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Original Article

Development of vascular complications and bladder carcinoma in diabetics using pioglitazone: A five-year Indian review

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ARTICLE INFO

Article history:
Received 23 October 2015
Accepted 13 June 2016

Keywords:
Diabetes mellitus type-2
Pioglitazone
Bladder carcinoma
Vascular complications
Thiazolidinedione

ABSTRACT

Background: Pioglitazone has better cardiovascular outcomes and a questionable relationship with bladder carcinoma in diabetes mellitus, type II (DM-2). We sought to evaluate the role of pioglitazone in the Indian population.

Methods: This is a retrospective study at an academic medical center in India. All DM-2 patients in 2008 with a new prescription of pioglitazone were age- and gender-matched with non-users. We excluded patients with gestational DM or DM type I. They were followed forward for five years and demographic data, micro- and macro-vascular complications, mortality, and bladder carcinoma were recorded. Two-tailed $p \leq 0.05$ was considered statistically significant.

Results: Two cohorts of 260 patients, with mean age of 58 ± 11 years with 413 (79.4%) males, were followed for five years. Pioglitazone users had higher hypertension, obesity, DM-2 family history (all $p < 0.003$), and use of insulin and oral hypoglycemics (all $p < 0.0001$) in comparison to non-users. HbA1c was not different between groups. Over five years, pioglitazone users had lesser retinopathy and myocardial infarctions (all $p < 0.01$). Five cases of bladder carcinoma were noted, all in the pioglitazone group, however without statistical significance. Baseline variables, including mean daily pioglitazone dose, were not statistically different between patients with and without bladder carcinoma. Nephropathy and MI were independent predictors for development of bladder carcinoma within pioglitazone users.

Conclusions: Pioglitazone users had significantly lesser myocardial infarctions and retinopathy despite more difficult to control DM 2. In an age- and gender-matched cohort of users and non-users, pioglitazone did not contribute to development of bladder cancer in the Indian population.

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http://dx.doi.org/10.1016/j.mjafi.2016.06.004
0377-1237/© 2016 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

Introduction

Thiazolidinediones (TZD) medications, which act on the proliferator-activated receptor gamma (PPAR-γ) a nuclear transcription factor, are used in the management of diabetes mellitus, type 2 (DM-2).[1] TZDs increase insulin sensitivity, reduce blood glucose and hemoglobin A1c (HbA1c) levels, inhibit adipose-tissue lipolysis, and inflammation and reduce blood pressure.[2] These medications offered a lot of hope for the management of DM-2 in which cardiovascular causes are responsible for nearly 75% of the deaths.[2] A landmark meta-analysis in 2007 showed a higher risk of myocardial infarction (MI) and cardiovascular mortality with rosiglitazone resulting in this medication being withdrawn from the market.[3] Subsequently, pioglitazone was promoted as the cardioprotective TZD with multiple studies demonstrating good cardiovascular profile in these patients.[2,4,5] More recently, a controversial correlation between pioglitaone and bladder cancer in male patients has been proposed, which has tapered our enthusiasm for this group of drugs.[1,4] However, most of these data are from the Western literature,[1,6] with data from Indian authors limited to expert opinions and case series despite India being the diabetic capital of the world.[7–14] Over the years, epidemiological data have highlighted the significant differences in cardiovascular risks and bladder carcinoma in the Indian population in comparison to other countries.[14,15] This lack of robust data had resulted in a Indian government ban on pioglitazone and subsequent rapid revocation in 2013 following global trends.[15] In this context, we sought to evaluate data on pioglitazone in the Indian population.

Material and methods

This retrospective cohort study was carried out at a tertiary care academic medical center in India. The Manipal University Institutional Ethics Committee exempted the study from obtaining written informed consent from individual patients due to its retrospective nature. All patients with between January and December 2008 with an International Classification of Diseases-10 code (ICD-10) of DM-2 with a new prescription of pioglitazone (TZD here forth) were reviewed. Patients with a diagnosis of type-1 or gestation diabetes mellitus were excluded from our study. Patient related information including demographic details, past medical history, oncological history, personal-social history and clinical presentations were recorded. Details on DM-2 including HbA1c, evidence of end organ damage and family history of DM-2 were collected. These patients were followed by chart review for a period of five years to assess for micro- and macro-vascular complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, cerebrovascular accident (CVA) and MI. Mortality during this period was also recorded.

For an anticipated hazard ratio of 1.2 in exposed individuals and an exposure rate of 0.485 in unexposed individuals from a previous study,[16] with precision of 15% at 95% level of confidence for a two-sided test, the calculated minimum sample size was 520. Age- and gender-matched cohorts of 260 patients with and without TZD therapy were followed for the development of malignancy. These patients were followed forward in time for a period of five years. Best attempts were made via the telephone and postal correspondence to contact patients lost to follow-up. Statistical analysis was performed using IBM SPSS Statistics (IBM Corp, Armonk, NY). The association between TZD exposure and outcomes of macro- and micro-vascular complications, patient status, and malignancy were analyzed using chi-square tests or Student's t-test for equal proportions. Where data were insufficient to meet statistical assumptions for chi-square test, Fisher's exact test or Mann–Whitney U-test was employed. All data are presented as mean ± standard deviation (SD), relative risks (RR) with 95% confidence interval (CI) or number (percentage). Logistic regression analysis is presented as odds ratio (OR) with 95% CI. Kaplan–Meier logistic regression analysis was used to calculate survival and hazard function statistics, with right censoring performed for the patients who did not have an event during the study duration. Cumulative survival and cumulative hazard was plotted against the event-time product. Two-tailed p-value of ≤0.05 was considered statistically significant.

Results

A total of 520 patients (all Asian Indian race) with DM-2 were studied in the period from January to December 2008. Of these patients, 413 (79.4%) were male with mean age of 58 ± 11 years. Age, gender, and smoking history matched cohorts of 260 new TZD users and non-users were created and followed over a period of five years. Detailed patient demographic characteristics and risk factors in TZD users and non-users are reported in Table 1. TZD users had lesser hypertension and obesity, but had a more prevalent family history of DM-2. TZD users had statistically significant higher usage of insulin, metformin, and sulphonylureas. HbA1c values were available for 160/520 (30.8%) patients with a mean value of 9.9 ± 2.5%, for the total cohort without statistically significant difference between both groups.

Over a five-year period, TZD and non-TZD patients were evaluated for development of micro-vascular (nephropathy, neuropathy, retinopathy) and macro-vascular (CVA, MI) complications. The TZD users had statistically significant higher incidence of neuropathy, but lesser retinopathy and MI as compared to the TZD non-users. Univariate analysis of complications in TZD and non-TZD users is presented in Table 2. In a logistic regression analysis of significant factors univariate variables from Table 1, TZD use remained an independent predictor of diabetic neuropathy as represented in Table 3.

Of the 520 patients, five (1.9%) patients developed bladder cancer over a five-year period. All five belonged to TZD users cohort with none detected in the non-TZD users (p-value 0.06). Over the five-year period, one patient developed bladder carcinoma at year one, second in year three, two additional patients in year four, and the last one in year five (Fig. 1). Mean survival time was 120.2 (95% CI 119.5–120.9) months with 515 patients censored at the end of the five-year duration due to absence of event occurrence. Among the TZD users, baseline characteristics of patients with and without bladder cancer are presented in Table 4. Patients with bladder cancer were all males, with no statistically significant differences in baseline

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