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RETROSPECTIVE ANALYSIS OF EMERGING DRUGS USE IN A QUEBEC WOMEN'S AND CHILDREN'S UNIVERSITY HOSPITAL AND PERSPECTIVES FOR SAFE AND OPTIMAL DRUG USE

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Abstract

Background
Only few medicines are licensed for children. The use of emerging drugs (unmarketed drug, off-label drug with poorly documented use, and/or costly drugs) might represent an essential alternative for pediatric patients.

Objectives
The objective of the study was to assess emerging drug uses rate and profile in our women's and children's centre to support the implementation of an appropriate policy.

Methods
We identified retrospectively emerging drugs used between 2013-01-01 and 2014-02-28, using computerized pharmacist software extraction of drugs used. Conventional oncologic drugs were excluded. Retrospective analysis of medical charts for patients who received an emerging drug and literature review for each drug were performed to determine efficacy and safety endpoints. Median delays between first intention and final decision to use the drug and between final decision and first administration were calculated. Proportion of patients who experienced a positive evolution under treatment or a side effect possibly related to the drug was calculated.

Results
A total of 26 emerging drugs were identified (89 patients, 99 uses). Median treatment duration was 66 days [1-1435]. Median delay between first evocation and final decision to use the drug was 2 days [0-333] and 0 day [0-404] between final decision and first administration. 52/99 (53%) of patients experienced a positive evolution under treatment and 26/99 (26%) experienced a side effect possibly related to emerging drug use.

Conclusions
This study allowed us to describe emerging drug uses in a women and children tertiary hospital. It led to the implementation of a local emerging drug use policy ensuring optimal and safe use of these drugs. There is a significant number of emerging drugs used in pediatric which shows positive improvement in 56% of patients.

Keywords: *pediatrics, unlicensed, off-label, emerging drugs*

Around the world, only few medicines are licensed for children. Before the implementation of pediatric regulations in the United States (US), the Food and Drug Administration (FDA) assessed that only 20% of approved medicines in the US were labeled for children.[1] Following this evaluation, the FDA Modernization Act (FDAMA), the Best Pharmaceutical for Children Act (BPCA) and the Pediatric Research Equity Act

(PREA) were adopted, respectively in 1997, 2002, and 2003, to promote pediatric research in the US. In 2013, the FDA Safety and Innovation Act (FDASIA) added requirements for clinical research in neonates. These 4 acts were followed by 615 new pediatric labels (as of February 29, 2016).[2] In Europe, in 2007, the European Medicines Agency (EMA) created the Pediatric Committee to promote and reward pediatric research, implementing the Pediatric Investigation Plans.[3] In Canada, the Paediatric Expert Advisory Committee (PEAC) was created in 2009, to provide a way to seek expert advice and public involvement for health products on the market designed for children, and pregnant and nursing women.[4] A 6-month extension of data protection is granted to the drug when manufacturers fulfilled requirements of pediatric clinical research. However, providing pediatric information is not mandatory in Canada.

Although pediatric regulations have been implemented in different countries, approved drugs in pediatrics are still lacking and off-label and unlicensed drug uses are still essential for children. A recent study from Europe found unlicensed and off-label drug use rates in children before implementation of pediatric regulations to be ranging from 0.2–36% for inpatients and between 0.3 and 16.6% for outpatients reduced to 0–11.4% for inpatients and between 1.26 and 6.7% for outpatients after the implementation regulations.[5] Off-label drug use rates decreased marginally from an 18–66% interval for inpatients and from a 10.5–37.5% interval for outpatients to 33.2–46.5% interval and to a 3.3–13.5% interval post-regulation, respectively. To overcome the lack of approved drugs, expanded accesses to non-marketed drugs have been implemented around the world. For example, in Canada, Health Canada created the Special Access Program (SAP) to provide "access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable."[6] In tertiary care hospitals, the use of SAP is more frequent due to more complex cases.

In this context, the use of emerging drugs, defined as un-marketed drugs, or off-label drug with poorly documented use, or very costly drugs, might represent an essential alternative for pediatric patients.

The aim of this study was to assess the emerging drug uses rate and profile in a women's and children's university hospital in Quebec to get an overview of these uncommon uses and to support the implementation of an appropriate emergent drug use policy in our centre.

METHODS

Health Care Setting

The study was conducted in a tertiary care women's and children's teaching hospital, in Montreal, Quebec, Canada. The centre is a 500-bed facility with more than 18,000 admissions, 100 000 patient-days, and 200,000 outpatient visits per year. The pharmacy department uses a closed drug formulary with the collaboration of a pharmacology and therapeutics committee. The local drug formulary includes 821 drug substances corresponding to 2,045 drug formulations currently used.

Definitions and Study Variables

First, we defined emerging drug criteria for our centre. Criteria identified to define a drug as being an emerging drug were the following:

- Every non-marketed drug in Canada, which had never or rarely been used in our centre, and is accessible through the Special Access Program of Health Canada, or
- Every marketed drug in Canada used for an unapproved and poorly documented use, and/or
- Every marketed drug considered very costly (> $CA 300 per dose) and for which pediatric use guidelines were not established in our centre.

Data Extraction

Considering these criteria, we identified retrospectively potential emerging drugs used between January 1, 2013 and February 28, 2014, using computerized pharmacist software (GesPharX8®, Québec, QC, Canada) extraction of all drugs used during this period.

Conventional oncologic drugs (other than immunotherapy and monoclonal antibodies) were excluded from our analysis. Most drugs used in oncology practice already undergo a thorough evaluation through Institution Review Board (research ethic committee) and decisions are usually made through a multidisciplinary process.

Data Analysis

A retrospective analysis of medical charts for every patient who received an emerging drug according to our criteria during the study period was performed. Data extracted from the computerized pharmacist software (GesPharX8®) was: birth date, start and end dates of emerging drug prescriptions, emerging drug prescribed, indication, dosage. Medical charts were retrieved for additional information: date of first evocation to use the emerging drug, date of final decision to use it, date of multidisciplinary meeting and pharmacy staff presence, documented written or verbal informed consent from patient or parents, alternatives used to treat the condition before the emerging drug prescription, definition of efficacy and safety endpoints, allowance or refusal of pharmacy department chief, results of efficacy and safety endpoints identified.

For all emerging drugs, a literature review was performed to determine efficacy and safety endpoints that should be monitored when using the drug. If prescribers did not clearly identify efficacy and safety parameters to monitor, we used the recommended endpoints retrieved in the literature review, and their monitoring was checked in patients' medical charts. Regarding the available alternatives to the emerging drug, we used guidelines and recommendations from different scientific and expert groups (Orphanet[7], Canadian Cancer Society[8]) or data issued from literature to determine what alternatives could have been used for the patient.

Endpoints

Emerging drugs profile in our centre was characterized by median delays between first intention of use and final decision to use the emerging drug, and between final decision to use it and first administration to patients. Mean number of alternatives used compared and mean number of available alternatives was also calculated. Also, proportion of prescriptions with a clear definition of efficacy and safety endpoints, proportion of patients who experienced a positive evolution under treatment and proportion of patients who experienced a side effect possibly related to the emerging drug use were calculated. Only descriptive statistics were performed.

RESULTS

Of all drugs used between January 1, 2013 and February 28, 2014 in our centre, 26 drugs matched our emerging drugs definition. Table 1 describes the profile of emerging drugs used between January 1, 2013 and February 28, 2014. Between January 1, 2013 and February 28, 2014, 89 patients received at least one emerging drug. Of them, 10 received two emerging drugs. Total number of emerging drugs uses was 99. Median age of patients at the beginning of the treatment was 4 years of age (0–18) and median treatment duration for patients who had discontinued treatment by the end of the study was 66 days (1–1435). The median delay between first evocation to use the emerging drug and first administration to patient was 5 days (0–404) and median delay between final decision to use the emerging drug and first administration was 0 days (0–404). The average ratio of used/available treatment alternatives were 2.2/3.6. The proportion of verbal informed consent mentioned in medical chart was 7% (7/99) and the proportion of written informed consent retrieved in medical charts was 12% (12/99). Only 33% of drug order had targeted efficacy parameters documented in medical charts (33/99). The proportion of patients who experienced a positive evolution under treatment was 53% (22/99). The proportion of drug orders with safety identified parameters was 10% (10/99) with a mean of 1.4 safety parameters/order. Finally, the proportion of patients who experienced a side effect possibly related to the emerging drug was 26% (26/99).

Regarding longer delays between the first intention and the final decision to use the emerging drug, they were due to an early first evocation of using emerging drug, before prescribers had tried every other available alternative for their patients.

Regarding the longer delays between final decision to use the emerging drug and first administration to patient, we reported different causes:

- Canakinumab: 61-days delay before getting approval from the company to get access to the drug (one patient).
- Galsulfase: 404-days delay between first reimbursement application and final acceptance from private insurance company (one patient).

TABLE 1 Profile of Emerging Drugs Used between January 1, 2013 and February 28, 2014

Emerging Drug	Indications of Use	Canadian Status	Emerging Status	Number of Patients
Aldesleukine (Interleukin-2)	Lymphoblastic leukemia, myeloblastic leukemia, neuroblastoma, atypical myelodysplasia	DIN	OLPD	10
Alpha-glucosidase	Pompe's disease	DIN	$$$	2
Bevacizumab intreavitreally	Maculopathy	DIN (compounding)	OLPD	1
Brentuximab	Hodgkin's disease	SAP	SAP	1
Canakinumab	Juvenile idiopathic arthritis	DIN	$$$	4
Cidofovir	Adenovirus systemic infection after bone-marrow transplant	SAP	SAP	5
Cidofovir (intralaryngeal)	Laryngeal papillomatosis	SAP	SAP	3
Défibrotide	Hepatic veino-occlusive disease	SAP	SAP	4
Eculizumab	Atypical hemolytic-uremic syndrome, chronic glomerulonephritis, Thromboembolic disease (including thrombotic thrombocytopenic purpura)	DIN	$$$ (atypical hemolytic-uremic syndrome), OLPD	8
Everolimus	Intracardiac rhabdomyoma associated with tuberous sclerosis	DIN	OLPD	2
Galsulfase	Type VI mucopolysaccharidosis (MPS VI)	DIN	$$$	1
Idursulfase	Type II mucopolysaccharidosis (MPS II)	DIN	$$$	1
Laronidase	Type I mucopolysaccharidosis (MPS I)	DIN	$$$	2
Liothyronine (triiodothyronine) injection	Neonatal cardiac surgery, euthyroid-sick syndrome	SAP	SAP	8
Mifepristone	Refractory meningioma associated with neurofibromatosis	SAP	SAP	1
Omalizumab	Severe allergic asthma, allergic bronchopulmonary aspergillosis	DIN	$$$ (severe allergic asthma), OLPD	5
Paliperidone palmitate	Acute schizophrenia	DIN	OLPD	2
PEG-Ademase	Severe combined immunodeficiency in ademase	SAP	SAP	1
Pyridoxal-5-phosphate	West syndrome, refractory epilepsy (focal seizures)	WCS (Compounding)	SAP	6
Rufinamide	West syndrome, refractory epilepsy (tonic-clonic seizures)	DIN	OLPD	6
Sacrosidase	Sucrase-isomaltase deficiency	SAP	SAP	1
Sargramostim (GM-csf)	Neuroblastoma	SAP	SAP	8
Sodium thiosulfate	Calciphylaxis	DIN	OLPD	1
Stiripentol	Dravet syndrome, refractory epilepsy (tonic-clonic or myoclonic seizures)	SAP	SAP	10

(*Continues*)

TABLE 1 (Continued)

Emerging Drug	Indications of Use	Canadian Status	Emerging Status	Number of Patients
Tocilizumab	Juvenile idiopathic arthritis	DIN	$$$	3
Ustekinumab	Refractory Crohn's disease	DIN	OLPD	3

$$$ = very costly drug (>300$ per dose); DIN = Drug identification number; OLPD = Off-label prescription drug; SAP = Special Access Program; WCS = Without Canadian status.
Note: a compounding is defined as a formulation compounded by the hospital pharmacy because no equivalent was available.

- Omalizumab: one patient had to wait to be 12 years old to access the treatment (11 when first application was filled) and another patient waited for 253 days before obtaining the reimbursement authorization from private insurance company.
- Sacrosidase: 141-days delay to get the authorization from private insurance company (one patient).

In order to illustrate differences in delays, available and used alternatives, safety and efficacy criteria definition and informed consent retrieved depending on the emerging drug, we detailed the 10 most prescribed emerging drugs uses in Table 2.

Triiodothyronine was only administered in intensive care unit and was considered as an emergency care drug. This is why delays were very short (a few hours only). Regarding aldesleukine (interleukin-2) and sargramostim (GM-csf), these 2 drugs were mostly used as a combination in the treatment of refractory neuroblastoma. Final decision to use these emerging drugs was made at the end of the prior cycle of treatment, approximately one month before the first administration of these emerging drugs.

DISCUSSION

The high prevalence rates of off-label and unlicensed drug uses are an issue around the world, especially in pediatrics.[5] Moreover, some studies have reported that off-label drug uses are closely related to an increased risk of developing side effects.[9] This risk seems to be more important when using a non-marketed or not-well known drug in a given environment. The treatment of patients includes more and more uses of drugs obtained through expanded access programs and/or off-label uses of marketed drugs. Additionally, the cost of these emerging therapies represents an important and growing burden of hospital budgets. As an example, a tool has been developed by the Memorial Sloan Kettering Cancer Center to explore drug pricing of new drugs.[10] Drug Abacus® calculates a theoretical price for a drug, taking into account dollars per life-year, toxicity, novelty of the drug, cost of development, rarity of the disease and burden of the disease and compare this calculated price to the actual US price. Mostly oncologic drugs are concerned by this tool.

For all these reasons, it is important to ensure that emerging drugs are properly used and their efficacy and safety are properly followed-up by health care providers. This proper use concerns diagnosis, prescription, distribution, administration, and follow-up. Local criteria obtained by consensus may also help to define in a detailed manner the indications and usage modalities. It can include, for example, the exact place in therapy (e.g., sacrosidase for refractory symptoms after a trial of a nutritional diet for 6 months), a specific diagnosis test to perform before initiating the treatment (e.g., CRIM status for alphaglucosidase use in Pompe's disease), a specific efficacy endpoint (e.g., ADAMTS13 dosage for eculizumab efficacy in thrombotic microangiopathies) or a specific safety follow-up (e.g. tubulopathy caused by cidofovir injections).

Our study showed that several medications could match our criteria of emerging drug and be defined as emerging drugs. They included monoclonal antibodies, enzymatic-replacement therapies, or antiepileptic drugs. Almost half of them were not marketed in Canada at the time of the study. Most of them (20/26) were considered very expensive, such as over $300 CAD per dose. This number of emerging drugs seems to be reasonable for a women and children university hospital, with most of patients suffering from refractory and complex conditions.

TABLE 2 Details of the 10 Most Prescribed Emerging Drugs Uses

Substance	Patients (*n*)	Median delay (1st evocation and final decision)	Mean available alternatives (*n*)	Mean used alternatives (*n*)	Informed content (*n*)	Efficacy assessment (*n*)	Safety assessment (*n*)	Side effects
Stiripentol	10	1 day [0-67]	7.1	3.5	0	Yes - 4/10	Yes - 0/10	Behavioural disorders, ataxia, drowsiness
						No – 4/10	No – 5/10	
						Unknown – 2/10	Unknown – 5/10	
Aldesleukine	10	24 days [0-120]	9.4	6.2	2	Yes – 0/10	Yes - 2/10	Cytopenia
						No – 1/10	No – 6/10	
						Unknown – 9/10	Unknown – 2/10	
Triiodothyronine	8	0 day	0.4	0.1	0	Yes – 4/8	Yes – 3/8	Unknown
						No – 0/8	No – 0/8	
						Unknown – 4/8	Unknown – 5/8	
Eculizumab	8	8 days [1-333]	3.0	2.0	2	Yes – 6/8	Yes – 5/8	Unknown
						No – 1/8	No – 1/8	
						Unknown – 1/8	Unknown – 2/8	
Sargramostim	8	29 days [0-98]	1	1	1	Yes – 4/8	Yes – 0/8	Hyperleuco., AST/ ALT/ creatinine elevation
						No – 2/8	No – 6/8	
						Unknown – 2/8	Unknown – 2/8	
Rufinamide	6	1 day [0-91]	9.2	6.6	0	Yes – 2/6	Yes – 1/6	Drowsiness, vomiting
						No – 0/6	No – 2/6	
						Unknown – 4/6	Unknown – 3/6	
Pyridoxal-5-phosphate	6	0 day [0-32]	5.0	2.4	0	Yes – 3/6	Yes – 0/6	Unknown
						No – 1/6	No – 0/6	
						Unknown – 2/6	Unknown – 6/6	
Omalizumab	5	49 days [1-253]	3.0	3.0	4	Yes – 5/5	Yes – 3/5	Unknown
						No – 0/5	No – 0/5	
						Unkown – 0/5	Unknown – 2/5	
Cidofovir	5	3 days [0-7]	0	0	0	Yea – 4/5	Yes – 2/5	Tubulopathy, creatinine elevation agranulocytosis
						No – 0/5	No – 2/5	
						Unknown – 1/5	Unknown – 1/5	
Canakinumab	4	35 days [9-77]	4.0	2.5	1	Yes – 3/4	Yes – 3/4	Rash, hepatic cytolysis, epistaxis
						No – 1/4	No – 1/4	
						Unknown – 0/4	Unknown – 0/4	

Hyperleuco. = hyperleucocytosis; ALT = alanine transaminase; AST = aspartate transaminase.

Median decision-making process duration was 2 days and median authorization process was 0 days. It seems that these delays did not interfere in patients' optimal medical care. When longer delays in medical care were noted, they were caused by administrative delays, such as a long delay for obtaining a reimbursement authorization from private insurances. Those delays occurred for emerging drugs used to treat chronic conditions. Depending on emerging drugs and indications, the decision-making and follow-up processes were very different.

Only 35% of prescriptions were associated with efficacy endpoints definition and 53% of patients experienced a positive evolution under treatment based on a retrospective review of medical charts. For 14/99 prescriptions, we could not retrieve information about efficacy. Only 10% of prescriptions were associated with safety endpoints definition. For 39/99 prescriptions, we couldn't determine if the patient had experienced a side effect possibly related to the emerging drug use because of missing data (no written follow-up or no definition of safety criteria in medical charts or in literature review).

It seems that most prescribers and pharmacists are aware of the risks associated with the use of emerging drugs but this pilot retrospective evaluation confirms that a policy should be written and applied to harmonize and optimize the decision-making and follow-up process regarding emerging drugs. This policy should also reinforce collaboration of health care providers, especially prescribers and pharmacists.

Moreover, health authorities are asking for additional studies assessing efficacy in real life. For example, the National institute of excellence in health and social services of Quebec (INESSS – Institut national d'excellence en santé et services sociaux) promotes "clinical excellence and the efficient use of resources in the health and social services sector."[11] INESSS assesses the clinical advantages and costs of medications, and its decisions have an impact on coverage by the public insurance plan and hospitals. For some medicines, such as brentuximab, the INESSS requires that prescribers prove the efficacy of the treatment to allow patients to extend the initial duration of treatment, by using objectives parameters results. As another example, uses of emerging drugs in France are partly regulated by the activity based funding (tarification à l'activité – T2A). Costly drugs are reimbursed in addition to other funding. To get a complete reimbursement, hospitals must testify in patient files that these drugs are used within approved indications. Unfortunately, this system does not include a patient's follow-up process and seem to be focused mainly on financial considerations.

Considering the risks associated with emerging drug uses, it appears relevant and necessary to provide a more comprehensive framework for these drugs. A study conducted in the US in 2006 evaluated the presence of a policy concerning the innovative off-label uses.[12] Of 104 responders, only 18 hospitals had an innovative off-label medication use policy. Of these centres, 12 had a standardized method of data review and a peer-review process, eleven required an informed consent, 9 required approval from a Pharmacy and Therapeutics Committee, and 8 required a follow-up procedure for outcome. Drugs included in this policy were for example intravenous immunoglobulins, nitric oxide, cidofovir and daclizumab. For hospitals without an innovative off-label medication use policy, 37 had no leadership to champion the concept, 29 declared that this problem had never been addressed by physicians or pharmacists, 24 had a limited personnel to develop protocols, 10 considered that this issue was not a problem and 7 considered that this issue was the responsibility of the institutional review board.[12]

In our centre, we identified 10 key principles that should govern the use of an emerging drug (Table 3). A request form has been developed, containing justification of the emerging drug use: patient history, indication of use, literature associated with this use and quality of this literature (randomized controlled trials, observational studies, case reports, etc.), treatment regimen (1^{st} to $\geq 4^{th}$ line drug treatment regimen), doses of the emerging drug, efficacy and safety parameters defined by health care providers during multidisciplinary meetings (with clinical outcomes and expected delay to achieve the outcomes). To be considered, the request must be signed and supported by a treating physician and pharmacists. The medical and the pharmacy department directors, in association with a research assistant in charge of emerging drugs, analyze the emerging drug use request including a

TABLE 3 Ten Guiding Principles Governing Emerging Drugs Uses

1.	Indications	An emerging drug use should be directed by scientific support.
2.		An emerging drug should only be used if no efficient and adapted alternative is available.
3.	Guiding principles	A multidisciplinary meeting with a pharmacist and different health care providers should be organized to decide whether or not the drug should be used.
4.		Dosage prescribed should be based on scientific data (monograph, randomized clinical trials, or cohort studies). If unavailable, case reports data should be used.
5.	Process	Informed consent should be obtained from patient or patient's parents.
6.	Monitoring	Efficacy criteria should be defined and frequently monitored.
7.		Safety criteria should be defined and frequently monitored.
8.		A note in medical chart should be written to inform all health care providers that the patient is receiving an emerging drug.
9.		Decision to use an emerging drug should be questioned frequently depending on the efficacy and safety criteria results, to make sure the patient is not exposed to a potentially inefficient or unsafe drug.
10.	Ethics	If several patients receive the same emerging drug for the same unapproved and poorly documented indication, health care providers should write a clinical research protocol and enroll their patients after evaluation by an ethics committee.

literature scan. After approval, the drug is dispensed and health care providers and research assistant monitor defined efficacy and safety endpoints. A list of emerging drugs and indications of uses is available online for prescribers and is updated at every new emerging drug use identified.

The main objective of this new policy is to ensure a safer and more efficient use of emerging drugs for all of our patients, by making sure that all available and approved alternatives are used before an emerging drug is considered. If an emerging drug has to be used, this policy ensures that the drug is used properly, with an adequate efficacy and safety follow-up, and ensures that our pediatric patients are not exposed to inefficient or unsafe drugs.

Further studies, such as the evaluation of the policy 12 months after implementation, will be conducted to improve this new policy. Also, a study comparing this policy to other systems, such as the French system, is being conducted. These studies will allow us to improve this new emerging drugs use policy.

Our study has its limits: emerging drugs were identified retrospectively and a selection bias may be present. As performing a retrospective study, we could only retrieve written information in medical charts. Some information concerning efficacy and safety may have been discussed but not consigned in the patient chart and could not be retrieved. Additionally, only one research assistant reviewed medical charts and some misinterpretation could have occurred. However, the research assistant has been in contact with pharmacists to discuss a posteriori similar cases and a sufficient exposure to patient documentation was offered before the study. Finally, we excluded oncology drugs because a process was already in place in that sector. Delays and other global results may have been different if oncology drugs were included in the evaluation.

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