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Off Label Use as an Indicator of Therapeutic Need in Pediatrics

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Unapproved use of an approved drug is called "off-label" use. In line with European Medicine Agency's pharmacovigilance directive, off-label use "*relates to situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information (SmPC)* [1].

This term can mean that the drug is: Used for a disease or medical condition that it is not approved to treat or more widely, not only for different indication but also for different route of administration, dosage, formulation, population from those approved by the Regulatory Agencies on the basis of data provided by the owner at the time of an application (benefit/risk ratio).

The use a medicine in an unauthorized way allows to treat patients who, in the clinician's medical evaluation, would not have a therapeutic choice. This is due both to the absence of a therapeutic alternative use for the treatment of the patient and to the need to treat vulnerable populations (ie. patients with rare diseases, pediatrics, etc..) for which authorized therapies are not available.

The use of an off-label opens up the debate on one of the most delicate ethic aspects of the Medicine. The responsibility for the therapeutic choice and, therefore, for the off-label use falls on the prescriber who will have to ask the patient (or whoever takes his place), to sign an informed consent with which inform appropriately about the pros and cons of the chosen therapy.

Physicians must be able to make a decisions in the best clinical interest of their patients; in the case that they believe that the best interest of their patient is to use an off-label therapeutic treatment, this is allowed as long as the patient is fully informed, is made aware of any risks and is fully involved in the decision-making process.

There are therapeutic areas where the unauthorized use of a medicine is very wide, for example the pediatric field. The spread of off-label use in the pediatric field derives mainly from the difficulty in starting trials in this context, situation which it has long been reflected in a social and ethical paradigm. The pediatric population should be protected from research, but the difficulty in starting trials involving this population makes it "orphan" of authorized therapies. Ethical and, sometimes, methodological and economic issues make the pediatric trials "unattractive". Furthermore, children are not a homogeneous population; in fact, within this category it is possible to distinguish different groups based on age groups characterized by biological diversity and for which starting a trial would be an expensive and complex process [2].

Some studies have shown that most of the drugs used in newborns and infants are off-label or unlicensed and, according to a recent American study, would amount to 65% in settings such as intensive care [3,4].

In February 2017, an European Commission report containing the results of a study was made public [5], showing that in hospital there is a range of off-label use ranging from 13 to 69% in the pediatric population. A very important information obtained from this study also concerns the therapeutic areas most concerned. In the pediatric field, areas such as cardiovascular, infectious diseases, central nervous system, respiratory system and the alimentary tract and metabolism are the most interested [5].

Also in the report of the European Medicine Agency emerged that the most used off-label medicines belong to the category of antiarrhythmics, antihypertensive drugs, and drugs for the nervous system central [6].

Some literature reviews have also analyzed the potential association between off-label use and the risk of adverse events in pediatrics. It emerges that the incidence of adverse reactions was higher in patients treated off-label than in those who had received on-label treatment [7,8].

An analysis of the cardiovascular system medicines which are most used in pediatrics both through the evaluation of the information in the related SmPC both through a literature research and a research of the ongoing trials allowed to verify their off-label use and the main areas of use in clinical practice [9].

The analysis of the offlabel use of the main molecules belonging to the category of ACE inhibitors suggests a therapeutic need of authorized molecules for proteinuric nephropathies, post heart transplant vasculopathy, treatment of univentricular heart and as a support for the Fontan procedure, as well as for the treatment of anthracycline cardiotoxicity. Another emerging area concerns the treatment of Alport syndrome, a rare genetic condition for which ramipril is studied [10-22].

After ACE-I, beta-blockers are the most used but only propranolol is authorized for the indication childhood hemangiomas. Arterial hypertension, heart disease, arrhythmias, hyperthyroidism, migraine prophylaxis, portal hypertension at risk of varicose veins are the most registered area of offlabel use. Ongoing studies focus on ROP, a proliferative vitreo retinopathy, one of the most frequent causes of blindness in preterm infants.

Other studies focused on their use in the field of autistic spectrum in combination with intensive behavioral intervention, in patients with burn injuries, in a rare vascular neoplasia (Kaposiforme hemangioendothelioma) and in the neuroblastoma; also in Fontan intervention and in preventing heart failure in cancer survivors exposed at high doses of anthracyclines, this two last indications as for the Ace Inhibitors.

Finally, also beta blockers and in particolar atenolol is studied for a rare connective tissue disease, involving heart and blood vessels, ligaments and skeletal system, eyes and lungs called Marfan syndrome [23-57].

Off-label use is one of the topics most attentionate at international level and, although many studies carried out have various limitations, it is worth continuing to investigate to consolidate systematic monitoring activities.

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