Comparative risk of the incident cancer between histamine-2 receptor antagonists (Risk of cancer between H2RAs)

First published: 19/04/2021

Last updated: 23/04/2024

Study Planned

Administrative details

EU PAS number

EUPAS38902

Study ID

42946

DARWIN EU® study

No

Study countries

- [ ] France
- [ ] Germany
- [ ] Korea, Republic of
- [ ] Spain

☐ United Kingdom

☐ United States

Study description

Dietary N-nitrosodimethylamine (NDMA) has been shown to be carcinogenic in animals, however, evidence from population-based studies is inconlusive. The U.S. Food and Drug Administration has issued a statement on ranitidine because they may contain unacceptable levels of NDMA in 2019. To date, there have been several studies regarding association between NDMA exposure and risk of cancer, however, real-world evidence of cancer risk in relation with ranitidine is scarce. We aim to evaluate the comparative risk of incident cancer in patients exposed to various H2 receptor antagonists (H2RAs). We will conduct systematic, multinational study to estimate the relative risk of primary outcome (overall cancer except non-melanoma skin cancer) and secondary outcomes (overall cancer, overall cancer except thyroid cancer, 16 types of cancer, and cancer mortality) in ranitidine cohort. We will compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model after propensity score adjustment.

Study status

Planned

Research institutions and networks

Institutions

Yonsei University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

IQVIA

United Kingdom

First published: 12/11/2021

Last updated: 22/04/2024

Institution | Non-Pharmaceutical company | ENCePP partner

Ajou University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

IQVIA

United Kingdom

First published: 12/11/2021

Last updated: 22/04/2024

Institution | Non-Pharmaceutical company | ENCePP partner

NHIS South Korea, Hanyang University South Korea, Ajou University South Korea, Kangdong Sacred Heart Hospital South Korea, Columbia University US, Stanford University US, IQVIA US

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Seng Chan You

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/01/2021

Study start date

Planned: 18/01/2021

Date of final study report

Planned: 01/11/2021

Sources of funding

- Other

More details on funding

Ministry of Health & Welfare, Republic of Korea. grant number: HI19C0143

Study protocol

H2RACancerRisk_Protocol_V0.5.pdf (679.44 KB)

H2RACancerRisk_Protocol_V0.5.1.pdf (691.94 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Non-EU RMP only

Other study registration identification numbers and links

https://github.com/ohdsi-studies/ranitidinecancerrisk

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Main study objective:

To generate evidence for comparative safety of incident cancer of ranitidine compared with other H2 blockers

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A02BA) H2-receptor antagonists

H2-receptor antagonists

Medical condition to be studied

Neoplasm malignant

Additional medical condition(s)

The primary outcome was overall cancer except non-melanoma skin cancer. The secondary outcomes were overall cancer, 16 subtypes of cancer.

Population studied

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

200000

Study design details

Outcomes

Occurrence of malignant neoplasm except non-melanoma skin cancer for the first time in the person’s history, The secondary outcomes include overall cancer, 16 subtypes of cancer (lip, oral cavity and pharynx cancer, esophageal cancer, stomach cancer, colorectal cancer, liver cancer, pancreatic cancer, lung cancer, breast cancer, cervical cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, leukemia, thyroid cancer, gall bladder and biliary tract cancer) and death

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Data analysis plan

We use propensity score model to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The following covariates are used in the large-scale propensity score matching: demographics including age, gender and race, all recorded medication, medical history, exposed procedures, Charlson comorbidity index in the year prior to the index date in each database. We construct matched cohorts using 1:1 propensity score matching with a caliper of 0.2 on the logit scale. The

propensity scores were estimated by L1 regularized logistic regression, tuned by 10-fold cross validation. Cox proportional hazard models will be used to assess the hazard ratios with associated 95% confidence intervals (CIs) between the two cohorts using the CohortMethod R package (https://github.com/OHDSI/CohortMethod). Random-effect model meta-analysis will be performed to calculate summary hazard ratio for pooling effect estimates across databases.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

THIN® (The Health Improvement Network®)

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

THIN, SIDIAP

Data sources (types)

Administrative healthcare records (e.g., claims)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No