Brief Communication

Side effects of antineoplastic and immunomodulating medications reported by European consumers

Lise Aagaard¹, Ebba Holme Hansen²

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: Immunosuppressants (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 (Enbrel⁰), interferon beta (Betaferon⁰/Extavia⁰), and imatinib (Glivec⁰) with only few being serious.

Conclusion: In general, consumers reported a high number of ADRs from the use of antineoplastic and immunomodulating agents, and many of these were classified as non-serious. This indicates that consumers are interested 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

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...
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. 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. 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. EudraVigilance (EV) is the central database containing reports of suspected ADRs for medicinal products authorized in the European Economic Area (EEA). 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). 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. 

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.

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: Immunosuppressant (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

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. 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. 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. The different types of reported ADRs were classified according to the Medical Dictionary for Regulatory Activities SOC. Medicines were classified according to the anatomical therapeutic chemical (ATC) classification system 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.
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

| 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 |
| 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
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 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     |                 |

ADR = 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 (Tagrisso®) | 12 (12) |
|                          | Panitumumab (Vectibix®) | 3 (3) |
|                          | Rituximab (MabThera®) | 5 (5) |
|                          | Sunitinib (Sutent®) | 126 (19) |
|                          | Sorafenib (Nexavar®) | 2 (1) |
|                          | Temsirolimus (Torisel®) | 3 (1) |
|                          | Trastuzumab (Herceptin®) | 17 (17) |
|                          | Vinflunin (Javelin®) | 5 (5) |
| L02 (endocrine therapy)  | Fulvestrant (Faslodex®) | 15 (0) |
| L03 (immunostimulants)   | Interferon beta | 550 (19) |
|                          | Pegfilgrastim (Neulasta®) | 7 (7) |
| L04 (immunosuppressants) | Adalimumab (Humira®) | 120 (120) |
|                          | Anakinra (Kinerei®) | 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) |

ATC = Anatomical therapeutic chemical, ADRs = Adverse drug reactions
Aagaard and Hansen: Side effects of antineoplastic and immunomodulating agents

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 |
| Ankylosing 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 ≤ 5)              | 484|
| Total ADRs                  | 889|

ADRs = Adverse drug reactions

of important serious and rare events. 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.

ACKNOWLEDGMENTS

The authors wish to thank the European Medicines Agency for providing access to data and MSc Jesper Frederiksen for assistance with data handling.

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.

REFERENCES

1. Aagaard L, Strandell J, Melskens L, Petersen PS, Holme Hansen E. Global patterns of adverse drug reactions over a decade: Analyses of spontaneous reports to VigiBase™. Drug Saf 2012;35:1171-82.
2. Hansen EH. Technology assessment in a user perspective—Experiences with drug technology. Int J Technol Assess Health Care 1992;8:150-65.
3. Aagaard L, Hansen EH. Information about ADRs explored by pharmacovigilance approaches: A qualitative review of studies on antibiotics, SSRIs and NSAIDs. BMC Clin Pharmacol 2009:4-9.
4. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: A review of published literature and international experience. Br J Clin Pharmacol 2007;63:148-56.
5. Medawar C, Herxheimer A. A comparison of adverse drug reaction reports from professionals and users, relating to risk of dependency and suicidal behaviour with paroxetine. Int J Risk Saf Med 2003;16:5-19.
6. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: A retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf 2009;32:1067-74.
7. de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K. Adverse drug reaction reporting by patients in the Netherlands: Three years of experience. Drug Saf 2008;31:515-24.
8. Aagaard L, Hansen EH. Consumers’ reports of suspected adverse drug reactions volunteered to a consumer magazine. Br J Clin Pharmacol 2010;69:317-8.
9. Vilhelmsen A, Svensson T, Meeuwisse A, Carlsten A. What can we learn from consumer reports on psychiatric adverse drug reactions with antidepressant medication? Experiences from reports to a consumer association. BMC Clin Pharmacol 2011;11:16.
10. Van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: An 11-country survey. Drug Saf 2012;35:45-60.

11. European Commission. The EU Pharmacovigilance System. Available from: http://www.ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm. [Last accessed 2012 Dec 14].

12. European Medicines Agency. Note for guidance–Eudravigilance human – Processing of safety messages and individual case safety reports (ICSRs). EMA/H/20665/04/Final Rev. 2. Available from: http://www.ema.europa.eu/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015697.pdf. [Last accessed 2012 Dec 14].

13. Office Journal of the European Commission. Regulation (EC) no 1049/2001 of the European parliament and of the council of 30 May 2001 regarding public access to European Parliament, council and commission. L 145/43. Available from: http://www.europarl.europa.eu/register/.r1049_en.pdf. [Last accessed 2012 Dec 14].

14. Pharmacovigilance: Medicinal products for human use and veterinary products. Vol. 9. Available from: http://www.ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm. [Last accessed 2012 Dec 14].

15. MedDRA. Available from: http://www.meddrasso.com. [Last accessed 2012 Dec 14].

16. WHO Collaboration Centre for Drug Statistics Methodology. 2007. Available from: http://www.whocc.no/atc_ddd_index/. [Last accessed 2012 Dec 14].

How to cite this article: Aagaard L, Hansen EH. Side effects of antineoplastic and immunomodulating medications reported by European consumers. J Res Pharm Pract 2013;2:44-9.

Source of Support: Nil, Conflict of Interest: None declared.