

# THE USE OF BIOLOGICAL AND BIOSIMILAR DRUGS IN RHEUMATOLOGY AND DERMATOLOGY: ANALYSIS OF TWO PRESCRIBING CENTERS IN SICILY FROM 2019 TO 2020

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## SUMMARY

Two position papers from the Italian Medicine Agency (AIFA) and the recent (September 2022) statement by European Medicines Agency (EMA) highlighted that biosimilar medicines approved in the European Union (EU) are interchangeable with their reference medicine or with an equivalent biosimilar. AIFA statements assessed that biosimilars must be preferred both for naïve patients and patients already under treatment with biological medicines, for whom it is possible to apply the switch to the biosimilar products. Accordingly, the Sicilian Regional Health Systems has issued different acts to comply with the National directives, and to spread the use of biosimilars products.

This research aimed to evaluate the appropriateness of biosimilars prescriptions by two prescribing centers in Sicily. Specifically, the research was carried out during 2021, analyzing the prescription forms of the biological or biosimilar medicinal products at higher cost of two Sicilian prescribing centers, *i.e.*, Rheumatology and Dermatology centers, respectively from 2019 to 2020. To assess the prescribing appropriateness of these two centers, we evaluated the number of naïve patients treated with biosimilars, the amount of switching to the biosimilar products, and the motivations reported by clinicians, to justify the use of the biological products at higher cost.

Our analysis revealed that the number of biosimilar prescriptions at the time of the analysis was lower compared to the originators. Moreover, biosimilars have been prescribed but not for all the naïve patients, in contrast with the national and local directives. We also found that the switching from originators to biosimilars was negligible.

Finally, several motivations submitted by clinicians, related to prescription of drug with highest cost, were inappropriate and did not comply with Sicilian Regional Health System acts. The analysis revealed that, at the prescribing centers considered in this study, even if the number of biosimilar products at the time of the analysis was lower compared to the originators, biosimilars have been prescribed, but not for all the naïve patients, and the switching from originators to biosimilars was limited, confirming a high utilization of originators. Moreover, several reported motivations for prescription of high-cost biologics are considered inappropriate, according to the acts established by the Sicilian Regional Health System.

## Key words

*Biological drugs; biosimilar; originator; appropriateness; interchangeability.*

## Impact statement

Biosimilars are interchangeable to biologics at high cost, specifically in terms of safety and efficacy. However, several efforts are still needed to spread the use of biosimilars, in order to contribute to the sustainability of the Health Care System.

## INTRODUCTION

Biosimilar medicinal products represent an effective tool for the optimization of the health care resources, allowing the sustainability of the biological innovative therapies, guaranteeing superimposable efficacy, safety and quality profile at a lower cost compared to the originators. Prescription, interchangeability, and switching from originators to biosimilars are defined by the National Health Authorities; however, the European Medicines Agency on the 19<sup>th</sup> of September 2022 issued for the first time a statement on interchangeability, "confirming that biosimilar medicines approved in the European Union (EU) are interchangeable with their reference medicine or with an equivalent biosimilar" (1). Looking at the Italian regulation, the Italian Medicines Agency (AIFA) endorsed two different Position Papers, the first in 2013 and the second in the 2018, with the aim to boost the spread of biosimilar products use, and their prescribing appropriateness (2, 3). The Position Papers state that biosimilars should be used for naïve patients and as well as for patients already under treatment with the originators, assuming that biosimilar drugs are interchangeable with their originators. In line with the National dispositions, the Regional Health System in Sicily issued several local measures in order to promote the use of biosimilars, with the aim to prefer the biological medicinal products at the lower cost, as specified in the first Assessorial Decree (A.D.) 540/2014: "The inappropriate use of medicinal products correspond to therapies' efficacy lost, an increased risk of adverse events and unjustified increment of the pharmaceutical expenditure" (4). However, as specified by the article 2 of the D.A. 540/14, in specific circumstances, the clinicians might prefer the biological product at higher cost, specifying the motivations by fulfilling the dedicated form "prescribing form of the biologic or biosimilar product at higher cost" (figure 1). The forms must be transmitted to the Hospital Pharmacy, that within 30 days has the responsibility to address the forms to the dedicated regional technical committee, which then assesses the ap-

propriateness of the reported motivations. In order to optimize the use of biological products at higher costs, the Regional Health System issued two different acts, n. 9 of 4.08.2015 and n. 20 of 26.11.2018 (5, 6), that specify the motivations defined as inappropriate, that do not justify the choice of biological products at higher cost. The first act underlines that, forms claiming "therapeutic inefficacy and safety concerns related to the medicinal product", "intolerance/allergy" without a signaling form of suspected adverse reaction, are inappropriate (5). **Table I** reports the motivations considered inappropriate according to act n. 20(5) (**table I**).

Looking at the local dispositions issued in Sicily, the aim of this research was to analyze the prescribing forms of one Rheumatology prescribing center and one Dermatology prescribing center in Sicily, within 2019-2020, in order to assess which factors may limit the extent of use of biosimilars, and the appropriateness of prescriptions.

## MATERIALS AND METHODS

The research was carried out at the Pharmaceutical Department of the local health authority of Catania (Azienda Ospedaliera Provinciale di Catania), during the year 2021. We analyzed the prescription forms of the biological or biosimilar medicinal products at higher cost, issued with the A.D. 540/14 (**figure 1**) of two different prescribing centers: Dermatology and Rheumatology departments, both belonging to the Garibaldi Hospital in Catania, from 2019 to 2020. The data were collected in two electronic sheets, one for each center, respectively. Data have been anonymized and the following information have been retrieved: gender, diagnosis, originator or biosimilar, first prescription or therapy prosecution, motivation supporting the choice of the use of the biological product at higher cost, when occurred. The analysis excluded the prescribing forms in which the biological medicine was not specified or those used for non-biological drugs. To assess the prescribing appropriateness, we evaluated the

**SCHEDA DI PRESCRIZIONE FARMACO BIOLOGICO O BIOSIMILARE  
A MAGGIORE COSTO**

Centro prescrittore \_\_\_\_\_

Medico prescrittore (cognome e nome) \_\_\_\_\_

Tel. \_\_\_\_\_

E-Mail \_\_\_\_\_

Paziente (cognome e nome) \_\_\_\_\_

Luogo e data di nascita \_\_\_\_\_ Sesso  M  F

Codice fiscale \_\_\_\_\_ Residente \_\_\_\_\_

Tel. \_\_\_\_\_ Regione \_\_\_\_\_

ASP di residenza \_\_\_\_\_ Provincia \_\_\_\_\_

MMG / PLS \_\_\_\_\_

Diagnosi \_\_\_\_\_

Farmaco biologico originatore o biosimilare a costo maggiore prescritto \_\_\_\_\_

Prima prescrizione

Motivare la prescrizione del farmaco biologico originatore o biosimilare a costo maggiore:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Prosecuzione del Trattamento \*  
*\*(in caso di prosecuzione del trattamento non è necessaria la motivazione)*

Durata prevista per il trattamento \_\_\_\_\_

MMG  PLS  Reparto  D.H.  Ambulatorio

Data \_\_\_\_\_

Firma e timbro Medico prescrittore

**Figure 1.** Prescribing form of the biologic or biosimilar product at higher cost, A.D. 540/14.

**Table I.** Inappropriate motivations according to act n. 20 of 26.11.2018 (adapted table).

Type of motivations	Inappropriate motivations
Motivations about the patient's characteristics	<ul style="list-style-type: none"> <li>• Age (e.g., elderly patient, young patient...).</li> <li>• Pathological conditions that do not represent a contraindication according to the SPC (e.g., senile dementia, cardiovascular problems).</li> <li>• Agophobia not proven by the psychiatric documentation for patients who can't undergo parental therapies.</li> <li>• Patient in polytherapy.</li> </ul>
Motivations from clinical experience	<ul style="list-style-type: none"> <li>• Lack of experience with biosimilar.</li> <li>• Lacking experience with the medicine proposed by the DPC web platform.</li> <li>• Previous clinical experience.</li> </ul>
Motivations related to the medicine	<ul style="list-style-type: none"> <li>• Less efficacy compared to than the originator.</li> <li>• Therapeutic efficacy of the originator on the basis of the technical data sheet.</li> <li>• Patient unresponsive to the biosimilar without any documentation certifying its lack of efficacy.</li> <li>• Higher number of literature references for originator compared to the biosimilar (clinical trials, drug with proven efficacy).</li> <li>• Greater stability of the originator.</li> <li>• Incorrect" declaration of non-availability of the drug at lower cost in the distribution system (drug available in stock on the web PC platform).</li> <li>• Unique molecule, biosimilar not present.</li> <li>• Unavailability of infusion chairs for intra venous drugs.</li> <li>• Intolerance, allergy, toxicity (with the exception of specific technical warnings reported on the data sheet of the drugs).</li> </ul>

number of naïve patients treated with biosimilars, and the amount of patient already under treatment with originator that were switched to the biosimilar products. Therefore, for each patient the prescribing form was recorded as "first prescription" or "treatment prosecution". Finally, the motivations reported by clinicians, that justified the use of the biological products at higher cost have been scrutinized, in order to assess their appropriateness according to regional acts. Data analysis and graph design has been carried out with Office Excel.

## RESULTS

The prescription forms of 259 and 256 patients, respectively for Rheumatology and Dermatology prescribing centers, have been evaluated. However, 48 forms were excluded because it

was not possible to recognize the type of biological drugs used due to missing or uncompleted data, thereby, the analysis included the prescribing forms of 243 patients (159 females, 84 males) in Rheumatology, and 224 patients (64 females, 160 males) in Dermatology (**table II**). **Table III** shows the biological drugs used.

The most diagnosed disease at the Rheumatology center was rheumatoid arthritis (144 patients out of 243) and plaques psoriasis at the Dermatology center (192 patients out of 224). At Rheumatology center 162 patients were treated with 12 originators: abatacept, adalimumab, anakinra, belimumab, certolizumab, etanercept, infliximab, golimumab, sarilumab, secukinumab, tocilizumab, ustekinumab (**figure 2**). Eighty-one patients were treated with 5 biosimilars of 3 originators: 25 patients were treated with adalimumab biosimilars, 54 patients

**Table II.** Summary of the prescribing forms analyzed.

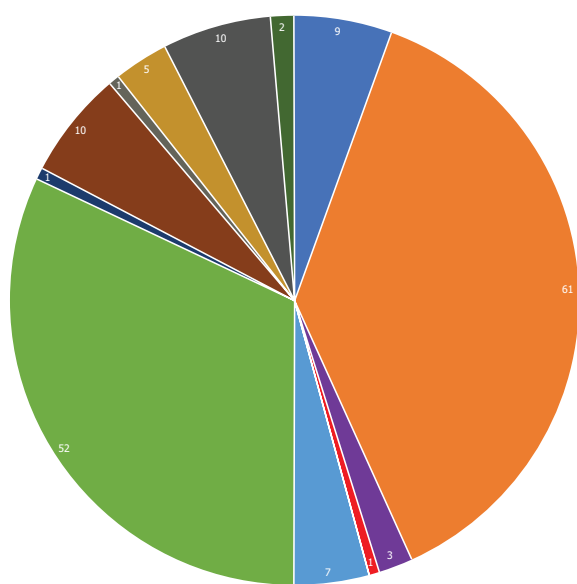
Prescribing center	N. patients for prescribing forms evaluated	Included prescribing forms	Excluded prescribing forms
Rheumatology	259	243	16
Dermatology	256	224	32

**Table III.** Originators and biosimilars used in the two prescribing centers.

Originator (active substances)	Biosimilar (branded name)	Therapeutic class	Prescribing centers
abatacept	no *	Recombinant DNA fusion protein T-cell costimulation modulator	Rheumatology
adalimumab	yes	Human mAB ** TNFi- $\alpha$ **	Rheumatology Dermatology
anakinra	no	DNA recombinant interleukin-1 antagonist	Rheumatology
belimumab	no	Human mAB B lymphocyte stimulator-specific inhibitor (BLyS)	Rheumatology
certolizumab	no	mAB Fab' fragment TNFi- $\alpha$	Rheumatology
dupilumab	no	mAB IL-4 inhibitor	Dermatology
etanercept	yes	Recombinant DNA fusion protein TNFi- $\alpha$	Rheumatology Dermatology
infliximab	yes	Mouse human chimeric mAB Anti-TNF- $\alpha$	Rheumatology Dermatology

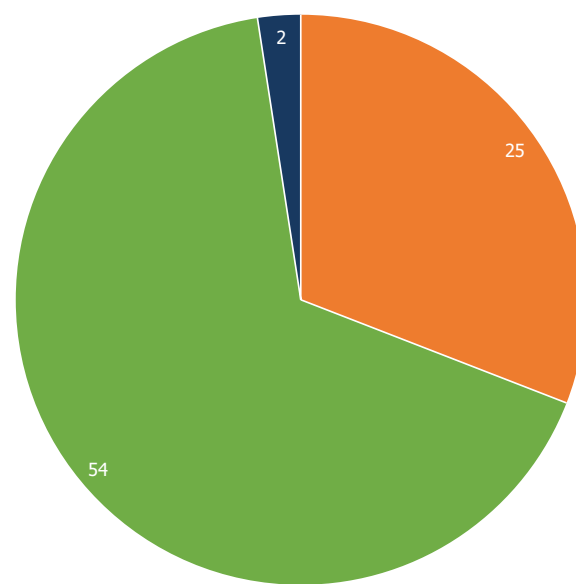
Originator (active substances)	Biosimilar (branded name)	Therapeutic class	Prescribing centers
ixekizumab	no	Humanized mAB IL-17° inhibitor	Dermatology
golimumab	no	Human mAB TNFi-α	Rheumatology Dermatology
guselkumab	no	Human mAB IL-23 inhibitor	Dermatology
omalizumab	no	Humanized mAB immunoglobulin E (IgE) inhibitor	Dermatology
sarilumab	no	Human mAB IL-6 inhibitor	Rheumatology
secukinumab	no	Human mAB IL-17° inhibitor	Rheumatology Dermatology
tocilizumab	no	Humanized mAB IL-6 inhibitor	Rheumatology
ustekinumab	no	Human mAB IL-12/23 inhibitor	Rheumatology Dermatology

\* Not available in the period 2019-2020; \*\* Monoclonal antibody (mAB); TNFi-α: Tumor Necrosis Factor Inhibitor.



■ abatacept ■ adalimumab ■ anakinra ■ belimumab  
■ certolizumab ■ etanercept ■ infliximab ■ golimumab  
■ sarilumab ■ secukinumab ■ tocilizumab ■ ustekinumab

**Figure 2.** Number of patients treated with originators at Rheumatology center.



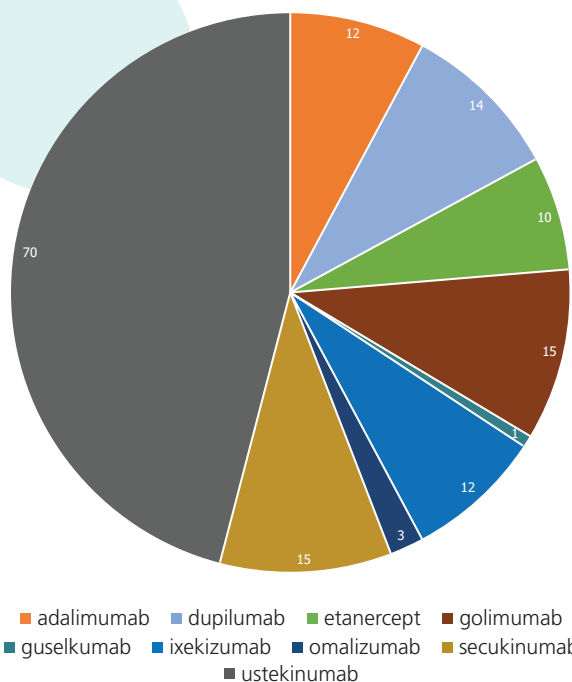
■ adalimumab ■ etanercept ■ infliximab

**Figure 3.** Number of patients treated with biosimilars at Rheumatology center.

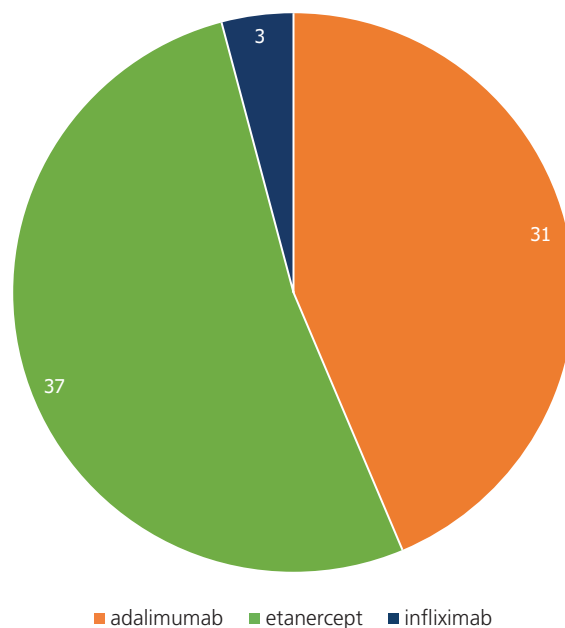
with etanercept biosimilars and 2 with infliximab biosimilar (**figure 3**).

At Dermatology center, 153 patients were treated with 9 originators: adalimumab, dupilumab, etanercept, golimumab, guselkumab, ixekizum-

ab, omalizumab, secukinumab, ustekinumab (**figure 4**), and 71 patients with 4 biosimilars of 3 originators: 31 patients treated with adalimumab biosimilar, 37 with etanercept biosimilars, 3 with infliximab biosimilar (**figure 5**).



**Figure 4.** Number of patients treated with originators at Dermatology center.



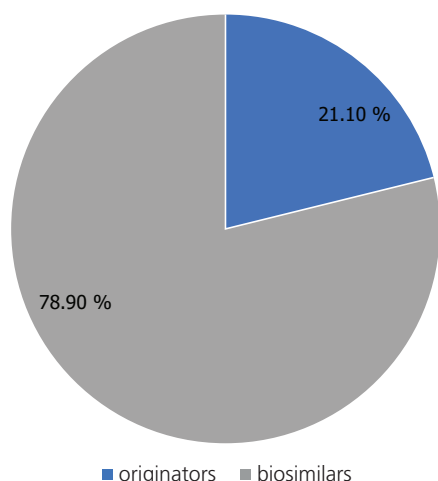
**Figure 5.** Number of patients treated with biosimilars at Dermatology center.

The most prescribed originators were adalimumab at the Rheumatology center, used in 25% of cases, and ustekinumab at the Dermatology center, used in 31.2% of cases. In both centers the most prescribed biosimilar drug was etanercept, used in 66.7% and 22.2% of patients, in Rheumatology and Dermatology, respectively (**figure 4** and **figure 5**).

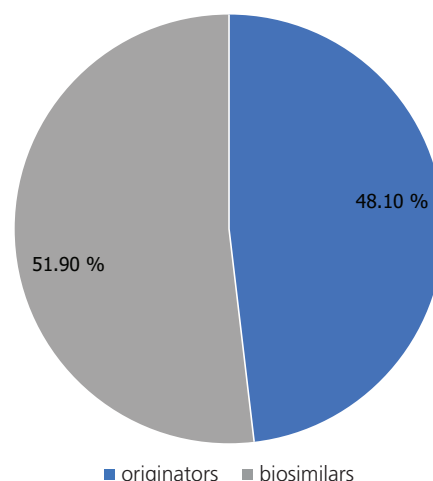
Analysis of prescriptions revealed that at both centers the amount of first prescriptions about naïve patients was lower than prosecutions. In particular, at the Rheumatology center, 78.9% of naïve patients were treated with biosimilars (30 out of 38 patients) (**figure 6**), and 51.9% of naïve patients were treated with biosimilars at Dermatology center (27 out of 52 patients) (**figure 7**). However, considering the patients already under treatment, biosimilar products were used just for 42 patients out of 196, and for 35 patients out 141, at Rheumatology and Dermatology centers, respectively. The number of switches from originators to biosimilars were 18 at the Rheumatology center, and just 2 at the Dermatology center. However, other types of switches occurred: from biosimilars to biosimilars, from

biosimilars to originators and from originators to other originators. Looking at the motivations justifying the use of biological drugs at higher cost, the analysis shows a high variability of motivations, not always considered appropriate, and often not reported, as required according to the regional acts. At the Rheumatology center, in 45 forms among the 243 included in the analysis, the motivations were missing. The retrieved motivations for prescription of biologic drug at higher cost, are hereby reported:

- patient with previous tuberculous disease: tuberculosis reactivation did not occur during therapy, so therapeutic continuity is required for clinical stability;
- QuantiFERON-TB positive patient: etanercept therapy showed safety in association with isoniazide, whereas data about safety of biosimilar are lacking;
- denied consent;
- patient in an exacerbation phase;
- complicated clinical status due to uveitis;
- authorization from the Hospital Director;
- therapeutic continuation is required due to important allergic history;



**Figure 6.** Biosimilars use among naïve patients at Rheumatology center.



**Figure 7.** Biosimilars use among naïve patients at Dermatology center.

- patient with favism, no hemolytic crisis with etanercept;
- patient informed about the efficacy of the biosimilar refuses the switch, despite the reassurance;
- prescription with originator, waiting about the whole evaluation of the clinical status, hypothesizing the switch to biosimilar at the next evaluation;
- waiting for the overall evaluation of the clinical status and for the acquisition of a greater awareness by the patient;
- biosimilar inefficacy;
- patient in stationary phase with complex clinical status;
- young age;
- aggressive disease complicated by comorbidities;
- clinical instability;
- stability of clinical status;
- originator delivered because the drug is in stock at the pharmacy;
- concomitant fibromyalgia;
- switch to certolizumab due to the patient's desire for pregnancy;
- active arthritis unresponsive to anti-TNF biosimilar and severe psoriasis;
- active arthritis, in overlap with connectivopathy complicated by pulmonary fibrosis, a clinical status that contraindicates the use of anti-TNF.

The most frequent reported motivation at the Rheumatology center was "waiting for the overall evaluation of the clinical status and for the acquisition of a greater awareness by the patient". This motivation was reported for 34 patients, among which just 6 underwent the switching from originator to biosimilar. The refusal of the use of the biosimilar by the patient was present for 12 patients. Whenever inefficacy of the biosimilar or allergy has been reported as motivation, the required signaling form of adverse event was present just in few cases.

Regarding the Dermatology center, among the forms of 153 patients treated with biological drugs at higher cost, 122 did not report the motivations, and, when available, they were the following:

- inefficacy;
- adverse events related to biosimilar;
- patient refuses the biosimilar, concerning a worsening of the response;
- patient refuses the switch;
- diabetic patient;
- QuantiFERON-TB positive patient, under treatment with isoniazide;
- Patient treated at Hematology department due to a monoclonal gammopathy;
- Patients treated in another health center;
- Benepali adverse effects (lack of ADR report).
- Unresponsive patients to adalimumab and ustekinumab (multi-failure);



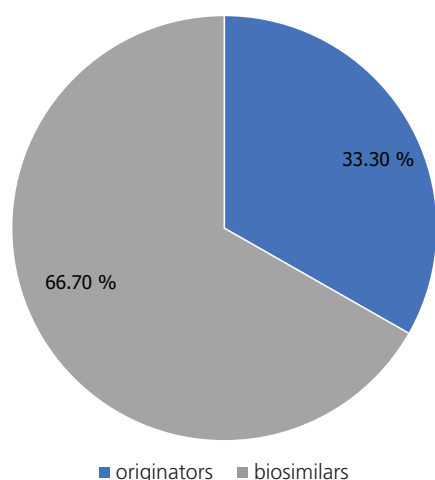
- Authorization by the Hospital Director;
- Patients with only one kidney.

The most frequent motivations analyzed were biosimilars inefficacy (6 patients) and refuse of the patient about the use of the biosimilar (6 patients).

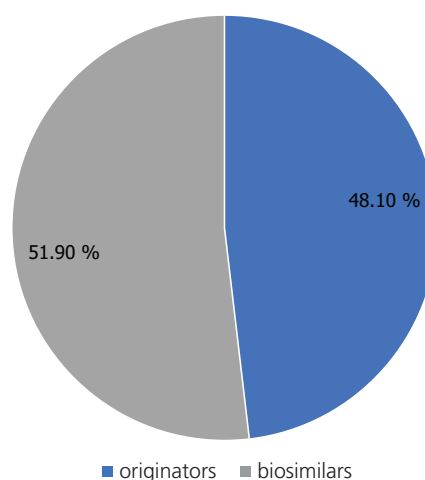
## DISCUSSION

The data obtained show that the biosimilar products have been used in both centers, however not for most of patients. In fact, the number of patients treated with originators was higher compared to number of patients treated with biosimilars, with a similar percentage in both centers, accounting for 66.7% in Rheumatology and 68.3% in Dermatology (figures 8 and figure 9). However, in order to interpret properly the data obtained from our analysis, it is necessary to underline that at the time of the research, the majority of the originators did not have the corresponding biosimilars, with exception for the immunosuppressors adalimumab, etanercept and infliximab. Based on this limitation and considering just these products that had biosimilars, the analysis shows that, biosimilars have been used more than corresponding originators (65.74% biosimilar prescription) in Dermatology center. While in the Rheumatology center the % of biosimilar prescription was 41.54%, compared

to corresponding originators. However, an exception was found for use of adalimumab at the Rheumatology center, where the originator was prescribed more than the corresponding biosimilar. Moreover, worthy of note that at the Dermatology center, only the biosimilar of infliximab was used, and no prescriptions with originator were found. The prescriptions analyzed partially comply with national and regional directives; biosimilars were not used for all the naïve patients, observing a higher number of biosimilar prescriptions at the Rheumatology center versus the Dermatology center (78.9% vs. 51.9%, respectively) and a limited number of switches from originators to biosimilars have been applied. Moreover, the motivations reported by clinicians to justify the choice of biological products and higher costs, were disparate and often not appropriate, i.e., not complying with the regional directives. Among the others, the most frequent inappropriate motivations were "age of the patient", "patient refusal", "waiting for the acquisition of a greater awareness by the patient", "biosimilar inefficacy" and "allergy or intolerance" without the required adverse event forms. Along with a high number of inappropriate motivations, a lot of forms with missing motivations have been found, especially in the Dermatology center (122 out of 153). Worthy of note is the frequent motivation reported for prescription, at both centers, of etanercept originator,



**Figure 8.** Biosimilars use among naïve patients at Dermatology center.



**Figure 9.** Biological utilization at Dermatology center.



i.e.: "The need to keep the clinical stability in patients with previous tuberculosis, obtained with etanercept". Therefore, there was concern that switching to the biosimilar, could compromise this stability. Moreover, in one case, it was reported that "there's no data about the safety of biosimilars regarding the latent tuberculosis". These concerns may arise from information reported in the Summary of Product Characteristics (SmPC) of etanercept, given that all anti TNF- $\alpha$  agents could increase the risk of infections. However, the risk is associated both to the originator as well the biosimilars, thus the clinician's concerns are not justified.

## CONCLUSIONS

The European regulatory authorization process establishes that the risks benefits ratio of the biosimilar products is the same of the originators. For this reason, AIFA considers biosimilars interchangeable products with the respective originators, for naïve patients and for patients already under treatment, that can be switched from originator to biosimilar at any time. This principle should drive the prescribing choices of clinicians, who have the possibility to assess if, in specific circumstances, it is necessary to maintain the use of the originator instead of the biosimilar; however, these circumstances, as underlined by AIFA, should be circumscribed to limited situations, contributing to the rationalization of the Italian NHS expenditures. Our study is characterized by two limitations: i) a short observation timeframe (2019-2020); ii) lower number of biosimilar products, at the time of the analysis, compared to the originators. Besides these limitations, our analysis revealed that, at the prescribing centers considered in this study, biosimilars have been prescribed, but not for all the naïve patients, as the national and local directives requirements,, and the switching from originators to biosimilars was limited, confirming a high utilization of originators. Moreover, several motivations have been reported but were considered inappropriate, according to

the acts established by the Sicilian Regional Health System. Looking at the results, even if it is undoubted that the biosimilars have the same benefit risk profile of the originator, it seems that it is still necessary to widespread the awareness about their efficacy and safety among clinicians and patients. This need determined the decision of EMA to issue the first statement on interchangeability about biosimilars on the 19 September 2022, after 15 years of biosimilars approvals. In fact, EMA stated that "at present the EU medicines regulatory network has identified the need to explicitly state that from a scientific point of view, biosimilars approved in the EU can be considered interchangeable. This is because the absence of a clear EU-wide position on interchangeability has been identified as a factor causing uncertainty among stakeholders on the use of biosimilars in clinical practice" (1).

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## ETHICS

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### Conflict of interests

There were no institutional or private fundings for this article.

## Authors' contributions

VD, MAS, DAM conceptualized the research. VD collected data. VD analyzed data. CMBP carried out formal analysis. VD wrote the manuscript. VD, CMBP, MAS, DAM revised, edited and approved the manuscript.

## Availability of data and materials

Raw data will be provided by the corresponding author under reasonable request of additional information.

## Ethical approval

N/A.

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