10 May 2022
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Data analysis plan

Population incidence rate of pemphigoid

Administrative details of the data analysis	
Condition/ADR(s)	Pemphigoid
Short title of topic	Pemphigoid incidence rates
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1. List of abbreviations

MAH	*Marketing Authorisation Holder*
EMA	*European Medicines Agency*
PRAC	*Pharmacovigilance Risk Assessment Committee*
RDA	*Rapid Data Analysis*

2. Rationale and background

Pemphigus and bullous pemphigoid are autoantibody-mediated blistering skin diseases. In pemphigus, keratinocytes in epidermis and mucous membranes lose cell-cell adhesion, and in pemphigoid, the basal keratinocytes lose adhesion to the basement membrane. Pemphigus lesions are mediated directly by the autoantibodies, whereas the autoantibodies in pemphigoid fix complement and mediate inflammation. In both diseases, the autoantigens have been cloned and characterized; pemphigus antigens are desmogleins (cell adhesion molecules in desmosomes), and pemphigoid antigens are found in hemidesmosomes (which mediate adhesion to the basement membrane). There are two major types of pemphigus, pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The rarer subgroup of pemphigus-like diseases is paraneoplastic pemphigus. The major type of pemphigoid is bullous pemphigoid (BP).

BP is characterized by diffuse truncal and limb tense blisters, urticarial plaques, intense pruritus and sparing of mucosal membranes. The pathogenesis of BP depends on the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors. Several trigger factors, such as drugs (e.g. furosemide, heparin, ibuprofen, captopril) or thermal or electrical burns, surgical procedures, trauma, ultraviolet irradiation, radiotherapy, chemical preparations, transplants and infections may induce or exacerbate BP. The presence of diabetes, stroke, Parkinson's disease, and dementia can be associated with BP compared to the general population.

The incidence of BP has increased over the past decades as a result of population aging with multiple comorbidities and exposure to drugs that may potentially trigger the disease, as well as improvement in the clinical diagnosis. Epidemiological studies of BP in Europe demonstrate the incidence ranges from 2.5 to 42.8 cases/million/year. The frequency of BP also increases in patients older than 80 years, with nearly 150-330 new cases/million/year at this age range. Patients with BP have increased mortality, ranging from 10% to 40% in the first year.

Pemphigoid is sometimes discussed as a potential ADR after treatment with some drugs. Recently it has been associated with some direct oral anticoagulant and some COVID-19 vaccines. To address such safety signals for COVID-19 vaccine and to be prepared for future regulatory discussions on signals focused on pemphigoid, population incidence rates for pemphigoid will be calculated across all six European databases.

3. Research question and objectives

The objective of this study is to address the following research questions:

- What is the incidence rate of pemphigoid stratified by age, sex and years of diagnosis?
- Where possible, what is the incidence of pemphigoid stratified by season of diagnosis (Autumn, Winter, Spring, Summer)?

4. Research methods

4.1. Study design

This will be a cohort study describing incidence rates (IRs).

4.2. Setting and study population

General and stratified IRs for pemphigoid will be calculated in six EU databases which cover primary health care users from France, Germany, UK, Spain, Italy and Romania.

4.3. Variables

Outcomes

To define pemphigoid, database specific codes mapping to ICD10: L12 (for the COVID-19 signal, this may be updated – either being expanded or more focussed – following input from pharmacovigilance colleagues).will be used as following:

L12.0 Bullous pemphigoid

L12.1 Cicatricial pemphigoid

L12.2 Chronic bullous disease of childhood

L12.3 Acquired epidermolysis bullosa

L12.8 Other pemphigoid

L12.9 Pemphigoid, unspecified

Specific codes used for each database are shown in Annex 2.***Stratification***

Results will be stratified by sex and age group (0-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years & ≥80 years). If possible, results will also be stratified by quarter (season of diagnosis): (Q1- Winter: 01January-31March; Q2-Spring: 01April-30June; Q3-Summer: 01July-30September; Q4-Autumn: 01October-31December). See table shell in Annex 3.

4.4. Data sources

The following databases will be used: IQVIA™ Disease Analyser France, IQVIA™ Disease Analyser France, IQVIA™ Disease Analyser France, IQVIA™ Disease Analyser Germany, IQVIA™ Medical Research Data (IMRD, UK), THIN® Spain, THIN® Italy, THIN® Romania

4.5. Statistical analysis

4.5.1. Main statistical methods

This study will describe the incidence of new onset pemphigoid diagnoses in patients contributing patient time to the databases listed above. Patients will be required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients will be excluded from the analysis if they have any prior history of the condition in the database.

The study period will be from 2015 to 2019. Population incidence rates from 2020 and 2021 (or the most recent data available) are included for interest only as the "true" background rates might be distorted by a change in the way in which patients interacted with healthcare services during the COVID-19 pandemic.

Numerator

The numerator will consist of the number of patients who experience the event of interest during the yearly or quarterly time period. Patients with a baseline history of pemphigoid will be excluded and will only be able to contribute one event.

Denominator

As with the numerators, patients with a baseline history of pemphigoid at the start of each quarter will be excluded. Patient follow-up time will be truncated at the occurrence of the first event after which they will not contribute to the analysis.

Analysis

Follow-up time will be calculated using the following formula:

follow up time (years) = ((end date for the period – start date for the period + 1))/365.25

Time will be truncated where patients enter or leave the study cohort part way through a time period or where they have an event. The incidence rate is the calculated as the number of events divided by the total follow up time:

incidence rate = (number of new onset events)/(total follow up time (years))

This will be presented as the number of events per 100,000 person-years and will be calculated for the entire population as well as stratified by year, quarter (where possible), gender and age group (see Annex 3 below for the table shells). Confidence intervals around incidence rates will be calculated using exact method.

Analyses will be performed by the EMA researchers, using the IHD platform for IQVIA™ Disease Analyser France and Germany and using SAS for IMRD, THIN® Spain, THIN® Italy and THIN® Romania.

4.5.2. Sensitivity analysis

Sensitivity analyses were not conducted.

4.6. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4.7. Limitations of the research methods

Diagnostic coding for pemphigoid is not known to have been validated in the primary care databases available. As a skin condition, it is likely to present in primary care. Although confirmation of the diagnoses required specialist input (incorporating biochemistry and histological investigation), it is thought likely that the nature of the diagnosis means that its recording in primary care records will be reasonably accurate and complete. However, this assumption should be treated cautiously.

The results will be carefully examined to see if there is any evidence of changes in healthcare utilisation during the COVID-19 pandemic (2020-present), which might have the potential to give misleading results. The results will be stratified by quarter to investigate if there is any seasonal trend.

5. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

For information entering the public domain such as publication in EU PAS register, and in accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database and <10 in IQVIA™ Disease Analyzer France, THIN® Spain, Italy and Romania) will be removed prior to publication of this report. Additional cells may have been redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

6. References

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Lee J, Seiffert-Sinha K, Attwood K and Sinha AA (2019) A Retrospective Study of Patient-Reported Data of Bullous Pemphigoid and Mucous Membrane Pemphigoid From a US-Based Registry. *Front Immunol* 10:2219. doi: 10.3389/fimmu.2019.02219

Persson, M., Harman, K., Vinogradova, Y., Langan, S., Hippisley-Cox, J., Thomas, K. and Gran, S. (2021), Incidence, prevalence and mortality of bullous pemphigoid in England 1998–2017: a population-based cohort study. *Br J Dermatol* **184**: 68-77. https://doi.org/10.1111/bjd.19022

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Lu, L, Chen, L, Xu, Y, Liu, A. Global incidence and prevalence of bullous pemphigoid: A systematic review and meta-analysis. *J Cosmet Dermatol* 2022; 00: 1– 18. doi:10.1111/jocd.14797

Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

The Health Improvement Network (THIN®) Italy

In THIN® Italy data collection started in 2000 and this database is currently able to provide clinical monitoring data of anonymised patients managed by 500 GPs in primary care (including patients'

history). The data source of THIN® Italy is electronic health care records. The entire database reaches 900,000 patients (active and non-active), from which 500,000 are currently actively followed. In order to be representative at national and macroregional level, physicians have been recruited in accordance with their universe distribution in terms of geography, age and gender.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and they are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The Health Improvement Network (THIN®) Romania

THIN® Romania is a primary care healthcare database, including only General Practitioners (574 GPs). The source of data is electronic health care records. Enrolled GPs and their patients are representative of the whole Romanian population in terms of location, demographics and prevalence from the point of view of main chronic health pathologies. Data collection started in 2012.

In Romania, the insured population (background sampled population) numbered 17.1 million individuals (data from 2012). Among these, 8.5 million individuals benefited of healthcare services, in the public system. The number of GPs who worked in the public healthcare system, in 2017 was aproximately 11,000 physicians. They recorded 76 million consultations and issued 71 million prescriptions (data from 2017). The number of deceased patients was of 297,000 individuals, and number of newborns in 2020 was of 179,000 individuals.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and they are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The Health Improvement Network (THIN®) Spain

THIN® Spain is mainly a primary care healthcare database, including practitioners (GP), specialists and pediatricians & nurses. It contains data from approximately 2,000 GPs and 2,400 specialists (cardiology, pulmonology, urology, etc.). THIN® Spain also includes partial activities related to the hospital. THIN® Spain is globally representative of the whole national demographics and prevalence on the main chronic health pathologies. THIN® Spain includes 3,000,000 individuals out of the overall population. Among these, 1,050,000 are active in the previous year and 1,800,000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals. New patients are automatically included into the database, and deceased patients identified in a specific field.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The THIN® Spain Database has been approved by two Ethics Committees, one from the Community of Madrid (Hospital Ramón Cajal) and one from the Community of Catalonia (Hospital Clinic de

Barcelona). These ethics committees reviewed the data collection, protection, and anonymization processes and positively approved THIN® Spain for observational research of medical products (upon protocol submission).

Annex 2 – Code lists

THIN® – Italy

code	label
M2IT.ICD9.694.2	DERMATITE ERPETIFORME GIOVANILE
M2IT.ICD9.694.5	PEMFIGOIDE
M2IT.ICD9.694.6	PEMFIGOIDE BENIGNO DELLE MUCOSE
M2IT.ICD9.694.60	PEMFIGOIDE BENIGNO DELLE MUCOSE SENZA MENZIONE DI INTERESSAMENTO OCULARE
M2IT.ICD9.694.61	PEMFIGOIDE BENIGNO DELLE MUCOSE CON INTERESSAMENTO OCULARE

THIN® - Romania

code	label
PHRO.ICD10.L120	Pemphigoid bulos
PHRO.ICD10.L121	Pemphigoid cicatrial
PHRO.ICD10.L122	Dermatoza
PHRO.ICD10.L123	Epidermoliza buloasa dobindita
PHRO.ICD10.L128	Pemphigoid

THIN® – Spain

code	label
FUES.CIE10.L12.0	PENFIGOIDE AMPOLLOSO
FUES.CIE10.L12.1	PENFIGOIDE CICATRICIAL
FUES.CIE10.L12.2	ENFERMEDAD AMPOLLOSA CRÓNICA DE LA INFANCIA
FUES.CIE10.L12.8	OTROS TIPOS DE PENFIGOIDE
FUES.CIE9.694.2	DERMATITIS HERPETIFORME JUVENIL
FUES.CIE9.694.5	PENFIGOIDE
FUES.CIE9.694.6	PENFIGOIDE BENIGNO DE LA MEMBRANA MUCOSA
FUES.CIE9.694.60	PENFIGOIDE BENIGNO MEMBRANA MUCOSA-SIN IMPLICACION OCULAR
FUES.CIE9.694.61	PENFIGOIDE BENIGNO MEMBRANA MUCOSA-CON IMPLICACION OCULAR

IMRD (UK)

clinicalcodeid	term	readtermid
5684019	Acquired epidermolysis bullosa	M1453
10833016	Juvenile dermatitis herpetiformis	M142
57191017	Mucous membrane pemphigoid	M146
57192012	Cicatricial pemphigoid	M1460-1
127980014	Bullous pemphigoid	M1450
142845014	Pemphigoid	M145
308664012	Pemphigoid NOS	M145z
308669019	Benign mucous membrane pemphigoid	M146z
309311010	[X]Other pemphigoid	Myu12
399920011	Benign mucous membrane pemphigoid with no eye involvement	M1460
485794012	Ocular pemphigoid	M1461
267631000006119	Ocular pemphigoid	F4Cy1
403571000006114	[X]Ocular pemphigoid	FyuC6
5128231000006113	Prebullous pemphigoid	^ESCTPR512823
6049801000006118	Ocular cicatricial pemphigoid	^ESCTOC604980

IQVIA™ Disease analyzer – France

ICD10 code	term
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid (Benign mucous membrane pemphigoid)
L12.2	Chronic bullous disease of childhood (Juvenile dermatitis herpetiformis)
L12.3	Acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified

IQVIA™ Disease analyzer – Germany

ICD10 code	term
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid (Benign mucous membrane pemphigoid)
L12.2	Chronic bullous disease of childhood (Juvenile dermatitis herpetiformis)
L12.3	Acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified

Annex 3 – table shell

strata	***events***	***follow-up time (person years)***	***Rate per 100,000 (95% CI)***
overall			
2016			
2017			
2018			
2019			
2020			
2021			
under 20 years			
20-29 years			
30-39 years			
40-49 years			
50-59 years			
60-69 years			
70-79 years			
80 years & over			
female			
male			
female under 20 years			
female 20-29 years			
female 30-39 years			
female 40-49 years			
female 50-59 years			
female 60-69 years			
female 70-79 years			
female 80 years & over			
male under 20 years			
male 20-29 years			
male 30-39 years			
male 40-49 years			
male 50-59 years			
male 60-69 years			
male 70-79 years			
male 80 years & over			
Q1 - Winter			
Q2 - Spring			
Q3 - Summer			
Q4 - Autumn			