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Persistance des traitements anti-TNFα et anti-IL17 dans la spondyloarthrite axiale : résultats d'une étude observationnelle multicentrique

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AVERTISSEMENT

La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

ABREVIATIONS LIST

ASAS: Assessment of SpondyloArthritis International Society

ASD: absolute standardised difference

AxSpA: axial spondyloarthritis

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BMI: body mass index

CRP: C-reactive protein

bDMARDs: biological disease-modifying antirheumatic drugs

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

IQR: interquartile range

PS: propensity score

RCT: randomised controlled trial

SD: standard deviation

SEC: sécukinumab

SpA: spondyloarthritis

TNF: tumour necrosis factor

LISTE DE ABRÉVIATIONS

ASAS : Assessment of SpondyloArthritis International Society

ASD : différence absolue standardisée

AxSpA : spondyloarthrite axiale

BASDAI : Bath Ankylosing Spondylitis Disease Activity Index

CRP : protéine C réactive

bDMARDs : anti-rhumatismaux modificateurs de la maladie de type biologique

ERC : essai contrôlé randomisé

HLA : antigène leucocytaire humain

IMC : indice de masse corporelle

IQR : écart interquartile

MICI : maladies inflammatoires chroniques de l'intestin

PS : score de propension

SD : déviation standard

SEC : sécukinumab

SpA : spondyloarthrites

TNF : facteur de nécrose tumorale

SOMMAIRE

PRÉAMBULE

Le travail scientifique présenté dans cette thèse de médecine fait l'objet d'une soumission d'article international en anglais. Il suit le plan suivant :

- Une introduction en français.
- L'abstract en anglais, tel qu'il a été soumis en complément de l'article reproduit juste après.
- L'article en anglais, tel qu'il a été soumis pour publication, dans le format imposé par le journal Rheumatology (introduction, matériel et méthodes, résultats, discussion).
- Une discussion en français, qui reprend pour l'essentiel la discussion en anglais de l'article.

Le document est ainsi structuré en application de la circulaire Toubon[1].

Les références présentées en fin de document, ainsi que les listes de figures et tables, résultent de la fusion des parties en anglais et en français. La numérotation est donc incrémentée dans l'ensemble du document, que les parties soient anglophones ou francophones.

[1] Circulaire du 19 mars 1996 concernant l'application de la loi no 94-665 du 4 août 1994 relative à l'emploi de la langue française. JORF n° 68 du 20 mars 1996 page 4258. NOR: PRMX9601403C

INTRODUCTION EN FRANÇAIS

Contexte

Les spondyloarthrites (SpA) sont un groupe de rhumatismes inflammatoires intéressant le squelette axial, mais aussi certaines articulations périphériques et les enthèses (zones d'ancrage à l'os des tendons, ligaments, fascias et capsules articulaires). Elles regroupent la spondyloarthrite axiale (AxSpA), la spondyloarthrite périphérique, les arthrites réactionnelles, le rhumatisme psoriasique, les spondyloarthrites associées aux entérocolopathies inflammatoires chroniques (MICI) (maladie de Crohn, rectocolite hémorragique) et des formes indifférenciées (1) .

La prévalence en France en 2010 est estimée à 0,43 % (2). L'âge au diagnostic est d'environ 26 ans. Les SpA concernent plus fréquemment les hommes que les femmes, avec un sex ratio en Europe de 3,8:1 (3).

Les SpA sont largement associées à la présence, chez les individus atteints, de l'allèle Human Leukocyte Antigen (HLA) B27 (4). Plusieurs études ont montré une augmentation du taux de Tumour Necrosis Factor α (TNFα) au sein des articulations sacro-iliaques des patients atteints de d'AxSpA (5). D'autres cytokines pro-inflammatoires comme l'interleukine 17A (IL-17A) et son récepteur sont également surexprimés dans les tissus atteints par la maladie (6,7).

Les principaux symptômes de l'AxSpA sont dus à l'inflammation des enthèses du rachis et des articulations sacro-iliaques. La lombalgie d'horaire inflammatoire est le premier signe chez 75 % des patients, elle s'accompagne d'une raideur matinale supérieure à 30 minutes, de réveils nocturnes douloureux et est habituellement soulagée par la prise d'un traitement par anti-inflammatoires non stéroïdiens (AINS). Des remaniements cartilagineux, ligamentaires et osseux peuvent entraîner des déformations, une raideur et *in fine* des

incapacités et une diminution de la qualité de vie (8).

La spondyloarthrite axiale est elle-même phénotypée en spondyloarthrite radiographique (rx-SpA) ou non-radiographique (nr-AxSpA) en fonction de la présence (ou non) d'anomalies sur les radiographies des articulations sacro-iliaques (9).

Le diagnostic de spondyloarthrite repose sur un faisceau d'arguments concordants : cliniques, anamnestiques, biologiques et d'imagerie. Des critères de classification ASAS (Assessment of SpondyloArthritis International Society) sont utilisés dans les études cliniques et en pratique pour aider au diagnostic d'AxSpA et de SpA périphérique. Certaines atteintes comme le psoriasis, l'uvéite antérieure aiguë, les MICI, sont les principales « manifestations extra-articulaires » (MEA) associées aux SpA (10) et font partie des critères ASAS.

La prise en charge thérapeutique a pour principal objectif de contrôler les symptômes de la maladie. Elle repose sur l'information et l'éducation du patient, la rééducation fonctionnelle nécessaire au moins à court et moyen termes (11) et des thérapeutiques médicamenteuses. En cas de spondyloarthrite active, les sociétés savantes de rhumatologie ASAS, EULAR (European Alliance of Associations for Rheumatology) et ACR (American College of Rheumatology) recommandent un traitement par AINS en 1re intention, puis par biomédicament (ou biological disease-modifying antirheumatic drug ou bDMARD) en cas d'échecs répétés des traitements AINS (12,13).

Jusque 2015-2016, les seuls biomédicaments utilisés et autorisés dans le traitement de l'AxSpA étaient les molécules ciblant le Tumour Necrosis Factor α (les anti-TNFα ou TNFi) : infliximab, étanercept, adalimumab, golimumab, certolizumab pegol. Ces 5 molécules ont prouvé leur efficacité dans des essais randomisés (14). Cependant, 15 à 32 % des patients interrompent leur traitement à 2 ans, soit du fait d'une inefficacité, soit du fait d'effets secondaires (15,16). Certains patients présentent aussi des contre-indications à cette

classe thérapeutique (17).

Un deuxième traitement, l'inhibiteur de l'IL-17A appelé secukinumab (Cosentyx®), a été approuvé dans le traitement de la SA par l'Agence européenne des médicaments (EMA) en 2015 puis recommandé par les sociétés savantes ASAS/EULAR après échec d'un premier TNFi (12,18,19). Trois essais randomisés contrôlés (ERC) de phase III chez des patients atteints de SA ont montré son efficacité avec un bon profil de tolérance (20–22). Un ERC de phase III en 2019 a montré les mêmes résultats chez des patients atteints de spondyloarthrite axiale non radiographique (23).

Objectifs

La persistance thérapeutique, indicateur indirect du succès d'un traitement à long terme, dépend à la fois de son efficacité et de son profil d'innocuité. Elle est définie par la période pendant laquelle un patient poursuit ledit traitement et peut être comparée en utilisant des analyses de survie (24). De récentes études en conditions de vie réelle ont comparé les TNFi et le SEC chez des patients ayant déjà reçu un ou plusieurs TNFi (25–27).

L'objectif principal de cette étude était de comparer la persistance thérapeutique des TNFi et du SEC dans le traitement des patients atteints d'AxSpA, le deuxième objectif était d'identifier les facteurs affectant la persistance de ces biomédicaments.

ARTICLE EN ANGLAIS

1. Abstract

Objectives: Biological disease-modifying antirheumatic drugs (bDMARDs) should be considered in patients with active axial spondyloarthritis (AxSpA) despite the use of nonsteroidal anti-inflammatory drugs. The objective of this study was to compare drug persistence in patients with active AxSpA treated with tumour necrosis factor inhibitors (TNFi) and secukinumab (SEC), an interleukin 17 inhibitor.

Methods: AxSpA patients from three tertiary care centres starting SEC or TNFi in 2016-2019 were included. Hazard-ratios (HR) for treatment discontinuation were calculated using propensity score and after overlap weighting.

Results: A total of 279 patients were included: 178 with TNFi, and 101 with SEC. The majority of them were diagnosed with radiographic sacroiliitis (63.4%), few were naïve to bDMARD (33.7% and 14.9% for TNFi and SEC, respectively). 77 matched pairs (mean values of the 10 imputed datasets) were found. Out of 279 patients, 128 (45.9%) discontinued treatment. In unadjusted analyses, a better drug persistence was observed with TNFi compared with SEC (HR for treatment discontinuation: 1.46; 95%CI: 1.03 to 2.08; p=0.033). The HR for treatment discontinuation in overlap-weighting and matched cohort were 1.46 (95%CI: 0.83 to 2.54; p=0.18) and 1.46 (95%CI: 0.86 to 2.50; p=0.16), respectively. Subgroup analyses (age, BASDAI at diagnosis, BMI) showed no significant difference between TNFi and SEC. Discontinuation due to inefficacy was the main reason for both treatments. The overall rate of adverse events leading to treatment discontinuation

was similar for both treatment groups (19.2% and 20.0% for TNFi and SEC, respectively).

Conclusion: Persistence with TNFi and SEC were similar in AxSpA patients. These results should be supplemented by randomized controlled trials.

2. Introduction

Axial spondyloarthritis (AxSpA) is a chronic inflammatory disease characterized by enthesitis and inflammation in the spinal and sacroiliac joints, which may cause irreversible damage, resulting in limited mobility, progressive disability and decreased quality of life (1). The current Assessment of SpondyloArthritis International Society (ASAS), the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recommend Nonsteroidal Anti-inflammatory drugs (NSAIDs) as first-line treatment for active AxSpA, followed by biological disease-modifying antirheumatic drugs (bDMARDs) for patients who are nonresponsive to NSAIDs (12,13).

Until recently, bDMARD choice was limited to tumour necrosis factor inhibitors (TNFi). However, up to 40% of patients with AxSpA do not respond to TNFi therapy (15,16) and TNFi may be contraindicated in other patients (17).

The fully human interleukin 17A (IL-17A) inhibitor secukinumab (SEC) was approved for use in AxSpA in 2015 by the European Medicines Agency and has also been recommended by ASAS/EULAR after failure of the first TNFi (12,18,19).

Three phase III randomized controlled trials (RCT) have shown that SEC may be effective in the treatment of active radiographic AxSpA patients, and may have a manageable safety profile (20–22). The same results were found in a 2019 phase III RCT including non-radiographic AxSpA patients (23).

Many patients have to switch from one bDMARD to another because of inefficacy or because of adverse events (AEs) (28). Drug persistence is a proxy indicator of long-term treatment success, as it is determined by both drug efficacy and safety profile. It is defined as the time a patient remains on a specific agent and is investigated using the technique of survival analysis (24).

Real-world studies have provided data on therapy outcomes among TNFi-experienced patients receiving a second TNFi or SEC (25–27). There are no head-to-head studies comparing persistence with TNFi and SEC in AxSpA patient*s*.

The primary objective of this study was to compare persistence with TNFi and SEC in AxSpA patient*s*, a second objective was to identify factors affecting the persistence of such bDMARDs.

3. Methods

Study Cohort

This multicentric, retrospective study included patients over 18 years old with AxSpA starting a bDMARD including: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and secukinumab in the period between 1st June 2016 and 31st December 2019 in three French rheumatology departments of hospitals. The study included all patients who received at least one dose of bDMARDs during the study period and had at least one follow-up visit.

Covariates

Demographic features (age, sex, time since AxSpA diagnosis, human leukocyte antigen B27 (HLA B27) status) and therapeutic data (prior bDMARDs use) were collected. Several potential maintenance predictors were tested: smoking status, evidence of MRI sacroiliitis, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and CRP at diagnosis. Chronic conditions that may have impacted persistence with biological drugs, such as fibromyalgia were further selected. Clinical disease activity scores (BASDAI) and biological parameters (CRP) were recorded during the follow-up. Information on the presence of extra-articular manifestations (EAMs) such as anterior uveitis, psoriasis and inflammatory bowel disease (IBD) prior to the start of the bDMARD treatment was collected. The following comorbidities were considered: coronary heart disease, heart failure, hypertension, stroke, diabetes, obesity, smoking, respiratory failure. This information was used to calculate the Charlson comorbidity index assessing the number of comorbid conditions for a patient (29).

Date and reasons of discontinuation – i.e. inefficacy, adverse events (AEs), sustained remission or others – were collected. Primary inefficacy was defined as the absence of a clinically improvement within the six-month period after treatment initiation, secondary

inefficacy was defined as a recurrence of AxSpA activity after an initial six-month response.

Outcome measures

The primary outcome of this analysis was drug persistence, calculated as the difference in months between initiation and discontinuation. Discontinuation date was defined as the date when the treatment was discontinued due to various reasons (reported events, inefficacy, bDMARD switch, death). Temporary discontinuation of treatment with the same drug of less than 3 months were ignored.

Statistical analysis

Categorical variables are expressed as numbers (percentage). Quantitative variables are expressed as mean ± standard deviation or median and interquartile range according to normality of distribution. Normality of distributions was checked graphically and using Shapiro-Wilk test. Baseline characteristics were described according to the treatment SEC and TNFi and the magnitude of the between-group differences was assessed by calculating the absolute standardized difference (ASD); an absolute standardized difference >10% was interpreted as a meaningful difference (30).

Persistence was estimated using the Kaplan-Meier method, considering treatment discontinuation (whatever the reason) as event of interest and by treating patients' loss of follow-up as censored events. The persistence with the two treatments were compared after taking the potential confounding factors by using the propensity score methods (31). Primary analysis was conducted using overlap weighting propensity score method (overlap-weighted cohort) (32) and secondary analysis (as sensitivity) using the propensity score matching method (matched cohort). The propensity score was estimated using a non-parsimonious multivariable logistic regression model, with treatment groups as dependent variable and all

predefined confounding factors (gender, smoking status, history of psoriasis, peripheral arthritis, ever enthesitis, radiographic sacroiliitis, positive HLA-B27, uveitis, dactylitis, current enthesitis, treatment line and history of fibromyalgia as categorical variables, age, years since diagnosis, BMI, CRP at diagnosis and Charlson score as quantitative variables) as covariates. Patients from the SEC treatment group were matched 1:1 to patients from the TNF inhibitors treatment group according to propensity score using the greedy nearest neighbor matching algorithm with a caliper width of 0.2 SD of logit of propensity score (33,34). To evaluate bias reduction , ASD were calculated after propensity score matching (30).

Because of missing data on propensity score calculation variables, the effect sizes in overlap-weighted and matched propensity score cohorts were estimated after handling missing values by multiple imputation using a regression switching approach (chained equations with m=10 imputations obtained) (35). Imputation procedure was performed under the missing at random assumption using all baseline characteristics listed in Table 1, treatment group and outcome (event status (treatment withdrawal) and log of event time) with predictive mean matching method for quantitative variables and logistic regression (binary, ordinal, or polynomial) for categorical variables(36).

In each imputed dataset, the propensity score and the overlap weight were calculated, and a matched cohort was assembled to provide both weighted-adjusted and matched effect sizes. Therefore effect sizes from each imputed dataset were combined using the Rubin's rules (37,38). In the overlap weighting cohort, the treatment effect size (hazard ratio of treatment withdraw for Secukinumab versus TNF inhibitors treatment) was estimated using a weighted Cox proportional hazard model (with overlap weights) and in matched-cohorts, using a Cox proportional hazard model with a robust sandwich variance estimator to account the matched design.

The heterogeneity in treatment effect size for persistence with treatment was further investigated following subgroups: age (<50 vs. ≥50 years), BASDAI score (<70 vs. ≥70) and BMI (<25 vs. 25 to 30 vs. ≥30 km/m2) by introducing a multiplicative term into Cox' regression models, both in overlap weighting and matched propensity score cohorts.

Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analysed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

Being a routine clinical practice study, Ethics Committee, Institutional Review Board and informed consent of eligible patients were not required. The study has been declared to the French National Commission for Information Technology and Civil Liberties (CNIL) (DECT number 2214454v0).

Data were analysed in anonymous form and identified each patient by a number.

4. Results

Baseline characteristics

Of the 279 patients included, 178 received TNFi and 101 received SEC. Mean (SD) age was 45.1 (12.9) years and 45.5% were women. Mean (SD) disease duration was 15.1 (11.5) years. The most common phenotype was radiographic AxSpA (n=144, 63.4%). Before matching, patients of the SEC group were older, more likely to present with peripheral joint manifestations, radiographic sacroiliitis, had a higher prevalence of male gender, HLA-B27 positive status, fibromyalgia and comorbidities. No patient with known IBD was treated with SEC, while the respective proportion of patients treated with TNFi was 4.5%. Mean disease duration and number of prior bDMARDs were higher in the SEC group. A few patients were naïve to bDMARD (33.7% and 14.9% for TNFi and SEC, respectively). Most patients (76.8%) received SEC according to the Ankylosing Spondylitis label (20), i.e. 150 mg every 4 weeks. The most common deviation was dose escalation (22.2%), other deviation was use of 300mg upon first-time (1.0%).

The main clinical characteristics of the patients in relation to type of treatment before and after propensity score matching are shown in Table 1. Seventy-seven matched pairs (mean values of the 10 imputed datasets) were found. As shown in Table 1, imbalance in pre-specified confounders were reduced after propensity-score matching, though with meaningful difference for number of prior bDMARDs use and dactylitis.

Table 1. Baseline characteristics of patients according to treatment before and after Propensity Score Matching.

Characteristics	Prematching			Postmatching		
	TNF inhibitors[6] n = 178	Secukinumab n = 101	ASD (%)	TNF inhibitors n = 77	Secukinumab n = 77	ASD (%)
Women[1]	86 (48.3)	41 (40.6)	15.6	43 (55.6)	43 (56.1)	1.1
Age (years)[1], mean ± SD	44.5 ± 13.1	46.2 ± 12.6	13.9	46.7 ± 14.9	46.1 ± 13.8	5.0
Years since diagnosis[1-2], median (IQR)	6 (4 to 11)	7 (5 to 17)	32.0	8 (4 to 15)	7 (5 to 15)	5.2
Body mass index (kg/m²)[1-3], mean ± SD	26.5 ± 5.6	26.9 ± 6.1	4.8	27.0 ± 7.3	26.7 ± 6.2	4.0
Smoker[1]			21.9			9.5
No	37/98 (37.8)	16/64 (25.0)		22 (29.0)	23 (30.6)	
Current smoker	43/98 (43.9)	29/64 (45.3)		34 (44.8)	33 (43.3)	
Former smoker	18/98 (18.4)	19/64 (29.7)		20 (26.2)	20 (26.1)	
Psoriasis ever[1]	35 (19.7)	16 (15.8)	10.0	13 (16.7)	13 (16.6)	0.2
Peripheral arthritis[1]	37 (20.8)	33 (32.7)	27.1	21 (27.5)	23 (30.3)	6.4
Enthesitis ever[1]	27 (15.2)	18 (17.8)	7.1	12 (16.0)	13 (17.0)	3.0
Radiographic sacroiliitis[1]	78/146 (53.4)	66/81 (81.5)	53.0	54 (70.7)	55 (71.2)	1.7
Positive HLA-B27[1]	101/152 (66.4)	70/89 (78.7)	22.8	57 (74.4)	56 (73.6)	1.9
Uveitis ever[1]	23 (12.9)	10 (9.9)	9.5	7 (9.6)	7 (9.5)	0.0
Dactylitis ever[1]	6 (3.4)	7 (6.9)	16.2	2 (2.6)	4 (4.7)	12.2
Current enthesitis[1]	12 (6.7)	11 (10.9)	14.7	6 (8.4)	7 (9.0)	2.2
CRP at diagnosis (mg/L)[1-4], median (IQR)	11 (3 to 22)	12 (3 to 23)	0.6	11.9 (4.0 to 24.0)	13.1 (3.1 to 24.5)	2.3
BASDAI at diagnosis[5], mean ± SD	60.3 ± 15.1	61.9 ± 15.6		62.2 ± 20.4	61.0 ± 16.0	
Charlson score[1]			12.6			6.7
0	102/164 (62.2)	57/98 (58.2)		44 (58.2)	48 (62.5)	
1	29/164 (17.7)	16/98 (16.3)		14 (18.2)	12 (15.0)	
≥2	33/164 (20.1)	25/98 (25.5)		18 (23.6)	17 (22.5)	
Number of previous bDMARDs[1]			45.6			11.6
0 (first-line treatment)	60 (33.7)	15 (14.9)		14 (17.9)	15 (19.6)	
1 (second-line treatment)	54 (30.3)	41 (40.6)		30 (39.4)	28 (36.4)	
2 (third-line treatment)	64 (36.0)	45 (44.6)		33 (42.6)	34 (43.9)	
Diabetes	4/161 (2.5)	4/97 (4.1)		3 (4.0)	3 (3.7)	
Hypertension	19/161 (11.8)	15/97 (15.5)		11 (14.3)	12 (15.4)	
Fibromyalgia[1]	8/161 (5.0)	10//97 (10.3)	19.1	7 (8.5)	6 (7.7)	3.1

Abbreviations: ASD: absolute standardized difference; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; HLA: human leukocyte antigen; IQR: interquartile range; SD: standard deviation; TNF: tumor necrosis factor.

Values are numbers (%) unless otherwise stated.

Values were calculated after handling missing data using multiple imputation procedure (m=17).

ASD are reported only for the variables used to calculate propensity score.

[1] Variables used to calculate propensity score.

[2] 19 missing values (n=14 vs. 5).

[3] 71 missing values (n=48 vs. 23).

[4] 53 missing values (n=41 vs.12).

[5] 39 missing values (n=30 vs.9).

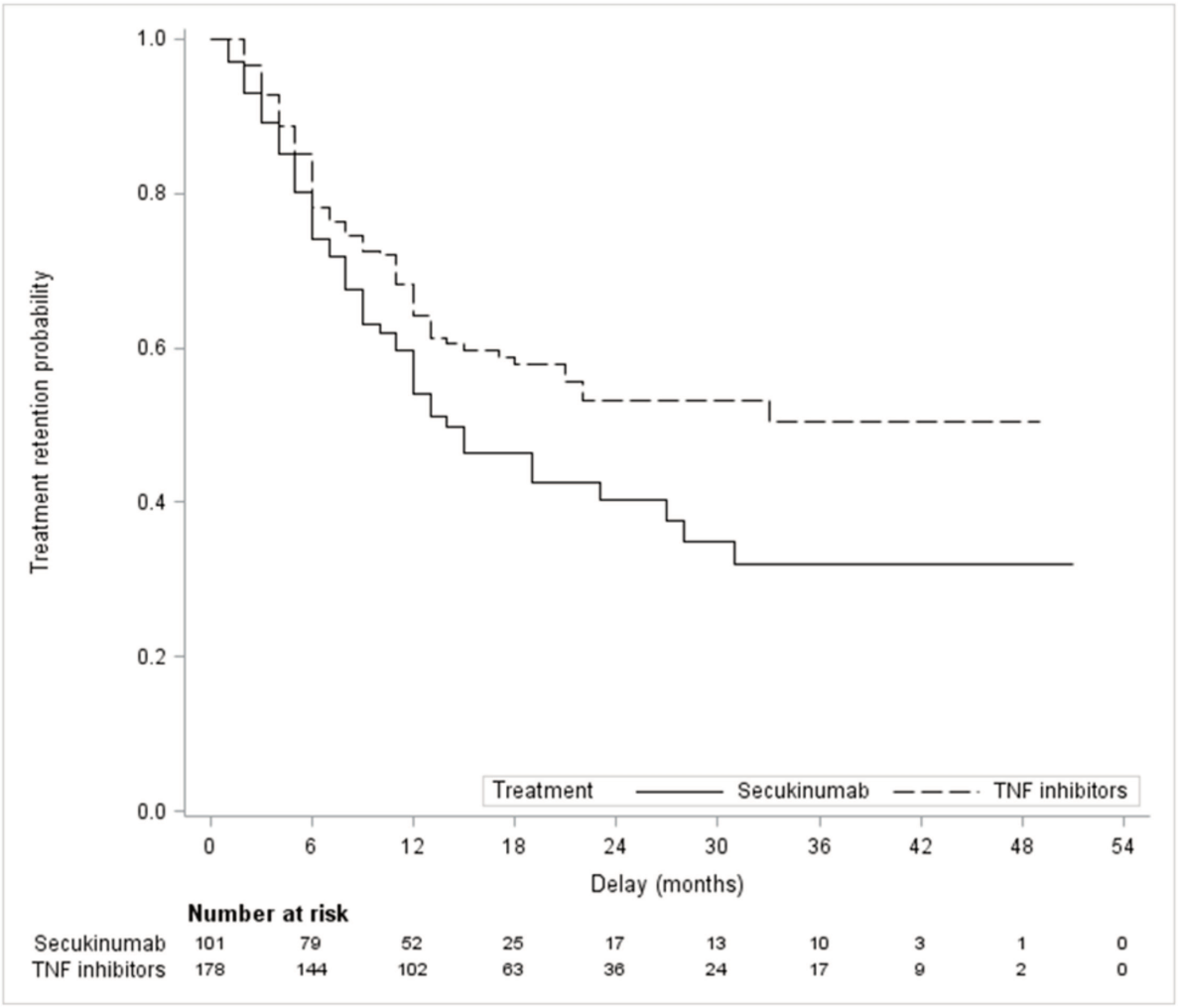
[6] Adalimumab (n=59), etanercept (n=37), certolizumab pegol (n=46), golimumab (n=33) and infliximab (n= 3)

Comparison of persistence with SEC versus TNFi

In unadjusted analyses, persistence with TNFi was higher compared to persistence with SEC (Hazard Ratio HR for treatment discontinuation: 1.46; 95%CI: 1.03 to 2.08; p=0.033) (Figs. 1 and 2). In the propensity score overlap weighting and matched cohorts, persistence with TNFi was not significantly higher than persistence with SEC (HR: 1.46; 95%CI: 0.83 to 2.54; p=0.18) and (HR: 1.46; 95%CI: 0.86 to 2.50; p=0.16), respectively).

The 6- and 12-months retention rates were 74.0% and 54.0% in the SEC group and 78.1% and 64.2% in the TNFi group. After 4 years of follow-up, the median retention duration for patients treated with SEC was 14 months. TNFi were discontinued in less than 50% of patients and thus calculation of the median duration was not possible.

FIG. 1 Persistence with SEC versus TNFi



Reasons for treatment discontinuation

Of the 178 patients treated with TNFi, 73 (41.0%) discontinued treatment. Of the 101 patients treated with SEC, 55 (54.5%) discontinued treatment (Table 2). Inefficacy was the reason for discontinuation in 76.7% of TNFi patients and 74.5% of SEC patients. Corresponding proportions for discontinuation due to adverse events were 19.2% of TNFi patients and 20.0% of SEC patients. Discontinuation of TNFi occurred due to clinical remission in 3 patients.

Adverse events leading to treatment discontinuation were heterogeneous. Important adverse events leading to TNFi discontinuation included infection (6 patients), injections site reaction (3 patients), abdominal pain (2 patients) along with one case each of new onset psoriasis, allergy, and hepatic cytolysis. Headaches accounted for 3 patients changing biologic in the SEC group. Other adverse events in the SEC group included dizziness (2 patients), infection (3 patients, including one case of Candida infection) along with one case each of new onset Crohn's disease, psoriasis flare-up, allergy, and progression of multiple sclerosis. There was one death and one chronic lymphocytic leukemia progression in the SEC group. Neither event was suspected of being treatment-related.

Table 2. Reason for treatment discontinuation according to treatment.

	TNF inhibitors n = 178	Secukinumab n = 101
Discontinued treatment, n (%)	73 (41.0)	55 (54.5)
Reason for discontinuation		
Primary non-response, n (%)	33 (45.2)	22 (40.0)
Secondary inefficacy, n (%)	23 (31.5)	19 (34.5)
Adverse events, n (%)	14 (19.2)	11 (20.0)
Hepatic cytolysis, n	1	0
Infection, n	6	3
Generalised drug eruption, n	1	1
Injection site reaction, n	3	0
Headache, n	0	3
Dizziness, n	0	2
Inflammatory bowel disease, n	0	1*
Abdominal pain, n	2	0
Paradoxical psoriasis, n	1	1
Remission, n (%)	3 (4.1)	0 (0.0)
Other, n (%)	0 (0.0)	3 (5.5)†

* One new-onset inflammatory bowel disease

† One death not treatment related, one progression of multiple sclerosis, one progression chronic lymphocytic leukemia

Subgroup analyses

No significant heterogeneity in treatment effect size for treatment persistence across key subgroups (age (<50 vs. ≥50 years), BASDAI score (<70 vs. ≥70) and BMI (<25 vs. 25 to 30 vs. ≥30 kg/m²)) was found in both overlap weighting and matched analyses (Figs. 2 and 3).

FIG. 2 Persistence with SEC and TNFi, before and after Overlap Weighting.

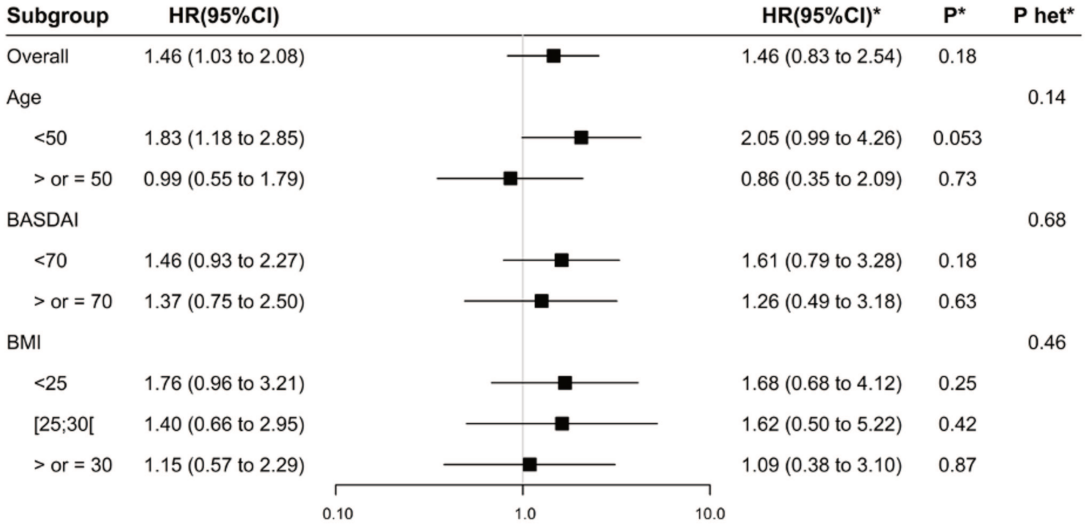
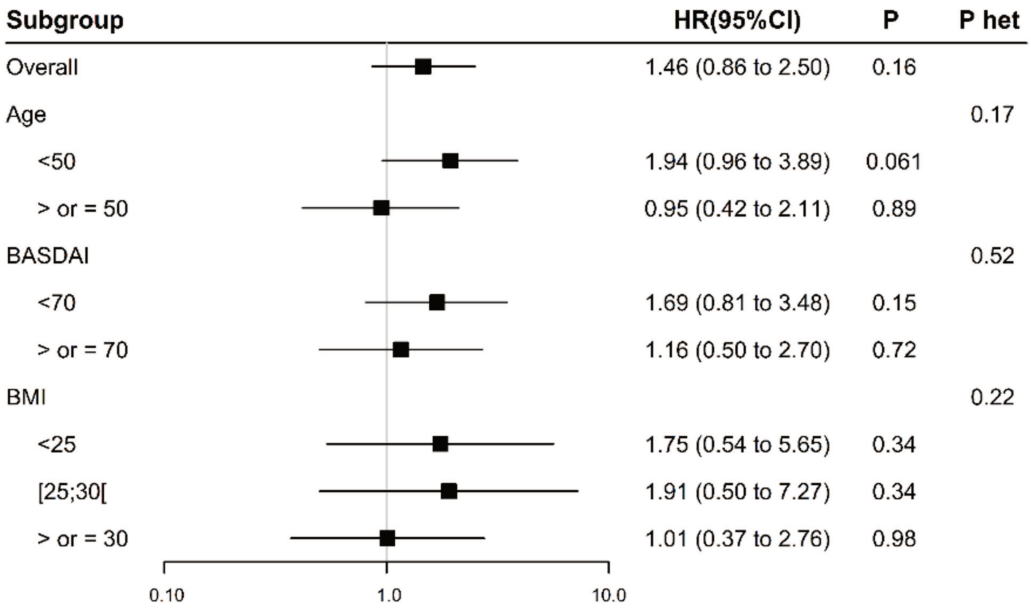


FIG. 3 Persistence with SEC and TNFi, before and after Propensity Score Matching.



Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; HR: hazard ratio.

Hazard ratios were calculated for patients treated with Secukinumab versus those treated with TNF inhibitors.

* after overlap weighting

5. Discussion

In this multicentric real-world study, persistence with SEC and TNFi were similar. Reaching very similar results through both propensity-score and IPTW adds to the robustness of the results.

These findings are in agreement with two recent propensity-matched studies involving AxSpA patients with previous exposure to TNFi (OR 1.14 and HR 1.14, respectively) (26,27). Glintborg et al. also showed no difference between at 1 year according to treatment line: 1st line HR 0.78, 2nd line HR 0.94, 3rd+ line HR 1.06 (39).

Michelsen et al. conducted a large study on 1860 patients treated with SEC in 16 European registries. They showed 6-month and 12-month SEC retention rates of 82% and 72%, respectively (40), which are higher than the 6-month and 12-month rates of 74% and 54% in our study. Similarly, a recent Italian study showed a 72.3% 12-month retention rate (41). Compared with both of these registries, few of our patients treated with SEC were naïve to bDMARD (14.9% vs 22.3% and 33%, respectively), which may explain the lower retention rate observed in our study. Interestingly, Michelsen et al. highlighted that patients who had used 1 bDMARD or ≥ 2 previous bDMARD were at higher risk of discontinuing SEC before 12 months compared with patients naïve to bDMARD (HR 1.78 and HR 2.33, respectively) (40). It is further noted that SEC retention is even higher in RCTs, a notable example being a 3-year SEC retention rate of 86% in study including 61.1% of patients naïve to bDMARD (22).

In our study, persistence with TNFi was higher than persistence with SEC in unadjusted analysis. This difference was likely due to the higher proportion of TNFi prescribed at first-line compared with SEC.

No differences were found between the two groups according to age, BASDAI at diagnosis

and BMI.

Baseline characteristics of the patients were consistent with European published data regarding spondyloarthritis (8,42), as well as with other real-world studies. Time since diagnosis was comparable with those reported in RCT (43) and real-world studies (40). Disease activity at enrolment, which is generally less severe than that reported in phase III RCT (43), was in line with other large studies (44). In accordance to current guidelines (12,13,45), SEC was mainly used in patients with primary inefficacy to a first TNFi. Furthermore and consistent with the same recommendations (12,13,45), none of the AxSpA patients included received comedication with sulfasalazine or methotrexate.

The main cause of discontinuation of TNFi and SEC was inefficacy, followed by adverse events. There were no substantial differences noted in the safety profile of SEC compared with TNFi. Only 8 serious infections requiring treatment discontinuation were reported, with no difference among the 2 groups. In a real-world cohort including 556 patients with spondyloarthritis treated with SEC, Flachaire et al. (46) have reported 46 (8,3%) discontinuation due to adverse events, a similar value to that seen in our study. Among the patients treated with TNFi, the most common adverse event was injection or infusion reaction, followed by infections, which is in line with other clinical studies (47). One newly diagnosed case of IBD was reported in a patient treated with SEC in our study, which is known to be associated with increased risk of IBD exacerbation (18,48). Psoriasis is commonly a reported paradoxical effect after administration of TNFα inhibitors for psoriasis, psoriatic arthritis, AxSpA, IBD, and rheumatoid arthritis (49). Exacerbations of psoriatic lesions are even more uncommon after exposure to SEC (50), but it was the reason for withdrawal in one case. IL-17A inhibition may increase IL-23 levels and thus up-regulate IL-17F, IL-22, and TNFα, which are important cytokines in psoriasis (51).

Strengths of our study include the large real-world cohort of AxSpA patients treated at

multiple centres. In France, initial prescriptions of SEC and TNFi are restricted to hospital doctors. Thus, our population is representative of all French AxSpA patients treated with these molecules. Data from daily practice match the outcomes of actual daily clinical care. To limit a potential bias by treatment in different calendar periods, we have only included patients after secukinumab's Marketing Authorization in France. Another strength of this study was to compare SEC and TNFi in a large real-world cohort of AxSpA patients. To the best of our knowledge, it is one of the first studies to do this direct comparison between TNFi and SEC in AxSpA. Patients with comorbidities or prior medications may have been excluded from RCTs, the results of our study are thus more generalizable to patients found in clinical practice.

The results of this study must be considered in light of some limitations. As with all observational studies, its main limitation is that part of the data was retrospectively collected. This probably did not influence drug persistence itself as variables related to such analyses (date of discontinuation and reason for discontinuation) are registered in daily practice. Additionally, though propensity score matching largely adjusts for baseline difference and reduces selection bias, it may omit residual confounders which impact outcomes. AxSpA patients treated with ixekizumab were too few in number to be compared to patients treated with TNFi or secukinumab and therefore could not be included in our study. Missing data worth noting included disease duration (6.8% missing data), body mass index (25.4% missing data), CRP at diagnosis (19.0% missing data) and BASDAI at diagnosis (14.0% missing data). Although we used a multiple imputation procedure to account for missing variables, we could not exclude the possibility of bias in estimates. BASDAI score was often unavailable because of the lack of a systematic assessment by physicians, thus we could not compare clinical response to both treatments.

The decision to discontinue and switch in our study was made by treating rheumatologist

and was not standardized. Comparison with the outcomes from other cohorts is difficult, partly because of selection bias and different management practices between countries. BASDAI cut-off of 7 was chosen, a cutoff of 4 is frequently used to define active disease, but this cut-off level does not have a firm justification (52). Kobelt and colleagues (53) demonstrated that BASDAI > 7 appears to be a significant threshold above which the impact on work capacities and the physical impairment are higher in AxSpA patients.

Conclusion

In this multicentric real-world retrospective study, persistence with TNFI and SEC were similar. In subgroups analyses, age, BASDAI at diagnosis and BMI did not favour any group. The findings of our study support AxSpA guidelines which recommend individualized care based on each patient's circumstances, and consideration of a patient's preference (13). Head-to-head studies are needed to determine the most appropriate individual treatment sequences and strategies.

DISCUSSION EN FRANÇAIS

Dans cette étude multicentrique de vraie vie, la persistance thérapeutique des TNFi était comparable à celle du SEC chez les patients atteints d'AxSpA. Les résultats obtenus par score de propension et par IPTW sont similaires, ce qui renforce la cohérence de l'étude.

Ces résultats sont en accord avec ceux de deux études récentes chez des patients atteints de SA ayant déjà reçu une 1re ligne de TNFi, en utilisant également un score de propension (OR 1,14 et HR 1,14, respectivement) (26,27). Une autre étude menée par Glintborg *et al.* n'a également pas montré de différence entre TNFi et SEC à 1 an : HR 0,78 en 1re ligne, HR 0,94 en 2nde ligne, HR 1,06 en 3ème ligne (39).

Michelsen *et al.* ont mené une vaste étude (1860 patients) regroupant 16 registres européens de patients atteints de SA traités par SEC. Les taux de rétention SEC à 6 mois et 12 mois de 82 % et 72 %, respectivement (40), supérieurs aux 74 % et 54 % de notre étude. Une récente étude italienne a également montré un taux de rétention à 12 mois de 72 % (54). À la différence de ces deux populations, très peu des patients traités par SEC dans notre étude étaient bio-naïfs (14,9 % contre 22,3 % et 33 %, respectivement), ce qui peut expliquer un taux de rétention plus faible. En effet, Michelsen *et al.* ont montré une diminution de la persistance du SEC chez les patients antérieurement traités par 1 bDMARD et ≥ 2 bDMARD par rapport aux patients bio-naïfs (HR 1,78 et HR 2,33, respectivement) (40). L'essai randomisé MEASURE 2 montrait un taux de rétention à 3 ans à 86 % dans un groupe SEC 150mg comptant 61,1 % de patients bio-naïfs (22).

L'analyse univariée montrait une persistance plus élevée dans le groupe TNFi comparée à celle du groupe SEC. Cette différence était probablement liée à la proportion plus élevée de TNFi prescrits en première ligne par rapport au SEC.

Aucune différence n'a été retrouvée entre les deux groupes en fonction de l'âge, du BASDAI

au moment du diagnostic et de l'IMC.

Les caractéristiques des patients étaient comparables à celles d'études épidémiologiques européennes (8,42) et d'autres études de vraie vie. La durée d'évolution de la maladie était comparable à celle rapportée dans les ECR (43) et les études de vraie vie (40). L'activité initiale de la maladie évaluée par le BASDAI, le plus souvent inférieure à celle rapportée dans les ECR de phase III (43), était comparable à celles d'autres études (44). Conformément aux recommandations actuelles (12,13,45), le SEC a majoritairement été prescrit chez des patients ayant présenté un échec primaire à un premier TNFi. En accord avec les mêmes recommandations (12,13,45), aucun des patients inclus ne recevait de csDMARDs (sulfasalazine ou méthotrexate) en plus du traitement à l'étude.

La principale cause d'arrêt du TNFi et du SEC était l'inefficacité, suivie des arrêts liés aux effets secondaires. Les deux biomédicaments ont montré le même profil de tolérance. Seules 8 infections graves nécessitant l'arrêt du traitement ont été signalées, sans différence entre les deux groupes. Dans une cohorte de vie réelle comprenant 556 patients atteints de spondyloarthrite traités par SEC, Flachaire *et al.* (46) ont rapporté 46 (8,3 %) interruptions en raison d'effets secondaires, une valeur similaire à celle observée dans notre étude. Parmi les patients traités par TNFi, l'effet secondaire le plus fréquent était la réaction au point d'injection ou à la perfusion, suivie des infections, ce qui rejoint le profil de tolérance rapporté dans d'autres études (39). Nous avons signalé un cas de MICI nouvellement diagnostiquée chez un patient traité par SEC, biomédicament associé à un risque accru d'exacerbation des MICI (18,48). Le psoriasis est un effet paradoxal des anti-TNFα (49). Les exacerbations de lésions psoriasiques sont plus rares pendant l'exposition au SEC (50), mais à l'origine d'une interruption de traitement chez un des patients inclus dans notre étude. L'inhibition de l'IL-17A peut augmenter les niveaux d'IL-23 et donc d'IL-17F, d'IL-22 et de TNFα, qui sont des cytokines centrales dans l'apparition des lésions de psoriasis (51).

Notre étude présente plusieurs forces. Tout d'abord, l'inclusion d'un grand nombre de patients traités dans plusieurs centres permet une bonne validité extrinsèque. Les traitements par SEC et TNFi étant des médicaments à prescription initiale hospitalière en France, notre population est représentative de l'ensemble des patients français atteints d'AxSpA et traités par ces molécules. Les données de vie réelle correspondent à l'expérience des soins cliniques quotidiens réels. Deuxièmement, pour limiter un biais lié au calendrier des mises sur le marché des biomédicaments, nous n'avons inclus de patients qu'après l'Autorisation de mise sur le marché du sécukinumab en France. Ensuite il s'agit à notre connaissance d'une des premières études de comparaison directe entre les TNFi et le SEC chez les patients AxSpA. Enfin les patients présentant des comorbidités ou déjà traités par biomédicaments sont souvent exclus des essais contrôlés randomisés, les résultats de notre étude sont donc plus généralisables aux patients rencontrés en pratique clinique.

Les résultats de cette étude doivent être interprétés en considérant certaines limites, la principale étant son caractère rétrospectif. Cela n'a probablement pas influencé la mesure du critère de jugement principal car les variables d'intérêt (date et raison d'arrêt) sont majoritairement recueillies en pratique quotidienne. Les patients AxSpA traités par ixekizumab étaient trop peu nombreux pour être comparés aux patients des groupes TNFi et secukinumab et n'ont donc pas été inclus dans notre étude. Les données manquantes constituent une autre limite des études rétrospectives, par exemple dans notre étude la durée de la maladie (6,8 % de données manquantes), l'indice de masse corporelle (25,4 % de données manquantes), la CRP au diagnostic (19,0 % de données manquantes) et le BASDAI au diagnostic (14,0 % de données manquantes). L'utilisation d'une procédure d'imputation multiple dans notre étude limite l'impact des données manquantes, mais peut faire disparaître certaines différences liées aux traitements. L'évolution du BASDAI au cours

du temps était souvent indisponible en raison de l'absence de recueil systématique par les médecins, la réponse clinique aux deux traitements n'a donc pas pu être comparée.

La décision d'interrompre et de relayer le traitement était prise par le rhumatologue traitant et n'était pas standardisée. Les biais de sélection et la variabilité des recommandations en vigueur dans les autres pays rendent également la comparaison avec les autres études plus complexe. Le seuil BASDAI de 7 a été choisi, un seuil de 4 est fréquemment utilisé pour définir une SpA active, sans preuve scientifique évidente (52). Kobelt *et al.* (53) ont démontré qu'un BASDAI > 7 chez les patients atteints d'AxSpA est un seuil significatif au-delà duquel l'impact sur les capacités de travail et la déficience physique sont plus élevés.

Conclusion

Cette étude de vraie vie incluant une cohorte de patients atteints d'AxSpA permet de conclure que TNFi et SEC semblent avoir la même persistance thérapeutique. Les analyses en sous-groupes n'ont pas mis en évidence de différence en fonction de l'âge, de l'IMC, du BASDAI au diagnostic. Ces deux biomédicaments sont bien tolérés.

Les résultats de cette étude confirment l'intérêt d'une prise en charge personnalisée et adaptée aux préférences et comorbidités de chaque patient.

Des études comparatives prospectives sont nécessaires pour identifier les séquences thérapeutiques les plus efficientes.

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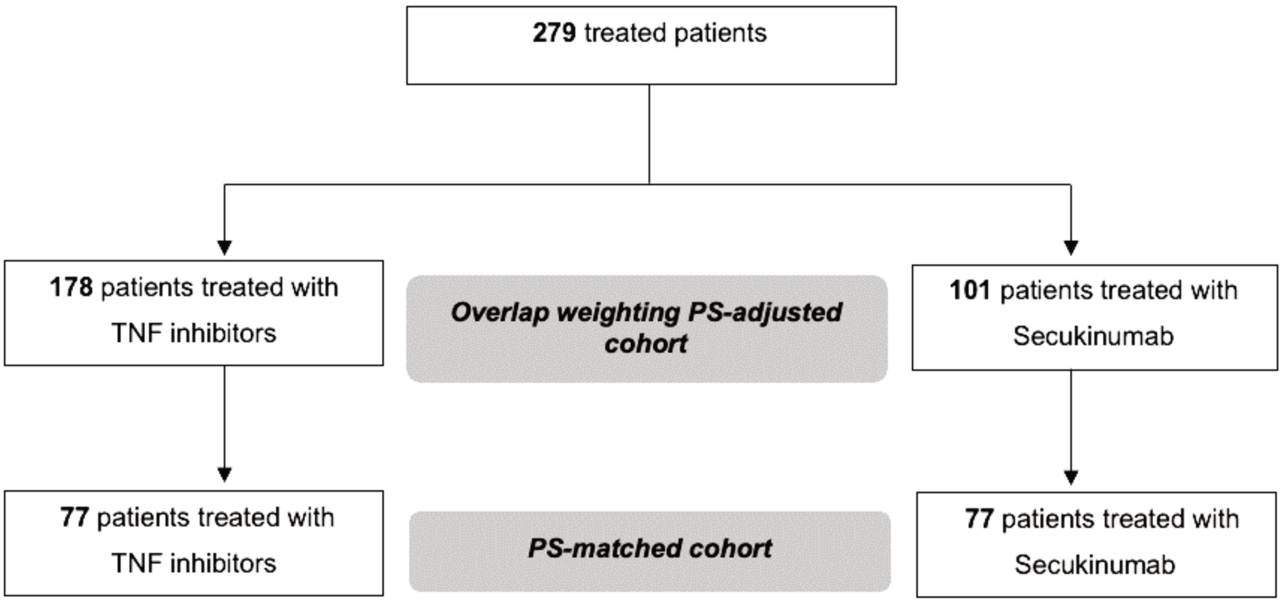
ANNEXES

Appendix 1. Flow Chart



Abbreviations: PS = propensity score ; TNF = tumour necrosis factor

AUTEUR : DELÉPINE Thibaut

Date de soutenance : 16 juin 2021

Titre de la thèse : Etude comparative de la persistance des traitements par anti-TNF α et anti-IL17 au sein d'une cohorte rétrospective de patients atteints de spondyloarthrite axiale.

Thèse - Médecine - Lille 2021

Cadre de classement : Médecine / Rhumatologie

DES + spécialité : Rhumatologie

Mots-clés : spondyloarthrite, persistance, anti-TNF, anti-IL17

Résumé :

Contexte : Les biomédicaments anti-TNFα (TNFi) et le sécukinumab (SEC) ciblant l'interleukine 17 sont indiqués chez les patients atteints de spondyloarthrite axiale (AxSpA) et dont la maladie reste active malgré plusieurs traitements anti-inflammatoires non stéroïdiens. Peu d'études comparent la persistance de ces traitements chez ces patients et les motifs d'arrêt sont variables (échec primaire, échappement secondaire, effets secondaires).

Méthodes : Nous avons réalisé une étude rétrospective multicentrique de patients atteints d'AxSpA ayant débuté un traitement par SEC ou TNFi entre 2016 et 2019. Le critère de jugement principal était la persistance thérapeutique définie comme la différence en mois entre l'initiation et l'arrêt du traitement. La probabilité comparée d'arrêt de chaque traitement est exprimée en hazard-ratio (HR) en utilisant un score de propension et après pondération.

Résultats : 279 patients ont été inclus : 178 traités par TNFi, 101 traités par SEC. 63,4 % présentaient une sacro-iliite radiographique, peu étaient naïfs de biothérapie (33,7 % dans le groupe TNFi, 14,9 % dans le groupe SEC). 128 patients (45,9 %) ont interrompu leur traitement. En analyse univariée, la persistance des TNFi était supérieure à celle du SEC (HR: 1,46, intervalle de confiance à 95 %, IC: 1,03-2,08). Les groupes d'appariement du score de propension contenaient 78 patients chacun. Les HR ajustés par le score de propension et après pondération ne révélaient pas de différence significative entre les groupes SEC et TNFi (HR = 1.46; IC à 95 %: 0,86; 2,50, p = 0,16 et HR = 1.46 IC à 95 %: 0,83 à 2,54, p = 0,16, respectivement). Des analyses en sous-groupes (âge, BASDAI au diagnostic, IMC) n'ont pas montré de différence entre TNFi et SEC. Le principal motif d'interruption des deux traitements était l'inefficacité. Le taux d'effets secondaires nécessitant l'arrêt du traitement était similaire pour les deux groupes.

Conclusion : Cette étude comparative rétrospective de vraie vie chez des patients atteints d'AxSpA ne met pas en évidence de différence de persistance thérapeutique entre les biomédicaments anti-TNFα et le sécukinumab. Ces résultats doivent être complétés par des essais contrôlés randomisés.

Composition du Jury :

Président : Monsieur le Professeur René-Marc FLIPO

Assesseurs : Monsieur le Professeur Bernard CORTET, Monsieur le Professeur Éric HOUVENAGEL**,** Monsieur le Docteur Jean-Guillaume LETAROUILLY