Pharmacoepidemiological study report abstract
Pioglitazone-5020/ER-9531

Pioglitazone Use and Risk of Bladder Cancer in Observational Studies: a Systematic Literature Review and Meta-Analysis

Authors: Juha Mehtälä, Houssem Khanfir, Fabian Hoti
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Title

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Keywords

Bladder cancer, Diabetes, Meta-analysis, Pioglitazone, Review

Rationale and background

Several studies have been published investigating the possible risk of incident bladder cancer in type 2 diabetes mellitus patients treated with pioglitazone with conflicting results. Furthermore, meta-analyses of published studies have been conducted, suggesting that pioglitazone use is associated with a small but statistically significant increase in the risk of bladder cancer. Most previous meta-analyses were conducted using studies published prior to 2013. Considering that more long-term observational studies investigating the possible risk of bladder cancer with pioglitazone use have been published since 2013, there is a need to review the accumulated real world evidence and update the previous meta-analyses.

Research question and objectives

The objective of this meta-analysis was to assess the association between bladder cancer and exposure to pioglitazone among subjects with type 2 diabetes mellitus in a meta-analysis of observational studies. This meta-analysis was aimed to answer the following questions:

- **Primary research question:** Are type 2 diabetes mellitus patients treated with pioglitazone at higher risk of bladder cancer compared to type 2 diabetes mellitus patients who are not treated with pioglitazone?

- **Secondary research question:** Is the risk of bladder cancer increased by cumulative exposure duration or cumulative dose of pioglitazone?

Study design

This meta-analysis was based on a systematic and comprehensive literature review conducted to identify eligible observational studies from peer-reviewed scientific journals.

Setting

Studies published prior to September 30, 2016 were identified using a specified search strategy. The reference section of each included study and previous meta-analysis resulting from the electronic search were used to identify additional records and screened for eligibility.

Study size

Of the 363 identified records, 23 were included in the review and 18 in the actual meta-analyses.

Variables and data sources

The following variables were extracted from eligible studies: authorship, year of publication, country or region of source data, setting (database used), study design (e.g. cohort, case-control, nested case-control), study period, inclusion and exclusion criteria, study population size, follow-up (summary measure), age (summary measure), proportion of male subjects, outcome identification, number of bladder cancer cases, type(s) of pioglitazone exposure studied, estimated effect sizes for pioglitazone – bladder cancer association, adjusting covariates used when estimating the association of risk between pioglitazone exposure and bladder cancer, any additional information that might guide the reviewers when assessing the risk of bias.

Results

After a systematic review of 363 identified records, 18 studies were included in the meta-analyses. For the bladder cancer outcome, the overall effect size for ever use vs. never use of pioglitazone was estimated at
1.16 (95% CI: 1.04, 1.28). Among cumulative exposure groups of <10 500 mg, 10 500 – 28 000 mg, and >28 000 mg, the effect sizes were 1.12, 1.09 and 1.41, with respective CIs (0.98, 1.30), (0.83, 1.42) and (1.06, 1.88). In the 10 500 – 28 000 mg and >28 000 mg exposure groups substantial heterogeneity between individual studies was found ($I^2 = 54\%$ and $55\%$, with p-values 0.075 and 0.066, respectively). Among cumulative duration groups of <12 months, 12 – 24 months, and >24 months, the effect sizes were 1.07, 1.19 and 1.38, with respective CIs (0.94, 1.22), (1.07, 1.32) and (1.04, 1.82). Substantial heterogeneity between individual studies was found in the >24 months exposure group ($I^2 > 82\%$, p-value 0.002). In the analysis (sensitivity I) including only studies/results which adjusted for lifestyle-related factors the treatment effect size was 1.18 (95% CI: 1.00, 1.40), but the result was not statistically significant (p=0.054). In the Bayesian model (sensitivity III) with an extra level of hierarchy (study country) to account for between-country variations, the overall effect size 1.17 was similar to the primary analysis, but the 95% credible interval (0.94 to 1.54) crossed 1.0 with the posterior probability of 7.1% for having a value smaller than 1.

Conclusion

In line with previous meta-analyses, we observed a small but statistically significant association between ever (vs. never) use of pioglitazone and bladder cancer risk; however, causality is not established and one cannot rule out alternative explanations. In the cumulative dose and duration analyses highest effect size was observed in the highest/longest exposure group, but substantial heterogeneity across individual studies was present. Importantly, when studies without adjustment for lifestyle factors were excluded, the effect size was not statistically significant. Also, when the imbalance in number of studies per country/overlap in subjects was addressed in the Bayesian sensitivity analysis, the 95% credible interval of the treatment effect size crossed 1.