Dihydropyrimidine dehydrogenase deficiency related toxicities to fluorouracil and fluorouracil related substances containing medicinal products - EudraVigilance analysis and literature review

First published: 20/01/2021

Last updated: 02/04/2024

Study Finalised

Administrative details

EU PAS number

EUPAS39122

Study ID

39123

DARWIN EU® study

No

Study countries

Netherlands

Study description

This study included a descriptive analysis of case reports to fluorouracil and related substances in EudraVigilance that could have resulted from dihydropyrimidine dehydrogenase deficiency (DPD). The study included several different potential case definitions of DPD including probabilistic phenotyping.

Study status

Finalised

Research institutions and networks

Institutions

European Medicines Agency (EMA)

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Contact details

Study institution contact

Pinheiro Luis luis.pinheiro@ema.europa.eu

Study contact

luis.pinheiro@ema.europa.eu

Primary lead investigator

Pinheiro Luis

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 26/03/2019

Actual: 26/03/2019

Study start date

Planned: 26/03/2019

Actual: 26/03/2019

Data analysis start date

Planned: 26/03/2019

Actual: 26/03/2019

Date of final study report

Actual: 19/06/2019

Sources of funding

- EMA

Study protocol

DPD deficiency toxicity and 5FU drugs - EV DAP - 20190326.pdf (155.1 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Other

If ‘other’, further details on the scope of the study

Case series review of Pharmacovigilance Data

Data collection methods:

Secondary use of data

Main study objective:

To identify and describe case reports to fluorouracil and fluorouracil related substances and, To identify and characterise case reports to these products where dihydropyrimidine dehydrogenase deficiency (DPD) was also reported.

Study Design

Non-interventional study design

Other

Non-interventional study design, other

Case-series, Probabilistic phenotyping with Machine Learning

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

FLUOROURACIL

CAPECITABINE

TEGAFUR

FLUCYTOSINE

Medical condition to be studied

Dihydropyrimidine dehydrogenase deficiency

Additional medical condition(s)

Dihydropyrimidine dehydrogenase deficiency related toxicity

Population studied

Short description of the study population

Case reports to fluorouracil and related substances in EudraVigilance that could have resulted from dihydropyrimidine dehydrogenase deficiency (DPD).

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)
- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- 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

126890

Study design details

Data analysis plan

Descriptive statistics was performed by substance, age, gender, indication for use, origin of reports, reaction and outcome for all case reports. Cases were highlighted according to whether they refer to a DPD patient or mention any term within the toxicity spectrum. Where feasible, boxplots of time to onset were plotted and stratified by product and indication for use. In addition, the proportion of cases with life-threatening or fatal reactions amongst DPD patients and those with DPD toxicity spectrum reactions was compared as were

the proportions of cases with immediate (1 - 2 days), short (3 – 21 days) and long (> 21 days) time-to-onset for DPD patients and those with DPD toxicity spectrum reactions. To estimate the number of likely DPD related cases, machine learning models were be run deployed. These identify patterns in the terms reported to DPD patients and detect similar patterns in cases were DPD status is unknown.

Documents

Study results

DPD deficiency toxicity and 5FU drugs - Final Report - 20190617_corr.pdf (1.38 MB)

Study publications

Correia Pinheiro L, Durand J, Dogné JM. An application of machine learning in p…

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), other

EudraVigilance

Data sources (types)

Spontaneous reports of suspected adverse drug reactions

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