Compassionate drug uses in Italy. Analysis of regional and local diffusion

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ORIGINAL ARTICLES AND REVIEWS

Abstract
Aims. Compassionate drugs are provided to patients with a specific disease and no further treatment option, most frequently via Early (or Expanded) Access Programs. In Italy, it often occurs that compassionate uses concern medicines whose price has not been negotiated yet (and therefore unavailable on the market), although their use has been approved in Europe. Thus, compassionate drug uses turn out to be a way to expedite the access to new innovative drugs with demonstrated efficacy. This study aims to investigate how widespread is the use of compassionate drugs throughout the Country.
Methods. We analyzed data from 20 early access programs implemented by 2 pharmaceutical companies in the last few years. Data were analyzed by the number of patients and centers in each Region and province, and a correlation was established between patients and centers in each Region and the resident population. A further analysis was carried out with the same criteria on the subpopulation of oncology patients, including more than 80% of total study population.
Results. In our sample, 7529 patients received compassionate drug treatments in 348 centers throughout Italy. A significant correlation exists between the resident population in each Region and the number of requesting centers ($r^2=0.877$) and patients treated ($r^2=0.844$) in the Region. Taking the value of the linear regression slope as the expected one, certain Regions show a better "performance", in terms of more patients treated than expected, namely Umbria, Emilia-Romagna, Lazio, Lombardy, Tuscany, Liguria and Friuli Venezia-Giulia.
Conclusions. In this study we showed that the use of compassionate drugs in Italy is diffused in a manner closely related to the population of each Region. A number of Regions – mostly but not exclusively from the South and Island areas – show a performance below the expectations, in terms of patients treated.

INTRODUCTION

Compassionate Drug Use (CDU) is one of the ways through which patients with a specific disease and no further treatment option can access unauthorized treatments. Compassionate drugs can be given for individual use; more often, the patients are included into specific Compassionate Use Programs (CUPs) [1]. In either case, the Company producing the drug approves the request and covers the cost of treatment [1]. Moreover, in Italy local Ethics Committees are in charge to evaluate and approve CDU requests, provided that the Company has declared the availability to supply the treatment free of charge [2, 3].

Although Italy adhered to the European Community (EC) Regulation n. 726/2004 by issuing a specific act in 2017 [2, 3], the term "unauthorized treatment" is currently interpreted in Italy in a peculiar way, i.e., as a treatment whose price has not been negotiated yet by the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA). Thus, a medicine can be considered as "unauthorized" even though it was approved by the European Medicine Agency (EMA). Proof of this is the fact that many drugs classified as Cnn (C *non negoziato*: hence, virtually available on the Italian market at a free price, waiting for price negotiation) are accessed by patients through CUPs.

We have recently published a study describing CDUs at the Fondazione Policlinico Gemelli in Rome, the largest academic hospital in Italy, in the period 2018-2021 [4]. We found that only 20 out of 463 requests of CDU received in the period under scrutiny were concerning drugs that had no indication approved by EMA/EC at the cutoff date of June 30, 2021 [4]. This finding suggests that the vast majority of CDU requests deals with

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medicines with at least one indication already approved in Europe; thus, CDUs and CUPs can be envisioned as a powerful tool to expedite the access to innovative treatments with demonstrated efficacy, while the complex (and often time-consuming) marketing procedures are still under way.

In such a scenario, it was interesting to investigate how diffuse is the CDU practice in Italy and verify whether the access to innovative treatments granted by CUPs is widespread throughout Italy or it is limited to specific areas. To this end, we have analyzed the databases provided by two pharmaceutical companies which implemented a large number of CUPs in Italy in the last few years.

MATERIALS AND METHODS

The databases were provided by Bristol Myers Squibb (BMS) Italia and Roche Italia S.p.A. Data from BMS included two products, nivolumab and luspatercept, which accounted for five and two CUPs respectively. Data from Roche included ten products, which were provided as compassionate drugs through three (atezolizumab), or two (pralsertinib, risdiplam) or a single CUP (alectinib, emicizumab, entrectinib, glofitamab, ocrelizumab, polatuzumab vedotin and trastuzumab emtansine) respectively, to a total of 14 CUPs. Emicizumab was not included in our analysis since only one patient was treated within the CUP. All the CUPs were closed at the time the Companies provided the data, except for praseltinib CUPs, which are planned to close on October 22, 2022, and glofitamab CUP, which was activated on March 3, 2022, and is currently ongoing. Overall, twenty CUPs 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 treated 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 treated in that Center. Our analysis did not include the physicians.

For each CUP, data were analyzed per number of patients and number of Centers in each Region. Twenty-one Regions were considered, 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) (https://www.istat.it). Since the same Center could be involved in more than one CUP, data were re-analyzed considering any requesting Center regardless of the number of CUPs involving that Center. This second wave of analysis also included the provinces (districts) to which Centers belong. Moreover, data were also analyzed per therapeutic areas, with a special focus on oncology, which accounted for more than 80% of treated patients.

Having defined the number of patients and Centers from each Region, we calculated the correlation between the percent of Italian population resident in each Region, as estimated by the Italian Institute of Statistics (Istituto Nazionale di Statistica, ISTAT) on January 1, 2022 [5], and the regional percentage of patients and Centers over the total in Italy. A sort of "efficiency index" was also obtained for each Region by calculating the ratio between the number of patients and the number of Centers. All statistics used in this study are descriptive, except the correlations between regional populations and the number of Centers and patients in each Region, which required a linear regression analysis carried out with a PrismTM v.6 computer program (GraphPad, San Diego CA, USA).

RESULTS

The drugs and indications included in this analysis are reported in *Table 1*. The products are listed per number of patients enrolled. Out of twenty programs, sixteen involved indications in oncology/onco-hematology (6080 patients, 80.75% of total), three involved neurological/neuromuscular disorders (1246 patients, 16.55% of total) and one involved an indication in non-malignant hematology (203 patients, 2.7% of total). Half of the CUPs had a relatively low number of patients, i.e. less than 200, either because they were concerning rare diseases (e.g., spinal muscular atrophy) or oncology patients with low-incidence diseases or rare mutations, or else because of a recent start of the program.

For each CUP, we analyzed the number of patients (*Table 2*) and Centers (*Table 2S available online as Supplementary Material*) involved in each of the twenty-one Regions. The CUPs are listed in order of magnitude, from the highest number of patients or Centers onward. The tables also report the absolute numbers and the percentages of patients and Centers in the four Italian macro-areas, as defined by AIFA, i.e., North, Center, South and Islands [5].

As explained in Materials and Methods, the above analysis overestimates the number of Centers, since any single Center may be involved in more than one CUPs. At variance, *Table 3* shows the analysis whereby each requesting Center is considered once, regardless of the number of requests coming from that Center. In this analysis, the Centers are reported per Region and per province (district), in order to gain more insight into the diffusion of CDUs throughout the Country.

Table 4 reports the values and their relative percent over the total of the patients and the Centers, as resulting from the analysis shown in *Table 2* and *3*, respectively. Per each Region these data are reported along with the regional population [5] and the relative percent over the total of the country. The ratio between the patients and the Centers per each Region is also reported. These data served to estimate the correlation between the regional population and patients receiving compassionate drugs in that Region (*Figure 1A*) or between the regional population and the requesting Centers in the Region (*Figure 1B*).

There is a good correlation between regional populations and the number of patients treated in each Region (r^2=0.844; Y=1.031X − 0.145); even closer correlation exists between regional populations and the number of requesting Centers (r^2=0.877; Y=0.875X + 0.593). *Figure 1* also shows that some dispersion exists around the

Table 1
Drugs included in the analysis and indications for which a Compassionate Use Program (CUP) was activated

Company	Medicine	Indication	Centers	Patients
BMS	Nivolumab 1	Non-squamous Non-Small Cell Lung Cancer (NSCLC)	187	2186
Roche	Trastuzumab emtansine	HER 2 positive early-stage Breast Cancer (eBC)	206	1248
Roche	Ocrelizumab	Primary Progressive Multiple Sclerosis (PPMS)	85	1045
BMS	Nivolumab 2	Squamous Non-Small Cell Lung Cancer (NSCLC)	113	530
BMS	Nivolumab 3	Renal cell carcinoma (RCC)	108	519
BMS	Nivolumab 4	Unresectable malignant pleural mesothelioma	64	246
Roche	Alectinib	Advanced ALK positive Non-Small Cell Lung Cancer (NSCLC) pretreated with crizotinib	67	226
Roche	Atezolizumab 1	Bladder cancer	68	222
BMS	Luspatercept 1	Transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)	64	215
BMS	Luspatercept 2	Transfusion-dependent anaemia associated with beta-thalassaemia	36	203
BMS	Nivolumab 5	Classical Hodgkin lymphoma (cHL)	68	195
Roche	Polatuzumab vedotin	Patients with relapsed/ refractory diffuse large B cell Lymphoma (r/r DLBCL) ineligible for haematopoietic stem cell transplantation and who have received prior therapy	70	167
Roche	Risdiplam 1	Spinal Muscolar Atrophy 2 (SMA2)	32	152
Roche	Atezolizumab 2	Metastatic non squamous Non-Small Cell Lung Cancer (NSCLC)	47	127
Roche	Atezolizumab 3	Locally advanced or metastatic Triple Negative Breast Cancer (TNBC)	50	94
Roche	Pralsetinib1	Adult patients with unresectable or metastatic RET gene fusion positive Non-Small Cell Lung Cancer (NSCLC) who are not candidates for treatment with approved therapeutic alternatives	30	65
Roche	Risdiplam 2	Spinal Muscolar Atrophy 1 (SMA1)	18	49
Roche	Pralsetinib 2	Adult patients with advanced or metastatic RET mutant medullary thyroid carcinoma (MTC) or RET gene fusion positive thyroid carcinoma requiring systemic therapy who are not candidates for treatment with approved therapeutic alternatives	8	15
Roche	Entrectinib	Metastatic or locally advanced solid tumor with NTRK translocation or Non-Small Cell Lung Cancer with ROS-1 rearrangement	10	14
Roche	Glofitamab	Patients with relapsed/ refractory diffuse large B-cell lymphoma (r/r DLBCL) or relapsed/ refractory high-grade lymphoma (r/r HGL) or relapsed/ refractory transformed follicular lymphoma (r/r trFL) or relapsed/ refractory primary mediastinal lymphoma (r/r PMBCL)	9	11
			1340	7529

theoretical slope, with certain Regions performing "better that expected" (i.e., the observed value is above the theoretical slope) concerning the number of patients treated or Centers or both, and other Regions vice versa (i.e., with the observed value being below the theoretical slope). *Figure 2A* and *B* show the variability over the percent population in each Region.

Figure 3 shows the patients/Centers ratio in each Region. The average ratio in the Country is 21.64 patients per Center. Nine Regions out of twenty-one present ratios higher than the mean for Italy, with Umbria, Emilia-Romagna, Lazio and Campania having more than 30 patients per Center on average.

The analysis on the subpopulation of oncology patients shows a similar trend compared to the general population, with an important difference: the gap between better- and worst-performing Regions is increased, with some Regions performing even better,

namely Emilia-Romagna, Tuscany, Umbria and Friuli-Venezia Giulia, and the other way round for Piedmont, Campania, Puglia and Sicily (*Table 5*). Such increased dispersion around the theoretical slope translates into a weaker correlation between the regional populations and the percent of patients treated ($r^2=0.783$), although the goodness-of-fit remains statistically significant.

DISCUSSION

This investigation included twenty CUPs from two major pharmaceutical companies, and involved twelve new drugs, 348 prescribing Centers and 7529 patients throughout Italy. In its repository on CUPs, AIFA has registered 69 CUPs (including 36 closed programs, 2 temporarily closed programs and 31 ongoing programs) at the cutoff date of July 21, 2022 [6]. In AIFA repository, the number of patients enrolled in the CUPs is not

Table 2
Patients enrolled in Compassionate Use Programs (CUPs) in each Italian Region

DRUGS	North									Center					South					Islands		Total
	PI	VdA	LO	BZ	TN	VE	FVG	LI	ER	TU	UM	MA	LA	AB	MO	CAM	PU	BA	CAL	SI	SA	
Nivolumab 1	60	3	381	11	-	76	56	86	305	265	106	31	359	33	7	90	93	4	22	149	49	2186
Trastuzumab emtansine	95	1	244	19	22	86	17	57	121	92	15	26	148	19	-	93	59	13	18	88	15	1248
Ocrelizumab	72	-	137	6	2	62	10	42	54	19	10	19	183	43	63	120	75	9	11	108	-	1045
Nivolumab 2	12	1	106	-	-	12	14	14	79	62	27	6	56	6	2	52	33	1	3	31	13	530
Nivolumab 3	13	-	83	5	1	31	26	14	83	68	14	15	58	5	-	54	11	-	8	20	10	519
Nivolumab 4	35	-	55	3	-	20	5	17	27	39	5	1	9	-	-	13	7	2	1	2	8	246
Alectinib	13	1	28	-	-	18	12	2	18	28	10	5	54	3	-	14	12	1	-	2	5	226
Atezolizumab 1	15	-	32	3	-	13	11	3	29	55	-	4	18	11	-	11	6	-	2	4	5	222
Luspatercept 1	31	-	64	-	-	4	3	5	15	11	2	9	10	12	-	14	12	-	2	9	9	215
Luspatercept 2	27	-	34	-	-	9	-	1	9	10	1	-	4	-	-	-	28	-	6	29	45	203
Nivolumab 5	9	-	46	-	-	9	1	9	28	10	3	2	16	6	-	23	14	1	5	10	3	195
Polatuzumab vedotin	12	-	19	1	-	11	10	13	19	17	4	2	17	6	-	6	14	1	3	8	4	167
Risdiplam 1	13	-	38	2	4	6	10	9	10	10	1	4	22	-	-	5	11	-	1	4	2	152
Atezolizumab 2	3	-	21	3	-	20	8	1	14	19	1	5	20	3	-	5	1	-	2	1	-	127
Atezolizumab 3	6	-	15	2	3	12	1	6	4	3	-	2	15	-	-	10	4	-	-	11	-	94
Pralsetinib 1	6	-	13	-	-	3	-	1	13	4	5	-	16	-	-	-	1	-	-	-	3	65
Risdiplam 2	5	-	12	-	-	2	2	1	8	-	-	2	8	-	-	7	1	-	-	1	-	49
Pralsetinib 2	-	-	5	-	-	2	-	-	4	-	1	-	3	-	-	-	-	-	-	-	-	15
Entrectinib	4	-	5	-	-	-	-	-	3	1	-	-	-	-	-	-	-	-	1	-	-	14
Glofitamab	1	-	2	-	-	2	1	1	1	-	-	-	-	-	-	-	2	-	-	1	-	11
TOTAL	432	6	1340	55	32	398	187	282	844	713	205	133	1016	147	72	517	384	32	85	478	171	7529
			3576 (47.5%)							2214 (29.4%)					1090 (14.5%)					649 (8.6%)		

PI = Piedmont, VdA = Val d'Aosta, LO = Lombardy, BZ = Autonomous Province of Bolzano, TN = Autonomous Province of Trento, VE = Veneto, FVG = Friuli-Venezia Giulia, LI = Liguria, ER = Emilia-Romagna, TU = Tuscany, UM = Umbria, MA = Marche, LA = Lazio, AB = Abruzzo, MO = Molise, CAM = Campania, PU = Puglia, BA = Basilicata, CAL = Calabria, SI = Sicily, SA = Sardinia.

recorded [6]. Since we analyzed 17 closed programs, our sample represents about 50% of all closed CUPs, which is highly representative of the overall scenario.

After the analysis per Region of the patients and Centers involved in CUPs, we verified the hypothesis that CDUs are evenly diffused in the Country, by correlating the regional data of patients and Centers with the population in each Region. There is indeed a significant relationship between inhabitants on the one hand, and patients and Centers on the other hand (*Figure 1A and B*). Assuming the value corresponding to the theoretical slope as the expected value in each Region, we observed some variability, with: 1) Tuscany, Liguria, Friuli Venezia-Giulia, Umbria and Molise showing more patients and more centers than expected, 2) Lombardy, Lazio and Emilia-Romagna showing more patients and less Centers than expected, 3) Veneto, Piedmont, Marche, Abruzzo, province of Bolzano and Val d'Aosta showing less patients and more Centers than expected, and 4) Campania, Puglia, Sardinia, Sicily, Calabria, Basilicata and province of Trento showing less patients and less Centers than expected (*Figure 2*). In such ranking, those Regions having more patients than expected should be considered as having a good "performance" regardless of the lower number of Centers involved. In fact, enrolling patients within a low number of Centers not necessarily is to be envisioned as a negative paradigm.

Another analysis was carried out looking at the ratio between patients and Centers in each Region (*Figure 3*). Concerning the gap between Regions with better and worst performance, this analysis provided almost overlapping results with the previous analysis, with the only exception of Campania, which presented a high patient/Center ratio in front of a relatively low number of patients enrolled. Taken collectively, the results of regression analysis and the patients/Centers ratios show a trend toward a worst performance in the areas of South and Islands. However, such trend is counterbalanced by negative parameters in such northern Regions as Piemonte, Val d'Aosta, Veneto, and Trentino-Alto Adige. Thus, a clearcut conclusion that Regions of the Center/North Italy are better served than Regions of the South/Island cannot be drawn at this time.

A highly important factor for the diffusion of CDUs in the Country is the presence of Centers of clinical excellence at local level. We haven't carried out a quantitative analysis of this parameter. Here we provide only a paradigmatic example of the relevance of excellence Centers for CDUs: a single Center in Molise (i.e., "Neuromed" based in Pozzilli, district of Isernia) recruited

Table 3
Centers involved in Compassionate Use Programs (CUPs) in each Italian Region and district

Region	Districts and number of requesting Centers												Total
Lombardy	Milan 18	Brescia 7	Bergamo 6	Varese 6	Como 4	Monza 3	Pavia 3	Cremona 2	Sondrio 2	Lecco 1	Lodi 1	Mantova 1	54
Lazio	Rome 27	Latina 3	Frosinone 2	Viterbo 1									33
Piedmont	Turin 15	Cuneo 6	Alessandria 3	Verbania 3	Biella 2	Novara 2	Asti 1	Vercelli 1					33
Tuscany	Florence 9	Siena 7	Pisa 4	Livorno 2	Lucca 2	Prato 2	Arezzo 2	Pistoia 1	Grosseto 1	Massa Carrara 1			31
Veneto	Verona 7	Padova 6	Vicenza 5	Treviso 4	Venice 4	Belluno 2	Rovigo 1						29
Sicily	Catania 8	Messina 5	Palermo 5	Caltanissetta 3	Ragusa 2	Agrigento 1	Siracusa 1	Trapani 1					26
Emilia-Romagna	Modena 5	Bologna 4	Reggio Emilia 3	Rimini 3	Ferrara 2	Parma 2	Ravenna 2	Forlì – Cesena 1	Piacenza 1				23
Puglia	Bari 6	Lecce 5	Taranto 4	Brindisi 3	Foggia 2	BAT 1							21
Campania	Naples 11	Salerno 3	Avellino 1	Benevento 1	Caserta 1								17
Marche	Ancona 4	Pesaro Urbino 3	Ascoli Piceno 2	Fermo 2	Macerata 2								13
Abruzzo	Chieti 5	L'aquila 3	Teramo 2	Pescara 1									11
Liguria	Genova 4	Imperia 3	Savona 3	La Spezia 1									11
Calabria	Catanzaro 3	Cosenza 3	Reggio Calabria 2	Crotone 1									9
Sardinia	Cagliari 5	Sassari 3	Nuoro 1										9
Friuli VG	Udine 3	Pordenone 2	Trieste 2	Gorizia 1									8
Umbria	Perugia 5	Terni 1											6
Trentino (Bolzano)	Bolzano 5												5
Basilicata	Potenza 2	Matera 1											3
Molise	Isernia 2	Campobasso 1											3
Trentino (Trento)	Trento 2												2
Val d'Aosta	Aosta 1												1
													348

Table 4
Absolute values and relative percentages of regional populations, Centers and patients included in Compassionate Use Programs (CUPs) in each Region, with the relevant Patient/Center ratio, in Italy

Region	Population (January 1st, 2022)	% over Italian population	Centers	Centers % of the total in Italy	Patients	Patients % of the total in Italy	Patients/ Centers ratio
Lombardy	9,965,046	16.89	54	15.5	1337	17.8	24.76
Lazio	5,715,190	9.69	33	9.48	1018	13.5	30.85
Campania	5,590,681	9.48	17	4.89	517	6.87	30.41
Veneto	4,854,633	8.23	29	8.33	401	5.29	13.83
Sicily	4,801,468	8.14	26	7.47	478	6.35	18.38
Emilia-Romagna	4,431,816	7.51	23	6.61	844	11.2	32.46
Piedmont	4,252,279	7.21	33	9.48	432	5.74	13.09
Puglia	3,912,166	6.63	21	6.03	384	5.10	18.29

Table 4
Continued

Region	Population (January 1st, 2022)	% over Italian population	Centers	Centers % of the total in Italy	Patients	Patients % of the total in Italy	Patients/ Centers ratio
Tuscany	3,676,285	6.23	31	8.91	713	9.47	23.00
Calabria	1,844,586	3.13	9	2.59	85	1.13	9.44
Sardinia	1,579,181	2.68	9	2.59	171	2.27	19.00
Liguria	1,507,438	2.56	11	3.16	282	3.75	25.63
Marche	1,489,789	2.53	13	3.74	133	1.77	10.23
Abruzzo	1,273,660	2.16	11	3.16	145	1.95	13.18
Friuli Venezia Giulia	1,197,295	2.03	8	2.30	187	2.48	23.37
Umbria	859,572	1.46	6	1.72	205	2.72	34.16
Trentino (Trento)	542,158	0.92	2	0.57	32	0.43	16.00
Basilicata	539,999	0.92	3	0.86	32	0.43	10.66
Trentino (Bolzano)	535,774	0.91	5	1.44	55	0.73	11.00
Molise	290,769	0.49	3	0.86	72	0.96	24
Valle d'Aosta	123,337	0.21	1	0.29	6	0.08	6
TOTAL	58,983,122		348		7529		

63 patients within the CUP for Ocrelizumab, out of 72 patients in total from Molise, in three CUPs. Thus, the activity of a single center in a single CUP placed Molise among the Regions with better performance in Italy. Another aspect somewhat related to the presence and activity of Centers of excellence is the phenomenon of "health tourism", a condition which often sees the involvement of patients needing CDUs because of the lack of therapeutic options. Unfortunately, the available data do not allow to analyze this phenomenon, and its impact on the diffusion of CDUs in the Country.

The analysis per therapeutic areas focused on oncology, which accounted for more than 80% of the whole sample of population. Two important differences emerged compared to the overall sample: 1) there is one less "good performing" Region, i.e., Molise, which recruited 87.5% of the patients in a non-oncologic area; 2) the gap between "good performing" and "bad-performing" Region is increased, as shown in *Table 5*.

In conclusion, this study shows that thousands of patients with limited therapeutic options could take advantage from CDUs in the last few years in Italy. Diffusion of CDUs throughout the Country is widespread, in close correlation to the density of population in each Region. Regions with a larger number of patients treated also show a higher number of requesting Centers, and/or a higher patients/Centers ratio. Based on these parameters, certain Regions can be envisioned as "better performing", namely Umbria, Emilia-Romagna, Lazio, Lombardy, Tuscany, Liguria and Friuli Venezia-Giulia. The role of the Centers of clinical excellence in such performances has been briefly discussed.
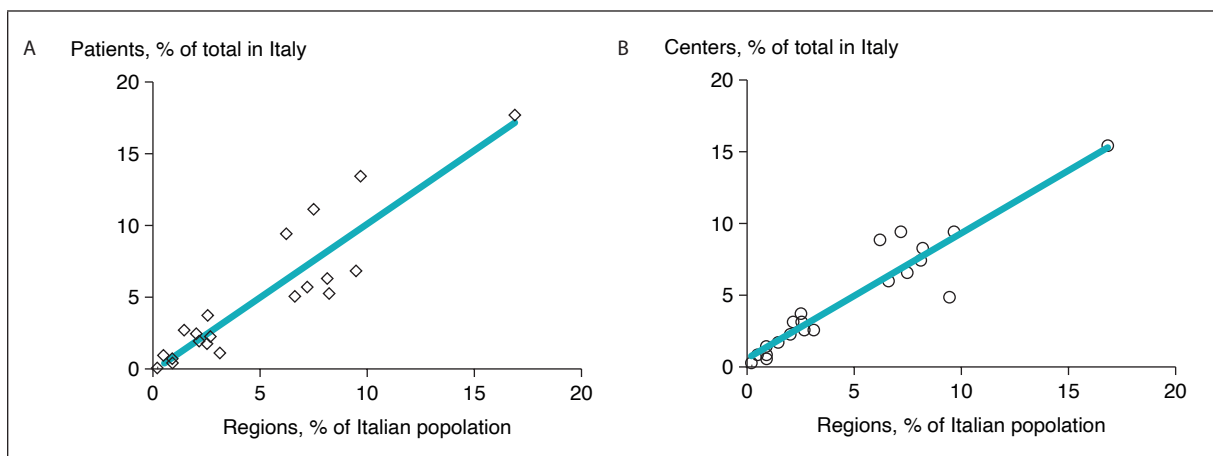

Figure 1
Panel A: The number of patients treated with compassionate drugs in each Region (on the Y axis) is directly related to the number of inhabitants in the Region (on the X axis). Panel B: The number of Centers recruiting each Region (on the Y axis) is directly related to the number of inhabitants in that region (on the X axis). Data are expressed as the percent of total population in Italy.
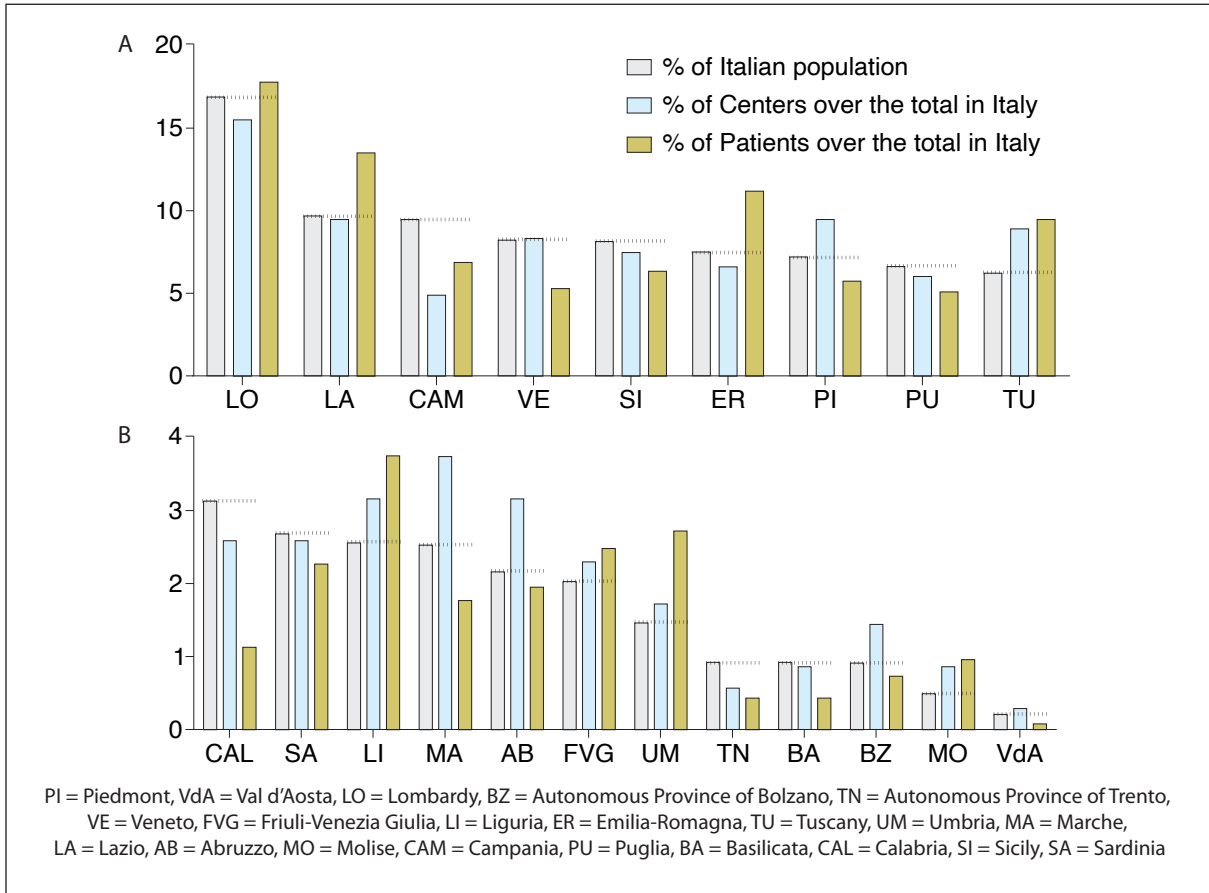
Figure 2

The figure shows the number of inhabitants, of recruiting Centers, and of patients treated with compassionate drugs in each Region. All data are expressed as percentages over the total in Italy. Panel A: Regions with more than 3.5-million inhabitants. Panel B: Regions with less than 2-million inhabitants.
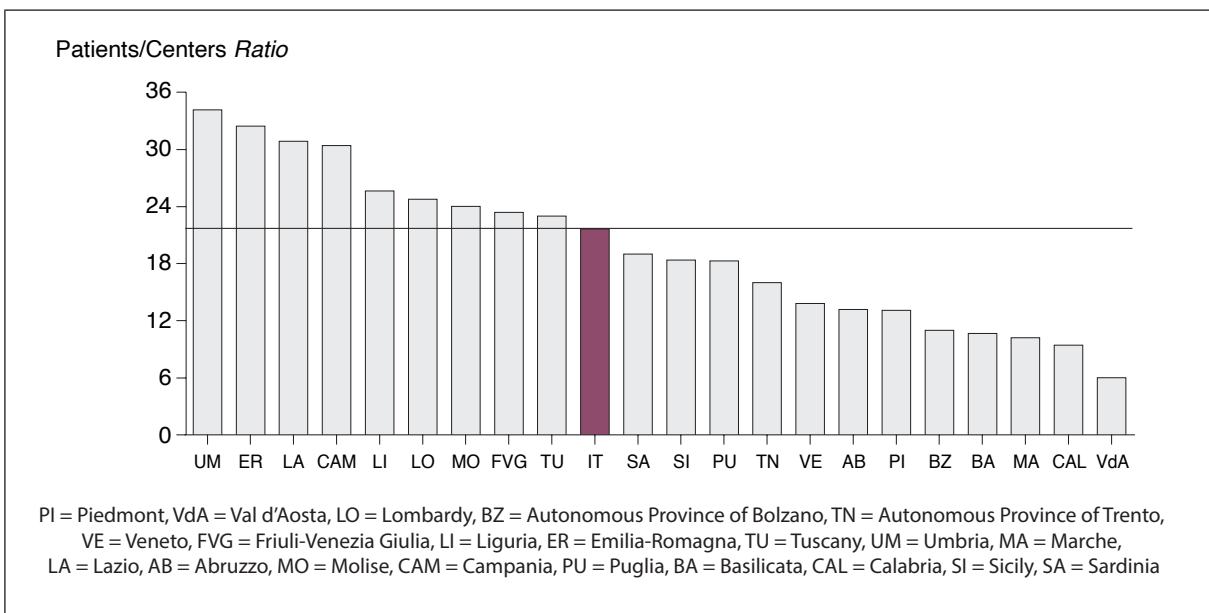

Figure 3

The figure shows the ratio between the number of patients treated and the number of centers in each Region. The value for Italy is reported in red.

Table 5
Analysis of the subpopulation of oncology patients in Italy

Region	Population (January 1st, 2022)	% over Italian population	Patients	Patients % of the total in Italy		Oncology patients	Oncology patients % of the total in Italy	
Lombardy	9,965,046	16.89	1337	17.8	+ 0.91%	1119	18.04	+ 1.15%
Lazio	5,715,190	9.69	1018	13.5	+ 3.81%	799	13.14	+ 3.45%
Campania	5,590,681	9.48	517	6.87	- 2.61%	385	6.33	- 3.15%
Veneto	4,854,633	8.23	401	5.29	- 2.94%	319	5.24	- 2.99%
Sicily	4,801,468	8.14	478	6.35	- 1.79%	336	5.52	- 2.62%
Emilia-Romagna	4,431,816	7.51	844	11.2	+ 3.99%	763	12.5	+ 4.99%
Piedmont	4,252,279	7.21	432	5.74	- 1.47%	315	5.18	-2.03%
Puglia	3,912,166	6.63	384	5.10	- 1.53%	269	4.42	- 2.21%
Tuscany	3,676,285	6.23	713	9.47	+3.24%	674	11.1	+ 4.80%
Calabria	1,844,586	3.13	85	1.13	- 2.00%	67	1.1	- 2.03%
Sardinia	1,579,181	2.68	171	2.27	- 0.41%	124	2.04	- 0.64%
Liguria	1,507,438	2.56	282	3.75	+ 1.19%	229	3.76	+ 1.20%
Marche	1,489,789	2.53	133	1.77	- 0.76%	108	1.77	- 0.76%
Abruzzo	1,273,660	2.16	145	1.95	- 0.21%	104	1.71	- 0.45%
Friuli Venezia Giulia	1,197,295	2.03	187	2.48	+ 0.45%	165	2.71	+ 0.68%
Umbria	859,572	1.46	205	2.72	+ 1.26%	193	3.17	+ 1.71%
Trentino (Trento)	542,158	0.92	32	0.43	- 0.49%	26	0.42	- 0.50%
Basilicata	539,999	0.92	32	0.43	- 0.49%	23	0.38	- 0.54%
Trentino (Bolzano)	535,774	0.91	55	0.73	- 0.18%	47	0.77	- 0.14%
Molise	290,769	0.49	72	0.96	+ 0.47%	9	0.15	- 0.34%
Valle d'Aosta	123,337	0.21	6	0.08	- 0.13%	6	0.1	- 0.11%
TOTAL	58,983,122		7529			6080		

Authors' contributions

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

Conflicts of interest statement

The Authors declare no conflict of interest.

REFERENCES

1. Watson TA. Global perspective on compassionate use and expanded access. Ther Innov Regul Sci. 2017;51:143-5. doi: 10.1177/2168479017694848
2. European Medicines Agency. Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (Ec) No 726/2004. London: EMEA; 2007.
3. Ministero della Salute. Decreto 7 settembre 2017. Disciplina dell'uso terapeutico di medicinale sottoposto a sperimentazione clinica (17A07305). Gazzetta Ufficiale – Serie Generale n. 256, 2 novembre 2017. Available from: www.gazzettaufficiale.it/eli/id/2017/11/02/17A07305/SG.
4. Pilunni D, Daloisio V, Campopiano R, Pani M, Navarra P. Compassionate drug uses and saving for the national health system: the case study of Fondazione Policlinico Gemelli. Eur Rev Med Pharmacol Sci. 2021;25:6365-77. doi: 10.26355/eurrev_202110_27010
5. Agenzia Italiana del Farmaco. L'uso dei farmaci in Italia. AIFA; 2022. Available from: www.aifa.gov.it/uso-dei-farmaci-in-italia.
6. Agenzia Italiana del Farmaco. Farmaci a uso compassionevole. AIFA; 2022. Available from: www.aifa.gov.it/farmaci-a-uso-compassionevole.