Switch pattern of biological drugs (originator and biosimilars) for the treatment of chronic immune-mediated inflammatory diseases through an Italian network of regional administrative databases: the VALORE Project

Summary

Abstract

In September 2022 EMA stated that biosimilars are comparable to their reference products in terms of safety and immunogenicity and are therefore interchangeable. However, for a single active ingredient numerous biosimilars are marketed and switching patterns among biological drugs might be very various and complex. The aim of this study was to describe the pattern of switch and swap among incident users of biological drugs approved for IMIDs in dermatology, rheumatology, and gastroenterology. A retrospective cohort study was conducted using the claims data of nine Italian regions from 2010 to 2020 (VALORE project). Incident users of biologic drug with an indication for IMIDs were included. Characteristics of patients, pattern of switch and swap among biological drugs with related predictive factors will be described by therapeutic indication. We are confident to finalize the results of this study by the end of December 2022.

Introduction

Biological drugs revolutionized the treatment of numerous chronic diseases in different therapeutic areas, and in particular in dermatology, rheumatology and gastroenterology.[1] 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 chronic immune mediated inflammatory diseases (IMIDs), a large number of biosimilars concerning anti-TNF alpha inhibitors have been marketed, while for other more recent biological drug classes such as interleukin inhibitors patent expiry has not been occurred yet (Table A1 and Figure A1 of the appendix).

Switching between biological drugs, both originator and biosimilar, in patients affected by chronic diseases is a frequent phenomenon in clinical practice (about 20% during the first year of therapy).[4–7] A large body of evidence from randomized clinical trial, observational studies using administrative databases and spontaneous reporting databases[8] showed no differences in terms of efficacy and safety between biological drug users who switched between originator and biosimilar and vice versa vs. non-switchers.

In September 2022 EMA stated that biosimilars are comparable to their reference products in terms of safety and immunogenicity and are therefore interchangeable.[9] However, for a single molecule numerous biosimilars are marketed and switching patterns among biological drugs might be very various and complex.[10] Nonmedical switching could also lead patients to a nocebo effect if not well motivated to patients who know little about biosimilars.[11,12] A study conducted in Netherland in patients using etanercept reported that one out of seven patients switched back to the originator after biosimilar switching due to perceived loss of effect.[13] Also a systematic review of clinical trials and observational studies reported similar results on TNF-alfa inhibitors where patients who switched back were 8%.[14]

For these reasons, it is essential to explore what is happening in clinical practice in the various therapeutic areas (rheumatological, dermatological and gastrointestinal). The assessment of the frequency and predictive factors of multiple switches, switch back, swap (patients adopting an alternative class of biological agents with a different mechanism of action) by therapeutic indication can shed a light on utilization patterns of these drugs.

Objective

Primary objective: To describe the pattern of switch and swap among incident users of biological drugs approved for IMIDs in different therapeutic areas (dermatology, rheumatology and gastroenterology).

Secondary objective: To identify potential predictive factors of switch and swap among incident users of biological drugs approved for IMIDs.

Methods

Data source

This study will use the claims databases from nine Italian regions (Tuscany, Veneto, Lazio, Emilia-Romagna, Friuli-Venezia-Giulia, Apulia, Sicily, Autonomous Province of Trento, Lombardy) involved in the VALORE project. More information about the datasource is reported in detail in another study.[15] In addition to databanks described, also hospital discharge record and exemptions were available. 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

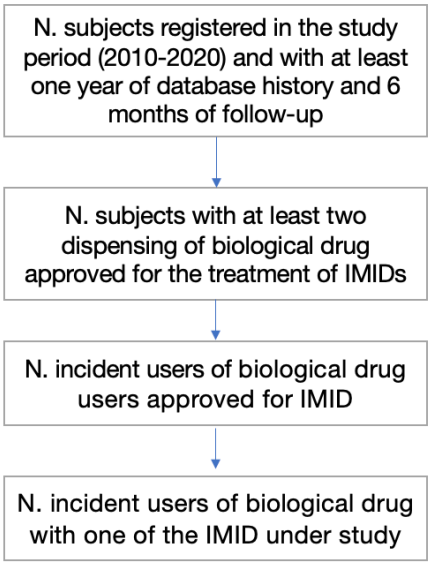
A cohort, retrospective, multicenter study will be conducted.

Cohort selection

The regional claims databases previously described from 2010 to 2020 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 biologic drug (approved for IMIDs – see table A1 of the appendix) dispensing during the study period. The first date of a biological drug dispensing will be considered as the *index date* and the biological drug the *index drug*. Only incident users of biological drugs will be included, i.e. biological drugs users with no dispensing of the same drug within one year prior to index date; 2) At least one year of look-back period in the database and at least six months of follow up after index date (a sensitivity analysis will be conducted to evaluate pattern of switch for those patients with less than 6 months of follow up); 3) Patients with any of these indications: rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis); dermatological diseases (psoriasis, arthritis psoriatic) or gastroenterology diseases (Crohn's disease and ulcerative colitis) (see variable section for the identification of exposure and indication of use) (Figure 1).
Each patient included in the study will be followed till end of the study period, death, or emigration from the region, whichever came first.

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



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

<u>Cohort characterization</u>
Incident users stratified by class of biological drugs (TNF-alpha inhibitors, anti-interleukin drugs and selective immunosuppressant) and by indication of use (rheumatological, dermatological and gastroenterological indications) 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, tDMARDs, NSAIDs, corticosteroids), comorbidities (other record IMIDs during follow-up, record of infections, diabetes, hypertension, stroke, BPCO, acute myocardial infarction and heart failure in the year before index date) and Charlson Comorbidity index.

Table 1. Characteristics of incident users of biological drugs with IMID by class and indication of use

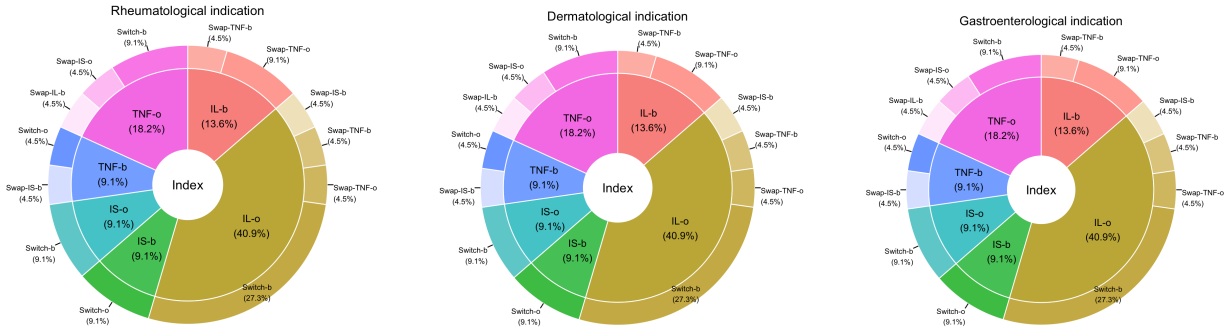
	TNF-alpha inhibitors	Anti-interleukin	Selective immunosuppressant	Overall
Rheumatological indications / single rheumatological indications				
Female, n (%)				
Median age, years [IQR]				
Age bands, n (%)				
≤18				
19-44				
45-64				
65-79				
≥80				
Type of Index drug, n (%)				
Originator				
Biosimilar				
Index drug (single AI)				
Infliximab				
Etanercept				
Adalimumab				
…				
Previous use of other drugs approved for IMID				
cDMARDs				
tsDMARDs				
NSAIDs				
Corticosteroids				
Comorbidities				
Previous infections				
AMI				
Heart failure				
Stroke				
Diabetes				
Hypertension				
BPCO				
Dermatological IMIDs / single indication				
Gastrointestinal IMIDs / single indication				
Dermatological indications / single dermatological indications				
##Same as rheumatological##				
Gastroenterological indications / single gastroenterological indication				
##Same as rheumatological##				

<u>Pattern of switch and swap</u>

Pattern of switch/swap will be described by indication (see variable section for switch / swap definition). Starting from the index drug, we will describe switching to biosimilar or originator, swapping to other classes different from the index drug class (to TNF-alfa originator/biosimilar, to anti-interleukin originator/biosimilar or to selective immunosuppressant originator/biosimilar) or no switching (only incident drug users with at least two biological drugs dispensing will be included in the analysis) by using proportions. After the second layer, also the switch back will be described. This analysis will be performed 1) considering only the first year of follow up after the index date 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).

The pattern of switch and swap will be represented using a nested sliced donut charts or a branched sun burst chart or an arrow diagram as shown in the article of Ingrasciotta et al.[4] (see figure 2).

Figure 2. Nested sliced donut charts/ or sunburst chart/ or arrow diagram per indication (dummy figure)



IL-o: interleukin originator; IL-b; interleukin biosmiliar; IS-b; Immunosuppressive biosmiliar; IS-o; Immunosuppressive originator; TNF-o: TNF alpha inhibitor originator; TNF-b; TNF alpha inhibitor biosimilar.

The absolute frequency in terms of switch, multiple switch, switch back and swap will be reported in table 2. In this analysis also the switch between biosimilars of the same active ingredient will be evaluated. Whether possible, the analysis will be stratified by sex and age (≤18/19-44/45-64/65-79/≥80).

Table 2. Frequency of switch and swap among biological drugs (originator and biosimilars) by indication and drug class (dummy table)

	TNF-alpha inhibitors	**Anti-interleukin**	**Selective immunosuppressant**	**Overall**
Rheumatological indications				
No switch/no swap, n (%)				
Switch, n (%)				
Switch to biosimilar (same AI)				
Switch to originator (same AI)				
Switch to biosimilar (different AI)				
Switch to originator (different AI)				
Multiple switch				
Switch back				
Swap, n (%)				
Swap to TNF-alfa inhibitors*	-			
Swap to anti-interleukin*		-		
Swap to selective immunosuppressant*			-	
Dermatological indications				
##Same as rheumatological##				
Gastroenterological indications				
##Same as rheumatological##				

AI: active ingredient; * only biological drugs

<u>Median time to switch and swap</u>

Time to switch and swap will be described (table 3) using a Kaplan Meier approach stratifying by indication and class of biological drugs. Patients will be followed from index date to first switch to biosimilar / originator, switch back, swap (to biological TNF-alfa inhibitor, to anti-interleukin, to

selective immunosuppressant), multiple switch (2nd switch or swap). Also in this case, if possible, analysis will be stratified by sex and age (≤18/19-44/45-64/65-79/≥80) Median time will be also calculated.

Cox Models

A multivariate COX proportional hazards model will be used to analyze predictors of single switch / swap / multiple switches / switch back. To select only medical switch only switch to different active principles will be considered. Results of the Cox model will be reported as HR with 95%CI and represented using forest plots. Analyses will be stratified by indication of the index drug (i.e. rheumatological, dermatological and gastroenterological indication). Variables included in the models will be age (≤18/19-44/45-64/65-79/≥80), sex (female/male), type of index drug (originator/biosimilar), index class of biological drug (TNF-a/anti-interleukin/selective immunosuppressant), comorbidities, previous use of drugs and use of drugs before event - 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 respected a time-dependent approach will be used.

Variables definition

Exposure:

Using drugs dispensation data, the following variables will retrieved.

- Index drug: For each index drug active ingredient (ATC) and originator/biosimilar information (AIC). The list of biological drugs to be included in the study is reported in Table A1.
- Record of biological drug during follow-up: active ingredient (ATC) and originator/biosimilar information (AIC).
- Class of biological drug: each active ingredient will be classified according to mechanism of action (TNF-alpha inhibitors/ anti-interleukin drugs/ selective immunosuppressant). See table A1 for classification.

Events:

- Switch: Patients with a record of any biological drug (of the same class) other than the index biological drug (different ATC or different AIC) during follow-up will be considered as switcher. Each switch will be characterized as 1) switch to originator or 2) switch to biosimilar. The type of active ingredient and AIC will be retrieved. Medical switch will be defined as a switch to an active principle different from the previous one.
- Swap: Patients with a record of any 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. The type of active ingredient and AIC will be retrieved.
- Multiple switch: Patients will be characterized as multiple switchers if switch/swap occurs ≥2 times during follow up.
- Switch back: As for multiple switchers, also switching back to previous type of biological drug (same ATC) for which they were previously exposed 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.

Other variables:

- 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 specific algorithms described elsewhere: Psoriasis and psoriatic arthiritis,[16–20] Chron disease and Ulcerative colitis, [21] Rheumatoid arthritis, [22] and ankylosing spondylitis. [23]
- Previous use of drugs: Record of one of these drugs in the one year before index date using dispensing data: cDMARDs, tsDMARDs, NSAIDs, Corticosteroids.
- Use of drugs from index date to event: Record of one of these drugs from index date to event (switch, swap, 2nd switch/swap, switch back) will be retrieved: cDMARDs, tDMARDs, NSAIDs, Corticosteroids.
    - Note: Time in which these records will be searched will be different on the basis of event (see time to switch/swap variable).
- Comorbidities: Previous record (1 year before index date) of 1) infections, 2) heart failure 3) Acute myocardial infarction 4) diabetes 5) hypertension 6) BPCO, 7) Other IMIDs for which an algorithm is available
- Charlson Comorbidity index (If possible) See reference Quan et al. [24]

As for codes please check table A2 in the appendix.

Sensitivity analyses

1) Switch pattern of patients with less than 6 months of follow-up
2) Whether necessary analysis was conducted according to active ingredient

Limitations

Missing information such as duration of the disease is missing. Moreover, as for drugs such as NSAIDs information in administrative data may be lacking. Finally, we will use as proxy of medical switch in the COX analysis a switch to another active ingredient (this proxy is not validated).

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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	Concomitant treatment	Condition	Original (bold) and biosimilars approved by EMA
TNF-alpha inhibitors	Infliximab - L04AB02	Rheumatoid arthritis	+ MTX	Adults: 1) active disease previously treated with DMARDs or MTX 2) severe, active and progressive disease not previously treated with MTX or DMARDs	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		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	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		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	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		Psoriatic arthritis	+ MTX or alone (intolerance)	Adults: active and progressive disease not responders to DMARDs	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		Ankylosing spondylitis	-	Adults: severe, active disease not responders to conventional therapy	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		Psoriasis	-	Adults: moderate to severe disease not responders to MTX, ciclosporin or PUVA	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
	Etanercept - L04AB01	Rheumatoid arthritis	+ MTX or alone (intolerance)	Adults: 1) moderate to severe active disease not responders to DMARDs or MTX; 2) severe, active and progressive disease not previously treated with MTX	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		Juvenile idiopathic arthritis	-	Pediatric (2+): polyarthritis and extended oligoarthritis not responders or intolerant to MTX	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		Psoriatic arthritis	-	Adults: active and progressive disease not responders to DMARDs Pediatric (12+): not responders or intolerant to MTX	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		Axial spondylarthritis	-	Adults: 1) severe, active disease not responders to conventional therapy; 2) severe non-radiographic disease with objective signs of inflammation not responders to NSAIDs	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		Plaque psoriasis	-	Adults: Moderate to severe disease not responders or intolerant to systematic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Chronic disease inadequately controlled or intolerant to systematic therapy or phototherapy	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
	Adalimumab - L04AB04	Rheumatoid arthritis	+MTX or alone (intolerance)	Adults: 1) moderate to severe active disease not responders to DMARDs or MTX; 2) severe, active and progressive disease not previously treated with MTX	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Juvenile idiopathic arthritis	+ MTX or alone (intolerance)	Pediatric (2+): active polyarticular disease not responders to DMARDs; Pediatric (6+): active enthesitis-related disease polyarticular disease not responders or intolerant to conventional therapy	**Humira®,** Hulio®, Hyrimoz®, Amgevita® Idacio® Imraldi® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®

		Axial spondylarthritis	-	Adults: 1) severe, active disease not responders to conventional therapy; 2) severe non-radiographic disease with objective signs of inflammation not responders to NSAIDs	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Psoriatic arthritis	-	Adults: active and progressive disease not responders to DMARDs	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Psoriasis	-	Adults: moderate to severe disease who are candidate to systemic therapy	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Plaque psoriasis	-	Pediatric (4+): Severe chronic disease not responders to topical therapy or phototherapy	**Humira®,** Hulio®, Hyrimoz®, Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Hidradenitis suppurativa	-	Adults and adolescent (12+): moderate to severe active disease not responders to conventional therapy	**Humira®,** Hyrimoz® Amgevita® Idacio® Imraldi® Hefiya® Libmyris® Amsparity®
		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	Adults: **Humira®,** Hyrimoz® Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity® Pediatric: **Humira®,** Hulio®, Hyrimoz® Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		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	Adults: **Humira®,** Hyrimoz® Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity® Pediatric: **Humira®,** Hyrimoz® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
		Uveitis	-	Adults: non-infectious intermediate, posterior and panuveitis not responders or intolerant to corticosteroids Pediatric (2+): chronic non-infectious anterior disease not responders or intolerant to conventional therapy	Adults: **Humira®,** Hyrimoz® Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity® Pediatric: **Humira®,** Hulio® Hyrimoz® Amgevita® Idacio® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
	Certolizumab – L04AB05	Rheumatoid arthritis,	+MTX or alone (intolerance)	Adults: 1) moderate to severe active disease not responders to DMARDs or MTX; 2) severe, active and progressive disease not previously treated with MTX or DMARDs	**Cimzia®**
		Axial spondylarthritis		Adults: 1) severe, active disease not responders to NSAIDs; 2) severe non-radiographic disease with objective signs of inflammation not responders to NSAIDs	**Cimzia®**
		Psoriatic arthritis	+MTX or alone (intolerance)	Adults: active and progressive disease not responders to DMARDs	**Cimzia®**
		Plaque psoriasis		Adults: Moderate to severe disease candidates to systemic therapy	**Cimzia®**
	Golimumab L04AB06	Rheumatoid arthritis	+ MTX	Adults: 1) moderate to severe active disease not responders to DMARDs or MTX; 2) severe, active and progressive disease not previously treated with MTX	**Simponi®**
		Juvenile idiopathic arthritis	+ MTX	Pediatric (2+): active polyarticular disease not responders to DMARDs;	**Simponi®**
		Axial spondylarthritis		Adults: 1) severe, active disease not responders to conventional therapy; 2) severe non-radiographic disease with objective signs of inflammation not responders to NSAIDs	**Simponi®**
		Psoriatic arthritis	+MTX or alone	Adults: active and progressive disease not responders to DMARDs	**Simponi®**
		Ulcerative colitis		Adults: moderately to severely active disease not responders to corticosteroids/6-MP or AZA or intolerant	**Simponi®**
Anti-interleukin	*Anakinra – L04AC03*	Rheumatoid arthritis	+ MTX	Adults: sign and symptoms of the disease not responders to MTX alone	**Kineret®**
		COVID-19		Adults: with pneumonia requiring supplement oxygen at risk of severe respiratory failure	**Kineret®**

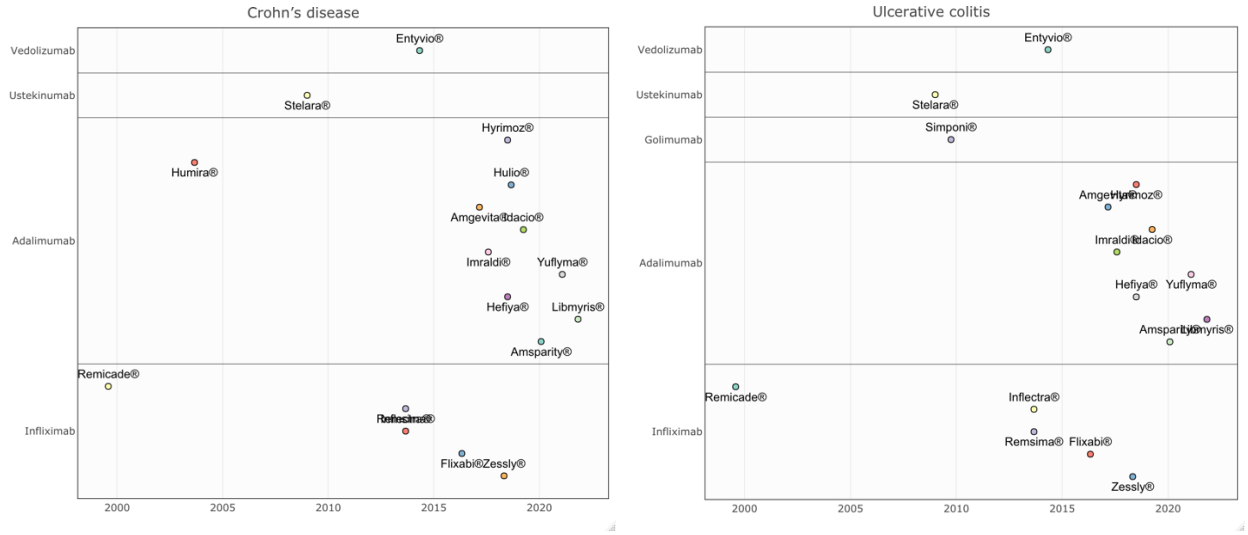
		Periodic fever syndrome		Pediatric (8 months+) and adults: autoinflammatory periodic fever syndromes	**Kineret®**
		Cryopyrin-Associated Periodic Syndromes		Pediatric and adults	**Kineret®**
		Familial Mediterranean Fever	+ Colchicine (if appropriate)		**Kineret®**
		Still's Disease	+/- DMARDs	Pediatric (8 months+) and adults: 1) systemic features of moderate to high disease activity, 2) disease activity after NSAIDs	**Kineret®**
	Tocilizumab - L04AC07	Rheumatoid arthritis	+ MTX or alone (intolerance)	Adults: 1) moderate to severe active disease not responders to DMARDs or TNF antagonists; 2) severe, active and progressive disease not previously treated with MTX	**RoActemra®**
		COVID-19		Adults: with pneumonia requiring supplement oxygen or mechanical ventilation receiving corticosteroids	**RoActemra®**
		Juvenile idiopathic arthritis	+ MTX or alone (intolerance)	Pediatric (2+): 1) active systemic disease not responders to NSAIDs and corticosteroids 2) polyarthritis not responders to MTX	**RoActemra®**
		Cytokine release syndrome		Pediatric (2+) and adults: CART-T cell induced severe disease	**RoActemra®**
	Secukinumab - L04AC10	Plaque psoriasis		Adults: Moderate to severe disease candidates to systemic therapy	**Cosentyx®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders to DMARDs	**Cosentyx®**
		Axial spondylarthritis		Adults: 1) active disease not responders to conventional therapy; 2) active non-radiographic disease with objective signs of inflammation not responders to NSAIDs	**Cosentyx®**
	Ustekinumab - L04AC05	Crohn's disease		Adults: moderate to severe active disease not responders to conventional therapy of TNF alfa antagonist	**Stelara®**
		Ulcerative colitis		Adults: moderately to severely active disease not responders to conventional therapy or biologic or intolerant	**Stelara®**
		Plaque psoriasis		Adults: Moderate to severe disease not responders or intolerant to systematic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Moderate to severe disease inadequately controlled or intolerant to systematic therapy or phototherapy	**Stelara®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders to DMARDs	**Stelara®**
	Ixekinumab - L04AC13	Plaque psoriasis		Adults: Moderate to severe disease candidates to systematic therapy	**Taltz®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders to DMARDs	**Taltz®**
	Brodalumab - L04AC12	Plaque psoriasis		Adults: Moderate to severe disease candidates to systematic therapy	**Kyntheum®**
	Sarilumab - L04AC14	Rheumatoid arthritis	+ MTX or alone (intolerance)	Adults: 1) moderate to severe active disease not responders or intolerant to DMARDs	**Kevzara®**
	Guselkumab - L04AC16	Plaque psoriasis		Adults: Moderate to severe disease candidates to systematic therapy	**Tremfya®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders or intolerant to DMARDs	**Tremfya®**
	Tildrakizumab - L04AC17	Plaque psoriasis		Adults: Moderate to severe disease candidates to systematic therapy	**Ilumetri®**
	Risankizumab - L04AC18	Plaque psoriasis		Adults: Moderate to severe disease candidates to systematic therapy	**Skyrizi®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders or intolerant to DMARDs	**Skyrizi®**

Selective immunosuppressants	*Abatacept – L04AA24*	Rheumatoid arthritis	+ MTX	Adults: 1) moderate to severe active disease not responders to DMARDs or MTX or TNF alfa antagonists; 2) highly active and progressive disease not previously treated with MTX	**Orencia®**
		Psoriatic arthritis	+ MTX or alone	Adults: active disease not responders or intolerant to DMARDs or MTX (addiotional systematic therapy not required)	**Orencia®**
		Juvenile idiopathic arthritis	+ MTX or alone (intolerance)	Pediatric (2+): polyarthritis not responders to DMARDs	**Orencia®**
	Vedolizumab - L04AA33	Crohn's disease		Adults: moderate to severe active disease not responders to conventional therapy of TNF alfa antagonist	**Entyvio®**
		Ulcerative colitis		Adults: moderately to severely active disease not responders/intolerant to conventional therapy or TNF alpha inhibitors	**Entyvio®**
		Pouchitis		Adults: moderate to severe active disease who undergone proctocolectomy and ileal pouch anal anastomosis and not responders to antibiotics	**Entyvio®**
	Rituximab - L01XC02(old)/ L01FA01	Non-Hodgkin lymphoma	Chemotherapy (adult point 1 and pediatric); CHOP (point 4)	Adults: 1) Untreated with stage III-IV follicular lymphoma; 2) Manteinance therapy (monotherapy); 3) Stage III-IV follicular lymphoma chemoresistant or second or subsequent relapse; 4) C20 positive diffuse large B cell lymphoma Pediatric (6 months +):Untreated C20 positive diffuse large B cell lymphoma / Burkitt lymphoma /Burkitt leukemia or Burkitt.like lymphoma	**Mabthera®** Ruxience® (no pediatriac) Truxima® (no pediatriac) Blitzima® (no pediatric) Riximyo® (no pediatric) Rixathon® (no pediatric)
		Chronic lymphocytic leukemia	Chemotherapy	Patients with previously untreated and relapsed/refractory CLL	**Mabthera®** Ruxience® (no pediatriac) Truxima® (no pediatriac) Blitzima® (no pediatric) Riximyo® (no pediatric) Rixathon® (no pediatric)
		Rheumatoid arthritis	+ MTX	Adults: severe active disease not responders to DMARDs including TNF alfa antagonists	**Mabthera®** Ruxience®, Truxima® Riximyo® Rixathon®
		Granulomatosis	+ glucocorticoids	Adults: severe active disease with polyangiitis and microscopic polyangitiis	**Mabthera®** Ruxience®, Truxima® Riximyo® Rixathon®
		Pemphigus vulgaris		Patients with moderate to severe disease	**Mabthera®** Ruxience® (no pediatriac) Truxima® (no pediatriac) Riximyo® (no pediatric) Rixathon® (no pediatric)

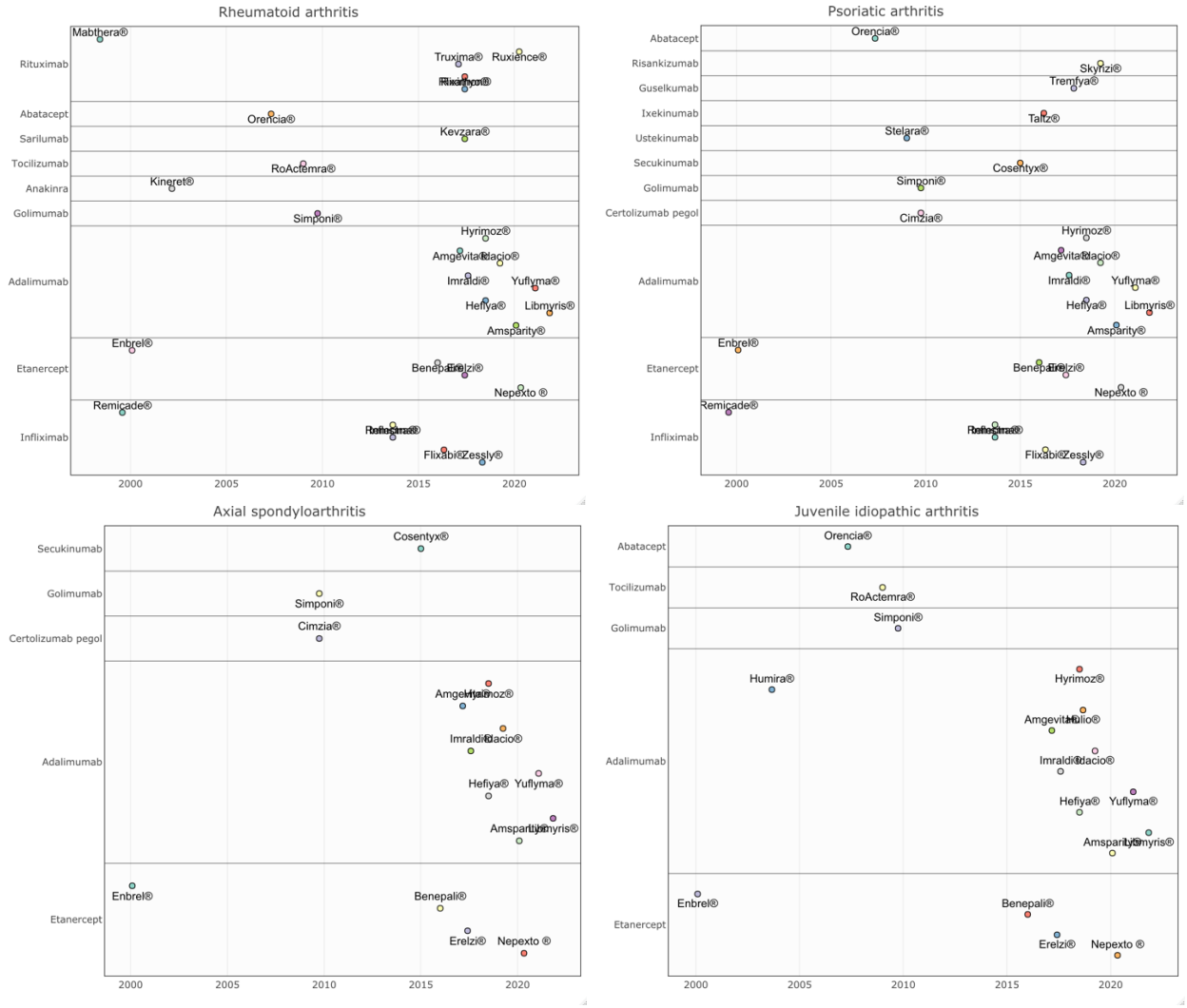
6-MP: 6-mercaptopurine; AZA: azathioprine; DMARDs: disease-modifying antirheumatic drugs; MTX: Methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; PUVA: psoralen and ultraviolet-A light

Figure A1. Timeline of approval of biological drugs (and corresponding biosimilars) for IMIDs.

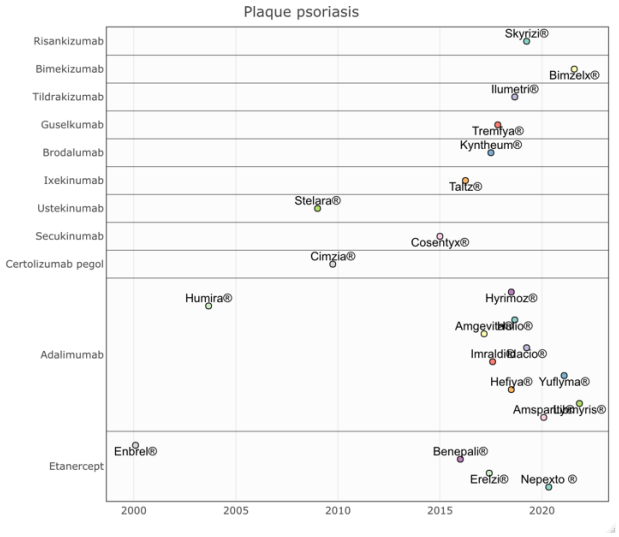
Gastrointestinal diseases



Rheumatological diseases



Dermatological disease



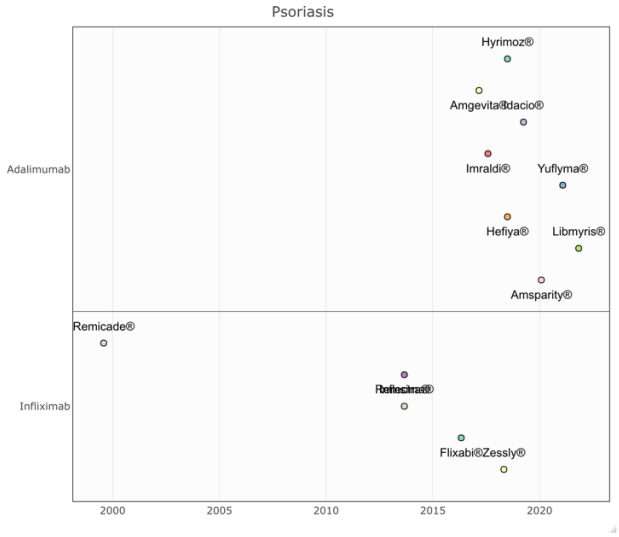


Table A2. Codes for variable identification

Variable	Definition	Databanks					
		Hospital discharge records (HDR)	**Exemption registry (EXE)**	**Dispensing from hospital pharmacies (DDRUG)**		**Dispensing from community pharmacies (DRUG)**	
		ICD9CM	**ICD9 /exemption codes**	**ATC**	**AIC**	**ATC**	**AIC**
Biologic drug use	Record of biologic drug from index date to end of follow up DDRUG			TNF-alfa (L04AB02, L04AB01, L04AB04, L04AB05, L04AB06) interleukin (L04AC03, L04AC07, L04AC10, L04AC05, L04AC13, L04AC12, L04AC14, L04AC16, L04AC17, L04A) selective inhibitors (L04AA24, L04AA33, L01FA01/ L01XC02)	Not attached file excel but available upon request		
Indication of use							
Rheumatoid Arthritis	SDO OR EXE OR DDRUG/DRUG	714*	006 OR 006.714* OR 714*	Auranofin (M01CB03) OR sodio aurotiosolfate (M01CB02) OR baricitinib (L04AA37) or leflunomide L04AA13) or filgotinib L04AA45) or sarilumab (L04AC14)		Auranofin (M01CB03) OR sodio aurotiosolfate (M01CB02) OR baricitinib (L04AA37) or leflunomide L04AA13) or filgotinib L04AA45) or sarilumab (L04AC14)	
Psoriatic arthritis	HDR or EXE or (PsO and DDRUG/DRUG)	696.0 OR (696.1 AND 721*)	045.696.0 OR 696.0	Abatacept (L04AA24) OR anakinra (L04AC03) OR azathioprine (L04AX01) or certolizumab (L04AB05) or golimumab (L04AB06) or hydroxychloroquine (P01BA02) or leflunomide (L04AA13) or rituximab (L01FA01/ L01XC02) or sulfasalazine (A07EC01) or tocilizumab (L04AC07)		Abatacept (L04AA24) OR anakinra (L04AC03) OR azathioprine (L04AX01) or certolizumab (L04AB05) or golimumab (L04AB06) or hydroxychloroquine (P01BA02) or leflunomide (L04AA13) or rituximab (L01FA01/ L01XC02) or sulfasalazine (A07EC01) or tocilizumab (L04AC07)	
Axial spondylarthritis	SDO OR EXE	720.0	720.0 or 054.720.0 or 054				

Crohn's disease	HDR or EXE	555*	555 or 009.555				
Ulcerative colitis	HDR OR EXE OR (EXE and DDRUG/DRUG)	556*	556 or 009.556	Golimumab (L04AB06) or Budenoside (R03BA02) or mesalazine (A07EC02) or balsalazide (A07EC04)		Golimumab (L04AB06) or Budenoside (R03BA02) or mesalazine (A07EC02) or balsalazide (A07EC04)	
Psoriasis	HDR OR EXE OR DDRUG	696.1	045.696.1 or 696.1	Brodalumab (L04AC12) or tildrakizumab (L04AC17) or Risankizumab (L04AC18) or calcipotriol (D05AX02)		Brodalumab (L04AC12) or tildrakizumab (L04AC17) or Risankizumab (L04AC18) or calcipotriol (D05AX02)	
Comorbidities							
Infections	≥1 record in the year before index date (primary or secondary position)	**Herpes Zoster** (053.x), **Herpes simplex** (054.x) **Tuberculosis** (010.x-018.x), **Candida** (112.x), **Bacteremia/ Sepsis** (038,78552,7907,99591,99592), **Hepatitis** (070.3, 070.2, 070.9,070.1), **HIV** (042.x) **Pulmonitis** (480.x, 481.x, 482.x, 483.x,484.x, 485.x, 486.x,487.x), **Fungal infections** (039.x; 110.x; 111.x; 112.x; 114.x; 115.x; 116.x; 117.x; 118; 202.1x; 484.6; 484.7; 711.6x), **Conjunctivitis** (077.8), **Upper respiratory tract infections** (465.x; 460.x; 461.x; 462.x, 463.x; 464.x, 487.1), **COVID-19** (480.3; 079.82), **Infection of central nervous system** (00321, 0360,0361,045, 046,047, 048,049, 0530,0543, 05472,05601, 05821, 05829,062, 063,064,06641, 0721,0722, 09181,0942, 09481,09882, 10081,130,320, 321, 3230, 3231,3232, 3234,3236,324) **Osteomyelitis** (003.24), pyelonephritis (590.*), **Bronchitis** (466.x; 490.x), **Urinary infections** (595.x; 597.x; 599.x), **Gastrointestinal infections** (009.0;009.1) endocarditis (03642, 07422, 0932,09884,421, 42292) **skin infection / soft tissue infections** (035, 0400, 56961, 681,682, 686, 72886, 7854)		Herpes zoster (D06BB03 J05AB01, S01AD03) Fungal infections (J02A*)		Herpes zoster (D06BB03 J05AB01, S01AD03) Fungal infections (J02A*)	
acute myocardial infarction (y/n)	≥1 record in the year before index date (any position)	410.xx, 411.xx, 412, 413.x, 414.xx					

Heart failure	≥1 record in the year before index date (any position)	428.x 398.91 402.01 402.11 402.91 404.01 404.11 404.91 404.03 404.13 404.93					
BPCO		491.2x , 492.8, 496					
Stoke		433.x1 434.x1 435.x 436 437.1x 437.9x 438.x*					
Diabetes		250.x					
Hypertension		401.x–405.x 437.2					
Previous use of drugs or during follow up							
csDMARDs	Previous: in the year before index date/ and to be searched from the from index date to event			azathioprine (ATC: L04AX01), ciclosporin (ATC: L04AD01), chloroquine (ATC: P01BA01), sodium aurothiosulfate (ATC: M01CB01), auranofin (ATC:M01CB03), hydroxychloroquine (ATC: P01BA02), leflunomide (ATC: L04AA13), methotrexate (ATC: L04AX03), sulfasalazine (ATC: A07EC01 mesalazine (ATC: A07EC02), balsalazide (ATC: A07EC04)		azathioprine (ATC: L04AX01), ciclosporin (ATC: L04AD01), chloroquine (ATC: P01BA01), sodium aurothiosulfate (ATC: M01CB01) auranofin (ATC:M01CB03), hydroxychloroquine (ATC: P01BA02), leflunomide (ATC: L04AA13), methotrexate (ATC: L04AX03), sulfasalazine (ATC: A07EC01) mesalazine (ATC: A07EC02), balsalazide(ATC: A07EC04)	
tsDMARDs (JAKi)	Previous: in the year before index date/ and to be searched from the from index date to event			L01EJ*; baricitinib (L04AA37), tofacitinib (L04AA29), upadacitinib (L04AA44), abrocitinib (D11AH08)		L01EJ*; baricitinib (L04AA37), tofacitinib (L04AA29), upadacitinib (L04AA44), abrocitinib (D11AH08)	
NSAIDs	Previous: in the year before index date/ and to be searched from the from index date to event			M01A, N02BE01, N02BA01		M01A, N02BE01, N02BA01	
Corticosteroids	Previous: in the year before index date/ and to be searched from the from index date to event			H02AB, H02BX		H02AB, H02BX	