Switch pattern of biological drugs for the treatment of inflammatory bowel diseases through the VALORE distributed database network

Introduction

After their marketing approval, biological drugs changed the treatment of immune-mediated inflammatory disease such as inflammatory bowel (IBDs) which include Crohn disease and Ulcerative colitis.[1] Overall, five biological drugs are approved in Europe for IBDs (TNF-alpha inhibitors: Adalimumab, Infliximab and Golimumab; Anti-interleukin: ustekinumab; anti-integrin: Vedolizumab). In particular, vedolizumab and ustekinumab are approved in patients who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα inhibitors or have medical contraindications to such therapies. (**Table 1 and Table A1**)

Table 1. Biological drugs approved for IBD by EMA

Drug	Pharmacological class	Indication	RoA	Maintenance posology
Adalimumab	TNF-alfa	CD, UC	SC	40/80mg every two weeks
Infliximab	TNF-alfa	CD, UC	IV, SC	5 mg/kg every 8 weeks (IV), 120mg every 2 weeks (SC)
Golimumab	TNF-alfa	UC	SC	patient < 80 kg: 50 mg every 4 weeks. - patient ≥ 80 kg: 100 mg every 4 weeks.
Ustekinumab	Anti-interleukin	CD, UC	IV (Induction), SC (Maintenance)	90 mg SC at week 8 and then every 12 weeks
Vedolizumab	Anti-integrin	CD, UC	IV, SC	300 mg every 8 weeks (IV), 108 mg SC every 2 weeks

CD: Crohn disease, IV: Intravenous; RoA: Route of administration; SC: Subcutaneous; UC: Ulcerative colitis

Due to their high cost, biological drugs threaten the sustainability of the Italian National Health Service[2] and, therefore, it is crucial to ensure their appropriate use in clinical practice. Since 2006, following the patent expiry of some biologic drugs, the first biosimilar drugs have been introduced in the European market. They are defined by the European Medicines Agency as biologic drugs similar to the originator in terms of quality, efficacy and safety.[3] In the context of inflammatory bowel diseases (IBDs) such as Crohn disease and ulcerative colitis, a large number of biosimilars concerning anti-TNF alpha inhibitors (adalimumab and infliximab) have been marketed, while for other more recent biological drug classes such as interleukin or integrin inhibitors patent expiry has not been occurred yet.

Switching between biological drugs, both originator and biosimilar, in patients affected by IBD is a frequent phenomenon in clinical practice (from 5 to 30% during the first year of therapy).[4,5] Moreover, in September 2022 EMA stated that biosimilars are comparable to their reference products in terms of safety and immunogenicity and are therefore interchangeable.[7] However, for a single molecule numerous biosimilars are marketed and switching patterns among biological drugs might be very various and complex.[8] Nonmedical switching could also lead patients to a nocebo effect if not well motivated to patients who know little about biosimilars.[9,10] For these reasons, it is essential to explore what is happening in clinical practice in patients affected by IBDs.

Objective

Primary objective: To describe the pattern of switch and swap among incident biological drug users approved for IBDs.

Secondary objective: 1) To identify potential predictive factors of multiple switches and switch-back among incident users of biological drugs approved for IBDs. 2) To assess the treatment persistence to single active ingredients according to biological treatment line.

Methods

Data source

This study will use the claims databases from thirteen Italian regions (Veneto, Lazio, Lombardy, Apulia, Friuli-Venezia-Giulia, Sardinia, Emilia-Romagna, Calabria, Tuscany, Marche, Sicily, Abruzzo, Umbria) involved in the VALORE project. More information about the datasource is reported in detail in another study.[13] An R-based tool for distributed analyses developed by the Italian National Institute of Health (The ShinISS) was employed by each center to locally elaborate patient data using a common data model, sharing only a fully anonymized dataset for central analysis, in compliance with EU General Data Protection Regulation regulations.

Study design

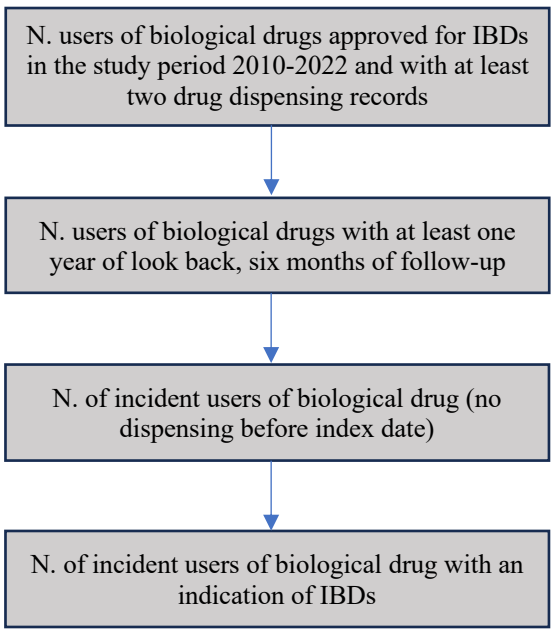
A descriptive, cohort, retrospective, multicenter study will be conducted.

Cohort selection

The regional claims databases previously described will be considered. From this source, subjects will be included in the study based on the presence of all the following criteria: 1) At least two records of biological drugs (approved for IBDs – see table A1 of the appendix) dispensing during the study period (2010 to 2022). The first date of a biological drug dispensing will be considered as the *index date* and the biological drug as the *index drug*. Only incident users of biological drugs will be included, i.e. biological drugs users with no prior dispensings of a biological drug; 2) At least one

year of look-back period in the database and at least one year of follow up after index date; 3) Patients with any of these indications: Crohn's disease and ulcerative colitis (see variable section for the identification of exposure and indication of use) Moreover, patients with a record of ustekinumab before September 1st 2018 will not be considered because the indication for use of IBD was not yet available. Furthermore, if the algorithm assigns an indication for use of UC but there are previous dispensations of ustekinumab before October 2019, the approval date for colitis, the indication will become non-colitis, and the subject will be excluded from the cohort. (**Figure 1**).
Each patient included in the study will be followed till death or loss of follow-up in the database (i.e., emigration from the region or end of data availability in the database), whichever came first.

Figure 1. Flow chart of biological drug users included in the study



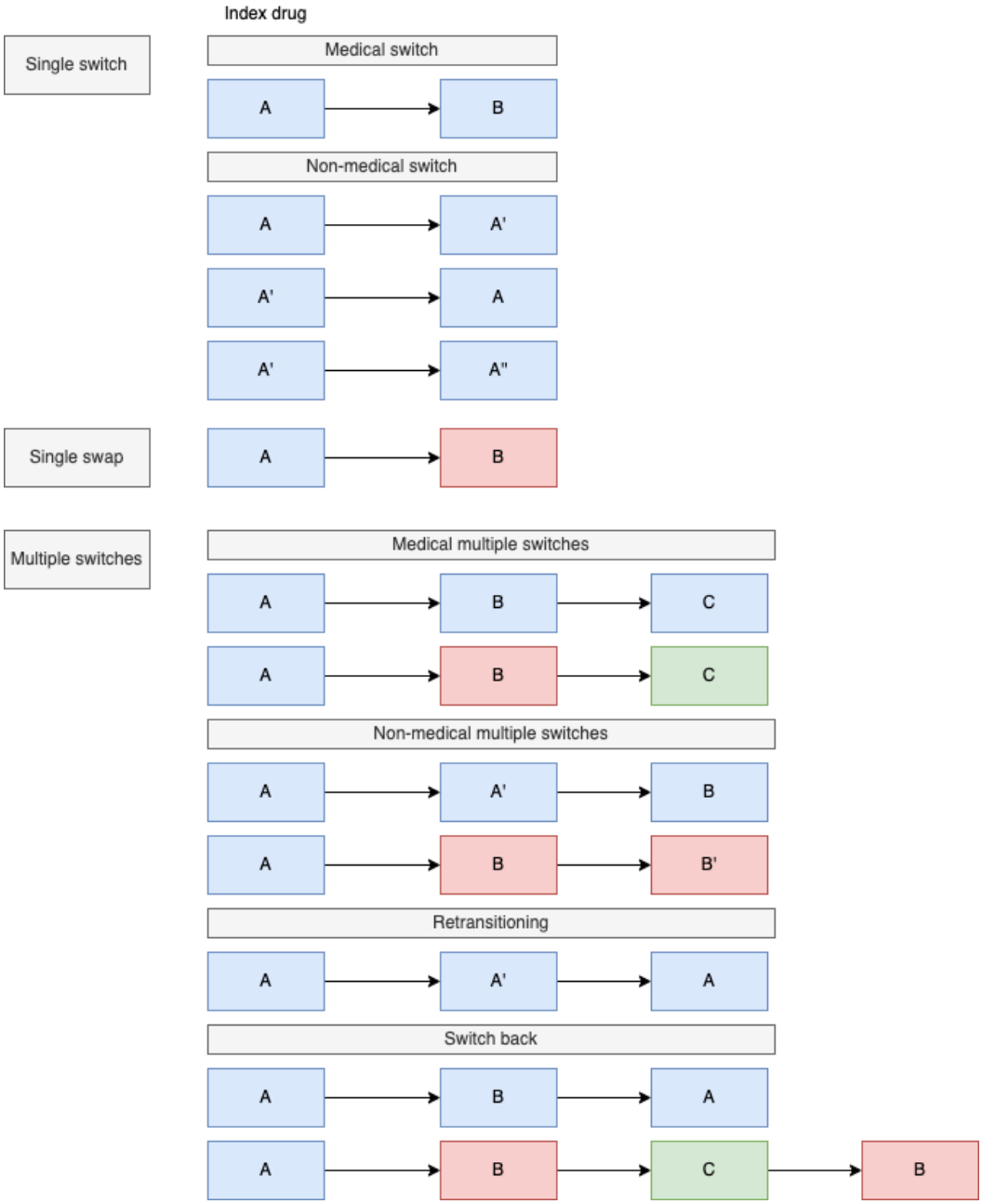
Drug exposure
All drugs mentioned in **Table 1** will be considered to identify biological drug exposure.
Using drugs dispensation data, the following variables will be retrieved. 1) Index drug: For each index drug active ingredient and originator/biosimilar information; 2) Biological drug utilization during follow-up: active ingredient and originator/biosimilar information; 3) Class of biological drug: each active ingredient will be classified according to mechanism of action (TNF-alpha inhibitors/ anti-interleukin drugs/ anti-integrin). See **Table 1** for classification.

Switch/Swap definition
- Single switch: Patients with at least one record of a single biological drug (of the same pharmacological class) other than the index biological drug during follow-up will be considered as single switcher. Each switch will be characterized as 1) switch to originator or 2) switch to biosimilar. The active ingredient will be retrieved. Medical switch will be defined as a switch to an active principle different from the previous one.
- Single swap: Patients with at least one record of asingle biological drug of a different class other than the class of index biological drug during follow-up will be considered as swapper. Each swap will be characterized as 1) swap to originator or 2) swap to biosimilar.

- Multiple switches: Patients will be characterized as multiple switchers if switch/swap occurs ≥2 times during follow-up. See **Figure 2** for the definition of medical and non-medical multiple switches.

  Among multiple switchers also two cases will be explored:
  - Switch back: Switching back to previous type of biological drug (same active ingredient, independently from pharmacological class) for which they were previously exposed will be retrieved (From A to B and from B to A).
  - Retransitioning: Is defined as switching from an originator to a biosimilar and back to the originator.

Figure 2. Definitions of switch, swap and multiple switches



Legend: Different letter = Different biological active ingredient; Different color = Different pharmacological class; Letters with ' = biosimilars (i.e. A' is the biosimilar of the originator drug A; A'' is a different type of biosimilar respect to A')

Moreover, the following variables related to exposure will be retrieved:

- Time to event: number of days between the date of the index drug dispensing and switch/swap occurrence. This variable will be calculated also for multiple switcher (time from index date to second switch/swap) as well as for switch back and retransitioning.
- Line of biological drug treatment: according to switch and swap occurrence the treatment will be assigned with a specific number which represents the biological drug treatment line (i.e., if a patient had adalimumab as index drug and then switch to infliximab and then swap to ustekinumab, adalimumab would represent the first line, infliximab the second and ustekinumab the third).
- Treatment coverage: Defined daily dose (DDD) will be used to define dispensation coverage of a single drug dispensation .

Other variables definition

All the codes and the related time windows used to extract such information from the analytical datasets of VALORE distributed database network are detailed in Table A2.

- Demographic characteristics: Gender (0: male; 1: female) and age (years) at index date
- Year of cohort entry (year)
- Region
- Indication: Indication of use will be retrieved using a META-algorithm developed and validated from the VALORE distributed database network.
- Previous use of drugs: Record of one of these drugs in the one year before index date using dispensing data: cDMARDs, tsDMARDs, NSAIDs, Corticosteroids.
- Comorbidities: Cardiovascular disease, diabetes, previous infection, depression, other dermatological or rheumatological IMIDs (i.e., psoriasis/psoriatic arthritis, rheumatoid arthritis, spondylarthritis) to be searched in the look-back period

Analysis plan

Descriptive analyses will be conducted to assess demographic and clinical characteristics of biological drug users in relation to indication of use. In particular, the following analysis will be performed:

Cohort characterization

Incident users stratified by class of biological drugs (TNF-alpha inhibitors, anti-interleukin drugs and anti-integrin) and on the basis of occurrence of at least one switch/swap during follow up, will be characterized at baseline in terms of sex, age, type of index drug (originator/biosimilar), previous use of other drugs approved for IMID (cDMARDs, JAK-i, NSAIDs, corticosteroids), and comorbidities (hypertension, MACE, diabetes, previous infections, depression other IMIDs in the look-back period). See **Table 2** for representation and **Table A2** for variable definition**.**

Table 2. Characteristics of incident users of biological drugs with IMID by class and indication of use

	TNF-alpha inhibitors		Anti-interleukin		Anti-integrin		Overall	
	At least one switch/swap	No switch/swap	At least one switch/swap	No switch/swap	At least one switch/swap	No switch/swap	At least one switch/swap	No switch/swap
Female, n (%)								
Median age, years [IQR]								
Age bands, n (%)								
≤18								
19-44								
45-64								
65-79								
≥80								
Type of Index drug, n (%)								
Originator								
Biosimilar								
Index drug (single AI)								
Adalimumab								
Etanercept								
Infliximab								
Golimumab								
Ustekinumab								
Vedolizumab								
Indication of use								
Crohn disease								
Ulcerative colitis								
Previous use of other drugs approved for IMID								
cDMARDs								
JAK-i								
NSAIDs								
Corticosteroids								
Comorbidities								
Hypertension								
MACE history								
Diabetes								
Gastrointestinal infections								
Other infections								
Depression history								

Pattern of switch and swap

The absolute frequency, mutually exclusive, in terms of single switch, single swap, multiple switches, by pharmacological class and active ingredient will be reported in **Table 3**. This analysis will be performed 1) considering only the first one, three and five years of follow up after the index date (only patients with at least 1 year, three year and five years of follow up will be counted as denominator, respectively) and 2) for the entire duration of follow-up. Whether possible, the analysis will be stratified by sex (female/male) and age (≤18/19-44/45-64/65-79/≥80).

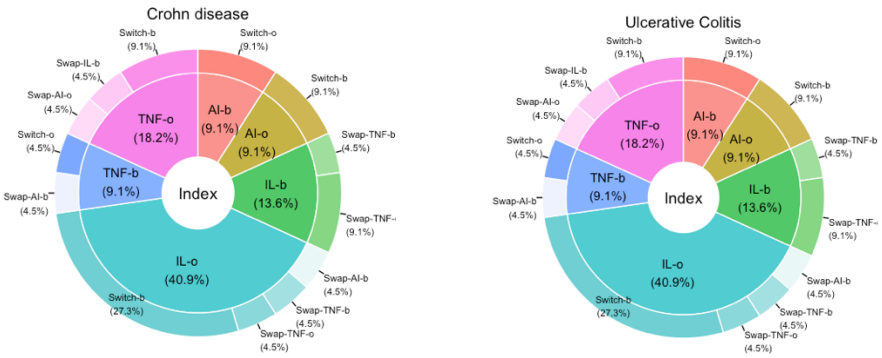
Table 3. Frequency of single switch, swap, multiple switches and switch-back among incident users of biological drugs by pharmacological class at 1, 3 and 5 years of follow-up

	TNF-α inhibitors	Anti-IL	Anti-integrin	Overall
First year of follow-up				
n (with at least 12 months of follow-up)				
Single switch, n (%)				
Medical single switch				
Switch to originator (different AI)				
Switch to biosimilar (different AI)				
Non-medical single switch				
Switch to originator (same AI)				
Switch to biosimilar (same AI)				

	TNF-α inhibitors	Anti-IL	Anti-integrin	Overall
Single swap, n (%)				
Swap to TNF-α inhibitors				
Swap to anti-interleukin				
Swap to selective immunosuppressant				
Multiple switches, n (%)				
Medical multiple switches				
Non-medical multiple switches				
Switch back, n (%)				
Retransitioning, n (%)				
At least one switch or swap, n (%)				
Three years of follow-up […]				
Five years of follow-up […]				

The pattern of switch and swap will be represented using a sun burst chart or sunkey diagram.

Figure 2. Sunburst chart of pattern of switch/swap by pharmacological class (dummy figure) and active ingredient per indication



IL-o: interleukin originator; IL-b; interleukin biosmiliar; AI-b; Anti-integrin biosmiliar; AI-o; Anti-integrin originator; TNF-o: TNF alpha inhibitor originator; TNF-b; TNF alpha inhibitor biosimilar.

Time to switch and swap

Time to switch and swap will be described using a Kaplan Meier approach stratifying class of biological drugs/active ingredient according to indication. Time to 1) first medical switch/swap, 2) non-medical switch, 3) switch back, 4) multiple switches. Median time for such events will be also calculated.

Retransitioning

Retransitioning (from originator to biosimilar and back to originator) will be described by TNF-alpha inhibitors active substance (i.e. adalimumab and infliximab). Among those patients with index drug adalimumab and infliximab who switch to the same biosimilar active ingredient the proportion of those with a record of retransitioning to the originator will be obtained according to indication of use. This information can be used as a proxy of the nocebo effect with biosimilar drugs since no pharmacotherapeutic rationale about retransitioning exists. Median time to retransition (from first dispensation of biosimilar drug to retransitioning to originator will be calculated). This analysis will be stratified by indication.

Table 5. Frequency and median time to retransitioning among patients with a non-medical switch to biosimilar

Drugs	Patients with non-medical switch to biosimilar, n	Retransitioning, n (%)	Median time to retransition, days [IQR]
Crohn disease			
Adalimumab			
Infliximab			
Ulcerative colitis			
Adalimumab			
Infliximab			

Persistence to first- and second-line treatment

If a subject has more than 60 days treatment gap between the estimated end of exposure of previous dispensing and the start of the next one (if any), or switched/swapped to another active ingredient he/she will be defined as discontinuer.

Persistence to biological treatment at one, three and five years according to drug classes and treatment line (first-line – i.e. index drug, second-line) will be calculated. As for the definition of persistence and treatment lines see exposure paragraph. This analysis will be stratified by indication of use.

Table 6. Persistence of first- and second-line biological treatment at one year, three and five years according to pharmacological class

	n	Median treatment duration, days (IQR)	Persistence 1 year, n (%)	Persistence 3 years, n (%)	Persistence 5 years, n (%)
First line treatment					
TNFi					
Anti-IL					
Anti-integrin					
Overall					
Second line treatment					
First line not persistent at 1 year					
TNFi -> TNFi					
TNFi -> Anti-IL					
TNFi-> Anti-integrin					
Anti-IL -> Anti-IL					
Anti-IL -> TNFi					
Anti-IL -> Anti-integrin					
Anti-integrin -> TNFi					
Anti-integrin -> Anti-IL					
Overall					
First line persistent at 1 year					
TNFi -> TNFi					
TNFi -> Anti-IL					
TNFi-> Anti-integrin					
Anti-IL -> Anti-IL					
Anti-IL -> TNFi					
Anti-IL -> Anti-integrin					
Anti-integrin -> TNFi					
Anti-integrin -> Anti_IL					
Overall					

Determinants of multiple switches at three years of follow-up

A multivariate COX proportional hazards model will be used to analyze predictors of multiple switches (medical), switch back and retransitioning at three years of follow-up. Results of the Cox model will be reported as HR with 95%CI and represented using forest plots. Variables included in the models will be age (≤18/19-44/45-64/65-79/≥80), sex (female/male), indication (Crohn disease/Ulcerative colitis), type of index drug (originator/biosimilar), index class of biological drug (TNF-a/anti-interleukin/anti-integrin), comorbidities, previous use of drugs such as cDMARDs (y/n), tDMARDs (y/n), NSAIDs (y/n), Corticosteroids (y/n). Assumption of proportionality of COX model will be checked for each variable included in the model. The assumption of proportionality of risk will be checked for each covariate and if it will not be respected a time-dependent approach or stratification approach will be used.

Statistical analysis

As for descriptive analysis, continuous variables will be described by means and standard deviation or by median and interquartile range (in case of outliers). Categorical variables will be described by patient counts and percentages. Determinants of switching will be analyzed by using COX regression model and a conditional regression model (nested case control study). All determinants will be analyzed both univariately and using multivariate model (determinants from univariate analysis with p value <0.05)

Sensitivity analysis

- As for persistence, 1) an analysis considering a gap of 45 days instead of 60 will be performed; 2) Stratification according to indication of use of the index biological drug (Crohn disease/ Ulcerative colitis)

References

1. Su, C. G. & Lichtenstein, G. R. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *Gastroenterology* **125**, 1544–1546 (2003).
2. Blackstone, E. A. & Joseph, P. F. The economics of biosimilars. *Am Health Drug Benefits* **6**, 469–478 (2013).
3. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 13.
4. Bressler, B. Is there an optimal sequence of biologic therapies for inflammatory bowel disease? *Therap Adv Gastroenterol* **16**, 17562848231159452 (2023).
5. Zhdanava, M. *et al.* Treatment persistence among bio-naïve patients with Crohn's disease initiated on ustekinumab or adalimumab. *Curr Med Res Opin* **39**, 533–543 (2023).
6. Ebbers, H. C., Muenzberg, M. & Schellekens, H. The safety of switching between therapeutic proteins. *Expert Opin Biol Ther* **12**, 1473–1485 (2012).
7. EMA. Biosimilar medicines can be interchanged. *European Medicines Agency* https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged (2022).
8. Trifirò, G., Marcianò, I. & Ingrasciotta, Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. *Expert Opin Biol Ther* **18**, 309–315 (2018).
9. Fleischmann, R., Jairath, V., Mysler, E., Nicholls, D. & Declerck, P. Nonmedical Switching From Originators to Biosimilars: Does the Nocebo Effect Explain Treatment Failures and Adverse Events in Rheumatology and Gastroenterology? *Rheumatol Ther* **7**, 35–64 (2020).

10. Peyrin-Biroulet, L., Lönnfors, S., Roblin, X., Danese, S. & Avedano, L. Patient Perspectives on Biosimilars: A Survey by the European Federation of Crohn's and Ulcerative Colitis Associations. *J Crohns Colitis* **11**, 128–133 (2017).
11. Meijboom, R. W. *et al.* Incidence of and Reasons and Determinants Associated with Retransitioning from Biosimilar Etanercept to Originator Etanercept. *BioDrugs* **35**, 765–772 (2021).
12. Meijboom, R. W., Gardarsdottir, H., Egberts, T. C. G. & Giezen, T. J. Patients Retransitioning from Biosimilar TNFα Inhibitor to the Corresponding Originator After Initial Transitioning to the Biosimilar: A Systematic Review. *BioDrugs* **36**, 27–39 (2022).
13. Trifirò, G. *et al.* Large-Scale Postmarketing Surveillance of Biological Drugs for Immune-Mediated Inflammatory Diseases Through an Italian Distributed Multi-Database Healthcare Network: The VALORE Project. *BioDrugs* **35**, 749–764 (2021).
14. Ingrasciotta, Y. *et al.* How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013. *BioDrugs* **29**, 275–284 (2015).
15. Lee, H. *et al.* Validation of claims-based algorithms to identify patients with psoriasis. *Pharmacoepidemiol Drug Saf* **30**, 868–874 (2021).
16. Eder, L. *et al.* Identifying and Characterizing Psoriasis and Psoriatic Arthritis Patients in Ontario Administrative Data: A Population-based Study From 1991 to 2015. *J Rheumatol* **47**, 1644–1651 (2020).
17. Dobson-Belaire, W., Goodfield, J., Borrelli, R., Liu, F. F. & Khan, Z. M. Identifying Psoriasis and Psoriatic Arthritis Patients in Retrospective Databases When Diagnosis Codes Are Not Available: A Validation Study Comparing Medication/Prescriber Visit-Based Algorithms with Diagnosis Codes. *Value Health* **21**, 110–116 (2018).
18. Wu, J. J. *et al.* Treatment Switch Patterns and Healthcare Costs in Biologic-Naive Patients with Psoriatic Arthritis. *Adv Ther* **37**, 2098–2115 (2020).
19. Pezzolo, E. *et al.* Psoriasis severity matters when dealing with all-cause mortality in psoriasis patients: a record linkage analysis in Northern Italy. *Arch Dermatol Res* **313**, 255–261 (2021).
20. Di Domenicantonio, R. *et al.* Occurrence of inflammatory bowel disease in central Italy: a study based on health information systems. *Dig Liver Dis* **46**, 777–782 (2014).
21. Convertino, I. *et al.* Validation of algorithms for selecting rheumatoid arthritis patients in the Tuscan healthcare administrative databases. *Sci Rep* **11**, 20314 (2021).
22. Dubreuil, M. *et al.* Validity of ankylosing spondylitis diagnoses in The Health Improvement Network. *Pharmacoepidemiol Drug Saf* **25**, 399–404 (2016).
23. Quan, H. *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* **43**, 1130–1139 (2005).

Appendix

Table A1. Biological drugs (originator/biosimilars) for the treatment of chronic immune-mediated inflammatory diseases in the dermatological, rheumatological, gastroenterological areas (all approved indications) by mechanism of action

Class	Drug - ATC	Indication	Condition
TNF-alpha inhibitors	*Infliximab - L04AB02*	Crohn's disease	Adults: 1) moderately to severely disease not responders to corticosteroids/immunosuppressant or intolerant; 2) treatment of fistuling active disease not responded to previous antibiotics/immunosuppressant Pediatric (6-17 y/o): severe active disease not responders to corticosteroids/immunosuppressant or intolerant
		Ulcerative colitis	Adults: moderately to severely active disease not responders to corticosteroids/6-MP or AZA or intolerant Pediatric (6-17 y/o): severe active disease not responders to corticosteroids/6-MP or AZA or intolerant
	Adalimumab - L04AB04	Crohn's disease	Adults: moderate to severe active disease not responders to corticosteroids/immunosuppressant or intolerant Pediatric (6+): Moderately or severly active disease not responders or intolerant to conventional therapy
		Ulcerative colitis	Adults: 1) moderately to severely active disease not responders to corticosteroids/6-MP or AZA or intolerant Pediatric (6-17 y/o): moderately to severely active disease not responders to corticosteroids/6-MP or AZA or intolerant
	Golimumab L04AB06	Ulcerative colitis	Adults: moderately to severely active disease not responders to corticosteroids/6-MP or AZA or intolerant
Anti-interleukin	*Ustekinumab - L04AC05*	Crohn's disease	Adults: moderate to severe active disease not responders to conventional therapy or TNF alfa antagonist
		Ulcerative colitis	Adults: moderately to severely active disease not responders to conventional therapy or biologic or intolerant
Anti-integrin	*Vedolizumab - L04AA33*	Crohn's disease	Adults: moderate to severe active disease not responders to conventional therapy or TNF alfa antagonist
		Ulcerative colitis	Adults: moderately to severely active disease not responders/intolerant to conventional therapy or TNF alpha inhibitors

6-MP: 6-mercaptopurine; AZA: azathioprine; DMARDs: disease-modifying antirheumatic drugs; MTX: Methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs;

Table A2. Variable identification in the analytical dataset of the VALORE distributed database network

Variable	Definition	Databanks – Analytical dataset from the VALORE distribuited database network			
		Hospital discharge records (HDR) – ADS Caratterizzazione (VALORE)	**Exemption registry (EXE) - ADS Caratterizzazione (VALORE)**	**Dispensing from hospital pharmacies (DDRUG) - ADS Descrittivo (VALORE)**	**Dispensing from community pharmacies (DRUG) - ADS Descrittivo (VALORE)**
		VALORE Dictionary	**VALORE Dictionary**	**VALORE Dictionary**	**VALORE Dictionary**
Indication of use	**META-algorithm**				
Comorbidities					
Hypertension	≥1 record in the look-back period (any position)	r_iperten	Ese_iperten	antiper	antiper
MACE history	≥1 record in the look-back period (any position)	R_evcereb, r_imapregr, r_ima, r_scomp			
Diabetes	≥1 record in the look-back period (any position)	R_diabete	Ese_diabete	antidiab	antidiab
Intestinal infections history	≥1 record in the look-back period (any position)	r_intinf			
Other Infections history	≥1 record in the look-back period (any position)	r_herpes_simplex, r_herpes_zoster, r_artinf, r_batteri, r_cuteinf, r_respinf, r_fung_visc, r_fung_superf, r_gineinf, r_infez_occhio, r_nervinf, r_urinf, r_polm, r_covid, r_sepsi, r_tbc_extra, r_tbc_polmonare, r_tbc_primaria, r_uve			
Depression	≥1 record in the look-back period (any position)	R_depre		Antidep	Antidep
Previous use of drugs					
csDMARDs	In the year before index date			Balsa, Balsa.uc, Mesa, mesa.uc, mesa, MTX, MTX.alg, MTX.crohn, sulfa	Balsa, Balsa.uc, Mesa, mesa.uc, mesa, MTX, MTX.alg, MTX.crohn, sulfa
tsDMARDs (JAKi)	In the year before index date			bari, tofa, upad	bari, tofa, upad
NSAIDs	In the year before index date			fans	fans
Corticosteroids	In the year before index date			glucocort, corticost	glucocort, corticost