

# Compassionate drug uses in Italy. Analysis at single-center level

Daniela Pilunni<sup>1</sup>, Maria Erica Blandino<sup>1</sup> and Pierluigi Navarra<sup>2</sup>

<sup>1</sup>Farmacia Prodotti Sperimentali, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>2</sup>Dipartimento di Sicurezza e Bioetica, Sezione di Farmacologia, Facoltà di Medicina e Chirurgia,

Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

## Abstract

**Aims.** Using a database from two pharmaceutical companies that managed several compassionate use programs in the last few years in Italy, we have previously analyzed the data by the number of patients and centers in each region and province, showing that the use of compassionate drugs is largely diffused in the country, in a manner directly related to the size of population of each region. In the present study we used the same database to expand the analysis to single-center level, aiming to test the hypothesis whether, despite a good diffusion of compassionate drug uses in each region, the majority of them concentrates within a relatively low number of centers.

**Methods.** Data from different programs were grouped per center, and the centers were ordered per the number of compassionate uses dispensed, and per region. Two cutoff levels, at 75% and 90%, were drawn to look at the number of centers accounting for such percentages of compassionate uses in each region.

**Results.** Out of 343 centers throughout Italy, 93 and 156 centers (i.e., 27.11% and 45.48% of the total) account for about 75% and 90% of all compassionate drugs dispensed in Italy. In 6 regions out of 20 (Valle d'Aosta, Liguria, Umbria, Lazio, Molise and Campania) the centers accounting for 75% of all compassionate drugs dispensed are located in a single town. Forty and 20 out of the 93 centers dispensing 75% of all compassionate drugs are academic hospitals and research hospitals (Istituti di Ricovero e Cura a Carattere Scientifico, IRCCS), respectively.

**Conclusions.** In this study we have demonstrated that, in spite of widespread diffusion of compassionate drug uses in all Italian regions, their management is restricted to a relatively low number of dispensing centers in each region.

## Key words

- compassionate drug
- compassionate drug use
- early access program
- expanded access program
- Italy

## INTRODUCTION

Compassionate drug use (CDU) is one of the manners to provide unauthorized treatments to patients with no further treatment options, along with the inclusion of patients in clinical trials, off-label prescriptions, or medicine import. Most often, compassionate drugs are given through the inclusion of patients into specific early access programs or expanded access programs (EAPs) managed by the companies producing the drug [1, 2]; this is especially true if the company has already applied, or is going to apply, to get the drug approved in a given indication. Less frequently, the compassionate drug is prescribed for individual use, outside any EAP. In both cases, the company scrutinizes the individual requests for approval, and provides the drug for free [1, 2].

In the European Community (EC) Regulation n. 726/2004, compassionate drugs are referred to as "unauthorized medicinal products" [3]. However, in Italy the notion of compassionate drug includes not only

medicines that are not approved yet in the EC, but also medicines with one or more indications approved by European Medicines Agency (EMA)/EC, whose price has not been negotiated yet with the Italian drug agency (Agenzia Italiana del Farmaco, AIFA). As a matter of fact, the latter category is not available for use in the clinical practice even if approved in the EC.

In a previous study on the CDU requests processed in a big Italian academic hospital in the period 2018-2021 [4], we showed that more than 95% of the CDUs (i.e., 443 out of 463) was concerning drugs with at least one indication approved in the EC. Thus, CDUs (and EAPs) can be taken as an index of the access to *approved* innovative treatments in advance to their availability on the market. In this perspective, we have previously investigated how diffuse CDUs are in Italy by analyzing the databases of two pharmaceutical companies running several EAPs in the last few years in the country [5]. We analyzed the data by region and

district, showing that the use of compassionate drugs is widespread, and is closely related to the population of each region. However, this analysis did not consider the relative weight of centers of excellence and/or large hospitals present into the region. For this reason, in the present study we re-analyzed the above database at single-center level, showing that, despite a good diffusion of CDUs in each region, the large majority of CDUs was managed by a relatively low number of centers.

## MATERIALS AND METHODS

The databases were provided by Bristol Myers Squibb (BMS) Italia and Roche Italia SpA. The data from BMS included seven EAPs and two products, nivolumab and luspatercept, which accounted for five and two EAPs respectively. The data from Roche included ten products, which were provided as compassionate drugs through three (atezolizumab), or two (pralsetinib, risdiplam) or a single EAP (alectinib, emicizumab, entrectinib, glofitamab, ocrelizumab, polatuzumab vedotin and trastuzumab emtansine) respectively, to a total of 14 EAPs. Emicizumab was not included in our analysis since only one patient was treated within the EAP. Overall, twenty EAPs involving twelve products were included in our analysis.

The two databases had similar structure; BMS data were based on the physician requesting the drug, and each string of information included: 1) the name of the physician, 2) the clinical center and 3) the number of patients enrolled in that center.

Roche data were based on the center requesting the drug, and included: 1) the clinical center, 2) the region where the center is located and 3) the number of patients enrolled in that center. Our analysis did not include the physicians.

Twenty-one regions were considered in our analysis, according to the approach used by AIFA, which takes separate the “autonomous provinces” of Bolzano and Trento (actually belonging to the same region, Trentino-Alto Adige) [6]. For each of the 343 prescribing centers, the total number of dispensed CDUs was calculated. The centers were grouped per region and ordered per number of CDUs managed. All statistics used in the study were descriptive.

The number of centers dispensing CDUs in each region are reported from the region with the higher number of dispensing centers downward. Two cutoff thresholds were set at 75% and 90%, respectively.

## RESULTS

Compared to our previous report, which showed 348 centers dispensing CDUs in Italy in the study period [5], in the present re-analysis we found 343 dispensing centers. Careful single-center analysis carried out here let emerge that a number of centers were counted twice in the previous study, accounting for the discrepancy. Likewise, here we counted a slightly lower number of patients (7508 vs the previous 7529). Such 0.28% difference can be considered an acceptable margin of error.

Starting from the region with the higher number of dispensing center, we found that in Lombardy 13 and 23 centers out of 54 account for 75.59% and 90.17% of the CDUs, respectively. In Lazio, 7 and 12 centers out of 32

account for 76.11% and 90.42% of the CDUs, respectively. In Piedmont, 7 and 15 centers out of 32 account for 76.35% and 90.40% of the CDUs, respectively. In Tuscany, 8 and 14 centers out of 31 account for 76.02% and 90.88% of the CDUs, respectively. In Veneto, 7 and 12 centers out of 28 account for 73.65% and 90.14% of the CDUs, respectively. In Sicily, 8 and 13 centers out of 26 account for 73.82% and 90.34% of the CDUs, respectively. In Emilia-Romagna, 7 and 10 centers out of 23 account for 77.84% and 91.82% of the CDUs, respectively. In Puglia, 6 and 11 centers out of 20 account for 76.98% and 91.09% of the CDUs, respectively. In Campania, 4 and 7 centers out of 16 account for 71.95% and 91.10% of the CDUs, respectively. In Marche, 4 and 8 centers out of 13 account for 71.42% and 91.73% of the CDUs, respectively. In Liguria, 1 and 4 centers out of 11 account for 75.26% and 90.94% of the CDUs, respectively. In Abruzzo, 3 and 4 centers out of 11 account for 76.30% and 92.59% of the CDUs, respectively. In Sardinia, 4 and 5 centers out of 9 account for 78.30% and 88.16% of the CDUs, respectively. In Calabria, 4 and 5 centers out of 9 account for 80.00% and 90.59% of the CDUs, respectively. In Friuli Venezia Giulia, 2 and 3 centers out of 8 account for 70.59% and 89.84% of the CDUs, respectively. In Umbria, 1 and 2 centers out of 6 account for 69.86% and 96.17% of the CDUs, respectively. In the autonomous province of Bolzano, 2 centers out of 5 account for 90.90% of the CDUs. In the autonomous province of Trento, 1 center out of 2 account for 96.87% of the CDUs. In Basilicata, 2 and 3 centers out of 3 account for 71.86% and 100.00% of the CDUs, respectively. In Molise, 1 center out of 3 account for 87.50% of the CDUs. In Valle d'Aosta, there is a single center dispensing CDUs.

Detailed data of dispensing center in each region are reported as *Supplementary Material* available online. In these supplementary tables, the centers accounting for about 75% of the CDUs are highlighted in green; additional centers, accounting for up to 90% of the CDUs are highlighted in pale blue.

*Table 1* summarizes the data for the whole country. Overall, 93 centers out of 343 (i.e., 27.11% of the total) account for about 75% (74.82%±2.9%) of CDUs dispensed in Italy, whereas 156 centers out of 343 (i.e., 45.48% of the total) account for about 90% (91.14%±2.2%) of CDUs dispensed in Italy.

## DISCUSSION

In this study we have demonstrated that, despite a good diffusion of CDUs in all Italian regions (with a number of centers involved and patients treated in each region broadly proportional to the inhabitants of the region) [5], the handling of CDUs is restricted to a relatively low number of dispensing centers in each region. In fact, about 75% of all CDUs were managed by less than 30% of the centers, and about 90% of all CDUs were managed by less than 50% of the centers throughout the country. In 6 regions out of 20 (i.e., 30% of total), namely Valle d'Aosta, Liguria, Umbria, Lazio, Molise and Campania, the centers accounting for 75% of dispensed CDUs were concentrated in a single town; this fact has a special relevance for those regions with large

**Table 1**

Centers accounting for the majority (about 75% in column 3, and about 90% in column 4 from the left) of CDUs dispensed in each Region

Region	N. of Centers	N. of Centers accounting for ≈75% of CDUs	N. of Centers accounting for ≈90% of CDUs
Lombardy	54	13	23
Lazio	32	7	13
Piedmont	32	7	15
Tuscany	31	8	14
Veneto	28	7	12
Sicily	26	8	13
Emilia-Romagna	23	7	10
Puglia	20	6	11
Campania	16	4	7
Marche	13	4	8
Liguria	11	1	4
Abruzzo	11	3	4
Sardegna	9	4	5
Calabria	9	4	5
Friuli Venezia Giulia	8	2	3
Umbria	6	1	2
Autonomous province of Bolzano	5	2	2
Basilicata	3	2	1
Molise	3	1	3
Autonomous province of Trento	2	1	1
Valle d'Aosta	1	1	1
<b>Total</b>	<b>343</b>	<b>93 (27.11%)</b>	<b>156 (45.48%)</b>

CDU: compassionate drug use.

populations, i.e., Lazio and Campania, whose major centers are all located in Rome and Naples, respectively.

These findings are somewhat expected, reflecting the hub-and-spoke organizational model of the National Health System (NHS). Consistent with this concept is the fact that 40 out of the 93 centers dispensing 75% of all CDUs are academic hospitals and 20 out of 93 centers are research hospitals (IRCCS), with 8 centers being both academic hospitals and IRCCS.

Which are the drawbacks of this situation? One obvious consideration is that, since CDUs have been defined as an important manner to provide critical patients with innovative treatments, some inequity exists on this regard between the patients living near the major CDUs dispensing centers and those living in less served areas. Again, this condition can be conveyed within the general hub-and-spoke organization model of NHS.

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**Ethics approval**

Ethical approval was not required for this study.

**Authors' contributions**

DP analyzed the data and critically reviewed the manuscript. MEB analyzed the data. PN conceived the study, supervised data analysis and drafted the manuscript.

**Conflicts of interest statement**

The Authors declare no conflict of interest.

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