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MEETING REPORT

Workshop on the Italian Pharmacovigilance System in the International Context: Critical Issues and Perspectives

Janet Sultana[1] · Ugo Moretti[2] · Antonio Addis[3] · Pia Caduff[4] · Annalisa Capuano[5] · Agnes Kant[6] · Joan-Ramon Laporte[7] · Marie Lindquist[4] · June Raine[8] · Daniele Sartori[4] · Gianluca Trifirò[1] · Marco Tuccori[9] · Mauro Venegoni[2] · Eugene van Puijenbroek[6] · Roberto Leone[2]

1 Introduction

The field of pharmacovigilance has evolved significantly since the turn of the millennium, from spontaneous reporting to complex pharmacoepidemiologic studies, to the implementation of new methodologies for proactive pharmacovigilance and risk minimisation measures and, more recently, the attempts to use big data for post-marketing drug safety assessment [1]. Pharmacovigilance in Italy is no exception to such progress; the quality and quantity of spontaneous reporting have improved significantly, the number of centres of excellence dedicated to pharmacoepidemiology and pharmacovigilance has increased notably, partnerships and collaborations with Regional Pharmacovigilance Centres are being consolidated and the presence of pharmacovigilance experts at the Italian Drug Agency has increased [2, 3]. The availability of funding for pharmacovigilance, partly dedicated to the running of regional pharmacovigilance centres and partly dedicated to funding regional and multi-regional drug safety projects, has catalysed the creation and maintenance of Regional Pharmacovigilance Centres in almost all Italian regions. Partnerships between the Italian Drug Agency and the Regional Pharmacovigilance Centres have been ongoing for several years now, and have led to better signal management, whether for drugs or for vaccines.

In order to discuss the strengths, weaknesses and opportunities for pharmacovigilance in Italy, a workshop was held at the International School of Pharmacology "Giampaolo Velo" of Ettore Majorana Foundation in Erice (Italy) from the 9th to the 12th September 2018 on the topic "the Italian Pharmacovigilance System in the international context: critical issues and perspectives" (http://www.ccsem.infn.it/ef/emfcsc2018/posters/pdf/farmacologia.pdf). The workshop was organised by Annalisa Capuano from the University of Campania, Roberto Leone and Ugo Moretti from the University of Verona, Marie Lindquist from the Uppsala Monitoring Centre and Gianluca Trifirò from the University of Messina. The speakers and attendees included a variety of stakeholders, such as Italian pharmacovigilance officers working in National Agency and Regional Pharmacovigilance Centres as well as international pharmacovigilance experts, pharmacoepidemiologists, experts in drug regulatory affairs of regulatory agencies and industry and research scientists. June Raine from the Medicines and Healthcare Products Regulatory Agency (MHRA) provided an overview of pharmacovigilance systems at the international level while Carmela Santuccio provided her insight on the same theme at the national level in Italy. The impact of pharmacovigilance in an international context was discussed by Agnes Kant, based on her work at

✉ Roberto Leone
roberto.leone@univr.it

1 Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

2 Veneto Regional Pharmacovigilance Centre, University of Verona, Piazzale Ludovico Antonio Scuro n.10, 37134 Verona, Italy

3 Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

4 Uppsala Monitoring Centre, Uppsala, Sweden

5 Campania Pharmacovigilance Regional Centre, Naples, Italy

6 Netherlands Pharmacovigilance Centre Lareb, WHO Collaborating Centre for Pharmacovigilance in Education and Patient Reporting, 's Hertogenbosch, The Netherlands

7 Fundació Institut Català de Farmacologia, Hospital Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain

8 Medicines and Healthcare products Regulatory Agency, Canary Wharf, London, UK

9 Toscana Pharmacovigilance Regional Centre, Pisa, Italy

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the Lareb Pharmacovigilance Centre in the Netherlands, while the impact of pharmacovigilance in the Italian setting was discussed by Antonio Addis, from the Department of Epidemiology, Regione Lazio. Another topic of the workshops concerned the integration of different data sources in pharmacovigilance, of which the international context was discussed by Daniele Sartori from the Uppsala Monitoring Centre and the Italian context was discussed by Gianluca Trifirò. The last topic to be presented at the workshop was how to bring pharmacovigilance into the healthcare setting. This was discussed by Joan-Ramon Laporte (Autonomous University of Barcelona) from an international perspective and Annalisa Capuano from the Italian perspective.

The talks given by the above-mentioned speakers were followed by discussions, which led to a series of proposals aimed at improving Italian pharmacovigilance. These proposals are discussed in detail in this article and concern the following three themes: (1) increasing training and improving communication, (2) better use of data sources in Italian pharmacovigilance and (3) better allocation of resources and improved organisation.

2 Increasing Training and Improving Communication

Continued professional development for students and healthcare professionals and information campaigns for patients are essential to improve the appropriate and safe use of medications. Nevertheless, such training is rarely made available systematically [4]. In this context, the quality of the information is as important as independence from information providers with conflicts of interest [5]. Nevertheless, in recent years there has been a reduction of publicly funded and independent initiatives coordinated by the Italian Drug Agency aiming to educate healthcare professionals and patients about the appropriate and safe use of medicines in Italy.

Communication on drug use and safety, understood as a two-way approach tailored to a specific audience and which engages the recipient rather than just providing them with information, could also be improved. Indeed, recent research has shown that healthcare professionals appreciate and participate in two-way drug safety communication systems through apps [6]. There is currently a very large amount of information on drug use and safety, but in order to be useful, this must be meaningfully conveyed to the appropriate stakeholders. For example, communication could be improved by regularly publishing pharmacovigilance newsletters on the Italian Drug Agency website, as done by the MHRA in the UK, which publishes a monthly drug safety bulletin ("Drug Safety Update"), and by other competent national authorities. Survey-based research, however, indicated that the preferences of healthcare professionals in 26 European countries in receiving drug safety information were, in decreasing order, medicines reference book, national clinical guidelines, medical journal, personalised letter, summary of product characteristics/patient information leaflet and newspaper [7]. At present, only the information requiring urgent dissemination is published on the Italian Drug Agency website. Nevertheless, according to results from the same survey based in nine European countries, more healthcare professionals from Italy were informed and aware of selected safety concerns through communications requiring urgent dissemination, such as Direct Healthcare Professional Communication, than the other eight countries, suggesting that the Italian Drug Agency is effective in communicating such information [8]. There was a consensus on the importance of launching regular communications and ensuring they are not limited to regulatory decisions such as drug withdrawals or changes to the summary of product characteristics. It is particularly important to disseminate information regarding newer drugs with a potentially limited safety profile, whether such information is issued by the Italian Drug Agency or by other Italian entities, such as the regional pharmacovigilance centres. However, it was further suggested that these communications should address important issues such as the appropriateness of drug prescribing as well as the use and safety of older, widely used medications. Furthermore, some initiatives are currently launched by single Italian pharmacovigilance centres rather than being part of a more coordinated and broader approach. To optimise the use of resources, it is essential to coordinate individual communication initiatives as well as involve key stakeholders who can provide accurate and independent information. A well thought-out strategy is needed to this end. It is also essential to find new ways of issuing communications on drug use and safety that could reach out to larger numbers of healthcare professionals and patients as well as to measure the impact of such communication campaigns.

The impact of such communication campaigns should be properly measured and, given that social media may play a very important role in reaching out to healthcare professionals and patients quickly, it was agreed that efforts should be made to benefit from the full potential of such media. The recipient of medication-related information should be a strong determinant of the decision to use social media or otherwise, since healthcare professional perception of social media as a channel of drug safety information was not very good [8]. Moreover, it was highlighted that the quality and the completeness of timely communications related to medication safety, provided by independent sources, is key to maintaining the trust that the broader population has in the healthcare system.

3 Better Use of Data Sources in Italian Pharmacovigilance

The Italian healthcare system has become increasingly digitalised over the last few years; there has been an increase in the number of hospital wards that use electronic patient charts, practically all general practitioners and family paediatricians use specific data entry software in their routine practice, and many regions have implemented registries of vaccinations. For all these examples and several others, the collection and management of data concerning potential adverse reactions of drugs and vaccines is a primary component. It is increasingly important to initiate and sustain dialogue between such stakeholders and the Italian National Pharmacovigilance Network (known nationally as *Rete Nazionale di Farmacovigilanza*) with the aim of facilitating data sharing and/or linkage. It was agreed that better coordination in terms of data collection between the various Italian registries, be it national or regional ones, and the National Pharmacovigilance Network is urgently needed to avoid the current situation where the same patient-level data entry procedure must be duplicated or even triplicated in more than one registry.

There is also room for improvement regarding electronic spontaneous reports. As of a few years ago, it became possible to compile and submit electronic spontaneous reports online. Nevertheless, the number of paper-based spontaneous reports received by pharmacovigilance centres is very high compared with other countries, leading to a greater and avoidable workload for personnel who receive the reports and must manually record the contents electronically. It is also important to encourage spontaneous reports by patients. Applications downloaded to mobile phones or similar devices may play an important role in promoting patient-led drug safety reporting, as suggested by findings among European healthcare professionals in the IMI-WEB RADR project [6].

The need to create an informatics infrastructure allowing the integration of regional claims data, where healthcare claims for all Italian citizens are collected in each region, was highlighted by several speakers. This would allow more rapid independent research, be it by single groups of researchers or multi-regional research groups. The organisation and infrastructure for data integration should be launched in a pilot phase to ensure its feasibility before investing resources on a large scale. A good example of this is the Mini-Sentinel initiative [9], launched and supported by the Food and Drug Administration (FDA) in the US and later developed sustainably into a full and long-term drug safety programme. With the collaboration of a network of Italian pharmacoepidemiology and real-world data experts, an infrastructure of this kind would allow a timely and cost-effective method to respond to the urgent questions raised by the Italian Drug Agency and the European Medicines Agency, such as evaluation of the implementation and impact of risk minimisation measures, validation of safety signals and the general post-marketing monitoring of drug safety and efficacy. In this context, pharmacovigilance can serve as a bridge between medical research and clinical practice. Another important role of pharmacovigilance concerns the appropriate monitoring of the impact of regulatory decisions and updated guidelines. This should be the 'gold standard' for decision makers to understand the impact of such decisions on health outcomes and costs. Examples of studies using Italian healthcare claims data [10] or electronic medical records [11] to monitor the impact of regulatory decisions on health outcomes in the target populations are already available in our country. Irrespective of the use of data resources, it is essential that the Regional Pharmacovigilance Centres, healthcare professionals and researchers in the field of pharmacovigilance work closely with the Italian regional authorities to analyse the available drug utilisation data. The aim of such data analysis should primarily be that of identifying and addressing important drug-related issues, particularly regarding the appropriate use of medications. The knowledge generated by the analysis of real-world data should be shared effectively with healthcare professionals to promote the appropriate and safer use of medications. Finally, it was emphasised that data integration and assisted drug safety reporting could reduce workload and boost quality.

4 Better Allocation of Resources and Improved Organisation

In Italy, funding dedicated to pharmacovigilance activities has been systematically allocated for the past 20 years. Nevertheless, there is significant uncertainty concerning the amount of funding available and the timeframe in which it reaches its recipients. One suggestion to address this issue raised during the workshop concerned requesting the inclusion of pharmacovigilance activities among the essential healthcare activities ("*livelli essenziali di assistenza*") covered by the Italian National Healthcare System. This would make the receipt of funding more certain and would have the additional benefit of leading to better prioritisation of pharmacovigilance activities in Italy. Such prioritisation of drug-related issues could be based on the analysis of drug utilisation patterns, whether of widely used low to moderately costly drugs or of less commonly used but expensive drugs. It is essential to objectively measure the infrastructure, processes and outcomes of pharmacovigilance by bench-marking and monitoring processes, in order to clearly

document the benefits of pharmacovigilance in relation to its implementation costs. The Indicator-Based Pharmacovigilance Assessment Tool published by the Management Sciences for Health [12] is an example of sets of indicators but this is focused on processes rather than outcomes. A set of indicators measuring pharmacovigilance outcomes has yet to be developed. A general observation was made that quality indicators assessing spontaneous reporting should not focus only on increasing the quantity of spontaneous reports, but on increasing their quality and impact by promoting reporting for drug-related events of highest severity and novelty. Even though spontaneous reporting should always be encouraged in all settings, focusing on certain target populations, such as general practitioners or patients, or drug categories, such as vaccines, may lead to a larger impact.

Another issue that was raised regarding the allocation of resources concerns the routes through which funding by the Italian Drug Agency is allocated (i.e. primarily through pharmacovigilance projects). The timeframe for project approval is not certain, so it is therefore difficult to obtain regular funding to remunerate the pharmacovigilance work done. It was proposed that the portion of national funds reserved to support the work of the Regional Pharmacovigilance Centres should be made available on a regular basis, without waiting for the approval of pharmacovigilance projects. On the other hand, the regional authorities are strongly encouraged to commit to officially recognising the position that pharmacovigilance staff hold within the Regional Pharmacovigilance centre, such as through the creation of formal job positions with well defined and remunerated duties. Finally, it is important to empower the Regional Pharmacovigilance Centres to achieve other objectives, such as spreading awareness of pharmacovigilance among healthcare workers, training personnel at the Regional Pharmacovigilance Centres, and maintaining best practices in signal detection.

5 Conclusion

Pharmacovigilance in Italy has great potential, whether in relation to the availability of large amounts of healthcare data, the presence of strong networks of pharmacovigilance and pharmacoepidemiology experts pooling both data and expertise, or the availability of financial resources to support pharmacovigilance activity. It is hoped that the proposals brought forward in this workshop will lead to concerted action at the regional and national level to leverage the many resources available in Italy for the benefit of public health.

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Compliance with Ethical Standards

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