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Adverse events reported for hereditary angioedema medications: a retrospective study of spontaneous reports submitted to the EudraVigilance database, 2007–2013

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Abstract: Information about long-term safety issues from use of orphan drugs in treatment of hereditary angioedema (HAE) is limited and must be studied further. As clinical trials in patients with rare diseases are limited, prescribers and patients have to rely on spontaneous adverse drug reaction (ADR) reports for obtaining major information about the serious, rarely occurring, and unknown ADRs. In this study, we aimed to characterize ADRs reported for HAE medications in Europe from 2007 to 2013. ADR reports submitted for C1-inibitors and bradykinin receptor antagonists to the European ADR database, EudraVigilance (EV), were included in this study. The ADR reports were categorized with respect to age and sex of the patients, category of the reporter, type and seriousness of the reported ADRs, and medications. The unit of analysis was one adverse event (AE). Totally, 187 AEs were located in EV, and of these, 138 AEs were reported for Cinryze® (C1-inhibitor) (73% of the total) and 49 AEs for Firazyr® (icatibant) (26% of the total AEs). Approximately 60% of all AEs were serious, including three fatal cases. Less than 5% of AEs were reported in children. In total, 62% of AEs were reported for women and 38% for men. For both Cinryze® and Firazyr®, the majority of reported AEs were of the type "general disorders and administration site conditions". For Cinryze®, a large number of AEs of the type "HAE" and "drug ineffective" was reported, but only few of these were serious. For Firazyr®, several nonserious reports on injection site reactions were reported. In conclusion, this study showed that in EV, several ADR reports from use of HAE medications were identified, and a large number of these were serious, including fatal cases.

Keywords: orphan drugs, hereditary angioedema, adverse drug reactions, adverse events, C1-inhibitor, Cinryze®, icatibant, Firazyr®, EudraVigilance

Introduction

Hereditary angioedema (HAE) is an autosomal dominant and rare disease which is caused by either a diminished level (HAE type 1) or dysfunction (HAE type 2) of complement C1-inhibitor.[1–3] Complement C1-inhibitor deficiency causes an uncontrolled activation of the contact system with excessive bradykinin formation as the main outcome.[1–3] Symptoms of HAE are recurrent angioedema attacks without urticarial signs, typically characterized by swelling of the skin and/or mucosa. Angioedema episodes most frequently affect the extremities, abdomen, head/neck area, and the upper respiratory airways.[1–3] HAE patients do not respond to traditional angioedema treatments, for example, antihistamines, glucocorticoids, and epinephrine, and for many years, HAE patients have been treated off-label with androgens and/or tranexamic acid. Hence, the

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need for development of more effective and specific HAE treatments has been prevailing for both patients and health care professionals.[4–6] Traditionally, the pharmaceutical industry did not find it profitable to develop medicines for rare diseases, but with the worldwide implementation of national Orphan Diseases Acts, it has became more economically profitable to develop specific medications for treatment of HAE, the so-called orphan drugs.[7,8] In the European Union (EU), a rare disease is defined as any disease occurring in less than 5 in 10,000 people, and consequently, orphan drugs are being licensed under favorable conditions with respect to demonstration of efficacy and safety.[8] The EU Orphan Disease Act has led to the development of several new HAE-specific medical treatments, for example, C1-inhibitors,[9–11] bradykinin receptor antagonists (icatibant),[12,13] and the recombinant plasma kallikrein inhibitor ecallantide (Kalbitor®; Dyax Corp. Burlington, Vermont, USA).[14–16] Lack of sufficient knowledge of long-term safety aspects from use of orphan drugs in treatment of HAE patients makes spontaneous ADR reporting systems an important source of information about medicine safety.[17] As premarketing clinical trials within the area of rare diseases are scarce, clinicians and health authorities have to rely on spontaneous reports as the major source of new information on ADRs, particularly data on serious and rarely occurring ADRs.[17] Since 2012, researchers have been allowed to access the EU ADR database, EudraVigilance (EV), and this has opened for cross-national analysis based on a standardized reporting format.[18] By February 2016, no studies have systematically analyzed postmarketing safety data reported for orphan drugs licensed for treatment of HAE and submitted to national ADR databases in Europe.[19] The aim of this study was to characterize the adverse events (AEs) reported for orphan drugs licensed for treatment of HAE submitted to the EV database from 2007 to 2013.

Materials and methods

Study design

We retrospectively reviewed ADR reports submitted to the EV database for orphan drugs licensed for treatment of HAE in Europe. The reported AEs were analyzed with respect to their type and seriousness, age and sex of the patient, suspected medicines, and type of the reporter. The unit of analysis was one ADR. The age groups of the patients were categorized into two: children (0–17 year olds) and adults (≥18 year olds). AEs reported for HAE medications licensed through the central licensing procedure in the EU by the European Medicines Agency (EMA) were included in this study. The included HAE medications were Berinert® (CLS Behring, Danderyd, Sweden) Cinryze® (Shire, Danderyd, Sweden), and Ruconest® (Shire, Danderyd, Sweden) (C1-inhibitors – ATC code B06AC01) and Firazyr® (Shire, Danderyd, Sweden) (icatibant) (bradykinin receptor antagonist – ATC code B06AC02). Table 1 displays the characteristics of the included HAE medications, their approved indications and age groups, time of licensing in the EU, name of the marketing authorization holder, and occurrence and type of reported adverse drug reactions listed in the latest version of the official product information. Information about the orphan drugs was retrieved through the website of the EMA. The C1-inhibitor Berinert®, which is also licensed for acute and prophylactic treatment of HAE, was excluded from this study. Berinert® is not centrally authorized in the EU, and therefore, we could not get access to the ADR reports reported for Berinert® through EMA.

Material

The EV database contains information about all suspected spontaneous ADR reports and the ADRs reported in clinical trials and postmarketing for all medicinal products authorized in the EU.[20] ADR data should be transmitted electronically to the database in accordance with the International council on harmonisation of technical requirements for registration of Pharmaceuticals for human use (ICH E2B) (R2) standard.[21] The EV database is not publicly accessible, and authorization for data access was given by the EMA.[22] ADR information was provided for this study in anonymous form with encrypted personal identification.[23] Data extraction and data analyses of the raw material were comprehensive and time consuming. ADR information was extracted from the EV database with respect to the type of reporter and the criteria of seriousness and medications for which the AEs were reported. Criteria of seriousness were evaluated and made by the reporters and the evaluations were confirmed by the national regulatory agencies before forwarding the ADR data to the EV database. The reported AEs were coded according to their type and seriousness using the Council for International Organizations of Medical Sciences criteria by the academic staff in the national regulatory agencies.[24] ADR data were extracted from the EV database in Microsoft Excel files using the following criteria: patient's sex and age, medicines (active substance), adverse drug reaction, and severity.[22] The material comprised all ADR reports submitted to the EV database from 2007 to 2013. Data were extracted from the EV database and delivered to us as several large Excel files. In STATA® statistical software package (StataCorp LP, College Station, TX, USA), the Excel files were merged into one major file and the ADR reports were searched for duplicates. Data analysis including coding of ADR reports was conducted in an Access database. Each ADR report may refer

Table 1 Characteristics of orphan drugs licensed for treatment of hereditary angioedema in Europe and information about adverse drug reactions (frequency and type) available in the official product information

Medications (alphabetical order)	Indication for use	Population	Year of EU licensing	MAH	Adverse drug reactions (frequency and type)	PI* version (month/year)
Cinryze® (C1-esterase inhibitor human)	Angioedema • Acute • Prophylaxis	Adolescents Adults	2011	Shire Orphan Therapies GmbH	*Common:* Rash *Uncommon:* Abdominal pain Arthralgia Chest discomfort Contact dermatitis Cough Diarrhea Dizziness Erythema Headache Hot flush Hyperglycemia Injection site reactions Joint swelling Myalgia Nausea Phlebitis Pyrexia Pruritus Venous burning/thrombosis Vomiting *Not known*: Hypersensitivity reactions	12/2014
Firazyr® (icatibant)	Angioedema • Acute	Adults	2008	Shire Orphan Therapies GmbH	*Very common (≥1/10):* Injection site reactions Transaminase increased *Common (from ≥1/100 to <1/10):* Dizziness Erythema Headache Nausea Pyrexia Pruritus Rash	03/2013
Ruconest® (conestat alfa)	Angioedema • Acute	Adults	2010	Swedish Orphan Biovitrum	*Common (from ≥1/100 to <1/10):* Headache *Uncommon (from ≥1/1,000 to <1/100):* Abdominal discomfort Diarrhea Nausea Paresthesia Swelling Throat irritation Urticaria Vertigo	10/2013

Note: *PI: Product information available at the website of the European Medicines Agency (http://www.ema.europa.eu/ema/).
Abbreviations: EU, European Union; MAH, Marketing Authorization Holder; PI: product information.

to one or more suspected ADR(s) as well as to one or more medicinal products. In this study, we only included the AEs reported for medications, which were listed as suspect drug by the reporter, meaning that a causal relationship between the reported ADR and the drug was expected.

Classification of AEs by type and seriousness

The different types of reported AEs were classified according to the *Medical Dictionary for Regulatory Activities* System Organ Class (SOC).[24] Serious AEs were defined as: fatal,

life-threatening, requiring hospitalization or prolongation of existing hospitalization, and resulting in persistent or significant disability/incapacity in the reporter's assessment, in a congenital anomaly/birth defect, and other medically important conditions. All other AEs were classified as non-serious.[24] The scientific staffs working in the different national regulatory agencies made the seriousness evaluations, and these evaluations were forwarded to us together with the copies of the ADR reports.

Ethical approval

According to Danish law, no ethical approval was required for this study.

Results

From 2007 to 2013, a total of 79 individual ADR reports containing information about 187 AEs were found in EV for HAE medications licensed by the EMA (Table 2). For Cinryze®, a total of 60 ADR reports covering information about 138 AEs were reported, and for Firazyr®, the number was 19 reports and 49 AEs. No ADR reports were found for Ruconest® in the EV database. Health care professionals reported all ADR cases. In total, 62% of AEs were reported for women and 38% for men. Approximately 5% of AEs were reported in 0–17 year olds. Approximately 10% of ADR reports were found without information about patient age in EV.

AEs by seriousness

In total, 60% (n=116) of all reported AEs (n=187) were classified as serious, and among these, three fatal cases were reported (Table 2). For Cinryze®, the share of serious AEs was 57% (n=80) and for Firazyr®, it was 70% (n=36). The characteristics of the three fatal cases are displayed in Table 3. For Cinryze®, one fatal case of sudden death presumably due to "basilar artery thrombosis" was reported in a 52-year-old male, and one fatal case due to the AEs "cytomegalovirus infection" and "cytomegalovirus test positive" in a male infant was also found in EV for Cinryze®. For Firazyr®, one fatal case of sudden death presumably due to "myocardial infarction" was reported in a 67-year-old male.

Table 3 Fatal adverse drug reaction cases reported for Cinryze® and Firazyr® in Europe, 2007–2013

Case no	Year	Medicine	ATC group	Adverse drug reaction(s)	Age	Sex
1	2008	Cinryze®	B06AC01	Basilar artery thrombosis Death	52	Male
2	2010	Cinryze®	B06AC01	Cytomegalovirus infection Cytomegalovirus test positive Death	<1	Male
3	2012	Firazyr®	B06AC02	Myocardial infarction	67	Male

Note: ATC, Anatomical therapeutic chemical classification system.

AEs by type and seriousness

Table 4 shows the distribution of reported AEs by SOC, seriousness, and medicine. For Cinryze®, the largest shares of AEs were reported for the SOCs "general disorders and administration site conditions" (25% of the total AEs) and "skin and subcutaneous disorders" (25% of the total AEs). For Cinryze®, the majority of serious AEs were also found within the SOC "general disorders and administration site conditions" (60% of the reported AEs). For Firazyr®, majority of the reported AEs were of the type "general disorders and administration site conditions" (49% of the total AEs), and approximately 45% of these AEs were serious.

AEs by medication

Table 5 displays the number of reported AEs by medicines and seriousness. For Cinryze®, the largest number of reported AEs was "HAE" (n=25) and "drug ineffective" (n=10); however, only a few of these ADR cases were serious. For Firazyr®, a large number of nonserious ADR reports on injection site reactions were found in EV. For both Cinryze®

Table 2 Distribution of cases and adverse drug reactions (AEs) for orphan drugs licensed for treatment of HAE by medication, seriousness, age, and sex, found in the EudraVigilance database, 2007–2013

Medications (alphabetical order)				Sex			Age (years):		
	Cases (n)	AEs (n)	Serious AEs (n)	Male (n)	Female (n)	NA (n)	<17 (n)	≥18 (n)	NA (n)
Berinert®	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cinryze®	60	138	80	53	85	1	9	116	13
Firazyr®	19	49	36	18	30	0	0	41	8
Ruconest®	0	0	0	0	0	0	0	0	0
Total	79	187	116	71	115	1	9	157	21

Abbreviations: AE, adverse effect; HAE, hereditary angioedema; NA, no information available in EudraVigilance.

Table 4 Number of adverse drug reactions reported for HAE medications distributed by system organ class, seriousness (in parentheses), and medicine, 2007–2013

System organ class (alphabetical order)	Cinryze® Total (n) (serious)	Firazyr® Total (n) (serious)
Blood and blood forming organs	8 (8)	NA
Cardiac disorders	2 (2)	7 (7)
Congenital, familial, and genetic disorders	4 (4)	1 (1)
Gastrointestinal disorders	7 (7)	1 (1)
General disorders and administration site conditions	36 (25)	25 (12)
Hepatobiliary disorders	3 (3)	2 (2)
Immune system disorders	4 (4)	1 (1)
Infections and infestations	2 (2)	NA
Injury, poisoning, and procedural complications	6 (5)	NA
Investigations	1 (1)	3 (3)
Metabolism and nutrition disorders	2 (1)	NA
Musculoskeletal and connective tissue disorders	8 (0)	3 (3)
Nervous system disorders	3 (1)	1 (1)
Pregnancy, puerperium, and perinatal conditions	8 (9)	NA
Skin and subcutaneous disorders	33 (6)	5 (5)
Vascular disorders	6 (2)	NA
Total	138 (80)	49 (36)

Abbreviations: HAE, hereditary angioedema; NA, no information available in EudraVigilance.

and Firazyr®, only 10% of the reported AEs were already mentioned in the official product information.

Discussion

This is the first study conducted to analyze postmarketing ADR data reported for orphan drugs licensed for treatment of HAE in Europe and submitted to the EV ADR database. Only few ADR reports, all for the medications Cinryze® and Firazyr®, were found in EV, and a large number of these were serious. More than one half of AEs were reported for women, and physicians reported all the AEs. A large number of AEs reported for Cinryze® and Firazyr® were of the type "general disorders and administration site conditions". The majority of AEs reported for both Cinryze® and Firazyr® were not mentioned in the official product information.[17]

Reported AEs by type and seriousness

The majority of AEs reported for Cinryze® and Firazyr® were of the type "general disorders and administration site conditions", for example, injection site reactions, and this ADR pattern was expected due to their route of administration parenteral. Additionally, for Cinryze®, a large number of AEs of the type "skin and subcutaneous disorders"

Table 5 Number of reported adverse events by type (preferred term), seriousness (in parentheses), and medicine reported in Europe from 2007 to 2013

Adverse drug reaction (alphabetical order)	Cinryze® Total (n) (serious)	AE listed in PI (yes/no)	Firazyr® Total (n) (serious)	AE listed in PI (yes/no)
Abdominal pain	2 (2)	Y	1 (1)	N
Abortion	4 (4)	N	–	–
Acidosis	1 (1)	N	–	–
Acute respiratory failure	1 (1)	N	–	–
Adverse event	1 (1)	N	2 (2)	–
Anaphylactic shock	2 (2)	N	–	N
Angioedema	2 (0)	N	1 (1)	N
Anomaly of external ear congenital	1 (1)	N	–	N
Arteriospasm coronary	–	–	2 (2)	N
Arthralgia	2 (0)	Y	1 (1)	N
Asthenia	2 (0)	N	–	N
Basilar artery thrombosis	1 (1)	N	–	N
Blood pressure fluctuations	1 (1)	N	2 (2)	N
Bronchopneumonia	1 (1)	N	–	N
C1-esterase inhibitor decreased	1 (1)	N	–	N
Chest pain	–	Y	3 (3)	N
Chills	–	N	1 (0)	N
Circulatory collapse	1 (1)	N	–	–
Coagulation factor IX level increased	1 (1)	N	–	–
Coagulation factor VIII level increased	1 (1)	N	–	–
Condition aggravated	3 (1)	N	–	–
Cytomegalovirus infection	1 (1)	N	–	–
Cytomegalovirus test	1 (1)	N	–	–
Deep vein thrombosis	1 (1)	Y	–	–
Death	2 (2)	N	–	–
Dizziness	2 (2)	Y	1 (1)	Y
Drug abuse	2 (2)	N	–	–
Drug ineffective	10 (10)	N	2 (2)	N
Drug-specific antibody present	2 (2)	N	–	–
Eosinophilia	1 (1)	N	–	–
Erythema	3 (1)	Y	–	–
Exposure during breast feeding	2 (2)	N	–	–
Exposure during pregnancy	5 (5)	N	–	–
External auditory canal atresia	2 (2)	N	–	–
Fatigue	4 (0)	N	1 (1)	N
Feeling hot	1 (0)			
Fibrin D dimer increased	1 (1)	N	–	–
Headache	3 (1)	Y	–	–
Heart rate increased	1 (1)	N	–	–

(*Continued*)

Table 5 (*Continued*)

Adverse drug reaction (alphabetical order)	Cinryze® Total (n) (serious)	AE listed in PI (yes/no)	Firazyr® Total (n) (serious)	AE listed in PI (yes/no)
Hepatic enzyme increased	–	–	1 (1)	N
Hepatitis	3 (3)	N	4 (4)	N
Hernia	–	N	1 (1)	N
Hereditary angioedema	25 (3)	N	1 (1)	N
Hyperhidrosis	1 (0)	N	–	–
Hypersensitivity	1 (1)	N	–	–
Hypertension	–	–	1 (1)	N
Incorrect drug administration	3 (1)	–	–	–
Injection site reaction	5 (1)	Y	14 (2)	Y
Laryngeal edema	2 (1)	N	–	–
Leukocytosis	1 (1)	N	–	–
Loss of consciousness	–	–	2 (2)	N
Malaise	3 (1)	N	1 (1)	N
Muscle spasms/ tightness	2 (0)	N	1 (1)	N
Myocardial infarction	–	–	3 (3)	N
Nausea	2 (2)	Y	–	Y
Obstructive airways disorder	1 (1)	N	–	–
Edema peripheral	–	–	1 (1)	N
Off-label use	1 (1)	–	–	–
Pain	–	–	1 (1)	N
Pain in extremity	–	–	1 (1)	N
Paresthesia	–	–	1 (1)	N
Phlebitis	1 (1)	Y	–	–
Poor venous access	4 (0)	–	–	–
Pruritus	2 (0)	Y	–	–
Pulmonary embolism	1 (1)	N	–	–
Pyrexia	2 (2)	Y	–	Y
Swelling	1 (1)	N	1 (1)	N
Swollen tongue	1 (1)			
Systemic lupus erythematous	–	–	1 (1)	Y
Tachycardia	1 (1)	N	–	–
Urticaria	1 (1)	N	–	–
Vomiting	1 (1)	Y	–	–
Weight increased	1 (0)	N	–	–
Total	138 (80)	–	49 (36)	–

Abbreviations: AE, adverse event; PI: product information.

were also reported, and these reactions were all listed in the product information. The findings are in line with the ADR patterns reported in another study monitoring the safety of use of C1-inbibitors in different clinical settings in the US and in Europe.[25] Thromboembolic events due to administration of C1-inhibitors have been of concern and discussed in the literature.[26,27] In this study, only few cases were reported for Cinryze® ("basilar artery thrombosis" "increased level of coagulation factors IX and VIII", "deep vein thrombosis", "pulmonary embolism", and "tachycardia"). Analyses of postmarketing data submitted to the US Food and Drug Administration ADR database showed ten cases of thromboembolic events from use of Cinryze®.[28,29] More than one half of the AEs found in EV were serious; however, this reporting pattern was not surprising, since physicians – from a clinical perspective – may find it more relevant to report serious reactions than nonserious reactions.[30] Due to the increasing number of patients diagnosed with HAE, more patients will get access to treatment with orphan drugs, despite the problems with patients' access due to high prices and national restrictions in patients' access,[31] and therefore, a larger number of ADR reports occurring from use of these medications is expected to be reported in the future.[31–33]

Reported AEs by therapeutic groups and medications

The largest number of AEs was reported for the medication Cinryze®, which was expected since Cinryze® is frequently recommended and used in HAE patients.[4–6] As expected, no ADR reports were found for Ruconest®, because this medicine is not prescribed very often for treatment of HAE. For Cinryze®, a large number of AEs of the type "HAE" were reported, indicating that the medicine may increase the severity of the disease or that the patients/physicians have difficulties in distinguishing between disease symptoms and possible AEs from medication use. The use of orphan drugs in treatment of HAE is considered being low due to the small disease prevalence in EU, the price of the treatments,[28] and limited access to these treatments in some member states.[31] Therefore, we also expected a low number of ADR reports present in EV, and our assumption was confirmed. However, the many serious cases may also indicate that health care professionals and patients report only unknown and serious events, which is also mandatory for the health care professionals operating in the individual EU member states. However, it is also well-known that a high rate of underreporting is biasing the spontaneous reporting systems and probably a much higher number of AEs have occurred in real life.[34] Therefore, we encourage the health care professionals and consumers/patients to continue reporting of suspected AEs in order to increase knowledge about ADRs from use of orphan drugs.

Study limitations

The strength of this study is that it comprised all AEs reported for HAE medications in Europe, which were forwarded to the EV database during a 7-year period, hence a limitation

to this study is that we do not know to which extent the causality of the reported AEs can be confirmed, and this has implications for the interpretation of the findings. The respective pharmaceutical companies make causality assessment of ADR cases as a part of their legal obligations to monitor the safety of their marketed drugs. In this study, we did not evaluate the validity of the ADR reports since we only had access to the data entered into the EV database and not the ADR original reports; however, we expect the data to be valid, as they were predominantly entered into EV by the regulatory agencies. Spontaneous reporting systems suffer from various barriers, such as incomplete recognition of AEs, administrative barriers to reporting, and low data quality, all of which may result in underreporting of important serious and rarely occurring AEs.

Hence, AEs that are classified as being nonserious or already known may be underreported; however, this study provides information on the reported AEs, which contributes to broadening the knowledge on medicine safety. Hence, it is not possible to generalize from data reported to the EV database to the other EU member states, as the prescribing practice and disease diagnostic procedures may be very different. Although ADR reporting is mandatory in the EU, it is unknown whether the analyzed ADR data represent all information available in each country, and therefore, the actual ADR prevalence could not be estimated. Spontaneous reports are an important source of information about new and previously unrecognized AEs, and the value of spontaneous reporting schemes lies in their ability to act as hypothesis-generating procedures.[35] Therefore, EMA and the national regulatory agencies should continue to systematically survey and analyze AEs reported by health care professionals/consumers and patients in order to signal previously unknown and rarely occurring AEs presumably related to use of orphan drugs.

Conclusion

Only a few AEs from use of HAE medications were identified in the EV database, but a large majority of these were serious, including fatal cases. There is a need of more research into the prescribing of these medicines to patients with HAE, as well as tighter reporting of AEs for HAE medicines prescribed for this population, particularly from use in children and adolescents.

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Author contributions

LA and AB designed the study, analyzed data, and wrote the first version of the manuscript. LA carried out the sampling. Both authors saw and approved the final version of the manuscript. No sources of funding were used to assist in the preparation of this study.

Disclosure

The authors report no conflicts of interest in relation to the content of this manuscript.

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