Reviewer's report

Title: Can daily intake of aspirin and/or statins influence the behavior of non-muscle-invasive bladder cancer? A retrospective study on a cohort of patients undergoing transurethral bladder resection

Version: 2 Date: 17 June 2014

Reviewer: Teemu Murtola

Reviewer's report:

This manuscript describes a cohort study of 574 patients with non-muscle invasive bladder cancer (NMIBC) undergoing transurethral resection during 2008-2013. Disease recurrence after the primary operation was compared between patients who had used aspirin, statins, both or neither of studied the drug groups.

More recurrences and higher number of lesions at recurrence were observed in medication users overall compared to non-users. Among the medication users aspirin users had fewer recurrences compared to statin users, with the recurrence rate being comparable between aspirin users compared to medication non-users, but elevated in statin users compared to non-users.

I have the following comments:

Major compulsory revisions:

- The length of follow-up, as well as the end-points for study follow-up need to be described
- The conclusion that aspirin protects from NMIBC is an overinterpretation of the results. Figure 3 shows that there is very little difference in any of the end-points between aspirin users and medication non-users, with overlapping confidence intervals. What was the reference group for the p-values reported in this Figure? The medication non-users or statin users? I suspect the latter, whereas the former would be correct.
- You should re-do the analysis using Cox regression or Kaplan-Meier method with time-metric being the time since the primary TURB. This would be much more informative given that that it would take into account also the time to recurrence.

Minor essential revisions:

Abstract
- Conclusions, Page 3:
  - Overstatement in conclusions. A single observational study cannot confirm or refute causal associations, especially given the limitations mentioned above.
Background
- Page 4, 2nd paragraph, the sentence beginning “Using our cohort of patients and the results of other studies on epithelial neoplasms....”
  o This sentence remained unclear to me. What results from other studies did you use in your study?

Methods
- 1st paragraph: did you include only patients undergoing their primary TURB, or did you also include previously treated patients?
- 2nd paragraph: Describe the 21 women that were excluded in order to obtain statistically homogeneous comparison groups. What were the exact reasons for their exclusion?
- Page 6, 1st paragraph: Did you only consider medication usage at baseline (the time of primary TURB) or did you also include medication usage during the follow-up?

Results
- It can be observed in Table 1 that medication users, especially statin users had more often high-grade and pT1 disease, which could explain the higher number of recurrences among them. The difference was not statistically significant, but this could be due to low numbers of study participants. You should include stratified analyses comparing recurrence by medication use separately in those with high-grade disease and in those with low-grade disease. Also stratification by smoking status and presence of carcinoma in situ would be informative.

Table 1
- The proportions of men with carcinoma in situ should be added to the table.
- Report the numbers of patients who received intravesical instillation of chemotherapy at TURB. If you do not have this information, it should be mentioned as study weakness.

Figures
- What are the numbers reported inside the bars? Means or medians?

Discussion
- The p-values and proportions should not be repeated in this section, as they have already been reported in the Results-section.
- Page 10, 4th paragraph: this paragraph discusses the potential significance of COX-2 in bladder carcinogenesis. However, the similar disease recurrence in aspirin users and medication non-users observed in this study does not support this.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I previously, but not any more owned stock at Orion Pharma. I have received lecture fee from Janssen-Cilag. I have participated in scientific meetings at expense of Astellas Pharma, GlaxoSmithKline and Janssen-Cilag.