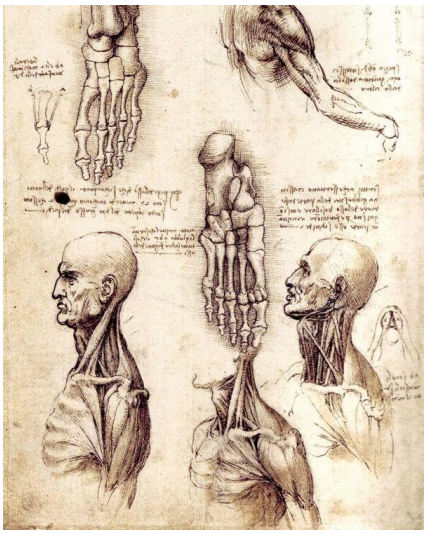
UtiLization pattErns, access to healthcare facilities and ecONomic Assessment of JAKi dRugs useD in rheumatOid arthritis patients in Tuscany: the LEONARDO study

Final Report



Authors

Marco Tuccori

Giuseppe Turchetti

Rosa Gini

Valentina Lorenzoni

Ersilia Lucenteforte

Sabrina Giometto

Claudia Bartolini

Olga Paoletti

Irma Convertino

Sara Ferraro

Emiliano Cappello

Giulia Valdiserra

Corrado Blandizzi

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1 Background

Rheumatoid arthritis (RA) is an immuno-mediated inflammatory disease (IMID) characterized by progressive joint erosion and articular damage, leading to loss of function and comorbidities. Its etiology is still under investigation, but the pathophysiology is linked to defects of the major histocompatibility complex class II genes. Cytokines play a key-role in the pathophysiology of RA and other IMIDs, such as ankylosing spondylitis, psoriatic arthritis (PsA), psoriasis, ulcerative colitis (UC) and Crohn's disease. In RA, several cytokines have been detected in the synovial tissues, such as tumor necrosis factor (TNF), IL(interleukin)-1, IL-6, IL-7, IL-15, IL-17, IL-18, IL-21, IL-23, IL-32, IL-33, and granulocyte-macrophage colony-stimulating factor.[1] Some of these cytokines, such as IL-1, TNF and IL-6, have been employed as pharmacological targets with variable degrees of therapeutic success. In particular, while targeting of IL-1 produces little improvements in RA, anti-TNF and anti-IL-6 drugs are associated with a good clinical response and disease remission.

Notably, cytokines induce transcription pathways through the activation of membrane receptors and signal transducers, making these downstream proteins suitable targets to obtain the therapeutic blockade of inflammatory processes.[2] A large proportion of these cytokines bind type I/II receptors and exert their actions through the Janus kinase (JAK) transduction pathway, which then regulates gene transcription through the activation of signal transducers and activators of transcription (STAT) nuclear factors. JAKs comprise a group of enzymes belonging to the family of tyrosine kinases and consist of four different subtypes (JAK1, JAK2, JAK3, and TYK2). JAK signals can induce the downstream activation of seven STAT factors (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6).[3] When cytokines bind a type I or II receptor, two linked JAK members are activated and initiate a sequence of phosphorylations leading to the downstream phosphorylation and dimerization of STAT factors. The STAT dimer then migrates into the nucleus where it binds specific DNA oligonucleotide sequences thus controlling gene transcription.[4] Each cytokine binds specific type I or II receptors and activate specific JAK pathways. For instance, IL-2, IL-7, IL-9, IL-15 and IL-21 bind γ-common chain receptors, which are coupled with JAK1 and JAK3, activate STAT3 and STAT5,

and are physiologically involved in lymphoid cell maturation, natural killer cell differentiation and B cell class switching.[4] IL-6 binds its receptors, transmembrane (IL-6R) and soluble (sIL-6R), and through a receptor component, the gp130 domain, it activates the JAK-STAT signaling. This pathway then ends with the nuclear translocation of phosphorylated STAT3 and the expression of responsive genes.[5]

The evidence that the blockade of IL-6 receptors modulates the JAK-STAT signaling paved the way to the development of the first-generation JAK inhibitors (JAKi) (e.g. tofacitinib, baricitinib), designated as targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDs), which demonstrated good efficacy in the treatment of RA. However, these drugs are characterized by non-selective inhibition of JAK subtypes with possible safety issues. Subsequently, the new generation of JAKi (including filgotinib and ruxolitinib), able to block more selectively specific JAK members, was developed with the intention of overcoming some safety issues, while preserving the clinical benefits.[4,6–9]

In 2020, the EULAR guidelines recommended the introduction of tsDMARDs as a second line pharmacological approach to the management of RA, along with anti-TNF drugs, included in the class of biologic (b) DMARDs. According to EULAR guidelines, first line therapy in RA patients includes "*MTX plus glucocorticoids (GCs) and stratification according to risk factors upon insufficient response to this therapy within 3 to 6 months. With poor prognostic factors, as presence of autoantibodies, high disease activity, early erosions or failure of two conventional synthetic (cs)DMARDs, any biologioc DMARD (bDMARD) or JAKi should be added to the csDMARD*". The combination of bDMARDs and tsDMARDs with csDMARDs is preferred; however, whenever csDMARDs are contraindicated, the combination of IL-6 inhibitors and tsDMARDs is reported to have some advantages compared with other bDMARDs. "*If a bDMARD or tsDMARD fails, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. If a patient is in persistent remission after having tapered GCs, one can consider tapering bDMARDs or tsDMARDs, especially if*

this treatment is combined with a csDMARD. If a patient is in persistent remission, tapering csDMARD could be considered."[10]

In Italy, there are currently two JAKi approved for treatment of moderate to severe RA: tofacitinib and baricitinib.

1.1 Tofacitinib

Tofacitinib, available in Italy since October 2018 as Xelyanz®, is a non-selective inhibitor of the JAK family members (pan-JAKi), with a moderate preferential affinity for JAK3 and JAK1[8]. These kinases play important roles in the process of inflammation associated with some autoimmune diseases, and tofacitinib helps reduce inflammation and other symptoms[11].

Tofacitinib was first approved by the U.S. Food and Drug Administration (FDA) in 2012 for RA patients, while the European Medicinal Agency (EMA) granted the marketing authorization for tofacitinib to treat adults with RA on March 2017. In 2018, this indication was extended to adults with psoriatic arthritis (PsA) or severe UC[11].

There are currently 175 trials involving tofacitinib recorded on ClinicalTrials.gov[12]. Phase 3 studies are investigating the efficacy and safety of tofacitinib in the treatment of juvenile idiopathic arthritis, AS and psoriasis. Considering the promising results obtained in a clinical trial conducted for juvenile idiopathic arthritis (A3921104)[13], the pharmaceutical corporation Pfizer communicated the intention of filing for this indication with the FDA in 2020[14].

Tofacitinib is currently employed to treat adults with moderate to severe RA and PsA in combination with methotrexate (MTX) after therapeutic failure, adverse events (AEs) or adverse drug reactions (ADRs) following treatment with one or more DMARDs. In addition, tofacitinib can be taken alone by patients with contraindications to MTX. The therapeutic indication for treatment of adult patients with moderate-to-severe active UC is limited to subjects with inadequate response, loss of response, or intolerance to either conventional therapy or a biologic agent. Tofacitinib is available as

tablets for oral administration. For treatment of RA and PsA, the recommended dose is 5 mg taken twice a day, while the recommended regimen for UC consists of 10 mg twice a day for the first 8 weeks and then 5 mg twice a day for maintenance[11].

Tofacitinib is metabolised by cytochrome P450 (CYP) 3A4 and interactions with medicinal products that modulate this activity are likely. Exposure to tofacitinib can increase in patients receiving potent CYP3A4 inhibitors or one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. The total daily dose should be reduced by half in patients receiving potent CYP3A4 inhibitors. By contrast, tofacitinib exposure is decreased when co-administered with potent CYP3A4 inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to alter significantly the pharmacokinetics (PK) of tofacitinib. In addition to pharmacokinetic interactions, the combination of tofacitinib with biologics should be avoided, due the possibility of enhanced immunosuppression and increased risk of infections[11]. Indeed, treatment with tofacitinib should be discontinued in patients who develop a serious infection, which is an expected side effect of this drug, or in those with abnormal blood tests.

Events of serious venous thromboembolism, including pulmonary embolism, some of which were fatal, and deep vein thrombosis, have been observed in patients taking tofacitinib[11]. On February 2019, the FDA announced, through a Drug Safety Communication, that a risk of blood clots in the lungs and death with the 10-mg dose regimen of tofacitinib in RA patients emerged in a post-marketing safety clinical trial commissioned by the US regulatory agency to Pfizer (A3921133)[14,15]. This study aimed at evaluating the two different dosages of tofacitinib (5 mg and 10 mg twice daily) in comparison with anti-TNF drugs, to better investigate the safety profile for cardiovascular, oncological and infectious complications. The trial revealed that tofacitinib 10 mg twice daily was associated with an increased risk of blood clots in the lungs and death in RA patients (study population). The dose of 10 mg twice daily was approved for UC, but not for RA (nor in USA or EU), and therefore the safety recommendations included also patients on treatment for UC. The EMA reviewed the study A3921133, evaluating patients with RA and an increased risk of cardiovascular

disease, along with data from earlier studies and consultations with experts in the field. All these combined data led the Agency to recommend that tofacitinib should be used with caution in all patients at high risk for thrombotic events[16]. In addition, the maintenance dosage of 10 mg twice daily should not be used in patients with UC, who are at high risk of blood clots, unless there is no suitable alternative treatment. Moreover, patients older than 65 years should be treated with tofacitinib only when there is no alternative treatment. Venous thromboembolism is currently labelled as a serious ADR with uncommon frequency[16].

The most common serious ADRs were serious infections (e.g. pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis). The other commonly reported ADRs over the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension[11].

Data on the use of tofacitinib are continuously monitored. Post-marketing pharmacovigilance helps find and evaluate AE reported with this drug.

EudraVigilance reports 25,404 cases of suspected ADRs associated with tofacitinib[17]. The majority of cases include suspected ADR related to general disorders and administration site conditions as well as to infections and infestations reaction groups, according to the System Organ Class (SOC) MedDRA classification (Table 1). The Italian Medicines Agency (Agenzia Italiana del Farmaco -AIFA-) public database (reazioni averse ai medicinali - RAM system) reports 171 cases of suspected ADRs associated with tofacitinib[18]. The highest frequency of ADRs are reported for the SOC general disorders and administration site conditions, followed by gastrointestinal disorders and infections and infestations.

Table 1. Suspected ADRs to tofacitinib extracted from the Eudravigilance European and AIFA public databases according to SOC classification. The table shows single drug-event pairs related to 25,404 suspected ADRs to tofacitinib from the Eudravigilance European database, as compared to 171 ADRs to tofacitinib from the AIFA public database.

SOC	EUDRAVIGILANCE N (%)	RAM N (%)
General disorders and administration site conditions	12228 (16.8%)	34 (19.9%)
Infections and infestations	10160 (13.9%)	21 (12.3%)
Musculoskeletal and connective tissue disorders	7604 (10.4%)	10 (5.8%)
Injury, poisoning and procedural complications	5991 (8.2%)	2 (1.2%)
Gastrointestinal disorders	5667 (7.8%)	29 (17.0%)
Nervous system disorders	4,877 (6.7%)	12 (7%)
Investigations	4,199 (5.8%)	7 (4.1%)
Respiratory, thoracic and mediastinal disorders	3,997 (5.5%)	7 (4.1%)
Skin and subcutaneous tissue disorders	2,690 (3.7%)	12 (7.6%)
Psychiatric disorders	1,871 (2.6%)	3 (1.8%)
Vascular disorders	1,806 (2.5%)	7 (4.1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1,788 (2.5%)	5 (2.9%)
Cardiac disorders	1,436 (2.0%)	4 (2.3%)
Immune system disorders	1,359 (1.9 %)	1 (0.6%)
Eye disorders	1,345 (1.8%)	-
Renal and urinary disorders	1,242 (1.7%)	2 (1.2%)
Metabolism and nutrition disorders	1,165 (1.6%)	1 (0.6%)

Table 2 shows details about the most reported Preferred Terms (PT) in Eudravigilance for the first five SOC group listed in table 1.

Table 2. Most detected PTs for the main SOCs reported for suspected ADRs to tofacitinib in Eudravigilance.

SOC	PT	(N, %)
General disorders and administration site conditions	Drug ineffective	3836 (31.4%)
	Condition aggravated	2592 (21.2 %)
	Therapeutic product effect incomplete	1039 (8.5%)
Infections and infestations	Pneumonia	2248 (22.1%)
	Nasopharyngitis	993 (9.8%)
	Infection	940 (9.3%)
Musculoskeletal and connective tissue disorders	Athralgia	1917 (25.2%)
	Joint swelling	1190 (15.6%)
	Back pain	641 (7.8%)
Injury, poisoning and procedural complications	Fall	1192 (19.9%)
	Contraindicated product administered	536 (8.9%)
	Product use issue	455 (7.6%)
Gastrointestinal disorders	Nausea	1310 (23.1%)
	Diarrhoea	1198 (21.1%)
	Abdominal discomfort	608 (10.7%)

As for the Italian System RAM, the most reported PT is drug ineffective, followed by nausea and headache.

1.2 Baricitinib

Baricitinib, available in Italy since the first months of 2018 under the brand name Olumiant®, is a drug approved for use in the European Union and the United States for treatment of RA. This drug acts by a preferential blockade of JAK1 and JAK2. It is indicated for treatment of moderate-to-severe active RA in adult patients, who have responded inadequately to, or who are intolerant to, one or more DMARDs. Baricitinib may be used as monotherapy or in combination with MTX, and is available as 2 mg and 4 mg film-coated tablets[19].

As reported by the baricitinib summary of product characteristics, three studies in about 2,500 patients showed that baricitinib improves symptoms, such as tenderness and joint swelling, in patients whose previous DMARDs did not work well enough. In these studies, baricitinib (alone or in combination with the DMARD MTX) resulted in more patients achieving an improvement of 20% or more of a standard symptom score (American College Rheumatology - ACR 20) than comparator medicines or placebo[19].

The EMA granted a marketing authorisation in the European Union (EU) in December 2016, via a centralised procedure, for baricitinib in the treatment of adults with moderate to severe active RA [20]. In Italy, baricitinib is reimbursed by the National Health Service as of 03/12/2017. [21] The FDA approved baricitinib in May 2018 for the 2 mg dosage only, while the application for the 4 mg dosage was rejected. Baricitinib packaging must have a boxed warning about the risk of serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections [22].

There are currently 69 clinical trials with baricitinib recorded on ClinicalTrials.gov. Phase 3 studies are currently underway for assessing the efficacy of baricitinib in the following diseases: systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis, moderate to severe atopic dermatitis, very severe alopecia areata, juvenile idiopathic arthritis, COVID-19-associated pneumonia[23].

In vitro, baricitinib is a substrate of organic anionic transporter (OAT)3, P-glycoprotein (Pgp), breast cancer resistance protein and multidrug and toxic extrusion protein 2-K. In a clinical pharmacology study, dosing of probenecid (an OAT3 inhibitor with strong inhibitory potential) resulted in approximately a 2-fold increase in AUC, without changes in the Tmax or Cmax of baricitinib. Thus, a concomitant administration of probenecid and baricitinib is possible with a modification of baricitinib posology. Ibuprofen and diclofenac, acting as moderate inhibitors of (OAT)3, do not affect the PK of baricitinib. In clinical studies, there were no clinically meaningful effects on exposure when baricitinib was coadministered with digoxin (Pgp substrate) or MTX (substrate of several transporters). In vitro, baricitinib is a substrate of CYP3A4, although less than 10% of the dose is metabolised via oxidation. In clinical pharmacology studies, co-administration of baricitinib with ketoconazole, fluconazole or rifampicin resulted in no clinically meaningful changes of baricitinib exposure[24].

The most commonly reported ADRs, occurring in ≥ 2 % of patients treated with baricitinib monotherapy or in combination with csDMARDs, were increased LDL cholesterol (33.6 %), upper respiratory tract infections (14.7 %) and nausea (2.8 %). Infections reported with baricitinib treatment included *Herpes zoster*. The most common AE found during these studies were upper respiratory tract infections, *Herpes zoster*, *Herpes simplex*, gastroenteritis, urinary tract infections, pneumonia, hypercholesterolaemia, thrombocytosis, nausea, Alanine amino transferase (ALT) increased and rash. Neutropenia, hypertriglyceridemia, AST increase, acne, face swelling, urticaria, pulmonary embolism, deep vein thrombosis, weight increase and creatine phosphokinase increase are other uncommon ADRs associated with baricitinib[19]. The reporting rates of infection-related ADRs for baricitinib, as compared to placebo, were: upper respiratory tract infections (14.7 % vs. 11.7 %); urinary tract infections (3.4 % vs. 2.7 %); gastroenteritis (1.6 % vs. 0.8 %); *Herpes simplex* (1.8 % vs. 0.7 %), and *Herpes zoster* (1.4 % vs. 0.4 %)[19]. Concerns about the toxicity of baricitinib have slowed its use in the United States[22].

EudraVigilance reports 2204 cases of baricitinib suspected ADRs[25]. The majority of cases include infections and infestations reaction group, according to the SOC Medical Dictionary for Regulatory Activities (MedDRA) classification (Table 3). The AIFA public database (RAM system) reports 443 cases of baricitinib suspected ADRs, and, in line with the European data, the majority of cases include infections and infestations (Table 3)[18].

Table 3. Suspected ADRs to baricitinib extracted from the Eudravigilance European and AIFA public databases according to SOC classification. The table shows single drug-event pairs related to 2204 suspected ADRs to baricitinib from the Eudravigilance European database, as compared to 443 suspected ADRs to baricitinib from the AIFA public database.

SOC	EudraVigilance N (%)	RAM N (%)
Infections and infestations	690 (31,3%)	152 (34,3%)
General disorders and administration site conditions	371 (16,8%)	98 (24,1%)
Gastrointestinal disorders	340 (15,4%)	82 (18,5%)
Investigations	330 (15,0%)	136 (30,1%)
Respiratory, thoracic and mediastinal disorders	282 (12,8%)	58 (13,1%)
Skin and subcutaneus tissue disorders	224 (10,2%)	38 (8,6%)
Nervous system disorders	189 (8,6%)	46 (10,4%)
Musculoskeletal and connective tissue disorders	185 (8,4%)	107 (24,2%)
Vascular disorders	166 (7,5%)	28 (6,3%)
Blood and lymphatic system disorders	116 (5,3%)	28 (6,3%)
Injury, poisoning and procedural complications	97 (4,4%)	30 (6,8%)
Metabolism and nutrition disorders	83 (3,8%)	15 (3,4%)
Neoplasms benign, malignant and unspecified	80 (3,6%)	7 (1,6%)
Psychiatric disorders	66 (2,0%)	8 (1,8%)
Cardiac disorders	62 (2,8%)	7 (1,6%)
Renal and urinary disorders	45 (2,0%)	16 (3,6%)
Eye disorders	40 (1,8%)	9 (2,0%)
Reproductive system and breast disorders	20 (0,9%)	7 (1,6%)
Ear and labyrinth disorders	16 (0,7%)	5 (1,1%)

The reports from the Italian pharmacovigilance system (RAM) show the following PT as the most frequently reported: blood cholesterol increase and *Herpes zoster*. A significant number of PT are in

the area of therapeutic failure, such as RA, arthralgia and joint pain[18]. Table 4 shows details about the most reported PT in Eudravigilance for the first six SOC groups listed in table 3.

Table 4. Most detected PTs for the main SOCs reported for suspected ADR cases to baricitinib in Eudravigilance.

SOC	PT	N (%)
Infections and infestations	Herpes zoster	196 (28,4%)
	pneumonia	63 (9,1%)
	nasopharyngitis	30 (4,3%)
General disorders and administration site conditions	drug ineffective	79 (21,3%)
	fatique	51 (13,7%)
	Malaise	35 (9,4%)
	asthenia	22 (5,9%)
Investigation	blood cholesterol increased	39 (11,8%)
	blood creatine phosphokinase increased	20 (6,1%)
	alanine aminotransferase increased	18 (5,5%)
Respiratory, thoracic and mediastinal disorders	dyspnoea	45 (16,0%)
	cough	35 (12,4%)
	oropharyngeal pain	23 (8,2%)
Gastrointestinal disorders	nausea	92 (27,1%)
	abdominal pain	28 (8,2%)
	vomiting	23 (6,8%)
	constipation	14 (4,2%)
Skin and subcutaneous tissue disorders	alopecia	28 (12,5%)
	rash	27 (12,1%)
	pruritus	13 (5,8%)
	erythema	12 (5,4%)

1.3 Other JAK inhibitors

Beside tofacitinib and baricitinib, other JAKi, displaying different patterns of JAK selectivity, have been developed with different indications, in an attempt of improving their safety profile while preserving clinical benefits[26]. Some of these JAKi have received approval or are currently under investigation for treatment of various IMIDs, including RA.

Peficitinib is an oral pan-JAKi approved in 2019 in Japan as a once-daily RA therapy in 100 and 150 mg/day regimens. The approval was based mainly on the results of two randomised, double-blind 52 weeks phase III trials (RAJ3[27] and RAJ4[28]) conducted in patients who had an inadequate response to MTX or to csDMARDs. Starting at week 12, peficitinib demonstrated superiority over placebo at both doses in reducing RA symptoms (RAJ3: ACR20 57.7% for 100 mg and 74.5% for 150 mg versus 30.7% for placebo. RAJ4: ACR20 58.6 for 100 mg and 64.4% for 150 mg versus 21.8% for placebo). Peficitinib was well tolerated up to 52 weeks and the ACR response was maintained. Its safety profile is similar to that of other JAKi.[27,28] The RAJ3 trial was conducted on the Japanese populations, but similar results were obtained also in a multicentre study conducted in USA, Mexico and some European countries[29]. Three clinical trials and one post-marketing surveillance study are currently ongoing on peficitinib in RA patients with inadequate response or intolerance to MTX[30].

Decernotinib (VX-509) is an oral selective JAK3 inhibitor that completed phase IIb. The efficacy of decernotinib was tested in RA patients in randomized control trials, both in monotherapy and combination with MTX or with DMARDs. In patients unsuccessfully treated with DMARDs, decernotinib monotherapy for 12 weeks showed disease improvements at doses of 50-150 mg twice a day compared to placebo[31]. At week 12, the ACR20 response rates were 61.0% for 50 mg, 65.0% for 100 mg, and 65.9% for 150 mg versus 29.3% for placebo[31]. Genovese et al. conducted a phase IIa[32] and IIb[33] clinical trials. In the phase IIa, patients with active RA, who had inadequate response to DMARD therapy, were treated with dosages of 25-150 mg of decernotinib twice daily in combination with a stable DMARD dose for 12 weeks[32]. The phase IIb evaluated the efficacy and safety of different

single doses twice-daily of decernotinib in combination with MTX, in adult patients with active RA, who had an inadequate response to MTX therapy[33]. The phase IIa trial showed the efficacy of decernotinib with an ACR20 response rate of 65% in RA patients receiving high doses[32]. In this trial, magnetic resonance imaging (MRI) was used to detect and measure inflammation and joint damage (RAMSIS score), showing an improvement with decernotinib as compared with placebo[32]. In phase IIb, decernotinib improved significantly the signs and symptoms of RA at weeks 12 and 24 as compared with the placebo group when it was administered in combination with all doses of MTX[33]. At week 12, the ACR 20 response rates ranged between 46.5 and 68.1% versus 18.3% for placebo, while at week 24 the ACR20 response rates ranged from 60.9 to 62.5% versus 16.9% for placebo[33]. The safety profile is similar to other JAKi, with the occurrence of common infections and serious infections, like the reactivation of *Herpes zoster*, tuberculosis or *Candida*, associated with immune suppression. Other common AE include nausea, diarrhoea, increased ALT, hypercholesterolemia and headache. AE are mainly dose dependent[31-33].

Upadacitinib (Rinvoq®) is an oral JAK1 inhibitor approved by FDA[34] and EMA[35] in 2019 for treatment of moderate-to-severe RA in patients with inadequate response or intolerance to DMARDs. The efficacy of upadacitinib was tested in the SELECT program, consisting of five clinical trials that compared upadacitinib monotherapy to MTX and the combination upadacitinib-MTX/DMARD to MTX/DMARD alone. The SELECT-EARLY[36] study compared upadacitinib to MTX-naïve RA patients for 12 weeks and the SELECT-MONOTHERAPY[37] study compared upadacitinib to MTX taken at stable doses from 14 weeks. In these two monotherapy trials, upadacitinib-treated patients showed a greater clinical response versus those on MTX: in the SELECT-EARLY[36] the ACR20 was 60.3% for 15 mg, 65.6% for 30 mg versus 28.3% for MTX at 12 week; in the SELECT-MONOTHERAPY[37] the ACR20 was 67.7% for 15 mg, 71.2% for 30 mg and 41.2% for MTX. The other two clinical trials (SELECT-NEXT[38] and SELECT-BEYOND[39]) compared patients with inadequate response to csDMARDs, bDMARDs or MTX to the add-on upadacitinib treatment. In all these trials, the add-on therapy showed significantly better clinical response in all regimens. Finally, in the SELECT-COMPARE[40] study,

a phase III trials that compared upadacitinib plus MTX to adalimumab and placebo in patients with inadequate response to MTX, from week 12 and till the end of the study, upadacitinib showed superiority versus placebo and adalimumab.

Filgotinib is an oral JAK1 inhibitor under approval by the FDA and EMA[41,42] for treatment of patients with moderate-to-severe RA. Several clinical trials evaluated filgotinib for inflammatory diseases. The Darwin program (DARWIN 1[43] and DARWIN 2[44]) consists of phase II trials aimed at providing data on the efficacy and safety of filgotinib as an add-on therapy to MTX and in monotherapy in patients with inadequate response to MTX. The tested doses ranged from 25 mg to 100 mg once or twice daily. The duration of the studies were 12 and 24 weeks. In DARWIN 1[43], all treatment arms differed significantly from placebo in both ACR50 and ACR70; ACR20 at 24 weeks was 54.9% for 50 mg once daily (OD), 61.2% for 100 mg OD, 60.6% for 50 mg twice daily and 79.8% for 100 mg bid versus 41.9% for placebo. In DARWIN 2[44], both ACR20 and ACR50 were significantly higher in all treatment arms as compared to placebo, with a dose-dependent positive relationship at 12 weeks. The phase III program, named FINCH, includes four trials. The FINCH trials compared co-therapy between filgotinib and MTX or a bDARMD with an active comparator (MTX, other csDMARD, or adalimumab). Only the results of the FINCH 2 trial are currently available[45]. In this study, patients with inadequate response to bDMARDs were randomized to filgotinib 200 mg, 100 mg or placebo. Like for other trials, the ACR20 was higher in the filgotinib arms (66% with 200 mg and 57.5% with 100 mg) as compared with placebo (31.1%), at week 12. Filgotinib was well tolerated in all clinical trials.

Solcitinib is a JAK1 inhibitor. To the best of our knowledge, this drug has currently no approved indication. The clinicaltrial.gov repository contains five completed clinical trials on the use of solcitinib for UC, psoriasis and systemic lupus erythematosus[46]. **Itacitinib** is a JAK1 inhibitor, currently under investigation for the treatment of graft-versus-host-disease[47]. There is only one explorative study, completed on March 2019, on the use of itacitinib in patients with active RA but data are still not available[48]. **Fedratinib** is a JAK2 inhibitor. It is approved by FDA for treatment of myelofibrosis[49].

There are not currently ongoing studies exploring its efficacy in IMIDs. **Ruxolitinib** is a JAK1 and JAK2 inhibitor approved by EMA and FDA for treatment of myelofibrosis and hydroxyurea-resistant or -intolerant polycythemia vera[50]. Only one explorative study on the tolerability and efficacy of ruxolitinib in RA has been completed, but, to the best of our knowledge, the results have not been published yet[51].

2 Objective

In this study, we identified and described new users of JAKi in Tuscany from 2018 (year of approval of the first JAKi in the treatment of severe to moderate RA) to 2019. In particular, we described their utilization in the Regional Healthcare System (RHS) facilities both before and after treatment initiation, providing also an evaluation of the economic impact associated with resource use, considering the perspective of the RHS. Finally, we provided also an estimation over time of the bDMARD new users with history of access to rheumatology wards in Tuscany.

3 Research questions

1. What was the utilization history of DMARDs in patients initiating JAKi drugs in Tuscany, during 10 years, leading to JAKi initiation?
2. What was the yearly direct cost of patients before initiating treatment with a JAKi in Tuscany?
3. What was the pattern of healthcare utilization (i.e., hospitalization, access to specialist visits) after initiating JAKi in Tuscany?
4. What was the estimated direct cost in the first sixth months after initiating JAKi in Tuscany?
5. What was the number of new users of bDMARDs among rheumatologic patients over time in Tuscany?

4 Methods

4.1 Study design

This is a descriptive, retrospective cohort study.

4.2 Data source

We used data retrieved from administrative healthcare databases of Tuscany. Particularly the study database was obtained linking records from 4 different administrative databases: hospital discharge (SDO) (cause of hospitalization [ICD-9 code], date of hospitalization and discharge, cost of hospitalization), emergency department (ED) admission (cause of ED admission [ICD-9 code], date of ED admission and discharge), of drug dispensations (drugs [ATC codes], gender, birth date, dates of drug dispensation, drug doses, drug costs), and specialist encounters (rheumatologic visits, date of rheumatologic visits, cost of visits)[52]. Data were linked among databases using an anonymous unique patient code.

4.3 Definition of cohorts

In order to answer the above research questions (RQ), we created three different study cohorts, as described in detail below.

For the RQ-1 and RQ-2, patients were identified by the first dispensation of a JAKi (Table 5) from January 1st, 2018 to December 31st, 2019. Cohort entry was defined by the first dispensation of a JAKi. We excluded patients with less than 10 years of records in the look back period, history of cancer or use of anti-cancer drugs in the look back period, as well as those aged ≤ 18 at the index date.

For the RQ-3 and RQ-4, patients were identified by the first dispensation of a JAKi from January 1st, 2018 to June 30th, 2019. Cohort entry was defined by the first prescription of JAKi. Only patients with at least six months of observation after cohort entry were included. We excluded patients with less than 10 years of records in the look back period, history of cancer or use of anti-cancer drugs in the look back period, as well as those aged ≤ 18 at index date.

In both the above analyses, patient observation was censored at the end of the study period, loss to follow-up, or death whichever came first.

For the RQ-5, patients were identified by the first prescription of a bDMARD (Table 5) from January 1st, 2014 to December 31st, 2019. Cohort entry was defined by the date of the first prescription of a bDMARD. We included patients with at least one visit in a Tuscan rheumatology ward in the year preceding the cohort entry. We excluded patients with less than 1 year of look back period.

Table 5. Study drugs.

Drug class	Drug name	ATC code
Targeted synthetic DMARDs (tsDMARDs) – JAKi	Tofacitinib	L04AA29
	Baricitinib	L04AA37
Conventional sysntetic DMARDs (csDMARDs)	Methotrexate	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

4.4 Data analysis

For RQ-1, we calculated the number of patients receiving their first JAKi in the study period (both overall and stratified by year, age, gender and by the first JAKi). Since in Italy the currently available JAKi have the sole indication of moderate-to-severe RA, we assumed that all the JAK users were RA patients, although an off-label use could not be excluded. We calculated the number of patients with history of DMARD dispensation before cohort entry, the number of dispensations, both overall and categorized (0, 1-3, 4-9, ≥10), the mean and median number of dispensations per patient, and of each DMARD before cohort entry. We calculated also the mean time from the first ever DMARD dispensation and cohort entry. Based on the time from the first ever DMARD to the cohort entry, patients were then categorized into five groups (<1 year; 1 ≤ years <2; 2 ≤ years < 3; 3 ≤ years < 5; 5 ≤ years ≤ 10). Mean time and time category were estimated as well, considering the time from the first ever bDMARD to cohort entry.

For RQ-2, we estimated direct health costs for the population of JAKi users over the five-year period before cohort entry, evaluating the costs for each year in the look back period. Both total direct health costs and costs associated with the different items included in the present analysis were evaluated: dispensed DMARDs, hospitalizations, specialist visits. Overall, the direct health costs born to the RHS accounting for the size of the study cohort were presented to assess the impact on the regional healthcare budget; mean patient cost/per year was estimated also to evaluate the average costs among the target population.

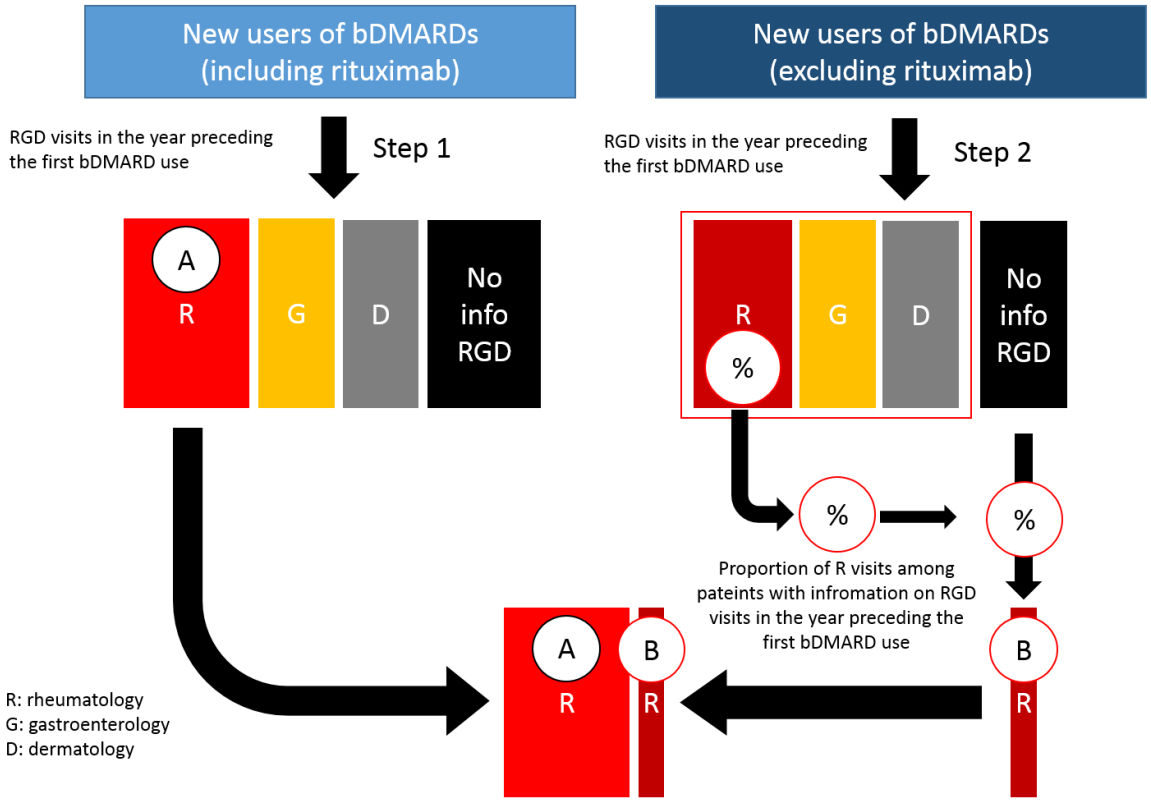
For RQ-3, we calculated the number of accesses to ED for any cause, hospitalizations for any cause and the number of rheumatologic visits during the 6-month follow up (both overall and stratified by drug). We calculated then the number of patients with at least one access to ED for any cause, hospitalization for any cause and the number of rheumatologic visits. In patients with at least

one access to ED during the follow-up, we estimated the mean time to the first ED access (overall and stratified by drug and gender). We calculated the same outcome for hospitalizations and rheumatologic visits. Finally, we described the most frequently reported causes for ED access and hospitalization (first cause reported on discharge records).

For RQ-4, we estimated the direct health costs of the population of JAKi users in the sixth month after the first dispensation. Like for RQ-2, both the total direct health costs and costs associated with the different items included in the present analysis (i.e, dispensed DMARD, hospitalizations, specialist visits) were evaluated. Overall, the direct health costs born to the RHS accounting for the size of the study cohort were presented to assess the impact on the regional healthcare budget; mean patient costs over the six-month period were assessed also to evaluate the average costs within the target population. Assuming an equal distribution of costs over one year, the estimation of the overall costs and mean patient cost/per year were provided as well.

For RQ-5, we estimated the number of new users of bDMARDs stratified by year of first bDMARD dispensation (figure 1). In the first step, we identified new users of bDMARDs (table 5) with a rheumatology visits in Tuscany in the year preceding the first dispensation of bDMARD (A). In this analysis, we identified a certain number of bDMARD users without information on rheumatology, gastroenterology or dermatology visits. These included patients receiving rituximab for hematology/oncology indications and patients with private visits or visited in other regions. We assumed that the proportion of new bDMARDs users among these patients was the same as those with rheumatology visits in the population of new bDMARD users with rheumatology, gastroenterology and dermatology visits. Then, in the second step, we identified new bDMARD users excluding rituximab. Among the patients with information on rheumatology, dermatology or gastroenterology visits, we identified the proportion (%) of those with rheumatology visits. Then, we used this proportion to assume the number of patients with rheumatology visits (B) among those without information on rheumatology, dermatology or gastroenterology visits. The final number of new bDMARD users in the rheumatology setting was given by the sum of A plus B.

Figure 1


New users of bDMARDs (including rituximab)
New users of bDMARDs (excluding rituximab)
RGD visits in the year preceding the first bDMARD use
Step 1
RGD visits in the year preceding the first bDMARD use
Step 2
A
R
G
D
No info RGD
R
%
G
D
No info RGD
%
%
Proportion of R visits among pateints with infromation on RGD visits in the year preceding the first bDMARD use
A
R
B
R
B
R
R: rheumatology
G: gastroenterology
D: dermatology

5 Results

5.1 Characteristics of JAK inhibitor users

We identified 450 new JAKi users in the period from January 1st 2018 to December 31st, 2019. Of these, 22 subjects were excluded because of a look back period shorter than 10 years; 55 subjects were excluded due to history of cancer in the look back period; 1 subject was excluded because of less than 18 years-old and 9 because of lack of demographic data. Thus, the final cohort included 363 patients (figure 2).

Figure 2

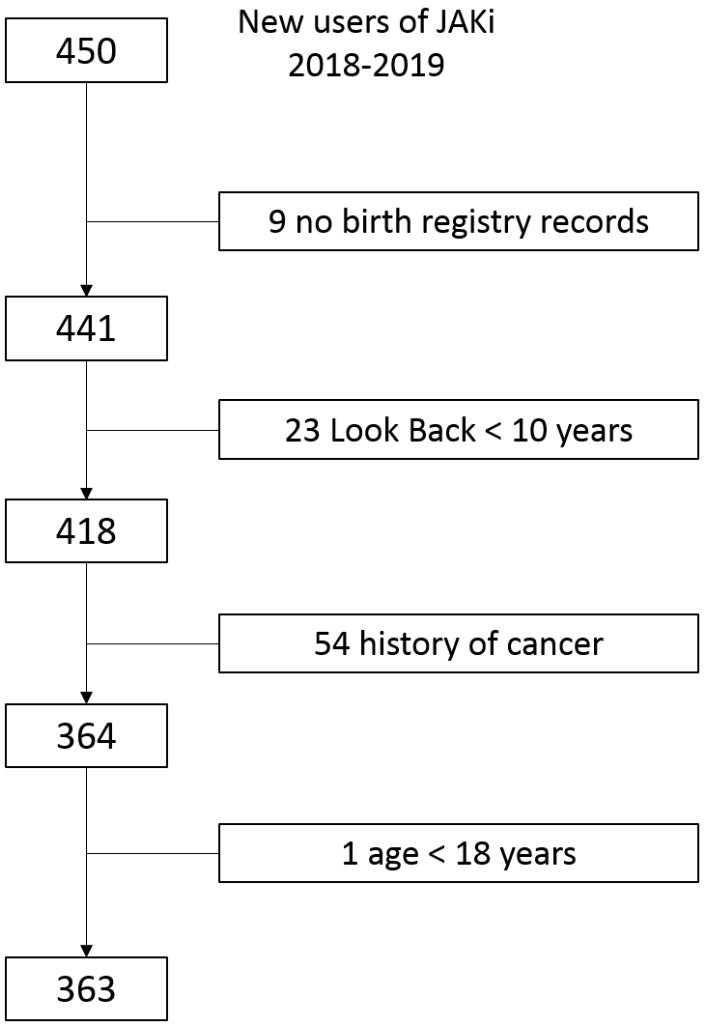


Table 6 summarizes the main characteristics of the final cohort, both overall and stratified by the two years of cohort entry.

Table 6 – Characteristics of JAKi users

	Overall	**2018**	**2019**
JAKi new users n	363	90	273
Female n (%)	293 (80.7)	73 (81.1)	220 (80.6)
Tofacitinib n (%)	78 (21.5)	1 (1.1)	77 (28.2)
Baricitinib n (%)	285 (78.5)	89 (98.9)	196 (71.8)
Age years (mean ± SD)	61.5 (13.6)	60.3 (11.9)	61.9 (14.1)
Age years (median ± IQR)	63 (52.5 to 71.5)	60 (52.3 to 69.8)	64 (53 to 73)

SD: standard deviation; IQR: interquartile range

Mean and median age of patients was about 60 years, with female patients representing the largest proportion of users (about 80%). This prevalence is in line with that expected in the medical literature for RA, a disease for which the women/men ratio is estimated to be around 3-4:1(ref). We found a higher number of baricitinib users, due to its earlier approval as compared with tofacitib (for tofacitinib there was only 1 new user in 2018 in this dataset).

5.2 History of DMARD use in JAK inhibitors users

When history of DMARD use in these patients was explored (table 7a), we found 29 new JAKi users (8%) without previous prescription of any DMARD. We cannot exclude that some of these patients used the JAKi as a first line treatment, but other explanations must be considered, such as previous private purchase of DMARDs (not captured by the regional administrative healthcare dataflow) or previous dispensations of DMARDs in other regions.

Among the DMARD users, 79% had a record of csDMARD supply, with hydroxychloroquine (44%), MTX (42%) and leflunomide (33%) being the most frequent. When considering patients with

history of anti-TNF use (60%), the most frequently supplied was etanercept (recorded in the history of 40% of JAKi users), followed by adalimumab (recorded in the history of 27% of JAKi users). The most frequently supplied non-anti-TNF bDMARD was abatacept (recorded in the history of 30% of JAKi users).

Table 7a. History of DMARD use in new users of JAKi (n = 363)

DMARDs	**Patients n (%)**
No use	29 (8.0)
Any use	334 (92.0)
csDMARDs	287 (79.1)
Methotrexate (L01BA01)	152 (41.9)
Leflunomide (L04AA13)	121 (33.3)
Azathioprine (L04AX01)	10 (2.8)
Cyclosporin (L04AD01)	15 (4.1)
Hydroxychloroquine (P01BA02)	161 (44.4)
Minocycline (A01AB23)	0 (0.0)
Mycophenolate (L04AA06)	2 (0.6)
Sulfasalazine (A07EC01)	39 (10.7)
anti-TNF bDMARDs	217 (59.8)
Adalimumab (L04AB04)	97 (26.7)
Certolizumab pegol (L04AB05)	60 (16.5)
Etanercept (L04AB01)	147 (40.5)
Golimumab (L04AB06)	42 (11.6)
Infliximab (L04AB02)	28 (7.7)
non anti-TNF bDMARDs	152 (41.9)
Abatacept (L04AA24)	110 (30.3)
Rituximab (L01XC02)	34 (9.4)
Tocilizumab (L04AC07)	74 (20.4)
Sarilumab (L04AC14)	0 (0.0)

Assuming that patients with only one type of DMARD recorded in the clinical history can be considered as second line therapy users of JAKi (and consequently, third line those with two types of DMARDs and fourth line those with all types of DMARDs in their history), JAKi appeared to be used in similar proportion as a second, third and fourth line treatment in RA patients (table 7b).

Table 7b. History of treatment lines for new JAKi users (n = 363)

Line	N (%)
First line (no history of any DMARD use)	**29 (8.0)**
Second line	**113 (31.1)**
Only csDMARD	81 (22.3)
Only anti-TNF bDMARDs	25 (6.9)
Only non-anti-TNF bDMARDs	7 (1.9)
Third line	**120 (33.1)**
csDMARDs + anti-TNF bDMARDs, but not non-anti-TNF bDMARDs	76 (20.9)
csDMARDs + non-anti-TNF bDMARDs, but not anti-TNF bDMARDs	29 (8.0)
Anti-TNF bDMARDs + non-anti-TNF bDMARDs, but not csDMARDs	15 (4.1)
Fourth line	**101 (27.8)**
csDMARDs + anti-TNF bDMARDs + non-anti-TNF bDMARDs	101 (27.8)

Table 7c summarizes the number of dispensations received in their history by new JAKi users of. Among the csDMARDs users, MTX users received a mean number of 23 dispensations. The majority of MTX users (93/152) received more than 10 dispensations. Among the anti-TNF bDMARDs users, etanercept users received a mean number of 26 dispensations. The majority of etanercept users (85/147) received more than 10 dispensations. Among the non-anti TNF bDMARDs users, tocilizumab users received a mean number of 23 dispensations. The majority of tocilizumab users (41/74) received more than 10 dispensations.

Table 7c. History of DMARDs dispensations

DMARD	**Overall Number of dispensation (n)**	**mean number of dispensation per patients (± SD)**	**Dispensations groups n (%)**			
			0	**1-3**	**4-9**	**≥10**
Conventional sysntetic DMARDs (csDMARDs)						
Methotrexate (n = 152)	3451	22.7 (23.6)	211	33 (22)	26 (17)	93 (61)
Leflunomide (n = 121)	2261	18.7 (22.0)	242	33 (27)	32 (27)	56 (46)
Azathioprine (n = 10)	172	17.2 (16.5)	353	3 (30)	1 (10)	6 (60)
Cyclosporin (n =15)	102	6.8 (9.9)	348	7 (47)	6 (40)	2 (13)
Hydroxychloroquine (n = 161)	2398	14.9 (17.8)	202	54 (33)	30 (19)	77 (48)
Minocycline (n = 0)	0	0 (0.0)	0	0	0	0
Mycophenolate (n = 2)	14	7.0 (7.1)	361	1 (50)	0 (0)	1 (50)
Sulfasalazine (n = 39)	252	6.5 (8.7)	324	23 (59)	6 (15)	10 (26)
Anti-TNF biologic DMARDs						
Adalimumab (n = 97)	1589	16.4 (20.1)	266	18 (19)	31 (32)	48 (49)
Certolizumab pegol (n = 60)	893	14.9 (17.7)	303	16 (27)	21 (35)	23 (38)
Etanercept (n = 147)	3762	25.6 (30.0)	216	26 (18)	36 (24)	85 (58)
Golimumab (n = 42)	512	12.2 (13.6)	321	8 (19)	18 (43)	16 (38)
Infliximab (n =28)	306	10.9 (14.9)	335	11 (39)	10 (36)	7 (25)
Non anti-TNF biologic DMARDs						
Abatacept (n = 110)	1843	16.8 (18.2)	253	29 (26)	28 (26)	53 (48)
Rituximab (n = 34)	234	6.9 (6.4)	329	14 (41)	11 (32)	9 (27)
Tocilizumab (n =74)	1734	23.4 (30.7)	289	7 (9)	26 (35)	41 (56)
Sarilumab (n = 0)	0	0 (0.0)	0	0	0	0

Table 7e reports the time from the date of the first ever DMARD (all DMARDs) and bDMARD (anti-TNF and non-anti TNF bDMARDs) to the date of the first dispensation of JAKi. The mean time from the beginning of treated disease to the use of JAKi is 7.2 years. It is important to note that the majority of JAKi users have an history of use of any DMARD starting between 5 and 10 years before. This could be suggestive of a potential channelling bias. Channeling bias may occur when a newly marketed drug and an established drug, despite similar therapeutic indications, are prescribed to patients with different prognostics characteristics. Over time, the prognostic characteristics of the patients who prescribed the two drugs may become more balanced as the newly marketed drug becomes more established. Reasons for channeling bias could be a belief in extra advantages of the new drug compared to the established drug, or simply because doctors do not know how else to treat a subgroup of patients due to intolerance or low response to established drugs. The latter situation seems to fit with that observed in this study. However, this situation is expected in the first years of availability of an innovative drug (i.e. a drug with a mechanism of action never exploited before, such as JAKi)[53]. This picture will likely change over years in parallel with the increasing of the use of JAKi.

Table 7e. Time from first DMARD and from first bDMARD to cohort entry

	First DMARD (n=334)	**First bDMARD** (n=253)
Mean time (± SD), years	7.2 (3.3)	4.5 (3.2)
< 1 year (n, %)	20 (6)	47 (19)
1 ≤ years < 2 (n, %)	20 (6)	26 (10)
2 ≤ years < 3 (n, %)	24 (7)	29 (11)
3 ≤ years < 5 (n, %)	26 (8)	41 (16)
5 ≤ years < 10 (n, %)	244 (73)	110 (44)

5.3 Resource use and economic impact among new JAK inhibitor users in the period preceding the first JAK inhibitor prescription

Table 8a details the number of ED accesses, hospitalizations and specialist visits for each of the 5 years before cohort entry considered in the present analysis. The table highlights a slight increase in the overall number of both ED accesses and hospitalizations approaching the cohort entry, while the total number of specialist visits slightly increased progressively from the 5th year to the 2nd year before the cohort entry.

Table 8a. Number of ED accesses, hospitalizations, and specialist visits in the years preceding the first prescription of JAKi

	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**
Ed accesses (n)	205	225	163	166	170
Hospitalizations (n)	113	111	98	84	84
Specialist visits (rheumatology) (n)	431	522	496	420	370

Looking at the number of patients that used at least once each of the considered resources, a slight increase from the 5th year to the 2nd year preceding the cohort entry was observed for the number (and percentage) of patients with at least one specialist visit. The number of patients with at least one hospitalization remained quite constant over the years, being comprised between 17.6% and 19.9% of the overall study cohort. Similar values were found for patients with at least one ED access, who represented about one third of the study cohort (Table 8b).

Table 8b. Distribution patients with at least one ED access, hospitalizations, and specialist visits in the years before the first prescriptions of JAKi

	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**
ED accesses (n, %)	122 (33.6%)	117 (32.2%)	108 (29.8%)	114 (31.4%)	107 (29.5%)
Hospitalizations (n, %)	66 (18.2%)	70 (19.3%)	69 (19.9%)	64 (17.6%)	67 (18.5%)
Specialist visits (rheumatology) (n, %)	179 (49.3%)	204 (56.2%)	175 (48.2%)	153 (42.1%)	137 (37.7%)

Table 8c displays the mean number of events per patient over the years and highlights no substantial difference in the mean number of events per patient/year for all type of contacts with the healthcare system considered in the analysis.

Table 8c. Resource use 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**
Mean (Min;Max) number per patient/year					
ED accesses	0.56 (0;7)	0.62 (0;6)	0.45 (0;6)	0.46 (0;5)	0.47 (0;7)
Hospitalizations	0.31 (0;11)	0.31 (0;5)	0.27 (0;9)	0.23 (0;3)	0.23 (0;3)
Specialist visits (rheumatology)	1.19 (0;8)	1.44 (0;11)	1.37 (0;12)	1.16 (0;12)	1.02 (0;12)

Overall direct health costs associated with the 363 patients included in the study cohort highlighted a slightly increase in costs born to the RHS that increased from 1,551,981 Euro in the 5th year before cohort entry to 1,898,227 Euro in the 2nd year before cohort entry (Table 8d).

The modest increase in the overall costs was driven essentially by a significant increase in the costs related to hospitalizations that almost doubled over the years, while the overall costs related to other resource use did not vary significantly over the years.

The differences highlighted for the overall economic impact determined by the patients included in the cohort translated into a slightly increase in the mean direct cost per patient/year from the 5th to the 2nd year preceding the cohort entry: 4,275.4 Euro per patient/year and 5,229.3 Euro per patient/year. As highlighted above, the increase was related to a significant increase in the costs associated with hospitalizations. Since the number of accesses to the resources remained stable over the time, the increase in the mean costs likely depends on an increase in the severity of complications requiring resource utilization. In our opinion, the pattern of costs and resource utilization over the time likely reflects a deterioration of the overall patients' conditions.

Due to unexpected issued in the interpretation of data related to resources spent during ED accesses, we prefer to provide a separate estimation of costs, including ED costs, in annex 1.

Table 8d. 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*	1,676,429	1,898,227	1,754,176	1,621,148	1,551,981
Drugs	1,147,654	1,438,147	1,376,923	1,283,628	1,273,034
Hospitalizations	521,431	450,207	368,797	329,850	271,317
Specialist visits (rheumatology)	7,344	9,873	8,455	7,670	7,630
Mean (min; max) cost per patient/year	4,618.3 (0;96,568.5)	5,229.3 (0;41,415.0)	4,832.4 (0;52,039.5)	4,466.0 (0;30,511.9)	4,275.4 (0;24,265.4)
Drugs	3,161.6 (0;15,574.2)	3,961.8 (0;19,892.2)	3,793.2 (0;19,795)	3,536.2 (0;17,745.4)	3,507.0 (0;19,474.4)
Hospitalizations	1,436.5 (0;93,050)	1,240.2 (0;39,399)	1,016 (0;34,677)	908.7 (0;26,676)	747.4 (0;20,507)
Specialist visits (rheumatology)	20.2 (0;193)	27.2 (0;601)	23.3 (0;476)	21.1 (0;476)	21 (0;476)

*costs did not include ED costs

5.4 Hospitalization and emergency department access patterns in JAK inhibitor users

We identified 276 new JAKi users in the period from January 1st 2018 to June 30th, 2019. Of these, 16 subjects were excluded because of a look back period shorter than 10 years; 34 subjects were excluded due to history of cancer in the look back period; 1 subject was excluded because less than 18 years-old and 4 because of lack of demographic data. The final cohort included 221 patients (figure 3).

Figure 3

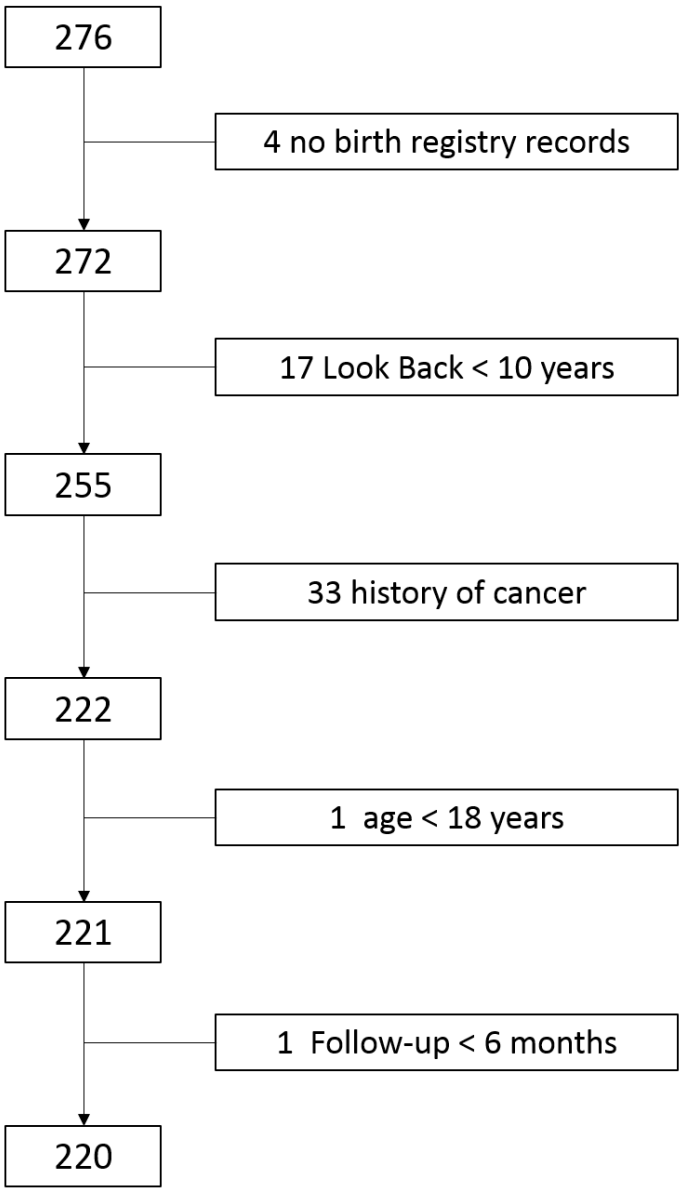


Table 9a summarizes the main characteristics of the final cohort, both overall and stratified for the two years of cohort entry. The mean and median age of patients was about 60 years, with female patients representing the largest proportion of users (about 80%). This prevalence is in line with that expected in the medical literature for RA, a disease for which the women/men ratio is estimated to be about 3-4:1. We found a higher number of baricitinib users, due to its earlier approval as compared with tofacitib (for tofacitinib there was only 1 new user in 2018).

Table 9a. Characteristics of JAKi users.

	Overall	**2018**	**2019**
JAKi new users	220	89	131
Female n (%)	179 (81.4)	73 (82.0)	106 (80.9)
Male n (%)	41 (18.6)	16 (18.0)	25 (19.1)
Tofacitinib n	42	1	41
Baricitinib n	178	88	90
Age (mean ± SD)	61.3 (13.0)	60.1 (11.8)	62.0 (13.7)
Age (median ± IQR)	62.0 (53.0 to 71.0)	60.0 (52.0 to 69.0)	63.0 (54.5 to 71.0)

During the first 6 months of utilization, JAKi users recorded 109 accesses to ED, 39 hospitalizations, and 64 rheumatology visits (table 9b). All rheumatology visits were recorded in patients receiving baricitinib (n=38) (table 9b). No rheumatology visits were recorded for tofacitinib in the first 6 months of use of the drug.

Table 9b. Number of emergency department (ED) admissions, hospitalizations and specialist visits (rheumatologic) follow-up 6 months

	Overall (n)	Baricitinib (n)	Tofacitinib (n)
Users	220	178	42
ED admissions (n)	109	68	41
Hospitalizations (n)	39	28	11
Specialist visits (rheumatology) (n)	64	64	0

The mean time to the first ED admission in patients with at least 1 ED admission (n=54) was 73 days (Table 9c). ED admissions were more frequent in male than female patients (34% vs 22%), and in baricitinib than tofacitinib users (26% vs 19%). The mean time to ED admission was shorter in male patients as compared to female patients, while it was similar in baricitinib users as compared to tofacitinib ones. Similar to ED admission, hospitalization was more frequent in male patients. The mean time to the first hospitalization (n=28) was 89.6 days, and it was longer in female patients as compared to male. While the frequency of hospitalization was almost the same in baricitinib and tofacitinib users, the mean time to the first hospitalization was shorter in baricitinib users as compared to tofacitinib ones.

Table 9c. Number of patients with at least 1 emergency department (ED) admission, hospitalization, and specialist visit (rheumatologic) and time to the first ED admission, hospitalization and specialist visits (follow-up 6 months)

	Overall (n = 220)	**Female (n = 179)**	**Male (n = 41)**	**Baricitinib (n = 178)**	**Tofacitinib (n = 42)**
Patients with ED admission n (%)	54 (25)	40 (22)	14 (34)	46 (26)	8 (19)
Time to first ED admission, days (mean ± SD)	73.5 (54.1)	77.8 (51.6)	61.2 (61.1)	73.2 (52.9)	75.1 (64.2)
Patients with hospitalization n (%)	28 (13)	19 (11)	9 (21)	22 (12)	6 (14)
Time to first hospitalization, days (mean ± SD)	89.6 (54.8)	92.9 (56.5)	82.6 (53.5)	86.6 (54.7)	100.3 (59.0)
Patients with specialist visits n (%)	38 (17)	30 (17)	8 (19)	38 (21)	0
Time to first specialist visit, days (mean ± SD)	60.9 (51.3)	63.1 (52.7)	53.0 (47.7)	60.9 (51.3)	NA

The main causes of ED access (table 9d) and hospitalization (table 9e) were comparable with those reported in the European and Italian spontaneous reporting systems of suspected ADRs (table 1-4, introduction).

Injury and poisoning (which likely include “fall”, the most frequently reported ADR in this category in spontaneous reporting systems) was the most frequent category of ED access. Skin disorders were one of the most frequent category of drug-related cause of ED admission in general[54]. In this case, we cannot exclude the presence of psoriasis or psoriatic arthritis as a concomitant

disease. Interestingly, and in line with concerns raised by the FDA and other regulatory authorities on JAKi[14,16,55], disorders of the cardiovascular system are frequently reported also. Of note, the combination of the categories "symptoms, signs, and ill-defined conditions" and "disease of the musculoskeletal system and connective tissue" may reflect situations of lack of efficacy or disease worsening, which have been frequently reported in the spontaneous reporting systems of ADRs.

Table 9d. Causes of access to emergency department (109 ED accesses in 54 JAKi users) during the first 6 months of JAKi use

Description	ICD-9 code	Cases (n, %)
Injury and poisoning	800-999	20 (18.3)
Diseases of the skin and subcutaneous tissue	680-709	15 (13.8)
Diseases of the circulatory system	390-459	12 (11.0)
Symptoms, signs, and ill-defined conditions	780-799	10 (9.2)
Diseases of the nervous system and sense organs	320-389	10 (9.2)
Diseases of the digestive system	520-579	8 (7.3)
Diseases of the musculoskeletal system and connective tissue	710-739	7 (6.4)
Diseases of the respiratory system	460-519	5 (4.6)
Diseases of the genitourinary system	580-629	3 (2.8)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	2 (1.8)
Infectious and parasitic diseases	001-139	2 (1.8)
Mental disorders	290-319	1 (0.9)
Complications of pregnancy, childbirth, and the puerperium	630-679	1 (0.9)
Diseases of the blood and blood-forming organs	280-289	1 (0.9)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	1 (0.9)

Cardiovascular problems seem to represent one of the main causes of hospitalization. This may reflect a peculiar cardiovascular safety problem of these drugs, as suggested by regulatory authority. However, since rheumatologic disease are risk factors for cardiovascular events[56], it is possible that these patients may have a high basal cardiovascular risk, because many of them have a long duration of treated disease, has observed in results showed in table 1e. Diseases of the

musculoskeletal system and connective tissue are another category of causes frequently reported in hospital discharge records. Analogously to what observed for ED admission, this may suggest a high frequency of “lack of efficacy” and “disease worsening” which have been reported frequently in ADRs spontaneous reporting systems.

Table 9e. Causes of hospitalization (39 hospitalizations in 28 JAKi users) during the first 6 months of JAKi use

Description	ICD-9 code	Cases (n, %)
Diseases of the circulatory system	390-459	27 (69.2)
Diseases of the musculoskeletal system and connective tissue	710-739	25 (64.1)
Diseases of the skin and subcutaneous tissue	680-709	15 (38.5)
Diseases of the respiratory system	460-519	13 (33.3)
Diseases of the nervous system and sense organs	320-389	10 (25.6)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	8 (20.5)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	6 (15.4)
Diseases of the genitourinary system	580-629	5 (12.8)
Infectious and parasitic diseases	001-139	5 (12.8)
Diseases of the blood and blood-forming organs	280-289	5 (12.8)
Diseases of the digestive system	520-579	2 (5.1)
Mental disorders	290-319	2 (5.1)
Neoplasms	140-239	2 (5.1)

5.5 Healthcare costs of JAK inhibitor users

Table 10a details information related to the direct costs generated by the 220 patients initiating JAKi and having a complete 6-month follow-up, both overall and considering the mean per patient costs over the 6-month period.

While the economic impact on the regional health care budget could not be compared with that estimated for the first cohort (RQ-2) owing to the different size of the population, the mean per patient costs appeared to be comparable with the estimates obtained for the overall cohort.

Table 10a. Cost in the first six months after the first JAKi prescription

	Cost (€)
Total cost*	**1,054,530**
Drugs	887,946
Hospitalization	165,624
Specialist visits (rheumatology)	960
Mean (Min;Max) cost per patient	**4,793.3 (607.5;50,306)**
Drugs	4,036.1 (607.5;8,387.9)
Hospitalization	752.8 (0;43,811)
Specialist visits (rheumatology)	4.4 (0;60)

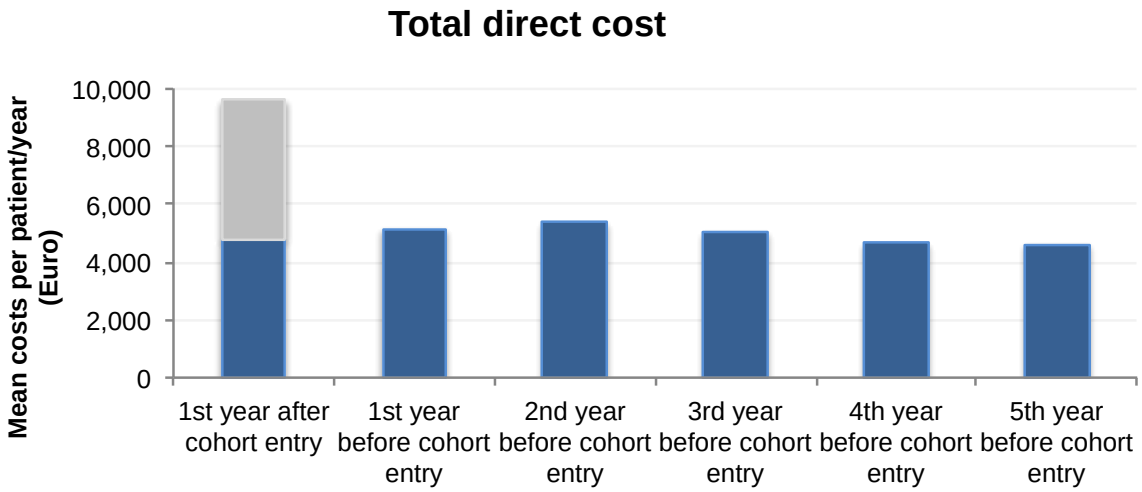
* Costs of ED accesses are not included

Indeed, if we assume an equal distribution of the costs over the 12 months of a calendar year, the estimation of the costs for the cohort of subjects having a complete six-month follow-up is provided in Figure 4 and 5, considering both the total mean direct costs per patient/year as well as the mean costs related to the different healthcare resources considered in the present analysis.

In detail, Figure 4 provides an overview of the expectation of total direct costs per patient/year, highlighting that the expected costs for the first year after cohort entry was estimated doubling the costs obtained over a six-month period. Expected costs in the first year after JAKi initiations appeared to be higher as compared to costs before treatment switch.

Anyway it is important to bear in mind that the adopted assumption may not be able to represent the path of costs that would have all over the year, thus not reflecting changes in the treatment pathway (associated adherence behaviour, treatment adjustment, etc.) and scheduling of follow-up visits that may occur all over the year (i.e., possibly overestimating some costs items and while underestimating others).

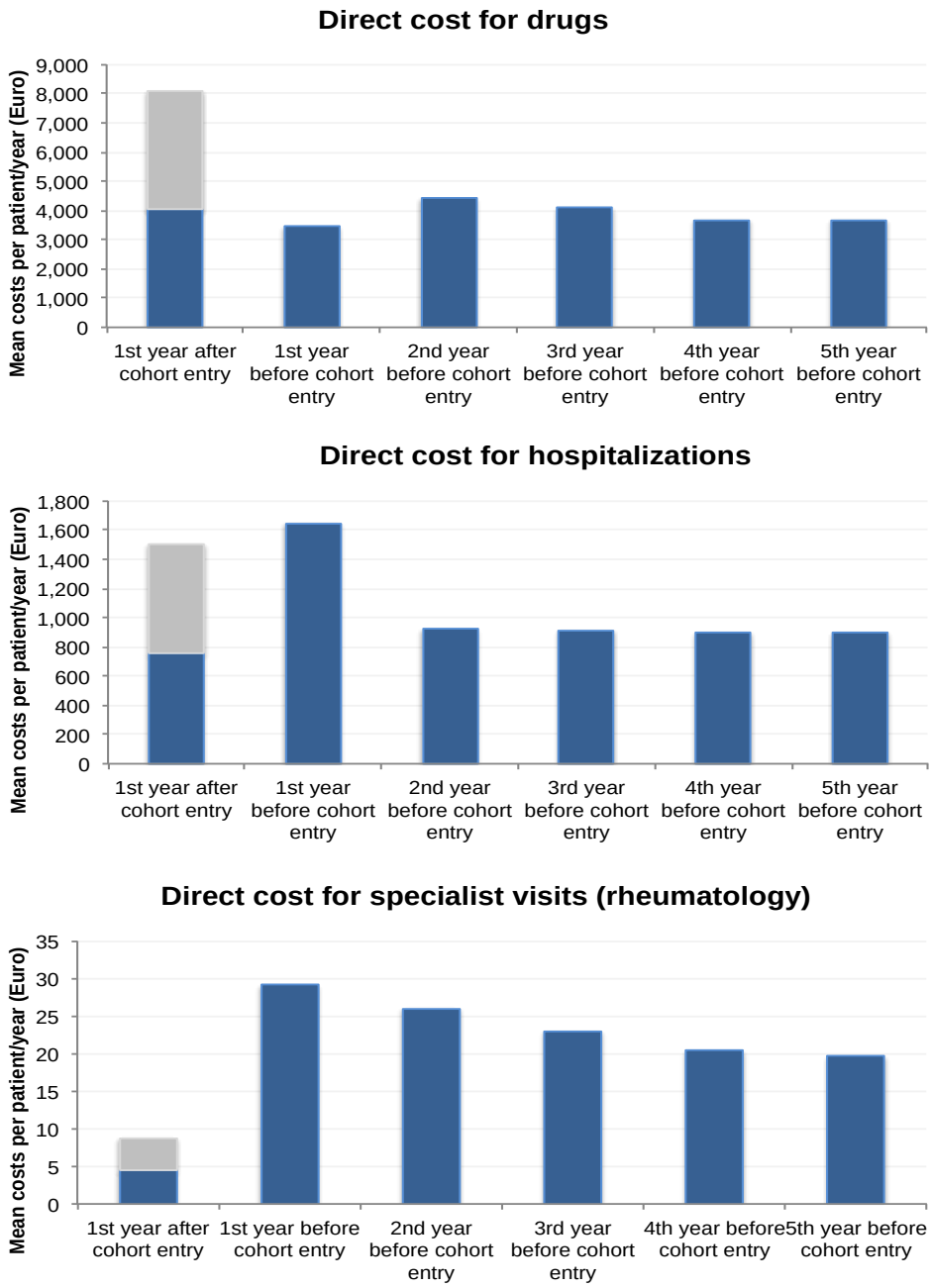
Figure 4



Likewise, figure 5 confirms the circumstance that the six-month observation period in this cohort likely was not able to fully capture costs comparable with those recorded in the previous years for the same patients, due to changes in treatment patterns and related visits. Of note, the ED costs are currently under evaluation, but these are not expected to impact significantly on the mean costs.

Figure 5 shows an increase of cost for drugs reflecting higher acquisition costs of new drugs. Of note, no differences in the costs during the year preceding the first JAKi prescription were observed for the cohort of subjects having a complete six-month follow-up with the first cohort of patients considered in the present analysis (RQ-2).

Figure 5



Due to unexpected issued in the interpretation of data related to resources spent during ED accesses, we prefer to provide a separate estimation of costs, including ED costs, in annex 2.

5.6 Use of bDMARD drugs in rheumatology wards in Tuscany

Table 11a and 11b summarize the number of new bDMARD users in Tuscany from 2014 to 2015. In this cohort we have extrapolated the patients using bDMARDs with supposed rheumatologic indications.

Table 11a. New users of bDMARDs with at least one visit in the year preceding the first bDMARD dispensation, stratified by year

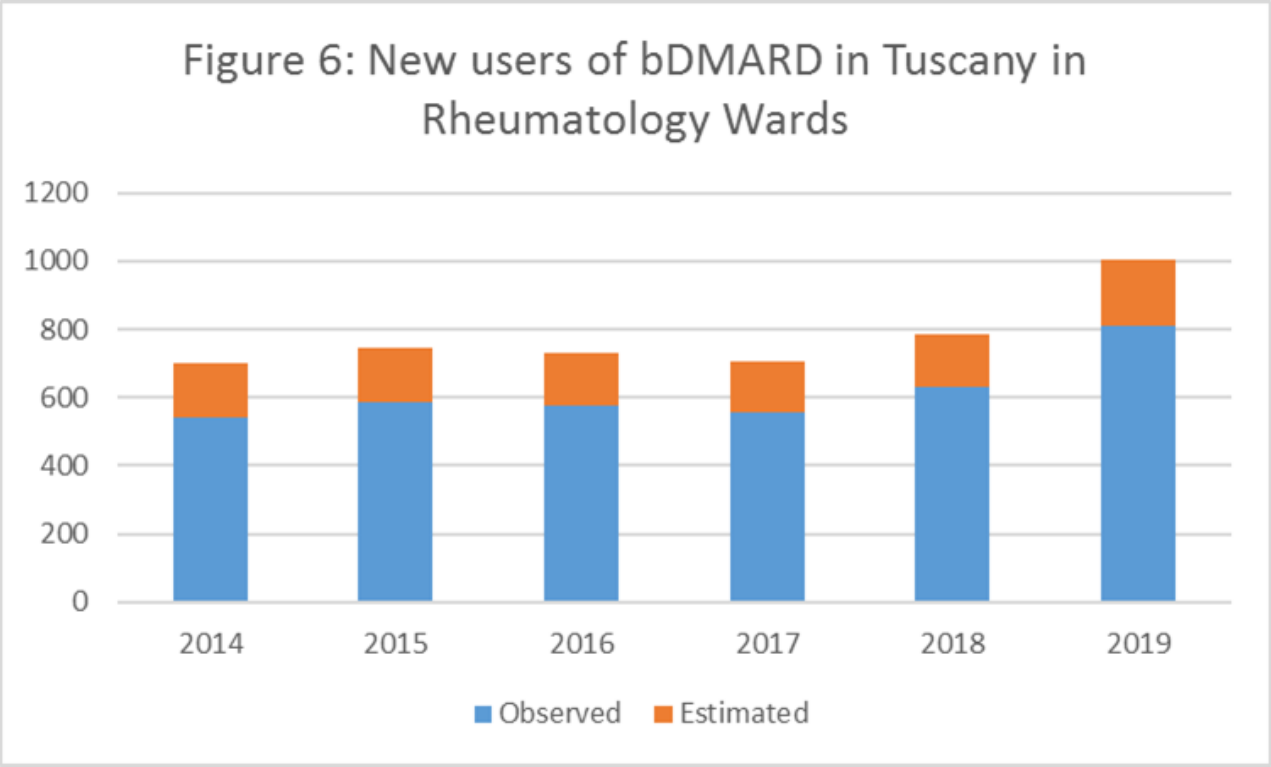
	2014	**2015**	**2016**	**2017**	**2018**	**2019**
Overall new users (including rituximab)	1528	1603	1628	2207	2300	2592
Subjects with information on rheumatology, gastroenterology, dermatology visit	814 (53.3)	927 (57.8)	903 (55.5)	1044 (47.3)	1198 (52.1)	1364 (52.6)
Rheumatologic visits (**A**)	543 (66.7)	588 (63.4)	577 (63.9)	557 (53.4)	633 (52.8)	810 (59.4)

Table 11b. New users of bDMARDs with or without at least one visit in the year preceding the first bDMARD dispensation, stratified by year

	2014	**2015**	**2016**	**2017**	**2018**	**2019**
Overall new users (excluding rituximab)	1047	1154	1114	1170	1296	1540
Subjects with information on rheumatology, gastroenterology, dermatology visits	708 (67.6)	812 (70.4)	793 (71.2)	811 (69.3)	952 (73.5)	1126 (73.1)
Rheumatologic visits	493 **(47.1)**	532 **(46.1)**	533 **(47.8)**	483 **(41.3)**	575 **(44.4)**	717 **(46.6)**
Subjects with no information on rheumatology, gastroenterology, dermatology visits	339 (100)	342 (100)	321 (100)	359 (100)	344 (100)	414 (100)
Assumed rheumatologic visits (**B**)	160 (**47.1**)	158 (**46.1**)	153 (**47.8**)	148 (**41.3**)	153 (**44.4**)	193 (**46.6**)
New users of bDMARD with at least one rheumatologic visit (**A+B**)	703 (46.0)	746 (46.7)	730 (44.8)	705 (31.9)	786 (34.2)	1003 (38.7)
Incidence of bDMARD users with at least one rheumatologic visit in Tuscany (x10.000 inhabitants/year)*	22	24	23	22	25	32

* Source for resident population: Italian Institute of Statistics (ISTAT)

As shown in figure 6, the use of bDMARDs in rheumatology wards was stable over the time with an increment in 2019. A possible explanation for this increase would be that the use of bDMARDs was favoured by the availability of new biosimilar medicinal products (for instance, the adalimumab biosimilar approved at the end of 2018), but this hypothesis should be verified.



A certain proportion of these new users of bDMARDs had likely used these drugs to treat RA. However, healthcare administrative databases cannot identify RA patients with accuracy and precision. A literature search was performed to assess the proportion of patients receiving bDMARDs for RA and rheumatologic diseases other than RA. Using MEDLINE without limit of time or language, we selected observational studies, performed on administrative healthcare databases or disease registries and conducted on new users of bDMARDs, in which the distribution of rheumatologic indications had been assessed. From each study, we collected information about the number and percentage of new bDMARD users for whom RA was recorded at least as one of the indications, as well as the number and percentage of new bDMARD users with record of rheumatologic indications

other than RA. We collected also information about the country where the study was performed, the period covered by patient enrolment and the type of data source.

Table 11c summarizes the results of this literature review. We identified 5 studies conducted on anti-TNF bDMARD new users. The results show that the new users of anti-TNF bDMARDs in a rheumatology ward had the indication for RA in a percentage that ranged from 57% to 88%. It is plausible that even in our patients the proportion of those receiving bDMARDs for RA lies in the same range with a certain approximation. This approximation is complicated by the following factors:

a) Our study included all bDMARDs, while the available literature studies were focused on anti-TNF bDMARDs only.
b) The percentage may vary across countries due to different prescription habits.
c) The percentage may vary in relationship with the calendar years on which the studies had been conducted. The drug-utilization patterns change over time in parallel with the prescriptive awareness, which in turn is influenced by the growth of scientific evidence and progressive availability of novel therapeutic tools.

Table 11c. Distribution of new TNF users in rheumatology setting by indication (observational studies, literature review)

Reference	New users of anti-TNF drugs for rheumatologic indications N	RA n (%)	Rheumatologic disease other than RA n (%)	Period (first use)	Country
Aydin et al., 2019[57]	411,383	363,020 (88)	48,363 (12)	2013-2015	Turkey
Howe et al., 2014[58]	1211	691 (57) (1st scenario) 776 (64) (2nd scenario)	520 (43) 435 (36)	February 1, 2008, and September 30, 2011	USA
Simard et al., 2011[59]	12,368	9302 (75)	3066 (25)	1999-2008	Sweden
Winthrop et al., 2013[60] & Baddley et al, 2014[61] (same database)	29,474	24,384 (83)	5090 (17)	1998-2007	USA

6 Final comments

According to the present analysis, over the first two years of marketing authorization, in Tuscany JAKi users had a history of disease treatment that meets the criteria reported in guidelines. Only 29 patients (8%) appear to have used these drugs as first line therapy (no DMARDs used before the JAKi). It is likely that some of these patients used DMARDs as first line through a dispensation that could not be tracked in Tuscany databases (for example, private purchase or dispensation in other regions). JAKi were used indifferently and in very similar proportions as second line therapy (only one type of DMARD delivered in the look back period), as third line (two types of DMARDs delivered in the look back period) and as fourth line (all types of DMARDs delivered in the look back period).

The majority of new JAKi users were mostly patients 60 years-old who had been treated for a rheumatologic disease for some years (in average about 7 years from the first DMARD, and about 4 years from the first bDMARD). This observation is in line with expectations. Indeed, when made available for the first time in the market, innovative drugs are used with priority in long-term patients, for whom a certain resistance towards previous available treatments is plausible. Even those this hypothesis should be verified, it would explain many of the observations made in the present study. The main implication would regard the frailty of subjects receiving these drugs, as suggested by the extent of accesses to the healthcare services (i.e., the progressive increase of the cost of resource utilization over the years can be likely explained by the progressive disease worsening), which were detected both in the period preceding the start of treatment with JAKi and in the subsequent one.

The cost of health facilities, as recorded for the new JAKi users in the five years preceding the start of treatment with JAKi, increased progressively. This is in line with the duration of treated disease and the prescription of JAKi to particularly frail patients. It should be noted that the extent of resource utilization remained constant in the face of cost increments, this pattern likely being related

to the fact that over the time the causes of resource utilization increased in terms of commitment and clinical relevance.

ED access and hospitalization for the new JAKi users occurred in a proportion of patients ranging from 20 to 30% and from 10% and 20%, respectively, and on average within 3 months from the start of treatment. The events that led to ED access or hospitalization were not related necessarily to the use of the drug, but are in line with the major categories reported by the spontaneous reporting systems, and include mainly trauma (falls) and clues of lack of efficacy and disease worsening.

Cardiovascular causes are often reported as causes of ED access and hospitalization. These events are reflected in the spontaneous reporting of ADRs and in concerns of regulatory agencies[14,16,55]. These types of access are however found both before and after the start of JAKi therapy and can also be explained by the fact that the underlying rheumatologic disease is an independent risk factor for cardiovascular events[56]. This hypothesis should be verified in further analytical studies.

The average direct costs per patient of new JAKi users, as estimated in the first six months of therapy, are higher as compared to the costs estimated for these patients in the years preceding the start of treatment with JAKi. The increase of the overall costs is driven by an increase of cost for drugs that reflect the higher acquisition costs for the innovative treatment. It is important to remark that yearly costs have been estimated by doubling the costs at six months. These yearly costs are likely overestimated because of remission, treatment adjustment and adherence behaviour modifications that may have occurred in the second part of the year.

In our analysis, the number of new bDMARD users remained constant over the time, with an increase in 2019. This observation does not reflect necessarily an increase in the incidence of RA (or other rheumatologic diseases) in Tuscany, but could rather depend on market-related reasons (e.g. availability of biosimilar adalimumab). Of note, a proportion of these patients has not been observed but estimated, based on an assumption to be verified. In this respect, it is important to remark that

the latter analysis does not provide an estimate of the possible candidates to the use of JAKi, but was intended to be used as a context information for a gross estimation of the incidence of RA in Tuscany.

7 List of acronyms

ACR: American College Rheumatology

ADR: adverse drug reaction

AE: adverse events

AIFA: agenzia italiana del farmaco (Italian Drug Agency)

ALT: alanine amino-transferase

bDMARD: biologic DMARD

COVID: CoronaVirus Disease

csDMARD: conventional synthetic DMARD

CYP: cytochrome P

DMARD: disease modifying anti-rheumatic drug

DNA: desoxyribonucleic acid

ED: emergency department

EMA: European Medicine Agency

EU: european union

FDA: food and drug administration

GCs: glucocorticoids

ICD: international classification of diseases

Il: interleukine

IMID: immune-mediated inflammatory disease

JAK: Janus kinase

JAKi: JAK inhibitor

ALTMedDRA. Medical Dictionary for Regualtory Activities

MTX: methotrexate

OAT: organic anionic transporter

PgP: P-glycoprotein

PsA: psoriasic arthritis

PT: preferred term

RA: rheumatoid arhritis

RAM: reazioni averse dei medicinali (adverse reactions to medicine)

RQ: research question

SDO: scheda dimissione ospedaliera (hospital discharge record)

SOC: system organ class

STAT: signal transducers and activators of transcription

TNF: tumor necrosis factor

tsDMARD: targeted synthetic DMARD

UC: ulcerative colitis

USA: united states of America

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LEONARDO study - Annex 1 – Cost of JAK inhibitor users in the years preceding the first dispensation of JAK inhibitors (including ED admissions)

Table 2d shows the costs of JAK inhibitor users in the years before the first dispensation of JAK inhibitors. Costs increased over years with a reduction in the year preceding cohort entry which is substantially related to the reduction of costs of drug treatments. A hypothesis that could explain such reduction could be the introduction on the clinical use of the biosimilar medicinal products of some largely used bDMARD (i.e. adalimumab). The cost of emergency department access is stable over time and it has a minimal impact on the overall costs.

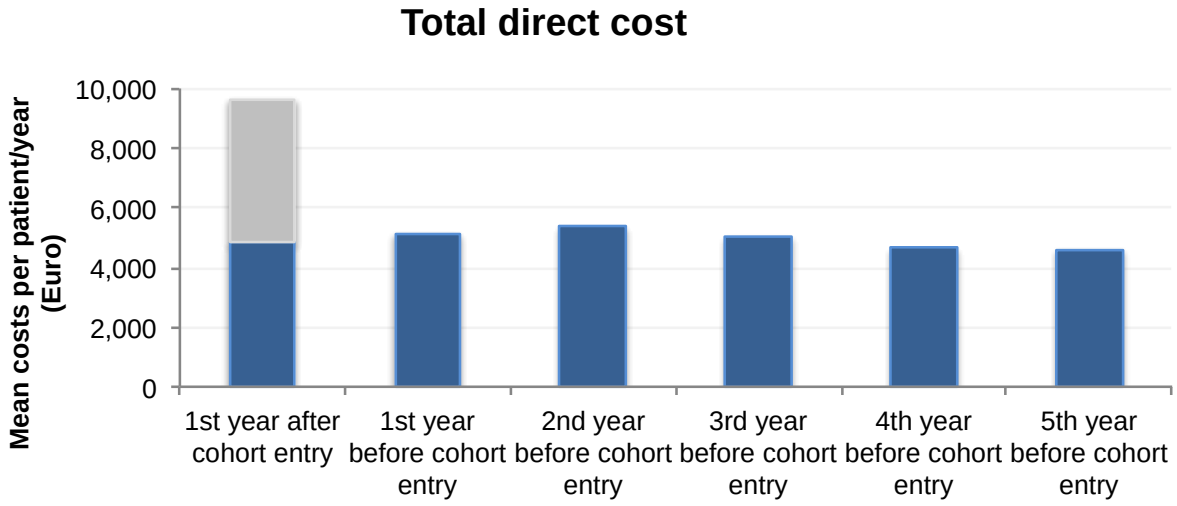
Table 2d – Cost in the years preceding the first JAKi prescription					
	In the 1st year before cohort entry	In the 2nd year before cohort entry	In the 3rd year before cohort entry	In the 4th year before cohort entry	In the 5th year before cohort entry
Total cost	**1,691,856**	**1,909,106**	**1,768,659**	**1,639,472**	**1,569,855**
Drugs	1,147,654	1,438,147	1,376,923	1,283,628	1,273,034
Emergency department access	15,428	10,879	14,483	18,324	17,874
Hospitalization	521,431	450,207	368,797	329,850	271,317
Specialist visits (rheumatology)	7,344	9,873	8,455	7,670	7,630
Mean (Min;Max) cost per patient/year	**4,660.8 (0;97,296.6)**	**5,259.2 (0;41,629.8)**	**4,872.3 (0;52,039.5)**	**4,516.5 (0;30,511.9)**	**4,324.7 (0;24,265.4)**
Drugs	3,161.6 (0;15,574.2)	3,961.8 (0;19,892.2)	3,793.2 (0;19,795)	3,536.2 (0;17,745.4)	3,507.0 (0;19,474.4)
Emergency department access	42.5 (0;1,072)	30.0 (0;1,121)	39.9 (0;872.4)	50.5 (0;1,468)	49.2 (0;2,849)
Hospitalization	1,436.5 (0;93,050)	1,240.2 (0;39,399)	1,016 (0;34,677)	908.7 (0;26,676)	747.4 (0;20,507)
Specialist visits (rheumatology)	20.2 (0;193)	27.2 (0;601)	23.3 (0;476)	21.1 (0;476)	21 (0;476)

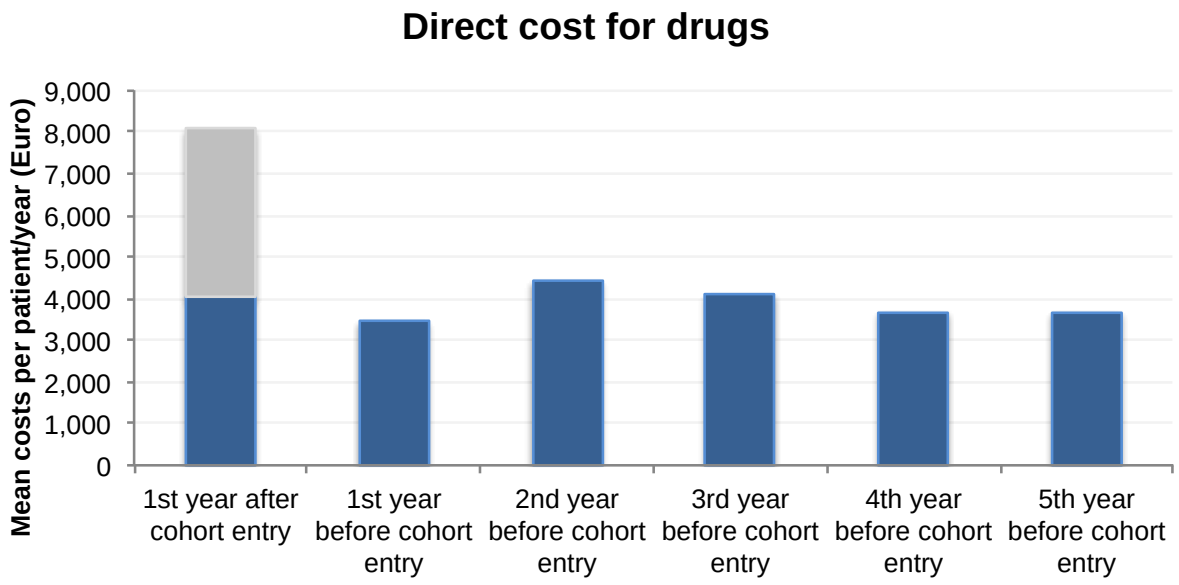
LEONARDO study - Annex 2 – Cost of JAK inhibitor users in the 6 months after the first dispensation of JAK inhibitors (including ED admissions)

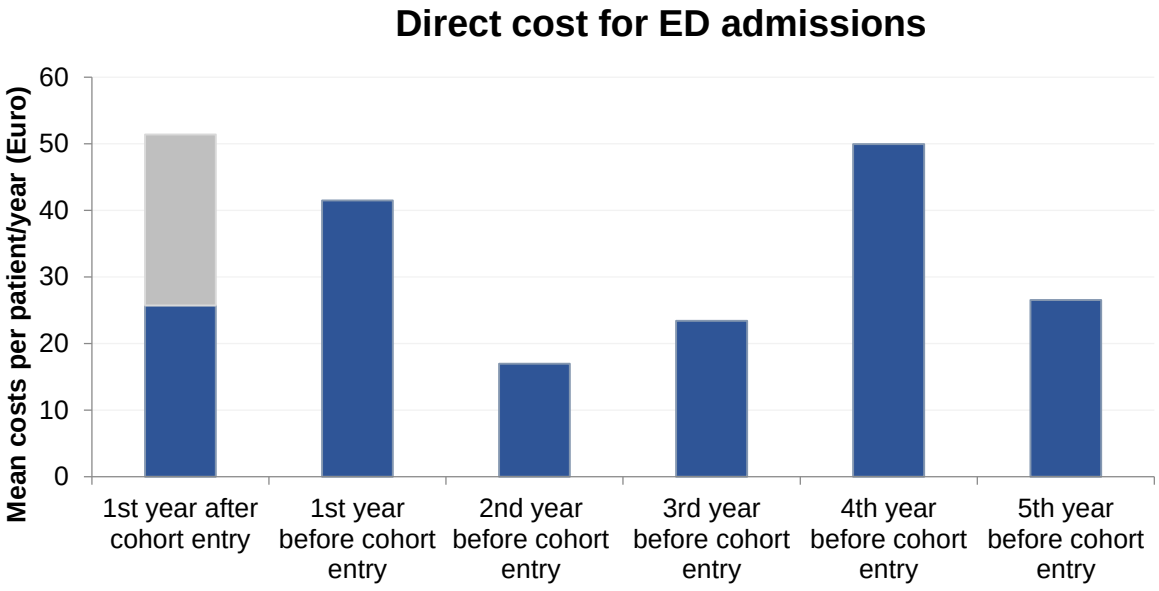
Table 2d shows the costs of JAK inhibitor users in the 6 months after the first dispensation of JAK inhibitors. The most important costs is hospitalization. The cost of emergency department has a minimal impact on the overall costs.

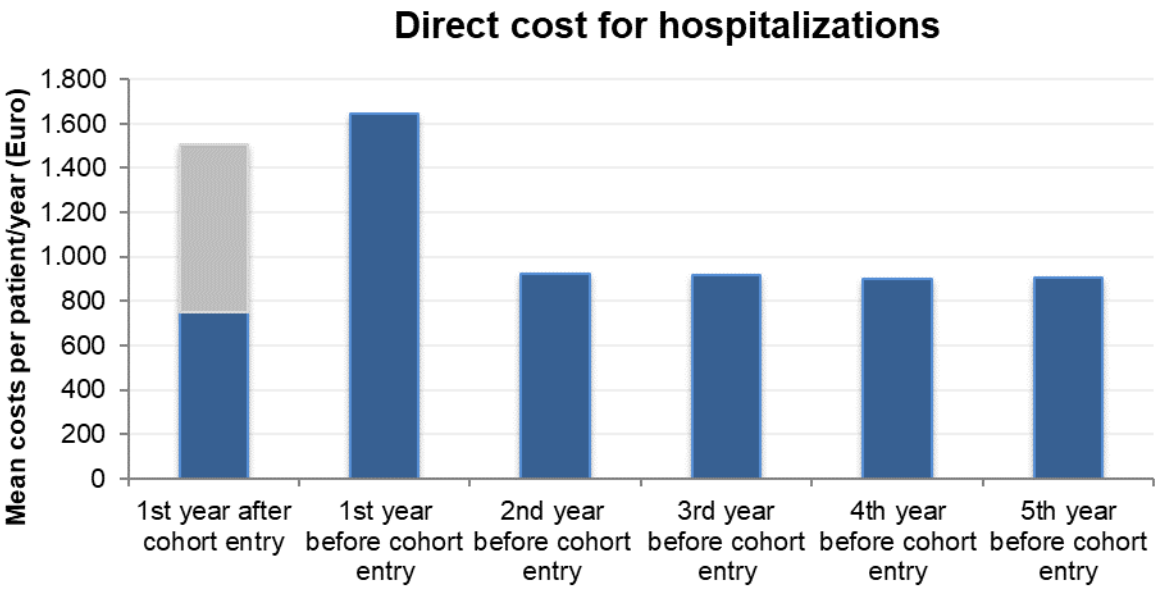
Table 2d. Cost in the first six months after the first JAKi prescription	
	Cost (€)
Total cost	**1,060,191**
Drugs	887,946
Emergency department access	5,661
Hospitalization	165,624
Specialist visits (rheumatology)	960
Mean (Min;Max) cost per patient	**4,819.1 (607.5;50,493)**
Drugs	4,036.1 (607.5;8,387.9)
Emergency department access	25.7 (0;1,371)
Hospitalization	752.8 (0;43,811)
Specialist visits (rheumatology)	4.4 (0;60)

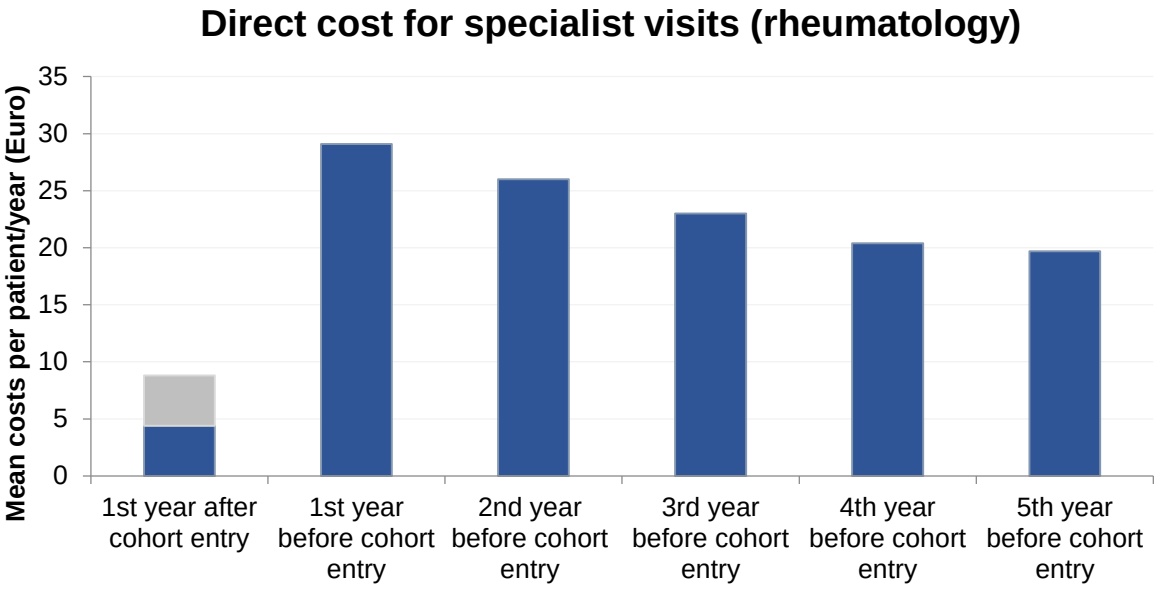
The following pictures show the trend of the costs before and after the introduction of JAKi in a population of JAKi users with at least 6 months of follow up. The increase of costs observed after the introduction of JAKi is leaded by the higher acquisition cost of drugs. Other items costs seems to remain stable or to have a small impact on overall costs.




Direct cost for drugs
Mean costs per patient/year (Euro)
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
1st year after cohort entry
1st year before cohort entry
2nd year before cohort entry
3rd year before cohort entry
4th year before cohort entry
5th year before cohort entry


Direct cost for ED admissions
Mean costs per patient/year (Euro)
60
50
40
30
20
10
0
1st year after cohort entry
1st year before cohort entry
2nd year before cohort entry
3rd year before cohort entry
4th year before cohort entry
5th year before cohort entry


Direct cost for hospitalizations
Mean costs per patient/year (Euro)
1.800
1.600
1.400
1.200
1.000
800
600
400
200
0
1st year after cohort entry
1st year before cohort entry
2nd year before cohort entry
3rd year before cohort entry
4th year before cohort entry
5th year before cohort entry


Direct cost for specialist visits (rheumatology)
Mean costs per patient/year (Euro)
35
30
25
20
15
10
5
0
1st year after cohort entry
1st year before cohort entry
2nd year before cohort entry
3rd year before cohort entry
4th year before cohort entry
5th year before cohort entry