Study protocol

UtiLization pattErns, access to healthcare facilities and ecONomic Assessment of JAKi dRugs useD in rheumatOid arthritis patients in Tuscany: the LEONARDO study

Version 1.0 – 10/06/2020

STUDY ESSENTIAL INFORMATION

Title	**Utilization patterns, access to healthcare facilities and economic assessment of JAKi drugs used in rheumatoid arthritis patients in Tuscany: the LEONARDO study**
Protocol version	1.0
EU PAS REGISTRY NUMBER	EUPAS35746
Version date	June 10th, 2020
Active substance object of the study	*JAK inhibitors* • Tofacitinib • Baricitinib
Promoter	Galapagos NV
Research question and objectives	This study will describe the population of JAK inhibitors new users in Tuscany between January 1st 2018 to December 31st 2019, including history of disease modifying anti rheumatic drugs (DMARDs) use, accesses to Emergency Department (ED), hospitalizations, access to specialist rheumatology encounters by means of real world data. This study will also provide an economic evaluation of these patients before and after the treatment with JAKi.
Country of study	Italy
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I. List of Abbreviations

ARS: agenzia Regionale di Sanità
ATC: anatomical therapeutic chemical
bDMARD: biologic disease modifying anti-rheumatic drug
csDMARD: conventional synthetic disease modifying anti-rheumatic drug
DMARD: disease modifying anti-rheumatic drug
ED: Emergency department
ENCEPP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD: international classification of diseases
IMID: Immuno-mediated inflammatory diseases
JAK: Janus Kinase
JAKi: Janus Kinase Inhibitor
RA: Rheumatoid Arthritis
SSSA: Scuola Superiore Sant'Anna
TNF: tumor necrosis factor
UADRM: Unit of Adverse Drug Reaction Monitoring
UniPi: University of Pisa

II. Investigators and institutions

Name	Role in the study	Institution
Marco Tuccori	Principal investigator	Unit of Adverse Drug Reaction Monitoring (UADRM) – University Hospital of Pisa, Pisa Italy (ENCEPP Centre)
Rosa Gini	Investigator	Agenzia Regionale di Sanità (ARS) Toscana, Florence, Italy (ENCEPP Centre)
Giuseppe Turchetti	Investigator	Scuola Superiore Sant'Anna (SSSA), Pisa, Italy
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Ersilia Lucenteforte	Investigator	Department of Clinical and Experimental Medicine, University of Pisa (UniPi), Pisa, Italy

*UADRM and UniPi represent the coordinating centre

III. Milestones

This is a study conducted on administrative healthcare database. Prospective collection of data is not scheduled. Below a summary of the timeline based on activities and responsibilities.

Activity	**Responsability**	**Expected timeline**
Complete study protocol	UniPi-UADRM, SSSA, ARS	July 1st 2020
Protocol EU PAS registration	UniPi-UADRM	July 1st 2020
Data extraction and data processing	ARS	July 7th 2020
Data analysis	UniPi-UADRM, SSSA	July 10th 2020
Report drafting	UniPi-UADRM, SSSA	July 15th 2020
Report reviewing	ARS	July 20th 2020
Report comments	Company	July 25th 2020
Report finalisation	UniPi-UADRM, SSSA, ARS	July 31st, 2020

1. BACKGROUND

JAK-inhibitors (JAKi) are a recently developed and approved class of drugs for the treatment of moderate-to-severe Rheumatoid Arthritis (RA) [1,2]. Janus kinases are a group of four intracellular tyrosine kinases mediating the signal transduction of multiple cytokines implicated in several functions including the activation of inflammation [2]. Their crucial role in sustaining chronic inflammation, by stimulating the activity of T and B cells, makes them an interesting pathway to target in RA and other immuno-mediated inflammatory diseases [3] (IMID)

Beside their indubitable efficacy, these drugs have been associated with safety concerns [4,5] that must be explored in details and might affect the cost of treatments. An appropriate use and monitoring of the population is recommended.

In 2018, two drugs belonging to the class of JAKi were approved in Italy for the treatment of moderate to severe RA: tofacitinib and baricitinib. Patients diagnosed with RA usually can respond to conventional disease modifying anti-rheumatic drugs (DMARDs) (i.e. methotrexate) for up to 3 years [6]. Then, these drugs usually start failing to provide the expected effect and a treatment with biologic DMARDs (bDMARDs) can be started. Real-life data demonstrate that within a timeframe of 3–5 years since first bDMARD introduction, about 50% of treated RA patients discontinue the biologic therapy and need to be managed with the choice of an alternative treatment option, such as JAKi [7]. Therefore, it is reasonable to expect that JAKi are used within 10 years from the first RA treatment, but these data should be verified.

In this study, we will identify and describe new users of JAKi in Tuscany from 2018 (year of approval in the treatment of severe to moderate RA) to 2019, and describe their utilization of the Regional Healthcare System facilities after treatment initiation, including an economic assessment. Since JAKi are used as second line in patients with moderate to severe RA non-responders to biologic DMARDs, we will provide an estimation over time of the new users of bDMARDs with and without history of access to rheumatoid arthritis wards in Tuscany.

2. RESEARCH QUESTIONS AND OBJECTIVES

1. What was the history of utilization of DMARDs in patients initiating JAKi drugs in Tuscany, during 10 years leading to JAKi initiation?
2. What was the yearly cost of patients before initiating treatment with a JAKi in Tuscany?
3. What was the pattern of Healthcare utilization (Emergency Department access, Hospitalization, access to specialist visits) after initiating JAKi in Tuscany?
4. What was the estimated cost per year after initiating JAKi in Tuscany?
5. What was the number of new users of anti-TNF in rheumatologic patients over time in Tuscany?

3. RESEARCH METHODS

3.1 Study design

This is a descriptive, retrospective cohort study.

3.2 Data source

Data will be retrieved from administrative healthcare databases of Tuscany. Particularly, the study will use records of hospital discharge (cause of hospitalization [ICD-9 code], date of hospitalization and discharge, cost of hospitalization), of emergency department admission (cause of Ed admission [ICD-9 code], date of ED admission and discharge, cost of Ed admission), of drug dispensations (drugs [ATC codes], gender, birth date, dates of drug dispensation, drug doses, drug costs), and of specialist encounters (rheumatologic visits, date of rheumatologic visits, cost of visits) [8]. Data were linked among the different databases using an anonymous unique patient code.

3.3 Cohort definition

3.3.1 Research questions 1 and 2

Inclusion criteria

Patients will be identified by the first prescription of a JAKi (table 1) between January 1st, 2018 and December 31st, 2019. Cohort entry will be defined by the first prescription of JAKi.

Exclusion criteria

a) Patients with less than 10 years of records in the look back period

b) Patients with history of cancer or use of anti-cancer drugs in the look back period

c) patients aged ≤ 18 at index date

3.3.2 Research questions 3 and 4

Inclusion criteria

Patients will be identified by the first prescription of a JAKi between January 1st, 2018 and June 30th, 2019. Cohort entry will be defined by the first prescription of JAKi. Only patients with at least six months of observation after cohort entry will be included.

Exclusion criteria

a) Patients with less than 10 years of records in the look back period

b) Patients with history of cancer or use of anti-cancer drugs in the look back period

c) patients with age ≤ 18

Patient observation will be censored at the end of study period, loss to follow-up, or death whichever comes first.

3.3.3. Research question 5

Inclusion criteria

Patients will be identified by the first prescription of an bDMARD (table 1) between January 1st, 2014 and December 31st, 2019. Cohort entry will be defined by the date of the first prescription of a bDMARD. We included patients with at least one visit in a Tuscan rheumatology ward before in the year preceding cohort entry.

Exclusion criteria

a) Patients with less than 1 year of look back period

Table 1 Study drugs

Drug class	**Drug name**	**ATC code**
Targeted synthetic DMARDs (tsDMARDs) – JAKi	Tofacitinib	L04AA29
	Baricitinib	L04AA37
Conventional sysntetic DMARDs (csDMARDs)	Metotrexate	L01BA01
	Leflunomide	L04AA13
	Azathioprine	L04AX01
	Cyclosporin	L04AD01
	Hydroxychloroquine	P01BA02
	Minocycline	A01AB23
	Mycophenolate	L04AA06
	Sulfasalazine	A07EC01
anti-TNF biologic DMARDs (bDMARDs)	Adalimumab	L04AB04
	Certolizumab pegol	L04AB05
	Etanercept	L04AB01
	Golimumab	L04AB06
	Infliximab	L04AB02
non-anti-TNF biologic DMARDs (bDMARDs)	Abatacept	L04AA24
	Rituximab	L01XC02
	Tocilizumab	L04AC07
	Sarilumab	L04AC14

3.4 Variables

For each subject in the cohort (research questions 1-4), the following variables will be computed:

- Use of any DMARD before cohort entry (yes or no)
- Number of dispensation of any DMARD before the cohort entry
- Number and causes of Emergency department admission before cohort entry
- Number and causes of Emergency department admission after the cohort entry
- Number and causes of hospitalization before the cohort entry
- Number and causes of hospitalization after the cohort entry
- Number of rheumatologic specialist visits before the cohort entry
- Number of rheumatologic specialist visits after the cohort entry
- Time from the date of the first ever dispensing of any DMARD to cohort entry
- Time from the date of the first ever dispensing of any anti-TNF DMARD to cohort entry
- Time from cohort entry to the date of the first access to emergency department
- Time from cohort entry to the date of the first hospitalization
- Time from cohort entry to the date of the first specialist visit (rheumatologic)
- Cost of patient accesses to emergency department
- Cost of patient hospitalizations
- Cost of DMARD drugs dispensed to patient
- Cost of patient accesses to specialist visits
- Unit costs of DMARD and JAKi drugs

3.5 Covariates

The following covariates will be considered in the analysis:

- Age at cohort entry
- Gender
- Type of JAKi dispensed at cohort entry (tofacitinib/baricitinib)
- Calendar year of cohort entry

4. DATA ANALYSIS

4.1 Research question 1

1) Count of patients receiving their first JAKi in the study period (overall and stratified by year, age, gender and by first JAKi) (output table 1a)
2) Count of patients with history of DMARD dispensation before cohort entry (output table 1b)
3) Count of number of dispensations, overall and categorized (0, 1-3, 4-9, ≥10), mean of number of dispensation per patient, and of each DMARDs before cohort entry (output table 1c and 1d)
4) Time, mean and categorized (<1 year; 1 ≤ years <2; 2 ≤ years < 3; 3 ≤ years < 5; 5 ≤ years ≤ 10), from the first ever DMARD dispensation and cohort entry (output table 1e)
5) Time, Time, mean and categorized (<1 year; 1 ≤ years <2; 2 ≤ years < 3; 3 ≤ years < 5; 5 ≤ years ≤ 10), from the first ever anti-TNF dispensation and cohort entry (output table 1e)

Output table 1a – Characteristics of JAKi users			
	Overall (n)	2018 (n)	2019 (n)
JAKi new users			
Female n (%)			
Male n (%)			
Tofacitinib			
Baricitinib			
Age (mean ± SD)			
Age (median ± IQR)			

SD: standard deviation; IQR: interquartile range

Output table 1b: History of DMARD use in new users of JAKi	
DMARD	**Patients n (%)**
No use	
Any use	
csDMARDS	
Metotrexate	
Leflunomide	
Azathioprine	
Cyclosporin	
Hydroxychloroquine	
Minocycline	
Mycophenolate	
Sulfasalazine	
anti-TNF biologic DMARDs	
Adalimumab	
Certolizumab pegol	
Etanercept	
Golimumab	
Infliximab	
non anti-TNF biologic DMARDs	
Abatacept	
Rituximab	
Tocilizumab	
Sarilumab	
csDMARDs and anti-TNF DMARDs only	
csDMARDs and non-anti-TNF DMARDs only	
Anti-TNF and non-anti-TNF DMARDs only	

Output table 1d: DMARDs dispensations						
DMARD	**Overall Number of dispensation (n)**	**mean number of dispensation per patients (± SD)**	**Dispensations groups**			
			0 (n)	**1-3 (n)**	**4-9 (n)**	**≥10 (n)**
Conventional sysntetic DMARDs (csDMARDs)						
Metotrexate						
Leflunomide						
Azathioprine						
Cyclosporin						
Hydroxychloroquine						
Minocycline						
Mycophenolate						
Sulfasalazine						
Anti-TNF biologic DMARDs						
Adalimumab						
Certolizumab pegol						
Etanercept						
Golimumab						
Infliximab						
Non anti-TNF biologic DMARDs						
Abatacept						
Rituximab						
Tocilizumab						
Sarilumab						

Output table 1d: Time from first DMARD and from first anti-TNF DMARD to cohort entry		
	First DMARD	First bDMARD
Number of non users (%)		
Number of ever users (%)		
Average time (± SD)		
< 1 year (n)		
1 ≤ years < 2 (n)		
2 ≤ years < 3 (n)		
3 ≤ years < 5 (n)		
5 ≤ years < 10 (n)		

4.2 Research question 2

1) Direct health cost of the population of JAKi users in the year before cohort entry (overall and stratified by type of cost, including cost of dispensed DMARD, cost of emergency department admission, cost of hospitalization, cost of specialist visits) (output table 2a)
2) Direct health cost of the population of JAKi users calculated for the second, the third, the fourth and the fifth year before cohort entry (overall and stratified by type of cost, including cost of dispensed DMARD, cost of emergency department admission, cost of hospitalization, cost of specialist visits) (output table 2a)

Table 2a – Cost in the years preceding the first JAKi prescription					
	In the 1st year before cohort entry	In the 2nd year before cohort entry	In the 3rd year before cohort entry	In the 4th year before cohort entry	In the 5th year before cohort entry
Total cost					
Drugs					
Emergency department access					
Hospitalization					
Specialist visits (rheumatology)					
Mean/Median cost per patient/year					
Drugs					
Emergency department access					
Hospitalization					
Specialist visits (rheumatology)					

4.3 Research question 3

1) Count of number of access to Emergency department for any cause during the follow up (overall and stratified by drug) (table 3a)
2) Count of number of hospitalizations for any cause during the follow up (overall and stratified by drug) (table 3a)
3) Count of number of rheumatologic visits during the follow up (overall and stratified by drug) (table 3a)
4) Count of patients with at least one access to Emergency Department during the follow up (overall and stratified by drug and gender) (Table 3b)
5) Count of patients with at least one hospitalization during the follow up (overall and stratified by drug and gender) (table 3b)
6) Count of patients with at least one rheumatologic visit during the follow up (overall and stratified by drug and gender) (table 3b)
7) In patients with at least one access in emergency department during the follow up, mean time to the first emergency department access (overall and stratified by drug and gender) (table 3b)
8) In patients with at least one hospitalization during the follow up, mean time to the first hospitalization (overall and stratified by drug and gender) (table 3b)
9) In patients with at least one rheumatologic visits during the follow up, mean time to the first rheumatologic visits (overall and stratified by drug and gender) (3b)
10) Count and percentage of causes of emergency department admission during the follow up (3c)
11) Count and percentage of causes of hospitalization during the follow up (3d)

Table 3a: Number of Emergency department (ED) admissions, hospitalizations, specialist visits (rheumatologic)

	ED admissions	Hospitalizations	Specialist visits
Overall (n)			
Tofacitinib (n)			
Baricitinib (n)			

Table 3b: Number of patients with at least 1 Emergency department (ED) admission, hospitalization, and specialist visit (rheumatologic)						
	ED admissions (n)	Time to first ED admission, days (mean ± SD)	Hospitalizations (n)	Time to first Hospitalization, days (mean ± SD)	Specialist visits (n)	Time to first specialist visit, days (mean ± SD)
Overall						
Female						
Male						
Tofacitinib						
Baricitinib						

Table 3c: Causes of access to Emergency department	
Cases (n, %)	Description (ICD-9)

Table 3d: Causes of Hospitalization	
Cases (n, %)	Description (ICD-9)

4.4 Research question 4

1) Direct health cost of the population of JAKi users in the sixth month after the first dispensation (overall and stratified by type of cost, including cost of dispensed DMARD, cost of emergency department admission, cost of hospitalization, cost of specialist visits (rheumatologic)) (table 4a)

Table 4a – Cost in first six months after the first JAKi prescription	
	Cost (€)
Total cost	
Drugs	
Emergency department access	
Hospitalization	
Specialist visits (rheumatology)	
Mean/Median cost per patient	
Drugs	
Emergency department access	
Hospitalization	
Specialist visits (rheumatology)	

4.5 Research question 5

1) Count of number of new users of bDMARDs with at least one rheumatologic visits, stratified by year of first bDMARD dispensation (table 5a). Since for some subject information on visits could be lacking, the count will be the sum of: A + B

A: for subjects with information on visits, we will consider new users of bDMARDs with at least one rheumatologic visits in the year before the date of the first bDMARD dispensation

B: for subjects without information on visits, we will consider new users of bDMARDs assuming the same distribution of the rheumatologic visits of subjects with information (A)

Table 5a – New users of bDMARDs with or without at least one visit in the year before the first anti-TNF dispensation, stratified by year

	2014	2015	2016	2017	2018
Overall new users					
Subjects with information on visit*					
Rheumatologic visits (A)					
Subjects with no information on visits*					
Assumed rheumatologic visits (B)					
New users of bDMARD with at least one rheumatologic visits (A+B)					

* rheumatology, gastroenterology or dermatology

5. QUALITY CONTROL

All data will be managed according to the Good Clinical Practice and the Good Pharmacovigilance Practice referred to the observational studies.

https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html)

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

6. PROTECTION OF HUMAN SUBJECT

This will be a retrospective study; consequently, all treatments have been performed according to the EULAR guidelines and the University Hospital procedures. Any insurance will not be needed.

All data will be managed according with EU data protection directive (95/46/EC), ePrivacy directive (2002/58/EC) and its revision (2009/136/EC) and the General data protection regulations (May 2018). The personnel of the Unit of Rheumatology of Pisa University Hospital involved in the study will manage clinical data according with the privacy protection. To ensure pseudo-anonymization of sensitive data we will use 3 K-anonymity, which are: 1) the unique ID code for patient, 2) the truncated ZIP code (dropped to the first 3 numbers, e.g. 561XX instead of 56126), 3) age as a range of 5 years (e.g. 50-55 years old instead of 53 aged).

Only personnel normally allowed to access patients' sensitive data (clinicians managing patients' care) will be involved in the process of pseudo-anonymization. The other persons involved in the present study will never have access to patients' individual sensitive data.

The agreement between Tuscan Region and ARS, based on the new EU data protection regulations will protect the decrypt process from patient sensitive data to anonymous ID code and vice versa.

7. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Due to the retrospective design of this study, the notification of adverse events detected during the study to the competent authority is not required.

8. DATA HOLDING

Data will be collect in excel file and the promoter and the Principal Investigator will store all documents related to Pathfinder study for at least seven years as electronic and/or paper folders.

9. AMENDMENTS AND DEVIATIONS

This is the original version of the protocol. No amendments or deviations reported.

10. PLAN FOR COMMUNICATION OF STUDY RESULT

Study results will be included in the report on drug use in Tuscany 2020 and presented in the related meeting scheduled for December 2020 in Florence. The study results will be published in a peer review journal and presented in national and international conferences.

11. REFERENCES

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