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Maintien thérapeutique des inhibiteurs de JAK et des bDMARDs dans la polyarthrite rhumatoïde

Camille Bie

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**MAINTIEN THERAPEUTIQUE DES INHIBITEURS DE JAK ET
DES bDMARDs DANS LA POLYARTHRITE RHUMATOIDE**

Sous la direction de Madame le Professeur Marie-Elise TRUCHETET

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M. le Professeur Thierry SCHAEVERBEKE
M. le Docteur Jean-Philippe VERNHES
M. le Professeur Pierre DUFFAU
M. le Professeur Christophe RICHEZ
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LISTE DES ABREVIATIONS

ACPA : anti-citrullinated protein antibodies

AE : adverse event

bDMARD : biological drug modifying arthritis rheumatic disease

BMI : body mass index

csDMARD : conventional synthetic drug modifying arthritis rheumatic disease

EULAR : European League Against Rheumatism

IFN : interferon

IL : interleukine

IL6ir : interleukine-6 receptor inhibitor

IQR : interquantile range

JAK : just another kinase

MTX : methotrexate

PR : polyarthrite rhumatoïde

RA : rheumatoid arthritis

RCT : randomized clinical trials

RF : rheumatoid factor

SD : standard deviation

STAT : signal transducer and activator of transcription

TNF : tumor necrosis factor

tsDMARD : targeted synthetic drug modifying arthritis rheumatic disease

INTRODUCTION

1.1 Stratégie thérapeutique dans la polyarthrite rhumatoïde : la place des inhibiteurs de JAK et des bDMARDs

Depuis les années 2000, l'évolution naturelle de la polyarthrite rhumatoïde (PR) a été révolutionnée par l'apparition de nouvelles thérapies et par une nouvelle approche stratégique globale. En effet on note ces dernières années une diminution globale de l'activité de la maladie, de la sévérité des atteintes articulaires et radiographiques, ainsi qu'une diminution de l'invalidité induite par la maladie (1,2).

Ces constatations sont le résultat de modifications profondes des stratégies thérapeutiques (3) :

- la reconnaissance de l'importance d'un diagnostic précoce avec la mise en route d'un traitement de fond le plus tôt possible ;
- l'utilisation d'outils standardisés permettant de suivre l'activité de la maladie régulièrement (tous les 1 à 6 mois selon le degré d'activité de la maladie) ;
- l'adoption du « *treat-to-target* » soit déterminer clairement un objectif thérapeutique (le plus souvent la rémission clinique ou au minimum une faible activité de la maladie) et modifier régulièrement les traitements jusqu'à l'atteindre.

Les dernières recommandations européennes de l' « European League Against Rheumatism » (EULAR) actualisées en 2019 pour la prise en charge de la PR conseillent la mise en place d'un traitement de fond le plus précocement possible avec en première intention l'introduction du méthotrexate éventuellement associé à une faible dose de corticoïdes (4).

Une des modifications notables dans les recommandations de ces dernières années concerne la stratégie thérapeutique en deuxième ligne thérapeutique avec l'arrivée des inhibiteurs de JAK (JAKi) comme nouvelle alternative thérapeutique. Il s'agit plus précisément de l'attitude proposée en cas de réponse jugée insuffisante au traitement de première ligne par csDMARDs en présence de facteurs de mauvais pronostic (activité de la maladie importante, taux élevés d'autoanticorps, présence d'érosions précoces, échec de deux ou plus csDMARDs).

Les recommandations de l'EULAR de 2013 proposaient seulement l'ajout d'un bDMARDs en deuxième ligne thérapeutique. Le tofacitinib pouvait être considéré comme une alternative en cas

d'échec d'un bDMARDs mais son autorisation de mise sur le marché (AMM) était très limitée dans les pays européens (5). En 2016 on recommande en deuxième ligne l'ajout d'un bDMARDs ou d'un tsDMARDs mais avec toujours une préférence soulignée pour l'initiation d'un bDMARDs (6). Enfin en 2019, on recommande l'introduction d'un traitement ciblé (bDMARDs ou tsDMARDs) en deuxième ligne sans distinction. Cette stratégie est également celle recommandée par la Société française de rhumatologie (7).

1.2 Mode d'action des JAK inhibiteurs

Les tsDMARDs constituent donc une nouvelle classe thérapeutique avec deux molécules ayant reçues l'AMM en 2017 en France dans le traitement de la PR : le baricitinib et le tofacitinib, toutes les deux appartenant à la famille des inhibiteurs de JAK.

Les JAK sont des enzymes qui permettent la transduction de signaux intra-cellulaires de diverses cytokines et jouent un rôle dans la différenciation et le cycle cellulaire de nombreuses cellules avec un rôle primordial pour les cellules du système immunitaire. La famille des JAK comprend 4 molécules : JAK1, JAK2, JAK3 et Tyk2.

Il s'agit de protéines avec une activité tyrosine kinase liées à des récepteurs transmembranaires pour différentes cytokines. Les JAK fonctionnent en association avec des facteurs de transcription intracellulaires appelés STAT formant ainsi la voie JAK-STAT.

La reconnaissance de la cytokine par le récepteur va activer la protéine JAK qui va provoquer la phosphorylation du récepteur transmembranaire nécessaire pour la fixation des protéines STAT. Ces dernières possèdent un résidu tyrosine qui sera à son tour phosphorylé par les JAK (8). Les facteurs de transcription phosphorylés pourront alors migrer dans le cytoplasme jusqu'au noyau pour permettre la transcription de gènes ciblés. Il s'agit le plus souvent de gènes impliqués dans la synthèse de molécules pro-inflammatoires.

Dans la PR, l'activation lymphocytaire et macrophagique mène à la production incontrôlée de cytokines pro-inflammatoires qui en interagissant avec la voie JAK/STAT permettent de maintenir l'inflammation synoviale, de promouvoir l'auto-immunité et de favoriser la destruction osseuse et cartilagineuse. Les inhibiteurs de JAK agissent de manière intra-cellulaire en se fixant sur leur cible de manière réversible et compétitive et permettent de bloquer partiellement l'activité tyrosine

kinase et donc la phosphorylation des protéines STAT. Leur action permet une modulation de la réponse immunitaire et une diminution de la production des cytokines pro-inflammatoires. (9)

L'efficacité du tofacitinib et du baricitinib en monothérapie ou en association au méthotrexate a été démontrée dans plusieurs essais randomisés (10-14) qui ont également permis de recueillir des données rassurantes quant à leur tolérance. Néanmoins ces études ont été réalisées sur une population sélectionnée avec des critères d'inclusion précis qui ne reflètent pas forcément la diversité de la population traitée dans la pratique courante. Les études des données cliniques en vie réelle apportent donc un complément d'information précieux aux essais cliniques randomisés malgré les limites induites par leur caractère observationnel (15).

1.3 Intérêt de l'évaluation du maintien thérapeutique en vie réelle

Le maintien thérapeutique peut se définir comme la persistance d'un traitement dans le temps, depuis son initiation jusqu'à l'arrêt ou la modification de la stratégie thérapeutique. Il s'agit d'une mesure intéressante car prenant en compte indirectement plusieurs facteurs tels que l'efficacité et la tolérance. En général un traitement va en effet être poursuivi tant qu'il est jugé suffisamment efficace par rapport aux effets secondaires engendrés.

Dans la PR le maintien thérapeutique des bDMARDs est étudié le plus souvent par le biais de registres et d'études observationnelles. Ces études permettent le suivi des traitements en vie réelle mais le critère du maintien est plus rarement le critère de jugement principal au profit de l'analyse directe de l'efficacité et des effets secondaires comme dans les essais cliniques. Les études observationnelles en vie réelle sont d'ailleurs à l'origine d'avancées majeures en rhumatologie. Elles ont par exemple permis la considération du méthotrexate comme « gold-standard » dans la prise en charge de la PR, l'efficacité de ce traitement n'avait pas été aussi clairement démontré dans les premiers essais randomisés (16).

L'utilisation des inhibiteurs de JAK étant plus récente en France il existe encore peu de données sur le maintien thérapeutique en vie réelle. Un registre national dénommé « MAJIK » est actuellement en cours de réalisation avec pour objectif le recueil de données biologiques et cliniques sur les patients traités par inhibiteurs de JAK en rhumatologie dans différentes indications selon l'AMM susceptible d'évoluer au cours du temps.

Le but de ce travail est d'étudier le maintien thérapeutique des inhibiteurs de JAK et des bDMARDs utilisés chez des patients atteints de PR au CHU de Bordeaux en pratique courante sur une période allant jusqu'à 2 ans après leur introduction. Les objectifs secondaires sont l'étude des éventuels facteurs prédictifs du maintien thérapeutique et des motifs d'arrêt des traitements en recueillant des données sur l'efficacité et les effets indésirables.

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ARTICLE SCIENTIFIQUE

MAINTENANCE OF JAK INHIBITORS AND bDMARDs IN RHEUMATOID ARTHRITIS

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ABSTRACT

Objective : The continuation rate of a drug is an indirect measure of effectiveness and tolerance. The aim of this study was to assess the therapeutic maintenance in real-life of biologic drug modifying rheumatic diseases (bDMARDs) and JAK inhibitors (JAKi) in rheumatoid arthritis (RA) over an 18-month period and to analyze factors predictive of treatment continuation as well as reasons for discontinuation.

Methods : This is a retrospective analysis of the medical records of RA patients followed at Bordeaux University Hospital who received a new prescription for a JAKi or a bDMARD between November 1, 2017 and October 10, 2018. Clinical and biological data were collected at baseline and up to a 18-month follow-up. Survival curves were constructed using the Kaplan-Meier method and comparison made by logrank testing. Factors associated with maintenance at 12 and 18 months were assessed by univariate and multivariate analyses.

Results : Among the 129 patients included, 47 were prescribed a JAKi, 43 a TNF inhibitor (TNFi) and 39 another bDMARD (abatacept, rituximab, IL6 inhibitor). At 18 months, the global therapeutic maintenance rate was 39% (45% for JAKi, 37% for TNFi and 33% for other bDMARDs). There was no significant difference in the crude overall drug retention between treatments ($p = 0,26$). Presence of corticosteroids at initiation was the only predictive factor associated with maintenance in both univariate and multivariate analysis showing a higher discontinuation at 18 months ($p = 0.05$). However concomitant csDMARDs therapy showed no association with continuation ($p = 0,87$). The main causes of discontinuation were global lack of efficacy at 51% and occurrence of adverse events (AE) at 38%.

Conclusion : This observational study has shown a similar drug retention between JAKi and other bDMARDs.

1.1 Introduction

The discovery and use of biological disease-modifying antirheumatic drugs (bDMARDs) have deeply improved the outcome of rheumatoid arthritis (RA) (1). The evidence of their efficacy and safety has been proved with multiple randomized clinical trials (RCTs) : the first bDMARDs ever used for RA were tumor necrosis factor inhibitors (TNFi) with five molecules available (2-6), followed by the use of interleukine 6 (IL-6) receptor antibodies (7), co-stimulation inhibitor CTLA4-Ig (abatacept) (8) and anti-CD20 monoclonal antibody (rituximab) (9).

More recently JAK inhibitors (JAKi) have been added to the therapeutic arsenal of RA with two new drugs : baricitinib and tofacitinib. These are the first targeted synthetic drug modifying arthritis rheumatic disease (tsDMARDs) to have the market authorization in RA treatment in France since 2017. This new therapeutic line is different from the previous bDMARDs. First JAKi have a singular mode of operation by affecting intracellular signalization using the JAK/STAT pathway (10). Moreover, the way of administration of JAKi is different with a daily oral administration compared to the others bDMARDs which have regular subcutaneous or intravenous administration, implying also a shorter half-life.

Their efficacy has been proved in several phase III clinical trials (11,12). They should be used, like TNFi and others bDMARDs, in case of insufficient response of RA with a csDMARDs. In the latest EULAR recommendation, the efficacy of the different therapeutic option was considered equivalent and therefore a JAKi or a bDMARDs can be used without distinction based on effectiveness in second line after csDMARDs failure (13).

In contrast with TNFi, studies of JAKi in real life are rarer given the recent use of this drugs outside of controlled studies especially in France. The aim of this monocentric retrospective study was to assess the drug survival of bDMARDs and JAKi used in RA in real life over a short period of 18 months. The beginning of the observation period was in October 2017 which means that we study the first prescription of JAKi in real life in the university hospital of Bordeaux. We also wanted to assess the predictive factors of treatment continuation and analyze the reasons for discontinuation.

1.2 Methods

1.2.1 Study design and population

This monocentric, retrospective study was conducted in the university hospital of Bordeaux. Two investigators collected anonymized data based on the medical charts of patients with a previous or new diagnostic of RA receiving a new prescription of bDMARDs or tsDMARDs between November 1, 2017 and October 10, 2018. A same patient could be included several times if the therapeutic strategy was modified during the period of interest and his baseline characteristics were updated accordingly. We included all patients whose age was over 18 with a confirmed diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (14) (supplementary Figure 1). All new prescription of bDMARDs or tsDMARDs were analyzed regardless of the number of previous therapeutic lines. We classified the patients in 3 subgroups based on the treatment they received : JAKi, TNFi or other bDMARDs (including rituximab, abatacept, tocilizumab and sarilumab).

1.2.2 Data collected

Baseline and follow-up data were collected using mainly hospital medical charts but in some cases we could directly reached the liberal referring rheumatologist, the general practitioner or the patient himself to collect information in order to limit missing data on principal outcomes. We gathered data on patient characteristics (age, sex, BMI, smoking, diabetes), disease characteristics (time since RA diagnosis, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) status, structural damages, extra-articular involvement, number of previous bDMARDs), clinical and biological data at baseline (swollen joint count (SJC) and tender joint count (TJC), patient evaluation of activity (0-10) DAS28-ESR, C-reactive protein (CRP)) and treatments associated with the new prescription (presence of csDMARDs, presence and dose of glucocorticoids). Disease activity follow-up data (SJC, TJC, PEA, DAS28-ESR and CRP) were collected at 3, 6, 12, 18 and 24 months if available.

1.2.3 Follow-up

Data were collected until April 10, 2020 with a maximum follow-up of 24 months.

1.2.4 Continuation rate

The continuation rate of a treatment corresponded to the pursuit of this treatment at the date of assessment. We considered that an interruption of treatment for more than 90 days even if only temporary was equivalent to a stop. We also counted as discontinuation major therapeutic modifications such as another treatment's addition when efficacy was judged insufficient by the rheumatologist referent (generally the start of a csDMARDs when it was not given at inclusion). Data were collected at 1, 3, 6, 12, 18 and 24 months. Reasons for treatment discontinuation were recorded and classified into categories : primary inefficacy, secondary inefficacy, partial efficacy, AE, surgery, patient's decision, remission or death. When there was more than one reason for treatment interruption, they were all taken into account.

1.2.5 Adverse events

All the AE reported by the rheumatologist in the medical chart during the time of study were collected. We classified the AE into categories : general disorders (such as nausea, asthenia, dizziness, asthenia, abdominal pain), allergy (local or systemic), infectious events, renal failures, hepatic disorders, cardio-vascular events, the occurrence of malignancy and hematologic laboratory changes. We notified if each AE was leading to a temporary or permanent discontinuation of treatment.

1.2.6 Statistical analysis

Quantitative variables were presented as mean \pm standard deviation (SD) or median \pm interquartile range (IQR) and qualitative variables as number and percentage. Kaplan-Meier estimates of the probability for drug maintenance were used, and the survival of the different treatments were compared using the log rank statistic. Data were analyzed by Student test or Mann-Whitney test depending on the result of Shapiro-Wilk test for normality for quantitative variables, and a chi-squared test was used for qualitative variables.

First univariate logistic regression analyses were performed to examine associations between potential baseline predictive factors and treatment continuation. The multivariate logistic regression model included all the parameters that had a p value of <0.10 in univariate analysis to identify independent factors. The following significant variables were then entered into the logistic regression analyses : structural damages, glucocorticoids at baseline, treatment with IL6

receptor inhibitor and serologic status. Analysis were made with the software STATA 13. A p-value < 0.05 was considered statistically significant.

1.3 Results

1.3.1 Baseline characteristics of patients

A total number of 129 patients were included in this study. 72% (93/129) of patients were women. The mean age was 58 years (SD ± 14) with a median history of disease of 5,3 years (64 months, IQR [21-207]). The mean BMI was 27 (SD ± 6), 56% of the patients with available data on BMI at baseline had a BMI over 25 (61/108) and 26% had a BMI equal or over 30 (28/108). A new prescription of JAKi occurred in 36% of patients (47/129) with 34 prescriptions of baricitinib and 13 of tofacitinib ; 33% of patients received a prescription of TNFi (43/129) with 26 prescriptions of etanercept, 9 of adalimumab, 7 of infliximab, 1 of golimumab and no prescription of certolizumab ; 30% (39/129) had another treatment with 15 prescriptions of tocilizumab, 7 of sarilumab, 12 of abatacept and 6 of rituximab (Table 1).

72% of the patients (93/129) were already on a csDMARDs when the new therapeutic line was introduced and 62% of them (80/129) were taking glucocorticoids with a mean dose of 6,6 mg (SD ± 10). There was no difference about markers of disease activity at baseline between the three groups (Table 1).

However disease duration was significantly higher in the JAKi group than in the TNFi group and the other bDMARDs group (both $p < 10^{-4}$). JAKi patients had also more structural damages (83% vs 49%, $p < 10^{-4}$ and 83% vs 54%, $p < 10^{-4}$), and a significant higher number of previous lines of bDMARDs (4 ± 2 vs 1 ± 1 , $p < 10^{-4}$ and 4 ± 2 vs 2 ± 1 , $p < 10^{-4}$).

	Global (n=129)	JAK inhibitors (n=47)	TNF inhibitors (n=43)	Others bDMARDs (n=39)
Patient characteristics				
Female gender, n (%)	93 (72)	37 (79)	33 (77)	23 (59)
Age, mean (SD)	58 (±14)	55 (±14)	55 (±14)	55 (±13)
Active smoking, n (%)	33 (27)	11 (26)	11 (27)	11 (29)
BMI, mean (±SD)	27 (±6)	28 (±7)	26 (±5)	27 (±7)
Diabete, n (%)	15 (12)	4 (9)	6 (14)	3 (8)
RA characteristics				
Disease duration (months), median (IQR)	64 [21-207]	188 [73-287]	30 [12-97]	31 [13-156]
Serologic status, n (%)				
RF - and ACPA-	10 (8)	3 (6)	5 (12)	2 (5)
RF + or ACPA +	19 (15)	11 (26)	4 (10)	4 (10)
RF + and ACPA +	98 (76)	31 (66)	34 (79)	33 (85)
Structural damages, n (%)	81 (63)	39 (83)	21 (49)	21 (54)
Extra-articular involvement, n (%)	36 (28)	16 (34)	10 (23)	10 (26)
Nb of previous bDMARDs, mean (±SD)				
0, n (%)	37 (29)	1 (2)	27 (63)	9 (23)
1-3, n (%)	62 (48)	21 (45)	15 (35)	26 (67)
>3, n (%)	30 (23)	25 (53)	1 (2)	4 (10)
Disease activity				
TJC, mean (±SD)	6 (±6)	6 (±6)	5 (±6)	7 (±7)
STC, mean (±SD)	4 (±4)	3 (±4)	4 (±4)	5 (±6)
PGA, mean (±SD)	5 (±2)	5 (±3)	6 (±2)	5 (±2)
DAS 28-ESR, mean (±SD)	4,5 (±1,5)	4,4 (±1,7)	4,4 (±1,2)	4,8 (±1,7)
Therapeutics				
Glucocorticoids at inclusion, n (%)				
None	49 (38)	13 (28)	22 (51)	14 (36)
≤ 5 mg	32 (25)	18 (38)	9 (21)	5 (13)
entre 5 et 10 mg	32 (25)	13 (28)	9 (21)	10 (26)
> 10 mg	15 (12)	2 (4)	3 (7)	10 (26)
Association with csDMARDs, n (%)	93 (72)	31 (66)	34 (79)	28 (72)
JAK inhibitors, n (%)				
<i>Baricitinib</i>	34 (26)			
<i>Tofacitinib</i>	13 (10)			
TNF inhibitors, n (%)				
<i>Adalimumab</i>	9 (7)			
<i>Etanercept</i>	26 (20)			
<i>Golimumab</i>	1 (1)			
<i>Infliximab</i>	7 (5)			
Others bDMARDs, n (%)				
<i>Tocilizumab/Sarilumab</i>	22 (17)			
<i>Rituximab</i>	5 (4)			
<i>Abatacept</i>	12 (9)			

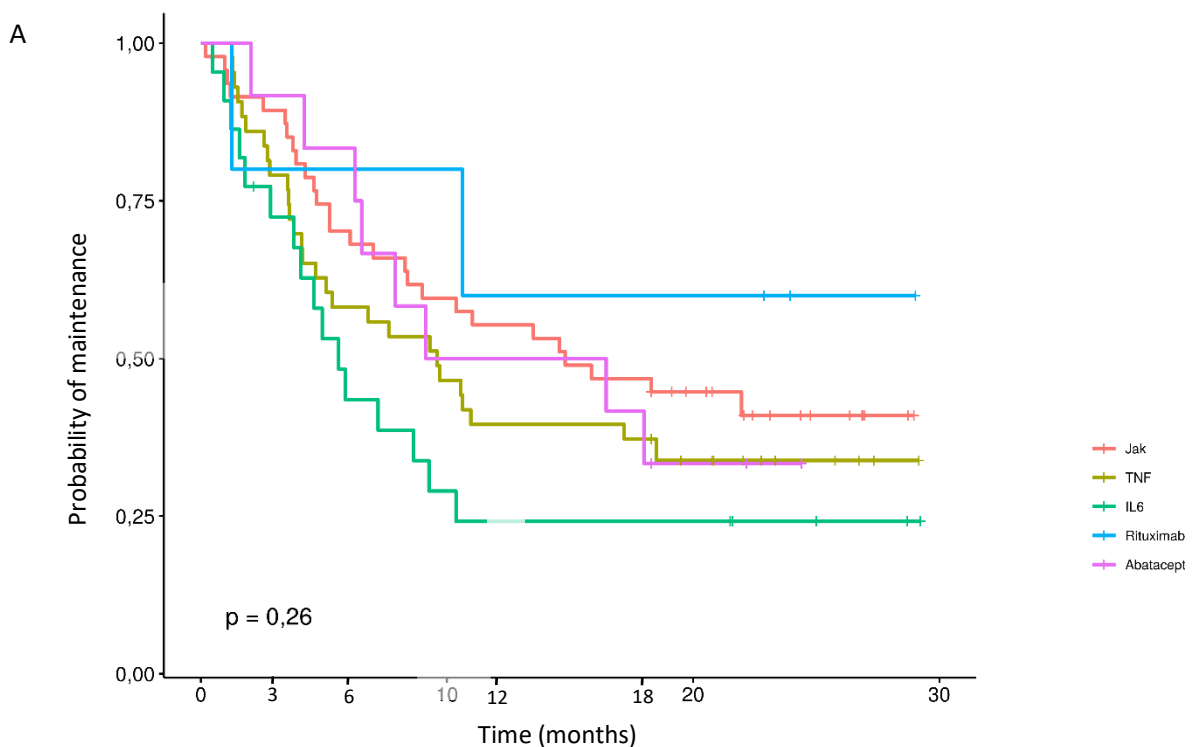
Table 1. Baseline characteristics of global population and description in 3 sub-groups based on treatment type.

SD = deviation standard ; BMI = body mass index ; IQR = interquartile range ; RF = rheumatoid factors ; ACPA = anti-citrullinated protein antibody ; bDMARD = biological DMARDs ; csDMARDs = conventional synthetic disease modifying antirheumatic drug ; JAK = Janus kinases ; TNF = tumor necrosis factor ; TJC = tender joint count ; SJC = swollen joint count ; PGA = pain global assessment ; ESR = erythrocyte sedimentation rate ; DAS 28-ESR = disease activity score for 28 joints using ESR.

1.3.2 Survival curves analysis of treatment continuation

The percentage of patients still receiving the same drug from the inclusion was estimated at 64% at 6 months, 44% at 12 months and 39% at 18 months. The global median duration of all treatments together was 311 days [124-616]. Using Kaplan-Meier estimates the percentage of patients still receiving the treatment in the JAKi group after 6, 12 and 18 months of follow-up was respectively 72%, 55% and 45% with a median duration of 365 days [157-659] ; 60%, 40% and 37% for the patients receiving TNFi at respectively 6, 12 and 18 months with a median duration of 291 days [108-555] ; and 56%, 36% and 33% for the patients receiving another bDMARDs at respectively 6, 12 and 18 months with a median duration of 237 days [113-645] (Figure 1).

Despite a tendency, no statistically significant difference in terms of survival was observed between the treatments (log-rank test, $p = 0,26$) even when JAKi were compared with all the other bDMARDs (log-rank test, $p = 0,21$) (Figure 1). We conducted additional analyses by removing the 5 patients with a treatment with rituximab. We assumed that the administration of rituximab every 6 months could alter our results by increasing continuation in the bDMARDs group. JAKi maintenance was still not significantly different compared to the other bDMARDs (log-rank test, $p = 0,14$) (Supplementary Figure 2).



Months	0	3	6	12	18
Global	129	103	82	57	50
JAKi	47	42	34	26	21
TNFi	43	33	26	17	16
IL6	22	14	9	5	5
Rituximab	5	4	4	3	3
Abatacept	12	10	9	6	5

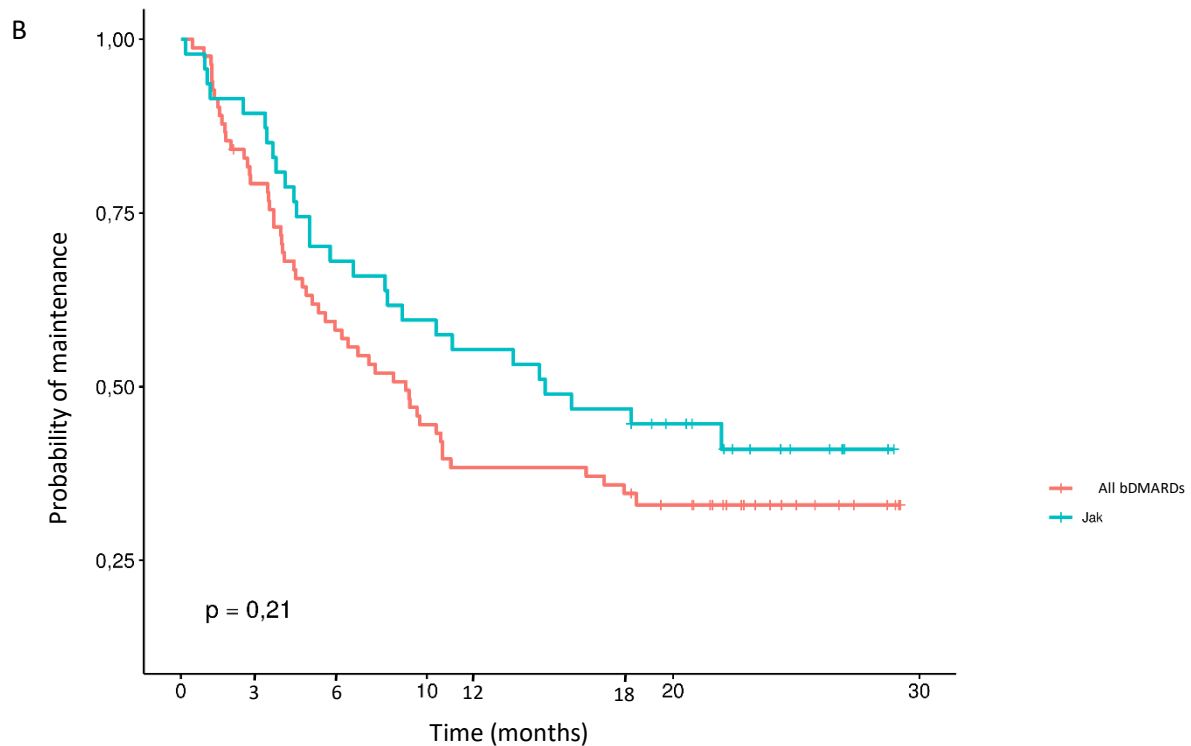


Figure 1. Kaplan–Meier survival analysis of persistence.

Comparison of survival rate between JAKi, TNFi and others bDMARDs including IL6ri, abatacept and rituximab (A). Comparison of survival rate between JAKi and all the other bDMARDs including TNFi, IL6ri, abatacept and rituximab (B). The number of patients on a drug at different time points is listed below the figure A.

1.3.3 Factors associated with continuation rate at 12 and 18 months in univariate and multivariate analysis

Univariate analysis showed that the presence of glucocorticoids and a higher dose of glucocorticoids at the moment of treatment’s initiation seemed to favour discontinuation at 18 months (respectively [odd ratio (OR) 0.35 (95% confidence intervals (CI) 0.17, 0.45), $p = 0,005$] and [OR 0.45 (95% CI 0.25, 0.82), $p = 0,03$]) as well as ACPA and/or RF positivity [OR 0.20 (95% CI 0.03, 0.84), $p = 0,05$] (Table 2). However we found no significant association between continuation and the nature of the treatment, the number of previous bDMARDs, the

concomitant use of csDMARDs or the characteristics of patients and disease such as gender, age or disease duration.

	Discontinuation at 18 months (n=79)	Continuation at 18 months (n=50)	p
Patient characteristics			
Female gender, n (%)	56 (71)	37 (74)	0,70
Age, mean (SD)	56,6 (±13,1)	58,4 (±14,4)	0,47
Active smoking, n (%)	19 (26)	14 (29)	0,67
BMI, mean (±SD)	26,1 (±5,8)	27,9 (±6,6)	0,16
Diabete, n (%)	9 (12)	6 (12)	0,92
RA characteristics			
Disease duration, median (IQR)	49 (12-207)	94 (31-216)	0,25
Serologic status, n (%)			0,05
RF - and ACPA-	3 (4)	7 (14)	
RF + or ACPA +	14 (18)	4 (8)	
RF + and ACPA +	60 (78)	38 (76)	
Structural damages, n (%)	45 (57)	36 (72)	0,09
Extra-articular involvement, n (%)	19 (24)	17 (34)	0,22
Nb of previous bDMARDs, mean (±SD)	1,9 (±2,1)	2,4 (±2,3)	0,20
0, n (%)	27 (34)	10 (20)	
1-3, n (%)	34 (43)	28 (56)	
> 3, n (%)	18 (23)	12 (24)	
Therapeutics			
Glucocorticoids at inclusion, n (%)	56 (71)	23 (47)	0,005
Dose of glucocorticoids at inclusion, n (%)			0,03
≤ 5 mg	20 (25)	12 (24)	
entre 5 et 10 mg	24 (30)	8 (16)	
> 10 mg	12 (15)	3 (6)	
Association with csDMARDs, n (%)	57 (72)	36 (73)	0,87
JAK inhibitors, n (%)	26 (33)	21 (42)	0,30
<i>Baricitinib</i>	18 (23)	16 (32)	
<i>Tofacitinib</i>	8 (10)	5 (10)	
TNF inhibitors, n (%)	27 (34)	16 (32)	0,80
<i>Adalimumab</i>	4 (5)	5 (10)	
<i>Etanercept</i>	18 (23)	8 (16)	
<i>Golimumab</i>	1 (1)	0	
<i>Infliximab</i>	4 (5)	3 (6)	
Others bDMARDs, n (%)	26 (33)	13 (26)	0,40
<i>Tocilizumab/Sarilumab</i>	17 (22)	5 (10)	0,09
<i>Rituximab</i>	2 (3)	3 (6)	
<i>Abatacept</i>	7 (9)	5 (10)	

Table 2. Predictive factors of treatment continuation at 18 months in univariate analysis.

SD = deviation standard ; BMI = body mass index ; IQR = interquartile range ; RF = rheumatoid factors ; ACPA = anti-citrullinated protein antibody ; bDMARD = biological DMARDs ; csDMARDs = conventional synthetic disease modifying antirheumatic drug ; JAK = Janus kinases ; TNF = tumor necrosis factor.

We performed supplementary univariate analysis with data at 12 months and we found an association with the presence of glucocorticoids at the moment of inclusion [OR 0.40 (95% CI 0.25, 0.82), p = 0,013], higher dose of glucocorticoids [OR 0.47 (95% CI 0.25, 0.82), p = 0,008] and treatment with IL6ir [OR 0.31 (95% CI 0.25, 0.82), p = 0,03], those factors were also associated with lower continuation (Supplementary Table 1).

Using multivariate analysis only glucocorticoids at baseline remains independently predictive of higher discontinuation at 18 months [OR 0.53 (95% CI 0.27, 0.57), p = 0,05] (Table 3).

Predictor	OR	12 months			18 months		
		95% CI	p	OR	95% CI	p	
Structural damages	1,67	0,75-3,9	0,22	1,66	0,88-24,6	0,23	
Presence of glucocorticoids	0,61	0,3-1,09	0,11	0,53	0,27-0,57	0,05	
IL6ir	0,35	0,10-1,04	0,07	0,48	0,1-3,9	0,21	
Serologic status	0,18	0,02-0,97	0,07	0,21	(0,04-1)	0,08	

Table 3. Predictive factors of treatment continuation in multivariate analysis.

OR = odd ratio ; CI = confidence intervals ; IL6ri = IL6 receptor inhibitor

1.3.4 Analysis of treatment discontinuation

We found 90 events leading to treatment discontinuation. The main causes of treatment discontinuation were occurrence of AE, primary inefficacy and partial efficiency with a global percentage of respectively 38%, 21% and 20%. Considering all the discontinuation of treatments for lack of efficacy (primary, secondary, or partial efficiency) the percentage was 51% of all causes. The JAKi group had a higher proportion of discontinuation for AE and partial efficiency with respectively 45% (13/29) and 31% (9/29) of patients who stopped their treatment for those reasons ; meanwhile there was more discontinuation of treatment for primary inefficacy in the TNFi group than in the other groups (35% ; 11/31).

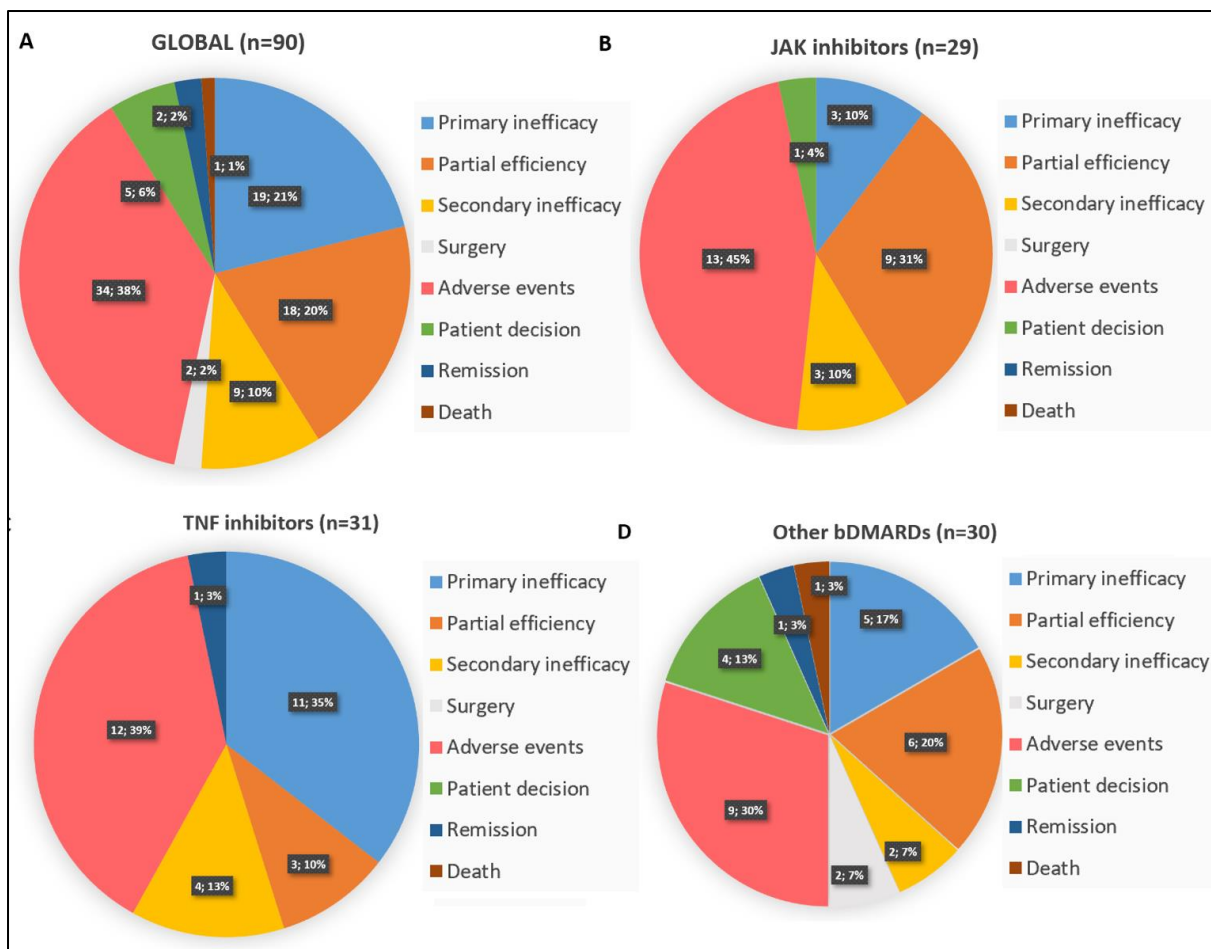


Figure 2. Descriptive analysis of the reasons for treatment discontinuation.

1.3.5 Analysis of the adverse events leading to treatment discontinuation

All AE during the period of study were collected (Supplementary Table 2). Among the 90 patients who have stopped their treatment in the time of study, 34 patients (38%) discontinued their treatment as a result of the occurrence of an AE. 5 patients had 2 simultaneous AE resulting in the decision to stop the treatment explaining the analysis of a total number of 39 AE. The distribution of those events were as followed : 38% (15/39) occurred in the JAKi group, 36% (14/39) in the TNFi group and 26% (10/39) in the other bDMARDs group including only IL6 inhibitors because we didn't find any occurrence of AE with rituximab or abatacept. Causes of discontinuation were multiple : 11 for infections ; 11 for general disorders ; 7 for allergic reactions (5 local and 2 systemics) ; 3 for hematologic disorders (moderate neutropenia with IL6i and JAKi, lymphopenia with TNFi) ; 2 for hepatic cytolysis (one with IL6i and one with JAKi) ; 2 for kidney failures (one with IL6i and one with TNFi) and 3 cardiovascular related events (acute coronary syndrome and lower limbs œdema due to fluid retention with IL6i, and aggravation of obliterant arteriopathy of lower limbs with JAKi) (Figure 3).

The infectious events leading to discontinuation were as followed : 3 infections of the upper respiratory tract (1 with TNFi, 1 with JAKi, 1 with IL6ir), 1 extensive herpes zoster (JAKi), 2 dental abscess (1 with JAKi, 1 with TNFi), 1 repeated urinary tracts infections (JAKi), 1 peritoneal infection due to mycobacterium tuberculosis (TNFi), 1 Fournier gangrene (TNFi), 1 diverticulitis (TNFi) and 1 recurrent herpes simplex infection (JAKi).

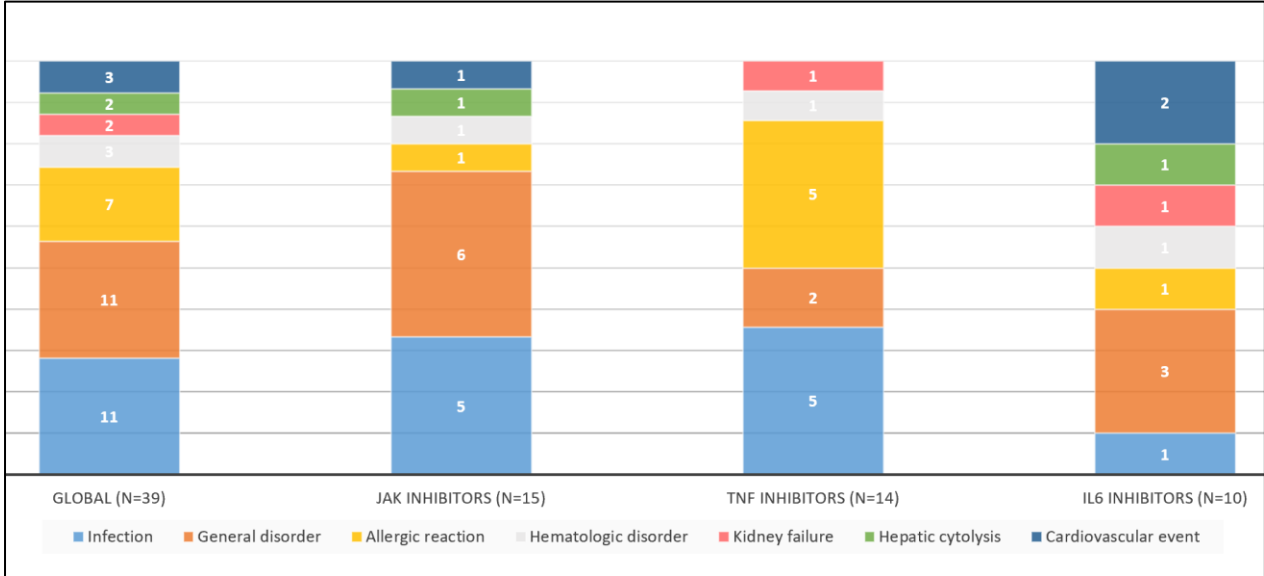


Figure 3. Adverse events leading to a discontinuation of treatment.

1.4 Discussion

In this study we assessed the continuation rate of bDMARDs and JAKi in a cohort of 129 patients in real-life and found that only 44% and 39% of patients were still receiving the same treatment at respectively 12 and 18 months. We found no significant statistical difference between JAKi and others bDMARDs regarding therapeutic maintenance over the time of our study.

Firstly we can focus on TNFi continuation since most of the studies in real-life about drug survival of bDMARDs in RA are focused on TNFi survival rate (15-18). Our percentage seems to be slightly lower than in the literature. For example in a meta-analysis based on observational studies only, the total continuation rate of TNFi was 57-72% at 12-24 months in first-line setting and 38-57% in second-line setting (19). They also found lower discontinuation with etanercept than with the others TNFi. The effectiveness in our study were too small to try to highlight this difference.

Other studies have also investigated non-TNFi bDMARDs retention in real life (20,21). Our results showed also higher discontinuation at early stages especially for IL6ir. This result does not seem

to follow the results of the few studies that compares retention rate of TNFi and non-TNFi bDMARDs with higher retention found with abatacept or tocilizumab within a much larger cohort (22). Data about JAKi retention in real-life are emerging in foreign countries where the prescription of tofacitinib has preceded France by several years (23). Retention of tofacitinib seemed similar to TNFi and non TNFi bDMARDs (24-27). The monocentric design of this study could be an explanation of the lower retention rate observed in our cohort compared to other larger observational study. As an university hospital it is possible that the patients treated have more severe diseases.

We did not find any significant difference in our study between JAKi and bDMARDs concerning the continuation rate over our short period of observation although JAKi seems to have a small advantage on continuation over time. The analysis of baseline characteristics of our population showed significant differences in patients initiating a JAKi compared to TNFi and other bDMARDs population. They have a longer disease duration, more previous therapeutics (csDMARDs and bDMARDs) and more frequent structural damages, probably meaning that their RA is also more severe and refractory. In real life JAKi have been more frequently initiated in patients who were running out of therapeutic options and had more difficult to treat diseases especially the year following their market authorization which correspond to our study follow-up. As an example, 30 patients in our cohort had received more than 3 previous bDMARDs and 83% of them were in the JAKi group. It could be interesting to assess the same data in a few years when the prescription of JAKi will probably be more comparable with the one of TNFi and others bDMARDs with more prescription in patients naive of bDMARDs as seen in Canada (28).

We found by analyzing the potential factors associated with the drug survival at 18 months that concomitant use of glucocorticoids and higher dose of glucocorticoids at the inclusion were negative predictors of treatment continuation. This has already been described in previous studies (29-32). One of the explanation might be that persistent use of glucocorticoids is often associated with disease severity and more difficult to treat RA (33) which can explain an early discontinuation of treatment for lack of efficacy. In our study we only assess the presence and dose of glucocorticoids at baseline and not their persistence during time which could indicate a difficult tapering and substantiate our hypothesis. Another possibility for this increased discontinuation could be a greater number of AEs caused by glucocorticoids, especially when given at high doses. We note that in our cohort discontinuation rate for lack of efficacy was 53%

for the patients with glucocorticoids and 46% for those who did not have glucocorticoids, while the discontinuation rate for AE's occurrence was respectively 33% and 46%. Furthermore, looking at the 12 patients with the highest doses of glucocorticoids at initiation (defined as strictly greater than 10 mg in our study) who discontinued their treatment, we found 7 stops of treatment for inefficacy, 2 for both inefficacy and tolerance reason, 1 for AE and 2 for other reasons. This tends to favour our first hypothesis despite the small number of patients analyzed.

Concerning the others predictive factors of discontinuation we found no significant statistical association. This could be explained by the small effectives and the lack of power of our study. In the literature several other predictive factors have been identified, female gender (30-32) and higher number of previous bDMARDs (30,31) are often considered as negative factors of continuation. Concomitant use of methotrexate or csDMARDs usually showed positive effect on bDMARDs continuation in particular with TNFi (30-32,34), whereas study about tocilizumab has showed no difference in drug retention between monotherapy and combination therapy (35). Others factors like age or disease duration has been associated with continuation but with more discordant results depending on the studies. Smoking has also been associated with higher discontinuation with TNFi (36).

Previous reports analyzing the causes of discontinuation in TNFi reported drug inefficacy as the first reason for discontinuation followed by the occurrence of AE's (37,38) which correspond our results for TNFi and also other bDMARDs and JAKi.

We can consider several limitations to our study. First the quality of the data collection from the patient medical charts was dependent on the physician who filled out this information and therefore some medical charts could be incomplete. The reasons for discontinuation were also left to the discretion of the medical practitioner without real standardized criteria. We sometimes reached directly the patients or referent practitioner in order to find missing data which could lead to memory bias. Concerning the data on efficacy there were too many missing data during the follow-up (58% of missing datas at 12 months and 72% at 18 months) to be able to follow the evolution of DAS28-ESR.

The period of inclusion was short to have sufficient data for each treatment separately. It leads to small number of patients limiting the power of the analysis conducted and preventing direct

comparison between each molecule that we had to gather in subgroups. Finally we only analyze predictive factors of retention at baseline but use of glucocorticoids or csDMARDs for example could be modified with time and we were not able to take those changes into consideration. It would be necessary to realize a more careful fulfilling of data registry especially during follow-up.

In conclusion, our study is one of the first in France to collect data about drug continuation with not only bDMARDs but also JAKi. The overall retention rate was slightly lower in our cohort than in other larger observational study with no difference between treatments. We found glucocorticoids as a factor of higher discontinuation but couldn't emphasize other predictive factors probably due to a too small number of patients included. Therefore national multicentric cohorts with long-term data collect will be needed to observe real-life behavior of JAKi in term of efficacy, safety and retention rate as it will be done from the national « MAJIK » registry on JAKi treated patients in all rheumatologic indications.

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SUPPLEMENTARY MATERIAL

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥ 6 weeks	1

Figure S1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (14).

	Continuation at 12 months (n=57)	Discontinuation at 12 months (n=72)	p
Patient characteristics			
Female gender, n (%)	41 (72)	52 (72)	0,97
Age, mean (SD)	56,6 (±12,7)	58,5 (±14,7)	0,42
Active smoking, n (%)	15 (28)	18 (26)	0,87
BMI, mean (±SD)	27,7 (±6,3)	26,1 (±6)	0,2
Diabete, n (%)	7 (12)	8 (11)	0,84
RA characteristics			
Disease duration, mean (±SD)	137,1 (±129,1)	107,2 (±116,6)	0,17
Serologic status, n (%)			0,06
RF - and ACPA-	8 (14)	2 (3)	
RF + or ACPA +	8 (14)	10 (14)	
RF + and ACPA +	40 (71)	58 (83)	
Structural damages, n (%)	40 (70)	41 (57)	0,12
Extra-articular involvement, n (%)	18 (32)	18 (25)	0,22
Nb of previous bDMARDs			0,21
0, n (%)	11 (19)	26 (36)	
1-3, n (%)	33 (58)	29 (40)	
> 3, n (%)	13 (22)	17 (24)	
Therapeutics			
Glucocorticoids at inclusion, n (%)	28 (49)	51 (71)	0,013
Dose of glucocorticoids at inclusion, n (%)			0,008
≤ 5 mg	12 (24)	20 (25)	
entre 5 et 10 mg	8 (16)	24 (30)	
> 10 mg	3 (6)	12 (15)	
Association with csDMARDs, n (%)	40 (70)	53 (74)	0,41
JAK inhibitors, n (%)	26	21	0,15
<i>Baricitinib</i>	20 (35)	14 (19)	
<i>Tofacitinib</i>	6 (10)	7 (10)	
TNF inhibitors, n (%)	16 (32)	27 (34)	0,26
<i>Adalimumab</i>	5 (10)	4 (5)	
<i>Etanercept</i>	8 (16)	18 (23)	
<i>Golimumab</i>	0	1 (1)	
<i>Infliximab</i>	3 (6)	4 (5)	
Others bDMARDs, n (%)	13 (26)	26 (33)	0,15
<i>Tocilizumab/Sarilumab</i>	5 (9)	17 (24)	0,026
<i>Rituximab</i>	3 (5)	2 (3)	
<i>Abatacept</i>	6 (11)	6 (8)	

Table S1. Predictive factors of treatment continuation at 12 months in univariate analysis.

SD = deviation standard ; BMI = body mass index ; IQR = interquartile range ; RF = rheumatoid factors ; ACPA = anti-citrullinated protein antibody ; bDMARD = biological DMARDs ; csDMARDs = conventional synthetic disease modifying antirheumatic drug ; JAK = Janus kinases ; TNF = tumour necrosis factor

	Global (n=129)	JAK inhibitors (n=47)	TNF inhibitors (n=43)	Others bDMARDs (n=39)
Patients having AE, n (%)	83 (64)	28 (60)	29 (67)	26 (67)
Nature of AE, n (%)				
Local allergy, n (%)	11 (9)	1 (2)	8 (19)	2 (5)
General allergy, n (%)	4 (3)	0	2 (5)	2 (5)
Number of infectious events	50	20	18	12
Patients having infectious events, n (%)	39 (30)	17 (36)	14 (33)	8 (21)
BK, n (%)	1 (1)	0	1 (2)	0
Herpes zoster, n (%)	2 (2)	1 (2)	0	1 (3)
Herpetic recurrence, n (%)	5 (4)	3 (6)	1 (2)	1 (3)
General disorder, n (%)	22 (17)	8 (17)	5 (12)	9 (23)
Hematologic laboratory changes, n (%)	10 (8)	4 (9)	2 (5)	4 (10)
Hepatic cytolysis, n (%)	5 (4)	2 (4)	1 (2)	2 (5)
Kidney failure, n (%)	3 (2)	0	1 (2)	2 (5)
Metabolic disorder, n (%)	6 (5)	3 (6)	2 (5)	1 (3)
Gastro-intestinal disorder, n (%)	7 (5)	3 (6)	1 (2)	3 (8)
Cardio-vascular event, n (%)	4 (3)	1 (2)	0	3 (8)
Malignancy occurrence, n (%)	1 (1)	0	1 (2)	0
Others, n (%)	8 (6)	3 (6)	2 (5)	3 (8)

Table S2. Descriptive analysis of all AE considering 3 subgroups.

AE = adverse events ; n = number

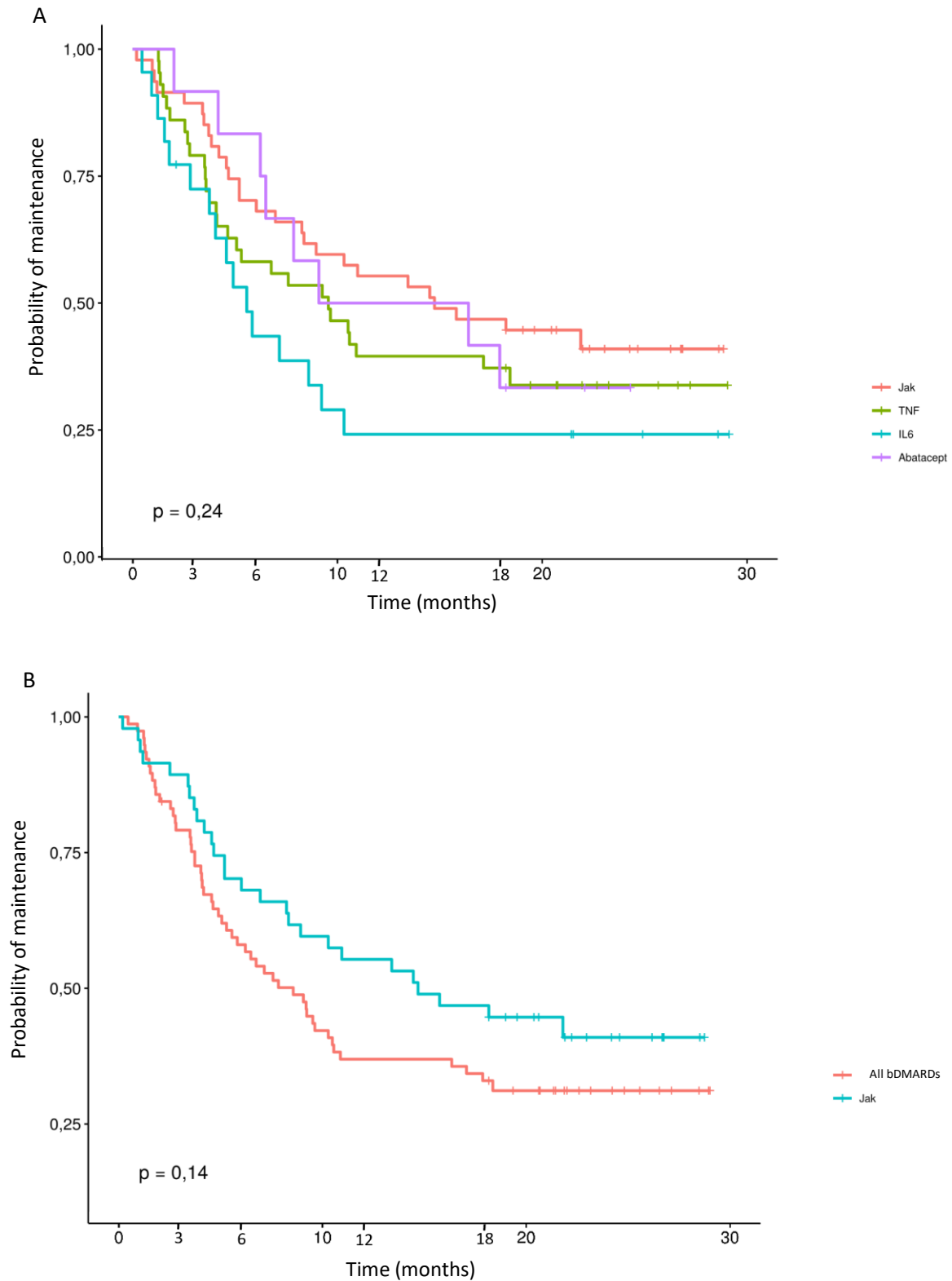


Figure S2. Kaplan–Meier survival analysis of persistence without rituximab.

Comparison of survival rate between JAKi, TNFi and others bDMARDs including IL6ri and abatacept (A).

Comparison of survival rate between JAKi and all the other bDMARDs including TNFi, IL6ri and abatacept (B).

SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés. J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

MAINTIEN THERAPEUTIQUE DES INHIBITEURS DE JAK ET DES bDMARDs DANS LA POLYARTHRITE RHUMATOÏDE

Objectif : Le maintien thérapeutique est une mesure indirecte de l'efficacité et de la tolérance d'un traitement. Le but de cette étude est d'étudier le maintien thérapeutique en vie réelle des biothérapies et des inhibiteurs de JAK (JAKi) dans la polyarthrite rhumatoïde (PR) sur une période de 18 mois et d'analyser les facteurs prédictifs de poursuite du traitement ainsi que les motifs d'arrêt.

Méthode : Il s'agit d'une analyse rétrospective des dossiers médicaux des patients atteints de PR suivis au CHU de Bordeaux ayant reçu une prescription d'inhibiteur de JAK ou de bDMARD entre le 1er novembre 2017 et le 10 octobre 2018. Nous avons recueilli les données cliniques et biologiques à l'inclusion puis au cours d'un suivi de 18 mois au minimum. Les courbes de survie ont été construites selon la méthode de Kaplan-Meier et la comparaison effectuée par le test du logrank. Les facteurs associés au maintien à 12 et 18 mois étaient évalués par analyses uni et multivariées.

Résultats : Parmi les 129 patients inclus, 47 ont bénéficié d'une prescription d'inhibiteur de JAK, 43 d'un anti-TNF alpha et 39 d'un autre bDMARD (abatacept, rituximab, anti IL6). A 18 mois, le taux de maintien thérapeutique global était de 39% (45% pour les inhibiteurs de JAK, 37% pour les anti-TNF alpha et 33% pour les autres bDMARDs). Il n'a pas été retrouvé de différence significative pour le maintien global entre les traitements ($p = 0,26$). Le seul critère prédictif associé au maintien thérapeutique à 18 mois retrouvé en analyse univariée et multivariée était la présence de corticoïdes à l'initiation qui semblait associé à un plus faible maintien thérapeutique ($p = 0,05$). Cependant l'utilisation concomitante d'un csDMARDs n'a pas semblé montrer d'association avec le maintien des traitements ($p = 0,87$). Les causes d'arrêt les plus fréquentes étaient le manque d'efficacité globale à 51% et la survenue d'effets secondaires à 38%.

Conclusion : Cette étude observationnelle a montré un taux de maintien thérapeutique comparable entre les JAKi et les autres bDMARDs étudiés.

Mots clés : Polyarthrite rhumatoïde, inhibiteurs de JAK, bDMARDs, maintien thérapeutique, étude en vie réelle

MAINTENANCE OF JAK INHIBITORS AND bDMARDs IN RHEUMATOID ARTHRITIS

Objectives : The continuation rate of a drug is an indirect measure of effectiveness and tolerance. The aim of this study was to assess the therapeutic maintenance in real-life of biologic drug modifying rheumatic diseases (bDMARDs) and JAK inhibitors (JAKi) in rheumatoid arthritis (RA) over an 18-month period and to analyze factors predictive of treatment continuation as well as reasons for discontinuation.

Methods : This is a retrospective analysis of the medical records of RA patients followed at Bordeaux University Hospital who received a new prescription for a JAKi or a bDMARD between November 1, 2017 and October 10, 2018. Clinical and biological data were collected at baseline and up to a 18-month follow-up. Survival curves were constructed using the Kaplan-Meier method and comparison made by logrank testing. Factors associated with maintenance at 12 and 18 months were assessed by univariate and multivariate analyses.

Results : Among the 129 patients included, 47 were prescribed a JAKi, 43 a TNF inhibitor (TNFi) and 39 another bDMARD (abatacept, rituximab, anti IL6). At 18 months, the global therapeutic maintenance rate was 39% (45% for JAKi, 37% for TNFi and 33% for other bDMARDs). There was no significant difference in the crude overall drug retention between treatments ($p = 0,26$). Presence of corticosteroids at initiation was the only predictive factor associated with maintenance in both univariate and multivariate analysis by showing a higher discontinuation at 18 months ($p = 0.05$). However concomitant csDMARDs therapy showed no association with continuation ($p = 0,87$). The main causes of discontinuation were global lack of efficacy at 51% and occurrence of adverse events (AE) at 38%.

Conclusion : This observational study has shown a similar drug retention between JAKi and other bDMARDs.

Keywords : Rheumatoid arthritis, JAK inhibitors, bDMARDs, drug maintenance, real-word study

Discipline : Rhumatologie

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