SAFETY AND COST OF DRUGS PRESCRIBED ACCORDING TO LAW 648/96

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Introduction: A medicinal product can be used safely and effectively in accordance with the terms established in the product information and approved during the marketing authorisation procedure. However, in real life medicinal products are not always used in accordance with these terms and the best available evidence may not be reflected in the product information. According to European Medicines Agency (EMA), off-label use refers to "situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information". It is the practice of prescribing drugs for unapproved indications or age group, dose or dosage frequencies, route of administration other than those listed in the specific summary of product characteristics. However, off-label prescribing is not currently regulated at European level but some countries adopted specific laws. In Italy, a comprehensive body of legislation has been produced in order to regulate off-label use (Law 648/1996; Law 94/1998). In particular, Law 648/1996establishes National Health System (NHS) can reimburse a drug (1) approved in other countries, or (2) currently used in clinical trials or (3) used for not approved indications. All these drugs must be included in specific lists (main list and annexes of consolidated use) based on new evidences resulting from at least phase II clinical trials. The inclusion of a drug in these lists may be promoted for example by clinicians, scientific societies, and patient associations. From 2014, Italy permits off-label use of less costly drugs safe and effective even in presence of approved treatment options with higher cost (Law 79/2014). Clinical and expenditure data related to the use of drugs included in the main list must be regularly sent to the Regulatory Authority. The aim of this project is to evaluate safety and cost of drugs used according to Law 648/1996, especially if the risk/benefit profile is not yet fully defined.

Methods: We analysed prescriptions performed in accordance with Law 648/96from 2018in 2Sicilian University Hospitals and collected through a dedicated electronic database. Safety of each drug was defined by the onset of adverse drug reactions (ADRs). Impact on hospital pharmaceutical expenditure was obtained from data sent to the Regulatory Authority.

Results: From January 2018to February 2019, 769prescriptions (first prescriptions and renewals) were performed according to Law 648/96, mainly from Hematology, Gynecology and Oncology Units. Low Molecular Weight Heparins (LMWHs) were the most prescribed drugs (28%), followed by epoetin zeta (13.3%). Few reports of suspected ADRs were available at the time of the preliminary analysis. These ADRs were not serious and were almost all associated with the use of mycophenolate mofetil to treat serious autoimmune disorders.The overall expenditure sustained until December 2018for treatments included in the main list was about € 846000, of which more than 50% refers to lenalidomide, eculizumab and arsenic trioxide.

Discussion and conclusions: Law 648/96represents a valuable opportunity for patients to be treated with drugs not yet approved with standard marketing authorization procedures, if efficacy and safety data support their use. However, the risk/benefit profile of these drugs could not be fully defined, in particular if they are currently used in clinical trials. These preliminary results show a widespread use of drugs according to Law 648/96, in particular in hemato-oncologic patients and pregnant women. No specific safety issue emerged so far from the ADR analysis. In the reference period a significant expenditure was recorded for treatments included in the main list, more than 50% related to 3high cost drugs. It is noteworthy that price of drugs included in the lists of Law 648/96are usually not negotiated by the Italian Medicines Agency.
The study is still ongoing and the expected date of conclusion is December 312020.