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REVIEW ARTICLE

Personalized Medicine and Adverse Drug Reactions: The Experience of An Italian Teaching Hospital

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Abstract: The personalized medicine is a model of medicine based on inherent difference given by the genetic heritage that characterizes us, diversity that can affect also our response to administered therapy. Nowadays, the term "adverse drug reaction" is identified with any harmful effect involuntary resulting from the use of a medicinal product; pharmacogenomics, in this field, has the aim to improve the drug response and to reduce the adverse reaction.

We analyzed all reports of adverse reaction collected in the Pharmacovigilance Centre database of an Italian University Hospital, at the Sant'Andrea Hospital Sapienza University of Rome, in a period of two years. Comparing the data result from our analysis with several studies found in literature, it is evident that adverse drug reactions represent an important problem in the management of a health care system. However, the development of pharmacogenetics and pharmacogenomics, allowing a personalized treatment, can improve clinical practice. This study highlights the great potential of pharmacogenomics in reducing adverse reactions and suggests the need for further pharmacogenomic clinical trials to better personalize drug treatment and to refine the current pharmacovigilance strategies.

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INTRODUCTION

The personalized medicine, emphasizing a clinical approach based on the uniqueness of each patient, has among its objectives to identify the preventive and/or therapeutic actions that best suits the needs of the single patient. It is known that a model of medicine aimed at the possibility of identifying the susceptibility of each person to possible diseases, measuring the risk, customizing the therapy according to the patient's genetic constitution and affecting the appropriateness of the drug administered, reduces the occurrence of adverse reactions [1]. Basic prerequisite is the inherent difference given by the genetic heritage that characterizes us, diversity that can affect our response to administered therapy, in particular to its effectiveness but also to the possible side effects According to the World Health Organization (WHO), an adverse drug reaction (ADR) is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." (WHO Technical Report No 498-1972). This definition does not include therapeutic failures and events due to errors in drug administration and non-compliance. Recently, with the European Directive 2010/84/EU and with the EU Regulation 1235/2010, published in the European Official Journal L. 348 on 31 December 2010, a new definition was introduced in the EU, in conformity with the terminology used by WHO but with important news. The term ADR (adverse drug reaction) is identified with any harmful effect involuntary resulting from the use of a medicinal product, in accordance with the instructions contained in the marketing authorization, to medication errors and also to uses not complying with the instructions contained in marketing authorization (including overdose, misuse, abuse of the medicine). The current definition does not depend on the type of the drug's usage and implies the need to report adverse reactions resulting from medication error, abuse, misuse, off label use, overdose and occupational exposure. Adverse reactions are a set of clinical manifestations due to unpredictable reactions of the organism. Despite the possibility

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that other factors may influence the individual's response to drugs, such as the diet, the environment, the age and lifestyle, the knowledge of the genetic characteristics of the person can facilitate the administration of therapies in a more effective and safe manner. In particular, the pharmacogenetics is interested in the individual response to drugs that a person may have, in terms of safety and efficacy properties. Its goal is to use the knowledge, methodology, and the gene to improve the administration of drugs under the double profile of their appropriateness and their non-harmfulness. This can be achieved through the selection of a drug already marketed or with the design of new targets stilled on the genetic characteristics of the patient but also on the variants of the same disease; or due to the prescription and the dosage calibrated on different metabolic properties related to the genetic constitution of the person. In fact, pharmacogenetics and pharmacogenomics, studying the relationship between the genotype, the level of expression of all genes in the genome and the phenotype, allowed discovering not only genetic variations related to some diseases but also various markers associated with an individual susceptibility to drug sensitivity and treatment [2].

The debate on the ethical and scientific substantiation of personalized medicine is particularly heated because while providing the possibility of great innovation, enhancing the appearance of the centrality of the individual patient characteristics, it requires considerable human and financial resources [3]. Keeping it in view, it is necessary to avoid the risk that may compress the protection of other healthcare sectors, without there being a real return and a fair balance between the expected benefits and the resources used [4-6]. The aim of this study is to analyze the phenomenon of the adverse drug reactions in Italy, and in particular at the Sant'Andrea Hospital in Rome and how these can affect the quality of care provided, thereby assessing the prospects for the future.

MATERIALS AND METHOD

The study was conducted in a hospital of 818 beds, with a total number of hospital admissions of around 160 000 per year, covering a population of more than 900 000 inhabitants in Rome, Italy. The study period was from 1 February 2014 to 28 February 2016. We used data collected in the Pharmacovigilance Centre database for hospital management located in the Department of Pharmacy and Clinical Pharmacology of the Sant'Andrea Hospital in Rome, an Italian University Hospital. All ADR reports in the database have been included, with data from each department of the structure, except Obstetrics. The reports were classified according to year and month in which the adverse reaction took place, drugs were used, therapeutic indication of the drug category and class of adverse event occurred. The drugs used were classified into pharmacological groups on the basis of the International Classification ATC (Anatomical Therapeutic Chemical classification system) controlled by the WHO. Adverse reactions have been labelled according to the World Health Organization - Adverse Reaction Terminology (WHO-ART) classification and divided into categories on the basis of the affected organs.

Statistical Analysis

A descriptive statistical analysis of categorical variables with the description of the frequencies (in absolute terms and in percentage) was performed. To assess the presence of associations between categorical variables, the statistical Chi-square test was executed, with analysis of the groups by year, type of adverse reaction and therapeutic indication. The level of statistical significance was set as 0.05.

RESULTS

During our study period (February 2014 - February 2016), a total of 274 reports of adverse drug reactions were collected: 121 in 2014, 122 in 2015 and 31 during the months of January and February 2016 (Fig. **1**).

Considering the context in which the examining of the adverse reactions occurred, 201 (74.4%) of the reports took place during the treatment of a chronic disease, 44 (16.3%) in patients with an acute disease, 22 (8.1%) in the course of a prophylactic treatment and 3 (1.1%) during a diagnostic imaging procedure (Fig. **2**).

The association between ADR reports and the therapeutic indication class was statistically significant (Chi-square 92.16, and $p < 0.001$). The most relevant therapeutic indications were infectious diseases (32.5% of cases), neurological diseases (17.9% of cases), psychiatric diseases (10.9% of cases), neoplastic diseases (10.6% of cases) and immunorheumatological diseases (10.2% of cases). These results

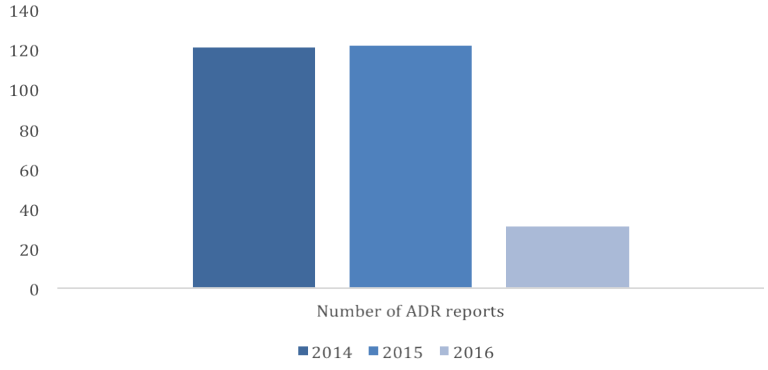

Fig. (1). Number of ADR reports collected during the study period. For the year 2016 are shown only the data for the months of January and February.

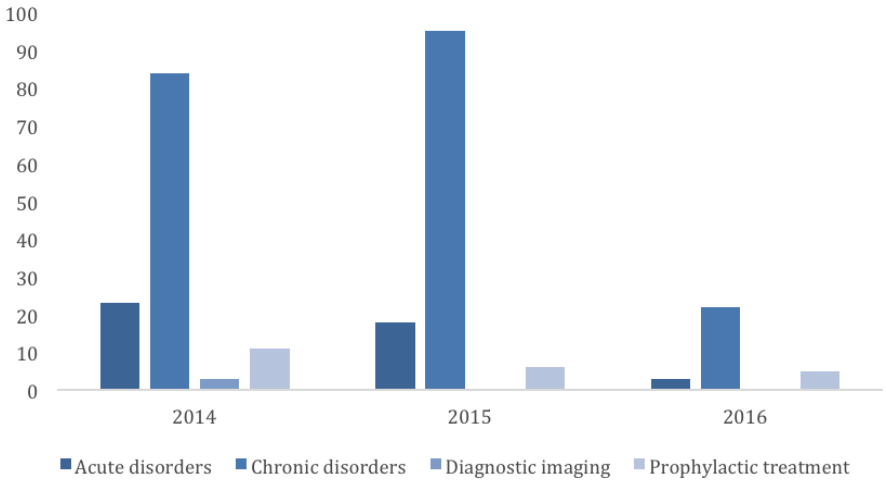

Fig. (2). Distribution of adverse drug reactions reports depending on the year and the context in which they occurred.

coincide with those obtained by the association between ADRs and drug category of the administered drug. In particular, 36.5% of ADRs concern antineoplastic and immunomodulating agents, 26.6% anti-infectives for systemic use, 17.2% drugs for the treatment of diseases of the nervous system.

The analysis of the class of antineoplastic and immunomodulating agents showed that the subcategory of biological drugs is associated with ADR reports in 20.8% of cases, consisting of a total of 57 reports, distributed according to the active principle and the disease is shown in Table **1**. In the subcategory of biologics, a significant impact of ADR reports was observed during therapy for neoplastic diseases (9 cases), but also, of particular importance, for rheumatoid arthritis (10 cases) and multiple sclerosis (9 cases).

Regarding the association between the subcategory of biological drugs and the reported adverse reaction, it was noted that out of a total of 57 reports, 19 (32,75%) consisted of drug ineffectiveness, including in particular, all the 5 cases of therapy with Ranibizumab for the treatment of macular degeneration.

An important association is observed between ADR reports and biopharmaceuticals for therapy of neoplastic diseases in general, but also particularly, for rheumatoid arthritis (10 cases) and multiple sclerosis (9 cases). Ineffectiveness represented a common adverse effect, occurring in 55 cases (20%). The absolute frequencies of cases of ineffectiveness by the pharmacological group and the therapeutic indication are shown in Table **2**.

Analyzing the specific therapeutic indication, it appears that from a total of 89 cases of ADRs associated with infectious disease, 35 (39.3%) occurred during therapy for chronic HCV hepatitis; of 49 cases of neurological disease, 34 (69.4%) took place in the course of treatment for multiple sclerosis; of 30 cases associated with psychiatric pathology, 18 (60%) were of bipolar disorder (2 unspecified, 14 type I and 2 type II); of 28 cases related with immunorheumatological disease, 11 (39.3%) occurred during therapy for rheumatoid arthritis.

In particular, the analysis of the involved drugs showed a high frequency of adverse reactions during antiviral therapy for HCV. The distribution of ADR reports for the drugs used for the treatment of HCV according to the period is shown in Table **3**.

Among antivirals, the drug most associated with adverse reactions proved to be the Boceprevir (12 reports, all in 2014), followed by Telaprevir (7 reports of which 6 in 2014 and 1 in 2015). Moreover, the association between Boceprevir and type of ADR showed 4 reports for skin rash and itching, 5 reports for alterations in laboratory parameters as hypertriglyceridemia and hyperuricemia, 2 reports for ineffectiveness.

Another relevant fact is the high frequency of ADRs associated with the drug Asenapine for which a total of 25 reports were collected of which, 16 consisted of drug ineffectiveness, 6 of dysesthesia, 2 of sedation and 1 of extrapyramidal disorder. In 62.5% of cases, Asenapine was administered for the treatment of bipolar I disorder; in the remaining cases, Asenapine was administered for manic state, dysthymic disorder, cyclothymic disorder and depression.

With regard to the type of ADR reported, 26.6% involved a combination of adverse effects, 15.7% comprised alterations in laboratory parameters, 13.5% included dermatologic adverse effects, 12.8% was drug ineffectiveness and 10.9% involved neurological adverse effects.

In addition, during the study period, three fatal cases were reported of which, two miscarriages were associated with administration of Fingolimod and a cardiac arrest due to the administration of the iodinated contrast Iopromide.

With regard to the drug Fingolimod, used for the treatment of multiple sclerosis, it was observed that on a total of 41 ADR signs associated with this disease, 19 were interested in precisely the drug Fingolimod with 13 reports of ineffectiveness and 2 miscarriages. The latter finding is consistent with the literature data about the frequency of miscarriages during treatment with Fingolimod [7].

Table 1. Distribution of ADR reports according to the active principle and the disease. Out of a total of 57 reports, 21 were related to the treatment of a rheumatic disease, while 10 were associated with the treatment of a neurological disease.

	Rheumatic Diseases	Neurological Diseases	Neoplastic Diseases	Immunological Disorders	IBD	HCV	AMD	Compassionate Use	Undefined Indication	Total
Abatacept	3								1	4
Etanercept	2									2
Adalimumab	6				2					8
Alemtuzumab								1		1
Certolizumab	1									1
Denosumab			2							2
Golimumab	3									3
Infliximab	1									1
Natalizumab		4								4
Nivolumab			3							3
Ranibizumab							5			5
Rituximab			4							4
Tocilizumab	3									3
Immunoglobulins	2	1		3						6
Interferons		5				5				10
Total	21	10	9	3	2	5	5	1	1	57

Table 2. The absolute frequencies of cases of ineffectiveness by the pharmacological group and the therapeutic indication.

	Rheumatic Diseases	Neurological Diseases	Psychiatric Diseases	Neoplastic Disorders	IBD	HCV	AMD	Hematological Diseases	Undefined Indication	Total
Blood and blood forming organs								2	1	3
Antiinfectives for systemic use						2				2
Antineoplastic and immunomodulating agents	12	13		1	2		5			33
Nervous system		1	16							17
Total	12	14	16	1	2	2	5	2	1	55

Table 3. ADR reports during treatment for chronic hepatitis C.

	2014	2015	2016	Total
ADR reports during treatment for infectious diseases	55	30	4	89
ADR reports during treatment for chronic hepatitis C	24	10	1	35

DISCUSSION

The Future: Pharmacovigilance, Pharmacogenetics and Pharmacogenomics

Pharmacovigilance, monitoring the safety of medicines, is the scientific activity relating to the detection, assessment, understanding and prevention of side effects and other problems related to drugs. The European Union (EU) has introduced a rigorous system to evaluate the safety of a medicinal product after it has obtained the marketing authorization and to take appropriate action, where this is necessary to protect public health. The EU's system provides different activities, including the collection and analysis of data, evaluation of reports, studies and risk management. Reports of adverse

reactions have increased dramatically in the last decade, thanks to new European legislation that includes reports on medication error, abuse, misuse, use outside the indications registered, overdose and occupational exposure. A good pharmacovigilance system collects information on the risks of medicinal products under the double and important aspect of the protection of the individual patient's health but also public health.

With the application of the new legislation mentioned above, also in Italy, direct reporting of suspected ADRs was introduced by the patient or by the health care worker, including among others, both figures in the decision-making process. In fact, in Italy, thanks to an ever greater attention to the issue together with the new European regulations, there has been an increase in reports of ADRs: according to data AIFA, Italy ranks since 2010 above the standard of 300 reports per million inhabitants, that is the Gold Standard according to the World Health Organization, showing the efficiency of the pharmacovigilance system [8]. However, the key objective has been achieved of promoting and protecting public health by reducing the number and severity of ADRs; a better use of medicines means not only to report but also to analyze and interpret data in order to understand the nature of the effects unwanted and, where possible, prevent them.

This fits well with the use of pharmacogenetics and pharmacogenomics, namely the study of the genes that determine the response to drugs: receptors of drugs, enzymes responsible for the transport of drugs and enzymes responsible for the metabolism. These are two disciplines of pharmacology and, generally pharmacogenetics refers to effects involving a limited number of genes, often involving drug metabolism, while pharmacogenomics involves the study of complex multi-gene patterns within the genome [9]. In realty, there is no agreement on the difference between the two and they are often used interchangeably. In fact, the term "pharmacogenetics" is that originally defined while the term "pharmacogenomics" is more recent, having been born after the success of the human genome project [10-12]. So, some Authors suggested that the difference is just that pharmacogenetics analyses a single gene whereas pharmacogenomics studies many genes or the entire genome [13]. However, the development of technologies applied to these sciences has made it possible to use them in clinical practice, more and more usefully. The goal of these new sciences is to better apply the knowledge of genome in medical practice, improving the treatment and the drug response. Nowadays, it is possible in several fields of application such as, first of all, for antineoplastic and immunomodulatory drugs [14-19].

The analysis carried out at our University Hospital provides results that reflect both the Italian trend of the past years [20] and the European one: most reports concern, in fact, antineoplastic and immunomodulating, antimicrobics and the central nervous system drugs (according to the International Classification ATC drug). The antineoplastic and immunomodulatory drugs are most frequently associated with adverse reactions (including an important and frequent reaction, the ineffectiveness) mainly for two reasons: the diseases for which they are prescribed, as they are chronic diseases often associated with different comorbidity, and the fact that these biological drugs belong to the category of medications which represent difficult therapeutic response [21-25].

The data of our observation agree with this trend by highlighting the high frequency of ADR reports in combination with biologics in about half of the cases consisting of ineffectiveness of the drug. Particularly interesting is the evidence of ineffectiveness in all cases in which the drug Ranibizumab was used in the treatment of macular degeneration. In fact, several authors [26] found that the gene may affect the development of this disease and the response to drug treatment; in particular, a recent study [27] has proven the association between polymorphisms of Complement Factor H (CFH) and the effectiveness of drug therapy, demonstrating the great utility that the pharmacogenomics can have in clinical practice.

Furthermore, interesting is the observation of the high frequency of adverse reactions associated with therapy for the treatment of Hepatitis C (35 cases in total, including 24 cases in 2014); the drugs most associated with adverse reactions in our observation were the boceprevir and telaprevir, both reported in the year 2014. Several observational studies had already shown in the past the possibility of frequent adverse events associated with the hiring of these two drugs, but one study in particular [28], published in February of 2015 has been noted as most of the patients (95%) treated with these two drugs had suffered an adverse reaction and appeared as the most frequent adverse events being dermatological ones, according to the data obtained from our work. These results are consistent in showing how, in practice, Boceprevir and Telaprevir are associated with a high frequency of adverse reactions [29-30]. The pharmacovigilance of our hospital, in this case, was efficient as shown in results from the net reduction (less than half) of adverse events due to HCV therapy from 2014 to 2015. This efficiency can still be improved by further studies as well as by the use of pharmacogenomics: for example, a recent study of May 2016 [31] offered an analysis of data derived from the sequence of HCV showing the association between the subtypes of the virus and the resistance to the different drugs generally used in therapy; this work is a useful approach to the understanding of the mutations at the base of mechanisms of resistance to the drug and can be useful to optimize the antiviral therapy.

Another result of great importance derived from this study appears to be the high frequency of ADRs associated with the drug Asenapine, of which there are a total of 25 reports, of which 16 consist of ineffectiveness. The Asenapine is a second generation antipsychotic medication, recently introduced in Italy, which has an action multi-receptor with different levels of affinity for various receptors; these characteristics are the basis of the several adverse effects [32], not present in the older generation antipsychotic drugs, and of the efficacy profile [33-35]. Most of the studies in the literature concern the evaluation of the effectiveness of the Asenapina compared to other antipsychotics or to placebo, but for the treatment of schizophrenia [36]; in such cases, however, better efficiency is not seen in the use of the Asenapine. Some authors in a study, aimed to evaluate the effectiveness of this drug in bipolar I disorder [37] as they felt the need for a longer observation time and further studies

to answer this question. Of particular importance, however, appears the fact that Asenapine is extensively metabolized from the isoform CYP1A2 of cytochrome P450 as well as direct glucuronidation from uridina difosfatoglucoroniltransferasis (UGT). It is well known that CYP1A2 polymorphisms affecting drug metabolism and various studies show the correlation between these polymorphisms and response to the therapy with Olanzapine [38]. Therefore, pharmacogenomic studies on Asenapine would allow a better understanding of the high frequency of ineffectiveness of this drug optimizing therapy.

CONCLUSION

Observing these data, probably similar to those of other Hospitals in different countries, the first reflection to make is that the ADRs represent an important chapter to be considered in the management of a health care system and for the increasing number of drugs introduced into clinical practice, both for the relevant cost in terms of mortality/morbidity and economically [39]. These costs are expected to rise considering the fact that more and more drugs are being placed in the market and more and more individuals are receiving multiple medications at once (polypharmacy). The second reflection is that ADRs represent real "drug-induced disease" that poses a problem of differential diagnosis as very challenging.

The first step for a correct management of the problem is to form an adequate pharmacovigilance system with the purpose to promptly report all serious ADRs that may especially occur after the drug is placed in the market [40, 41].

Nowadays, there are a lot of therapies for important diseases such as infections, cardiovascular disease, cancer and mental disorders. However, drug therapy is often not curative and may also cause adverse effects. The tendency to create drugs for extended use and not for an individual has shown that the therapeutic response is closely interindividual. Any drug can be therapeutic for some individuals and ineffective for others as some individuals show adverse effects while others do not. Pharmacogenomics offers us a choice: to opt for approach "a single drug cures all" to that of "personalized medicine." In this perspective, the pharmaceutical industry should incorporate pharmacogenomics into development phases of a drug, especially during clinical trials Phase II. Identifying specific genetic profiles for patients may create the basis for the approval and marketing of a specific medicine for a population [42-45].

This study suggests that this can be possible, highlighting the great potential of genetic tests in prevention to adverse reaction [46]. The great problem is the lack of big clinical trials. In fact, in many clinical trials, a large number of patients have been recruited for the purpose of solving the problem of the variability of response between patients. However, despite the inclusion of a large number of patients, currently the identification of rare ADR (less than 1 in 1000) is a big challenge. In fact, rare ADRs can be demonstrated only by observing large populations of patients exposed to the drug.

One solution is to carry out safety studies on the vast drug and heterogeneous populations prior to approval of the drug in the market. This, however, can significantly increase the time and cost of drug development, invariably delaying the availability of new medicines. An alternative solution would be the use of pharmacogenetics not only as a tool to develop new therapeutically useful molecules, but also to refine the current pharmacovigilance strategies. Pharmacogenomics could then effectively be added to existing systems that provide physicians with guidelines for a prescription as much as possible without risk for patients, thus making it more secure.

Finally, we would like to fully agree with the statement that "It would be painfully ironic if, in our pursuit of personalized medicine in the sense of medicine tailored to persons' genomes, we inadvertently abandon our pursuit of personalized medicine in the sense of medicine that shows respect for persons" [47]. Certainly, this needs reciprocal respect between patient and doctor, and PM will have to have a vision of the involvement of citizens as educated, engaged, resourceful, and responsible partners rather than passive recipients of health care [48]. Once again, the technological and socio-economic difficulties are proposed as critical to the development and success of PM. The institutional level will have to be careful and understand the importance of educating citizens in PM and to propose solutions to address such challenges.

Responsible innovation anticipates and evaluates the potential implications and societal expectations of technology in ways that are democratic, equitable, and sustainable (European Commission, 2013) [1, 49-50].

LIST OF ABBREVIATIONS

ADR = Adverse Drug Reaction

PM = Personalized Medicine

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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AUTHORS' ROLES

All authors contributed equally to manuscript drafting and critical discussion and approved the final version.

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