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The effect of withdrawal of rosiglitazone on treatment pathways, diabetes control and patient outcomes: A retrospective cohort study ☆

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ABSTRACT

Aims: To describe the withdrawal of rosiglitazone and the impact upon glycaemic control; intensification of therapy; and progression to major adverse cardiovascular events (MACE), cancer and mortality.
Methods: Data were from the Clinical Practice Research Datalink (CPRD), a longitudinal UK database. Rosiglitazone use was profiled from launch (2000) until withdrawal (2010). Patients discontinuing from July 2010 were included in the analysis to ascertain the impact on glycaemic control; therapy intensification; and progression to MACE, death and cancer. For comparison, patients were matched to those maintained on pioglitazone as a control group.
Results: Rosiglitazone use peaked in May 2007. Of patients prescribed rosiglitazone at discontinuation 54.1% patients used a dual-therapy regimen; most commonly with metformin (46.7%). 65.1% patients remained at the same stage of the diabetes pathway following discontinuation. 51.7% of patients replaced rosiglitazone with pioglitazone. Patients discontinuing were more likely (HR = 2.29), to subsequently intensify therapy than controls. After discontinuation of rosiglitazone there was a significant increase in HbA1c, from a median of 6.9% to 7.3%. In matched analysis, there was a significantly greater increase in HbA1c for rosiglitazone patients (0.33% versus 0.10%). Following discontinuation, crude rates for MACE, cancer and mortality were 8.4, 17.9 and 15.8 pkpy, respectively. None was significantly different in the matched analysis.
Conclusion: Withdrawal of rosiglitazone was associated with worsening glucose control and subsequent intensification of treatment regimen.

1. Introduction

Rosiglitazone, a thiazolidinedione (TZD), acts by increasing sensitivity to endogenous insulin and consequently reducing blood glucose. It was first licensed in the United Kingdom (UK) in 2000, but in 2007 safety concerns were raised, especially in relation to the potential for increased risk of myocardial infarction (MI) (Nissen & Wolski, 2007; US Food and Drug Administration, 2007). Following an evaluation by the European Medicines Agency (EMA) in September 2010 (European Medicines Agency, 2010), rosiglitazone was withdrawn from the UK market. At that time it was estimated that there were approximately 55,000 patients prescribed rosiglitazone as monotherapy, and 35,000 patients prescribed rosiglitazone in combination with metformin (NHS Choices, 2010).These patients were therefore switched to an alternative glucose-lowering regimen.

Although UK general practice data relating to TZDs have been extensively studied (Gallagher, Smeeth, Seabroke, Leufkens, & van Staa, 2011), little is known about the impact on patient outcomes following rosiglitazone withdrawal. We aimed to determine whether switching patients from stable treatment with rosiglitazone to alternative glucose-lowering regimens led to a loss of glucose control, and consequently intensification of anti-diabetes medication. Furthermore, to determine whether discontinuation of rosiglitazone was associated with adverse clinical outcomes.

2. Methods

2.1. Data source

The study was conducted using data from the Clinical Practice Research Datalink (CPRD) (The Medicines & Healthcare products Regulatory Agency (MHRA)); a longitudinal, anonymised database derived from over 650 UK primary-care practices. CPRD contains data from over 13 million people. Available data included medical history,

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investigation results and prescriptions. Diagnoses in CPRD are recorded using the Read code classification and have been validated in a number of studies, with results showing a high positive predictive value (Herrett, Thomas, Schoonen, Smeeth, & Hall, 2010).

2.2. Selection of patients

All patients initiating rosiglitazone were extracted to profile use from launch in 2000 until 2012. For the discontinuation analysis, patients were selected if they had discontinued rosiglitazone from 1st July 2010, and consequently switched to an alternative regimen. For comparative analyses, patients discontinuing rosiglitazone were compared with patients maintained on pioglitazone, an alternative TZD. Index date was defined as the date of rosiglitazone discontinuation. Matched pioglitazone control patients had to have initiated therapy before the index date and discontinued afterwards, and were matched dynamically at a ratio of 1:1. Dynamic matching algorithms allowed the baseline characteristics of the rosiglitazone patient which are known at the index date – to be matched to those of the control, which are fluid. Matching criteria were: age (± 5 years), gender, history of major adverse cardiovascular event (MACE) or cancer, stage in the treatment pathway (see below), year of rosiglitazone initiation (± 1 year), smoking status, and HbA1c (± 1.0%). Baseline differences between cohorts were assessed by univariate analysis appropriate to the distribution of the variable. All results were reported with two-sided p values.

2.3. Analysis

Pattern of use of rosiglitazone from launch (2000) to 2012 was analysed to determine the impact of the initial warnings concerning rosiglitazone in 2007 and the subsequent withdrawal in 2010. Analysis was presented by patients initiating or discontinuing, and aggregate number of patients receiving rosiglitazone.

The pattern of substitution following discontinuation of rosiglitazone after July 2010 was described by treatment stage according to the usual treatment pathway for glucose lowering: oral monotherapy (T1); oral dual therapy (T2); oral triple therapy (T3); therapy comprising more than three oral agents (T4) and injection-based therapy (T5).

Baseline characteristics at the date of discontinuation were presented for patients defined by therapy stage (groups T1 through T5). Substitution of rosiglitazone was described by change in treatment-pathway stage: static—remaining on the same stage of the treatment pathway (having rosiglitazone substituted for another oral agent); intensification of treatment (having rosiglitazone substituted with either two or more oral agents or an injectable agent); de-intensification of treatment (having no replacement therapy).

2.4. Intensification

Intensification of therapy following substitution was characterised. Intensification was defined as a progression along the treatment pathway from the stage that the patient switched to following rosiglitazone discontinuation. The number and proportion of patients intensifying treatment were presented by treatment pathway stage.

Two Cox proportional hazard models were created to consider patient factors that predicted discontinuation, comprising firstly all patients who had discontinued rosiglitazone therapy and secondly, patients discontinuing rosiglitazone with the matched pioglitazone patients.

Two sub-group analyses patients were performed. The first compared those who remained static with those who either intensified or de-intensified treatment. The second, restricted to patients intensifying or static on initial switch, compared those who replaced rosiglitazone with either pioglitazone, a DPP-4 inhibitor, sulfonylurea or metformin.

2.5. Change in glucose control

The nearest HbA1c observation for each patient within −180 and +90 days of discontinuation was used as the baseline value. The nearest value (±180 days) of the anniversary of discontinuation (discontinuation date +365 days) was recorded and the difference compared using the paired *t*-test.

Change in HbA1c was also presented by taking 60-day rolling averages from baseline for the first year following treatment discontinuation. For those remaining on static therapy, difference in HbA1c by therapy substitution was compared using one-way analysis of covariance (ANCOVA). To determine if change in HbA1c was greater than expected with the natural progression of diabetes, change in HbA1c was compared between patients discontinuing rosiglitazone and matched pioglitazone controls using ANCOVA.

2.6. Safety analysis

The primary endpoints for the safety analysis were all-cause mortality, MACE (MI or ischaemic or haemorrhagic stroke) and cancer. Patients with a prior history of a study endpoint were excluded from any relevant analysis. All diagnoses for MACE and cancer were classified by Read codes recorded within the patients' records.

The number of events and crude rates for patients discontinuing rosiglitazone were presented. Time to each clinical endpoint was presented using Kaplan–Meier curves. Two Cox proportional hazard models were created to consider other patient factors that predicted each endpoint, comprising all patients who had discontinued rosiglitazone therapy and those with matched patients continuing on pioglitazone therapy.

In the Cox models for intensification and safety additional covariates were age, gender, diabetes duration, systolic blood pressure, HbA1c, cholesterol, BMI, smoking status, lipid-lowering and anti-hypertensive therapy. Baseline morbidity was characterised by number of primary-care contacts in the previous year and by Charlson co-morbidity index. Covariates were added to the Cox models with a threshold for covariate retention of significance $p \leq 0.20$.

Patients were followed from index date to date of event or censorship. Cases were censored at either the patient's last contact date or the last data-collection point for their particular practice.

3. Results

The number of patients receiving rosiglitazone increased from 2000, reaching a peak in May 2007 (n = 18,278), when safety concerns were first publicised. The subsequent decline in rosiglitazone is characterised by an increase in discontinuations and a rapid decrease in patients initiating. In the months prior to September 2010, there was an increase in discontinuations followed by a sharp spike of discontinuation as rosiglitazone was withdrawn from the market. The pattern of initiation, discontinuation and total patients prescribed rosiglitazone from August 2000 to December 2010 is illustrated in Fig. 1.

3.1. Discontinued patients

3680 eligible patients discontinuing rosiglitazone from 1st July 2010 were identified. Of these, 3526 (95.8%) were included in the analysis group. The reasons for exclusions are shown in supplementary Fig. 1. Baseline characteristics by the stage in the treatment