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# Adherence to biotherapies and to comorbidities screening recommendations for SpA patients in current practice

Lauriane Vacher

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**ADHÉSION AUX BIOTHÉRAPIES ET AUX RECOMMANDATIONS  
DE PRISE EN CHARGE DES COMORBIDITÉS DES  
SPONDYLOARTHrites EN PRATIQUE COURANTE**

THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

SPÉCIALITÉ : MÉDECINE INTERNE ET IMMUNOLOGIE CLINIQUE

SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

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*[Données à caractère personnel]*

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## Abbreviations

AS : Ankylosing Spondyloarthritis  
ASAS : Assessment of Spondyloarthritis international Society  
ASDAS : Ankylosing Spondylitis Disease Activity Score  
axSpA : axial Spondyloarthritis  
BASDAI : Bath Ankylosing Spondylitis Disease Activity Index  
BASFI : Bath Ankylosing Spondylitis Functional Index  
bDMARDs : biological Disease Modifying Anti Rheumatic Drugs  
bsDMARDs : biosimilar Disease Modifying Anti Rheumatic Drugs  
CVD : Cardiovascular Disease  
CASPAR : Classification Criteria for Psoriatic Arthritis  
CD : Crohn's disease  
CHU : Centre Hospitalo-Universitaire  
CRP : C-Reactive Protein  
csDMARDs : conventional synthetic Disease Modifying Anti Rheumatic Drugs  
DAMPS : Damage Associated Molecular Patterns  
ER : Endoplasmic Reticulum  
ERAP : Endoplasmic reticulum aminopeptidase  
EULAR : European League Against Rheumatism  
HLA-B27 : Human Leucocyte Antigen B27  
IBD : Inflammatory Bowel Disease  
IFN  $\gamma$  : Interferon  $\gamma$   
IL-23 (R) : Interleukine-23 (Receptor)  
KIR : Killer Immunoglobulin Receptor  
LILR : Leukocyte immunoglobulin-like Receptor  
MHC : Major Histocompatibility Complex  
MRI : Magnetic Resonance Imaging  
mSASS : modified Stoke Ankylosing Spondylitis Spinal Score  
NK cell : Natural killer cell  
(n)r-axSpA : (non)radiographic axial Spondyloarthritis  
NSAIDs : Non Steroidal Anti Inflammatory Drugs  
PAMPS : Pathogen Associated Molecular Patterns  
PsA : Psoriatic Arthritis

RA : Rheumatoid Arthritis

SAPHO Syndrome : Synovitis Acne Pustulosis Hyperostosis Osteitis Syndrome

SFR : Société Française de Rhumatologie

SIJ : Sacroiliac joint

SpA : Spondyloarthritis

TCR : T cell Receptor

Th17 : T helper 17

TNF $\alpha$  : Tumor Necrosis Factor  $\alpha$

TNFi : TNF inhibitors

UC : ulcerative colitis

## **I. Introduction**

Spondyloarthritis (SpA) correspond to a variety of chronic inflammatory rheumatic diseases sharing articular and extra-articular manifestations. This disease framework includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel diseases (IBD), undifferentiated spondylitis, and syndrome of Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO syndrome). These varied diseases share common clinical manifestations and genetic origin. Clinical joint involvement is defined by an inflammation; the location of which may be axial and affecting the spine or sacroiliac joint (SIJ), or peripheric, and concerning peripheric joints or entheses. Extra-articular involvement, present in 5 to 10 % of patients, may be ocular, with the presence of uveitis, or cutaneous, with psoriasis, or involve the digestive tract in the context of chronic IBD, such as Crohn's disease (CD) and ulcerative colitis (UC).

### **a. Spondyloarthritis**

#### **1. Epidemiology**

The prevalence of SpA varies according to subtype and geographical area. It ranges from 0.20 % in South-East Asia to 1.61 % in Northern Arctic communities; whereas prevalence of AS is ranged from 0.02% in Sub-Saharan Africa to 0.35% in Northern Arctic communities; and prevalence of PsA from 0.01% in the Middle East to 0.19% in Europe. Prevalence of the other SpA subgroups is difficult to estimate due to a very small number of studies, but it is estimate around 0.0 to 0.2% for reactive arthritis, around to 0.0 to 0.1% for SpA related to IBD, and 0.0 to 0.7% for undifferentiated SpA.(1)

The overall prevalence of SpA was estimated at 0.3% in France in 2001.(2) A retrospective study found lower prevalence in Great Britain, but an increase since the early 2000s (from 0.13%  $\pm$ 0.006 to 0.18%  $\pm$ 0.006), rising predominantly among women and patients aged  $\geq$ 60. By contrast, AS incidence declined initially between 1998 and 2007, followed by a further increase between 2007 and 2017. It may be explained by an improvement in the diagnosis of AS for incidence, and improved patient survival for prevalence. Due to delayed referral to a rheumatologist and diagnosis difficulties, an overall median time from first symptom to rheumatology referral was 4.87 years and 8.31 to diagnosis. This delay was longer in women (6.71) than in men (5.65). (3)

The sex ratio was usually described as 1.5 men to 1 woman, but in recent years it seems to be getting closer to 1:1, with more women being diagnosed, probably because of the use of Magnetic Resonance Imaging (MRI) for the diagnosis of non-radiographic SpA (nr-SpA). (4)

## 2. Physiopathology

Although many factors and mechanisms have been identified, the detailed physiopathology of SpA is still unclear. Recent progress has been made, which has led to a better understanding of risk factors and disease origin.

A familial aggregation of AS in 20 to 30% of patients is observed, with a strong association with uveitis, enterocolopathies, psoriasis, indicating common predisposing factors to the different forms of AS. Genetic studies have made a significant contribution to our understanding of pathology. Human Leukocyte Antigen B-27 (HLA-B27) is a class I major histocompatibility complex (MHC) antigen present in 50 to 90% patients with a SpA, and predominantly in patients with AS (85 to 95% of White, Hispanic and Han Chinese patients but only 50 to 84% in Middle East and North Africa, and in American Black patients). Less than  $\leq$  8% of the general population overall carries HLA-B27. Among them, 5% of HLA-B27 positive individuals in the general population will get SpA.(5) However, the presence of HLA-B27 is also considered as an important factor that is highly associated with the development of AS in Caucasian patients and related for an earlier disease onset and higher family aggregation. Absence of HLA-B27 is related to a higher frequency of peripheral arthritis, dactylitis, and extra-articular manifestations.(6) DESIR cohort also found association between HLA-B27 positive in patients with recent onset AS and axial inflammation (spine and SIJ), radiographic damage of the SIJ, decreased disease activity and lower frequency of psoriasis. It is not associated with physical function and MRI structural lesions of the SIJ.(7)

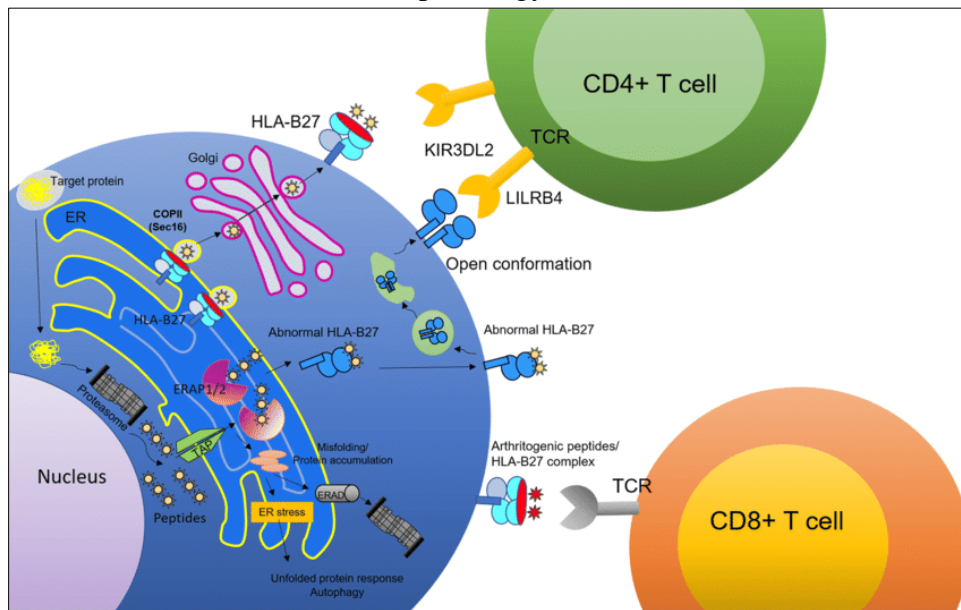
The HLA-B27 family has a high degree of genetic polymorphism. The most common HLA-B27 subtype, HLA-B\*27:05, is distributed ubiquitously worldwide and is strongly associated with AS. Some populations have other HLA-B\*27 subtypes, positively associated with AS, or not. Studies show that specific HLA-B27 subtypes also modulate specific AS manifestations, including peripheral joint involvement and uveitis in certain populations. The role that HLA-B27 plays in the pathogenesis of AS is the subject of much investigation. Several mechanisms have been proposed:

- Presentation by HLA-B27 of a peptide imitating a microbial antigen, to the  $\alpha\beta$  T cell receptor (TCR) on CD8+ T cells or to the killer immunoglobulin receptor (KIR) on

natural killer cells (NK cells). Although no specific peptide has been found, AS patients have a reduced cytotoxic CD8<sup>+</sup> T cell profile in their peripheral blood, and a stimulation in the inflamed joint.(8)

- Misfold of HLA-B27 heavy chains in the endoplasmic reticulum (ER) compared to other HLA-B alleles, causing their accumulation, degradation, leads to a proinflammatory unfolded protein response, activates the innate immune response and upregulates proinflammatory cytokines such as interferon gamma (IFN $\gamma$ ) and interleukin (IL)-23, and other cytokines from T helper 17 (Th17) pathway.(9)
- Formation of homodimers from HLA-B27 heavy chains, recognized by KIR and leukocyte immunoglobulin-like receptors (LILR). However, this predisposition is not certain, because of propriety shared by HLA-B27 subtypes not associated with AS.(10)
- Alteration of intracellular signalling pathway by HLA-B27 that causes intracellular bacterial persistence and upregulated cytokine production.(11)
- Recognition of HLA-B27, through the trimolecular complex of HLA-B27 heavy chain,  $\beta$ 2-microglobulin, or of free HLA-B27 heavy chains or HLA-B27 homodimers, by the TCR on CD4<sup>+</sup> T lymphocytes, generating an autoimmune response.(12)
- Alteration of gut microbiomes, noticed in HLA-B27–positive individuals, which influences disease susceptibility.(13)

Figure 1 – Proposed pathological roles of HLA-B27, adapted from A. Nakamura, *Seminars in Immunopathology*, 2021

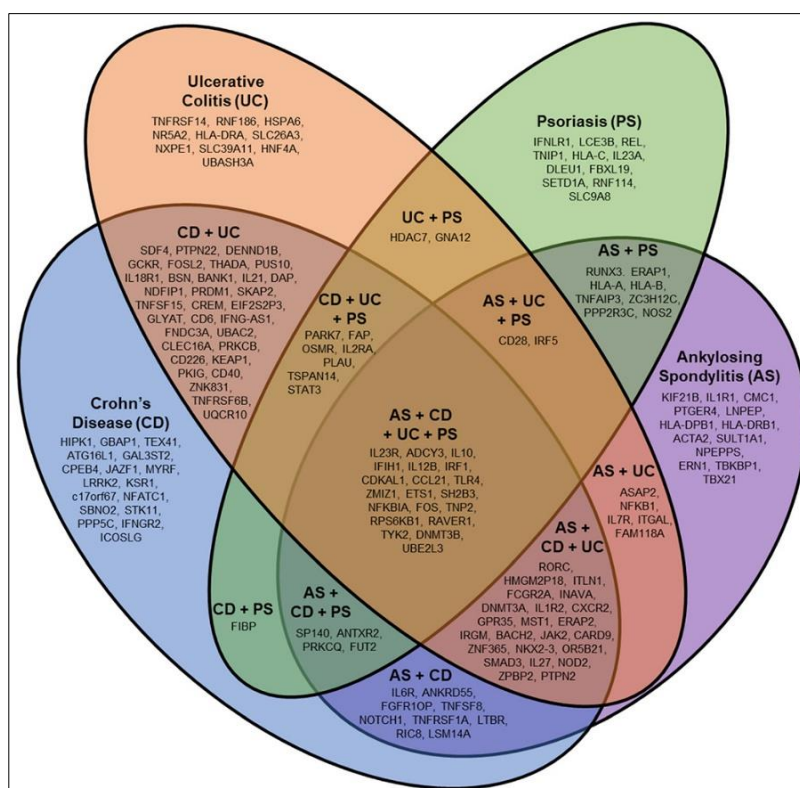


*TAP : Transporter associated with antigen processing ; ERAD : Endoplasmic Reticulum Associated Protein Degradation ; COPII : Coat Protein Complex II.*

Some studies have identified and characterized the role of one hundred susceptibility genes or loci outside the MHC locus genes. Some of them are associated between AS, CD, UC, and psoriasis. Other important genes are those coding for endoplasmic reticulum aminopeptidase (ERAP1 and ERAP2) and IL23 receptor (IL23R). ERAP corresponds respectively to a metallopeptidase that trims proteins during presentation to type 1 HLA and to the plasma cell receptor of a key cytokine implicated in the Th17 pathway.



Figure 2 – Susceptibility genes for AS, Crohn's disease, ulcerative colitis, and psoriasis, adapted from M Hwang, Clin Rheumatol, 2021

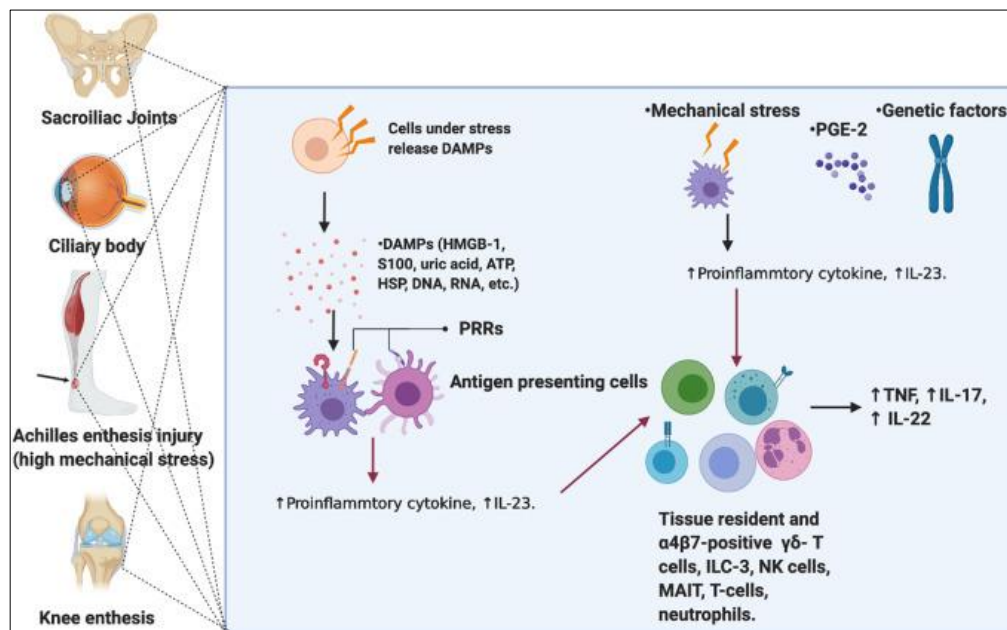


On the other side, gut involvement is frequent in patients with AS, explaining that intestinal microbiome could participate to pathologic mechanism, especially in those who are already genetically susceptible. The inoculation of commensal bacteria such as *Bacteroides vulgatus* into transgenic animals contributed to the development of arthritis. Moreover, the transfer of the HLA-B27–transgenic rats from their sterile environment to a conventional rat colony led to the development of SpA symptoms.(14) Additionally, patients with AS have increased gut permeability, which exposes more potentially pathogenic gut microbes, with their Pathogen-Associated Molecular Patterns (PAMPs) and changes immune profile. For example, Paneth cells are specialized secretory host-defence epithelial cells, and secrete IL-23, able to activate IL-23 responsive cells. These activated cells recirculate from the gut to sites of inflammation in SpA pathogenesis.(15) Clinical example is reactive arthritis, appearing a few weeks after intestinal or genital microbiologic infection, and presence of bacterial antigens in the joint fluid.

Besides, the role of key cytokines such as Tumor Necrosis Factor (TNF-  $\alpha$ ) and IL-2, and the significant impact of biomechanical factors on enthesitis and synovitis has been

demonstrated.(16) In case of micro-trauma and mechanical stress, the enthesis produces Damage Associated Molecular Pattern (DAMPs) and neo-vascularisation from the bone and underlying tissue. This leads to inflammatory lesions following repeated and significant movements. SpA could be linked to an increased susceptibility to mechanical stress and a failure to resolve inflammation.

Figure 3 – Enthesitis based model, in early phase of SpA, adapted from K. Sharif, Rheumatology, 2020

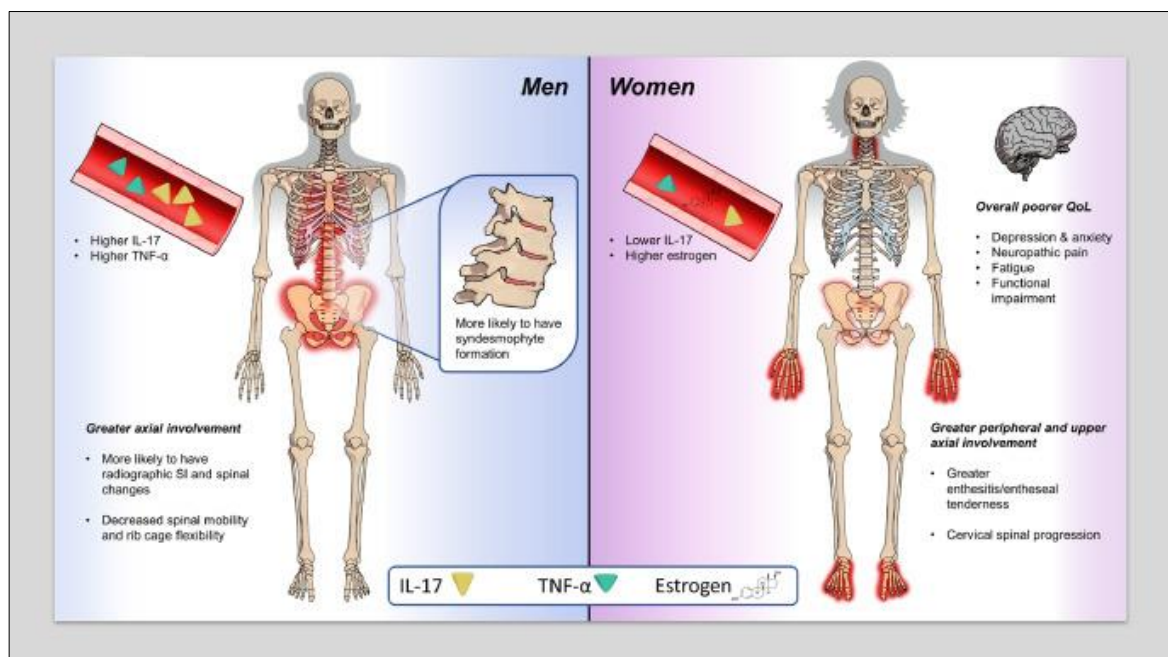


*HMGB-1 : High Mobility Group Box 1 protein ; ATP : Adenosine Triphosphate ; HSP : Heat Shock Proteins ; DNA : Deoxyribonucleic acid ; RNA : Ribonucleic acid ; PRR : Pattern Recognition Receptors ; PGE-2 :Prostaglandin E2 ; ILC-3 : Type 3 Innate Lymphoid cells ; MAIT : Mucosal-associated invariant T cell*

Despite the equivalent prevalence of HLA-B27 between men and women, AS affects more men than women (approximately 2:1 ratio), but not nr-axSpA, where an equal proportion of men and women, or more women than men, is described.(17) In SpA, gender difference exists in terms of age, type and severity of clinical manifestations and response to treatment. AxSpA men have more radiographic damages compared to women, who have a longer diagnostic delay, higher disease activity, and a lower efficacy of treatment. Independently of radiographic damage, AS men have a better quality of life over time.(18,19) Concerning clinical AS manifestations, women usually have more peripheral arthritis, dactylitis, and enthesitis

compared to men.(20) Genetic polymorphism is described with shared gene expression patterns in men and women, although men showed additional variations in gene expression.(21) The same study showed that men with AS had higher levels of IL-17, TNF- $\alpha$ , and IL-18 and greater number of Th17 cells in peripheral blood than woman and controls, whereas IL-6 levels are elevated in the blood of women with AS. Moreover, hormonal differences could play a role. In basic research, development of inflammatory arthritis was suppressed in SKG mice (who harbours a point mutation in the ZAP-70 gene yielding reduced T-cell receptor (TCR) signalling, develops multi-organ inflammation under microbial influence), treated with 17 $\beta$ -oestradiol and expression of the inflammatory cytokines TNF- $\alpha$ , IFN- $\gamma$ , IL-6, and IL-17A were all significantly reduced.(22) The differences observed in men are probably due to genetic factors predisposing to AS development, and to immunological and lifestyle differences.

Figure 4 – Differences between men and women with AS, adapted from G.C. Whright, Semin Arthritis Rheum, 2020



Furthermore, environmental factors are added, such as smoking, a sedentary lifestyle and obesity. Smoking may play a role in disease activity and the structural evolution of SpA. In a Chinese study, patients who were active smokers had significantly more active AS, and lower functional capacity scores, even though biological inflammation was not higher. Its role could lie on epigenetic modification by DNA methylation. In terms of lifestyle, patients who engaged

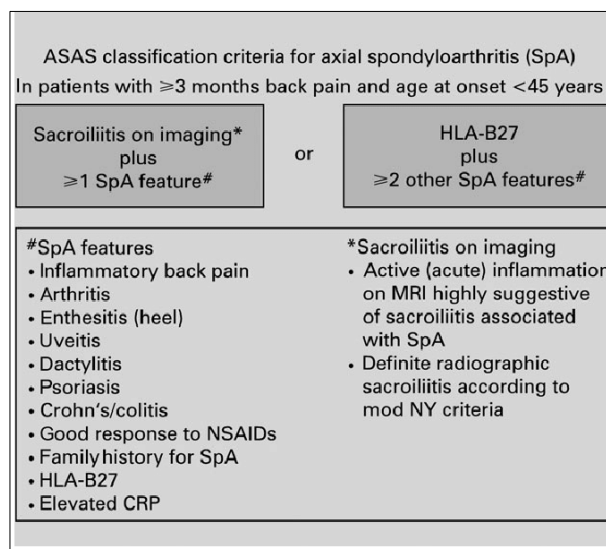
in regular physical activity showed a reduction in disease activity, and an increase in their quality of life and physical capacity.(23)

Overall, it remains unclear how interactions between genes, microbes, mechanical stress, gender, and other environmental and lifestyle factors predispose patients to the development of AS. The exact mechanisms are complex and multifactorial.

### 3. Diagnosis

The diagnosis of SpA is based on a range of clinical, biological, and radiological factors, the definition of which has evolved considerably in recent years. The presence of radiological sacroiliitis used to be an essential criterion for a diagnosis of AS according to the modified New York criteria. In view of the need to identify early forms of SpA in order to prevent a deteriorating course, new definitions have emerged, in particular nr-SpA, with the presence of sacroiliitis (diagnosed by MRI) and/or the presence of the HLA B27 antigen.

Figure 5 – ASAS Criteria for SpA classification, 2009



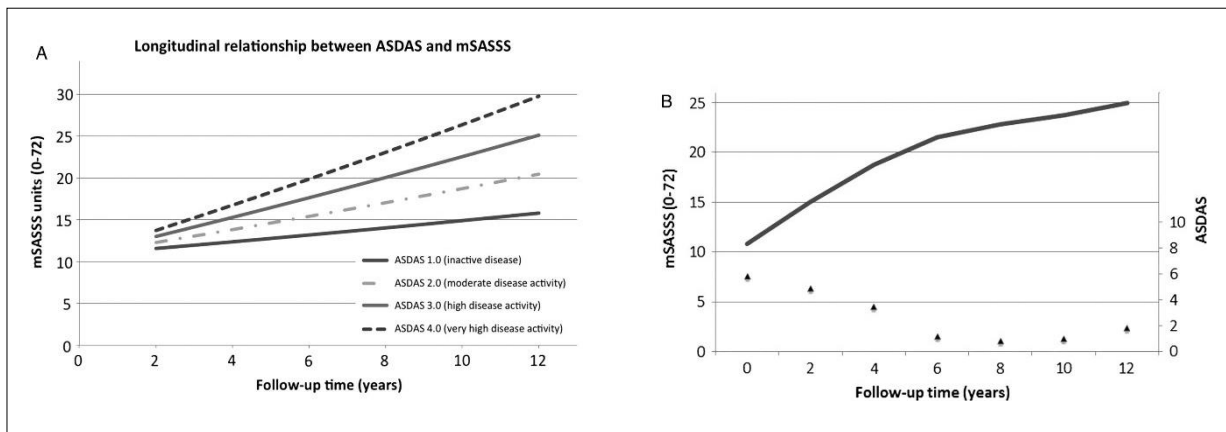
The new classification approach has also differentiated between the two predominant manifestations of SpA, axial and peripheral. The basis of the new classification is the shared features of SpA, such as sacroiliitis, arthritis and enthesitis, as well as common genetic markers and a positive family history.

In addition, extra-articular manifestations may be part of different diseases. For example, psoriasis is included in the CASPAR score for the classification of psoriatic arthritis, as well as in the ASAS score.

#### 4. Evolution

Disease-related inflammation is an important risk factor for prognosis and progression of structural damage. In the study conducted by Sofia Ramiro and al., based on the OASIS cohort, which followed 217 patients with axial spondylitis for 12 years, the influence of high disease activity on the radiographic progression of patients was demonstrated, as shown below (figure 6).(24) A greater impact of disease activity on radiographic progression was also found in the earliest phase of the disease.

Figure 6 – Longitudinal relationship between ASDAS and mSASSS, adapted from S. Ramiro, Ann Rheum Dis, 2014

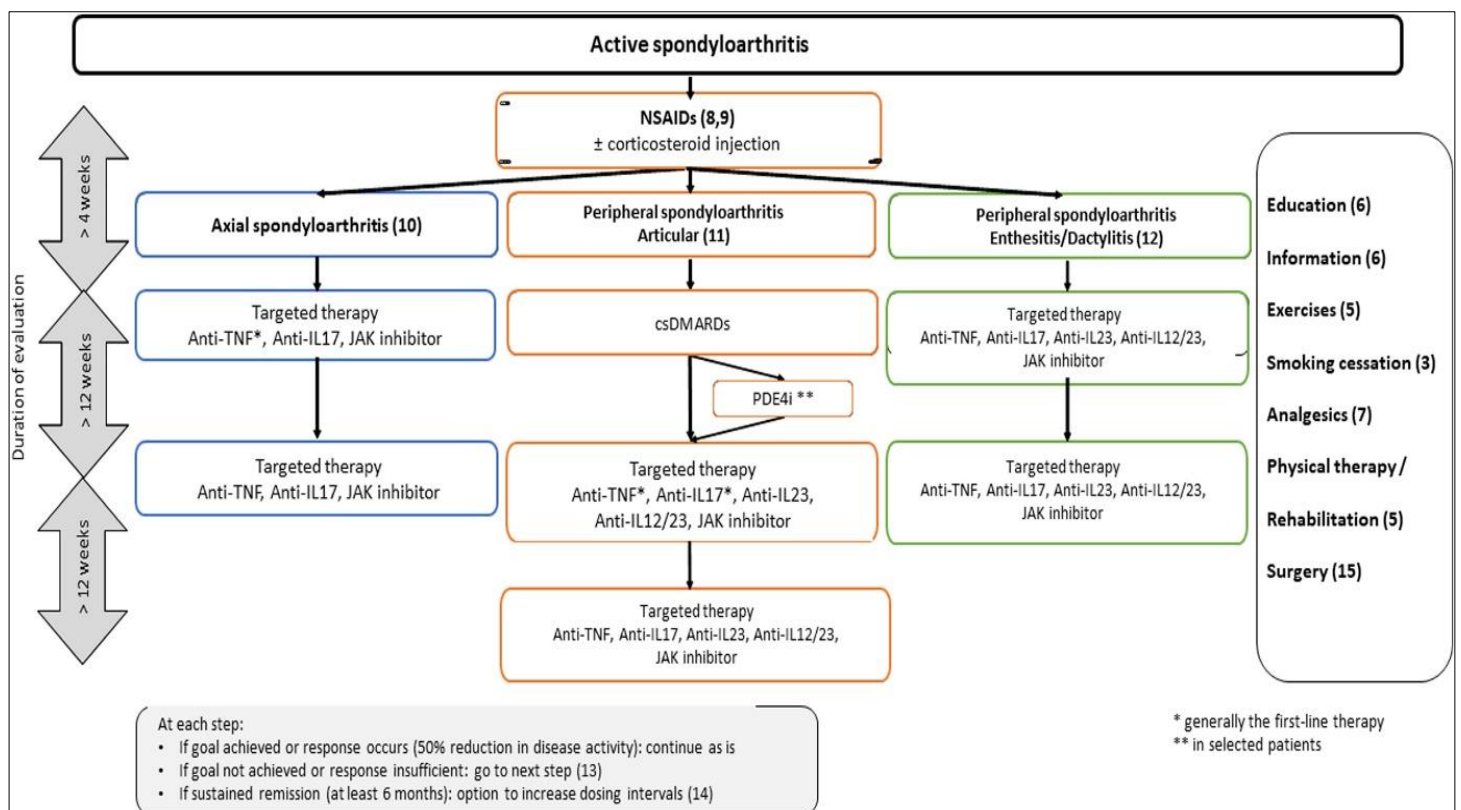


#### 5. Therapeutics

Therapeutic management depends on the clinical phenotype of SpA, as well as the extra-articular manifestations. It requires multidisciplinary collaboration with general practitioners, rheumatologists, as well as other health professionals. The aim is to limit the social and professional impact of the disease. By reducing chronic inflammation, the progression of structural damage is reduced, as cardiovascular damage. The main therapeutic objective is therefore to achieve clinical remission, or failing that, the lowest possible level of activity, defined by an Ankylosing Spondylitis Disease Activity Score (ASDAS) of less than 1.3.

The French Society of Rheumatology has recently published new recommendations for the management of SpA, including pharmacological and non-pharmacological measures, as well as treatment modalities based on the dominant phenotype and extra-articular manifestations.(25) NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are also the first-line pharmacological treatment for the different presentations. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as Sulfasalazine, Methotrexate and Leflunomide, may be indicated in refractory forms of peripheral arthritis, but are not indicated in isolated axial and enthesitis. Sometimes local corticosteroid injections may also be indicated. If the conventional treatment response is inadequate, biological and/or targeted synthetic DMARD should be considered. Clinical phenotype and the presence of extra-articular manifestations are the main parameters which influence DMARD prescription as shown in figure 6.

Figure 6 – Overall treatment strategy to spondyloarthritis, adapted from SFR recommendations, JBS, 2022



The treatment of axSpA has been revolutionised by the introduction of biological agents targeting TNF $\alpha$ , IL-17 or IL-23. These cytokines are crucially involved in the pathophysiological process of the disease. Biotherapies have shown significant clinical efficacy, particularly in terms of pain, physical function, and quality of life. In the short term, biologics have been shown to have no effect on the process of new bone formation but may slow the rate of radiographic progression in the long term. One study also showed that a delay in starting TNFi drugs was associated with greater structural progression, although the visible effect on structural progression was itself delayed.(26) Early treatment targeting most at risk patients most could therefore be of interest to prevent the occurrence of radiological lesions and the associated loss of function.

Although bDMARDs have been shown to inhibit radiographic progression, the biological mechanism behind this effect is not known. There may be a direct role for inhibition of inflammation. New studies are underway on the direct interaction with the developmental pathways of bone formation (notably via the Wnt and DKK-1 pathways).

## **6. Response to treatment**

Composite scores have been developed to assess response to treatment. For ax-SpA, the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and the ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) are commonly used in clinical practice (Supplemental figures 1 and 2). Clinical remission is defined as a score < 2 on the BASDAI and <1.3 on the ASDAS-CRP. High clinical activity, on the other hand, is defined as >4 on the BASDAI and >2.1 on the ASDAS-CRP. Clinical evolution is also important in assessing response to treatment, with clinical response defined as a 50% or 2-point reduction in the BASDAI score and a 1.1-point reduction in the ASDAS-CRP score. With regard to treatment, clinical improvement at 3 months is required in order to maintain treatment in place, with the initial treatment objective being achieved at 6 months.

BASFI is a functional index which makes it possible to assess the degree of functional impotence of patients suffering from spondyloarthropathies (Supplemental figure 3).

## **b. Comorbidities**

Patients with chronic musculoskeletal diseases are also frequently suffering from comorbidities that may be related to the overall spectrum of the disorder (such as IBD, uveitis or psoriasis), the consequence of chronic inflammation (such as cardiovascular disease), related to therapy (such as gastric ulcer or infection), or just concomitantly by coincidence. The presence of such comorbidities may alter the level of the treatment target, since the risk of aggravating the comorbid condition may outweigh the benefit conveyed by more intensive therapy to achieve the treatment target of the musculoskeletal manifestations.

### **1. Inflammation and comorbidities**

The presence and persistence of a biological inflammatory syndrome, as well as high disease activity (assessed by the ASDAS and BASDAI scores) are also considered to be risk factors for cardiovascular events. The mechanisms underlying the higher risk of cardiovascular disease (CVD) in patients with autoimmune rheumatic diseases are not fully understood. It appears that chronic low-grade systemic inflammation leads to prolonged endothelial activation, accompanied by a pro-thrombotic and pro-coagulant effect. Atherosclerosis is also influenced by other traditional CVD risk factors, including metabolic syndrome, which is higher in these patients. Innate immune pathways, which are dysregulated in these patients, may also play a role in accelerating atherosclerosis.

In the COMORA and COMOSPA studies, Dougados *et al.* found an increase in the prevalence of CVD, infections, and the development of certain malignant tumours in patients with rheumatoid arthritis (RA) and AS. In addition, osteoporotic fractures are more frequently observed in patients with RA and AS and can significantly alter functional prognosis.(27,28) The most important individual comorbidities were hypertension (with a prevalence of 23%), dyslipidaemia (17%) and obesity (14%).(29) It should be noted that, compared with a control population, patients with ax-SpA had a significantly higher prevalence of depression and heart failure (OR of 1.80 and 1.84 respectively). Comorbidities were also associated with higher disease activity, functional impairment and decrease in quality of life, work productivity or mortality.



Screening for cardiovascular disease seems all the more important, given that the risk of cardiovascular mortality in chronic inflammatory rheumatism is 20 to 40% higher than in the general population, due to the associated chronic inflammation. A 2008 retrospective study including 1843 SpA patients found a relative risk of ischaemic heart disease of 1.2 compared with the general population, atherosclerosis of 1.5, peripheral artery disease of 1.6, heart failure of 1.8 and stroke of 1.7.(30) The usual risk factors, such as smoking, diabetes, arterial hypertension, dyslipidemia, are more frequent in patients with SpA. However, they do not explain the increased risk observed, as after adjusting for the usual cardiovascular risk factors, the relative risk of cardiac events is still higher.(31) The determining element which seems to explain the increase in cardiovascular risk is inflammation which plays an important role in all phases of atheroma and potentiates the effect of usual risk factors. In parallel, treatments can affect cardiovascular risk by targeting inflammation, but can also have adverse events. Glucocorticosteroids increase the dyslipidemic profile, whereas NSAIDs increase risk of myocardial infarction.(32)

Beside the increased risk of lung cancer, smoking is a known risk factor for poor prognosis and poorer response to TNFi in AS.(33)

Obesity and overweight are also important comorbidities due to their association with more severe diseases and a poorer response to the efficacy of certain therapies.(33) Management of obesity, with weight loss, allows better management of inflammation and joint symptoms.

A low risk of serious infections was described in patients not exposed to TNFi, between 0% and 0.9%, while the risk of serious infections was also higher in those treated with TNFi, from 0% to 2.9%.(34)

The risk for malignancy between patients with SpA and the general population is comparable.(35) However, SpA patients with IBD may have a greater risk of gastrointestinal cancer. Crohn's colitis and ulcerative are associated with a high risk of colorectal adenocarcinoma, while the risk of small bowel adenocarcinoma in patients with Crohn's enteritis is greatly elevated in comparison with the general population.(36) TNFi have not reported an increased risk for malignant diseases in this population and appears to be similar to IL17 inhibitors.(37,38)

Osteoporosis is strongly associated with spondyloarthritis. In AS, Van der Weijden *et al.* showed a high overall prevalence of 51 to 54% reduction in Bone Mineral Density and 13-16% osteoporosis.(39) The study by Gratacos *et al*, in which loss of bone mineral density in AS was only observed in the presence of persistent disease, strongly suggests that the inflammatory

activity of the disease itself plays a major role in the pathophysiology of the initial bone mineral disorders observed in these patients.(40) In addition to the role of inflammation, sedentary lifestyle could be one of the factors responsible for the initial bone mineral disorders. Several authors have shown that patients with SA had a fourfold risk of fracture over their lifetime compared with unaffected ankylosing spine. The meta-analysis by Westerveld *et al.* reports overall mortality in the 3 months following the fracture of 17.7% in AS.(41)

Anxiety and depression make up a significant proportion of comorbidities, for which there are few current recommendations due to the difficulty of screening and the existence of few standard scores.

The difficulties of managing SpA have recently been highlighted, in a context of frequent associated pathologies such as fibromyalgia, which can be confused with the residual activity of the disease itself and can lead to an overestimation of the disease's activity, leading to over-treatment.

Overall, mortality is increased in patients with SpA, and circulatory disease is the most frequent cause of death. The duration and intensity of inflammation are associated with reduced survival. In order to improve long-term survival in AS, early detection and NSAIDs, as well as screening for cardiovascular risk factors and other associated co-morbidities, are necessary.

## **2. Recommendations**

Given the greater frequency of co-morbidities in inflammatory rheumatic diseases, it is necessary to optimize screening and follow-up. However, in the context of specialised care, medical prevention is sometimes sub-optimal compared with the general population. This is because rheumatic pathology may be given priority, with a tendency to minimise other desirable areas of health, not only by the specialist but also by other health referrers, due to the loss of responsibility within the professionals caring for the patient. In addition, certain comorbidities may themselves have an impact on results. Higher disease activity and higher levels of functional impairment might be indicators of severe disease resulting in the development of comorbidities.(42)

Given the need for better management of co-morbidities in order to prevent cardiovascular risk factors, reduce mortality, limit the functional impact and improve patients' quality of life, EULAR (European League Against Rheumatism) has proposed a summary of screening recommendations for daily practice. An annual assessment of cardiovascular risks in SpA is

proposed, and also a standardized systematic collection of variables to be collected during diagnosis and follow-up for optimal management of axial SpA in daily practice.(43)

Figure 7 – Points to consider for reporting, screening and preventing selected comorbidities in daily practices, adapted from A. Baillet, EULAR initiative, BMJ, 2016

Overarching principles	Mean (SD) level of agreement	
A. Comorbidities such as cardiovascular diseases, malignancies, infections, osteoporosis, peptic ulcer and depression should be carefully assessed and managed in patients with chronic inflammatory rheumatic diseases.		9.8 (0.5)
B. All clinicians including health professionals such as nurses, treating general practitioners and rheumatologists and patients through self-administered questionnaires and self-management programmes play a key role in the screening and detection of comorbidities.		9.5 (0.9)
C. Comorbidities should be subject to a systematic, standardised periodical review (eg, at least every 5 years) for those with a chronic inflammatory rheumatic disease.		9.4 (0.8)
Points to consider	Level of evidence	Mean (SD) level of agreement
<b>Cardiovascular diseases</b>		
1. History of myocardial infarction, pectoris angina, stent, stroke, transient ischaemic attack, heart failure and lower limb peripheral arterial disease should be documented.	5	9.7 (0.5)
2. Cardiovascular risk factors such as smoking status, body mass index, history of hypertension, hypercholesterolaemia, renal insufficiency and HEART-SCORE index should be documented.	1b	9.5 (0.9)
3. Current cardiovascular treatments such as antihypertensive therapy, antiplatelet therapy, diabetes insulin or non-insulin therapies, lipid-lowering agents and anticoagulants should be documented.	5	9.6 (0.7)
<b>Malignancies</b>		
4. History of malignancies should be documented.	5	9.6 (0.8)
5. Screening procedures for malignancy (including mammography, pap smear, visit to a dermatologist, faecal occult blood test, colonoscopy) and for malignancy risk factors (including family history of breast or colon cancer and personal history of inflammatory bowel disease) should be documented.	1b	8.9 (1.4)
<b>Infections</b>		
6. History of tuberculosis should be documented including prior results of chest X-ray, tuberculin skin test, interferon- $\gamma$ release assay and BCG vaccination.	2a	9.8 (0.5)
7. History of serious infections, opportunistic infections and chronic viral infections should be documented.	5	9.6 (0.5)
8. Vaccination status for infections including influenza, <i>Streptococcus pneumoniae</i> , herpes zoster, human papillomavirus, poliomyelitis, diphtheria, tetanus and hepatitis B should be documented.	1b	9.5 (0.7)
<b>Peptic ulcer</b>		
9. History of gastroscopy-proven peptic ulcer should be documented.	5	9.1 (0.9)
10. Risk factors for peptic ulcer such as age >65 years, proton pump inhibitor intake, personal history of complicated ulcer, <i>Helicobacter pylori</i> infection, current use of aspirin, non-steroidal anti-inflammatory drugs, corticosteroids and anticoagulants should be documented	5	9.1 (0.9)
<b>Osteoporosis</b>		
11. History of osteoporotic fracture should be documented.	5	9.5 (0.7)
12. Risk factors for osteoporosis including body mass index <19, physical inactivity, glucocorticoid exposure, alcohol intake, family history of femoral neck fracture, secondary osteoporosis, bone mineral density should be collected and the FRAX global risk should be calculated where applicable.	2b	9.0 (1.2)
13. Current or prior osteoporosis treatments including calcium/vitamin D supplementation, bisphosphonates, strontium ranelate, raloxifene, teriparatide and denosumab should be documented.	5	9.5 (0.7)
<b>Depression</b>		
14. History of depression, current depression and prior screening for depression should be documented.	5	9.0 (1.2)
15. Current treatments for depression should be collected.	5	9.2 (0.9)

An initial study carried out by the Anna Molto *et al.* in 2020 assessed the impact of a consultation to screen patients with axial spondyloarthritis for comorbidities at one year. The patient group who benefited from screening and information on comorbidities were more favourable in their short-term follow-up and management.(44) In addition, effective treatment can lead to an improvement in physical activity, with a consequent reduction in the risk of hypertension, obesity and diabetes, helping to reduce the cardiovascular risk itself. Indeed, the

role of TNFi on comorbidities has been widely demonstrated. There is an improvement in the lipid profile under TNFi treatment, as well as a reduction in insulin resistance. Controversial studies to be reviewed. There is a reduction in the progression of atherosclerosis with long-term TNFi, which may contribute to reducing the cardiovascular mortality risk itself.(45)

There is therefore a parallel to treat patients for their inflammatory pathology in order to reduce the activity of the disease and reduce the inflammation that maintains cardiovascular risk; and managing the patient's co-morbidities in order to prevent the onset of complications and optimise the effect of the treatment.

### **c. Adherence to recommendations and treatments**

Drug adherence is defined by the World Health Organization as the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider. Drug adherence is usually conceived as drug intake with 2 complementary notions: compliance and persistence over time. Threshold of 80% is usually considered for adequate adherence (meaning that more than 80% of the prescribed doses are taken by the patient). However, adherence is a complex outcome measure, which is influenced at different endpoints by miscellaneous parameters such as demographics education, employment, financial income, and health system. Lack of adherence can be either intentional or non-intentional. Adherence to bDMARDs in SpA is moderate over the long-term, with reported rates of adherence at twelve months at 80% (ranging from 71% to 94% across registries), and lower in nr-axSpA patients, with 12-month retention rates at 73% (70%-76%).

Suboptimal patient adherence compromises therapeutic efficacy and could increase disease activity. In consequence, non-adherence may lead to complications and unnecessary treatment switches. Thus, adherence is a key issue in chronic rheumatoid disease, which needs to be integrated into the comprehensive patient care and the factors of non-adherence have to be identified. Lack of adherence to treatments is multifactorial, and a great variability of the results exists in precedent studies, probably because of multiple definition of adherence, measurement methods, and associated factors analysed.(46) In retrospective studies, occurrence of adverse side events, number of previous biologic therapies, female gender, nr-axSpA patients, obesity

and functional disability negatively impacted the persistence on first line TNFi.(47,48) Main predictive factors identified in patient-reported outcomes are persistent pain, treatment history, self-administration of injections, negative beliefs about treatment, and a lack of perceived medical and social support.(49) Patients perceive DMARDs as strong medications with alarming side events that intensify their disease identity. Confidence in medical care, positive experiences with DMARDS among other patients, and an expectation that medications will help maintain participation in life can motivate patients to use DMARDs. Creating a supportive environment for patients to voice their concerns may improve treatment satisfaction, adherence, and health outcomes.(50)

For this reason, adherence should be assessed at each outpatient visit, at least using an open question, to identify risk factors associated with nonadherence. Some questionnaires exist to assess this therapeutic cognizance and adherence, such as Biosecure and CQR19 (Supplemental figures 4 and 5). Patient information and education, and patient/physician shared decision, are key to optimise adherence. Other techniques such as standardised education sessions, motivational interviewing and cognitive behavioural therapy may be useful.(51)

Although systematic comorbidity screening seems time-consuming and difficult to implement in practice, COMEDRA and COMOSPA studies emphasized that systematic comorbidity screening provides a better management of these comorbidities in almost all patients.(52)

#### **d. Study objective**

In rheumatoid arthritis, bDMARDs withdrawal for adverse events is more often observed in patients who did not adhere to recommendations for optimal comorbidity management.(53) The correlation between bDMARD adherence and comorbidities is dramatically missing for SpA patients. We hypothesized that adherence to co-morbidities recommendations would be associated with improved bDMARD adherence in patients with SpA.

**The main objective of the study was to evaluate causes of bDMARDs withdrawal rate of at 12 months in patients with spondyloarthritis.**

## **II. Materials and methods**

### **a. Study population**

This study is a retrospective, monocentric, observational, non-randomised and open-label cohort. It is part of the SCORIC cohort, named « Cohorte monocentrique prospective évaluant l'adhésion des patients aux recommandations de dépistage systématique des comorbidités chez des patients atteints de rhumatismes inflammatoires chroniques sous traitement de fond », that analysed all patients with chronic inflammatory rheumatism (CECIC, IRB : 5891). It is registered in clinicaltrials.gov (NCT05613712). Patients received an information note and signed an informed consent for inclusion. The data used in the description of the population were taken from the hospital charts (Supplemental figure 6).

Eligible patients were recruited since December 2016 by the rheumatology department of the university hospital of Grenoble. They have a diagnosis of chronic inflammatory rheumatic disease according to their rheumatologist and initiate bDMARD. On a day hospital, they receive an initiation consultation of bDMARD, as well as systematic screening for comorbidities.

For this study, patients were included from November 2016 to April 2022. They should be eighteen years or older, with a diagnosis of spondyloarthritis, confirmed by a rheumatologist. They attended a consultation with systematic screening for comorbidities in the day hospital of the rheumatology department of the CHU Grenoble-Alpes and received at least one comorbidity follow-up recommendation. They were able to understand and accept protocol modalities. Exclusion criteria were having difficulties in understanding the French language, disorders of higher functions incompatible with an education program, history of alcoholism, drug addiction, severe psychological problems which could eventually invalidate the patient's adherence to the protocol and the data collected.

#### **1. Demographic and disease-related data**

Besides usual demographic data, gender, age, disease duration, smoking status, we collected at baseline the following disease-related outcomes: axial and/or peripheral involvement, presence of MRI and/or radiological sacroiliitis, HLA-B27 positivity, CRP, BASDAI, BASFI, presence of extra-articular manifestation such as uveitis, psoriasis or IBD.

The following information regarding treatment was also recorded: treatment with csDMARDs, type of bDMARD, line of bDMARD, systemic steroids.

**At 12 months we recorded assessed whether patients were still adherent to their baseline DMARD or whether they withdrew baseline bDMARD.**

## **2. Comorbidity-related recommendations**

During this standardized program, certain information was collected, such as demographic data, validated tests related to chronic inflammatory rheumatic diseases, received treatments or in progress, and information related to screening for comorbidities. These data were evaluated by a rheumatologist and a specialist nurse. The comorbidities were listed according to the recommendations of EULAR and concerned cardio-vascular disease, obesity, infection, cancer, osteoporosis, sleep apnea syndrome and addiction. Patients also benefited from a systematic time of observance carried out by a clinical pharmacist, during which the safety criteria concerning the drugs was checked, and potential barriers to observance were identified. The goal was to provide an optimal pharmaceutical care plan targeting individual characteristics through unintentional adherence and intentional problems. At the end of day hospital, patients received a written report with updated follow-up and screening advice. This same report was also sent to the referring doctors who treat them. The initial consultation data, compliance with the recommendations relating to comorbidities and the evolution of the disease at twelve months were collected in computer files on the Easily software of the Grenoble University Hospital. Data were supplemented by telephone call if information was missing at 12-month follow-up. To limit missing data, each patient could be called up to four times.

**At 12 months we assessed whether patients followed baseline recommendations regarding comorbidity management. Patients were considered adherent to recommendation when they follow  $\geq 80\%$  baseline recommendations.**

### **b. Statistical Analysis**

The subjects were described at inclusion by their age, gender, form of pathology, duration of evolution, presence of HLA-B27, associated pathologies, inflammatory markers, presence of sacroiliitis, validated score index for activity and functionality with BASDAI and BASFI, treatments by csDMARDs, and treatments by bDMARDs. For patients lost to follow-up, impute missing data were made with “recommendations not followed” and “bDMARD

withdrawal”, because recommendations were probably not followed if they stopped their hospital follow-up, and the annual hospital prescription could not be renewed. Descriptive statistical summaries were used to report quantitative parameters, using mean and standard deviation after checking the application conditions or by median and percentiles 25<sup>th</sup> and 75<sup>th</sup>, depending on the distribution of the data. For categorical parameters, numbers and percentages were used.

Quantitative parameters were compared between groups using Student's t test or Mann-Whitney test due to low sample size or when normality was rejected. Qualitative parameters were compared between groups using Chi-square test or Fisher's exact test outside of application conditions. Maintenance of bDMARDs was analysed by Kaplan-Meier curves with a 95% confidence interval and compared with the log-rank test. Integration of explanatory variables was used with the Cox model. Significant variables with univariate analyses have been used for the Cox model. P-values of less than 0.05 were considered statistically significant. No adjustment of statistical threshold for multiple comparisons was made.

Statistical analyses were performed using R++.

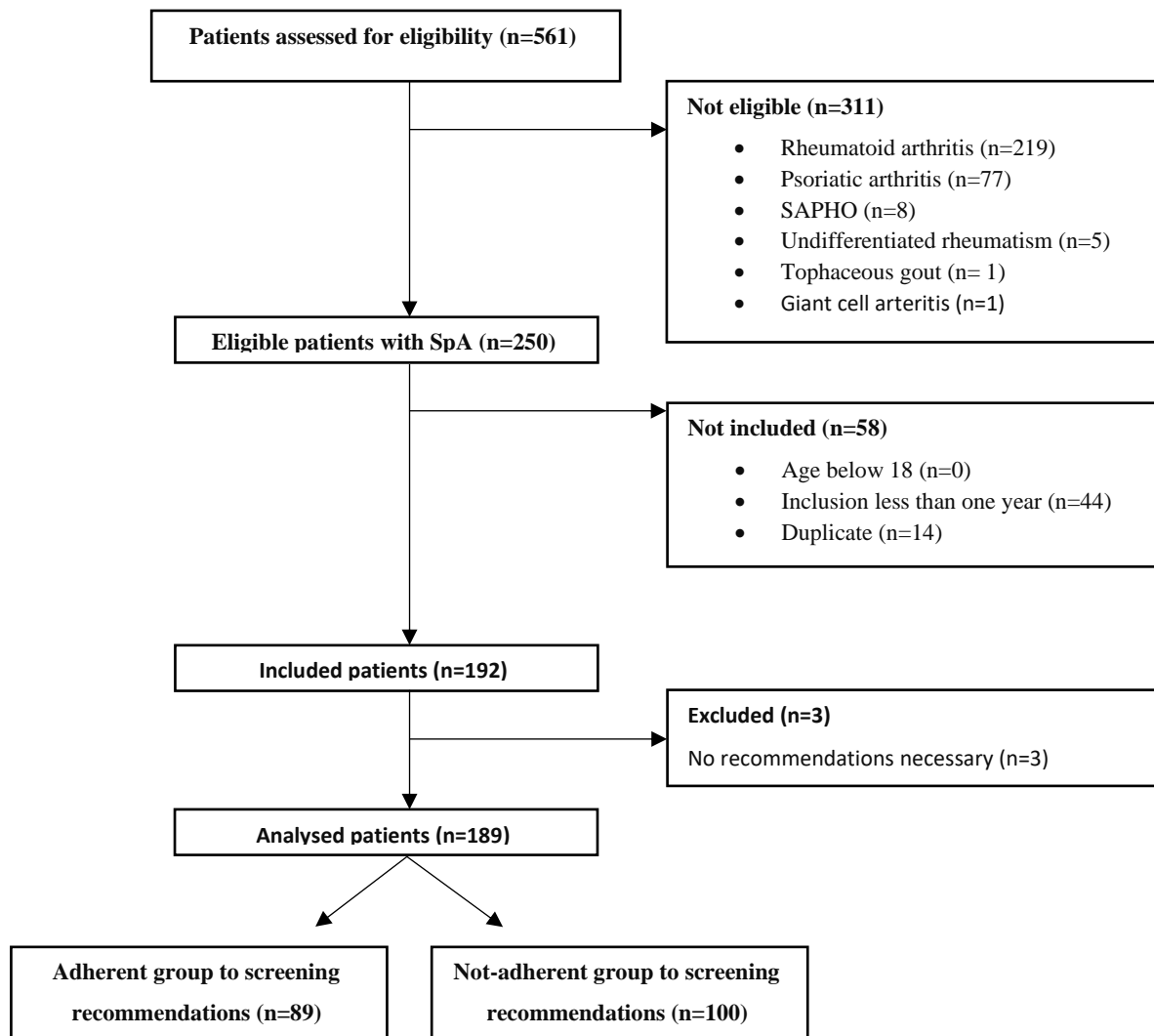
### **III. Results**

#### **a. Study population**

A total of one hundred eighty-nine patients were included in the study, involving hundred patients in the “not-adherent in screening recommendations group” and eighty-nine in “adherent group”. The flow chart is detailed in figure 1.



Figure 8 – Trial flowchart



Demographic of included patients are shown in Table 1. Mean age of the patients was 43 years ( $\pm 13$ ). Most of the SpA patients were male ( $n = 105$ , 56%); mean disease duration was 8 years ( $\pm 10$ ). A total of 87 patients had isolated axial SpA (47%), and 91 patients had both axial and peripheral SpA (49%). Most patients had history of sacroiliitis with 146 patients (80%) and HLA B-27 with 119 patients (67%). Patients had low levels of inflammation with median CRP at 8 ( $\pm 11$ ) mg/L. Mean scores BASDAI and BASFI were respectively 5 ( $\pm 2$ ) and 38 ( $\pm 23$ ). Among 53/189 patients (28%) with extra-articular involvement, 28 (15% SpA patients) had uveitis, 10 (5%) had IBD, 5 (3%) had psoriasis, and 4 (3%) combined damages. A total of 37 patients (20%) had associated csDMARDs, Methotrexate or Sulfasalazine. Concomitant steroids concerned only 14 patients (7%). TNFi were initiated in 138 patients (73%), IL-17 inhibitors in 49 patients (26%) and IL-12/IL-23 inhibitors in 2 patients (1%).

Majority of them were bsDMARDs (n=132/189 patients, 70%); and were on first line of bDMARDs (110/189 patients, 59%).

### **b. Adhesion to recommendations for comorbidity management**

The mean number of recommendations regarding comorbidities at baseline was 4 ( $\pm 2$ ). Cardiovascular recommendations concerned 71 patients (38%). A total of 43 patients (23%) were smoking. Other recommendations in each group are described in Supplemental figure 7. The univariate analysis showed that male patients and current smokers were less likely to follow recommendations with respectively Odds ratio 0.5 CI95% [0.3-0.9] and Odds ratio 0.3 CI 95% [0.1-0.6]. Both parameters remained statistically associated with non-adhesion to recommendations in the multivariate analysis.

Table 1 – Study population

	Non-adherence to screening recommendations n=100 (53%)	Adherence to screening recommendations n=89 (47%)	Overall 189 (100%)	p- value
<b>Gender, Female, n (%)</b>	33 (33%)	51 (57%)	84 (44%)	<b>0.001</b>
Male	67 (67%)	38 (42%)	105 (56%)	
<b>Age (year), mean (SD)</b>	42 (13%)	45 (12)	43 (13)	0.25*
median [Q1, Q3]	42 [32, 52]	43 [36, 54]	43 [34, 52]	
<b>Dis. Duration (year), mean (SD)</b>	9 (11)	7 (9)	8 (10)	0.16
median [Q1, Q3]	6 [1, 12]	4 [1, 10]	5 [1, 11]	
<b>Axial SpA, n (%)</b>	43 (43%)	45 (51%)	87 (47%)	0.63
<b>Peripheral</b>	4 (4/9)	5 (1%)	9 (5%)	
<b>Both axial and peripheral SpA</b>	51 (51%)	40 (47%)	91 (49%)	
<b>Sacroiliitis, n (%)</b>	79 (79%)	67 (46%)	146 (80%)	0.58
<b>HLA B-27 positive, n (%)</b>	67 (56%)	52 (44%)	119 (67%)	0.11
<b>CRP (mg/L), mean (SD)</b>	8 (11)	7 (10)	8 (11)	0.25
median [Q1, Q3]	5 [2, 11]	4 [1, 8]	4 [1, 8]	
<b>BASDAI, mean (SD)</b>	5 (2)	5 (2)	5 (2)	0.63*
median [Q1, Q3]	5 [4, 7]	5 [4, 6]	5 [4, 6]	
<b>BASFI, mean (SD)</b>	39 (23)	36 (22)	38 (23)	0.21
median [Q1, Q3]	39 [22, 56]	32 [19, 46]	37 [20, 55]	
<b>Extra-articular manifestations, n (%)</b>				0.97
None	73 (73%)	63 (70%)	136 (72%)	
IBD	5 (5%)	5 (6%)	10 (5%)	
Psoriasis	2 (2%)	3 (3%)	5 (3%)	
Uveitis	14 (14%)	14 (16%)	28 (15%)	
Psoriasis and uveitis	1 (1%)	1 (1%)	2 (1%)	
IBD and uveitis	0 (0%)	1 (1%)	1 (1%)	
Psoriasis, IBD and uveitis	1 (1%)	0 (0%)	1 (1%)	
<b>csDMARDs, n (%)</b>	20 (20%)	17 (19%)	37 (20%)	1.00
<b>Steroids, n (%)</b>	6 (6%)	8 (9%)	14 (7%)	0.6
<b>bDMARDs mode of action, n (%)</b>				0.65
TNF $\alpha$ inhibitor	70 (70%)	68 (76%)	138 (73%)	
IL-17 inhibitor	29 (29%)	20 (22%)	49 (26%)	
IL-12/23 inhibitor	1 (1%)	1 (1%)	2 (1%)	
<b>bsDMARDs, n (%)</b>	30 (30%)	27 (27/57)	57 (30%)	1.00
<b>1st line of bDMARDs, n (%)</b>	53 (53%)	57 (64%)	110 (59%)	0.11
<b>Cardiovascular recommendations, n (%)</b>	38 (38%)	33 (37%)	71 (38%)	1
<b>Current smokers, n (%)</b>	33 (33%)	10 (11%)	43 (23%)	<b>&lt;0.001</b>
<b>Total number of recommendations,</b>				0.55
mean (SD)	4 (2)	4 (2)	4 (2)	
median [Q1, Q3]	4 [3, 5]	4 [2, 5]	4 [2, 5]	
<b>Adverse events, n (%)</b>	18 (18%)	13 (14%)	31 (16%)	0.56
<b>Primary inefficacy, n (%)</b>	13 (13%)	19 (21%)	31 (17%)	0.17
<b>Secondary inefficacy, n (%)</b>	17 (17%)	11 (12%)	28 (15%)	0.42

\*parametric p-value. Other p-value are non-parametric.

Dis. Duration : Disease duration ; HLA-B27 : Human Leucocyte Antigen B27 ; CRP : C-Reactive protein ;  
BASDAI : Bath Ankylosing Spondylitis Disease Activity Index ; BASFI : Bath Ankylosing Spondylitis Functional

Index ; IBD : Inflammatory Bowel Disease ; cs/bDMARDs : conventional/biological Disease Modifying Anti Rheumatic Drugs ; bsDMARDs : biosimilar Disease Modifying Anti Rheumatic Drugs

### **c. bDMARD withdrawal at 12 months**

The sample was divided into two groups: continuation of bDMARD at 12 months (n=129, 72%) and bDMARDs withdrawal at 12 months (n=53; 28%). Table 3 shows the factors analysed in the univariate study.

The Fisher's test showed that continuation of bDMARDs at 12 months is not correlated with adherence to screening recommendations (odds ratio [OR] 95% confidence interval [CI] 0,5-1,7; p = 0.74). Male gender was significantly associated with more continuation of bDMARD at 12 months (**2,8 OR 1.4-5.3 [95% CI]; p = 0.002**). bDMARD withdrawal was more important with patients included in 2019 (49% of bDMARD withdrawal among them), whereas withdrawal is less important between 21 and 33% in patients included in 2017, 2018, 2020, 2021, 2022 (p = 0.04). Duration of evolution pathology, involvement, presence of HLA B-27 or associated pathologies were not associated significantly with continuation of bDMARD. Majority of patients with sacroiliitis continues bDMARDs (n=101 patients, 71%), and majority of patients also without sacroiliitis continues bDMARDs (n=31 patients, 89%). Systemic inflammation (i.e., baseline CRP level) was not associated with bDMARDs withdrawal. Disease activity at inclusion was associated with bDMARD withdrawal. Disability was not associated with bDMARD withdrawal. Concomitant csDMARDs was not correlated with bDMARD withdrawal. bDMARD mode of action was significantly correlated with bDMARD withdrawal: more patients with introduction of TNF $\alpha$  inhibitor continue their bDMARD (102 patients, 76%), whereas more patients with IL-17 inhibitors or IL-12/23 inhibitor discontinue their bDMARDs at 12 months, respectively 16 patients (33%) and 2 patients (100%); bsDMARDs were not associated with bDMARD withdrawal. Smoking status was not associated with bDMARDs continuation. Total number of recommendations was not associated also with bDMARD continuation.

Primary inefficacy was the most important statistically significant reason for bDMARD withdrawal at 12 months (**OR 0.007-0.08 [95% CI]; p < 0.001**) whereas secondary inefficacy is not correlated with bDMARD withdrawal (**OR 0.3-1.8 [95% CI]; p=0.5**). Occurrence of adverse events was also statistically significant reason for bDMARDs withdrawal (**OR 0.07-0.4 [95% CI]; p<0.001**).

Table 2 – bDMARD adherence at 12 months

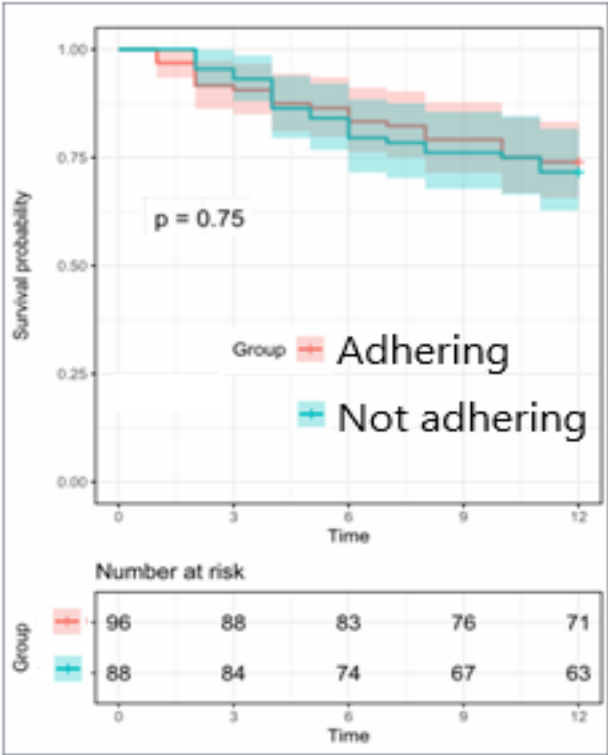
	bDMARDs adherence at 12 months 136 (72%)	bDMARDs withdrawal at 12 months 53 (28%)	Overall 189 (100%)	p-value	OR [95% CI]
<b>Adherence to screening recommendations, n (%)</b>	63 (46%)	26 (49%)	89 (47%)	0.74	[0.5 ; 1.7]
<b>Gender, Female, n (%)</b>	51 (39%)	33 (60%)	84 (44%)	<b>0.002</b>	<b>[0.2 ; 0.7]</b>
Male,	85 (63%)	20 (37%)	105 (56%)		
<b>Age (year), mean (SD)</b>	43 (12)	45 (13)	44 (13)	0.5*	
median [Q1, Q3]	42 [37, 52]	44 [34, 53]	43 [35, 52]		
<b>Dis. Duration (year), mean (SD)</b>	9 (11)	8 (9)	8.28 (10)	0.6	
median [Q1, Q3]	5 [1, 11]	5 [1, 12]	5 [1, 12]		
<b>Axial SpA, n (%)</b>	61 (47%)	22 (42%)	83 (44%)	0.54	
<b>Peripheral</b>	8 (6%)	1 (2%)	9 (5%)		
<b>Both axial and peripheral SpA</b>	63 (48%)	27 (51%)	90 (48%)		
<b>Sacroiliitis, n (%)</b>	101 (78%)	42 (81%)	143 (76%)	<b>0.03</b>	
<b>HLA B-27, n (%)</b>	87 (65%)	28 (53%)	115 (61%)	0.15	
<b>Extra-articular manifestations, n (%)</b>				0.33	
None	97 (75%)	36 (69%)	133 (70%)		
IBD	6 (4%)	4 (8%)	10 (5%)		
Psoriasis	4 (3%)	1 (2%)	5 (3%)		
Uveitis	22 (17%)	6 (12%)	28 (15%)		
Psoriasis and uveitis	2 (1%)	0 (0%)	2 (1%)		
IBD and uveitis	2 (1%)	1 (1%)	3 (1%)		
Psoriasis, IBD and uveitis	0 (0%)	1 (1%)	1 (1%)		
<b>CRP (mg/L), mean (SD)</b>	8 (10)	7 (14%)	8 (11)	0.08	
median [Q1, Q3]	5 [1, 11]	3 [1, 6]	4 [1, 8]		
<b>BASDAI, mean (SD)</b>	5 (2)	6 (2)	6 (2)	<b>0.04*</b>	
median [Q1, Q3]	5 [4, 6]	6 [5, 7]	5 [4, 6]		
<b>BASFI, mean (SD)</b>	37 (22)	40 (23)	38 (23)	0.52	
median [Q1, Q3]	37 [20, 55]	40 [25, 57]	37 [20, 55]		
<b>csDMARDs, n (%)</b>	25 (19%)	11 (22%)	36 (20%)	0.68	
<b>bDMARDs mode of action, n (%)</b>				<b>0.04</b>	
TNF $\alpha$ inhibitor	102 (18%)	32 (62%)	134 (71%)		
IL-17 inhibitor	32 (25%)	16 (31%)	48 (25%)		
IL-12/23 inhibitor	0 (0%)	2 (4%)	2 (1%)		
<b>bsDMARDs, n (%)</b>	42 (32%)	12 (23%)	54 (29%)	0.37	
<b>1st line of bDMARDs, n (%)</b>	82 (63%)	23 (44%)	105 (56%)	0.09	
<b>Current smokers, n (%)</b>	28 (21%)	13 (25%)	41 (22%)	0.55	
<b>Former smokers, n (%)</b>	5 (4%)	1 (2%)	6 (15%)	0.64	
<b>Total number of recommendations, mean (SD)</b>	4 (2)	4 (1)	4 (2)	0.3	
median [Q1, Q3]	4 [2, 5]	4 [3, 5]	4 [2, 5]		
<b>Adverse events, n (%)</b>	12 (9%)	19 (37%)	31 (17%)	<b>&lt;0.001</b>	[0.07 ; 0.4]
<b>Primary inefficacy, n (%)</b>	4 (3%)	28 (54%)	32 (17%)	<b>&lt;0.001</b>	[0.007 ; 0.08]
<b>Secondary inefficacy, n (%)</b>	19 (15%)	9 (17%)	28 (15%)	0.5	[0.3 ; 1.8]

\*parametric p-value ; Other p-value are non-parametric.

Dis. Duration : Disease duration ; HLA-B27 : Human Leucocyte Antigen B27 ; CRP : C-Reactive protein ; BASDAI : Bath Ankylosing Spondylitis Disease Activity Index ; BASFI : Bath Ankylosing Spondylitis Functional Index ; IBD : Inflammatory Bowel Disease ; cs/bDMARDs : conventional/biological Disease Modifying Anti Rheumatic Drugs ; bsDMARDs : biosimilar Disease Modifying Anti Rheumatic Drugs

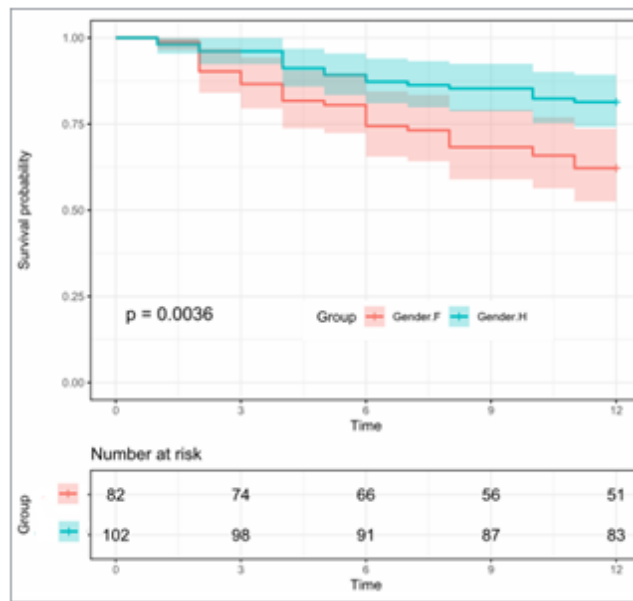
We showed in the univariate Cox analysis that bDMARDs adherence was similar for patients who adhere screening recommendations and those who did not adhere screening recommendations (log-rank  $p=0.75$ , fig 9).

Figure 9 – Kaplan-Meier curve of bDMARDs withdrawal at 12 months according to adherence to screening recommendations



The rate of bDMARDs continuation was greater among men who adhere screening recommendations than among women who adhere to screening recommendations ( $p=0.025$ , figure 10).

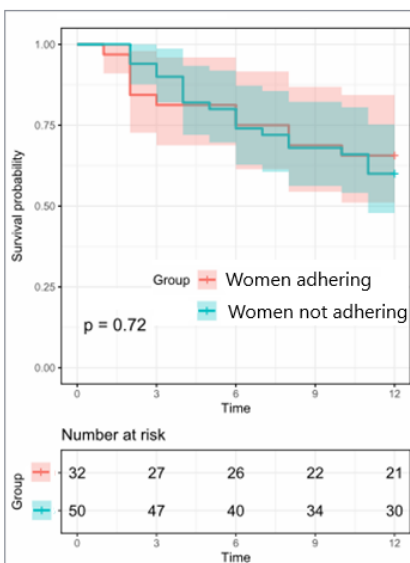
Figure 10 – Kaplan-Meier curves of bDMARDs withdrawal at 12 months according to gender



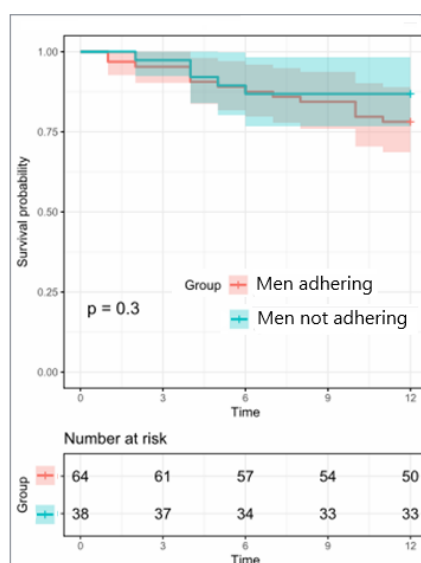
In the univariate Cox analysis (figure 11), male gender significantly prevented bDMARDs discontinuation, **Hazard ratio 0.4 IC95% [0.2-0.7]**. In the multivariate Cox model analysis male gender remained statistically associated with bDMARD adherence, **odds ratio 2.7 CI95% [1.3-5.8], p=0.003** whereas other outcomes associated with bDMARD continuation, i.e. sacroiliitis, disease activity BASDAI>4 and bDMARD mode of action were not statistically significant anymore.

Figure 11 – Kaplan-Meier curves of bDMARDs withdrawal at 12 months according to gender and adherence to screening recommendations

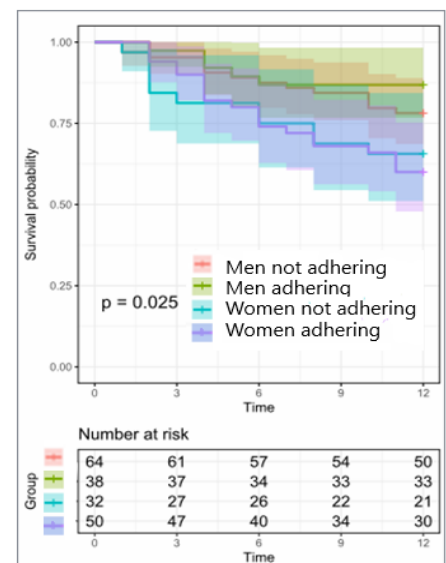
A. Female SpA patients



B. Male SpA patients



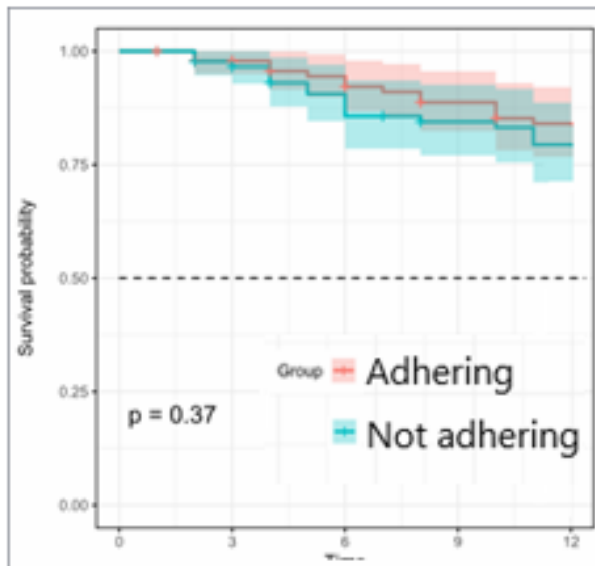
C. Overall SpA patients



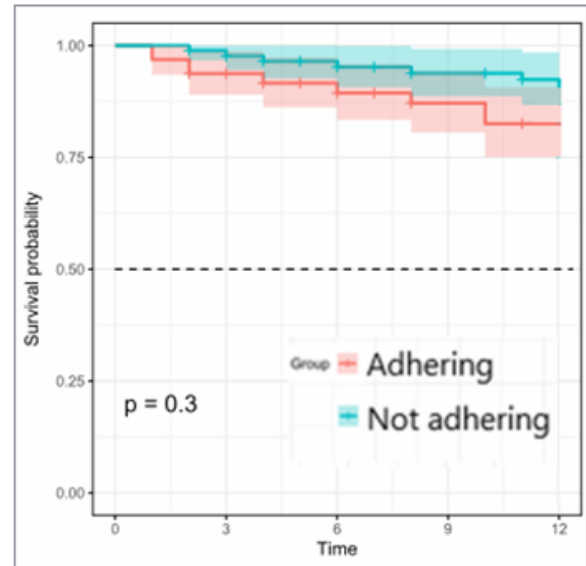
bDMARD withdrawal for either of adverse events or efficacy was not associated with adherence to the guidelines (Figure 13).

Figure 13 – Kaplan Meier curves of bDMARDs withdrawal at 12 months for outcomes of adverse events or inefficacy according to adherence to screening recommendations

A. Adverse events



B. Inefficacy



#### IV. Discussion

Our study overall probability of bDMARDs continuation at 12 month was 72%. This level is consistent with previous data, but it took part of the lowest, with a twelve-month continuation ranging from 71% to 94% across registries.(54)

In univariate analysis, bDMARDs continuation rates did not differ significantly between patients who adhere to screening recommendations and those who are not adhere but are statistically significant higher in male gender than female gender, whereas men adhere less to screening recommendations than women. These last results are consistent with previously data.(55) Supplementary analysis with adherence to screening recommendations in each gender did not show differences (Figure 11). Outcome of SARS-Cov2 period and difficulties to maintain efficient follow-up should be noted, as shown by a flare of bDMARDs withdrawal in 2019. One study also founded that proportion of therapy withdrawal increased during the pandemic.(56) It might be more interesting to evaluate the bDMARDs adhesion and withdrawal according to the evolution of disease activity and BASDAI score at twelve months. bDMARDs mode of action was significantly associated with bDMARDs adherence in the



univariate analysis with a better adherence with TNF $\alpha$  inhibitor than with IL-17 inhibitor or IL-12/23 inhibitor. However, in the multivariate analysis the differences between bDMARDs mode of action were not statistically significant because of the small number of patients treated with IL-17 or IL-12/23 inhibitors. No other factor among age, disease duration, involvement, presence HLA B-27, biologic inflammation with CRP rate, functional impairment with BASFI score, concomitant csDMARDs, biosimilars or line of bDMARDs, was statistically associated with the maintenance of bDMARD. Moreover, the number of comorbidities was not significant in terms of bDMARDs adherence at 12 months in our study.

The main cause of bDMARDs withdrawal was the primary inefficacy (54% of withdrawal, OR 0.007-0.08) then occurrence of adverse event (37% of withdrawal, OR 0.07-0.4). These data were consistent with retrospective studies.(57,58)

In the multivariate Cox model analysis, we showed that SpA male patients had an almost three-fold higher likelihood for bDMARD adherence than women SpA patients. Other potential factors such as adherence to screening recommendations, disease duration, sacroiliitis, systemic inflammation (i.e. CRP), disease activity BASDAI, concomitant csDMARDs, line and type of bDMARDs were not associated to bDMARD continuation in the multivariate Cox model.

Adherence to screening recommendations could be considered as a factor in overall compliance and seems to be independent from bDMARDs adherence in our study. Loss of efficacy and adverse events may occur, leading to a reduction in the persistence of treatment. withdrawal due to intolerance is considered as intentional non-adherence. In view of results, it could imply a different behaviour between adherence to recommendations and therapeutic adherence. One of the observations of this study is the preponderance of biotherapies withdrawal in women, whereas they adhere more in screening recommendations. These results have been reported in a few studies.(59) One possibility is that women are more likely to be part of nr-axSpA than men, and nr-axSpA often have poorer treatment adherence than in AS.(48) This study should reduce this risk by including patients with MRI involvement. In addition, in the univariate analysis, there was a greater maintenance of bDMARDs in the absence of radiographic or MRI sacroiliitis. Another possibility is that SpA women have a greater risk of developing associated fibromyalgia, which is not relieved by biotherapies, and may contribute to their early withdrawal. In literature, sex ratios (female to male) were approximately 3:2 and 1:3 in patients with and without fibromyalgia.(60) Furthermore, gene expression profiles, inflammation levels and hormonal modulation are different between men and women and could have a role to modulation with bDMARDs.(61) The underlying

pathophysiological differences across gender must be investigated to understand these differences and lead to appropriate best disease management.

Our study comports some limits. First point our retrospective analyses makes it possible to integrate a large amount of data, although the majority of data was prospective. It is more difficult to collect data from patients in routine care. This limitation was minimised at inclusion by using standardised letters. On the other hand, follow-up of comorbidities and bDMARDs maintenance at 12 months were more complicated to collect. Some patients therefore had to be called in order to collect certain data, increasing the risk of memory bias. Missing data concerning bDMARD continuation at 12 months and adherence to screening recommendations were imputed as withdrawal and non-adherence respectively. It could be overestimate bDMARD withdrawal rate. This bias is unlikely as outcome measure was missing for only 5 patients for whom we attributed bDMARD withdrawal. Another limit is the recruitment, tertiary care centre. It is likely that included patient, already more adherent and are more likely to adhere to recommendations for hospital physician. However, patients included in this study were referred from both rheumatologists working in private practice and in a Rheumatology tertiary centre. Moreover, the monocentric design of this study, which leads to an external validity bias. Results could be underestimate in real life.

Another limitation could be due to the lack of statistical power associated with the preliminary nature of the study, in which the number of subjects required was not calculated. However, all patients attending the day hospital for initiation of bDMARDs were screened for eligibility, and the study included a large total of 189 patients.

Another possible bias is the threshold of 80% to define adherence rate of screening recommendations. It is usual threshold used with medications adherence and particularly in study of bDMARDs adherence. But it could be less adapted to screening recommendations.

Finally, anxiety and/or depression comorbidities were not assessed, because of existence of few standard scores and the difficulty of management afterwards.

In conclusion, probability of bDMARDs continuation at 12 month is 71% in real-world study of patients with SpA. Female gender was associated with better adherence to systematic screening recommendations for comorbidities and with less therapeutic retention of a bDMARD at 12 months in patients with SpA. Better adherence to screening recommendations was not associated with bDMARDs continuation in SpA. In this study, bDMARDs withdrawal for outcome of adverse events was not decreased by adherence to recommendations screening. The introduction of a consultation dedicated to the introduction of bDMARDs and screening for comorbidities has enabled this treatment to be initiated and optimised in patients with SpA. bDMARDs withdrawal was indicative of difficulties in adherence over time, despite initial joint multi-professional medical, paramedical, and pharmaceutical management. Closer initial clinical monitoring, with systematic research into patient adherence, could help optimise long-term adherence in these patients.

Adherence to screening recommendations is not a predictive factor to continuation of bDMARD, whereas gender seems to have different continuation of bDMARD. Identifying the factors that lead to the best responses to biotherapies is a major challenge e to achieve optimal personalised treatment without delay.

## References

1. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res.* sept 2016;68(9):1320-31.
2. Saraux A, Guillemin F, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of spondyloarthropathies in France: 2001. *Ann Rheum Dis.* oct 2005;64(10):1431-5.
3. Crossfield SSR, Marzo-Ortega H, Kingsbury SR, Pujades-Rodriguez M, Conaghan PG. Changes in ankylosing spondylitis incidence, prevalence and time to diagnosis over two decades. *RMD Open.* déc 2021;7(3):e001888.
4. Li Z, van der Linden SM, Khan MA, Baumberger H, Zandwijk H van, Khan MK, et al. Heterogeneity of axial spondyloarthritis: genetics, sex and structural damage matter. *RMD Open.* mai 2022;8(1):e002302.
5. Hwang MC, Ridley L, Reveille JD. Ankylosing spondylitis risk factors: a systematic literature review. *Clin Rheumatol.* août 2021;40(8):3079-93.
6. Arévalo M, Gratacós Masmitjà J, Moreno M, Calvet J, Orellana C, Ruiz D, et al. Influence of HLA-B27 on the Ankylosing Spondylitis phenotype: results from the REGISPONSER database. *Arthritis Res Ther.* 3 oct 2018;20(1):221.
7. Chung HY, Machado P, Heijde D van der, D'Agostino MA, Dougados M. HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis. *Ann Rheum Dis.* 1 nov 2011;70(11):1930-6.
8. Gracey E, Yao Y, Qaiyum Z, Lim M, Tang M, Inman RD. Altered Cytotoxicity Profile of CD8+ T Cells in Ankylosing Spondylitis. *Arthritis Rheumatol Hoboken NJ.* mars 2020;72(3):428-34.
9. Navid F, Holt V, Colbert RA. The enigmatic role of HLA-B\*27 in spondyloarthritis pathogenesis. *Semin Immunopathol.* avr 2021;43(2):235-43.
10. Lim Kam Sian TCC, Indumathy S, Halim H, Greule A, Cryle MJ, Bowness P, et al. Allelic association with ankylosing spondylitis fails to correlate with human leukocyte antigen B27 homodimer formation. *J Biol Chem.* 27 déc 2019;294(52):20185-95.
11. Sahlberg AS, Ruuska M, Colbert RA, Granfors K, Penttinen MA. Altered PKR Signalling and C/EBP $\beta$  Expression is Associated with HLA-B27 Expression in Monocytic Cells. *Scand J Immunol.* févr 2012;75(2):184-92.

12. Boyle LH, Goodall JC, Opat SS, Gaston JS. The recognition of HLA-B27 by human CD4(+) T lymphocytes. *J Immunol Baltim Md* 1950. 1 sept 2001;167(5):2619-24.
13. Berland M, Meslier V, Berreira Ibraim S, Le Chatelier E, Pons N, Maziers N, et al. Both Disease Activity and HLA-B27 Status Are Associated With Gut Microbiome Dysbiosis in Spondyloarthritis Patients. *Arthritis Rheumatol Hoboken NJ*. janv 2023;75(1):41-52.
14. Rath HC, Herfarth HH, Ikeda JS, Grenther WB, Hamm TE, Balish E, et al. Normal luminal bacteria, especially *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. *J Clin Invest*. 15 août 1996;98(4):945-53.
15. Sharif K, Bridgwood C, Dubash S, McGonagle D. Intestinal and enthesitis innate immunity in early axial spondyloarthritis. *Rheumatol Oxf Engl*. 1 oct 2020;59(Suppl4):iv67-78.
16. McGonagle D, Stockwin L, Isaacs J, Emery P. An enthesitis based model for the pathogenesis of spondyloarthritis. additive effects of microbial adjuvant and biomechanical factors at disease sites. *J Rheumatol*. oct 2001;28(10):2155-9.
17. Grintborg B, Sørensen IJ, Østergaard M, Dreyer L, Mohamoud AA, Krogh NS, et al. Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry. *J Rheumatol*. janv 2017;44(1):59-69.
18. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Curr Rheumatol Rep*. 12 mai 2018;20(6):35.
19. Marzo-Ortega H, Navarro-Compán V, Akar S, Kiltz U, Clark Z, Nikiphorou E. The impact of gender and sex on diagnosis, treatment outcomes and health-related quality of life in patients with axial spondyloarthritis. *Clin Rheumatol*. 2022;41(11):3573-81.
20. Landi M, Maldonado-Ficco H, Perez-Alamino R, Maldonado-Cocco JA, Citera G, Arturi P, et al. Gender differences among patients with primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease in an iberoamerican spondyloarthritis cohort. *Medicine (Baltimore)*. déc 2016;95(51):e5652.
21. Gracey E, Yao Y, Green B, Qaiyum Z, Baglaenko Y, Lin A, et al. Sexual Dimorphism in the Th17 Signature of Ankylosing Spondylitis. *Arthritis Rheumatol Hoboken NJ*. mars 2016;68(3):679-89.

22. Jeong H, Bae EK, Kim H, Eun YH, Kim IY, Kim H, et al. Estrogen attenuates the spondyloarthritis manifestations of the SKG arthritis model. *Arthritis Res Ther.* 7 sept 2017;19(1):198.
23. Sveaas SH, Smedslund G, Hagen KB, Dagfinrud H. Effect of cardiorespiratory and strength exercises on disease activity in patients with inflammatory rheumatic diseases: a systematic review and meta-analysis. *Br J Sports Med.* juill 2017;51(14):1065-72.
24. Ramiro S, Van Der Heijde D, Van Tubergen A, Stolwijk C, Dougados M, Van Den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis.* août 2014;73(8):1455-61.
25. 2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis | Elsevier Enhanced Reader [Internet]. [cité 21 janv 2023]. Disponible sur: <https://reader.elsevier.com/reader/sd/pii/S1297319X22000033?token=1EAA27395E598B70762A693D083A8CF1BEA53DBEC71676D17BAB6FE28A7520C13B6A68F40815634468EBEEA7B0EDEA69&originRegion=eu-west-1&originCreation=20230121113514>
26. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor  $\alpha$  inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum.* oct 2013;65(10):2645-54.
27. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis.* janv 2014;73(1):62-8.
28. Moltó A, Etcheto A, Heijde D van der, Landewé R, Bosch F van den, Molano WB, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis.* 1 juin 2016;75(6):1016-23.
29. Zhao SS, Robertson S, Reich T, Harrison NL, Moots RJ, Goodson NJ. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. *Rheumatology.* 1 oct 2020;59(Supplement\_4):iv47-57.
30. Han C, Robinson DW, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol.* nov 2006;33(11):2167-72.

31. Solmaz D, Kalyoncu U, Tinazzi I, Bakirci S, Bayindir O, Dogru A, et al. Current Smoking Is Increased in Axial Psoriatic Arthritis and Radiographic Sacroiliitis. *J Rheumatol.* 1 sept 2020;47(9):1354-8.
32. Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, Folke F, Charlot M, Selmer C, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation.* 24 mai 2011;123(20):2226-35.
33. Zurita Prada PA, Urrego Laurín CL, Guillén Astete CA, Kanaffo Caltelblanco S, Navarro-Compán V. Influence of smoking and obesity on treatment response in patients with axial spondyloarthritis: a systematic literature review. *Clin Rheumatol.* 1 mai 2021;40(5):1673-86.
34. Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. *Ann Rheum Dis.* oct 2010;69(10):1756-61.
35. Hellgren K, Dreyer L, Arkema EV, Glintborg B, Jacobsson LTH, Kristensen LE, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. *Ann Rheum Dis.* 1 janv 2017;76(1):105-11.
36. Keller DS, Windsor A, Cohen R, Chand M. Colorectal cancer in inflammatory bowel disease: review of the evidence. *Tech Coloproctology.* janv 2019;23(1):3-13.
37. Hou L qiong, Jiang G xue, Chen Y fei, Yang XM, Meng L, Xue M, et al. The Comparative Safety of TNF Inhibitors in Ankylosing Spondylitis—a Meta-Analysis Update of 14 Randomized Controlled Trials. *Clin Rev Allergy Immunol.* 1 avr 2018;54(2):234-43.
38. Kim HW, Kim EH, Lee M, Jung I, Ahn SS. Risk of cancer, tuberculosis and serious infections in patients with ankylosing spondylitis, psoriatic arthritis and psoriasis treated with IL-17 and TNF- $\alpha$  inhibitors: a nationwide nested case-control analysis. *Clin Exp Rheumatol.* juill 2023;41(7):1491-9.
39. van der Weijden M a. C, Claushuis T a. M, Nazari T, Lems WF, Dijkmans B a. C, van der Horst-Bruinsma IE. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol.* nov 2012;31(11):1529-35.
40. Gratacós J, Collado A, Pons F, Osaba M, Sanmartí R, Roqué M, et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a followup study. *Arthritis Rheum.* nov 1999;42(11):2319-24.

41. Westerveld LA, van Bommel JC, Dhert WJA, Oner FC, Verlaan JJ. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. *Spine J Off J North Am Spine Soc.* 1 mai 2014;14(5):729-40.
42. Redeker I, Callhoff J, Hoffmann F, Marschall U, Haibel H, Sieper J, et al. The prevalence and impact of comorbidities on patients with axial spondyloarthritis: results from a nationwide population-based study. *Arthritis Res Ther.* 10 sept 2020;22(1):210.
43. Baillet A, Gossec L, Carmona L, Wit M de, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis.* juin 2016;75(6):965-73.
44. Molto A, Gossec L, Poiraudeau S, Claudepierre P, Soubrier M, Fayet F, et al. Evaluation of the impact of a nurse-led program of systematic screening of comorbidities in patients with axial spondyloarthritis: The results of the COMEDSPA prospective, controlled, one year randomized trial. *Semin Arthritis Rheum.* 1 août 2020;50(4):701-8.
45. Simard JF, Neovius M, Askling J, ARTIS Study Group. Mortality rates in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: drug-specific comparisons in the Swedish Biologics Register. *Arthritis Rheum.* nov 2012;64(11):3502-10.
46. López-González R, León L, Loza E, Redondo M, Garcia de Yébenes MJ, Carmona L. Adherence to biologic therapies and associated factors in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis: a systematic literature review. *Clin Exp Rheumatol.* 2015;33(4):559-69.
47. Serrano-Benavente B, Valor L, Del Río Blasco T, Janta I, González Benítez R, Nieto-González JC, et al. Long-Term Retention Rate of Golimumab in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, and Spondyloarthritis in a Real-Life Setting. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* 1 janv 2022;28(1):e150-5.
48. Lopalco G, Venerito V, Cantarini L, Emmi G, Salaffi F, Di Carlo M, et al. Different drug survival of first line tumour necrosis factor inhibitors in radiographic and non-radiographic axial spondyloarthritis: a multicentre retrospective survey. *Clin Exp Rheumatol.* 2019;37(5):762-7.
49. Betegnie AL, Gauchet A, Lehmann A, Grange L, Roustit M, Baudrant M, et al. Why Do Patients with Chronic Inflammatory Rheumatic Diseases Discontinue Their Biologics? An Assessment of Patients' Adherence Using a Self-report Questionnaire. *J Rheumatol.* avr 2016;43(4):724-30.



50. Kelly A, Tymms K, Tunnicliffe DJ, Sumpton D, Perera C, Fallon K, et al. Patients' Attitudes and Experiences of Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis and Spondyloarthritis: A Qualitative Synthesis. *Arthritis Care Res.* avr 2018;70(4):525-32.
51. Gossec L, Molto A, Romand X, Puyraimond-Zemmour D, Lavielle M, Beauvais C, et al. Recommendations for the assessment and optimization of adherence to disease-modifying drugs in chronic inflammatory rheumatic diseases: A process based on literature reviews and expert consensus. *Joint Bone Spine.* janv 2019;86(1):13-9.
52. Hubac J, Tribouillard H, Gastaldi R, Romand X, Gaudin P, Allenet B, et al. Implementation of comorbidities' systematic screening program in daily practice in France. *Joint Bone Spine.* déc 2020;87(6):663-5.
53. Reyes-Rivet L, Bellier A, Baillet A, Pham T, Gaudin P, Allenet B, et al. Adherence to EULAR's recommendations on comorbidity management minimizes the discontinuation of bDMARDs for intolerance in patients with chronic inflammatory rheumatic diseases. *Joint Bone Spine.* 1 déc 2021;88(6):105234.
54. Ørnbjerg LM, Brahe CH, Askling J, Ciurea A, Mann H, Onen F, et al. Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis.* nov 2019;78(11):1536-44.
55. Glintborg B, Østergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis.* 1 nov 2010;69(11):2002-8.
56. Ciurea A, Papagiannoulis E, Bürki K, von Loga I, Micheroli R, Möller B, et al. Impact of the COVID-19 pandemic on the disease course of patients with inflammatory rheumatic diseases: results from the Swiss Clinical Quality Management cohort. *Ann Rheum Dis.* févr 2021;80(2):238-41.
57. Favalli EG, Pontikaki I, Becciolini A, Biggioggero M, Ughi N, Romano M, et al. Real-life 10-year retention rate of first-line anti-TNF drugs for inflammatory arthritides in adult- and juvenile-onset populations: similarities and differences. *Clin Rheumatol.* août 2017;36(8):1747-55.
58. Samartín-Ucha M, Pego-Reigosa JM, Álvarez-Payero M, Martín-Vila A, Pineiro-Corrales G, Rodríguez-Rodríguez M, et al. Medication persistence on biological therapies prescribed for the treatment of chronic inflammatory arthropathies: a real-world data study. *Eur J Hosp Pharm Sci Pract.* nov 2021;28(Suppl 2):e47-50.

59. Lubrano E, Perrotta FM, Manara M, D'Angelo S, Addimanda O, Ramonda R, et al. The Sex Influence on Response to Tumor Necrosis Factor- $\alpha$  Inhibitors and Remission in Axial Spondyloarthritis. *J Rheumatol*. 1 févr 2018;45(2):195-201.
60. Son SM, Kim DS, Lee JS. Fibromyalgia in Axial Spondyloarthritis: A Meta-analysis. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis*. 1 janv 2022;28(1):e222-7.
61. Wright GC, Kaine J, Deodhar A. Understanding differences between men and women with axial spondyloarthritis. *Semin Arthritis Rheum*. août 2020;50(4):687-94.

# Supplementary data

## Supplemental figure 1. BASDAI Score

**BASDAI**  
Bath Ankylosing Spondylitis  
Disease Activity Index  
in French language



Nom: \_\_\_\_\_

Date: \_\_\_\_\_

Marquer d'un trait la réponse à chacune des questions en vous référant **aux dernières 7 jours**



<b>1</b>	Où situeriez-vous votre degré global de fatigue?	absent 0 1 2 3 4 5 6 7 8 9 10 extrême	Evaluation par docteur <input type="checkbox"/>
<b>2</b>	Où situeriez-vous votre degré global de douleur au niveau <u>du cou, du dos et des hanches</u> dans le cadre de votre spondylarthrite ankylosante?	absent 0 1 2 3 4 5 6 7 8 9 10 extrême	<input type="checkbox"/>
<b>3</b>	Où situeriez-vous votre degré global de douleur / gonflement articulaire en dehors du cou, du dos et des hanches?	absent 0 1 2 3 4 5 6 7 8 9 10 extrême	<input type="checkbox"/>
<b>4</b>	Où situeriez-vous votre degré global de gêne pour les zones sensibles au toucher ou la pression?	absent 0 1 2 3 4 5 6 7 8 9 10 extrême	<input type="checkbox"/>
<b>5</b>	Où situeriez-vous votre degré global de raideur matinale depuis votre réveil?	absent 0 1 2 3 4 5 6 7 8 9 10 extrême	$\frac{\textcircled{1} + \textcircled{5}}{2}$ <input type="checkbox"/>
<b>6</b>	Quelle est la durée de votre raideur matinale à partir de votre réveil?	0 1 2 3 4 5 6 7 8 9 10 0 1 2 3 4 5 6 7 8 9 10 0 1 2 3 4 5 6 7 8 9 10 1/2 1 1 1/2 2 heures ou plus	

BASDAI =

$$\text{BASDAI} = (\textcircled{1} + \textcircled{2} + \textcircled{3} + \textcircled{4} + \frac{\textcircled{5} + \textcircled{6}}{2}) / 5$$

## Supplemental figure 2. ASDAS-CRP Score

ASDAS-CRP	$0.12 \times \text{Back Pain} + 0.06 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.07 \times \text{Peripheral Pain/Swelling} + 0.58 \times \ln(\text{CRP}+1)$
ASDAS-ESR	$0.08 \times \text{Back Pain} + 0.07 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.09 \times \text{Peripheral Pain/Swelling} + 0.29 \times \sqrt{\text{ESR}}$
<p>ASDAS, Ankylosing Spondylitis Disease Activity Score; <math>\sqrt{\text{ESR}}</math>, square root of the erythrocyte sedimentation rate (mm/h); <math>\ln(\text{CRP}+1)</math>, natural logarithm of the C-reactive protein (mg/L) + 1. Back pain, patient global, duration of morning stiffness and peripheral pain/swelling are all assessed on a visual analogue scale (from 0 to 10cm) or on a numerical rating scale (from 0 to 10). Back pain, BASDAI question 2: "How would you describe the overall level of AS neck, back or hip pain you have had?". Duration of morning stiffness, BASDAI question 6: "How long does your morning stiffness last from the time you wake up?". Patient global: "How active was your spondylitis on average during the last week?" Peripheral pain/swelling, BASDAI question 3: "How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?"</p>	

Supplemental figure 3. BASFI Score

**BASFI**  
**Bath Ankylosing Spondylitis**  
**Functional Index**  
 in French language



Nom: \_\_\_\_\_

Date: \_\_\_\_\_

Marquer d'un trait la réponse à chacune des questions en vous référant aux dernières 7 jours



- 1** Pouvez-vous mettre vos chaussettes ou collants sans l'aide de quelqu'un ou de tout autre moyen extérieur (ex : petit appareil vous aidant à mettre vos chaussettes) ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 2** Pouvez-vous vous pencher en avant pour ramasser un stylo posé sur le sol sans l'aide d'un moyen extérieur ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 3** Pouvez-vous atteindre une étagère élevée sans l'aide de quelqu'un ou d'un moyen extérieur ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 4** Pouvez-vous vous lever d'une chaise sans accoudoir sans utiliser vos mains ou toute autre aide ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 5** Pouvez-vous vous relever de la position « couché sur le dos » sans aide ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 6** Pouvez-vous rester debout sans soutien pendant 10 minutes sans ressentir de gêne ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 7** Pouvez-vous monter 12 à 15 marches, en ne posant qu'un pied sur chaque marche, sans vous tenir à la rampe ou utiliser tout autre soutien ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 8** Pouvez-vous regarder par dessus votre épaule sans vous retourner ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 9** Pouvez-vous effectuer des activités nécessitant un effort physique (ex : mouvements de kinésithérapie, jardinage ou sports) ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible
- 10** Pouvez-vous avoir des activités toute la journée, que ce soit au domicile ou au travail ?

sans aucune difficulté 0 1 2 3 4 5 6 7 8 9 10 impossible

Évaluation par docteur

BASFI =

$BASFI = (1+2+3+4+5+6+7+8+9+10) / 10$

## Supplemental figure 4. Test Biosecure

1. Quelle est votre biothérapie actuelle ? Veuillez cocher une seule réponse.

- Enbrel (etanercept)
- Humira (adalimumab)
- Rémicade (infliximab)
- Mabthéra (rituximab)
- Oencia (abatacept)
- RoActemra (tocilizumab)
- Autre .....
- Je ne sais pas

2. Je peux arrêter ma biothérapie si mon rhumatisme va parfaitement bien (rémission). Veuillez cocher une seule réponse

- oui                       non                       je ne sais pas

3. Les infections sont plus fréquentes sous traitement par biothérapie.  
Veuillez cocher une seule réponse.

oui  non  je ne sais pas

4. Parmi les situations suivantes, lesquelles nécessitent des précautions particulières ou des modifications de votre biothérapie :

		Oui	Non	Je ne sais pas
4.1	Boire du lait	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.2	Voyager à l'étranger	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.3	Se faire opérer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.4	Faire du jogging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.5	Se faire extraire une dent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.6	Boire un verre de vin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.7	Manger bio	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.8	Envisager d'avoir un enfant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Qui dois-je prévenir que je suis sous biothérapie ?

Veuillez cocher une réponse pour chaque personne.

		Oui	Non	Je ne sais pas
5.1	Mon médecin traitant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.2	Mon employeur	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.3	Mon dentiste	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.4	L'anesthésiste en cas d'intervention chirurgicale	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.5	Le responsable de mon cours de gym	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.6	Le maître nageur de la piscine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.7	Le banquier qui gère mon compte	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Sous biothérapie, tous les vaccins sont contre-indiqués.

Veuillez cocher une seule réponse.

vrai  faux  je ne sais pas

7. Sous biothérapie une femme doit utiliser une contraception efficace.

Veuillez cocher une seule réponse.

vrai  faux  je ne sais pas

## 8. Veuillez cocher la bonne réponse pour chaque situation.

Parmi les situations suivantes, lesquelles nécessitent des précautions particulières ou des modifications de votre biothérapie :

		Oui	Non	Je ne sais pas
8.1	L'apparition d'une fièvre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.2	Avoir des envies fréquentes d'uriner	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.3	Se faire une entorse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.4	L'apparition d'une toux	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.5	Être essoufflé sans raison	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.6	Être constipé	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.7	Avoir des brûlures en urinant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.8	Grossir de 3 kg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.9	Maignir de 1 kg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### MISES EN SITUATION

Les biothérapies peuvent être faites en injections sous-cutanées à la maison, ou en perfusions à l'hôpital, c'est pourquoi les situations ci-dessous reprennent ces 2 cas. Merci de répondre en tenant compte de votre cas.

#### Cas n°1

Françoise a une polyarthrite traitée par biothérapie. Pendant les vacances de Noël, son mari et sa fille ont de la fièvre à 38°5, ils toussent et ont le nez qui coule. Le médecin leur a donné un traitement. Il a dit qu'ils n'avaient pas besoin d'antibiotiques car c'était un virus. Au bout d'une semaine, à son tour Françoise a les mêmes symptômes : toux, fièvre à 38°5, nez qui coule.

Avec laquelle ou lesquelles des décisions de Françoise êtes-vous d'accord ?

		Oui	Non	Je ne sais pas
1	Françoise prend le traitement donné par le médecin à son mari, car il a été efficace sur lui.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Elle attend un peu avant de contacter le médecin car son mari et sa fille ont guéri en quelques jours.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Elle fait sa biothérapie car c'est seulement un virus (elle fait son injection en sous-cutané ou sa perfusion prévue).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



### Cas n°2

Pierre a un rhumatisme inflammatoire traité par biothérapie. La veille de la biothérapie (perfusion ou injection), il a une grosse bronchite : toux grasse et rocailleuse, fièvre à 38°5. Son médecin lui prescrit un antibiotique qu'il commence le soir même. Il décide de ne pas faire sa biothérapie (il ne fait pas son injection en sous-cutané ou prévient pour annuler sa perfusion prévue).

Laquelle ou lesquelles des affirmations suivantes vous semblent vraies ?

		Oui	Non	Je ne sais pas
1	Pierre a eu raison de ne pas faire sa biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Pierre a eu raison de commencer les antibiotiques dès que possible.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Lorsque Pierre aura à nouveau une bronchite, il saura quel antibiotique il pourra prendre si son médecin n'est pas disponible.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Maintenant qu'il a commencé son antibiotique, Pierre va pouvoir faire sa biothérapie le lendemain.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Pierre a eu raison d'appeler son médecin.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Cas n°3

Christine est partie en vacances avec sa famille cet été. Pendant le séjour, elle s'est bien reposée et son rhumatisme ne la fait plus souffrir. Elle n'a pris que quelques jours ses anti-inflammatoires et finalement elle décide de ne pas continuer sa biothérapie (injection en sous-cutané ou perfusion). À son retour, une de ses amies lui demande : « pourquoi devrais-tu reprendre ta biothérapie puisque tu n'as plus mal ? »

Avec laquelle ou lesquelles des réponses suivantes de Christine êtes-vous d'accord ?

		Oui	Non	Je ne sais pas
1	Je vais reprendre ma biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Si mon rhumatisme ne m'a pas fait souffrir pendant 3 semaines, c'est qu'il est probablement guéri.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### Cas n°4

En octobre, Aline, 53 ans, a entendu que le vaccin contre la grippe était arrivé. Elle est sous biothérapie depuis 6 mois. Elle hésite à se faire vacciner.

Avec laquelle ou lesquelles des affirmations suivantes d'Aline êtes-vous d'accord ?

		Oui	Non	Je ne sais pas
1	Je vais faire mon vaccin.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Je risque d'avoir une réaction importante au vaccin à cause de la biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Le vaccin est contre-indiqué à cause de la biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Je vais voir mon médecin pour lui en parler.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### Cas n°5

Nicolas est sous biothérapie pour un rhumatisme inflammatoire. Nicolas aime jardiner : il s'est fait une coupure à l'index droit en replantant un rosier.

Avec laquelle ou lesquelles des affirmations suivantes êtes-vous d'accord ?

		Oui	Non	Je ne sais pas
1	Il faut tout de suite nettoyer la plaie, et mettre un pansement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	La plaie a plus de risque de s'infecter.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Il faut mettre tout de suite Nicolas sous antibiotique.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Nicolas peut faire le vaccin contre le tétanos même s'il est sous biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Cas n°6

Nadine est sous biothérapie et rencontre un chirurgien pour une intervention de la cataracte. Il lui propose de l'opérer dans 10 jours.

Avec laquelle ou lesquelles des affirmations suivantes êtes-vous d'accord ?

		Oui	Non	Je ne sais pas
1	L'intervention est définitivement contre-indiquée.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Elle est d'accord pour cette date car autant le faire le plus vite possible.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Elle refuse cette date car elle doit d'abord discuter d'arrêter sa biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Elle prévient le chirurgien qu'elle est sous biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Elle prévient l'anesthésiste qu'elle est sous biothérapie.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### SI VOUS AVEZ UNE BIOTHERAPIE SOUS-CUTANEE

Merci de répondre aux questions suivantes :

9. Veuillez cocher une seule réponse.

Le traitement par biothérapie doit être conservé :

- Au réfrigérateur
- Au congélateur
- À température ambiante
- Je ne sais pas

### Cas n°7

Christelle doit faire son injection sous-cutanée de biothérapie. Pour faire son injection :

1. Cochez ci-dessous, l'erreur qui s'est glissée dans ce qu'a fait Christelle.

- Elle sort le produit et attend un moment.
- Elle désinfecte la peau.
- Elle fait l'injection sur le ventre ou les cuisses.
- Elle jette l'aiguille usagée à la poubelle.

2. À votre avis, qu'a-t-elle oublié ? (une seule phrase)

.....  
.....  
.....

Numéro de question	Thème de la question	Bonne réponse valant 1 point	Points du patient
1	Quelle est votre biothérapie actuelle ?	Biothérapie juste	
2	Je peux arrêter ma biothérapie si mon rhumatisme va parfaitement bien.	non	
3	Les infections sont plus fréquentes sous traitement par biothérapie.	oui	
4	4.1 - Boire du lait	non	
	4.2 - Voyager à l'étranger	oui	
	4.3 - Se faire opérer	oui	
	4.4 - Faire du jogging	non	
	4.5 - Se faire extraire une dent	oui	
	4.6 - Boire un verre de vin	non	
	4.7 - Manger Bio	non	
	4.8 - Envisager d'avoir un enfant	oui	
5	5.1 - Mon médecin traitant	oui	
	5.2 - Mon employeur	non	
	5.3 - Mon dentiste	oui	
	5.4 - L'anesthésiste	oui	
	5.5 - Le responsable de mon cours de gym	non	
	5.6 - Le maître nageur	non	
	5.7 - Le banquier	non	
6	Vaccins	faux	
7	Contraception	vrai	
8	8.1 - L'apparition d'une fièvre	oui	
	8.2 - Des envies fréquentes d'uriner	oui	
	8.3 - Une entorse	non	
	8.4 - Une toux	oui	
	8.5 - Un essoufflement	oui	
	8.6 - Une constipation	non	
	8.7 - Des brûlures urinaires	oui	
	8.8 - Grossir	non	
	8.9 - Maigrir	non	
Cas 1	1 - Françoise prend le traitement.	non	
	2 - Elle attend un peu.	non	
	3 - Elle fait sa biothérapie.	non	

Numéro de question	Thème de la question	Bonne réponse valant 1 point	Points du patient
<b>Cas 2</b>	1 - Ne pas faire sa biothérapie.	vrai	
	2 - Commencer les antibiotiques.	vrai	
	3 - Lorsque Pierre aura à nouveau...	faux	
	4 - Maintenant qu'il a commencé...	faux	
	5 - Pierre a eu raison d'appeler son médecin.	vrai	
<b>Cas 3</b>	1 - Je vais reprendre ma biothérapie.	oui	
	2 - Si mon rhumatisme ne m'a ...	non	
<b>Cas 4</b>	1 - Je vais faire mon vaccin.	oui	
	2 - Je risque d'avoir une réaction.	non	
	3 - Vaccin contre-indiqué	non	
	4 - Je vais voir mon médecin.	oui	
<b>Cas 5</b>	1 - Il faut tout de suite nettoyer.	oui	
	2 - La plaie a plus de risque de s'infecter.	oui	
	3 - Sous antibiotique	non	
	4 - Il peut faire le vaccin contre le tétanos.	oui	
<b>Cas 6</b>	1 - L'intervention est contre-indiquée.	non	
	2 - Elle est d'accord pour cette date.	non	
	3 - Elle refuse cette date.	oui	
	4 - Elle prévient le chirurgien.	oui	
	5 - Elle prévient l'anesthésiste.	oui	
<b>Patient sous biothérapie IV : fin ici</b>		<b>Somme des points</b>	
<b>Total sur 100 : somme x 1.92</b>		<b>Total sur 100</b>	
<b>Patient sous biothérapie SC</b>			
<b>7</b>	Le traitement par biothérapie doit être conservé.	Réfrigérateur	
<b>Cas 6</b>	1 - Cochez l'erreur	Jeter l'aiguille à la poubelle	
	2 - Qu'a-t-elle oublié ?	Se laver les mains	
<b>Patient sous biothérapie SC : fin ici</b>		<b>Somme des points</b>	
<b>Total sur 100 : somme x 1.82</b>		<b>Total sur 100</b>	

## Supplemental figure 5. Test CQR19

### Table 1 The full compliance questionnaire for rheumatology (CQR19)

From: [A 5 item version of the Compliance Questionnaire for Rheumatology \(CQR5\) successfully identifies low adherence to DMARDs](#)

	Questions
Q1	If the rheumatologist tells me to take the medicines, I do so
Q2*	I take my anti-rheumatic medicines because I then have fewer problems
Q3*	I definitely don't dare to miss my anti-rheumatic medications
Q4	If I can help myself with alternative therapies, I prefer that to what my rheumatologist prescribes
Q5*	My medicines are always stored in the same place and that's why I don't forget them
Q6*	I take my medicines because I have complete confidence in my rheumatologist
Q7	The most important reason to take my anti-rheumatic medicines is that I can still do what I want to do
Q8	I don't like to take medicine. If I can do without them, I will
Q9	When I am on vacation, it sometimes happens that I don't take my medicines
Q10	I take my anti-rheumatic drugs, for otherwise what's the point of consulting a rheumatologist?
Q11	I don't expect miracles from my anti-rheumatic medicines
Q12	If you can't stand the medicines you might say: "throw it away, no matter what"
Q13	If I don't take my anti-rheumatic medicines regularly, the inflammation returns
Q14	If I don't take my anti-rheumatic medicines, my body warns me
Q15	My health goes above everything else and if I have to take medicines to keep well, I will
Q16	I use a dose organizer for my medications
Q17*	What the doctor tells me, I hang on to
Q18	If I don't take my anti-rheumatic medicines, I have more complaints
Q19	It happens every now and then, I go out for the weekend and then I don't take my medicines

# Supplemental figure 6. Example of a day hospital report for initiation of biotherapy and screening of comorbidities in chronic inflammatory rheumatic diseases



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## PÔLE APPAREIL LOCOMOTEUR CHIRURGIE REPARATRICE ET ORGANES DES SENS

CLINIQUE UNIVERSITAIRE DE  
RHUMATOLOGIE  
[www.rhumatologie-grenoble.com](http://www.rhumatologie-grenoble.com)

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C. Tiertant, Encadrant Secrétariats Médicaux  
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**Avis urgents** : réservé aux médecins  
Demande à faire au secrétariat

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- Consultation de rhumatologie  
- Consultation médico-chirurgicale  
- Filière ostéoporose  
- Consultation sourds et malentendants  
- Consultation arthroprothèse  
RHUMATISMES INFLAMMATOIRES  
- Consultation avec échographie articulaire  
- Initiation / renouvellement de biothérapie  
- Consultation de transition pédiatrique  
- Centre de compétence FAIR des AJI

**Recherche Clinique** : Niveau 2  
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RHUMATISMES INFLAMMATOIRES  
MALADIES AUTO-IMMUNES  
Biothérapies, Comorbidités, Bilans

**Rhumatologie Interventionnelle** :  
Niveau 1  
Responsable : Pr P. Gaudin  
GESTES RADIO / ECHO-GUIDES  
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REEDUCATION  
- Module du dos  
- Module de la polyarthrite  
- Module de la spondylarthrite  
- Réentraînement à l'effort / fibromyalgie  
- Consultation multidisciplinaire sclérodermie

Echirolles, le jeudi 16 septembre 2021

### Compte-rendu d'Hospitalisation de Jour du Concernant Monsieur TEST Rhumato, né TEST le 01/01/1980 pour initiation de biothérapie et dépistage des comorbidités dans la polyarthrite rhumatoïde

**Rhumatologue référent** : Dr

Patient vu ce jour dans le cadre du suivi personnalisé de sa polyarthrite rhumatoïde.

Pour rappel, Monsieur TEST, âgé de 41 ans souffre de polyarthrite rhumatoïde  
Choisissez un élément., anti-CCP Choisissez un élément., Choisissez un élément. à  
ce jour, diagnostiquée en Cliquez ici pour entrer une date..

Ce rhumatisme est associé à des atteintes extra articulaires :  
- Cliquez ici pour entrer du texte..

**Antécédents** :  
- Médicaux :  
- Chirurgicaux :  
- Allergies :

#### 1. LE RHUMATISME INFLAMMATOIRE

La prise en charge thérapeutique a conduit à la décision de mise sous biothérapie.

**A. L'activité (inflammation) de la polyarthrite rhumatoïde a été évaluée ce  
jour sur les éléments suivants :**

- Réveils nocturnes dus à la douleur :  oui  non  
- Dérouillage matinal : Cliquez ici pour entrer du texte. minutes  
- EVA douleur (0-100) : Cliquez ici pour entrer du texte.  
- EVA maladie (0-100) : Cliquez ici pour entrer du texte.  
- Nombre d'articulations douloureuses : Cliquez ici pour entrer du  
texte./28.  
- Nombre d'articulations gonflées : Cliquez ici pour entrer du texte./28.  
- CRP : Cliquez ici pour entrer du texte. mg/l  
- VS : Cliquez ici pour entrer du texte. mm 1<sup>ère</sup> H  
- DAS 28 VS = Cliquez ici pour entrer du texte.  
- Echographie ostéo-articulaire réalisée par le Dr Cliquez ici pour entrer  
du texte..

**B. L'histoire des traitements de fond de la polyarthrite rhumatoïde a été  
revue :**

Traitements de fond interrompus :

Molécule	Dose et voie d'administration	Motif d'arrêt
		Choisissez un élément.
		Choisissez un élément.
		Choisissez un élément.
		Choisissez un élément.
		Choisissez un élément.
		Choisissez un élément.

Traitements de fond en cours (molécule/dose et voie d'administration) :

- Cliquez ici pour entrer du texte.

Bilan pré-biothérapie (si besoin) :

- Quantiféron ou Elispot tuberculose :
- Sérologies Hépatite C – B / VIH 1 et 2 :

Après validation de l'indication et de l'absence de contre-indication par le Dr Gastaldi, l'injection sous-cutanée de **(nom commercial/forme/dosage)** a été réalisée par une IDE du service.

Des conseils techniques sur l'injection, les précautions et consignes d'usages ont été apportés au patient par cette même infirmière formée à l'éducation thérapeutique.

Une surveillance de 2 heures environ a ensuite été respectée pour surveiller la tolérance immédiate au traitement.

## 2. LES COMORBIDITES

A l'aide de la biologie du Cliquez ici pour entrer une date. et des éléments du dossier médical apportés par le patient nous avons également recherché l'existence de MALADIES ASSOCIEES (ou comorbidités).

### A. Risque de maladie cardio-vasculaire :

#### a. *Risque global :*

Afin de savoir si Monsieur TEST justifie une surveillance cardio-vasculaire particulière, il a été recherché les facteurs de risque selon la méthode HEART SCORE qui prend en compte l'âge, le sexe, le tabagisme, la tension artérielle et le rapport cholestérol total/HDL-cholestérol.

Ce risque est estimé à Cliquez ici pour entrer du texte. %.

Ainsi, il a été proposé : Choisissez un élément.

#### b. *Dyslipidémie :*

Afin de savoir si des mesures devraient être prises pour lutter contre un éventuel trouble lipidique, nous avons pris en compte les valeurs du HEART SCORE et du taux de LDL à : Cliquez ici pour entrer du texte. g/L.

HEART SCORE® (%) (recalibré pour la SA)	CIBLE	Valeurs de cholestérol LDL			
		< 0,70 g/L < 1,8 mmol/L	0,70 < 1,00 g/L 1,8 à < 2,5 mmol/L	1,00 à 1,90 g/L 2,5 à < 4,9 mmol/L	> 190 mg/dL > 4,9 mmol/L



< 1	3 mmol/l 1,15 g/l	pas d'intervention	pas d'intervention	RHD	RHD ± traitement si non contrôlé
≥ 1 à < 5	3 mmol/l 1,15 g/l	RHD	RHD	RHD ± traitement si non contrôlé	RHD ± traitement si non contrôlé
≥ 5 à < 10 ou haut risque	2,5 mmol/l 1,00 g/l	RHD ± traitement	RHD ± traitement	RHD + traitement immédiat	RHD + traitement immédiat
≥ 10 ou très haut risque	1,8 mmol/l 0,70 g/l	RHD ± traitement	RHD + traitement immédiat	RHD + traitement immédiat	RHD + traitement immédiat

Ainsi, selon les recommandations ci-dessus, il a été proposé : Choisissez un élément..

**c. Diabète :**

Afin de savoir s'il existait un risque de diabète, il a été réalisé :

- une glycémie veineuse à jeun : Cliquez ici pour entrer du texte. mmol/l
- Au vu de ces résultats, il est prévu : Choisissez un élément..

**d. HTA :**

Afin de savoir s'il existait un risque lié à une maladie hypertensive, chez ce(tte) patient Choisissez un élément.,

Tension artérielle ce jour :

- Membre supérieur droit : Cliquez ici pour entrer du texte./Cliquez ici pour entrer du texte. mmHg, gauche : Cliquez ici pour entrer du texte./Cliquez ici pour entrer du texte. mmHg
- Membre inférieur droit : Cliquez ici pour entrer du texte./Cliquez ici pour entrer du texte. mmHg, gauche : Cliquez ici pour entrer du texte./Cliquez ici pour entrer du texte. mmHg.
- Il a été conseillé Choisissez un élément..
- IPS droit : Cliquez ici pour entrer du texte., gauche : Cliquez ici pour entrer du texte..

Il a été conseillé Choisissez un élément..

**e. Surpoids :**

Afin d'estimer le risque lié à un éventuel surpoids, il a été noté ce jour :

- Poids Cliquez ici pour entrer du texte. kg, taille Cliquez ici pour entrer du texte. m, soit un indice de masse corporelle (IMC) de Cliquez ici pour entrer du texte. (normal : < 25 / surpoids : entre 25 et 30, obésité > 30)
- le périmètre abdominal : Cliquez ici pour entrer du texte. cm (normes : <94 cm chez les hommes et <80 cm chez les femmes).

Ainsi, il a été indiqué :

- la poursuite d'un régime alimentaire équilibré.
- la pratique d'une activité physique régulière.
- la possibilité de réaliser un bilan diététique.

**B. Risque de maladie infectieuse :**

**a. Rappelons tout d'abord que chez ce/cette patient:**

- Antécédents infectieux : Cliquez ici pour entrer du texte.
- Dose actuelle de corticothérapie : Cliquez ici pour entrer du texte. mg/j.

**b. La dernière visite chez le dentiste remonte à Cliquez ici pour entrer du texte. mois / plus de Cliquez ici pour entrer du texte. ans.**

On préconise une visite annuelle. De plus on recommande d'effectuer au moins deux fois par jour un brossage des dents avec une pâte dentifrice contenant une association d'un agent antibactérien et d'un copolymère et un bain de bouche antiseptique en solution.

**c. Le statut vaccinal a été vérifié. Nous recommandons :**

- vaccination contre la grippe saisonnière dès lors qu'il est disponible : Choisissez un élément.,
- vaccination contre le pneumocoque : schéma PREVENAR 13 puis PNEUMOVAX : Choisissez un élément. ,
- vaccination contre Diphtérie/Tétanos /Polio : M. TEST Choisissez un élément.,
- vaccination contre la COVID 19 :

**C. Risque de maladie cancéreuse :**

Rappelons tout d'abord que chez ce/cette patient, Choisissez un élément..

**a. Dépistage du cancer de la peau**

Comme il est recommandé, une consultation annuelle pour dépistage de lésions suspectes doit être réalisée chez les patients traités par biothérapie. Choisissez un élément..  
Au total, nous recommandons à M. TEST au moins une visite par an auprès d'un dermatologue.

**b. Dépistage du cancer du côlon et du rectum.**

Tout d'abord, nous avons recherché les facteurs prédisposant à cette affection et notamment la notion d'un cancer du côlon ou du rectum avant l'âge de 50 ans dans la famille, antécédents de maladie digestive inflammatoire, antécédent familial de polypose, coliques.

Chez ce/cette patient, nous Choisissez un élément. de facteur prédisposant. Choisissez un élément.

**c. Dépistage du cancer de la prostate**

Tout d'abord, nous avons recherché les facteurs prédisposant à cette affection :

- Antécédent familial
- origine afro-antillaise
- la présence de symptômes urinaires

Choisissez un élément.

**d. Dépistage du cancer du sein**

Choisissez un élément.

La dernière mammographie ayant été effectuée le Cliquez ici pour entrer du texte. la prochaine mammographie est à prévoir vers Cliquez ici pour entrer du texte..

**e. Dépistage du cancer du col de l'utérus**

Nous rappelons à la patiente que ce dépistage repose sur la pratique d'un frottis par an à partir de l'âge de 25 ans et que leur répétition doit être simplement tous les 5 ans si les deux premiers frottis n'ont pas retrouvé d'anomalie.

La patiente est âgée de 41 ans, son dernier frottis remonte à Cliquez ici pour entrer du texte. mois/an(s), nous lui recommandons donc le prochain frottis vers Cliquez ici pour entrer du texte..

**D. Risque de fracture ostéoporotique :**

A l'heure actuelle, M. TEST Choisissez un élément..

Choisissez un élément.

La densitométrie osseuse de ce jour retrouve :

- T score du col du fémur à Cliquez ici pour entrer du texte.
- T score du rachis lombaire à Cliquez ici pour entrer du texte..

L'apport calcique quotidien est de : Cliquez ici pour entrer du texte. mg / jour

On évalue (outil FRAX) ainsi un risque de fracture majeure de Cliquez ici pour entrer du texte. % à 10 ans et un risque de fracture du col du fémur de Cliquez ici pour entrer du texte. % à 10 ans.

Nous proposons donc :

- un traitement anti ostéoporotique de type Cliquez ici pour entrer du texte.
- une supplémentation en vitamine D
- une supplémentation calcique
- une augmentation des apports calciques naturels
- une surveillance simple.

#### **E. Risque de syndrome d'apnée du sommeil :**

Les questionnaires suivants ont été réalisés lors de la venue de M. TEST :

- Berlin : Cliquez ici pour entrer du texte. (<2 : faible/ ≥2 : forte probabilité d'apnée du sommeil)
- Epworth : Cliquez ici pour entrer du texte. (<8 : pas de dette de sommeil ; 9-14 déficit de sommeil ; ≥15 signes de somnolence diurne).

Compte tenu des résultats de ces tests, Choisissez un élément.

#### **F. Les consommations toxiques :**

Les questionnaires suivants ont été réalisés lors de la venue de M. TEST :

- Fagerström : Cliquez ici pour entrer du texte. (0-3 peu dépendant ; 4-6 dépendant ; 7-10 très dépendant)
- CAGE-DETA : Cliquez ici pour entrer du texte. (≥2 : trouble de la consommation).

Choisissez un élément.

#### **G. Prise en charge pharmacologique et rééducative :**

Le questionnaire suivant a été réalisé lors de la venue de M. TEST :

- Morisky : Cliquez ici pour entrer du texte.

Lors de son passage à l'hôpital, le/la patient a été vu par Cliquez ici pour entrer du texte., Choisissez un élément., qui a noté Cliquez ici pour entrer du texte..

#### **AU TOTAL**

Après avoir fait une synthèse avec tous les participants et après consultation auprès du Docteur GASTALDI Romain, M. TEST sort du service avec les conseils suivants :

- **En ce qui concerne la polyarthrite rhumatoïde :**

Le traitement par Cliquez ici pour entrer du texte. à la posologie de Cliquez ici pour entrer du texte. a été administré par voie sous-cutanée. Des conseils concernant l'injection ont été donnés par une IDE spécialisée dans l'éducation thérapeutique.

- **En ce qui concerne le traitement médicamenteux autre :**

o

- **Enfin, en ce qui concerne la prise en charge et/ou le dépistage des maladies potentiellement associées à la polyarthrite rhumatoïde,** nous recommandons Cliquez ici pour entrer du texte..

Il est recommandé à M. TEST de montrer ce présent compte-rendu à tous les médecins impliqués dans sa prise en charge et notamment au Docteur Cliquez ici pour entrer du texte., rhumatologue, qu'il/qu'elle doit revoir en consultation.

Bien confraternellement.



Nom du patient : TEST  
Prénom du patient : RHUMATO  
IPP :

Edité par : @Easily  
Pages :6/7

Dr Laurent GRANGE,  
PH

Pr Athan BAILLET,  
PU-PH

Dr Romain GASTALDI,  
PH

le

**L'hospitalisation de jour a été justifiée par :**

- Une fragilité particulière du patient  oui  non
  - Un terrain à risque  oui  non
  - Un besoin de surveillance particulier  oui  non.
- ⇒ Si oui les éléments ont été précisés dans le CR

**Un produit de la réserve hospitalière a été administré**

oui  non

⇒ Si oui les éléments ont été précisés dans le CR

**Prestations intellectuelles réalisées au cours de l'HDJ :** (nom, qualité des intervenants)

-  
-

**Actes techniques réalisés au cours de l'HDJ :** (un intervenant ne peut être comptabilisé à la fois comme effectuant un acte intellectuel et technique)

- Recueil des constantes, réalisation du bilan sanguin et coordination de la journée par une IDE

**Supplemental figure 7 – Recommendations rate in adherent group and not adherent group**

	Non adherence to screening recommendations 100 (53%)	Adherence to screening recommendations 89 (47%)	Overall 189 (100%)
<b>Recommendations</b>			
<b>Cardiovascular diseases</b>	38 (38%)	33 (37%)	71 (38%)
<b>SAOS</b>	21 (21%)	10 (11%)	31 (16%)
<b>Smoking</b>	33 (33%)	10 (11%)	43 (23%)
<b>Vaccinations</b>			
Influenza	55 (55%)	40 (45%)	95 (50%)
Pneumococcus	47 (47%)	37 (42%)	84 (44%)
DTP	29 (29%)	36 (40%)	65 (34%)
<b>Osteoporosis</b>	9 (9%)	2 (2%)	11 (6%)
<b>Dermatology</b>	65 (65%)	63 (70%)	128 (68%)
<b>Dentist</b>	31 (31%)	31 (35%)	62 (33%)
<b>Gastrology</b>	7 (7%)	9 (10%)	16 (8%)



THÈSE SOUTENUE PAR : Lauriane Vacher

TITRE :

Adhésion aux biothérapies et aux recommandations de prise en charge des comorbidités des spondyloarthrites en pratique courante

CONCLUSION :

Contexte : Dans la littérature, les données rapportant l'influence des comorbidités sur l'observance du bDMARD sont rares.

Objectif : Evaluer l'impact d'un programme multidisciplinaire de dépistage systématique des comorbidités SpA sur le maintien thérapeutique des bDMARD à 12 mois.

Patients et méthodes : Les données relatives au dépistage des comorbidités ont été collectées selon les recommandations EULAR lors de l'initiation d'un bDMARD. L'adhésion aux recommandations et le maintien thérapeutique des bDMARD ont été évalués à 12 mois. Le groupe adhérent est défini comme ayant plus de 80 % des recommandations suivies à 12 mois.

Le critère d'évaluation principal était le maintien du bDMARD à 12 mois. Les critères secondaires étaient les taux d'arrêt à 12 mois des bDMARD pour effets indésirables, et/ou d'inefficacité selon le respect des recommandations.

Les variables qualitatives ont été analysées à l'aide du test du Chi-2. Pour les variables quantitatives, le test t de Student a été utilisé dans le cas des variables gaussiennes et le test de Wilcoxon Rank dans le cas des variables non gaussiennes. Le délai d'arrêt du bDMARD a été analysé à l'aide des courbes de Kaplan-Meier. Un modèle de Cox expliquant le maintien du bDMARD à 12 mois a été généré en induisant des paramètres statistiquement significatifs de l'analyse univariée.

Résultats : 561 patients avec un rhumatisme inflammatoire chronique ont été examinés pour leur éligibilité ; l'analyse porte sur 189 patients SpA. Un total de 89 patients (47 %) appartenait au groupe adhérent et 100 patients (53 %) au groupe non adhérent aux recommandations à 12 mois. Les hommes étaient significativement moins adhérents aux recommandations (38/105=36 % contre 51/84=61 % chez les femmes), Odds ratio 0.5 IC 95 % [0.3-0.9]. Les patients fumeurs adhéraient significativement moins aux recommandations (10/43=23 % contre 79/176=45 % chez les non-fumeurs, Odds ratio 0.3 IC 95 % [0.1-0.6]). En analyse multivariée, le genre masculin était associé avec l'absence d'adhésion aux recommandations, Odds ratio 0,4 IC 95 % [0,2-0,7] ; de même que le tabagisme, Odds ratio 0,3 IC 95 % [0,1-0,6].

A 12 mois, les bDMARDs ont été arrêtés chez 52 patients (29 %). L'arrêt du bDMARD était lié à un événement indésirable chez 31 patients (17 %) et à une réponse insuffisante chez 27 patients (32 %). L'observance des anti-TNF était supérieure à celle des autres bDMARDs (76 % versus 67 % pour les anti-IL17 et les anti-IL12/23, Odds ratio 5,1 IC 95 % [2,8-11,4]). Le BASDAI initial moyen était significativement plus élevé chez les patients ayant interrompu le bDMARD à M12 (5,0 (2,0) contre 6,0 (2,0), p = 0,04). Les patients atteints de sacro-iliite ont interrompu significativement plus de bDMARD (29 % contre seulement 11 % chez les patients sans sacro-iliite, Odds ratio 3,2 IC 95 % [1,1-9,2]). Les femmes ont arrêté le bDMARD significativement plus souvent (39 % contre seulement 19 % chez les hommes, Odds ratio 2.4 IC 95 % [1.3-4.6]).

Conclusion : Le genre féminin était associé à une meilleure adhésion aux recommandations de dépistage systématique des comorbidités et à un meilleur maintien thérapeutique au bDMARD à 12 mois chez des patients atteints de spondyloarthrite. L'adhésion au dépistage systématique des comorbidités n'était pas associée à un meilleur maintien des bDMARDs.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 22/09/23

LE DOYEN DE LA FACULTÉ DE MÉDECINE



Pr Olivier PALOMBI

Pr Olivier PALOMBI  
Doyen de l'UFM de Médecine  
Par délégation  
du Président de l'UGA

LE PRÉSIDENT / LA PRÉSIDENTE DU JURY



Pr Laurence Bouillet

# Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ **Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

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

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

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

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

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

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

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

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

”

## Résumé

**Contexte :** Dans la littérature, les données rapportant l'influence des comorbidités sur l'observance du bDMARD sont rares.

**Objectif :** Evaluer l'impact d'un programme multidisciplinaire de dépistage systématique des comorbidités SpA sur le maintien thérapeutique des bDMARD à 12 mois.

**Patients et méthodes :** Les données relatives au dépistage des comorbidités ont été collectées selon les recommandations EULAR lors de l'initiation d'un bDMARD. L'adhésion aux recommandations et le maintien thérapeutique des bDMARD ont été évalués à 12 mois. Le groupe adhérent est défini comme ayant plus de 80 % des recommandations suivies à 12 mois. Le critère d'évaluation principal était le maintien du bDMARD à 12 mois. Les critères secondaires étaient les taux d'arrêt à 12 mois des bDMARD pour effets indésirables, et/ou d'inefficacité selon le respect des recommandations. Les variables qualitatives ont été analysées à l'aide du test du Chi-2. Pour les variables quantitatives, le test t de Student a été utilisé dans le cas des variables gaussiennes et le test de Wilcoxon Rank dans le cas des variables non gaussiennes. Le délai d'arrêt du bDMARD a été analysé à l'aide des courbes de Kaplan-Meier. Un modèle de Cox expliquant le maintien du bDMARD à 12 mois a été généré en incluant des paramètres statistiquement significatifs de l'analyse univariée.

**Résultats :** 561 patients avec un rhumatisme inflammatoire chronique ont été examinés pour leur éligibilité ; l'analyse porte sur 189 patients SpA. Un total de 89 patients (47 %) appartenait au groupe adhérent et 100 patients (53 %) au groupe non adhérent aux recommandations à 12 mois. Les hommes étaient significativement moins adhérents aux recommandations (38/105=36 % contre 51/84=61 % chez les femmes), Odds ratio 0.5 IC 95 % [0.3-0.9]). Les patients fumeurs adhéraient significativement moins aux recommandations (10/43=33 % contre 79/176=54 % chez les non-fumeurs, Odds ratio 0.3 IC 95 % [0.1-0.6]). En analyse multivariée, le genre masculin était associé avec l'absence d'adhésion aux recommandations, Odds 0,4 IC95% [0,2-0,7] ; de même que le tabagisme, Odds ratio 0,3 IC 95% [0,1-0,6]. A 12 mois, les bDMARDs ont été arrêtés chez 53 patients (28 %). L'arrêt du bDMARD était lié à un événement indésirable chez 31 patients (17%) et à une réponse insuffisante chez 27 patients (32 %). L'observance des anti-TNF était supérieure à celle des autres bDMARDs (76 % versus 67 % pour les anti-IL17 et les anti-IL12/23, Odds ratio 5,1 IC 95 % [2,8-11,4]). Le BASDAI initial moyen était significativement plus élevé chez les patients ayant interrompu le bDMARD à M12 (5,0 (2,0) contre 6,0 (2,0), p = 0,04). Les patients atteints de sacro-iliite ont interrompu significativement plus de bDMARD (29 % contre seulement 11 % chez les patients sans sacro-iliite, Odds ratio 3,2 IC 95 % [1,1-9,2]). Les femmes ont arrêté le bDMARD significativement plus souvent (39 % contre seulement 19 % chez les hommes, Odds ratio 2.4 IC 95% [1.3-4.6]).

**Conclusion :** Le genre féminin était associé à une meilleure adhésion aux recommandations de dépistage systématique des comorbidités et à un moins bon maintien thérapeutique au bDMARD à 12 mois chez des patients atteints de spondylarthrite. L'adhésion au dépistage systématique de comorbidités n'était pas associée à un meilleur maintien des bDMARDs.



## Abstract

**Background:** Spondyloarthritis (SpA) is associated with an increased prevalence of comorbidities which may impact on treatment strategies and outcomes. In the literature, data reporting the influence of comorbidities on bDMARD adherence are rare.

**Objective:** We aimed to evaluate the impact of a multidisciplinary systematic screening program for SpA comorbidities on therapeutic maintenance of bDMARDs at 12 months.

**Patients and Methods:** Data relating to screening for comorbidities were collected according to EULAR recommendations when initiating a bDMARDs, from December 2016 to April 2022. Adherence to recommendations and therapeutic maintenance of the bDMARD were assessed at 12 months. The adherent group is defined as having more than 80% of the recommendations followed at 12 months. The primary endpoint was maintenance of bDMARD at 12 months. The secondary endpoints were the withdrawal rates at 12 months bDMARDs for adverse events, and/or for ineffectiveness depending on adherence to recommendations. Qualitative variables were analysed using the Chi-square test. For quantitative variables, the Student t test was used in the case of Gaussian variables and the Wilcoxon Rank test in the case of non-Gaussian variables; bDMARD withdrawal time was analysed using Kaplan-Meier curves. A Cox model explaining the maintenance of bDMARD at 12 months was generated by including statistically significant parameters in the univariate analysis.

**Results:** 561 patients with chronic inflammatory rheumatism were screened for eligibility; the analysis concerns 189 SpA patients. A total of 89 patients (47%) were in the adherent group and 100 patients (53%) in the non-adherent group to the recommendations at 12 months. Men were significantly less adherent to the recommendations (38/105=36% compared to only 51/84=61% among women, Odds ratio 0.5 IC 95 % [0.3-0.9]). Smoking patients adhered significantly less to the recommendations (10/43=23 % compared to 79/176=45% among non-smokers, Odds ratio 0.5 IC 95 % [0.1-0.6]). In the multivariate analysis gender was associated with withdrawal, Odds ratio concerning men Odds 0,4 IC95% [0,2 -0,7]. Smoking was inversely associated with adherence, Odds ratio 0.3 IC95% [0.1-0.6]. At 12 months, bDMARDs were stopped in 55 patients (29%). bDMARD withdrawal was linked to an adverse event in 31/189 (17%) patients and to an insufficient response in 27/189 (32%) patients. Adherence to anti-TNF was higher than other bDMARDs (76% versus 67% for anti-IL17 and anti-IL12/23, Odds ratio 5.1 95% CI [2.8-11.4]). Mean initial BASDAI was significantly higher in patients who discontinued bDMARD at M12 (5.0 (2.0) vs. 6.0 (2.0), p=0.04). Patients with sacroiliitis interrupted significantly more bDMARDs (29% compared to only 11% in patients without sacroiliitis, Odds ratio 3.2 95% CI [1.1-9.2]). Women discontinued bDMARD significantly more often (39% compared to only 19% in men, Odds ratio 2.4 IC 95% [1.3-4.6]).

**Conclusion:** Female gender was associated with better adherence to systematic screening recommendations for comorbidities and with poorer bDMARD continuation at 12 months in patients with spondyloarthritis. Adherence to comorbidities screening recommendations was not associated with better bDMARD continuation at 12 months.