners. A large research study on type 2 diabetes (UKPDS) has shown us that diabetes is a progressive disease characterized by deterioration of pancreatic β-cell function and increasing insulin deficiency [5-8]. Diabetes, particularly in the early years after diagnosis, involves interplay between insulin resistance and insulin sensitivity complicated by overproduction of glucose by the liver and incretin deficiency. Diabetes is a multifactorial disease requiring several treatments targeted to particular defects.

The relevance of this paper is that it reviews the experience with rosiglitazone in a general practice setting in which the use of the drug is quite different from the use in a controlled clinical trial. A wide variety of patients were treated with different duration of diabetes, different HbA1c levels and different comorbidities and concurrent medications. It is generally accepted that to minimize the risk of microvascular and macrovascular complications of diabetes, glucose levels should be controlled to an HbA1c level of < 7%, which is equal to a mean plasma glucose of 9.5 mmol/l.

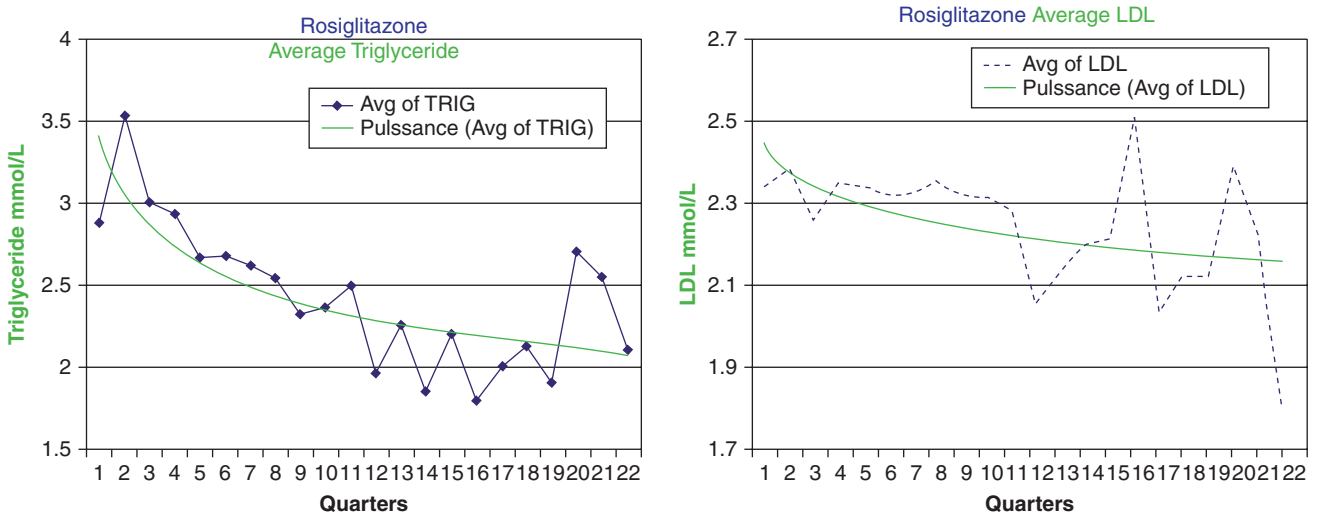

Figure 4. Average triglyceride and average LDL observed following commencement of rosiglitazone therapy.
LDL: Low-density lipoprotein.

Although the cornerstone of treatment of diabetes is lifestyle measures of diet and exercise, most people require pharmacotherapy to achieve control.

The first choice of medication for treatment is metformin in a therapeutic dose of up to 2000 mg/day, which will lower HbA1c levels by about 1 – 1.5%.

When further medications are required, the choice of medication needs to be individualized to the patient. Because diabetes is characterized by a progressive deterioration in β-cell function, the appropriate medication choices depend on where the patient is on the continuum of increasing insulin deficiency. In the early stages of the disease, when insulin resistance predominates, it is logical that our therapeutic efforts be directed toward pancreatic preservation. TZDs are the only medications that have demonstrated preservation of β-cell function [14,15], although incretins are showing some promise in animal studies. In the past, we have tended to start TZD when traditional treatment with SU or metformin failed; by this time, there has already been extensive β-cell failure and we are unlikely to see very much benefit. The place for TZD therapy is early in the course of the disease. TZD has the advantage of decreasing insulin resistance and preserving β-cell function but at the cost of increased fluid retention and weight gain. Similarly, DPP-4 inhibitors and GLP-1 analogues are only effective when there is suffi-cient residual β-cell function to augment. In theory, the co-administration of a TZD with an incretin therapy has some logical appeal and there are now studies being conducted to investigate this.

All drugs have risks and benefits. Whenever we prescribe medications, we have to weigh the risks against the benefits and determine what is in the best interest of the patient. Rosiglitazone and the TZD class of medications to which it belongs have been a real breakthrough in the treatment of diabetes not only because of the glucose lowering effect of increasing glucose disposal but also because of preservation of the insulin producing ability of the pancreas. Rosiglitazone has shown in several studies that it lowers blood glucose levels significantly and for a longer period of time than any other treatment. All treatments before TZD in the market failed because of the progressive deterioration of the pancreas. Rosiglitazone was the first drug that showed the potential to slow or possibly stop the deterioration of pancreatic function. This was also the first drug of its class in Canada that improved insulin resistance, which is a core defect in type 2 diabetes. Subsequent research has not only confirmed that rosiglitazone slows pancreatic deterioration but also that it is the most effective treatment that we have to prevent diabetes (the DREAM trial) [16].

In individual, major, well-controlled studies of rosiglitazone, there has been no associated increase in risks of heart attack although the meta-analysis by Nissen and Wolski in 2007 did suggest a small degree of increased risk. A study done on another member of the same class of medication (PROactive Study) using pioglitazone suggested a reduction in cardiac events in people taking the drug [20,21]. We have always known that this class of medication may predispose the patient to fluid retention and that people with severe heart disease may not be able to tolerate this extra fluid load, possibly developing congestive heart failure. We can treat with amiloride or spironolactone diuretics to decrease this risk (loop diuretics and thiazides are less effective) and we can do an echocardiogram before treatment to see that our patients have adequate cardiac reserve to be able to tolerate the potentially increased fluid load.

The Nissen meta-analysis published in the *New England Journal of Medicine* in May 2007 looks only at certain studies and suggests that there may be a relative risk increase for

heart attack in people taking rosiglitazone [22]. We need to put this in perspective and realize that the actual (absolute) risk of heart attack in these studies was very small and the apparent increase in risk may not be of any clinical significance. We need more data and need to look closely at the studies that are now being conducted to observe specifically the risks of cardiac events.

A continuing study, the RECORD trial (Rosiglitazone Evaluation for Cardiac Outcomes and Regulation of glycemia in Diabetes), is looking at the incidence of vascular disease with TZDs. An interim report in 2008 did not show increased cardiovascular end point risk. Full results will not be available until 2009, but it is reassuring that the FDA is monitoring interim results (as is the study's Safety Monitoring Committee) and according to the FDA website (21 May 2007), these results contradict the findings of the article on rosiglitazone published in the NEJM [22]. Moreover, the DREAM and ADOPT trials certainly show that there is no significant increase in the risk of myocardial infarction with rosiglitazone [16,17].

For the moment, rosiglitazone is a safe and effective drug. Patients can find it reassuring that on 31 July 2007, an expert committee reporting to the FDA voted 22-1 to keep rosiglitazone on the market.

We should also be reassured by websites of the CDA, The Endocrine Society and the American Diabetes Association (in a joint statement with the American Heart Association and the American College of Cardiology), which all agree that we need more information and that the article in the NEJM on rosiglitazone should not influence us to unduly stop a medication that is clearly working [22]. Those of our patients taking a TZD for the treatment or prevention of diabetes may be assured that these are safe, effective medications with a unique mechanism of action and are the only known medications to preserve pancreatic β-cell functioning. Although there are risks and benefits with all medications, both the scientific community and the regulatory agencies are monitoring safety issues and if there are significant concerns the medical community will be advised.

Although glycemic control is of primary importance in controlling microvascular complications, the results of glycemic control have less impact on macrovascular risks. All persons with diabetes should receive comprehensive macrovascular risk reduction with statin to lower LDL to ≤ 2 mmol/l and treatment of hypertension to a target of BP < 130/80 and ACE (or ARB) inhibition for vascular preservation and ASA for thrombosis prevention.

Declaration of interest

The authors do not have any known or suspected conflicts of interest with regard to the subject matter of this manuscript.

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