Comparative risk of the incident cancer between ranitidine versus other histamine-2 receptor antagonists

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Background

Ranitidine is a histamine H2-receptor antagonist (H2RAs) commonly have been used to treat gastroesophageal reflux disease and peptic ulcer disease and it was top over-the-counter H2RA brand in the USA in 2013. Recent study confirmed that oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine (NDMA) by nitrosation of ranitidine under stomach-relevant pH conditions in vitro, and the potential cancer risk from ranitidine was suggested.

In 2019, The US Food and Drug Administration (FDA) has asked doctors and patients to withdraw all ranitidine products from the market as of September 2019, after low levels of the probable human carcinogen NDMA were detected. NDMA is known as one of the most potent animal carcinogens and has been shown to be a potent carcinogen across all species that have been investigated. Hence, the International Agency for Research on Cancer has classified NDMA as “probably carcinogenic to humans” (group 2A).

Even though there have been several studies regarding association between NDMA exposure and risk of cancer, real-world evidence of cancer risk in relation with ranitidine is scarce. Recent Danish nationwide cohort study found that NDMA exposure in contaminated valsartan was not associated with increased risk of cancer. It means that the real-world evidence could be uncertain.

Hence, this multinational large-cohort study aimed to identify whether ranitidine has higher cancer risk compared with other H2RAs.

Methods

This study is an observational, comparative cohort study based on the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM). We compared the incidence of cancer between ranitidine and other H2RAs including famotidine, roxatidine, and lafutidine. We identified eligible patients who started to use the H2RA longer than 30 days. Primary outcome is overall cancer except non-melanoma skin cancer from 1 year after the treatment initiation to end of observation. Secondary outcomes include overall cancer, overall cancer except thyroid cancer, 16 types of cancer, and cancer mortality.

Large-scale propensity score (PS) matching is used to balance the differences in baseline characteristics between febuxostat and allopurinol group. The outcome model includes all covariates that were also included in the propensity model, and is fitted using a L1 regularized conditional Cox regression with prior. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable. We employ 99 negative outcomes (eg, candidiasis of skin and tenia pedis) to address potential systematic bias. We conducted sensitivity analyses with various time-at-risk windows and methods adjusting PS.

The analytic software package and the detailed analytic plan are available at github (https://github.com/ohdsi-studies/RanitidineCancerRisk). Here, we report the preliminary results from Korean National Sample Cohort and Ajou hospital EHR database.

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Results

Here, we report only incidence results not to unblind the whole results before completing network study.

The incidence of primary outcome (overall cancer except skin cancer) was 20.9 and 19.4 per 1000PYs in ranitidine and other H2 blocker group in NHIS-NSC, respectively. The incidence of outcome was low in the AUSOM database, but results for the incidence rate difference of AUSOM was similar to those of NHIS-NSC. The results were consistent across different PS adjustment strategies

Database	Analysis	Target incidence	Comparator	IRD
NHIS-NSC	1:1 PS matching, ITT, with 1-year lag period*	20.9	19.4	1.5
	PS stratification, ITT, with 1-year lag period	21.9	19.5	2.4
	No PS matching, ITT, with 1-year lag period	21.9	19.5	2.4
AUSOM	1:1 PS matching, ITT, with 1-year lag period*	12.1	10.9	1.2
	PS stratification, ITT, with 1-year lag period	11.9	10.4	1.5
	No PS matching, ITT, with 1-year lag period	11.9	10.4	1.5

*Primary analytic setting; incidence indicates number of outcomes per 1000 person-years; IRD, incidence rate difference

We found substantial heterogeneity in incidence of primary outcome across the different time-at-risk settings. The incidence of cancer in ranitidine users is numerically higher than other H2 blocker users in on-treatment analysis without lag period, which warrants further investigation.

Database	Analysis	Target incidence	Comparator	IRD
NHIS-NSC	1:1 PS matching, ITT, with 1-year lag period*	20.9	19.4	1.5
	1:1 PS matching, ITT	23.7	20.8	2.9
	1:1 PS matching, on-treatment	42.9	35.2	7.7
	1:1 PS matching, on-treatment, with 1-year lag period	23.0	28.4	-5.4
AUSOM	1:1 PS matching, ITT, with 1-year lag period*	12.1	10.9	1.2
	1:1 PS matching, ITT	13.3	12.5	0.7
	1:1 PS matching, on-treatment	33.8	13.4	20.4
	1:1 PS matching, on-treatment, with 1-year lag period	9.8	23.3	-13.5

*Primary analytic setting; incidence indicates number of outcomes per 1000 person-years; IRD, incidence rate difference

Conclusions

In this preliminary result, we did not find substantially numerical difference in incidence of cancer between ranitidine use and other H2 blocker use. The results are sensitive to the setting for follow-up duration.

We are recruiting global OHDSI collaborators for this study. If you are interested in joining this study, please contact: **seng.chan.you@ohdsi.org**

- Acknowledgment : This work was supported by the Bio Industrial Strategic Technology Development Program (20001234) funded By the Ministry of Trade, Industry & Energy (MOTIE, Korea) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea [grant number: HI16C0992].