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Influence des co-médications sur la réponse aux anti-TNF dans la spondyloarthrite axiale

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Par MASSON Maëva

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**Influence des co-médications sur la réponse aux anti-TNF dans la
spondyloarthrite axiale**

Sous la direction de : Monsieur le Professeur Thierry SCHAEVERBEKE

Membres du jury :

Mme le Professeur Marie-Elise TRUCHETET	Présidente
Mr le Docteur Jean-Philippe VERNHES	Rapporteur et examinateur
Mme le Docteur Marie KOSTINE	Examinatrice
Mr le Professeur Charles CAZANAVE	Examineur
Mr le Professeur Thierry SCHAEVERBEKE	Directeur

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Abréviations :

Français:

AINS = Anti-Inflammatoires Non-Stéroïdiens

CLI = Cellules Lymphoïdes Innées

CMH = Complexe Majeur d'Histocompatibilité

IEC = Inhibiteurs de l'Enzyme de Conversion

IL = Interleukine

IPP = Inhibiteurs de la Pompe à Proton

MICI = Maladies Inflammatoires Chroniques de l'Intestin

SpA = Spondyloarthrite

Anglais:

ACE-i = Angiotensin Converting Enzyme inhibitor

ATB = Antibiotics

ASDAS = Ankylosing Spondylitis Disease Activity Score

Ax-SpA = Axial Spondyloarthritis

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

MTX = Methotrexate

NSAIDs = Non-steroidal anti-inflammatory drugs

ODM = Oral Diabetes Drug

PPIs = Proton Pump Inhibitors

SpA = Spondyloarthritis

TNF-i = Tumor Necrosis Factor inhibitor

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INTRODUCTION

Le terme de spondyloarthrite (SpA) regroupe des rhumatismes inflammatoires chroniques partageant certaines de leurs manifestations cliniques ainsi qu'un terrain génétique commun. La physiopathologie est complexe résultant de l'intrication de plusieurs facteurs génétiques, environnementaux et inflammatoires/auto-immuns. Ce travail de thèse se focalise sur les patients présentant une forme axiale de la pathologie. Le diagnostic sur l'association de plusieurs critères (**Figure 1**) (1).

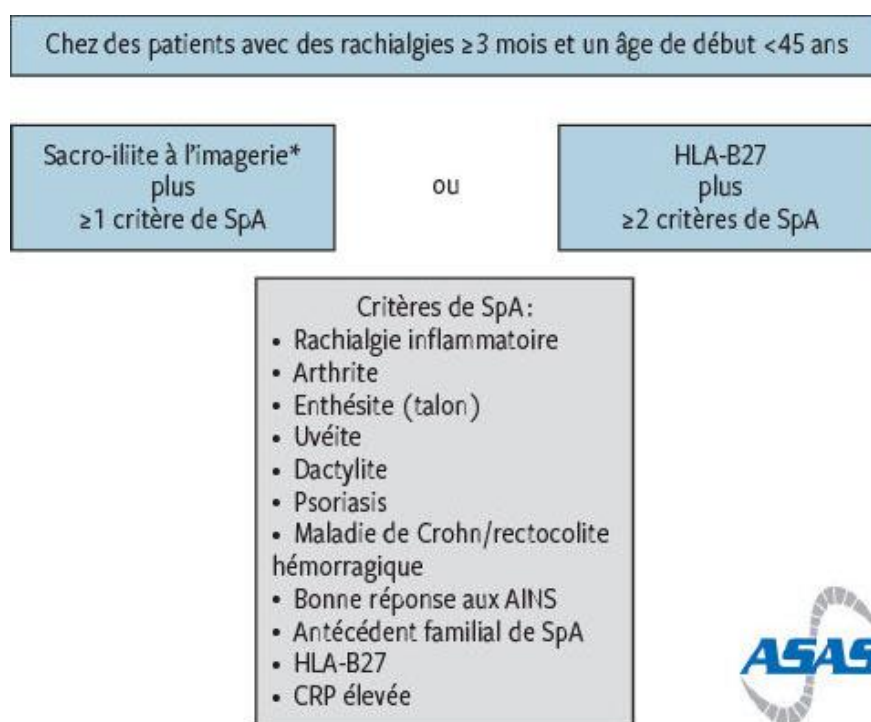


Figure 1. Assessment in spondyloarthritis international society classification criteria for axial spondyloarthritis. Rudwaleit *et al.* Ann Rheum Dis 2009 (1)

La contribution génétique la plus connue est la présence du gène de l'antigène leucocytaire humain HLA-B27. Il existe plus de 100 sous-types alléliques, le B27*05 étant le plus répandu. D'autres facteurs génétiques entrent compte, plusieurs études d'association pangénomique (genome-wide association study, GWAS) ont permis d'identifier au moins 113 variants génétiques, dont 80% indépendant du complexe majeur d'histocompatibilité (CMH) (2–4). Parmi eux on retrouve le gène ERAP (Endoplasmic reticulum aminopeptidase) codant pour des enzymes présentes dans le réticulum endoplasmique responsables du découpage des peptides afin d'obtenir la longueur adéquate pour se lier aux molécules HLA de classe I. Des

polymorphismes d'ERAP-1 auraient pour conséquence une augmentation d'expression des homodimères de la chaîne lourde libre du HLA-B27 à la surface de la cellule, ce qui pourrait indirectement stimuler la réponse Th17. D'autres gènes ont été identifiés, impliqués dans la voie de l'interleukine-23/17 ou dans la différenciation et l'activation lymphocytaire. Enfin, le rôle de facteurs environnementaux dans le déclenchement et l'activité de la SpA a été mis en évidence, comme le tabac, les événements de vie stressants ou l'environnement bactérien (5).

Spondyloarthritis et microbiome:

On connaît l'association entre SpA et maladies inflammatoires chroniques de l'intestin (MICI). De nombreux arguments témoignent du rôle du microbiote dans la pathogénie des MICI (6,7). 5 à 10% des patients atteints de SpA présentent également une MICI et inversement environ 30% des patients atteints de MICI présentent des manifestations de SpA (8). Des études ont montré que jusqu'à 60 % des patients atteints de SpA présentaient une inflammation intestinale subclinique (9–12). Van Praet *et al.* ont même suggéré un lien entre l'inflammation intestinale et SpA axiale, avec un œdème osseux en regard des articulations sacro-iliaques plus important chez les patients présentant une inflammation intestinale chronique associée (13). Par ailleurs, certaines infections digestives (*Salmonella* sp., *Shigella* sp., *Yersinia* sp. et *Campylobacter* sp) et uro-génitales (*Chlamydia* sp.) peuvent être à l'origine d'arthrites réactionnelles. Environ 20% des patients développent un tableau de SpA dans les 10 à 20 ans suivant.

Le microbiote joue un rôle majeur dans l'immunité intestinale mais aussi systémique comme cela peut être illustré grâce aux modèles murins axéniques ou germ-free qui présentent une moindre expression de peptides anti-microbien et production d'IgA, une hypoplasie des plaques de Peyer ou une population de lymphocytes T moins diversifiée, ainsi que des anomalies ne se limitant pas à l'épithélium intestinal, avec des organes lymphoïdes secondaires hypoplasiques (14). En l'absence de toute pathologie, il existe une homéostasie entre l'hôte et son microbiote limitant la translocation des micro-organismes et de leurs produits à travers la barrière épithéliale grâce au maintien de la couche de mucus et des jonctions serrées entre les cellules épithéliales. L'effet du microbiote sur le système immunitaire fait également intervenir divers métabolites comme les acides gras à chaîne courte (AGCC), tels que le propionate, l'acétate ou le butyrate (15). L'inflammation subclinique observée dans la SpA ou MICI se caractérise par une perte de cette fonction de barrière. L'immunité de type 3 caractérisée par la production IL-23 dépendante d'IL-17 et d'IL-22 par les cellules lymphoïdes innées 3 (CLI 3), les lymphocytes T $\gamma\delta$ et T CD4⁺ Th17, joue un rôle dans la défense contre les bactéries

extracellulaires et champignons. Des études chez l'homme ont démontré une augmentation du nombre de CLI 3 dans l'intestin des patients atteints de SpA (16) ainsi que le recrutement de polynucléaires neutrophiles et de cellules système phagocytaire mononucléé. L'observation de CLI 3 provenant de l'intestin dans la circulation et au niveau des tissus enflammés chez les patients atteints de SpA suggère une recirculation des CLI du site muqueux vers les tissus lymphoïdes et potentiellement les enthèses et articulations (**Figure 2**).

Concernant les modèles animaux, les rats transgéniques HLA-B27 développent spontanément un phénotype similaire à celui observé chez l'homme, avec des lésions inflammatoires intestinales, articulaires et cutanées constituant un modèle intéressant pour appréhender la physiopathologie des MICI et SpA. Taurog *et al.* ont rapporté que les rats transgéniques HLA-B27 élevés dans un environnement sans germes ne développaient pas de manifestation intestinale ou articulaire. Ces résultats soutiennent le concept selon lequel l'inflammation intestinale et articulaire sont étroitement liées sur le plan pathogénique (17). De même, Asquith *et al.* ont mené une étude sur des individus sains porteur de l'allèle HLA-B27 ayant montré qu'il existait une composition du microbiote intestinal distincte de celle observée chez les sujets HLA-B27 négatifs (18). Plusieurs études ont récemment été réalisées chez des patients atteints de SpA, permettant d'étudier le microbiote intestinal dans des échantillons de selles ou des biopsies intestinales. Breban *et al.* ont comparé le microbiote de 3 groupes d'individus: SpA, polyarthrite rhumatoïde (PR) ou témoins (19). Une raréfaction de la diversité microbienne a été observée dans le cas des deux maladies. Un autre constat était une surreprésentation de l'espèce *Ruminococcus gnavus*, bactérie commensale ayant la capacité de cliver et dégrader le mucus intestinal, dans le groupe de patients SpA par rapport aux témoins et aux patients atteints de PR, même en l'absence de MICI associée.

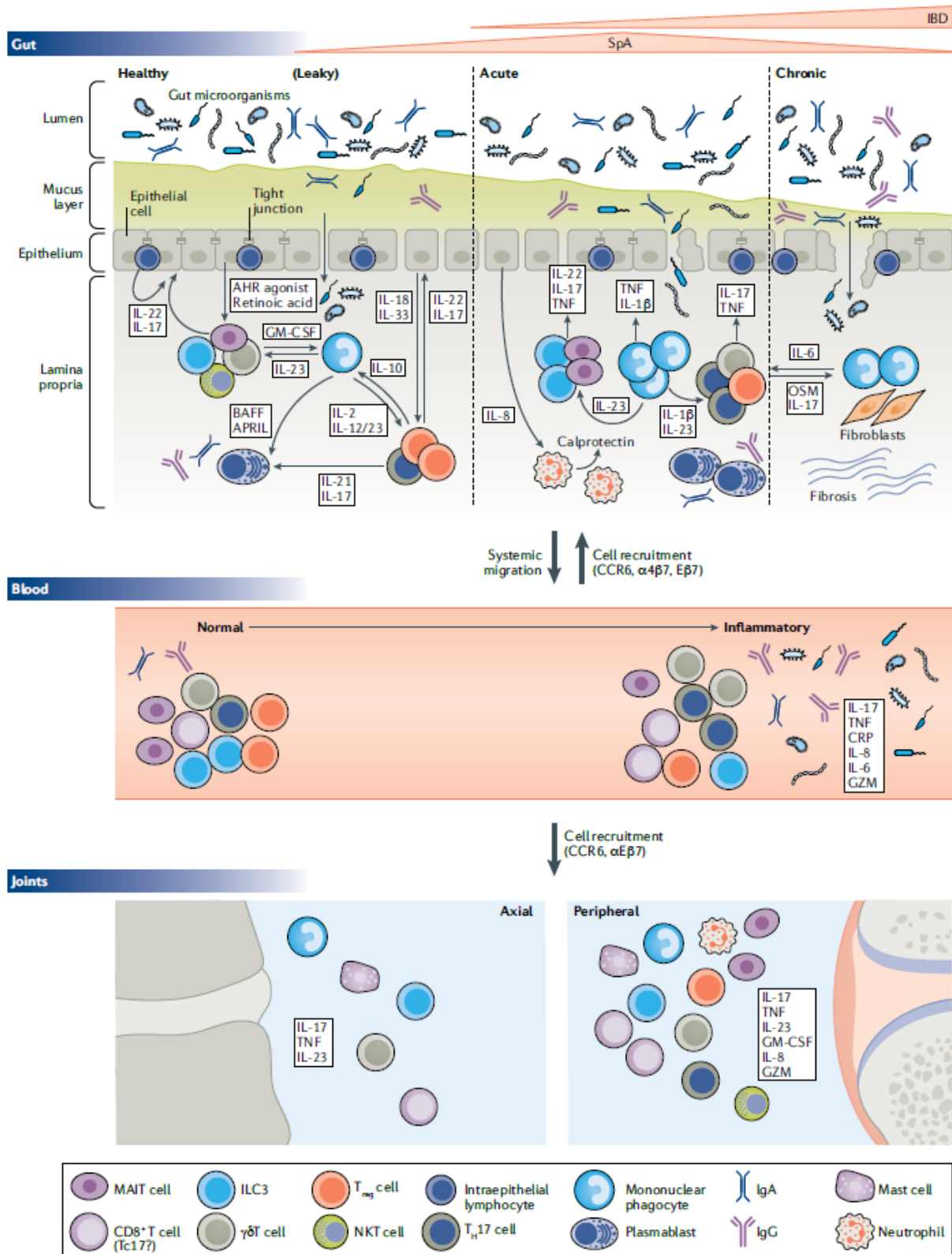


Figure 2. Immunological changes in the gut–joint axis of inflammation in SpA. Gracey *et al.* Nat Rev Rheumatol 2020 (20).

Intéraction hôte-microbiome-médicaments:

La pharmacomicrobiomique est une discipline émergente basée sur l'interaction entre le microbiome et les médicaments (absorption, distribution, élimination). Le microbiote intestinal comptabilise 10^{12} à 10^{14} micro-organismes (21). Il est principalement représenté par quatre phyla: protéobactéries, actinobactéries, firmicutes et bacteroidetes, les deux derniers représentant environ 90% (22,23). Seulement 20 à 30% des espèces sont cultivables. Au cours des dernières années, de nouvelles technologies telles que la métagénomique ou la spectrométrie de masse ou MALDI-TOF (Matrix Assisted Laser Desorption Ionization - Time of Flight) ont permis d'identifier et/ou de quantifier phylogénétiquement les composants du microbiote intestinal (24,25). Des projets tels que Meta-HIT (26) ou Human Microbiome Project (27) de caractérisation du microbiome ont accéléré l'étude de cette discipline. Outre les médicaments, d'autres facteurs peuvent interagir avec le microbiote (environnement, alimentation, facteurs génétiques), rendant l'étude du dialogue microbiome-médicaments complexe. Le microbiote peut avoir des effets directs sur les médicaments mais également avoir des effets indirects en influençant la biodisponibilité des médicaments ou la réponse aux médicaments via son interaction avec les systèmes immunitaire et métabolique de l'hôte (**Figure 3**).

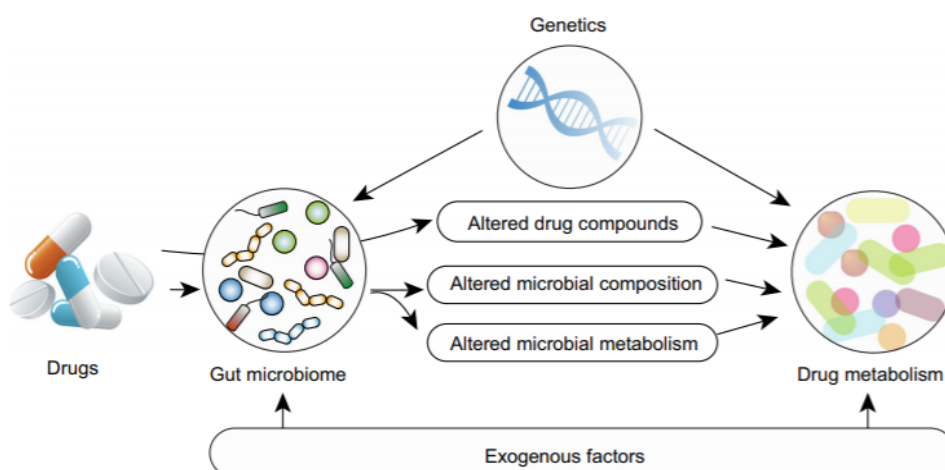


Figure 3. Host-microbe-diet interactions in drug metabolism. Doestzada *et al.* Protein Cell 2018 (28).

S'il n'est pas surprenant que les antibiotiques aient un impact sur la fonction et composition du microbiote intestinal (29,30), d'autres médicaments couramment prescrit ont également une influence (**Tableau 1**). Maier *et al.* ont analysé plus de 1 000 médicaments contre 40 souches bactériennes intestinales et ont constaté que 24 % des médicaments tels que les IPP, les statines,

antidépresseurs ... inhibaient la croissance d'au moins une souche *in vitro* (31). D'autres études, basées sur l'analyse du microbiote via des méthodes de métagénomique de patients exposés ou non à un médicament abondent dans le même sens (32).

<i>Corticoïdes</i>	Augmentation de la proportion relative de Firmicutes et d'Actinobacteria (33)
<i>IPP</i>	Pullulation bactérienne de l'intestin grêle (Small Intestinal Bacterial Overgrowth), surreprésentation bactérienne du tractus digestif haut (34,35)
<i>Metformine</i>	Diminution des espèces productrices de butyrate (36)
<i>Méthotrexate</i>	Diminution du phylum Bacteroidetes, pas de diminution de la diversité microbienne (37)
<i>Statine</i>	Augmentation des genres <i>Lactobacillus</i> et <i>Bifidobacterium</i> (38,39) Augmentation de la proportion d' <i>Akkermansia muciniphila</i> et <i>Faecalibacterium prausnitzii</i> (40)

Tableau 1. Exemple de modification du microbiote intestinal par des médicaments non-antibiotiques.

L'apport de la pharmacomicrobiomique peut être illustré par l'exemple des immunothérapies anticancéreuses (inhibiteurs des checkpoint immunitaires, ICI). Il a été montré par Routy *et al.* (41) que l'administration d'un traitement antibiotique préalablement à l'initiation d'ICI altérerait la réponse anti-tumorale chez l'homme et la souris. Une surreprésentation de Firmicutes chez les patients répondeurs a été mise en évidence, ainsi que d'une espèce appartenant à l'ordre des Verrucomicrobiales, *Akkermansia muciniphila*. L'apport oral de cette bactérie aux souris non répondeuses a permis de restaurer l'efficacité des ICIs. Depuis, d'autres études ont évalué l'influence des co-médications sur la réponse aux ICIs tels que les IPP ou les corticoïdes, qui pourraient avoir un impact négatif, cependant ces résultats reposent à l'heure actuelle sur des études observationnelles rétrospectives. Récemment, a vu le jour le premier essai clinique de phase 1 sur l'apport de la transplantation fécale comme traitement complémentaire (42). Par ailleurs, Buti *et al.* ont proposé un score pronostique basée sur l'exposition cumulative aux antibiotiques, IPP et/ou corticoïdes (43). Concernant les anti-TNF, les données sont pour le moment plus restreintes. Liu *et al.* (44) ont montré qu'un traitement par etanercept chez la souris (modèle protéoglycane) restaurait une composition similaire au microbiote des souris contrôles. Cette observation a également été faite chez l'homme. Yi *et al.* ont conduit une étude sur 127 patients atteints de spondylarthrite

ankylosante dont 67 ont bénéficié d'une biothérapie (etanercept ou infliximab) et 123 patients contrôles (45). Concernant le possible impact du microbiote intestinal sur la réponse aux anti-TNF, Bazin *et al.* (46) ont analysé le microbiote intestinal de 19 patients atteints de SpA à l'introduction et à trois mois du début du traitement par anti-TNF. L'activité de la maladie tenait compte des scores BASDAI et ASDAS. Il n'a pas été montré de différence significative de la composition quantitative et qualitative du microbiote des patients répondeurs en comparaison à celui des patients non répondeurs à trois de traitement. En revanche, a été observé que l'ordre Burkhoriales tenait une proportion significativement plus importante dans le microbiote des patients répondeurs avant introduction de l'anti-TNF.

Le microbiome intestinal apparaît comme un acteur important dans le domaine de la médecine personnalisée. La pharmacomicrobiomique pourrait donc avoir au moins deux applications cliniques: la première serait de combiner le microbiome et le profil génétique d'un patient donné afin de mieux prédire la réponse à certains traitements; la seconde serait de moduler le microbiome intestinal afin de potentialiser l'efficacité des médicaments à l'échelle individuelle. Considérant le rôle potentiel du microbiote intestinal dans la physiopathologie de la SpA comme dans la réponse thérapeutique, l'objectif de cette étude était d'étudier l'influence des co-médications connues pour interférer avec le microbiote intestinal sur la réponse thérapeutique à un premier TNF-i chez des patients suivis au CHU de Bordeaux SpA axiale et de valider les résultats dans une cohorte de réplication.

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Influence of Commonly Used Co-Medications on the Response To TNF-Inhibitors in Axial Spondyloarthritis Patients

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Abstract:

Objective: Considering the potential role of the gut microbiota in the pathophysiology of spondyloarthritis (SpA) as in the therapeutic response to biologics, we studied the influence of co-medications known to interfere with the microbiota with the therapeutic response to TNF-inhibitor (TNF-i) in SpA patients.

Methods: This was a retrospective cohort including patients having axial SpA (ax-SpA). Patients were classified as responder (R) or non-responder (NR) according to the BASDAI (< 40/100) value at month 6 or to the clinician judgment. We collected co-medication administered 1 month before and during the first 3 months of the TNF-i treatment. A replication cohort was built for external validation of the results. Multivariate logistic regression models adjusted for potential confounders were applied to evaluate the relationship between co-medications and TNF-i response.

Results: We included 188 patients of whom 135 (72%) were considered as R. In univariate analysis, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs),

antibiotics and psychotropic drugs intakes were significantly associated with a higher proportion of NR patients, unlike for corticosteroids, methotrexate (MTX), angiotensin-converting enzyme inhibitors and statins use. NSAIDs, PPIs and antibiotics intakes were considered as independent factors associated with TNF-i failure in multivariate analysis. 185 patients were included in the replication cohort, including 127 (69%) R patients. In multivariate analysis, although 88% of patients taking PPIs were also given NSAIDs, PPIs remained associated with a poorer response to a first TNF-i ($p < 0.001$).

Conclusion: Co-medication with PPIs was significantly associated with a decreased chance to respond to TNF-i. The hypothesis that this effect is due to their interference with the gut microbiota is only speculative but, regardless of the reason for this interaction, clinicians should be aware of the potential negative effect of PPIs on TNF-i.

Key words: TNF-inhibitors, axial spondyloarthritis, proton pump inhibitors, microbiota

What is already known about this subject?

Altered microbiota composition is suspected to be involved in the pathophysiology of spondyloarthritis (SpA) as potentially in the therapeutic response.

Pharmacomicrobiomics is an emerging field based on the crosstalk between microbiome and drugs. Commonly used drugs such as non-steroid anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), methotrexate (MTX), antibiotics or metformin have been reported to influence gut microbiota, and thus are potential candidates to modulate response to TNF-inhibitors (TNF-i).

What does this study add?

This is the first study to evaluate the association between concomitant commonly used drugs and response to a first TNF-i in ax-SpA. PPIs, one of the most frequently prescribed classes, were an independent factor of TNF-i failure. This result was validated in a replication cohort.

How might this impact on clinical practice or future developments?

PPIs are often over-prescribed and used for inappropriate indication and duration. Clinicians should be aware of its potential negative effect on TNF-i and limit prescription of PPIs only for patients who will gain a clinical benefit.

INTRODUCTION

The pathogenesis of spondyloarthritis (SpA) is complex and related to many factors, and the reason why some patients fail to respond to tumor necrosis factor inhibitors (TNF-i) remains unclear. SpA and inflammatory bowel disease (IBD) share genetic risk factors. As in IBD, accumulating evidence has suggested that gut microbiota may be involved in the development of SpA (1–3). Clinical studies have shown that up to 60% of patients with SpA had subclinical gut inflammation (4–6). Van Praet *et al.* have suggested a link between gut inflammation and progressive disease in axial SpA, with a higher degree of bone marrow oedema of sacroiliac joints in patients with chronic gut inflammation (7). Some data suggest the influence of gut microbiota composition on the response to TNF-i. Bazin *et al.* (8) analysed gut microbiota of 19 SpA patients. High proportion of Burkholderiales at baseline was associated with the clinical response at month 3. TNF-i have also been shown to restore the perturbed microbiome observed in proteoglycan-induced SpA mice (9) and in patients with ankylosing spondylitis to that of healthy controls (10).

Relationship between drugs and microbiota is complex, the human gut microbiota can influence drug responses and efficacy, while these drugs can also impact the gut bacteria (11,12). Vich Vila *et al.* analysed relations between commonly used drugs and the gut microbiome. Antibiotics were unsurprisingly linked with gut microbiome changes as already described (13,14); but 18 other medications were associated with microbial modifications, among which proton pump inhibitors (PPIs) and metformin, that showed with antibiotics the strongest associations (15), and thus are likely to influence the therapeutic response to TNF-i. Furthermore, it has been shown that the clinical response to immunotherapy in cancer may be altered by commonly used co-medication (16–18). This could be driven by gut microbiota as supported by a study conducted by Routy *et al.* (19) in which fecal microbiota transplantation from responder patients to mice restored the efficacy of immune checkpoint inhibitors.

Considering the potential role of the gut microbiota in the pathophysiology of SpA as in the therapeutic response, the aim was to study the influence of co-medications known to interfere with the gut microbiota on the therapeutic response to a first TNF-i in axSpA patients

from the University Hospital of Bordeaux in a retrospective cohort and to validate the results in a replication cohort.

MATERIAL AND METHODS

Patient selection:

We retrospectively reviewed the charts of all patients suffering from ax-SpA who initiated a first TNF-i treatment according to the recommendations of the French Society of Rheumatology (20) in our rheumatology department of the university hospital of Bordeaux in France between 2009 and 2019. The other selection criteria to be included in the study were the diagnosis of ax-SpA according to the ASAS criteria 2009 (radiographic or non-radiographic) (21), to have at least a 6-month follow-up after treatment initiation, to be aged of 18 years or more at treatment initiation. Patients who discontinued TNF-i within the first 6 month for allergy, severe infection or pregnancy were excluded. Cohort formed by included patients was named cohort 1. To validate our results, we built a replication cohort (cohort 2) using the same chart extraction procedure from four other French university hospitals: Brest, Toulouse, Saint-Etienne and Besançon.

Data collection

Demographic details and disease characteristics were collected including: age at diagnosis and TNF-i initiation, presence of sacroiliitis at magnetic resonance imaging (MRI) and/or X-Rays, HLA-B27 status, peripheral and extra-articular manifestations, baseline and at month 6 (M6) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and C-reactive protein (CRP) level (mg/l), body mass index (BMI) and smoking status.

Regarding co-medications, we collected all drugs known to interfere with the gut microbiota and frequently prescribed including : non-steroidal anti-inflammatory drugs (NSAIDs), PPIs, methotrexate (MTX), corticosteroids, antibiotics, antifungal and antiviral agents, metformin and other oral antidiabetes drugs, insulin, aspirin, statins, angiotensin converting enzyme inhibitors (ACE-i), morphine, and antiepileptics, antidepressants and anxiolytics gathered under the name of psychotropic drugs, that were administered 1 month before and during the first 3 months of the TNF-i treatment for > 5 days for antibiotics and at least 1 month for other co-medications. The class and route of administration of antibiotics, the indication and dose of PPIs (half, simple or double), the dose and route of administration of MTX and dose of corticoids were also collected.

Statistical analysis

Patients were classified as responder (R) or non-responder (NR) according to the BASDAI < 40/100 value at month (M) 6 or to the clinician judgment when BASDAI was not available. Remission was defined by a BASDAI < 20/100 at M6. We analyzed patient demographics and disease characteristics at baseline using standard descriptive statistics. Quantitative data were expressed as mean \pm standard deviation in the case of normal distribution or medians (interquartile range, IQR) otherwise, and qualitative variables as numbers and percentages. For comparison of characteristics of cohorts 1 and 2, we performed the Fisher's test or Chi2 test for categorical variables. Quantitative variables were compared by the Student's test if the conditions for test validity were met (normal distribution and homogeneous variances). If these conditions were not fulfilled, a Mann Whitney test was used.

We only considered for statistical analysis, drugs given to more than 5% of patients. Based on data from the literature, the following factors were included as potential confounders: age, gender, disease duration, BASDAI and CRP level at baseline, magnetic sacroiliitis, positive HLA-B27 (22,23), Body Mass Index (BMI) and current smoking (24,25). Because of missing baseline data, multiple imputation by chained equations was used. Logistic regression was performed to impute for binary variables and predictive mean matching for continuous variables (26,27). Variables with more than 20% missing data were not entered into the analysis, thus BMI and smoking status was not included (S1 and S2 Tables). Univariate and multivariate logistic regression models were used to assess and account for confounders to determine if a co-medication was an independent factor of TNF-i failure. Sensitivity analysis was carried out by performing the analysis using BASDAI50 at month 6 as criteria for response to TNF-i.

Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided p-value ≤ 0.05 was considered statistically significant. All analyses were computed on STATA 13.1 software.

RESULTS

Study population

A total of 188 patients having ax-SpA were included in cohort 1. Disease characteristics and demographic information are summarized in Table 1. Respectively, 159 (87%) and 119 (72%) patients had radiographic or magnetic sacroiliitis. Peripheral manifestations were present in 98 patients (52%). 111 patients (72%) had positive HLA-B27. HLA-27 status was missing for 35

patients. Median BASDAI at baseline was 49 (IQR [43;59]). Etanercept and Adalimumab were the TNF-i the most prescribed. MTX was combined with TNF-i in 52 patients and sulfasalazine in 4 patients. Concerning co-medications, NSAIDs, PPIs, MTX, corticosteroids, antibiotics, ACE-i and psychotropic drugs were included in the analysis (Figure 1). NSAIDs and PPIs were the drugs administered the most, respectively in 59 and 34% of patients.

Efficacy according to co-medications

Among 188 patients from cohort 1, 135 (72%) were considered as R. Median BASDAI at M6 was 30.5 [20; 42]. In univariate analysis, disease duration, age, gender, positive HLA-B27, peripheral manifestation and presence of magnetic sacroiliitis did not influence the response to TNF-i (Table 2).

59.1% of patients who received NSAIDs were R, compared to 88.2% of patients not treated with NSAIDs ($p < 0.0001$). 42.2% of patients receiving PPIs were R compared to 86.3% of patients PPI free ($p < 0.0001$) (Figure 2). 77% patients received half dose of PPI and 23% standard doses. PPIs were prescribed in line with the French guidelines (gastroesophageal reflux disease, history of gastro-duodenal ulcer and in prevention of NSAID-induced peptic ulcer disease in at-risk patients) in 46% of patients; and in 44% of patients in case of NSAIDs co-prescription. 55.8% of patients who were given antibiotics were R, compared to 75.7% of patients who did not ($p=0,013$). 43 patients received antibiotics, among 13 received a combination of rifampicin and isoniazid for 3 months to treat a latent tuberculosis. 27.8% of patients treated with psychotropic drugs were R, compared to 75.9% of patients not receiving such treatment ($p = 0.005$). Differences were not statistically significant for corticosteroids ($p = 0.39$), MTX ($p = 0.0522$) and ACE-i ($p = 0.059$). In multivariate analysis, PPIs, NSAIDs and antibiotics intakes were considered as independent factors associated with TNF-i failure (respectively $p < 0.001$; $p = 0.01$ and $p = 0.025$) (Table 3).

Replication cohort

A total of 185 patients were included in cohort 2. There was no significant difference among patients from both cohorts except for uveitis frequency, disease duration, presence of magnetic sacro-iliitis and peripheral manifestation. Golimumab was more used, unlike infliximab (Table 1). 127 patients (69%) were considered as R. Median BASDAI at M6 was 25 [10; 45]. R patients were older with a median age of 42 [32;54] years old versus 39 [27;47] for NR patients ($p=0.018$) (Table 2).

Same co-medications than in cohort 1 were included in the analysis except for ACE-i that were given to fewer than 5% of patients. In univariate analysis, 59,4% of patients who received NSAIDs were R, compared to 81% of patients not treated with NSAIDs ($p= 0,0022$). 43,3% of patients receiving PPIs were R compared to 83% of patients PPI free ($p< 0.0001$) (Figure 3). Indication for PPIs was present in 45% of patients and in 35% when these drugs were co-prescribed with NSAIDs. Differences were not statistically significant for antibiotics ($p= 0,136$), psychotropic drugs ($p= 0,20$), corticosteroids ($p = 0.796$) and MTX ($p = 0.065$) (Figure 3). Although 88% of patients taking PPIs were also given NSAIDs, PPIs intake remained associated in multivariate analysis with a poorer response to TNF-i ($p< 0.001$) (Table 3).

Influence of co-medications on remission

BASDAI at M6 was available for 138 and 143 patients in the cohort 1 and 2, respectively. Remission was achieved in 48 (35%) and 66 (46%) patients, in cohort 1 and 2 respectively. In cohort 1, 21.6% of PPI users achieved remission compared to 42% of patients PPI free (OR= 2.69, [1.22; 5.94], $p=0.014$). In cohort 2, 48% of PPI users had a BASDAI ≤ 20 compared to 54% of patients PPI free (OR= 2.46, [1.22;4.98], $p=0.012$). No significant difference was noted with other co-medications in both cohorts. In multivariate analysis, PPIs users still have a decreased chance to respond to TNF-i in both cohorts (respectively $p=0.009$ and $p = 0.046$), independently of NSAIDs intake (S3 Table).

Sensitivity analysis

Sensitivity analysis was performed using BASDAI50 or clinician judgement if BASDAI was not available to define clinical response. Respectively, 77 (41%) and 74 (40%) patients were considered as NR. In multivariate analysis, similar results were found, except for antibiotics intake in the cohort 1, that was no longer significant (S4 Table).

DISCUSSION

In this study, we found that a co-medication with PPIs was significantly associated with a decreased chance of therapeutic response to a first TNF-i in ax-SpA patients, independently from other co-medications, in particular NSAIDs, or potential confounders. Similar results were found with NSAIDs and antibiotics in cohort 1, but it was not confirmed in cohort 2.

To our knowledge, this study was the first to investigate the influence of commonly used drugs on the response to TNF-i therapy in patients with ax-SpA. The influence of PPIs in SpA has not been evaluated yet. The potential deleterious effect of PPIs has been suggested in other disorders: Lu *et al.* conducted a meta-analysis of 5 randomised controlled studies in patients with inflammatory bowel disease (IBD) (28) including 889 and 147 patients on infliximab with and without PPIs, respectively. PPI users were less likely to achieve remission even after adjusting for confounders (OR = 0.45, $p < 0.001$), but the indication of prescription was not specified for most patients and other medications were not taken into consideration. Influence of PPIs intake has been investigated in rheumatoid arthritis (RA) in a prospective cohort study (29). Regular PPI users had a 44% higher risk of developing RA as compared with non-regular users (adjusted Hazard Ratio = 1.44; 95% CI, 1.10-1.89) and the risk increased with the duration of PPI use. Prolonged PPI exposure was associated with several adverse events as increased risk of community-acquired pneumonia, potentially due to translocation into the lungs from upper gastrointestinal bacterial overgrowth (30); or of osteoporosis or fractures through a decrease in calcium absorption by induced hypochlorhydria (31,32). Nevertheless, these associations have been mainly raised by observational studies.

The mechanisms underlying explaining the observed negative association between PPIs use and the response to TNF-i in ax-SpA patients remain unclear. A hypothetical explanation is that gut microbiota may mediate this association. Gut microbiome is known to play a role in SpA, as shown by studies on HLA-B27 transgenic rats raised in a germfree environment that do not develop joint or intestinal inflammation (33). Breban *et al.* found that SpA patients had a distinct microbiome compared to healthy controls and RA patients, and that *Ruminococcus gnavus* appears specific as a marker of disease activity (34). Gut microbiome could become a prognostic factor in response to TNF-i (8,35), even if results need to be confirmed in larger studies. PPIs can affect the gut microbiome composition and function (36–39) through pH-dependent and pH-independent mechanisms resulting in small intestinal bacterial overgrowth (40), and could facilitate enteric infections, particularly to *Clostridium difficile* (41). PPI-induced microbiota modifications lead to over-representation of upper gastrointestinal microbiota to more distal parts of the digestive tract. This hypothesis of a modulation of inflammatory and/or immune response via a modulation of the gut microbiota is the basement of the so-called pharmacomicrobiomic (42).

The main mechanism of action of PPIs involves the formation of a covalent linkage to cysteine residues in the H⁺/K⁺ ATPase pump on gastric cells, but omeprazole has also been reported to bind with cysteine-free proteins, even at neutral pH (43), raising the potential off-

target effects of PPIs. It has been shown that omeprazole is an agonist of the aryl hydrocarbon receptor (AhR) (44,45). AhR is a ligand-activated transcription factor that can bind to a wide spectrum of molecules (e.g. microbiota dependant metabolites, pharmaceuticals, environmental toxicants), and modulate diverse processes, depending on the ligand (46–48), potentially explains discrepancies between its pro and anti-inflammatory effects. AhR *-/-* mice developed more severe symptoms and higher levels of pro-inflammatory cytokines in induced colitis models (49), whereas in RA models, a decrease in IL-1 β and IL-6 levels was noted (50). Murine models of RA have also demonstrated that AhR activation could contribute to RA disease progression and severity, and increased numbers of IL17-expressing cells in the joints (51).

PPIs are increasingly used and over-prescribed. Lasalle *et al.* identified more than 15 million of PPI users in France in 2015, being almost a quarter of the French population, including 7 million of new users. PPIs were prescribed without clear indication in 32.4% of the cases. Main indication was a co-prescription with NSAIDs for 53.5%, among 79.7% had no risk factor justifying a prophylactic treatment with PPIs (52). PPI use in association with NSAIDs was not justified in about 60% of the patients in the present study. Besides the indication, another concern is the duration, PPIs are frequently prescribed for longer periods than is recommended (53). In SpA, few modifiable predictor factors of response are known except smoking habits and body weight. Our results need to be confirmed in further prospective studies, and studies are also needed to explain the potential mechanisms, this could be interesting for clinical practice, raising the possibility to actively intervene on a predictive factor of response.

Our study has some limitations, mainly inherent in the retrospective design of the study, with limitations of reporting and selection bias. Despite adjustment for potential confounders, residual confounding effects may still exist. Statistical analysis could not be adjusted for smoking status and BMI because it was missing in a substantial proportion of the chart of the patients. Strongest evidence regarding PPI-induced dysbiosis is based on microbiota analysis before and after medium-term PPI use (4 to 8 weeks) (54). Regarding the effect of long-term use, data are based on unique microbiome analysis and on self-reported PPIs use (39). Most PPIs users were already taking these drugs when addressed to the hospital to start TNF-i, we were not able to estimate the exact duration of PPIs intake. Finally, as an observational study, this study cannot be used to demonstrate causality between PPI use and TNF-i failure.

In conclusion, a co-medication with PPIs was significantly associated with a decreased chance to respond to a first TNF-i. The hypothesis that this effect is due to their interference

with the gut microbiota is only speculative but, regardless of the reason for this interaction, clinicians should be aware of its potential negative effect on TNF-i.

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Table 1. Demographic and disease characteristics of patients included in the study.

	Cohort 1 (188 patients)	Cohort 2 (185 patients)	
Age at initiation of TNF-i , years, median [IQR]	40 [33.5; 50]	41 [30; 52]	p = 0.66
Age at diagnosis , years, median [IQR]	37 [28; 45]	32 [24; 43]	p = 0.09
Duration of the disease , years, median [IQR]	1 [0; 4]	2 [0; 8]	p = 0.049
Women/Men , nr (%)	67 (36) /121 (64)	78 (42) /107 (58)	p = 0.2
BMI (kg/m ²), median [IQR]	24,4 [22,2; 28,1]	24,5 [21,8; 27,4]	p = 0.83
Peripheral involvement nr (%)	98 (52)	57 (31)	p < 0.01
Magnetic sacroiliitis nr (%)	159 (87)	126 (78)	p = 0.02
Radiographic sacroiliitis , nr (%)	119 (72)	110 (66)	p = 0.29
HLA-B27 positive nr (%)	111 (73)	125 (73)	p = 0.99
Extra-articular manifestations nr (%)			
- Ocular	2 (1)	12 (6)	p = 0.006
- IBD	5 (2)	7 (4)	p = 0.57
BASDAI at M0 , median [IQR]	49 [43; 59]	52 [44; 63]	p = 0.06
CRP (mg/L) at M0 , median [IQR]	7 [3; 17]	8 [3; 18.5]	p = 0.55
TNF-i nr (%)			
- Adalimumab	81 (43)	82 (44)	p = 0.87
- Etanercept	64 (34)	41 (22)	p = 0.059
- Infliximab	37 (20)	15 (8)	p = 0.024
- Golimumab	4 (2)	34 (19)	p = 0.001
- Certolizumab	2 (1)	13 (7)	p = 0.06
Combination with cDMARDs nr (%)			
- MTX	51 (27)	25 (13)	p = 0.008
- SSZ	5 (3)	3 (2)	p = 0.66

nr = number; IQR = Inter-Quartile Range; TNF-i = Tumor Necrosis Factor Inhibitor; BMI = Body Mass Index; M0 = month 0; IBD = Inflammatory Bowel Disease; cDMARDs = conventional Disease Modifying Anti-Rheumatic Drugs ; MTX = Methotrexate, SSZ = Salazopyrine

Table 2. Univariate analysis of influence of baseline disease characteristics on the response to TNF-inhibitors.

	Cohort 1 (188 patients)	Cohort 2 (185 patients)
	Odd Ratio (95% Confidence Interval)	
Gender	0.65 (0.34;1.26)	1.43 (0.76; 2.72)
Duration of the disease	0.98 (0.95 ;1.03)	1.02 (0.99 ; 1.06)
Age at TNF-i initiation	1.01 (0.99; 1.045)	0.97 (0.95; 0.99)
Magnetic sacroiliitis	1.14 (0.42; 3.10)	0.48 (0.25; 1.02)
BASDAI at M0	1.00 (0.98; 1,00)	1.02 (0.99; 1.04)
CRP level at M0	0.99 (0.97; 1.01)	0.999 (0.98; 1.02)
Positive B27	0.97 (0.49; 2.08)	0.81 (0.69; 1.66)
Peripheral involvement	0.98 (0.52 ;1.85)	0.79 (0.4 ; 1.56)

TNF-i = TNF-inhibitor; M0 = month 0.

Table 3. Univariate and multivariate analysis of the association between co-medication with therapeutic response to TNF-inhibitors.

	Cohort 1 (188 patients)		Cohort 2 (185 patients)	
	Odd Ratio (95% Confidence Interval)			
	Univariate analysis	Multivariate analysis*	Univariate analysis	Multivariate analysis*
NSAIDs	6.1 (2.68;13.9)	3.62 (1.36; 9.66)	2.91 (1.47 ; 5.77)	1.09 (0.46; 2.57)
PPIs	8.6 (4.23 ;17.6)	5.69 (2.37; 13.69)	6.4 (3.25 ;12.7)	5.92 (2.58; 13.59)
Antibiotics	2.47 (1.21 ;5.03)	2.84 (1.14; 7.10)	1.87 (0.84 ; 4.16)	
Psychotropic drugs	5.16 (1.64 ;16.2)	2.01 (0.52; 7.75)		1.94 (0.75; 4.97)
Corticosteroids	1.01 (0.3 ;3.38)		1.11 (0.39;3.11)	
Methotrexate	0.94 (0.46; 1.93)		2.29 (0.97 ; 5.38)	
ACE-i	1.48(0.73 ;9.49)			
Statin	0.31 (0.3 ;5.21)			

*Adjusted for age, gender, disease duration, HLA-B27 status, BASDAI and CRP at baseline, presence of magnetic sacroiliitis and peripheral manifestation.

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPIs = Proton Pump Inhibitors; ACE-i = Angiotensin Converting Enzyme Inhibitors.

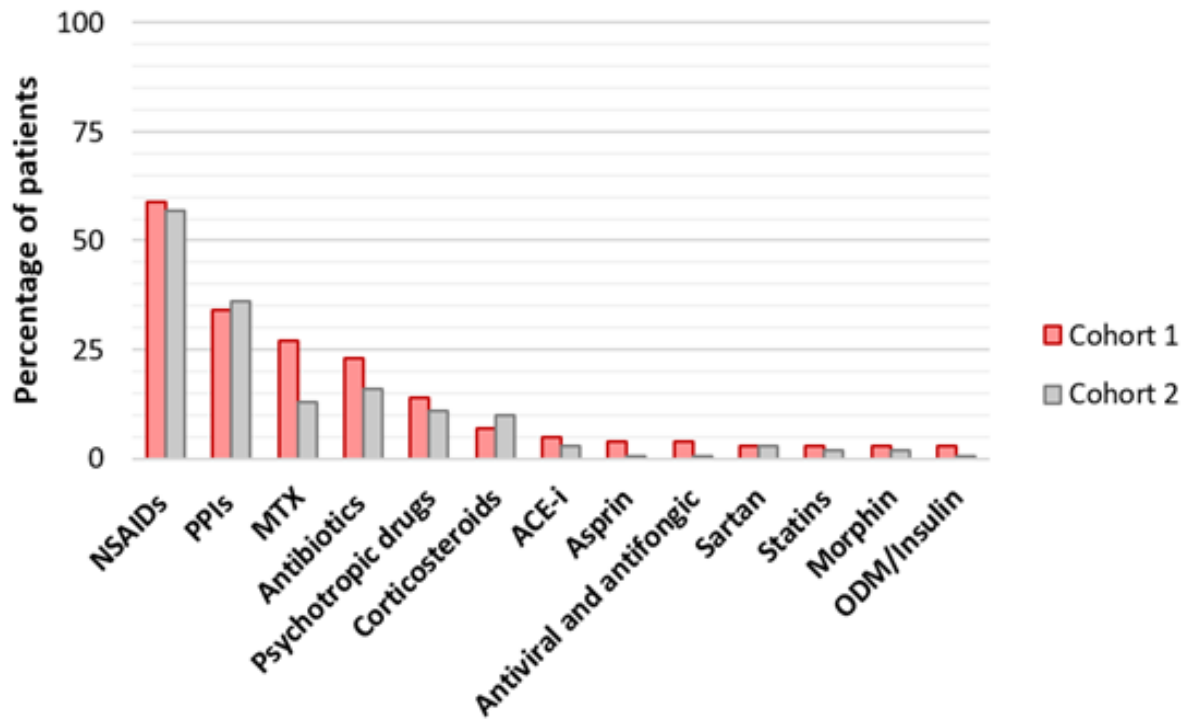


Figure 1. Concomitant drugs (%) in both cohorts. NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; PPIs= Proton Pump Inhibitors; MTX = Methotrexate; ACE-i= Angiotensin Converting Enzyme Inhibitors; ODM = Oral Diabetes Drug

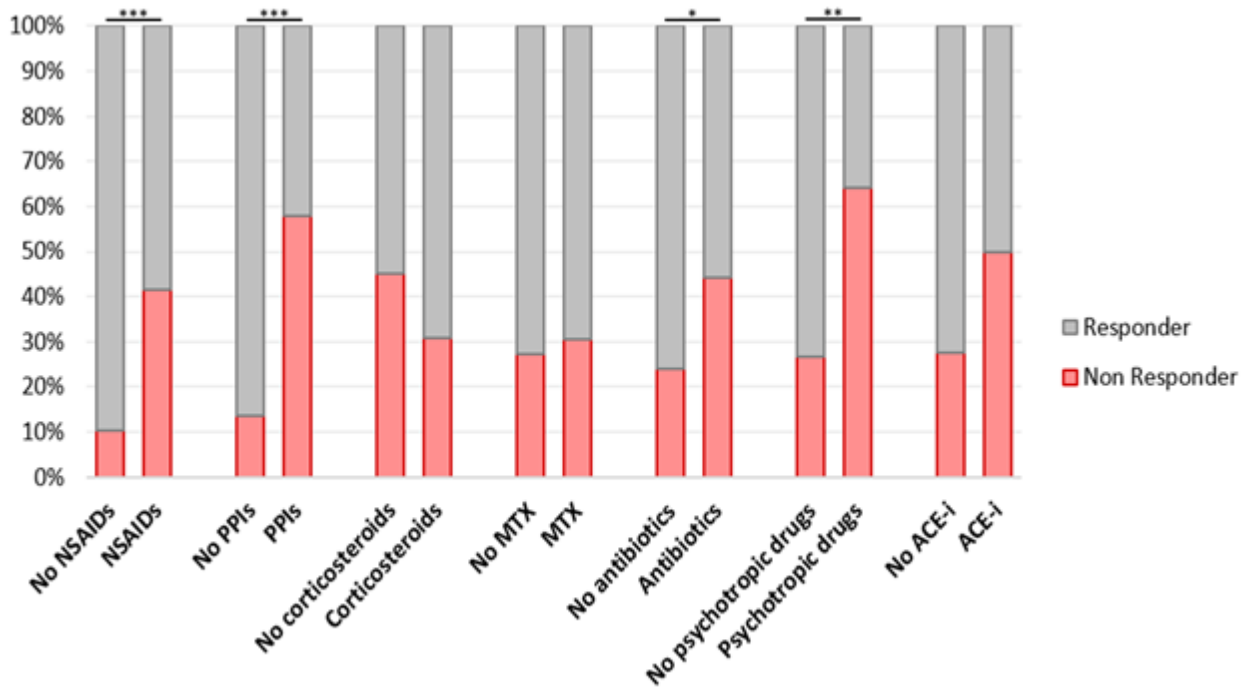


Figure 2. Proportion of responder and non responder patients from cohort 1 according to co-medication. *** $p < 0.001$, ** $p < 0.01$; * $p < 0.05$. NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; PPIs= Proton Pump Inhibitors; MTX = Methotrexate; ACE-i= Angiotensin Converting Enzyme Inhibitors; ODM = Oral Diabetes Drug

Figure 3.

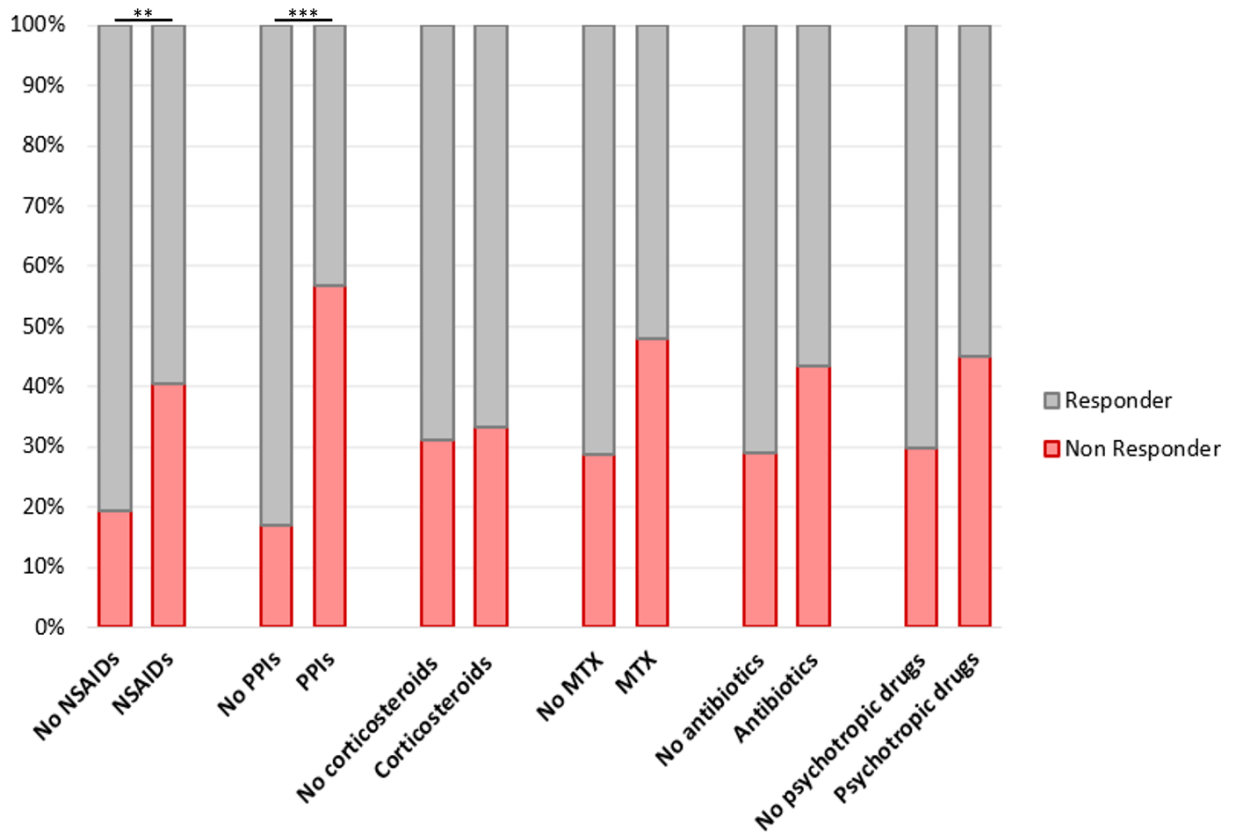


Figure 3. Proportion of responder and non responder patients from cohort 2 according to co-medication. *** $p < 0.001$, ** $p < 0.01$; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; PPIs= Proton Pump Inhibitors; MTX = Methotrexate; ODM = Oral Diabetes Drug

Supplementary data:**S1 Table.** Missing data.

	Cohort 1	Cohort 2
Age at TNF-i initiation (%)	0 (0)	0 (0)
Disease duration (%)	0 (0)	1 (< 1)
Peripheral manifestation, nr (%)	0 (0)	0 (0)
CRP level at M0, nr (%)	1 (<1)	8 (4)
Magnetic sacroiliitis, nr (%)	6 (3)	22 (12)
BASDAI at M0, nr (%)	10 (5)	7 (4)
B27 status, nr (%)	35 (18)	13 (7)
BASDAI at M6, nr (%)	50 (26)	42 (23)
BMI, nr (%)	66 (35)	91 (49)
Smoking status, nr (%)	170 (90)	168 (91)

BMI = Body Mass Index. M0 = month 0; nr = number, TNF-i = TNF-inhibitor.

S2 Table. Pattern of missing data of covariates included in multivariate model before imputation.

Percent	Pattern							Percent	Pattern						
	1	2	3	4	5	6	7		1	2	3	4	5	6	7
74	1	1	1	1	1	1	1	74	1	1	1	1	1	1	1
17	1	1	1	1	1	1	0	11	1	1	1	1	0	1	1
4	1	1	1	1	1	0	1	5	1	1	1	1	1	1	0
2	1	1	1	1	0	1	1	4	1	1	1	0	1	1	1
1	1	1	1	1	1	0	0	4	1	1	1	1	1	0	1
<1	1	1	1	0	1	1	1	2	1	1	1	1	0	1	0
<1	1	1	1	1	0	0	1	<1	1	0	1	0	1	1	0
<1	1	1	1	1	0	1	0								

1 means complete data

Pattern: 1 = age at TNF-i initiation; 2 = disease duration; 3 =peripheral manifestation; 4 = CRP at M0; 5 = magnetic sacroiliitis; 6 = BASDAI at M0; 7 = B27 status.

S3 Table. Univariate and multivariate analysis of the association between co-medication and remission.

	Cohort 1 (138 patients)		Cohort 2 (143 patients)	
	Odd Ratio (95% Confidence Interval)			
	Univariate analysis	Multivariate analysis*	Univariate analysis	Multivariate analysis*
NSAIDs	1.57 (0.77; 3.19)		1.63 (0.83; 3.22)	
PPIs	2.69 (1.22; 5.94)	3.46 (1.36; 8.75)	2.46 (1.22;4.98)	2.44 (1.01; 5.85)
Antibiotics	2.40 (0.90; 6.39)		1.41 (0.57; 3.5)	
Psychotropic drugs	4.59 (0.57; 37.80)		3.5 (0.93; 13.1)	
Corticosteroids	5.29 (0.65; 43.06)		1.55 (0.43; 5.55)	
Methotrexate	1.81 (0.77; 4.26)		1.40 (0.51; 3.86)	
ACE-i	0.51 (0.12; 2.14)			
Statin	0.70 (0.15; 3.25)			

*Adjusted for age, gender, disease duration, HLA-B27 status, BASDAI and CRP at baseline, presence of magnetic sacroiliitis, peripheral manifestation and NSAIDs use.

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPIs = Proton Pump Inhibitors; ACE-i = Angiotensin Converting Enzyme Inhibitors.

S4 Table. Univariate and multivariate analysis of the association between co-medication with therapeutic response to TNF-inhibitors according to BASDAI50.

	Cohort 1 (188 patients)		Cohort 2 (185 patients)	
	Odd Ratio (95% Confidence Interval)			
	Univariate analysis	Multivariate analysis*	Univariate analysis	Multivariate analysis*
NSAIDs	4.31 (2.24; 8.29)	4.61 (2.02; 10.54)	2.26 (1.22; 4.18)	1.05 (0.48; 2.28)
PPIs	6.53 (3.49; 12.73)	2.47 (1.13; 5.40)	5.61 (2.92; 10.78)	5.38 (2.47; 11.72)
Antibiotics	2.11 (1.06; 4.20)	2.24 (0.98; 5.14)	1.63 (0.74; 3.57)	1.46 (0.58; 3.64)
Psychotropic drugs	3.90 (1.18; 12.92)	1.37 (0.35; 5.38)	3.17 (1.20; 8.37)	
Corticosteroids	1.47 (0.49; 4.38)		0.95 (0.35; 2.57)	
Methotrexate	1.35 (0.71; 2.58)		1.76 (0.75; 4.10)	
ACE-i	2.21 (0.60; 8.10)			
Statin	1.82 (0.47; 6.99)			

*Adjusted for age, gender, disease duration, HLA-B27 status, BASDAI and CRP at baseline, presence of magnetic sacroiliitis and peripheral manifestation.

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; PPIs = Proton Pump Inhibitors; ACE-i = Angiotensin Converting Enzyme Inhibitors.

SERMENT D'HIPPOCRATE

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 déshonorée et méprisée si j'y manque.

Influence des co-médications sur la réponse aux anti-TNF dans la spondyloarthrite axiale

Introduction : Considérant le rôle potentiel du microbiote intestinal dans la physiopathologie de la spondyloarthrite (SpA) ainsi que dans la réponse thérapeutique aux biothérapies, nous avons étudié l'influence des comédications connues pour interférer avec le microbiote sur la réponse aux inhibiteurs du TNF (TNF-i) chez des patients atteints de SpA.

Méthodes: Il s'agit d'une cohorte rétrospective incluant des patients atteints de SpA axiale, qui ont été classés comme répondeurs (R) ou non-répondeurs (NR) selon la valeur BASDAI (< 40/100) au mois 6 ou selon le jugement du clinicien. Ont été recueilli les co-médications administrées 1 mois avant et pendant les 3 premiers mois du traitement. Une cohorte de réplication a été créée pour valider les résultats. Des modèles de régression logistique ont été utilisés pour évaluer la relation entre comédications et réponse aux TNF-i.

Résultats : 188 patients ont été inclus dont 135 (72%) considérés comme NR. En analyse univariée, la prise d'anti-inflammatoires non stéroïdiens (AINS), d'inhibiteurs de la pompe à protons (IPP), d'antibiotiques et de psychotropes était associée à une plus grande proportion de patients NR, contrairement aux corticostéroïdes, méthotrexate, inhibiteurs de l'enzyme de conversion de l'angiotensine et statines. Les AINS, IPP et antibiotiques ont été considérées comme des facteurs indépendants associés à l'échec des TNF-i en analyse multivariée. 185 patients ont été inclus dans la cohorte de réplication, dont 127 (69%) patients R. Bien que 88% des patients prenant des IPP aient également reçu des AINS, les IPP restaient associés à une moins bonne réponse à un premier TNF-i ($p < 0,001$).

Conclusion: Une prise concomitante d'IPP était significativement associée à une moindre chance de réponse aux TNF-i. L'hypothèse d'une interférence avec le microbiote intestinal n'est que spéculative, mais quelle que soit la raison de cette interaction, les cliniciens doivent être conscients de l'effet négatif potentiel des IPP sur les TNF-i.

Influence of Commonly Used Co-Medications on the Response To TNF-Inhibitors in Axial Spondyloarthritis Patients

Objective: Considering the potential role of the gut microbiota in the pathophysiology of spondyloarthritis (SpA) as in the therapeutic response to biologics, we studied the influence of co-medications known to interfere with the microbiota with the therapeutic response to TNF-inhibitor (TNF-i) in SpA patients.

Methods: This was a retrospective cohort including patients having axial SpA (ax-SpA). Patients were classified as responder (R) or non-responder (NR) according to the BASDAI (< 40/100) value at month 6 or to the clinician judgment. We collected co-medication administered 1 month before and during the first 3 months of the TNF-i treatment. A replication cohort was built for validation of the results. Multivariate logistic regression models adjusted for potential confounders were applied to evaluate the relationship between co-medications and TNF-i response.

Results: We included 188 patients of whom 135 (72%) were considered as R. In univariate analysis, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), antibiotics and psychotropic drugs intakes were significantly associated with a higher proportion of NR patients, unlike for corticosteroids, methotrexate (MTX), angiotensin-converting enzyme inhibitors and statins use. NSAIDs, PPIs and antibiotics intakes were considered as independent factors associated with TNF-i failure in multivariate analysis. 185 patients were included in the replication cohort, including 127 (69%) R patients. In multivariate analysis, although 88% of patients taking PPIs were also given NSAIDs, PPIs remained associated with a poorer response to a first TNF-i ($p < 0.001$).

Conclusion: Co-medication with PPIs was significantly associated with a decreased chance to respond to TNF-i. The hypothesis that this effect is due to their interference with the gut microbiota is only speculative but, regardless of the reason for this interaction, clinicians should be aware of the potential negative effect of PPIs on TNF-i.

Discipline: Médecine

Mots clés : spondyloarthrite axiale, anti-TNF, microbiote, pharmacomicrobiomique

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