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Brief Communication

Side effects of antineoplastic and immunomodulating medications reported by European consumers

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ABSTRACT

Objective: To characterize adverse drug reactions (ADRs) reported by European (EU) consumer for antineoplastic and immunomodulating medications.

Methods: ADRs reported by consumers of antineoplastic and immunomodulating medications (anatomical therapeutic chemical [ATC]) group L from 2007 to 2011 and located in the EU ADR database, EudraVigilance, were analyzed. Data were categorized with respect to age and sex, category, and seriousness of reported ADRs and medications. The unit of analysis was one ADR.

Findings: We located 9649 ADRs reported for antineoplastic and immunomodulating medications, which approximately 15% of were serious, including 26 deaths. Less than 5% of ADRs were reported in children. Totally 73% of ADRs were reported for women and 27% for men. The majority of ADRs were of the type "general disorders and administration site conditions" (54% of total ADRs), followed by "skin and subcutaneous disorders" (7% of total ADRs), and "infections and infestations" (6% of total ADRs). Reports encompassed medicines from the therapeutic groups: Imunosupressants (ATC group L04) (90% of all ADRs), immunostimulants (ATC group L03) (6% of all ADRS), and antineoplastic agents (ATC group L01) (4% of all ADRs). Many ADRs were reported for etanercept (Enbrel®), Interferon beta (Betaferon®/Extavia®), and imatinib (Glivec®) with only few being serious.

Conclusion: In general, consumers reported a high number of ADRs from the use of antineoplastic and immunostimulant medications and many of these were classified as non-serious. This indicates that consumers are interesting in reporting ADRs, but since the investigated substances potentially have the risk of causing many ADRs, we expected a higher number of serious ADRs.

Keywords: Adverse drug reactions; antineoplastic agents; consumers; eudravigilance; immunomodulating agents; pharmacovigilance

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INTRODUCTION

Antineoplastic and immunomodulating medications are licensed for treatment of various types of cancer and immune diseases, and these medications have the potential to lead to serious adverse drug reactions (ADRs).[1] Many of the medicines, i.e., cancer medications, are tested under favorable conditions, meaning that the medications are tested in a few clinical trials of short duration, including fewer patients than clinical testing of conventional drugs.[2] Due to the favorable licensing conditions, knowledge about ADRs is limited at the time of marketing, and information of long-time safety issues is unknown.[2] Spontaneous reports are an important source of information about new and previously unrecognized ADRs occurring after the time of marketing.[3] Consumers can provide first-hand information about patients' experiences with medicines and possible ADRs.[4] Studies of consumer ADR reports submitted to national pharmacovigilance databases in Denmark, the Netherlands, Sweden, and the United Kingdom, showed that patients are

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more likely to report ADRs from the nervous and psychiatric systems than health-care professionals. Studies also showed, that consumers submit information about ADRs not reported by physicians and that consumer reporting may be considered a supplement to traditional ADR reporting by health-care professionals.[5-9] The published consumer studies, all conducted on small national datasets showed that consumers are willing to report ADRs, but we do not know to which, extent similar findings are applicable for other countries. Until June 2012, consumer reporting was officially accepted in 5 European (EU) countries: Denmark, the Netherlands, Norway, Sweden, and the United Kingdom.[10] The new EU pharmacovigilance legislation, which came into force in June 2012 has made it possible for consumers in all EU countries to report ADRs directly to the health authorities.[11] EudraVigilance (EV) is the central database containing reports of suspected ADRs for medicinal products authorized in the European Economic Area (EEA).[12] EV was set up in December 2001 to facilitate the electronic reporting of ADRs in the EEA countries between the pharmaceutical companies, regulatory agencies, and the European Medicines Agency (EMA).[12] Since 2012, researchers have been allowed to access information about ADR data in the database and this has laid the foundation for cross-national analyses based on a standardized reporting format.[13]

The objective of this study was to investigate ADR reports on antineoplastic and immunomodulating medications submitted by consumers to the EV ADR database in Europe during the 1st 5 years of electronic reporting.

METHODS

The study comprised all ADR reports located in the EV database and reported by consumers for antineoplastic and immunomodulating medications (ATC group L) occurring from 2007 to 2011. The content of the reports was analyzed with respect to seriousness, categories of ADRs classified by system organ class (SOC) and medications. The unit of analysis was one ADR. Patient age was grouped into: Children (0-17-year-olds) and adults (18 + year-olds). ADR information was provided for this study in anonymous form with encrypted person identification and extracted from the EV database in large Microsoft Excel files using the following criteria: Patient's sex and age, medicines (active substance), and type and seriousness of reported ADRs. In compliance with EU regulation (EC) no. 1049/2001, EMA ensures that the protection of privacy and integrity of individuals is guaranteed, and therefore, individual country-specific ADR information could not be disclosed.[13] The reported ADRs were coded with respect to type and seriousness by academic staff in the national regulatory agencies using the Council for International Organizations of Medical Sciences criteria.[14] Serious ADRs are divided into the following categories: Fatal, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, in a congenital anomaly/birth defect, and other medically important conditions. Other ADRs were classified as non-serious.[14] The different types of reported ADRs were classified according to the Medical Dictionary for Regulatory Activities SOC.[15] Medicines were classified according to the anatomical therapeutic chemical (ATC) classification system[16] in which medicinal products are classified at five levels. The medicinal products reported are referenced based on their active substance, and in this article we present ADR data at ATC level 1 and 5.[16]

RESULTS

During the study period, a total of 7434 consumer ADR reports containing information about 35349 ADRs were located in EV. Of these, 9644 ADRs were submitted for antineoplastic and immunomodulating medications (ATC group L). In total, 14% of these ADRs were classified as serious and of these, 26 fatal cases were reported. The characteristics of the fatal cases are displayed in Table 1. The largest number of fatal cases (n = 16) was reported for etanercept (ATC group L04AB01) followed by six fatal cases reported for adalimumab (ATC group L04AB04). Totally, 73% of ADRs were reported for women and 27% for men. Less than 1% of ADRs were reported in children. The majority, 54% of ADRs were of the type "general disorders and administration site conditions," followed by "skin and subcutaneous disorders" (7% of total ADRs), and "infections and infestations" (6% of total ADRs) [Table 2]. Table 3 displays the number of ADRs reported by consumers distributed on therapeutic groups and seriousness. ADR reports encompassed medicines from the therapeutic groups: Immunosupressant (ATC group L04) (90% of all ADRs), immunostimulants (ATC group L03) (6% of all ADRs), and antineoplastic agents (ATC group L01) (4% of all ADRs). Except for immunostimulants, the majority of ADRs were serious. In particular, a large number of ADRs were reported for etanercept (Enbrel®) (n = 8462), interferon beta (Betaferon®/Extavia®) (n = 550), and imatinib (Glivec®) (n = 129). However, for interferon beta, the majority of reported ADRs were non-serious. Table 4 displays characteristics of serious ADRs reported for etanercept (Enbrel®). In total, 889 serious ADRs

Table 1: Fatal cases reported by consumers for antineoplastic and immunomodulating agents in Europe, 2007 to 2011

Case no.	Age (year)	Sex (M/F)	Medicine (s)	Adverse drug reaction (s)
1	18+	F	Adalimumab (Humira®)	Abscess
				Coma
				Epidermolysis
				Hepatic failure
				Pancreatic fistula
				Weight decreased
2	NA	F	Adalimumab (Humira®)	Death
3	18+	M	Adalimumab (Humira®)	Myocardial infarction
4	18+	M	Adalimumab (Humira®)	Death
5	18+	M	Adalimumab (Humira®)	Death
6	NA	F	Adalimumab (Humira®)	Death
7	0-17	M	Etanercept (Enbrel®)	Hemorrhage neonatal
				Neonatal aspiration
8	NA	M	Etanercept (Enbrel®)	Death
9	NA	F	Etanercept (Enbrel®)	Death
10	NA	M	Etanercept (Enbrel®)	Death
11	NA	M	Etanercept (Enbrel®)	Death
12	NA	M	Etanercept (Enbrel®)	Pneumonia
13	NA	F	Etanercept (Enbrel®)	Sepsis
14	NA	M	Etanercept (Enbrel®)	Pneumonia
15	NA	M	Etanercept (Enbrel®)	Swelling
				Hemorrhage neonatal
				Neonatal aspiration
16	NA	M	Etanercept (Enbrel®)	Death
17	NA	M	Etanercept (Enbrel®)	Death
18	18+	F	Etanercept (Enbrel®)	Death
19	18+	M	Etanercept (Enbrel®)	Death
20	NA	M	Etanercept (Enbrel®)	Exposure via semen
				Foetal exposure during pregnancy
				Multi-organ failure
21	18+	M	Etanercept (Enbrel®)	Pneumonia
22	0-17	M	Etanercept (Enbrel®)	Cardiac disorder
23	NA	F	Imatinib (Glivec®)	Abdominal neoplasm
				Neoplasm malignant
24	NA	NA	Imatinib (Glivec®)	Platelet count decreased
				Tumour hemorrhage
25	NA	M	Interferon-beta-1b (Betaferon®/Extavia®)	Dyspnoea
26	NA	M	Thalidomide (Thalidomide Celgene®)	Death

NA = Information not available

were reported; the most frequently reported ADR being abasia (n = 46), abdominal abscess (n = 43), abdominal adhesions/rigidity (n = 34), abdominal pain/discomfort (n = 17), and abnormal sensation in eye (n = 15). For imatinib, the largest numbers of reported ADRs were infection (n = 7), gastric disorder (n = 5), muscle spasm (n = 4), nausea (n = 4), and weight changes (n = 4).

DISCUSSION

This is the first study to systematically analyze ADRs for cancer medications reported by consumers to the EV database. The majority of ADRs were reported for immunosuppressants, particularly etanercept (Enbrel®), interferon-beta (Betaferon®/Extavia®) and imatinib (Glivec®). More than one half of reported ADRs were of the type "general disorders and administration site conditions." Few of the ADRs was rated as serious by the regulatory agencies, however fatal cases were found.

The largest number of ADRs was reported for etanercept (Enbrel®), and large shares of these were "injection site reactions." This is not surprising since the medication is administered to the patients as injections. This study showed that this type of ADR from a patient perspective is viewed as serious and

Table 2: Adverse drug reactions reported by European consumers for antineoplastic and immunomodulating agents by system organ class, 2007 to 2011

System organ class	ADRs (*N*)	% of total ADRs
General disorders and administration site conditions	5165	54
Skin and subcutaneous tissue disorders	703	7
Infections and infestations	540	6
Nervous system disorders	523	5
Gastrointestinal disorders	469	5
Musculoskeletal and connective tissue disorders	469	5
Injury, poisoning, and procedural complications	289	3
Respiratory, thoracic, and mediastinal disorders	278	3
Investigations	243	3
Psychiatric disorders	171	2
Eye disorders	165	2
Vascular disorders	94	1
Cardiac disorders	85	1
Surgical and medical procedures	63	1
Metabolism and nutrition disorders	61	1
Reproductive system and breast disorders	55	1
Blood and lymphatic system disorders	52	1
Neoplasm benign, malignant, and unspecified	50	1
Immune system disorders	49	1
Renal and urinary disorders	42	<1
Ear and labyrinth disorder	37	<1
Hepatobiliary disorders	24	<1
Social circumstances	8	<1
Endocrine disorders	7	<1
Pregnancy, puerperium, and perinatal conditions	5	<1
Congenital, familial, and genetic disorders	2	<1
Total ADRs	9649	

ADRs = Adverse drug reactions

Table 3: Distribution of adverse drug reactions reported by consumers for antineoplastic and immunomodulating agents by medication and seriousness (number of serious cases in parentheses), 2007 to 2011

Therapeutic group (ATC)	Medication	*N* (serious ADRs)
L01 (antineoplastic agents)	Bevacizumab (Avastin®)	50 (50)
	Dasatinib (Sprycel®)	3 (3)
	Everolimus (Afinitor®)	40 (40)
	Imatinib (Glivec®)	129 (129)
	Nilotinib (Tagisna®)	12 (12)
	Panituzumab (Vectibix®)	3 (3)
	Rituximab (MabThera®)	5 (5)
	Sunitinib (Sutent®)	126 (19)
	Sorafenib (Nexavar®)	2 (1)
	Temsirolimus (Torisel®)	3 (1)
	Trastuzumab (Herceptin®)	17 (17)
	Vinflumin (Javlor®)	5 (5)
Total L01		398 (285)
L02 (endocrine therapy)	Fulvestrant (Faslodex®)	15 (0)
Total L02		15 (0)
L03 (immunostimulants)	Interferon beta (Betaferon®/Extavia®)	550 (19)
	Pefilgrastrim (Neulasta®)	7 (7)
Total L03		557 (26)
L04 (immunosuppressants)	Adalimumab (Humira®)	120 (120)
	Anakinra (Kineret®)	2 (2)
	Canakinumab (Ilaris®)	3 (3)
	Eculizumab (Soliris®)	6 (3)
	Etanercept (Enbrel®)	8462 (889)
	Fingolimod (Gilenya®)	20 (13)
	Infliximab (Remicade®)	10 (7)
	Lenalidomide (Revlimid®)	3 (3)
	Sirolimus (Rapamune®)	52 (29)
	Thalidomide (Thalidomide Celgene®)	1 (1)
Total ATC L04		8674 (1069)
Total ATC group L		9649 (1380)

ATC = Anatomical therapeutic chemical, ADRs = Adverse drug reactions

harmful because this ADR is easily assessed, and obvious compared to many other types of ADRs that the patients cannot easily detect. Approximately, 15% of ADRs were serious, and this share was lower than in other studies on consumer reports;[5-9] we have no explanation for this reporting pattern.

The strength of our study is that the data comprised ADRs reported by consumers in Europe, which were forwarded to the EV database during a 5-year period. According to the EU regulation, we were not allowed to receive information about, the country of reporting. Therefore, we were unable to conduct further comparisons of consumer ADR reporting patterns between the EU countries, as well as compare the number of reports submitted to the EV database with ADR information presently stored in national pharmacovigilance databases. A major limitation to this study is that we do not know to which extent the causality of the reported ADRs can be confirmed, and this has implications for the interpretation of the findings.[4] In this study, we did not evaluate the validity of the consumer reports since we had access to the data entered into the EV database and not to the original reports. Spontaneous reporting systems suffer from various barriers such as incomplete recognition of ADRs, administrative barriers to reporting and low data quality, as well as lack of information about diagnosis, all of which may result in under-reporting

Table 4: Characteristics of serious adverse drug reactions for etanercept reported by European consumers, 2007 to 2011

Adverse drug reaction	*N*
Abasia	46
Abdominal abscess	43
Abdominal adhesions/rigidity	34
Abdominal pain/discomfort	17
Abnormal sensation in eye	15
Abortion spontaneous	14
Abscess jaw	12
Abscess limb	12
Ageusia	10
Aggression	10
Alcohol abuse	9
Alopecia	9
Fractures	9
Amyloidosis	8
Angina pectoris	8
Ankyloing spondylitis	8
Anosmia	8
Anxiety	8
Aortic aneurysm	8
Aphasia	7
Aphthous stomatitis	7
Arrhythmia	7
Arthralgia	6
Arthritis	6
Arthropathy	6
Arthropod bite	6
Asthenia	6
Atrial fibrillation	6
Autoantibody positive	6
Back pain	6
Bacterial test positive	6
Biliary tract disorder	6
Blepharitis	6
Blepharospasm	6
Blindness	6
Blood alcohol increased	6
Blood cholesterol increased	6
Blood glucose decreased	6
Others ($n \leq 5$)	484
Total ADRs	889

ADRs = Adverse drug reactions

of important serious and rare events.[4] ADRs that are classified as non-serious or already known may be over-reported; however, this study provides information about possible ADRs from the use of antineoplastic and immunomodulating medicines, and this information contributes to broadening the knowledge on medicine safety.

In general, consumers reported a high number of ADRs from antineoplastic and immunomodulating medications, and many of these were classified as non-serious. This indicates that consumers are interesting when it comes to reporting of ADRs, but since the investigated medications potentially have the risk of causing many ADRs, we expected a higher number of serious ADRs.

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AUTHORS' CONTRIBUTION

L. Aagaard and E.H. Hansen designed the study, analysed data and wrote the first version of the manuscript. L. Aagaard carried out the sampling. Both authors read and approved the final version of the manuscript. No sources of funding were used to assist in the preparation of this study.

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