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SHORT COMMUNICATION

Prevalence of Use and Cost of Biological Drugs for Cancer Treatment: A 5-Year Picture from Southern Italy

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Abstract

Background and Objectives Considering the clinical and economic burden of biological and non-biological targeted therapies in cancer treatment, it is necessary to explore how these drugs are used in routine care in Italy and how they affect the sustainability of the National Health Services. This study aimed to investigate the prevalence of use and costs of biological and non-biological targeted therapies for cancer treatment in a general population of Southern Italy in the years 2010–2014.

Methods This was a retrospective, observational study using data from the healthcare administrative databases of Messina Province for the years 2010–2014. In this study, users of biological and non-biological targeted therapies for cancer treatment were characterized and the prevalence of use and costs were calculated over time. The potential impact of biosimilars on the expenditure was also estimated.

Results Of a population of 653,810 residents in the Messina area during the study years, 2491 (0.4%) patients received at least one study drug. The most frequently used were monoclonal antibodies (mAbs) ($n = 1607$; 64.5%) and tyrosine kinase inhibitors (TKIs) ($n = 609$; 24.4%). mAbs were mainly used by females (60.3%) for metastasis due to an unspecified primary tumor, lymphomas, or breast cancer (24.2, 16.7, and 13.7%, respectively). Most users of small molecules were males (56.3%) being treated for multiple myeloma, metastasis due to unspecified primary tumor, leukemia, and lung cancer (13.1, 12.6, 9.5, and 8.9%, respectively). During the study years, the prevalence of use doubled from 0.9 to 1.8 per 1000 inhabitants; likewise, the related expenditure grew from €6.6 to €13.6 million. Based on our forecasts, this expenditure will grow to €25 million in 2020. Assuming a 50% biosimilar uptake (trastuzumab and rituximab), a potential yearly saving of almost €1 million may be achieved.

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Conclusions In recent years, the use and costs of biological and non-biological targeted therapies in cancer patients dramatically increased in a large population from Southern Italy. This trend may be counterbalanced by adopting biosimilars once they are available. Claims databases represent a valid tool to monitor the uptake of newly marketed biological drugs and biosimilars as well as other non-biological targeted therapies.

Key Points

In recent years, the use of biological and non-biological targeted therapies for cancer treatment rapidly increased and the corresponding costs almost doubled from €6.6 to €13.6 million.

Based on our forecasts, this expenditure will grow to €25 million in 2020 and the use of biosimilars may provide an annual savings of around €1 million.

Claims databases may represent a valid tool for monitoring the uptake of newly marketed biological drugs and biosimilars as well as other innovative targeted therapies.

1 Introduction

Biological drugs contain one or more active substances that may be produced or extracted from a biological system or through biotechnological procedures [1, 2]. In recent years, biological drugs have dramatically changed the pharmacological management of several high-burden diseases including specific cancer types. Most of the recently marketed drugs in oncology are monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs), which are highly innovative as they target specific molecules necessary for tumor growth and progression [3].

Considering the clinical and economic burden of biological and non-biological targeted therapies in cancer treatment, it is necessary to explore how these drugs are used in routine care and how they affect the sustainability of the National Health Services (NHSs). Once a biological drug loses its patent, the corresponding biosimilar may enter the market, thus guaranteeing an average 20–30% lower purchase cost than originators [4]. To date, the only biosimilar that has been approved by the European Medicines Agency (EMA) for cancer treatment is rituximab (2017), while trastuzumab and bevacizumab biosimilars are still currently under review [5].

The marketing of biosimilars may represent a great opportunity for saving money [6], and post-marketing monitoring systems using real-world data may be helpful for the assessment of their impact in clinical practice.

The aim of this retrospective, observational study was to analyze the use and costs of biological and non-biological targeted therapies for cancer treatment in a large area of Southern Italy in the years 2010–2014. In addition, possible economic savings due to the marketing of biosimilars for cancer treatment in future years was estimated.

2 Methods

2.1 Data Source

This retrospective, observational study was conducted using data extracted from the healthcare administrative databases of the Messina Local Health Unit, "G. Martino" Hospital, and Papardo Hospital during the years 2010–2014 (from 2011 to 2014 for Papardo Hospital). Each of these centers provided information on the total use of biological and non-biological targeted therapies for cancer treatment from all residents in Messina Province (Southern Italy).

In each center, specific databases collect anonymous data related to all the drugs that are reimbursed by the NHS and dispensed to both inpatients and outpatients. Data on drugs dispensed to inpatients are recorded by the specific ward as aggregate data (not at individual level), and were therefore not used for this study. In outpatients, systemic targeted therapies administered as subcutaneous injections or orally are dispensed by the hospital pharmacists to the patient, who will self-administer the drug. Systemic targeted therapies administered as an intravenous infusion are administered exclusively in the hospital setting, even to outpatients. However, the dispensing of biological and non-biological targeted therapies to outpatients is recorded at patient level through the dispensing database, which is routinely populated by the hospital pharmacy. This database includes data about the dispensed drug (i.e., market authorization code, brand name, Anatomical Therapeutic Chemical [ATC] classification system code, number of dispensed packages), the patient (date of birth, sex, citizenship, potential co-payment exemption codes), date of dispensing, and costs.

Each of the three centers has its own dispensing data flow, which is independent from that of the other centers. Furthermore, dispensing databases are generated for administrative reasons, and they routinely undergo quality checks in order to avoid duplicates. Users of the study drugs were identified and assigned an anonymous and unique identifier, thanks to which data from other claims

databases including hospital discharge diagnoses were able to be linked.

Claims databases containing hospital discharge diagnosis are coded using the *International Classification of Diseases, 9th revision, Clinical Modification* (ICD9-CM).

2.2 Study Population

All residents in the catchment area of Messina Province during the years 2010–2014 were considered for this study. From this source population, all patients receiving at least one dispensing of any of the study drugs during the study period were identified.

2.3 Study Drugs

The biological and non-biological targeted therapies approved for cancer treatment and available in Italy during the study years were classified into mAbs, fusion proteins, immunomodulatory agents, and small molecules, the latter being further categorized as TKIs, mammalian target of rapamycin inhibitors (mTOR-i), and proteasome inhibitors. A complete list of the study drugs and related indications for use is available in Electronic Supplementary Materials Table S1.

2.4 Data Analysis

Data on the users of the study drugs were entirely anonymized and pooled. The index date (ID) was identified as the first date of a study drug being dispensed during the study years.

As the overall population is dynamic during a calendar year, the prevalence of the study drugs use was calculated as the number of study drug users (i.e., patients receiving at least one study drug during the years 2010–2014) divided by the estimate of the total number of residents in the catchment area provided by the National Statistics Office for each study year, stratified by calendar year and type of drug. For each calculated prevalence of use, lower and upper bounds of the corresponding 95% confidence interval were computed following the Wilson score interval [7]. In addition, the pharmaceutical expenditure for the study drugs was measured over time and stratified by type of drug.

Users of different types of study drugs were characterized in terms of age and sex, type of cancer, and previous use of chemotherapeutics. The type of cancer was identified based on the last ICD9-CM diagnosis code of tumor registered in the hospital discharge diagnosis database within 6 months prior to the ID. Distinction between a primary (i.e., the original site of the tumor) and secondary tumor (i.e., any additional sites where the tumor has spread, also called metastases of primary tumors) was possible using the specific ICD9-CM codes. The median number of dispensings per patient was calculated.

Moreover, costs related to dispensing the study drugs were calculated over time and the expected expenditure sustained by public hospitals in the Messina area until 2020 was predicted. Data on the pharmaceutical expenditure for the study drugs in the years 2015–2016 were provided by the centers included in this study. Given the available cost-related information for the years 2010–2016, a linear trend (which expresses data as a linear function of time) in the expenditure sustained by the three centers in the Messina area was estimated (equation: $y = 2E + 06x + 5E + 06$; $R^2 = 0.9966$). In particular, it allowed us to determine whether measurements exhibit an increasing trend that is statistically distinct from random behavior. Through statistical extrapolation of data for the years 2017–2020 (in respect of assumption of a linear trend, independence of observations, and homoscedasticity), the baseline trend was calculated (scenario n. 1). Considering the impact of rituximab and trastuzumab on the yearly expenditure (35%), we calculated the pharmaceutical expenditure until 2020, assuming that both biosimilar rituximab and trastuzumab were 25% cheaper than the corresponding reference products and hypothesizing an uptake equal to 20, 50, and 80% of the total amount of consumption of the two biological drugs (scenarios n. 2, 3, and 4, respectively,).

2.5 Ethics Statement

This study was conducted in the context of the "Progetto Osservazionale sulla Psoriasi–SOPso" project. The study protocol was notified to the Ethical Committee of the Academic Hospital of Messina, in agreement with current national legislation [8]. This study received unconditional funding from Novartis, which did not interfere in any stage of the study.

All statistical analyses were conducted using SAS® for Windows, Version 9.3 (SAS Institute, Cary, NC, USA). Figures were created using Microsoft Office (Microsoft Corp., Redmond, WA, USA).

3 Results

Overall, of a total population of 653,810 residents in the catchment of the Messina area during the years 2010–2014, 2491 (0.4%) patients had at least 6 months of database history and received at least one study drug for cancer treatment.

The most frequently used drugs were mAbs ($n = 1607$; 64.5%), followed by TKIs ($n = 609$; 24.4%) (Table 1). mAbs were mostly dispensed for the treatment of

Table 1 Characteristics of users of monoclonal antibodies and other non-biological targeted therapies (i.e. small molecules) for cancer treatment in the years 2010–2014 in Messina Province

Characteristic	mAbs $n = 1607$	Small molecules				Total $n = 2491$
		TKIs $n = 609$	Proteasome inhibitors $n = 203$	mTOR-i $n = 72$	Total $n = 884$	
Sex						
Male	638 (39.7)	382 (62.7)	95 (46.8)	21 (29.2)	498 (56.3)	1136 (45.6)
Female	969 (60.3)	227 (37.3)	108 (53.2)	51 (70.8)	386 (43.7)	1355 (56.4)
Age (years) [median (Q1–Q3)]	62 (53–71)	65 (56–74)	70 (61–77)	63 (54.5–71.5)	67 (58–75)	64 (54–72)
Age categories (years)						
< 45	158 (9.8)	44 (7.2)	3 (1.5)	4 (5.6)	51 (5.7)	209 (8.4)
45–64	759 (47.2)	246 (40.4)	60 (29.6)	35 (48.6)	341 (38.6)	1100 (44.2)
65–79	589 (36.7)	265 (43.5)	113 (55.7)	26 (36.1)	404 (45.7)	993 (39.9)
≥ 80	101 (6.3)	54 (8.9)	27 (13.3)	7 (9.7)	88 (10.0)	189 (7.5)
Follow-up (days) [median (Q1–Q3)]	327 (130–595)	313 (91–867)	320 (132–644)	225 (69–358.5)	305 (95.5–777)	319 (119–640)
Number of dispensing of the study drugs at ID [median (Q1–Q3)]	7 (3–14)	4 (2–12)	16 (8–25)	3 (1–6)	5 (2–16)	6 (3–14)
Type of cancer[a]						
Lymphatic tissue[b]	268 (16.7)	2 (0.3)	3 (1.5)		5 (0.6)	273 (11.0)
Breast (female)	220 (13.7)	10 (1.6)		4 (5.6)	14 (1.6)	234 (9.4)
Colorectal	148 (9.2)	3 (0.5)			3 (0.3)	151 (6.1)
Leukemia	77 (4.8)	84 (13.8)			84 (9.5)	161 (6.5)
Lung	24 (1.5)	79 (13.0)			79 (8.9)	103 (4.1)
Liver cancer	5 (0.3)	48 (7.9)			48 (5.4)	53 (2.1)
Multiple myeloma	4 (0.2)		116 (57.1)		116 (13.1)	120 (4.8)
Metastasis of unspecified primary tumor	389 (24.2)	102 (16.7)	1 (0.5)	8 (11.1)	111 (12.6)	500 (20.1)
Other types of cancer[c]	124 (7.7)	55 (9.0)	14 (6.9)	5 (6.9)	74 (8.4)	198 (7.9)
Not reported	348 (21.7)	226 (37.1)	69 (34.0)	55 (76.4)	350 (39.6)	698 (28.0)
Previous chemotherapy[d]						
Number of chemotherapeutics						
0	916 (57.0)	517 (84.9)	193 (95.1)	34 (47.2)	744 (84.2)	1660 (66.6)
1	220 (13.7)	49 (8.0)	9 (4.4)	34 (47.2)	92 (10.4)	312 (12.5)
2–3	422 (26.3)	42 (6.9)	1 (0.5)	4 (5.6)	47 (5.3)	469 (18.9)
≥ 4	49 (3.0)	1 (0.2)			1 (0.1)	50 (2.0)
Type of chemotherapeutics						
Cyclophosphamide	342 (21.3)	1 (0.2)	1 (0.5)		2 (0.2)	344 (13.8)
Fluorouracil	234 (14.6)	1 (0.2)		1 (1.4)	2 (0.2)	236 (9.5)
Doxorubicin	153 (9.5)		7 (3.9)	4 (5.6)	11 (1.2)	164 (6.6)
Epirubicin	161 (10.0)	1 (0.2)			1 (0.1)	162 (6.5)
Docetaxel	128 (8.0)	17 (2.8)		2 (2.8)	19 (2.1)	147 (5.9)
Vincristine	99 (6.2)		2 (1.0)		2 (0.2)	101 (4.1)
Oxaliplatin	71 (4.4)			1 (1.4)	1 (0.1)	72 (2.9)
Capecitabine	40 (2.5)	14 (2.3)		4 (5.6)	18 (2.0)	58 (2.3)
Paclitaxel	51 (3.2)	1 (0.2)		3 (4.2)	4 (0.5)	55 (2.2)
Gemcitabine	12 (0.7)	34 (5.6)		2 (2.8)	36 (4.1)	48 (1.9)
Vinorelbine	14 (0.9)	23 (3.8)		7 (9.7)	30 (3.4)	44 (1.8)
Carboplatin	17 (1.1)	24 (3.9)		1 (1.4)	25 (2.8)	42 (1.7)
Triptorelin	32 (2.0)	5 (0.8)		2 (2.8)	7 (0.8)	39 (1.6)
Fulvestrant	19 (1.2)			10 (13.9)	10 (1.1)	29 (1.2)

Table 1 continued

Characteristic	mAbs $n = 1607$	Small molecules				Total $n = 2491$
		TKIs $n = 609$	Proteasome inhibitors $n = 203$	mTOR-i $n = 72$	Total $n = 884$	
Bendamustine	27 (1.7)					27 (1.1)
Fludarabine	25 (1.6)					25 (1.0)
Others[e]	54 (3.4)	24 (3.9)	2 (1.0)	6 (8.3)	32 (3.6)	86 (3.5)

Data are given as *n* (%) unless otherwise specified

Patients ($n = 8$) who were dispensed two different drugs at the index date were excluded

Patients ($n = 2$) whose sex and age were not available were excluded

No users of fusion proteins or immunomodulatory agents could be identified during the study years, and these two drug categories are therefore not included

ID index date, *mAb* monoclonal antibodies, *mTOR-i* mammalian target of rapamycin inhibitors, *Q1–Q3* interquartile range, *TKIs* tyrosine-kinase inhibitors

[a]Type of cancer refers to the last cancer diagnosis registered within 6 months prior to the first dispensing of the study drugs, during the study period

[b]Neoplasms of lymphatic tissue include lymphosarcoma and reticulosarcoma, Hodgkin's disease, non-Hodgkin's lymphoma

[c]Other neoplasms include neoplasms of peritoneum, eye, brain, thyroid, bones and connective tissue, genitourinary system, pancreas, respiratory organs (other than lungs), skin, carcinomas in situ, monoclonal gammopathy, prostate, benign neoplasm, breast (males), bladder and kidney, esophagus, stomach, duodenum, trachea, larynx, nasal cavities and neoplasms of unspecified nature

[d]Chemotherapeutics were identified within 6 months prior to the first dispensing of the study drugs, during the study period

[e]Other chemotherapeutics include cisplatin, pemetrexed, vinblastine, temozolomide, bleomycin, dacarbazine, methotrexate, etoposide, eribulin, topotecan, azacitidine, cabazitaxel, mitoxantrone, tegafur, vindesine, fotemustine

metastasis due to unspecified primary tumor (24.2%), lymphomas (16.7%), breast cancer (13.7%), and colorectal cancer (9.2%); most mAb users were females (60.3%) and were 45–64 years old (47.2%). Small molecule users were more likely to be males (56.3%) and to be slightly older (65–79 years old; 45.7%), and were receiving the study drugs mostly due to multiple myeloma, metastasis due to unspecified primary tumor, leukemia, and lung cancer (13.1, 12.6, 9.5, and 8.9%, respectively). No users of fusion proteins or immunomodulatory agents could be identified during the study years, and these two categories are therefore not included in Table 1.

During the study years, the total prevalence of use of study drugs for cancer treatment doubled from 0.9 (in 2010) to 1.8 (in 2014) per 1000 inhabitants, mostly due to the increased use of small molecules (+ 120.8%) rather than mAbs (+ 88.4%) (Fig. 1, Electronic Supplementary Material Table S2).

Accordingly, the costs of the biological and non-biological targeted therapies for cancer treatment rapidly grew during the study years in Messina Province from €6.6 million in 2010 ($n = 591$) to €13.6 million in 2014 ($n = 1150$), with a total expenditure of around €50 million during the five observation years (Fig. 2). Likewise, the number of different biological and non-biological targeted therapies that were prescribed to the study population increased from 17 in 2010 to 21 in 2014 (data not shown).

In 2020, based on our predictions, the expenditure for monoclonal antibodies and other non-biological targeted therapies will grow to €25 million. Assuming a 50% uptake for trastuzumab and rituximab biosimilars, in 2020 a potential yearly saving of more than €1 million may be achieved in the Messina Province (Fig. 3). Even if the uptake of the two biosimilars peaked at 20%, a yearly potential saving of more than €400,000 may still be achieved. On the other hand, wider uptake (80%) may allow a yearly saving of around €1.7 million (Fig. 3).

4 Discussion

To our knowledge, this is the first observational study investigating the prevalence of use and the costs of monoclonal antibodies and other non-biological targeted therapies in oncology in a large area of Southern Italy using administrative healthcare databases.

Our results showed a dramatic increase in biological and non-biological targeted therapies use in oncology, considering both mAbs and small molecules. These data are in line with the National Report on Medicines Use in Italy in 2015 [9], which described an 18.2% increase in mAb consumption (ATC I level: L) in comparison with the previous year. There may be different reasons to explain the increasing number of cancer patients using the study

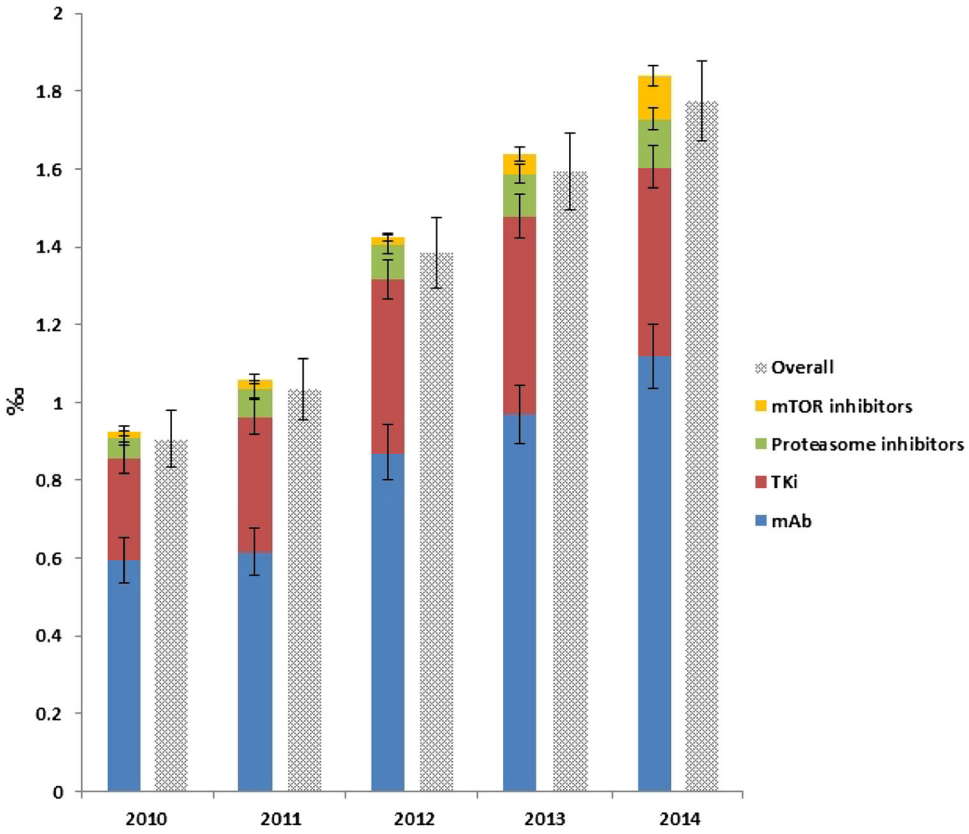

Fig. 1 Prevalence of biological and non-biological targeted therapies use for cancer treatment per 1000 inhabitants, stratified by calendar year. *mAb* monoclonal antibodies, *mTOR* mammalian target of rapamycin, *TKI* tyrosine kinase inhibitors

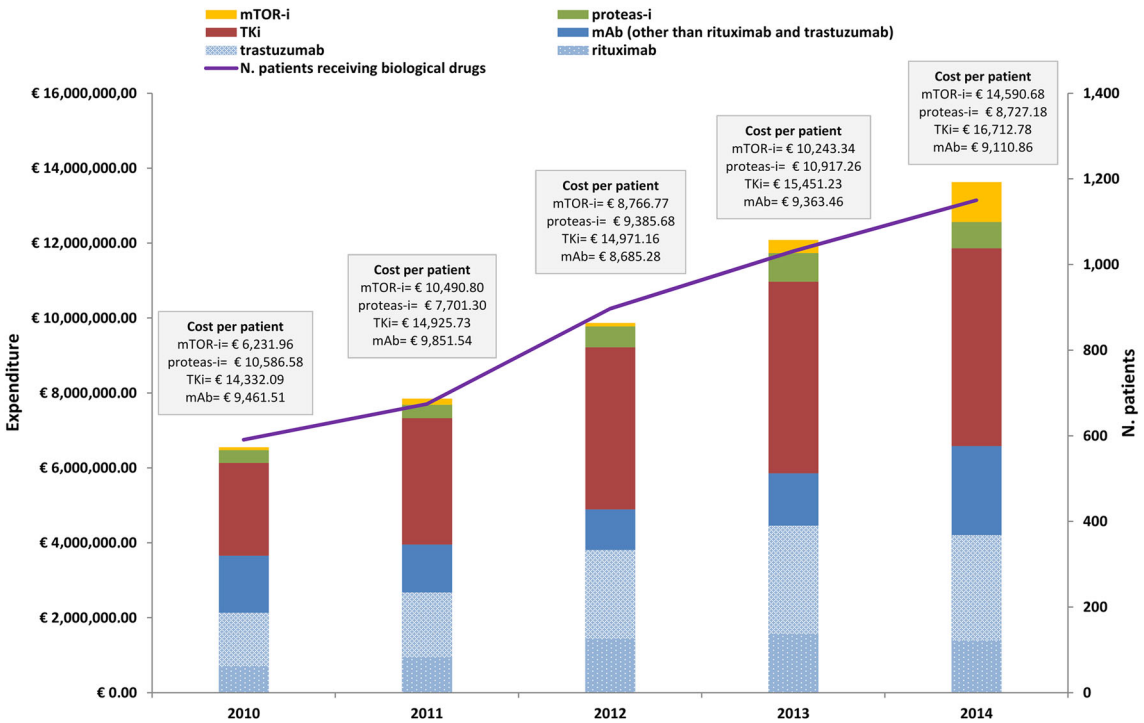

Fig. 2 Expenditure for the dispensing of biological and non-biological targeted therapies in oncology in Messina Province in the years 2010–2014, stratified by calendar year and type of drug. *mAb* monoclonal antibodies, *mTOR-i* mammalian target of rapamycin inhibitors, *proteas-i* proteasome inhibitors, *TKI* tyrosine kinase inhibitors

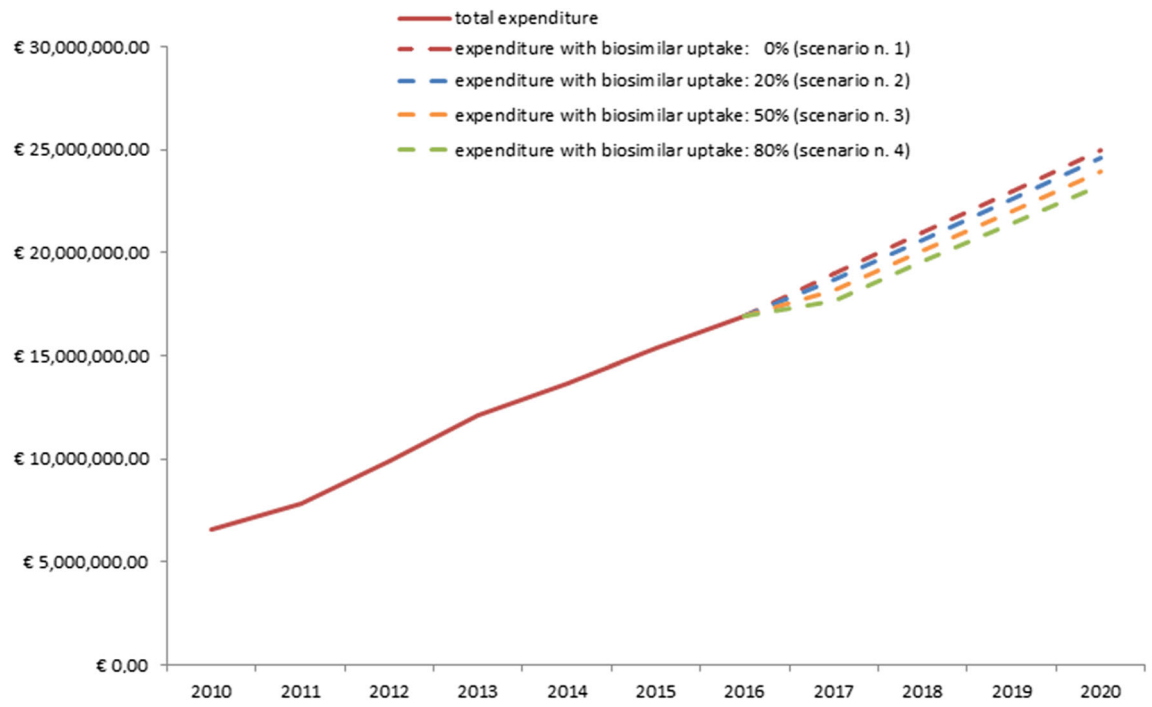

Fig. 3 Prevision of expenditure for biological and non-biological targeted therapies for cancer treatment in Messina area, assuming an uptake of trastuzumab and rituximab biosimilars of 0, 20, 50, and 80%

drugs. In recent years, an increasing number of biological and non-biological targeted therapies have been marketed in Italy, as confirmed by the increasing number of different ATCs for cancer treatment dispensed in Messina during the study years (from 17 in 2010 to 21 in 2014; data not shown). Furthermore, many biological and non-biological targeted therapies already approved for cancer treatment gained an extension to their indications of use, thus guaranteeing access to these innovative therapies to a larger number of patients. We observed an increase in the number of prevalent users over time, despite a decrease in the proportion of incident users (from 61.4% in 2011 to 54.4% in 2014; data not shown). These results reflect a growing number of patients taking monoclonal antibodies and other non-biological targeted therapies (small molecules) for a longer period of time, rather than an increase in those initiating treatment. During the study years, no users of fusion proteins or immunomodulatory agents could be identified. Specifically, use of aflibercept has only been approved in Sicily since November 2014 and we therefore could not identify any users of this drug. Due to their costs, many targeted therapies in oncology are included among the top 30 molecules for drug expenditure sustained by public hospitals, with trastuzumab, bevacizumab, and rituximab being the top three.

Rituximab lost its patent in 2013 and a biosimilar has been available on the European market since 2017, while biosimilars of trastuzumab and bevacizumab are currently under review by the EMA and will probably enter the market in the near future. In the USA, a bevacizumab biosimilar was approved in September 2017 [10], rituximab lost its patent in 2016 and the trastuzumab patent will expire in 2019 [11].

The assumptions taken into account for the forecast of the expected expenditure on monoclonal antibodies plus other non-biological targeted therapies in oncology until 2020 are as follows:

1. Biosimilars have been available on the European and Italian market since 2006 and they guarantee a 20–30% lower cost than the reference product [12]. Such cost reductions may reach significantly higher percentages when a larger uptake of biosimilars occurs, as demonstrated in Norway with infliximab [13]. When originally marketed in Italy, the biosimilars were around 25% cheaper than the corresponding reference products.
2. Biosimilar rituximab was marketed in Europe in 2017, trastuzumab has lost its patent and the corresponding biosimilar is under review by the EMA, while bevacizumab will lose its patent in 2022, although its biosimilar is already under review by the EMA [5, 14].
3. In recent years, several observational studies have evaluated the uptake of biosimilars in different Italian regions, highlighting a relevant heterogeneity across geographic areas [15, 16]. Results showed that the uptake of biosimilars ranged from 25 to 45% for

epoetins and from 25% to almost 90% for granulocyte colony-stimulating factors, depending on the region considered. This heterogeneity is likely to be due to different healthcare policy interventions promoting the use of the cheapest biological drug and to the skepticism of clinicians regarding the effectiveness and safety of biosimilars.

In 2016, a survey was conducted in Italy to explore clinicians' perceptions of biological drugs and biosimilars [17]. Most of the interviewed clinicians (60%) were rheumatologists, nephrologists, diabetologists, dermatologists, oncologists, gastroenterologists, and endocrinologists. Considering naïve patients, 27% of those interviewed usually prescribe an originator biological drug. Concerning patients already receiving treatment with biological drugs, 19% of the clinicians switched the therapy due to non-clinical reasons, i.e., to contribute to the sustainability of the NHS or to respect specific healthcare policies promoting the use of the cheapest biological drug. Only 28% of those interviewed consider biosimilars to be as effective and safe as the reference products.

In order to realistically predict expenditure, we assumed a 25% reduction in the purchase costs of those biological drugs for which the biosimilars are or will be available by 2020 (rituximab and trastuzumab). Considering the observed variability in the uptake of biosimilars, we hypothesized four different scenarios, assuming an uptake equal to 0, 20, 50, or 80% of the total consumption of the two biological drugs.

Assuming a 50% uptake of the biosimilars only for these two anticancer biological drugs, a potential saving of at least €1 million yearly in Messina Province was hypothesized, thus representing an important strategy to mitigate the constantly increasing expenditure for biological drugs in cancer treatment. However, the predicted expenditure in scenario n. 1 (Fig. 3) may be overestimated due to the potential decrease in the cost of the reference products after patent expiration. On the other hand, the future marketing of innovative and highly priced drugs for the treatment of cancer will likely increase pharmaceutical expenditure. In addition, patients treated first with the study drugs or with the biosimilars may switch to newly marketed innovative drugs, thus leading to an increase in total expenditure and to a lower uptake of biosimilars.

Marketing of biosimilars in oncology may also help the sustainability of NHSs while favoring access to medicines that may in some cases have an extremely significant impact on the clinical outcomes for cancer patients. In line with this, ipilimumab, trastuzumab emtansine, pertuzumab, and brentuximab vedotin have also been identified as innovative drugs by the Italian Drug Agency in light of the documented additional therapeutic value compared with the available alternative treatments [18].

In such a context, post-marketing monitoring systems using real-world data may allow rapid evaluations of the uptake, appropriate use, safety, and economic impact of the high-cost biological drugs and their corresponding biosimilars as well as other non-biological innovative targeted therapies in cancer patients, thus optimizing pharmaceutical expenditure. For most of the monoclonal antibodies and other non-biological targeted therapies approved for cancer treatment, the Italian Drug Agency implemented drug-specific monitoring registries as tools to monitor the appropriate use, effectiveness, and safety of those drugs that may facilitate post-marketing monitoring, although so far these registries have not been systematically used for scientific purposes [19]. On the other hand, an Italian network of claims databases has been successfully built for the post-marketing assessment of benefit–risk profiles of biologics/biosimilars in other therapeutic areas, thus demonstrating that these sources may also offer greater opportunities for exploring the clinical and economic impact of biological drugs and related biosimilars in oncology in the real-world setting [15, 16, 20].

4.1 Strengths and Limitations

Using administrative healthcare databases, including dispensing data and the hospital discharge diagnosis, this observational study investigated the prevalence of use and the costs of biological and non-biological targeted therapies in oncology in a large area from Southern Italy, covering a population of more than 650,000 people. Using the dispensing databases of three centers, we were able to capture all data regarding dispensing of the study drugs to outpatients resident in the Messina area. It is possible that patients resident in Messina receive the study drugs outside the catchment area (i.e., choose to be treated in other areas of Sicily or in other Italian regions), but this is unlikely. Due to the frequency of administration, especially for infusion study drugs, patients are much more likely to choose the closest oncology center.

As administrative databases do not include information about the indication for use, it is possible that using the diagnosis from the hospital discharge database may detect a diagnosis that is not the main indication for which the drug is used. To minimize the potential misclassification in terms of the indication of use, we considered the last cancer diagnosis within 6 months prior to the ID as the possible indication of use.

5 Conclusion

The use of and corresponding expenditure relating to monoclonal antibodies and other non-biological targeted therapies for cancer treatment has rapidly and dramatically increased, almost doubling over a 5-year period in a large

general population of Southern Italy. Significant uptake of biosimilars of trastuzumab and rituximab, which will be available shortly on the European Union market, may partly mitigate the pharmaceutical expenditure of biological drugs in cancer patients. On the other hand, real-world data are essential to rapidly monitor the benefit–risk profile and appropriate use of monoclonal antibodies and related biosimilars as well as other non-biological targeted therapies in routine care, with the final goal being to optimize pharmaceutical expenditure in oncology patients.

Author contributions Study concept and design: Gianluca Trifirò. Acquisition of data (Messina LHU): Carmela Sgroi. Acquisition of data (O.R. Papardo): Maria Pia Randazzo. Acquisition of data (A.O.U. "G. Martino"): Paolo Panagia, Rosanna Intelisano. Data management: Ilaria Marcianò. Analysis and interpretation of data: Simona Lucchesi, Ilaria Marcianò, Gianluca Trifirò, Giuseppe Altavilla, Mariacarmela Santarpia, Vincenzo Adamo, Tindara Franchina, Francesco Ferraù, Paolina Reitano. Preparation of manuscript: Simona Lucchesi, Ilaria Marcianò, Gianluca Trifirò, Mariacarmela Santarpia.

Compliance with Ethical Standards

Conflict of interest Gianluca Trifirò coordinates a research team at the University of Messina, which receives research grants for projects that are not related to the topic of the paper. Simona Lucchesi, Ilaria Marcianò, Paolo Panagia, Rosanna Intelisano, Maria Pia Randazzo, Carmela Sgroi, Giuseppe Altavilla, Mariacarmela Santarpia, Vincenzo Adamo, Tindara Franchina, Francesco Ferraù, and Paolina Reitano declare that they have no conflicts of interest.

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Ethical approval All procedures performed in this study were in accordance with the Ethical Standards of the Institutional Research Committee of the Academic Hospital of Messina (minutes n.9/2014, 21 July 2014), according to the current national law (8), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The manuscript does not contain clinical studies and all patients' data were fully anonymized. For this type of study, formal consent is not required.

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