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Étude des facteurs prédictifs du développement d'un rhumatisme psoriasique difficile à traiter chez les patients initiant une première biothérapie

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Abréviations

ASDAS	*Ankylosing Spondylitis Disease Activity Score*
axSpA	*Axial Spondyloarthritis*
BASDAI	*Bath Ankylosing Spondylitis Disease Activity Index*
BMI	*Body Mass Index*
bDMARD	*Biological Disease-Modifying AntiRheumatic Drug*
C2M-PsA	*Complex-to-manage PsA*
CASPAR	*Classification of Psoriatic Arthritis*
CI	*Confidence intervals*
CNIL	*Commission Nationale de l'Informatique et des Libertés*
csDMARD	*Conventional Synthetic Disease-Modifying AntiRheumatic Drug*
DAPSA	*Disease Activity in Psoriatic Arthritis*
D2M	*Difficult-to-manage*
D2T	*Difficult-to-treat*
EMA	*European Medicines Agency*
EULAR	*European Alliance of Associations for Rheumatology*
GRAPPA	*Group of Research and Assessment of Psoriasis Arthritis*
HBP	*High blood pressure*
IBD	*Inflammatory bowel disease*
IRD	*Inflammatory rheumatic disease*
MACE	*Major adverse cardiovascular events*
MDA	*Minimal Disease Activity*
PAD	*Peripheral arterial disease*
PsA	*Psoriatic arthritis*
RA	*Rheumatoid arthritis*

tsDMARD	*Targeted synthetic Disease-Modifying AntiRheumatic Drug*
UK	*United Kingdom*

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I. Introduction générale

Le rhumatisme psoriasique (PsA) est un rhumatisme inflammatoire souvent associé au psoriasis cutané. La prévalence mondiale est estimée entre 0,3 et 1 %. Chez les patients diagnostiqués avec un psoriasis cutané, la prévalence peut augmenter jusqu'à 30 % (1). La présentation clinique est variée et peut toucher les petites et grosses articulations, l'enthèse et le rachis. Le psoriasis peut également être associé à des manifestations extra-musculo-squelettiques telles qu'une maladie inflammatoire chronique de l'intestin (MICI) ou une uvéite (2).

La stratégie de traitement repose sur l'utilisation de traitements de fond (DMARDs) : les traitements de fond conventionnels synthétiques (csDMARDs), les DMARDs ciblés (tsDMARDs) et les DMARDs biologiques (bDMARDs) . L'objectif est de parvenir à une activité minimale de la maladie (MDA) (3), et à une rémission.

Malgré cet arsenal thérapeutique, un nombre important de patients restent symptomatiques et insuffisamment contrôlés, ce qui entraîne une altération de la qualité de vie. Cette situation a donné naissance au fait que certains patients sont susceptibles d'être « difficiles à prendre en charge » (D2M) ou « difficiles à traiter » (D2T) (4).

Cela a été mis en évidence pour la première fois dans la polyarthrite rhumatoïde (PR), autre rhumatisme où il existe une proportion significative de patients qui n'atteignent pas les objectifs thérapeutiques recommandés. En 2022, un groupe de travail de l'Alliance européenne des associations de rhumatologie (EULAR) (5) a proposé une définition pour caractériser cette population de patients.

L'objectif de ce groupe de travail était de proposer une définition commune pour les travaux ultérieurs visant notamment à identifier les facteurs de risque au moment du diagnostic chez les patients qui sont à risque d'évoluer vers une forme D2T de la PR. Ainsi, si les patients étaient diagnostiqués à un stade précoce, une prise en charge thérapeutique plus agressive pourrait être recommandée pour obtenir une rémission (6).

Par extension, cette définition a récemment conduit à la proposition d'une définition similaire pour un autre rhumatisme inflammatoire chronique : la spondylarthrite axiale (axSpA) (7). Ils ont établi une distinction entre les patients atteints de D2M et ceux qui étaient réfractaires au traitement. À l'heure actuelle, des investigations complémentaires sont nécessaires, mais elles représentent un challenge important en termes de compréhension approfondie de cette résistance thérapeutique et de prise en charge plus efficace de cette catégorie de patients.

Dans le cas du PsA, des définitions similaires sont actuellement manquantes alors que l'on estime qu'un grand nombre de patients atteints de PsA n'atteignent pas l'objectif du traitement (8). Le Groupe de recherche et d'évaluation du psoriasis et du rhumatisme psoriasique (GRAPPA) (9) et l'EULAR mènent actuellement deux travaux visant à proposer des définitions consensuelles du D2T PsA. Le GRAPPA a lancé un travail pour mieux définir le PsA réfractaire à l'aide d'une revue de la littérature (SLR) et de deux enquêtes auprès des professionnels de santé (HCP) du GRAPPA et des patients, qui ont abouti à la proposition de deux catégories distinctes mais liées : le PsA « complexe à gérer » (C2M-PsA) et le PsA « difficile à traiter ».

Dans l'attente de ces définitions, plusieurs groupes ont proposé leurs propres définitions basées sur l'analyse de cohortes.

Perrota *et al*. ont proposé une première définition à partir de celle de la PR D2T avec quelques changements en utilisant des critères composites spécifiques au PsA (10). Ils se sont basés sur une étude rétrospective de 106 patients suivis dans un centre tertiaire italien.

En 2022, Philippoteaux *et al*. (11) ont mené une étude sur une cohorte de 150 patients dans un centre tertiaire français. Les patients atteints de D2T PsA ont été définis comme des patients ayant reçu au moins 2 b/tsDMARD ayant un mécanisme d'action différent parmi les b/tsDMARD disponibles. Ils ont mis en évidence plusieurs facteurs de risque d'évolution vers un D2T PsA et ont suggéré d'adapter la définition du D2T PsA en utilisant un critère de temporalité.
Une autre étude de Vassilakis *et al* (12) a décrit la proportion de patients atteints de D2T PsA dans une cohorte grecque, en identifiant toutes les caractéristiques phénotypiques. Ils ont considéré comme D2T PsA potentiels les patients atteints de PsA dont la maladie durait depuis au moins 6 mois, qui n'avaient pas répondu à au moins 1 csDMARD et à au moins 2 bDMARDs/tsDMARDs ayant un mécanisme d'action différent, et dont l'activité de la maladie était au moins modérée et/ou qui n'étaient pas en MDA au moment de l'évaluation.

Cependant, toutes ces études étaient monocentriques et rétrospectives. Par conséquent, les caractéristiques identifiées étaient représentatives de la population du centre concerné.

De plus, les directives thérapeutiques diffèrent d'un pays à l'autre, ce qui pourrait avoir un impact sur la présentation clinique des patients atteints de D2T PsA si tous les

patients n'ont pas accès au même traitement.

En France, un traitement par csDMARDs doit être envisagé en cas d'échec des AINS, ainsi que des traitements infiltratifs. En cas de psoriasis, le méthotrexate est le traitement privilégié selon les recommandations de la Société française de rhumatologie (SFR) de 2022 sur la prise en charge des patients atteints de spondyloarthrite, y compris le PsA (13). Les b/tsDMARDS doivent être envisagées chez les patients qui ne répondent pas aux traitements conventionnels, ou qui présentent des lésions structurales périphériques, une MICI ou une uvéite réfractaire/récurrente (*Figure 1*).

Au Royaume-Uni, les patients doivent avoir essayé 2 csDMARD avant d'avoir accès à un b/tsDMARD, selon le National Institute for Health and Care Excellence (NICE) (14) (*Figure 2*).

Il n'existe actuellement aucune étude comparant les populations de patients atteints de D2T PsA dans différents pays.

L’objectif principal de notre étude était de déterminer les facteurs de risque de développement d'un D2T PsA chez les patients initiant un premier bDMARD, tel que défini par Philippoteaux *et al*, dans une population multicentrique. L’objectif secondaire était d'identifier les facteurs de risque de développer un rhumatisme psoriasique réfractaire dans la même population.

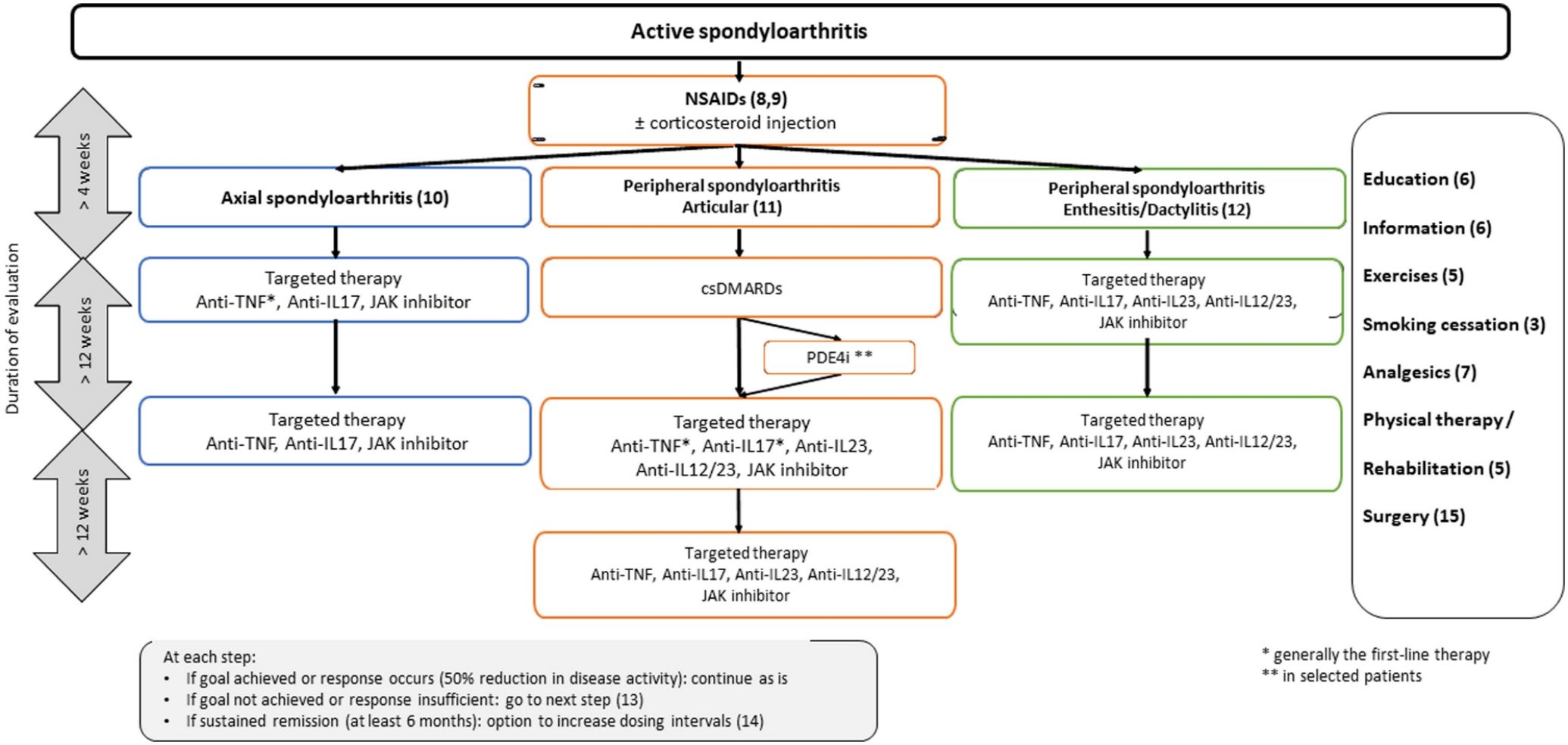


Figure 1: Overall treatment strategy for spondyloarthritis, including psoriatic arthritis, from the 2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis.
The numbers in parentheses refer to specific recommendations. At each step: if goal achieved or response occurs (50% reduction in disease activity): continue as is; if goal not achieved or response insufficient: go to next step; if sustained remission (at least 6 months): option to increase dosing interval.

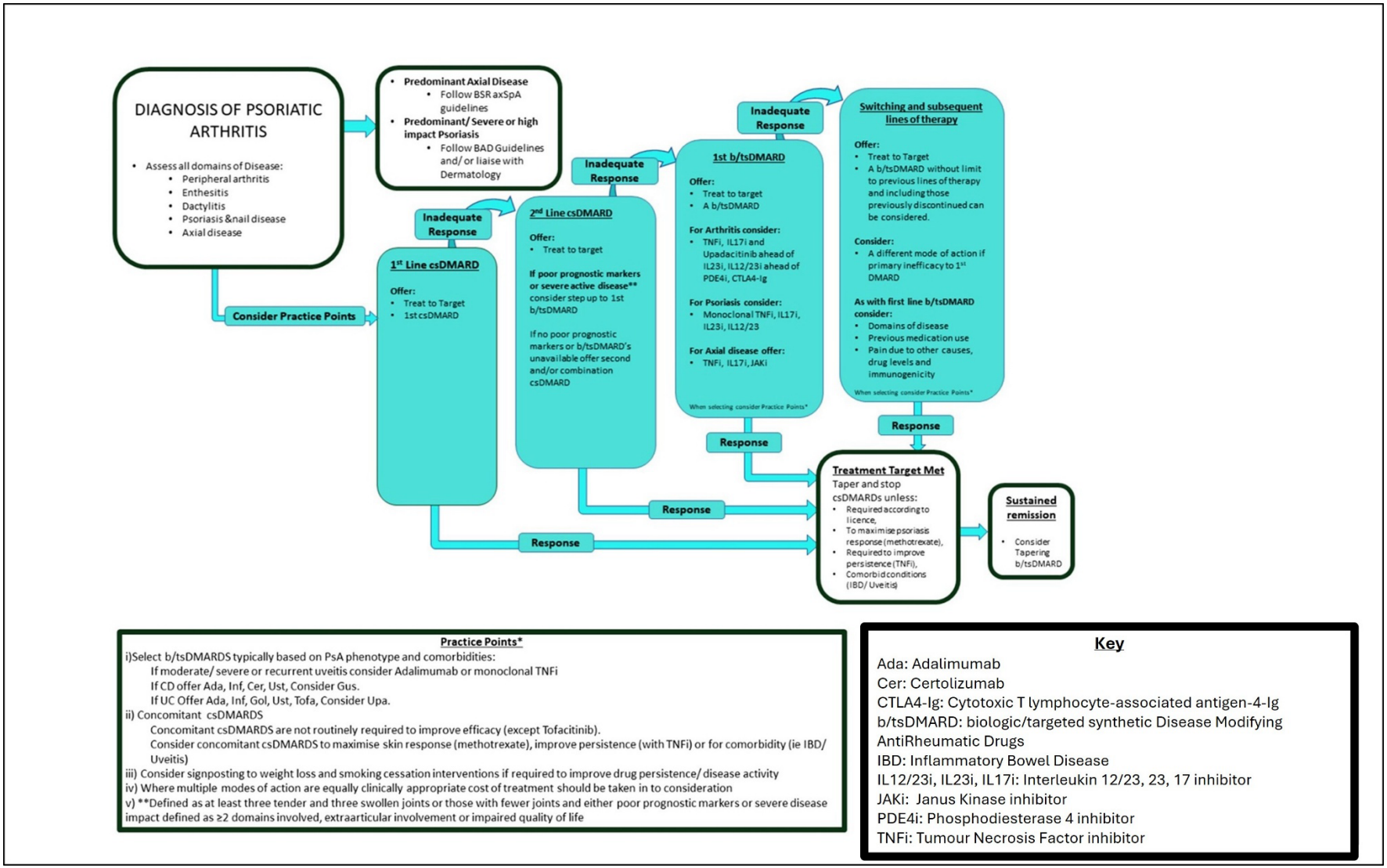


Figure 2: Summary algorithm for the treatment of an individual with PsA with b/tsDMARDS from the 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs.

II. Introduction

Psoriatic arthritis (PsA) is a type of inflammatory rheumatic disease (IRD) commonly associated with skin psoriasis. The global prevalence is estimated to range from 0.3 to 1%. In patients diagnosed with skin psoriasis, the prevalence increases to 30% (1). The clinical presentation is multifaceted and can affect both small and large joints, enthesis, and the spine. PsA can also be associated with extra-musculoskeletal manifestations such as inflammatory bowel disease (IBD) or uveitis (2).

The treatment strategy is based on the administration of Disease-Modifying Antirheumatic Drugs (DMARDs), with significant developments in biological and targeted DMARDs (b/tsDMARDs) occurring over the past few decades. The aim is to achieve remission or low disease activity (3).

Despite this therapeutic arsenal, a significant number of patients remain symptomatic and insufficiently controlled, resulting in impairment of the quality of life and mobility. This has given rise to the notion that some patients are likely to be ’difficult-to-manage’ (D2M) or ‘difficult-to-treat’ (D2T) (4).

This was highlighted for the first time in rheumatoid arthritis (RA), where a significant proportion of patients failed to attain their therapeutic goals. In 2022, a task force from the European Alliance of Associations for Rheumatology (EULAR) (5) proposed a definition to characterise this patient population. The objective of this task force was to propose a unique definition for future studies, especially for those who aim to identify risk factors at the time of diagnosis in patients who are at risk of progressing to a D2T

RA form. Consequently, if patients are diagnosed at an early stage, more intensive therapeutic management could be recommended to achieve remission (6).

Extending this definition has led to the proposition of a similar definition for another IRD: axial spondyloarthritis (axSpA), recently (7). They distinguished between D2M patients and those who were treatment-refractory. At present, further investigation is required, but it presents a significant challenge in terms of gaining a deeper understanding of therapeutic resistance and more effectively managing this category of patients.

In the case of PsA, similar definitions are currently lacking while it is estimated that a large number of PsA patients do not reach the treatment target (8). There are two ongoing works from the Group of Research and Assessment of Psoriasis Arthritis (GRAPPA) (9) and EULAR to propose consensual definitions of D2T PsA. GRAPPA initiated a comprehensive effort to better define refractory PsA with a scoping literature review (SLR) and two surveys among healthcare professionals (HCPs) from GRAPPA and among patients which led to the proposal of two distinct yet related categories: “complex-to-manage” PsA (C2M-PsA) and “difficult-to-treat” PsA.

Pending these definitions, several groups have proposed their own definitions based on the analysis of cohorts.

Perrota *et al*. proposed a first definition based on that of the D2T RA with some changes using composite measures specific to PsA (10). This definition was built on data of 106 patients from an Italian tertiary centre.

In 2022, Philippoteaux *et al.* (11) conducted a study among a cohort of 150 patients at a tertiary centre in France. D2T PsA patients were defined as patients who received at least 2 b/tsDMARDs with different mechanism of action among the b/tsDMARD

available. They highlighted several risk factors for progression to D2T PsA and further suggested adapting the definition for D2T by using a temporality criterion.

Another study from Vassilakis *et al* (12) described the proportion of D2T PsA patients in a Greek cohort, identifying any phenotypic characteristics. They considered as potential D2T PsA patients who had at least 6 months of disease duration, have failed to respond to at least one csDMARDs and at least two bDMARDs/tsDMARDs with a different mechanism of action, and had either at least moderate disease activity and/or were not in minimal disease activity (MDA) at the time of their assessment.

Nevertheless, all these studies were monocentric and retrospective in nature. Therefore, the characteristics identified were representative of the population of the centre concerned.

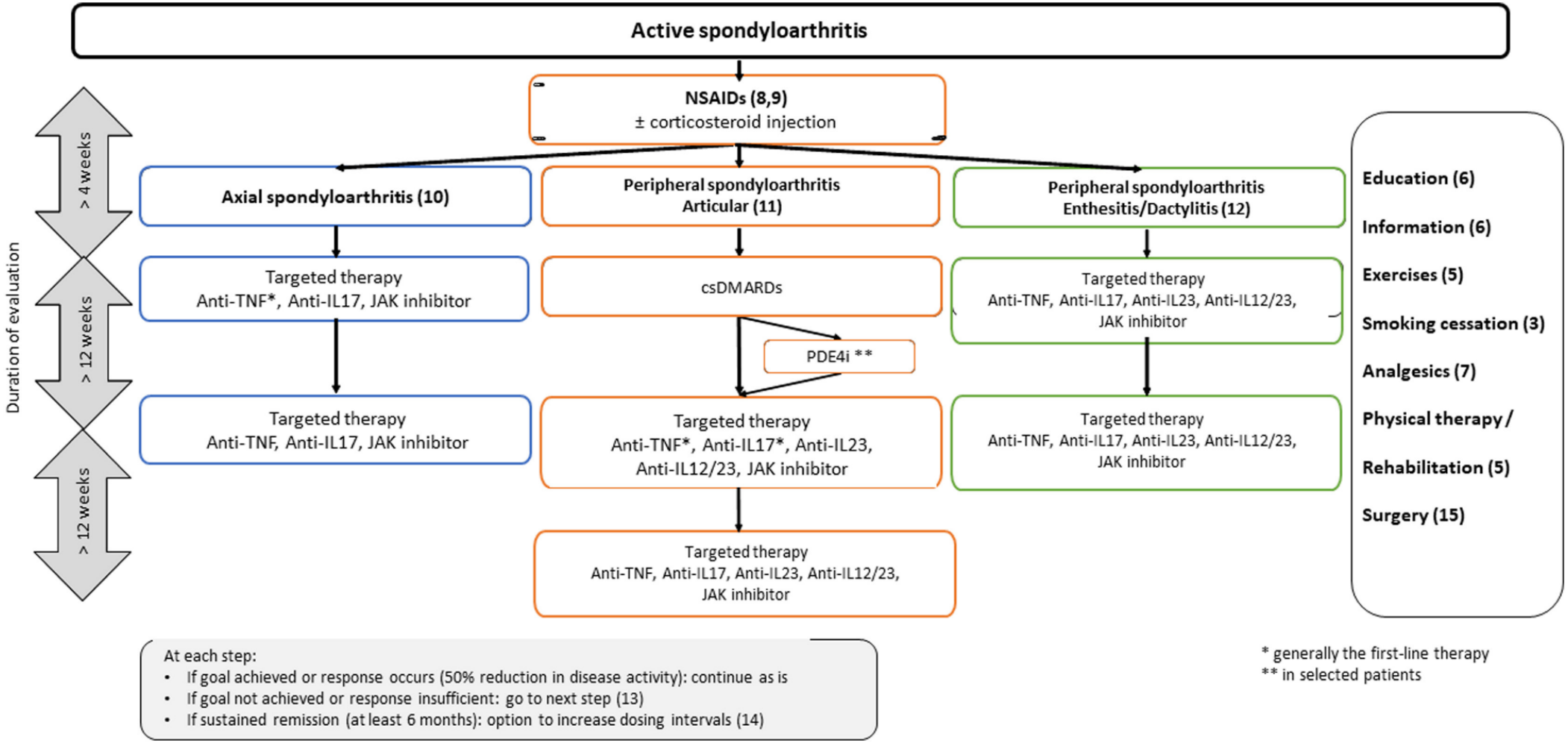
Moreover, therapeutic guidelines differ from country to country, and this could impact the clinical presentation of D2T PsA patients if not all patients have access to the same treatment.

In France, treatment with csDMARDs should be considered if NSAIDs have failed, along with local interventions. In cases of psoriasis, methotrexate is the preferred treatment according to the 2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including PsA (13) . Targeted therapies should be considered in patients who do not respond to conventional treatments, or have peripheral structural damage, active inflammatory bowel disease or refractory/recurrent uveitis (*Figure 1*).

While in the United Kingdom (UK), patients must have tried two csDMARDs before having access to a b/tsDMARD, according to the National Institute for Health and Care Excellence (NICE) (14) (*Figure 2*).

There are currently no studies comparing patients with D2T PsA populations between different countries.

The primary endpoint of our study was to determine the risk factors for developing D2T PsA in patients initiating a first bDMARD, as defined by Philippoteaux *et al*., in a multicentre population. The second endpoint was to identify the risk factors for developing refractory psoriatic arthritis (PsA) in the same population.



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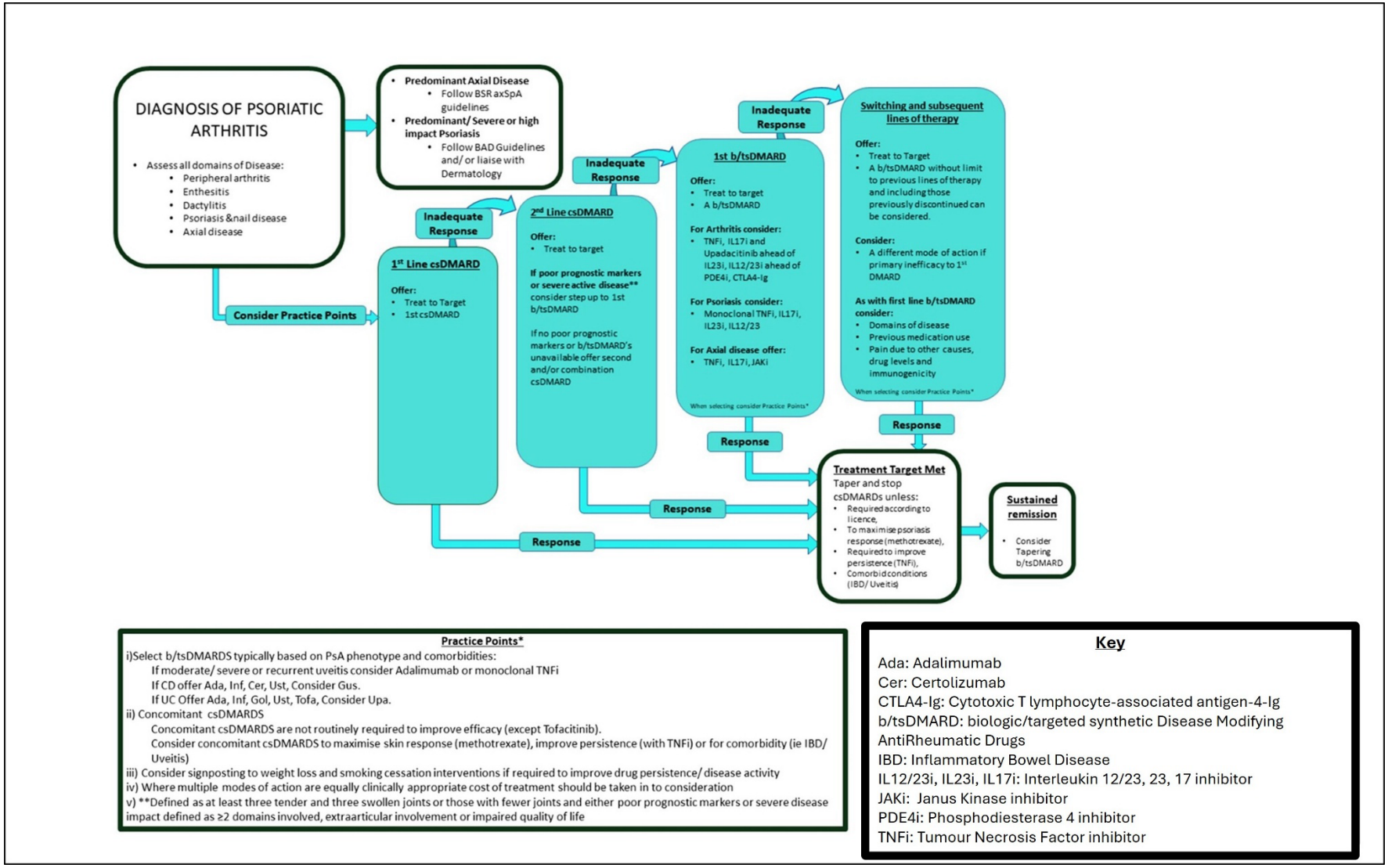

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III. Methods

Study design

We conducted a multicentre, observational, retrospective study in four different departments of rheumatology from September 2000 to December 2024. Three of the centres were located in northern France : one in a tertiary centre (Lille University Hospital) and two in secondary centres (Valenciennes and Saint-Philibert Hospitals). The last department was located in the Nuffield Orthopaedic Centre, a tertiary care centre in Oxford, United Kingdom.

Population, inclusion and exclusion criteria

Eligible participants aged ≥18 years had to have a clinical diagnosis of PsA confirmed by the ClAsSification of Psoriatic ARthritis (CASPAR) criteria (15) and were treated with a bDMARD or a tsDMARD. The main exclusion criteria were a diagnosis of another inflammatory rheumatic disease and a disease duration of less than 5 years.

Data collection

Clinical evaluation

Demographic and clinical data at baseline were collected from patients' medical records. Initiation of the first bDMARD was considered at the baseline time. Demographic data, including gender, age, weight, height, body mass index (BMI), and smoking status, were collected at baseline. Obesity was defined as a BMI of 30 kg/m² or greater. Smoking status was categorised into three categories: never smoked, previous smoker and active smoker. PsA characteristics at baseline were collected, including disease duration and PsA patterns.

Clinical PsA patterns

Clinical assessment encompassed the number of tender and swollen joints, enthesitis, dactylitis, inflammatory back pain, and buttock pain. Axial involvement in PsA was assessed by the rheumatologist based on the following criteria: axial clinical presentation (inflammatory back pain and/or inflammatory buttock pain), and suggestive typical imaging.

Presence of extra-articular manifestations such as psoriasis (cutaneous or nail), uveitis and inflammatory bowel diseases (IBD) at baseline was also reported. Disease activity was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (16), Ankylosing Spondylitis Disease Activity Score (ASDAS) (17) and Disease Activity in Psoriatic Arthritis (DAPSA) (18).

Imaging

Data from plain radiographs and MRI scans were collected at baseline and follow-up. Structural damage was considered to be present when peripheral and/or axial abnormal radiographic findings were observed. Axial structural damage included sacroiliitis, mostly asymmetrical, vertebral body squaring, parasyndesmophytes, syndesmophytes or facet joint fusion on radiographic or MRI findings. Peripheral structural damage was considered present when erosion, bone proliferation, periostitis and acro-osteolysis were found on plain radiographs. Patients could present with both structural damages.

Comorbidities

Main comorbidities were collected at baseline when reported in the medical records, including high blood pressure (HBP), dyslipidaemia, ischaemic cardiomyopathy,

diabetes mellitus, peripheral arterial disease, depression and fibromyalgia. Fibromyalgia diagnosis was based on the rheumatologist's opinion.

Laboratory Data

Laboratory data were collected at baseline (HLA and rheumatoid factor status, and CRP) and during follow-up (CRP).

Evolution of the phenotype of PsA

Several demographic and clinical characteristics at baseline were used to define eight phenotypes of PsA disease :

- Phenotype 1: Peripheral structural damage
- Phenotype 2: Axial structural damage
- Phenotype 3: Inflammatory bowel disease/uveitis
- Phenotype 4: Ischaemic cardiomyopathy/stroke
- Phenotype 5: Diabetes mellitus / dyslipidaemia
- Phenotype 6: Obesity
- Phenotype 7: Polyarticular PsA (i.e. > 3 involved joints)
- Phenotype 8: Dactylitis

The evolution of these eight phenotypes was assessed during four periods: before 1992, 1992-2002, 2003-2013, and 2014-2024.

Treatments

The history of treatment for every patient was reported, including csDMARDs (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine) and the b/tsDMARDs (TNF inhibitors, interleukin-17 inhibitors, interleukin-12/23 inhibitors, interleukin-23

inhibitors, interleukin-6 inhibitors, JAK inhibitors, anti-CD20 antibodies, and phosphodiesterase-4 inhibitors). Disease duration was defined as the time between diagnosis and initiation of the first bDMARD, the drug survival, the causes of discontinuation (primary failure, secondary failure, adverse events, pregnancy, dermatological failure, IBD, multiple sclerosis, patient's will) as well as the adverse events in case of discontinuation due to an adverse event.

Definition of D2T PsA

D2T PsA was defined following the definition mentioned in the Philippoteaux *et al* (11) study, such as:

- Failure of treatments of either of the following options:

• ≥ 2 b/tsDMARDS with different mechanisms of action within less than 2 years

Or

• ≥ 1 b/tsDMARDs within less than 2 years and a contraindication to one therapeutic class; i.e., a contraindication *to TNF inhibitors (multiple sclerosis, severe heart insufficiency*).

- Suggestive evidence of disease activity/progression, defined as ≥ 1 of the following:

• At least moderate activity (DAPSA ≥ 15)

• Signs (including biology and imaging) and/or symptoms suggestive of active disease (articular or rheumatological: uveitis, psoriasis, inflammatory bowel disease),

• Inability to reduce or discontinue NSAIDs,

• Disease controlled, but with persistent PsA symptoms causing reduced quality of life;

- Management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or patient.

Refractory PsA was defined as a failure of all four therapeutic classes, including TNF inhibitors, JAK inhibitors, interleukin-17 inhibitors, and interleukin-23 inhibitors.

Outcomes

The primary endpoint of this work was to determine the risk factors for developing D2T PsA in patients initiating a first bDMARD using the definition from Philippoteaux *et al* (11) in a multicentric population. The second endpoint was to determine the risk factors for developing refractory PsA in the same population.

Statistical analysis

Qualitative variables were described in terms of frequencies and percentages. Quantitative variables were described by the mean and standard deviation, or by the median and interquartile range in cases of non-Gaussian distributions. The normality of the distributions was verified graphically and using the Shapiro-Wilk test.

A comparison of patients with D2T PsA to those with non-difficult-to-treat PsA (nD2T PsA) was performed using logistic regression models adjusted for country (France vs. the UK). Factors with a p-value less than 0.05 were included in a multivariate logistic regression model, also adjusted for country. Co-linearity between parameters was checked using the variance inflation factor (VIF). Odds ratios (ORs) and their 95% confidence intervals (CI) were reported as the measure of association. A comparison was made between refractory PsA patients and non-refractory patients using the same methodology as previously described. However, the multivariate model was not performed due to the number of patients.

The significance level was set at 5%. Statistical analyses were performed using SAS software (SAS Institute version 9.4).

Ethics

As a retrospective study, an Ethics Committee and Institutional Review Board and informed consent from patients were not required, according to French law (JORF number 160 13th July 2018) . The study was performed in compliance with MR004 and received permission from Lille University Hospital, Hospital of Saint-Philibert, Hospital of Valenciennes, and was declared to the Commission Nationale de l'Informatique et des Libertés (CNIL).

Ethical permission was not sought in the UK but the data were collected as part of a retrospective audit of NHS Hospital data at Oxford University Hospitals NHS Trust. The project was registered as an audit within the hospital trust.

IV. Results

Study population

A total of 1170 patients were screened and 412 patients met our inclusion criteria. 145 were from Lille, 21 from Valenciennes, 134 from Saint-Philibert and 112 from Oxford. Among these patients, 320 were nD2T PsA (77.7%), 92 were diagnosed as D2T PsA (22.3%; 95% confidence interval [CI] 18.4-26.7) and 9 of them were diagnosed as refractory PsA (2.2%; 95% CI 1.0-4.1) (*Figure 3*).

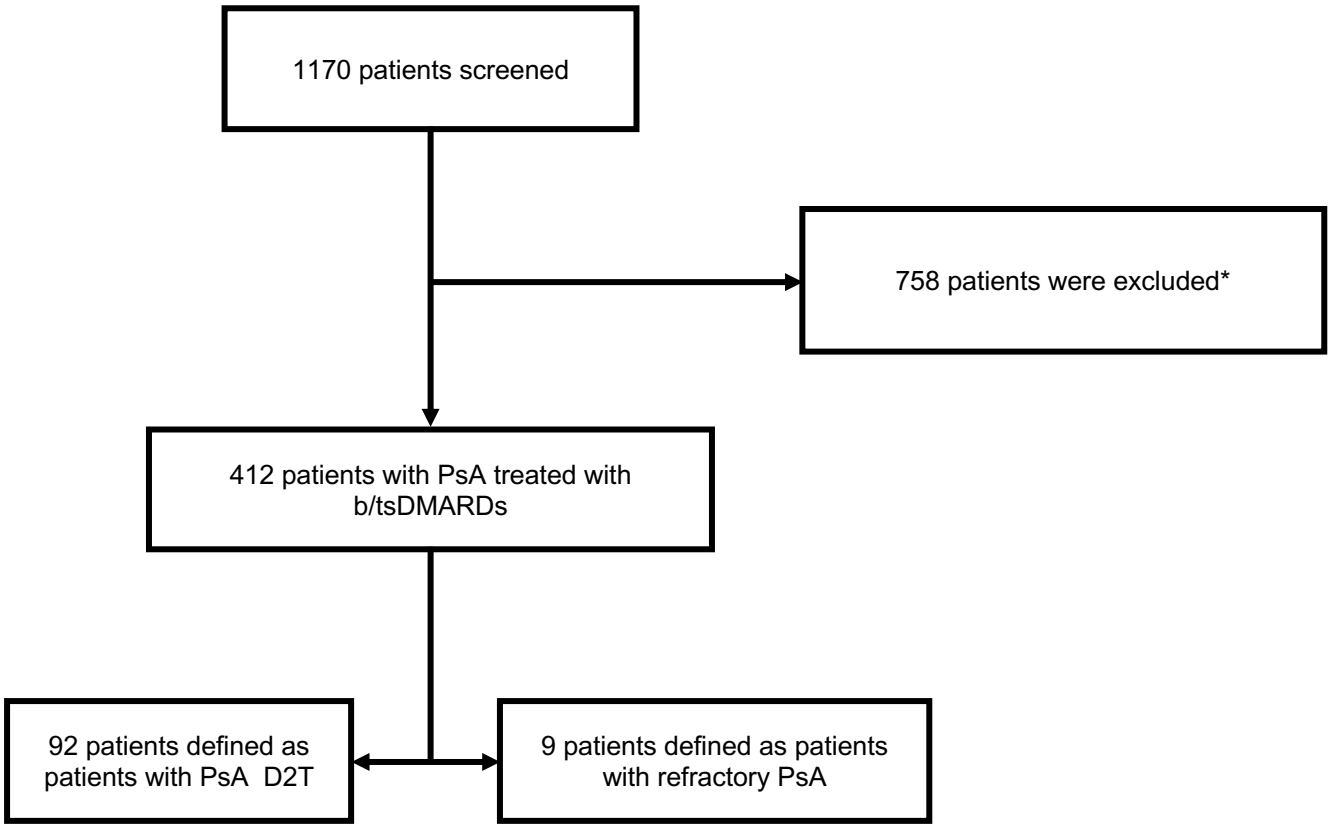

Figure 3: Flow chart of the study

***758 patients not included after screening** (32 PsA diagnosis incomplete according to CASPAR criteria, 36 PsA patients with rheumatoid arthritis, 132 PsA patients with time of follow-up <5 years, 101 patients treated with csDMARDs only, 251 axial spondyloarthritis, 21 SAPHO syndrome, 34 enteropathic spondylarthritis, 77 peripheral spondyloarthritis, 55 patients with axial and peripheral spondyloarthritis, 19 patients with juvenile spondyloarthritis).

Patients with D2T PsA

Among the 92 patients classified as patients with D2T PsA, 96.7% were from French centres and 3.3% were from the English centre (*Table 1*). No statistically significant difference was noted for demographic characteristics. Mean age was 56.1 ± 13.5 years and 55.1 ± 13.4 years; mean BMI was 28.5 ± 5.9 and 28.8 ± 6.0, respectively, for patients with D2T PsA and patients with nD2T PsA. The sex ratio was balanced (48.9% of patients with D2T PsA were female and 47.8% of patients with nD2T PsA were female). The median duration of the disease was 13.5 (8.5; 20.0) years and 11.0 (8.0-17.0) years, respectively, for patients with D2T PsA and patients with nD2T PsA.

Table 1: Baseline characteristics of patients with D2T PsA and those without PsA patients

Parameters	N	D2T PsA n = 92	N	Non D2T PsA n = 320	p value
Men	92	47 (51.1)	320	167 (52.2)	0.74
Age (years), mean ± SD	92	56.0 ± 13.5	319	55.1 ± 13.4	0.94
BMI, mean ± SD	77	28.5 ± 5.9	213	28.8 ± 6.0	0.73
PsA duration (years), median (IQR)	92	13.5 (8.5 ; 20.0)	320	11.0 (8.0 ; 17.0)	NA
Current smoker status	85	21 (24.7)	261	89 (34.1)	0.38
Clinical PsA characteristics at baseline					
Axial involvement	89	43 (48.3)	305	139 (45.6)	0.57
Peripheral involvement	92	89 (96.7)	312	289 (92.6)	0.15
Monoarthritic	90	6 (6.7)	312	33 (10.5)	-
Oligoarthritic (2-3 involved joints)	90	13 (14.4)	312	46 (14.7)	-
Polyarthritic (≥4 involved joints)	90	68 (75.6)	312	210 (67.1)	-
Dactylitis	83	14 (16.9)	301	90 (29.9)	**0.02**
Enthesitis	83	15 (18.1)	299	80 (26.8)	0.14
Tender joint count	51	5.5 ± 4.8	217	6.2 ± 6.6	0.41
Swollen joint count	51	2.5 ± 2.3	217	3.2 ± 3.0	0.37
BASDAI Baseline, mean ± SD	21	55.7 ± 20.6	73	45.7 ± 25.5	0.94
Uveitis	85	2 (2.4)	305	9 (3.0)	0.77
Psoriasis	88	70 (79.5)	311	275 (88.4)	NA
IBD	84	3 (3.6)	305	8 (2.6)	0.77
Baseline CRP (mg/L), median (IQR)	63	9.0 (3.0 ; 23.0)	267	7.0 (2.9 ; 17.3)	0.25
Positive HLA B27 status	80	12 (24.0)	148	52 (35.1)	0.15
Peripheral structural damage	80	36 (43.9)	231	92 (39.8)	0.53
Main comorbidities					
Diabete mellitus	92	15 (16.3)	317	34 (10.7)	0.34
Fibromyalgia	91	11 (12.1)	316	19 (6.0)	**0.03**
Depression	89	13 (14.6)	316	40 (12.7)	0.11
Ischaemic cardiomyopathy	92	9 (9.8)	318	11 (3.5)	**0.03**
TIA/Stroke	92	3 (3.3)	318	9 (2.8)	0.86
1st bDMARD line					
TNF inhibitors		81 (88.0)		278 (86.9)	NA
IL17 inhibitors		2 (2.2)		16 (5.0)	NA
IL12/23 inhibitor		5 (5.4)		14 (4.4)	NA
Abatacept		1 (1.1)		1 (0.3)	NA
IL 23 inhibitors		0 (0)		3 (0.9)	NA
Rituximab		1 (1.1)		0 (0)	NA
IL6 inhibitors		1 (1.1)		1 (0.3)	NA
Apremilast		1 (1.1)		7 (2.2)	NA

Values are expressed as number (%) unless otherwise stated. BASDAI: Bath Ankylosing Spondylitis Disease Activity; bDMARD: biological disease modifying antirheumatic drug; BMI: body mass index; CRP: C-reactive protein; D2T: difficult-to-treat; HLA: human leukocyte antigen IBD: inflammatory bowel disease; IQR: interquartile range; N: number of available observations; NA: not applicable; PsA: psoriatic arthritis; SD: standard deviation; TIA: transient ischaemic accident; TNF:Tumour Necrosis Factor.

Predictive factors of developing D2T PsA

In univariate analysis, fibromyalgia (OR=2.54; 95% CI 1.08-6.00; p=0.03) and ischaemic cardiomyopathy (OR=3.03; 95% CI 1.13-8.11; p=0.03), axial radiographic damage (OR=2.85; 95%CI 1.33-6.12; p=0.01) and dactylitis (OR=0.46; 95%CI 0.24-0.88; p=0.02) were found to be associated with D2T PsA.

In multivariate analysis, fibromyalgia and ischaemic cardiomyopathy were found to be associated with being D2T PsA, respectively OR 2.62 (95%CI 1.09-6.27; p=0.03) and OR 2.95 (95%CI 1.04-8.36; p=0.04). Dactylitis was also found to be associated with a protective factor against the occurrence of D2T PsA (OR 0.49; 95% CI 0.26-0.94; p = 0.03). Regarding axial radiographic damage, the multivariate analysis was not conducted due to a 43% rate of missing data.

Table 2: Multivariate analysis for D2T PsA predictive factors

	OR	**95% Confidence Interval**		**p-value**
Fibromyalgia	2.62	1.09	6.28	0.03
Ischaemic cardiomyopathy	2.95	1.04	8.36	0.04
Dactylitis	0.49	0.26	0.94	0.03

OR: Odd Ratio

Treatments

Initiation of a b/tsDMARDs

Most of patients had received csDMARD before initiating a b/tsDMARD: 85.7% (258/301) of nD2T PsA patients and 84.3% (75/89) of D2T PsA patients (*Figure 4*). In the large majority of cases, methotrexate was used in both populations: 84.3% for D2T PsA patients and 85.7% for nD2T PsA patients, followed by sulfasalazine: 29.9% for D2T PsA patients and 28.9% for nD2T PsA patients and leflunomide: 27% for D2T PsA patients and 26.2% for nD2T PsA patients.

Two csDMARDs were prescribed in several patients before initiating a first bDMARD: methotrexate and sulfasalazine in 56 patients, including 26 English patients; methotrexate and leflunomide in 61 patients, including 23 English patients and leflunomide and sulfasalazine in 5 patients, including 3 English patients. Methotrexate, leflunomide and sulfasalazine were prescribed in 26 patients, including 7 English patients. Two or more csDMARD were prescribed in 28 patients with D2T PsA (30.4% of the whole population of patients with PsA).

The mean time for initiating of b/tsDMARDs was 5.9 years for nD2T PsA and 5.2 years for D2T PsA.

When a b/tsDMARDs was initiated, the first line was a TNF inhibitor in both groups: 86.9% for nD2T PsA and 88% for D2T PsA. Among the TNF inhibitors, adalimumab was the most widely chosen: 42.4% for D2T PsA patients and 45.9% for nD2T PsA patients. For patients requiring second- or third-line treatment, the main bDMARD was another TNF inhibitor. After that, the lines of treatment varied between several molecules (*Table 2, Table 3*).

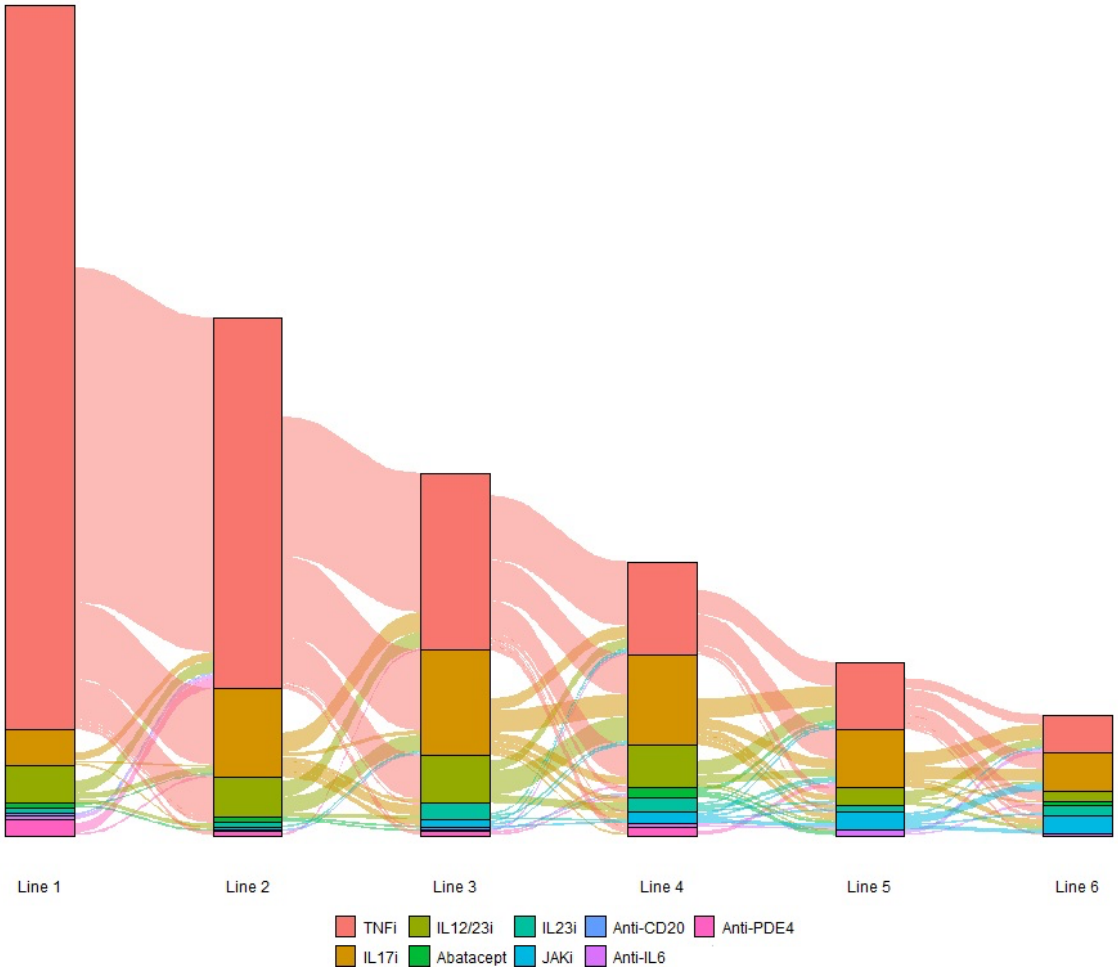

Figure 4: Treatment trajectories from first to sixth line for the population of the study

Table 2: Therapeutic lines for patients with D2T PsA

	1st line	2nd line	3rd line	4th line	5th line	6th line
TNFinhibitors	81	67	39	28	26	16
IL-17 inhibitors	2	13	28	26	20	13
IL-12/23 inhibitors	5	8	14	12	7	4
Abatacept	1	2	0	5	0	2
IL-23 inhibitors	0	1	3	3	2	5
JAK inhibitors	0	0	3	6	7	9
CD20 inhibitors	1	1	1	0	0	0
IL-6 inhibitors	1	0	1	2	3	2
PDE4 inhibitors	1	0	2	2	0	0

Each figure represents the number of patients receiving each therapeutic class, by therapeutic line

Table 3: Therapeutic lines for patients with nD2T PsA

	1st line	2nd line	3rd line	4th line	5th line	6th line
TNF-alpha inhibitors	278	117	49	18	7	3
IL-17 inhibitors	16	31	24	19	9	6
IL-12/23 inhibitors	14	12	10	9	2	1
Abatacept	1	0	0	0	0	0
IL-23 inhibitors	3	2	5	4	1	0
JAK inhibitors	0	1	1	0	2	0
CD20 inhibitors	0	0	0	0	0	0
IL-6 inhibitors	1	0	0	0	0	0
PDE4 inhibitors	7	2	0	2	0	0

Each figure represents the number of patients receiving each therapeutic class, by therapeutic line

Reason for discontinuation

Regarding the reasons for discontinuing b/tsDMARDs, the main reason for stopping the first line was secondary failure in nD2T PsA patients (79/170). For D2T PsA, primary failure occurred in 34 patients out of 92.

Concerning the following lines of treatment for nD2T PsA patients, b/tsDMARDs was stopped for primary and secondary failure, or adverse events. The proportion of patients strictly declined over time (6 patients at the 6th line). For D2T PsA patients, the main reason for discontinuation of b/tsDMARDs was primary failure for each line (*Table 4, Table 5*).

Table 4: Reason for discontinuation for patients with D2T PsA

	1st line N=92	2nd line N=92	3rd line N=86	4th line N=68	5th line N=52	6th line N=40
Primary failure	34	43	38	38	27	22
Secondary failure	27	27	22	16	7	10
Adverse events	19	12	17	10	8	5
Onset of IBD	0	1	0	0	0	0
Skin failure	8	9	8	5	8	4
Multiple sclerosis	1	0	0	1	0	0
Pregnancy	0	0	1	0	1	0
Patients' will	0	0	0	0	0	0

Each figure represents the number of patients by reason for discontinuation, according to therapeutic line.

Table 5: Reason for discontinuation for patients with nD2T PsA

	1st line N=177	2nd line N=98	3rd line N=54	4th line N=25	5th line N=10	6th line N=6
Primary failure	36	32	12	9	3	2
Secondary failure	79	34	19	7	1	2
Adverse events	37	18	17	7	3	1
Onset of IBD	0	0	0	0	0	1
Skin failure	10	8	5	2	2	0
Multiple sclerosis	0	2	0	0	0	0
Pregnancy	3	2	0	1	1	0
Patients' will	5	3	0	0	0	0

Each figure represents the number of patients by reason for discontinuation, according to therapeutic line.

Patients with refractory PsA

Only nine patients out of 412 were diagnosed as having refractory PsA. All of them were from French centres. The sex ratio was less balanced than in the nD2T PsA population, with 66.7% of males and 33.3% of females (*Table 6*). The mean age was 51.2 ± 11.1 years. The median duration of disease progression was also longer, at 20.0 (17.0; 25.0) years.

Comorbidities and clinical presentation

At baseline, all patients presented with a polyarticular condition and had a higher CRP level compared to patients with a non-refractory PsA (14.5 [3.0; 46.0] mg/L versus 7.0 [3.0; 18.0] mg/L).

Dactylitis was present in 28.7% of patients with a refractory PsA and 27.1% of patients with a non-refractory PsA. Regarding enthesitis, it was present in 42.9% of patients with refractory PsA, while it was present in 24.5% of patients with non-refractory PsA. Half of the patients with a refractory PsA had axial involvement at baseline. One data was missing for one patient. It was present in 46.1% of patients with non-refractory PsA.

Obesity was present in 62.5% of patients with a refractory PsA and 34.4% of patients with a non-refractory PsA.

Parameters	N	Refractory PsA n = 9	N	Non-refractory PsA n = 403
Men	9	6 (66.7)	403	208 (51.6)
Age (years), mean ± SD	9	51.2 ± 11.1	402	55.4 ± 13.5
BMI, mean ± SD	8	30.3 ± 3.9	282	28.7 ± 6.0
PsA duration (years), median (IQR)	9	12.0 (8.0; 18.0)	403	20.0 (17.0; 25.0)
Current smoker status	9	2 (22.2)	337	108 (32.0)
Clinical PsA characteristics at baseline				
Axial involvement	8	4 (50.0)	386	178 (46.1)
Peripheral involvement	9	9 (100.0)	395	369 (93.4)
Monoarthritic	9	0 (0.0)	394	39 (9.9)
Oligoarthritic (2-3 involved joints)	9	0 (0.0)	394	59 (15.0)
Polyarthritic (≥ four involved joints)	9	9 (100.0)	394	269 (68.3)
Dactylitis	7	2 (28.6)	377	102 (27.1)
Enthesitis	7	3 (42.9)	375	92 (24.5)
Tender joint count	5	6.6 ± 4.7	263	6.0 ± 6.3
Swollen joint count	5	3.0 ± 2.5	261	3.1 ± 2.9
BASDAI Baseline, mean ± SD	2	68.7 ± 4.7	92	47.5 ± 24.8
Uveitis	8	0 (0.0)	392	11 (2.9)
Psoriasis	9	8 (88.9)	390	337 (86.4)
IBD	8	0 (0.0)	392	11 (2.9)
Baseline CRP (mg/L), median (IQR)	6	14.5 (3.0; 46.0)	324	7.0 (3.0; 18.0)
Positive HLA B27 status	5	2 (40.0)	193	62 (32.1)
Peripheral structural damage	8	5 (62.5)	305	123 (40.3)
Main comorbidities				
Diabete mellitus	9	0 (0.0)	400	49 (12.3)
Fibromyalgia	9	0 (0.0)	398	30 (7.5)
Depression	9	1 (11.1)	396	52 (13.1)
Ischaemic cardiomyopathy	9	1 (11.1)	401	19 (4.7)
TIA/Stroke	9	0 (0.0)	401	12 (3.0)
1st bDMARD line				
TNF inhibitors		9 (100.0)		350 (86.8)
IL-17 inhibitors		0 (0.0)		18 (4.5)
IL-12/23 inhibitor		0 (0.0)		19 (4.7)
Abatacept		0 (0.0)		2 (0.5)
IL-23 inhibitors		0 (0.0)		3 (0.7)
Rituximab		0 (0.0)		1 (0.2)
IL-6 inhibitors		0 (0.0)		2 (0.5)
Apremilast		0 (0.0)		8 (2.0)

Table 6: Baseline characteristics of patients with refractory PsA and those without PsA patients

Values are expressed as a number (%) unless otherwise stated. BASDAI: Bath Ankylosing Spondylitis Disease Activity; bDMARD: biological disease modifying antirheumatic drug; BMI: body mass index; CRP: C-reactive protein; D2T: difficult-to-treat; HLA: human leukocyte antigen IBD: inflammatory bowel disease; IQR: interquartile range; N: number of available observations; NA: not applicable; PsA: psoriatic arthritis; SD: standard deviation; TIA: transient ischaemic accident; TNF:Tumour Necrosis Factor.

Treatments

All patients were initially treated with first-line csDMARDs. Methotrexate was used for 87.5% of patients, followed by sulfasalazine and leflunomide for 37.5% of patients. Regarding the prescription of csDMARDs in this population, two patients received methotrexate and leflunomide. One patient received methotrexate and sulfasalazine. One patient received methotrexate, sulfasalazine and leflunomide.

Then, the initiation of a b/tsDMARD was estimated at 11.0 (2.0; 23.0) years, compared to 3.0 (1.0; 8.0) years for patients with non-refractory PsA.

We also examined all the treatments prescribed for these patients (*Table 7*). The most common first-line b/tsDMARDs prescribed were TNF inhibitors. They generally received several IL-17 inhibitors before concluding that they were ineffective.

Table 7: Therapeutic lines for patients with refractory PsA.

	TNFi	IL23i	IL23/23i	JAKi	IL17i	Others
Patient 1	5	1	0	2	1	0
Patient 2	3	1	1	0	1	2
Patient 3	5	2	1	3	2	2
Patient 4	5	1	1	3	3	4
Patient 5	1	1	1	1	1	0
Patient 6	4	1	1	2	2	0
Patient 7	5	0	1	1	3	0
Patient 8	3	2	1	1	4	0
Patient 9	3	1	1	3	3	0

Each figure represents a number of b/tsDMARDs for each class.
Others : IL-6 inhibitors, Abatacept, CD20 inhibitors, PDE4 inhibitors

Reason for discontinuation

The reasons for discontinuation were more heterogeneous due to the small number of patients. These were mainly primary and secondary failures (*Table 8*).

Table 8: Reason for discontinuation for patients with refractory PsA

	1st line N=9	2nd line N=9	3rd line N=9	4th line N=9	5th line N=8	6th line N=8
Primary failure	4	2	4	4	6	4
Secondary failure	2	6	4	4	1	2
Adverse events	3	0	0	1	0	0
Onset of IBD	0	0	0	0	0	0
Skin failure	0	1	1	0	1	2
Multiple sclerosis	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Patients' will	0	0	0	0	0	0

Each figure represents the number of patients who discontinued the treatment for the same reason.

Phenotypes

We also looked at the evolution of baseline phenotypes over the decades (*Figure 4, Table 9*). Overall, the proportion of patients with peripheral structural damage, inflammatory bowel disease, uveitis, diabetes mellitus, and dyslipidaemia at baseline decreased over time. On the other hand, the proportion of patients with axial structural damage, ischaemic cardiomyopathy, stroke, obesity, polyarticular PsA (*i.e* ≥ four involved joints) and dactylitis was stable over time.

Table 9: Phenotype distribution depending on the year of diagnosis

	Year of diagnosis			
Phenotype	<1992 N=9	1992-2002 N=61	2003-2013 N=161	2014-2024 N=181
Peripheral structural damage	5/8 (62.5)	27/52 (51.9)	55/1232 (44.7)	41/130 (31.5)
Axial structural damage	1/6 (16.7)	16/50 (32.0)	43/112 (38.4)	37/122 (30.3)
Inflammatory bowel disease/uveitis	0/7 (0)	5/58 (8.6)	7/150 (4.7)	7/175 (4.0)
Ischaemic cardiomyopathy/stroke	2/9 (22.2)	0/61 (0)	14/159 (8.8)	11/177 (6.2)
Diabetes mellitus / dyslipidaemia	1/9 (11.1)	8/29 (27.6)	44/159 (27.7)	38/181 (21.0)
Obesity	2/6 (33.3)	16/53 (30.2)	39/122 (32.0)	58/147 (39.5)
Polyarticular PsA	7/8 (87.5)	49/60 (81.7)	111/157 (70.7)	11/178 (62.4)
Dactylitis	1/6 (16.7)	13/55 (23.6)	38/148 (25.7)	52/175 (29.7)

Data are expressed in numbers and percentages.

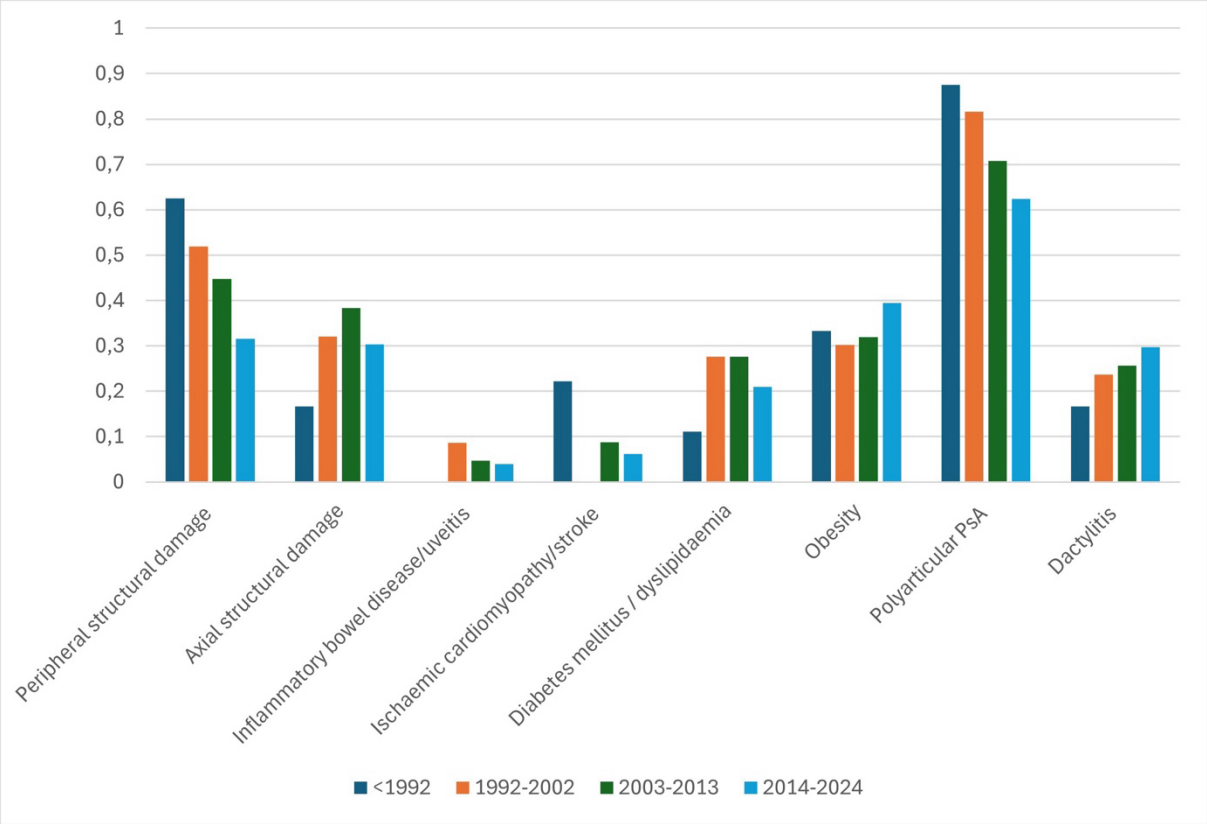

Figure 4: Evolution of phenotypes depending on the year of diagnosis

V. Discussion

Our study found that 22.3% of patients with D2T PsA and 2.2% of patients with refractory PsA were among the PsA population. The prevalence of patients with D2T PsA in our study falls within the range of those previously published (33.9% in the Perrota *et al.* study (10), 11.3% in the Philippoteaux *et al*. study (11), and 16.6% in the Vassilakis *et al.* study (12)).

Regarding the potential risk factors, ischaemic cardiomyopathy and fibromyalgia were found to be at elevated risk of developing D2T PsA. For patients with dactylitis at baseline, this seems to be a protective factor against developing a D2T form.

Ischaemic cardiomyopathy

The present study has identified an association between the presence of ischaemic cardiomyopathy and the risk of developing D2T PsA in patients. To our knowledge, this is the first time this factor has been identified.

Nevertheless, this phenomenon may also be explained by the fact that the presence of ischaemic cardiomyopathy or major adverse cardiovascular events (MACE) is considered a contraindication to the introduction of certain b/tsDMARDs. The results of the ORAL Surveillance study (19) led to recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency's (EMA) to use JAK inhibitors in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular issues (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer (20).

As a result, the therapeutic arsenal is limited for some patients.

Fibromyalgia, depression and anxiety

Regarding fibromyalgia, our study demonstrated a correlation between the presence of fibromyalgia and the probability of developing D2T PsA.

Evidence for this association has been demonstrated in several previous studies. The prevalence of this condition is estimated to range from 15% to 36% among patients diagnosed with PsA (22), with a greater proportion of female patients having a high number of tender joints (23). In instances where it is present, it poses a significant challenge to patient management. Patients can develop nociplastic pain, which is different from the inflammatory pain, and thus not controlled by DMARDs. Despite the absence of any signs of activity, this may result in an elevated level of rheumatic activity indices, an inaccurate estimation of the clinical presentation, false conclusions, failure to achieve the minimal level of activity, and a deterioration in quality of life (24).

Depression and anxiety in PsA are more frequent than in the general population. Their prevalence is estimated to be approximately 9-22% and 15-30%, respectively (24). These two conditions could have a significant impact on disease evaluation by the patients. In our study, the analyses did not reveal any association between anxiety, depression and the risk of evolving toward a D2T PsA. However, it has since been established that this parameter is challenging to evaluate and is not always given due consideration, which complicates interpretation in practice (24).

Dactylitis

Regarding dactylitis, the findings indicated that it possessed a protective effect against the development of D2T PsA.

This should be considered in the context of current recommendations for managing patients diagnosed with dactylitis. In France, for patients with dactylitis attributed to PsA who do not respond to symptomatic treatment, targeted therapy should be considered (13). In the United Kingdom, a targeted therapy is indicated when there is an inadequate response or intolerance to a csDMARD.

Consequently, it can be hypothesised that within this predominantly French cohort, the presence of dactylitis may act as a protective factor, attributable to a more aggressive management of the condition from the outset, with the prescription of a targeted therapy.

Patients with refractory PsA

Our study revealed a very low proportion of patients considered refractory.

We defined refractory patients as those resistant to all therapeutic classes, which may be considered a stringent definition. As the sample was too small, no statistical analysis could be carried out.

Haberman *et al*. chose to use a definition of failure of ≥ 4 b/tsDMARDs in a cohort of 960 patients from a North American tertiary centre (25). They were more likely to be female, obese, and have higher rates of axial involvement and depression, along with higher active disease activity.

Other factors

In our study, certain factors were found to be non-predictive of D2T PsA or refractory PsA, despite their description in the literature.

There is currently no consensus on the question of obesity as a risk factor for progression to D2T PsA. Research has indicated that patients diagnosed with PsA who have a higher BMI are less likely to achieve remission or minimal disease activity (26). This observation was confirmed in the Perrota *et al.* cohort (10), where it was identified as a risk factor for D2T PsA. However, this finding was not confirmed in the cohort of Philippoteaux *et al* (11). This was also the case for our study, despite a higher representation in patients with D2T PsA compared to those with nD2T PsA. In patients with refractory PsA, the proportion of obese patients was higher than in patients with a normal BMI.

Axial involvement is estimated to affect around 25-70% of PsA patients (27). Only 5% of PsA patients have a purely axial presentation, the majority having a polymorphic presentation (27). This reinforces the heterogeneity of the clinical presentation and the complexity of management strategies.

In our study, axial was not associated with a D2T PsA, on the contrary to Philippoteaux *et al.* (11) and Vassilakis *et al.*(28). It should be mentioned that the definition of axial involvement in PsA differs among studies (27, 28) and a broadly accepted definition is still awaited (30).

Treatments

Therapeutic strategies were broadly similar between the two countries. This is consistent with the development of new molecules during the study. In France, ustekinumab was approved in 2015 and secukinumab in 2018. Before the approval of these drugs, some patients were treated with IL6 inhibitors (tocilizumab, sarilumab) or CD20 inhibitors (rituximab) due to failure or contraindications to approved molecules.

Comparison between the English and French healthcare systems

The study also enabled a comparison to be made between the English and French systems.

b/tsDMARD initiation is approved after the failure of one csDMARD in France, whereas it is approved after the failure of two csDMARDs in the UK. The number of b/tsDMARDs is reimbursed regarding the county, whereas in France they are fully covered.

Consequently, the proportion of patients with D2T PsA in the UK is considerably lower than that of French patients when using the exact definition. We have observed that for our population, the initial prescription was primarily a TNF inhibitor, followed by a 2nd TNF inhibitor. Thus, if we follow the definition proposed by Philippoteaux *et al.* (11), the proportion of patients resistant to two molecules of a different therapeutic class within two years is very low. Only nine patients out of 112 had received at least 4 lines of treatment.

As for refractory PsA patients, no patient at the Oxford centre could be considered refractory, as none of these had received all four therapeutic classes.

Evolution of phenotypes

Regarding the phenotypes over the years, we noticed that structural peripheral involvement is decreasing. This is probably linked to the fact that patients are better screened as soon as they are diagnosed, and access to b/tsDMARDs is earlier, preventing an eventual structural evolution (31) (32).

However, we noticed that the cardiovascular burden persists, which could be partially explained by the high proportion of obesity among PsA patients. This is consistent with the literature (33).

Strengths of our study

This study is one of the first to focus on a large multicentre binational population. The number of patients included is close to the biggest published from the Greek cohort (12).

Using the data of patients from two healthcare systems with different conditions of approval for b/tsDMARD increased the external validity of our study. We only included patients with a follow-up of at least five years or more to have robust statistical analysis to determine predictor factors.

Limitations of our study

Nevertheless, our study has several limitations. The retrospective nature of the study was a potential limitation with a significant lack of data, leading to a decrease of power. The management of PsA is complex due to its heterogeneity and lacks clear recommendations. Follow-up was different for each patient, in terms of imaging, biology and evaluation criteria.

Additionally, there is a lack of a consensual definition of D2T PsA. We have used the definition of D2T PsA as defined in the study by Philippoteaux *et al*.(11), but EULAR and GRAPPA are developing alternative definitions. Furthermore, certain criteria in the definition could not be taken into account, such as DAPSA. Very few patients had activity scores completed, and these could not be applied to our population.

For the refractory patient population, a standardised definition is yet to be established. It is conceivable that such definitions would enable the same data to be used in the studies, allowing them to be compared.

In conclusion, this retrospective binational study found that fibromyalgia and ischaemic cardiomyopathy are potential risk factors for D2T PsA, whereas dactylitis appears to be a potential protective factor for D2T PsA.

This needs to be adapted with a consensual definition of patients with D2T PsA, thus enabling clinicians to identify patients at risk of progressing to D2T PsA and adapt treatment strategies at baseline.

VI. Discussion Générale

Notre étude a mis en évidence que parmi la population PsA, 22,3 % des patients atteints de D2T PsA et 2,2 % des patients souffraient de PsA réfractaire. La prévalence des patients atteints de D2T PsA dans notre étude se situe dans l'intervalle de prévalences publiés précédemment (33,9 % dans l'étude de Perrota *et al* (10), 11,3 % dans l'étude de Philippoteaux *et al* (11) et 16,6 % dans l'étude de Vassilakis *et al* (12)). En ce qui concerne les facteurs de risque potentiels, il a été constaté que la cardiopathie ischémique et la fibromyalgie étaient associées un risque de développer un D2T PsA. Pour les patients présentant une dactylite au diagnostic, cela semble être un facteur protecteur contre l'évolution vers une forme D2T PsA.

Cardiopathie ischémique

L'étude a identifié une association entre la présence d'une cardiomyopathie ischémique et le risque de développer un D2T PsA chez nos patients. A notre connaissance, c'est la première fois que ce facteur est identifié.

Néanmoins, ce phénomène peut également s'expliquer par le fait que la présence d'une cardiomyopathie ischémique ou d'événements cardiovasculaires majeurs (MACE) est considérée comme une contre-indication à l'introduction de certains b/tsDMARDs. Les résultats de l'étude ORAL Surveillance (19) ont conduit le Comité pour l'évaluation des Risques en matière de Pharmacovigilance (PRAC) de l'Agence européenne des médicaments (EMA) à recommander l'utilisation des inhibiteurs de JAK chez les patients suivants uniquement en l'absence d'alternatives thérapeutiques appropriées : les personnes âgées de 65 ans ou plus, celles présentant un risque

accru de problèmes cardiovasculaires majeurs (tels que crise cardiaque ou accident vasculaire cérébral), celles qui fument ou qui ont fumé pendant longtemps dans le passé et celles présentant un risque accru de cancer (21). L'arsenal thérapeutique est donc limité pour certains patients.

Fibromyalgie, dépression et anxiété

En ce qui concerne la fibromyalgie, notre étude a démontré une corrélation entre la présence de fibromyalgie et la probabilité de développer un D2T PsA.

Cette association a été démontrée dans plusieurs études antérieures. La prévalence de cette pathologie est estimée entre 15 et 36 % parmi les patients diagnostiqués avec un PsA (22), avec une plus grande proportion de patientes présentant un nombre élevé d'articulations douloureuses (23). Dans les cas où elle est présente, elle pose un défi important à la prise en charge du patient. Les patients peuvent développer des douleurs nociplastiques, différentes de la douleur inflammatoire, qui n'est donc pas contrôlée par les DMARD. Malgré l'absence de tout signe d'activité, il peut en résulter un niveau élevé des indices d'activité rhumatismale, une mauvaise estimation de la présentation clinique, des conclusions erronées sur l'incapacité à atteindre le niveau d'activité minimal et une détérioration de la qualité de vie (24).

La dépression et l'anxiété sont plus fréquentes dans le PsA que dans la population générale. Leur prévalence est estimée à environ 9-22 % et 15-30 % (23) pour chacune. Leur présence peut avoir un effet non négligeable sur l'évaluation de l'activité de la maladie par les patients. Dans notre étude, les analyses n'ont pas révélé d'association entre l'anxiété, la dépression et le risque d'évolution vers un D2T PsA. Cependant, il a été établi depuis que ce paramètre est difficile à évaluer et n'est pas toujours pris en

compte, ce qui complique l'interprétation en pratique (24).

Dactylite

En ce qui concerne la dactylite, les résultats semblent indiquer qu'elle a un effet protecteur contre l'évolution vers un D2T PsA.

Ces résultats doivent être replacés dans le contexte des recommandations actuelles sur la prise en charge des patients qui présentent une dactylite au diagnostic. En France, pour les patients atteints d'une dactylite attribuée au PsA qui ne répond pas au traitement symptomatique, une biothérapie doit être envisagée (13). Au Royaume-Uni, une biothérapie est indiquée en cas de réponse inadéquate ou d'intolérance à un csDMARD.

Par conséquent, on peut faire l'hypothèse que dans cette cohorte majoritairement française, la présence d'une dactylite peut agir comme un facteur protecteur, attribuable à une prise en charge plus agressive de la pathologie dès le départ, avec la prescription d'une biothérapie.

Patients réfractaires

Notre étude a révélé une très faible proportion de patients considérés comme réfractaires.

Nous avons défini les patients réfractaires comme étant résistants à toutes les classes thérapeutiques, ce qui peut être considéré comme une définition trop stricte. L'échantillon étant trop petit, aucune analyse statistique n'a pu être réalisée.

Haberman *et al*. ont choisi d'utiliser une définition d'échec de ≥ 4 b/tsDMARDs dans une cohorte de 960 patients d'un centre tertiaire nord-américain (25). Ces patients étaient plus souvent des femmes, obèses et présentaient des taux plus élevés

d’atteinte axiale et de dépression, ainsi qu’une activité active de la maladie plus importante.

Autres facteurs

Dans notre étude, certains facteurs se sont avérés non prédictifs du D2T PsA ou du rhumatisme psoriasique réfractaire, bien qu’ils aient été décrits dans la littérature.

Il n’existe actuellement aucun consensus sur la question de l’obésité en tant que facteur de risque d’évolution vers le PsA D2T. Des recherches ont montré que les patients diagnostiqués avec un psoriasis dont l’IMC est élevé ont moins de chances d’obtenir une rémission ou une activité minimale de la maladie (26). Cette observation a été confirmée dans la cohorte de Perrota *et al.* (10), où elle a été identifiée comme un facteur de risque de D2T PsA. Cependant, cette observation n’a pas été confirmée dans la cohorte de Philippoteaux *et al.* (11).Pour notre population, cette donnée n’a pas été prouvée dans l'analyse, malgré une représentation plus élevée dans le D2T PsA que dans le nD2T. Chez les patients atteints de PsA réfractaire, la proportion de patients obèses était plus élevée que chez les patients ayant un IMC normal.

On estime que l’atteinte axiale concerne environ 25 à 70 % des patients atteints de PsA (24). Seuls 5 % des patients atteints de PsA présentent un tableau purement axial, la majorité d’entre eux ayant un tableau polymorphe. Dans le cas du PsA, la douleur rachidienne est plus souvent moins inflammatoire que dans le cas de la SpA (27). Cela renforce l’hétérogénéité de la présentation clinique et la complexité des stratégies de prise en charge.

Dans la présente population, elle n'était pas associée au D2T PsA, contrairement à Philippoteaux *et al.* (11) et Vassilakis *et al.*(28). Il faut rappeler que la définition de l'atteinte axiale varie selon les études (27,29) et une définition consensuelle est toujours en attente (30).

Traitements

Les stratégies thérapeutiques étaient globalement similaires entre les deux pays. Ceci est cohérent avec le développement de nouvelles molécules au cours de l'étude. En France, l'ustékinumab a été approuvé en 2015 et le sécukinumab en 2018. Avant l'approbation de ces médicaments, certains patients étaient traités par des inhibiteurs de l'IL6 (tocilizumab, sarilumab) ou des inhibiteurs du CD20 (rituximab) en raison de l'échec ou de la contre-indication des molécules sur le marché.

Comparaison entre les systèmes de santé anglais et français

L'étude a également permis de comparer les systèmes anglais et français.

L'initiation d'un b/tsDMARD est approuvée après l'échec d'un csDMARD en France, alors qu'elle est approuvée après l'échec de deux csDMARD au Royaume-Uni. Le nombre de b/tsDMARDs est remboursé en fonction du comté, alors qu'en France, ils sont entièrement pris en charge.

Par conséquent, la proportion de patients atteints de D2T PsA au Royaume-Uni est considérablement plus faible que celle des patients français lorsque l'on utilise la définition. Nous avons observé que pour notre population, la prescription initiale était principalement anti-TNF alpha, suivi d'un second anti-TNF alpha. Ainsi, si l'on suit la définition proposée par Philippoteaux *et al*. la proportion de patients résistants à deux molécules d'une classe thérapeutique différente en l'espace de deux ans est très

faible. Seuls 9 patients sur 112 ont reçu au moins 4 lignes de traitement.

Quant aux patients réfractaires, aucun patient du centre d'Oxford n'a pu être considéré comme réfractaire, aucun d'entre eux n'ayant reçu les quatre classes thérapeutiques.

Évolution des phénotypes

En ce qui concerne les phénotypes au fil des années, nous avons remarqué que l'atteinte structurale périphérique diminuait dans notre étude. Ceci est probablement lié au fait que les patients sont mieux évalués dès le diagnostic, et que l'accès aux b/tsDMARDs est plus précoce, empêchant une éventuelle évolution structurale (27) (28).

Cependant, nous avons remarqué que la prévalence des comorbidités cardiovasculaires restait stable dans le temps, ce qui est en accord avec les données de la littérature (34).

Forces de l'étude

Cette étude est l'une des premières à porter sur une large population binationale multicentrique. Le nombre de patients inclus est proche du plus grand nombre publié dans la cohorte grecque (12).

L'utilisation des données de patients provenant de deux systèmes de santé ayant des conditions d'approbation différentes pour les b/tsDMARD augmente la validité externe de notre étude. Nous n'avons inclus que des patients ayant un suivi d'au moins cinq ans ou plus afin de disposer d'une analyse statistique solide pour déterminer les facteurs prédictifs.

Limites de notre étude

Notre étude présente néanmoins plusieurs limites. La nature rétrospective de l'étude était une limite potentielle avec un manque significatif de données, conduisant à une diminution de la puissance.

La prise en charge du PsA est complexe en raison de son hétérogénéité et manque de recommandations claires. Le suivi était différent pour chaque patient, en termes d'imagerie, de biologie et de critères d'évaluation.

De plus, il n'existe pas de définition consensuelle du D2T PsA. Nous avons utilisé la définition de D2T PsA telle que définie dans l'étude de Philippoteaux *et al*.(11), mais l'EULAR et le GRAPPA développent des définitions alternatives. De plus, certains critères de la définition n'ont pas pu être pris en compte, comme le DAPSA. Très peu de patients avaient des scores d'activité remplis et ceux-ci n'ont pas pu être appliqués à notre population.

Pour la population des patients réfractaires, une définition standardisée doit encore être établie. Il est nécessaire que de telles définitions permettent d'utiliser les mêmes données dans les études, ce qui permettrait de les comparer.

En conclusion, dans cette étude rétrospective binationale, la fibromyalgie et la cardiopathie ischémique se sont révélées être des facteurs de risque potentiels pour le D2T PsA, tandis que la dactylite semble être un facteur de protection potentiel pour le D2T PsA.

Ceci doit être adapté avec une définition consensuelle des patients atteints de D2T PsA, permettant ainsi aux cliniciens d'identifier les patients à risque d'évoluer vers le D2T PsA et d'adapter les stratégies de traitement au départ.

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Titre de la thèse : Étude des facteurs prédictifs du développement d'un rhumatisme psoriasique difficile à traiter chez les patients initiant une première biothérapie

Thèse - Médecine - Lille 2025
Cadre de classement : Rhumatologie
DES + FST/option : Rhumatologie
Mots-clés : rhumatisme psoriasique, difficile à traiter, réfractaires, rhumatisme inflammatoire chronique

Contexte : On manque aujourd'hui de facteurs de risque permettant d'identifier les patients à risques de développer un rhumatisme psoriasique difficile à traiter (D2T PsA). Des définitions GRAPPA/EULAR sont en cours de développement. L'objectif principal de ce travail était de déterminer les facteurs de risque de développer un D2T PsA chez les patients initiant une première biothérapie en utilisant la définition de Philippoteaux *et al*. L'objectif secondaire était de déterminer les facteurs de risque de développer un rhumatisme psoriasique (PsA) réfractaire dans la même population.
Méthode : Une étude rétrospective a été menée dans 3 centres secondaires et tertiaires en France et dans un centre tertiaire au Royaume-Uni. Nous avons inclus des patients d'au moins 18ans, ayant débuté une biothérapie avec un suivi d'au moins 5ans. Le D2T PsA a été défini comme l'échec de ≥ 2 b/tsDMARDs avec des mécanismes d'action différents en moins de 2ans. Le PsA réfractaire a été défini comme l'échec des anti-TNF alpha, anti IL-17, anti IL-23 et des JAKi. Les caractéristiques des D2T PsA ont été comparées à celles des patients non D2T à l'aide de modèles de régression logistique ajustés pour le pays. Les facteurs significatifs de 0,05 ont été introduits dans un modèle de régression logistique multivarié ajusté sur le pays. Les mêmes méthodes ont été appliquées pour comparer les patients atteints de PsA réfractaire à ceux non réfractaire. Néanmoins, l'analyse multivariée n'a pas été réalisée en raison de la taille limitée de l'échantillon.
Résultats : 412 patients ont été inclus : 92 D2T PsA (22,3 % ; IC à 95 %, 18,3-26,7) et 320 non D2T PsA (77,7 %). Les lignes thérapeutiques des patients ont été rapportées de la 1ère à la 6ème ligne. Une proportion plus élevée de patients atteints de D2T PsA présentait une dactylite, une fibromyalgie et une cardiomyopathie ischémique. En analyse multivariée, la fibromyalgie (OR = 2,62 ; IC à 95 % 1,09-6,28) et la cardiomyopathie ischémique (OR = 2,95 ; IC à 95 % 1,04-8,36) ont montré une association avec le risque d'être D2T PsA (OR = 0,49 ; IC à 95 % 0,26-0,94). 9 patients (2,2 %; 95 % CI 1,0-4,1) ont été classés comme réfractaires, sans analyse statistique devant le faible effectif.
Conclusion : Dans cette étude rétrospective binationale, la fibromyalgie et la cardiomyopathie ischémique se sont révélées être des facteurs de risque potentiels pour le D2T PsA, tandis que la dactylite était un potentiel facteur protecteur pour le D2T PsA.

Composition du Jury :

Président : Professeur FLIPO

Assesseurs : Professeur PASCART, Professeure COATES

Directeur de thèse : Docteur LETAROUILLY