boletim de FARMACO VIGILÂNCIA

VOLUME 22
NUMBER 5
MAY 2018

Dasatinib
risk of CMV reactivation

Quick Read
Patients with leukaemia under treatment with the chemotherapeutic agent dasatinib (Sprycel®) are at increased risk of complications from reactivation of latent cytomegalovirus infection.

Dasatinib is a tyrosine kinase inhibitor indicated in the treatment of adult patients with:

- *newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase;*
- *chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate;*
- *Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.*

Cytomegalovirus (CMV) is a member of the herpesviridae family which frequently affects immunosuppressed patients, not so much with an active infection but rather through reactivation of a latent infection. It commonly involves the retina and central nervous system in a context of immunosuppression and its severity parallels viral load. It is an important cause of morbidity and death in immunocompromised patients, including post-transplant, those on haemodialysis, with cancer, on immunosuppressive therapy, or infected with HIV.

In October 2017, during routine pharmacovigilance activities, the European Medicines Agency (EMA) detected several articles in the literature[1-9] supporting biological plausibility for dasatinib-associated cytomegalovirus reactivation.

Following a PRAC assessment of the cases stored in the European ADR report database, EudraVigilance, as well as of the available scientific literature and supplementary data provided by the MA Holder, product information texts for **Sprycel®** (dasatinib) are to be altered, namely in what concerns the infections and infestations item of SmPC **section 4.8 (Undesirable effects)**:

> Common: pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes).

Márcia Silva

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Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

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A web service for linking electronic clinical records to pharmacovigilance databases

Quick Read

Using information technology to extract adverse drug reactions and feed them into pharmacovigilance databases can contribute significantly towards simplifying and promoting ADR reporting.

Spontaneous reporting of ADRs is an efficient method to assess medicinal drug safety. It is widely known however, that underreporting hinders the effectivity of this process.[1,2]

It is also well known that one of the main reasons given by healthcare professionals for not reporting ADRs is their increasing work load.[3,4] To try and reduce the amount of effort put into ADR reporting, some information technology systems have been used and tested, such as automatic ADR detection software, clinical database analysis tools, or websites which actively inform healthcare professionals on ADRs.[5] Information systems can also be used to facilitate and promote ADR reporting by means of online reporting forms or **electronic clinical record (ECR) ADR extraction tools**[6,7].

In Portugal there is a multicentric gastroenterology research project (**GEDII (inflammatory bowel disease study group)**,[8] whose members (gastroenterology specialist physicians) use a common electronic clinical record for patient data collection. Their patients are usually being treated with innovative and "aggressive" medicines (e.g., immunomodulator agents) and this group's ECR includes a section for recording ongoing medication and any ADR that may supervene. Since the group's members already routinely fill in this section, the opportunity was seen to create a way to send the data onwards to the National Pharmacovigilance System. A computer-based communication channel (a web service) was thus set up by the **Porto Regional Pharmacovigilance Unit (UFP)** in cooperation with **the Community Medicine, Health Information and Decision-Making Department (MEDCIDS)**.

Before sending out the information this web service pseudo-anonymizes the patients' data (by changing their names into initials), in accordance with data protection regulations that the National Pharmacovigilance System has to abide by. Figure 1 shows the information flow from the ECR to the National Pharmacovigilance System:

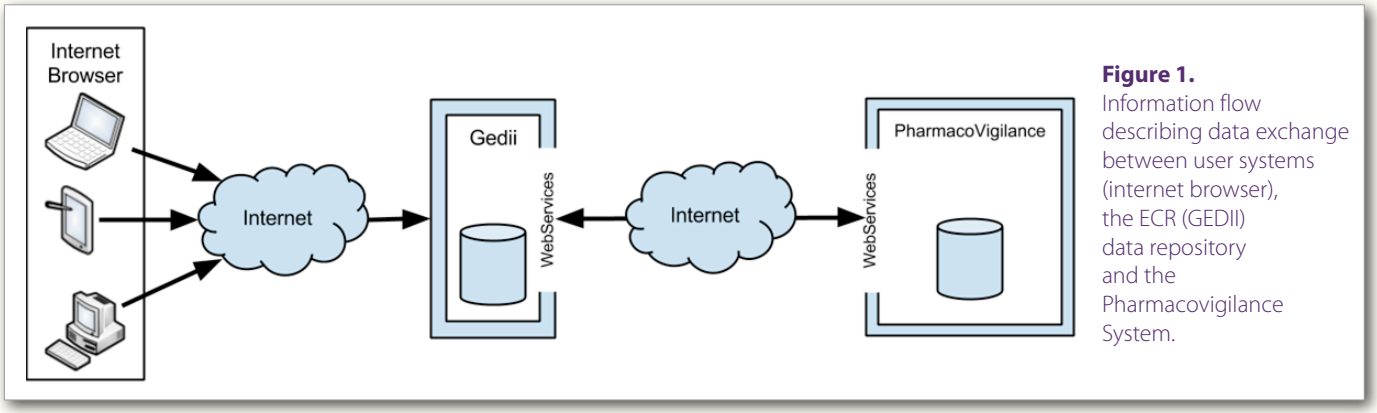

Figure 1. Information flow describing data exchange between user systems (internet browser), the ECR (GEDII) data repository and the Pharmacovigilance System.

In order to use this web service and send the data onwards the doctor needs to click on a permission button. Whenever that permission is not given by the doctor, the data remain stored in the GEDII clinical record only. The web service was implemented in April 2013 in 15 hospitals with a total of 39 users.[8] From April 2013 to February 2015, the GEDII doctors used it to report 167 ADRs, i.e. **10% of the total of ADRs** received in that period. Of the 167 reported ADRs, 118 (71%) were serious (according to the World Health Organization criteria)[9].

If one considers the physicians in the North of Portugal only, nine ADRs had been reported in the 23 months prior to the web service, and 121 ADRs in the ensuing 23 months – this is a 1,244% increase.

These results suggest that doctors could report more suspected ADRs if that did not mean an additional task superimposed on their routine activities. Information systems can make things easier and should be widely explored in that sense.

Taking into account the added value of this system, **Infarmed, I.P** is currently implementing an analogous strategy to make it possible for **other information systems** used by healthcare professionals to **get connected to the new ADR Portal**.

The National Pharmacovigilance System is available to facilitate the use of the web service described here by other clinical information systems used in Portugal.

Inês Ribeiro Vaz (UFP), Ricardo Cruz Correia (MEDCIDS)

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ADRs in the literature
Innovative study identifies and categorizes associations of adverse drug event risk factors

Zhou et al set out to review the scientific literature on risk factors most commonly studied in association with the occurrence of **adverse drug events (ADEs)**. The concept of ADE is rather broad and encompasses any untoward event related to the use of a medicine, including adverse drug reactions (ADRs).

This extensive review culminated in a detailed analysis of over one hundred articles in which at least one ADE risk factor had been studied. The authors then aggregated the identified risk factors. Though previous studies had already aggregated and analyzed risk factors, they had been restricted to the universe of ADRs and had excluded relevant risk factors such as the ones relating to healthcare service provision. Zhou et al grouped the ADEs into five categories and subdivided the latter into subtypes (Table 1). A total of 211 ADE risk factors were identified including genetic factors of recent and growing interest.

Patient related risk factors	Age; Gender; Weight; Ethnicity; Previous history of ADE; Socioeconomic status; Life style; Functional status; Treatment compliance.
Disease related risk factors	Comorbidity; GU disorders; CNS conditions; Vascular conditions; Mental and behavioural disorders; Disease complexity; Medical history and health condition.
Medication related risk factors	Polypharmacy; Medication for the cardiovascular system; Medication for the central nervous system; Anti-infectious medication; Antineoplastic medication.
Healthcare provision related risk factors	Service use (e.g., length of hospital stay or number of visits to family doctor); service provision (e.g., poor service coordination or admission to wrong service).
Genetic risk factors	Class I Major Histocompatibility Complex (MHC); ABC Transporters; Cytochrome P450; VKOR; Peptidase M13.

Table 1: Averse Drug Event (ADE) associated risk factor Categories and Subtypes.

When ordering risk factor subtypes by number of articles mentioning them (Figure 1), the **most studied** ones and which had been quoted in over ten articles were **polypharmacy, age, gender, comorbidity, inappropriate use or change of drugs, use of central nervous system or cardiovascular agents**.

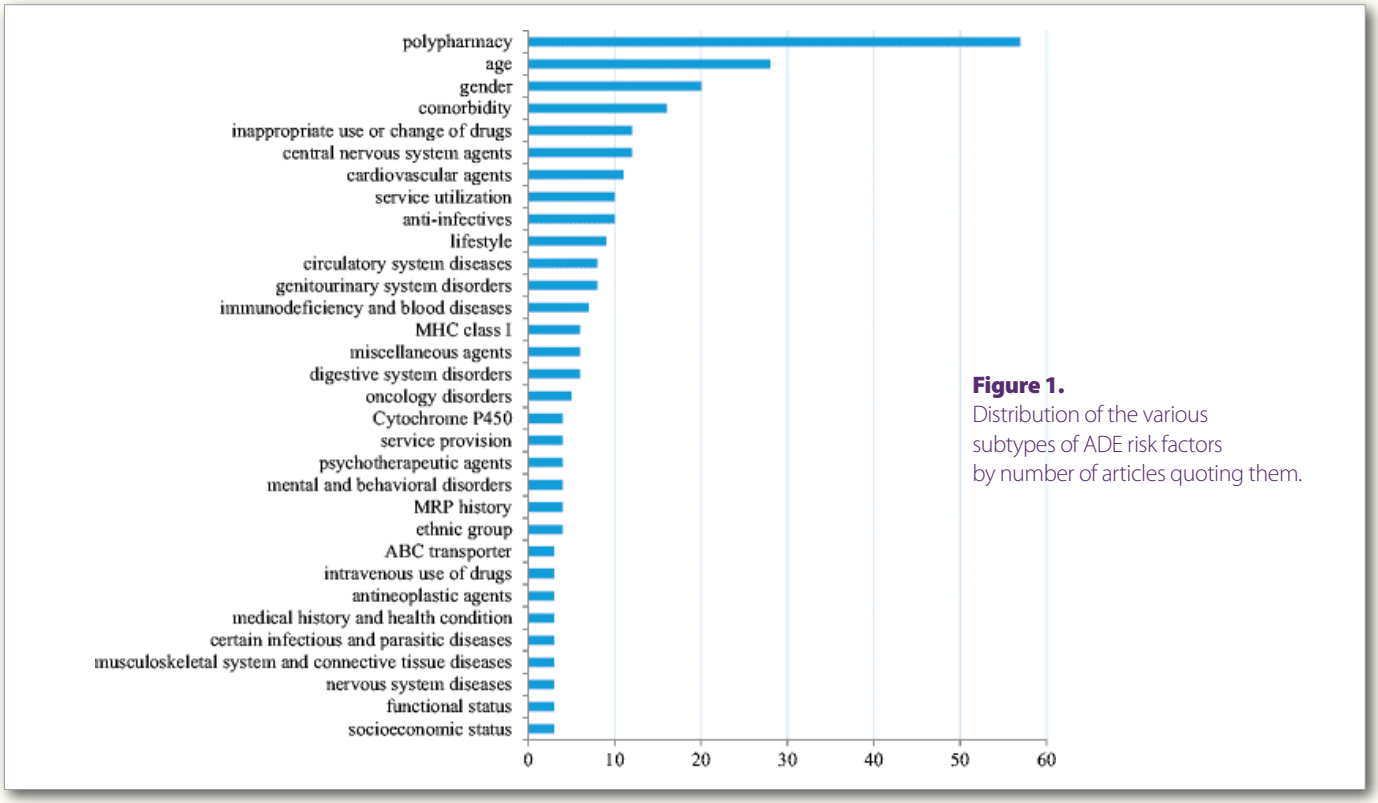

Figure 1.
Distribution of the various subtypes of ADE risk factors by number of articles quoting them.

ADRs in the literature
Innovative study identifies and categorizes associations of adverse drug event risk factors (cont'd)

By further analyzing risk factor subtype associations the authors identified a total of 40 association rules. The five rules with most association power can be seen in Table 2.

Association rules	Lift	Confidence
Polypharmacy, central nervous system agents → cardiovascular agents	8	0.5
Polypharmacy, cardiovascular agents → central nervous system agents	7.2	0.75
Age, comorbidity → gender, polypharmacy	6.98	0.8
Age, comorbidity, polypharmacy → gender	4.8	1
Age, lifestyle → gender	4.8	1

Table 2: Top 5 of ADE risk factor association rules.

By way of example, let us look at the first rule in Table 2: in half (confidence=0.5 i.e. 50%) of the articles researching both risk factor subtypes "polypharmacy" and "central nervous system agents", the "cardiovascular agents" factor was also studied. On the other hand, in a random selection of articles, whenever the "polypharmacy" and "central nervous system agents" were studied as ADE risk factors there is an 8-fold increased probability (lift=8) that the "cardiovascular agents" risk factor was also studied in the same article. Perhaps not surprisingly, age, gender, polypharmacy and comorbidity frequently emerge in association.

Finally, the medians of other ADE characteristics were also determined, such as **occurrence prevalence rate, occurrence preventability rate and seriousness rate**, which were respectively 19.5% [0,.9%-86.2%], 36.2% [2.63%-91%] and 16.0% [0.01%-47.4%].

One methodological aspect that begs questioning, is the fact that studies which were possibly very different were taken as equivalent (each was counted in as one unit). The authors do state that 94% of the reviewed studies used data from clinical trials, but it is well known that methodological quality and number of subjects can vary considerably across studies, an aspect that was not weighed in.

All in all, this is an innovative study in a field where much still needs to be done. Zhou L et al's article gives us new stepping stones to explore the subject further.

Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. Eur J Clin Pharmacol. 2018; 74(4):389-404.

Miguel Antunes

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

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