

**La stratégie de traitement par biothérapie de la maladie
de Still de l'adulte dépend de la dichotomie
phénotypique**
François Vercruysse

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U.F.R. DES SCIENCES MEDICALES

Thèse pour l'obtention du

DIPLOME D'ÉTAT DE DOCTEUR EN MEDECINE

Présentée et soutenue publiquement le 14 septembre 2018
Par Monsieur François Vercruysse
Né le 20 mars 1990 à Pau

**La stratégie de traitement par biothérapie de la
maladie de Still de l'adulte dépend de la dichotomie
phénotypique**

Président du Jury	Monsieur le Professeur Thierry Schaeverbeke
Membres du Jury	Monsieur le Professeur Christophe Richez Madame la Professeur Estibaliz Lazaro Monsieur le Docteur Jean-Philippe Vernhes
Directrice de thèse	Madame le Docteur Marie-Élise Truchetet
Rapporteur de thèse	Monsieur le Docteur Jean-Philippe Vernhes



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Prénom: **François**
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La stratégie de traitement par biothérapie de la maladie de Still de l'adulte dépend de la dichotomie phénotypique

Introduction: Le phénotype de la maladie de Still de l'adulte (MSA) peut être dichotomisé en une forme systémique et une forme articulaire chronique. A l'ère où les biothérapies et notamment le blocage des interleukines (IL)-1 et 6 jouent un rôle prépondérant dans son traitement, leurs place dans la stratégie thérapeutique reste à préciser. Cette étude avait pour objectif d'identifier des facteurs prédictifs cliniques ou biologiques de réponse préférentielle à l'anakinra ou au tocilizumab, et d'identifier si le choix de biothérapie et son délai d'initiation influençaient les chances de sevrage cortisonique.

Méthodes: Une étude exploratoire multicentrique rétrospective a inclus tous les patients atteints de MSA et ayant reçu une biothérapie dans trois hôpitaux régionaux jusqu'à 2018. Leur caractéristiques cliniques et biologiques au diagnostic et les données relatives aux traitements ont été recueillies. Une analyse univariée a été effectuée en utilisant le test statistique non-paramétrique de Mann-Whitney pour les variables quantitatives et le test exact de Fisher pour les variables qualitatives.

Résultats: Vingt-sept patients ont été inclus. Tous les patients sauf un ont atteint la rémission soit sous anakinra soit sous tocilizumab. La réponse au traitement dépendait du phénotype clinique : la présence d'arthrite et un phénotype articulaire chronique étaient associés à une réponse thérapeutique préférentielle pour le tocilizumab ($p=0.017$ et $p=0.0009$ respectivement), alors qu'une forme systémique et l'absence d'arthrite étaient associées à une réponse thérapeutique préférentielle à l'anakinra ($p=0.017$ et $p=0.0009$ respectivement). Le tocilizumab était associé à de meilleures chances de sevrage cortisonique ($p=0.029$) quel que soit son délai d'initiation ou sa place en terme de ligne thérapeutique.

Conclusion: Cette étude souligne l'importance de la dichotomisation phénotypique de la MSA et ses implications thérapeutiques. Ces résultats devraient nous permettre de mieux catégoriser les patients atteints de MSA et nous aider à codifier leur traitement.

Mots-clés: *Maladie de Still de l'Adulte, Traitements Biologiques, Corticoïdes, Maladies auto-inflammatoires*

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Adult-Onset Still's Disease Biological Treatment Strategy Depends on the Phenotypic Dichotomy

Objectives: Adult-onset Still's disease (AOSD) phenotype can be dichotomized in systemic or chronic articular forms. As biologicals and particularly interleukin (IL)-1 and IL-6 blockers play a more and more prominent role in the treatment, their place requires clarification. This study aimed to identify factors predictive of treatment response to anakinra or tocilizumab, and investigate whether the choice of biotherapy and delays in the initiation of biotherapy influenced the likelihood of steroid discontinuation.

Methods: A multicenter exploratory retrospective study included all patients diagnosed with AOSD and receiving biological treatments in three regional hospitals until 2018. Clinical and biological characteristics at diagnosis and treatment related data were collected. The non-parametric Mann-Whitney test was used to perform univariate analysis for quantitative variables, and Fisher's exact test was used for qualitative variables.

Results: Twenty-seven patients were included. All but one patient achieved remission with either anakinra or tocilizumab. Treatment responses depended on disease phenotype: the presence of arthritis and a chronic articular phenotype were associated with a preferential response to tocilizumab with $p=0.0009$ and $p=0.017$ respectively, whereas the systemic form and the absence of arthritis were associated with a preferential response to anakinra with $p=0.0009$ and $p=0.017$ respectively. Tocilizumab increased the likelihood of corticosteroid withdrawal ($p=0.029$) regardless of delays in initiation or when it was initiated relative to other treatment in the overall therapeutic strategy.

Conclusion: This study highlights the therapeutic implications of the phenotypic dichotomy of AOSD and should help us better codify AOSD treatment.

Keywords: *Adult-Onset Still's disease, Biologicals, Corticosteroids, Miscellaneous Rheumatic and Inflammatory Diseases*

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Liste des abréviations

Français

MSA : Maladie de Still de l'Adulte

CIVD : coagulation intra-vasculaire disséminée

SAM : syndrome d'activation macrophagique

Anglais

AOSD: Adult-Onset Still's Disease

IL: interleukin

INF: interferon

TNF: tumor necrosis factor

rHLH: reactive hemophagocytic lymphohistiocytosis

bDMARD: biological disease-modifying antirheumatic drugs

SoJIA: systemic-onset juvenile idiopathic arthritis

CRP: C-reactive protein

LDH: lactate dehydrogenase

NSAIDs: nonsteroidal anti-inflammatories

csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs

ENT : ear-nose-throat

CK: creatine kinase

Anti-ENA: anti-extractable nuclear antigen

ANCA: antineutrophil cytoplasmic antibody

ACPA: positive anticitrullinated protein antibody

ANA : antinuclear antibodies

Anti-DNA: antideoxyribonucleic acid

RF: rheumatoid factor

IQR: interquartile range

RCT: randomized controlled trial

JAK: janus kinase

« La médecine est un art qu'on exerce, en attendant qu'on le découvre. »
- Emile Deschamps

« L'art de la médecine consiste à distraire le malade pendant que la nature le guérit. »
- Voltaire

Introduction

Ce travail de thèse s'inscrit dans le contexte de l'élaboration d'une cohorte nationale sur la maladie de Still nommée RaDiCo-ACOSTILL ayant pour but de fédérer autour des patients un consortium de cliniciens pour mieux décrire la maladie, de constituer une biobanque afin d'effectuer des études physiopathogéniques et de constituer une file active de patients suffisamment importante pour de futurs essais thérapeutiques.

La Maladie de Still de l'Adulte (MSA) est une maladie inflammatoire systémique rare décrite par Eric George Bywaters en 1971 affectant principalement le jeune adulte et se manifestant par des symptômes similaires à ceux de l'Arthrite Juvénile Idiopathique à début systémique (SoJIA) décrite chez l'enfant par Sir George Frederic Still en 1897. Elle affecte autant les hommes que les femmes, son incidence annuelle est estimée entre 0.16 et 0.62 pour 100 000 personnes, et sa prévalence aux environs de 1 à 24 par millions.

Les symptômes cardinaux sont classiquement une fièvre hectique volontiers vespérale ; des arthralgies et/ou arthrites ; une éruption cutanée typiquement saumonée, évanescence, vespérale et concomitante du pic fébrile ; et une odynophagie. On observe également régulièrement une polyadénopathie et une splénomégalie. Les anomalies biologiques sont dominées par un syndrome inflammatoire majeur, une hyperferritinémie avec un effondrement de sa fraction glycosylée, et d'éventuelles anomalies hématologiques.

La physiopathologie de la MSA est encore imparfaitement comprise. Il s'agit d'une maladie auto-inflammatoire d'origine multifactorielle : une génétique prédisposante non mendélienne ; des facteurs environnementaux (principalement infectieux) ; et un déséquilibre immunologique impliquant une hyperactivation ou dérégulation du macrophage, du polynucléaire neutrophile et de l'inflammasome.

Récemment, il a été mis en évidence une dichotomie entre deux phénotypes majeurs de MSA : une forme dite « systémique » au cours de laquelle la fièvre, l'éruption cutanée, l'atteinte hématologique, parfois des atteintes viscérales et un syndrome inflammatoire biologique marqué sont au premier plan ; et une forme rhumatologique dite « articulaire chronique » au cours de laquelle un tableau de polyarthrite prédomine accompagné de marqueurs biologiques d'inflammation souvent moins élevés.

Cette représentation dichotomique de la MSA est non seulement alimentée par des observations cliniques mais aussi par des profils cytokiniques différents. Ce déséquilibre cytokinique se ferait plutôt en faveur de l'IL-1 β IL-18 and IFN- γ dans la forme systémique, alors que l'IL-6 IL-8 le TNF-alpha et l'IL-17 prévaudraient dans la forme articulaire chronique.

Le cours de la maladie est imprédictible et peut prendre de multiples évolutions : mono-poussée, forme polycyclique, formes chroniques systémiques ou articulaires. Le pronostic de la MSA est donc triple: fonctionnel pour les formes érosives polyarticulaires chroniques ; vital plus particulièrement lors des formes systémiques par la survenue de sérite ou d'un syndrome d'activation macrophagique pouvant aboutir à une coagulation intravasculaire disséminée (CIVD); et enfin iatrogène étant donné l'exposition fréquente de ces patients à de fortes doses prolongées de corticoïdes avec les effets indésirables qu'on leur connaît, et du fait des complications notamment infectieuses des traitements biologiques prescrits.

Ce polymorphisme clinique et pronostique représente un défi majeur et complique la prise en charge et la stratégie thérapeutique initiale d'une MSA au diagnostic. Elle explique également en partie l'absence de recommandations consensuelles sur la stratégie thérapeutique notamment concernant les traitements biologiques au cours de la MSA. La prise en charge d'une MSA est donc actuellement encore largement empirique ou basée sur de trop rares case-reports ou études rétrospectives.

Cependant les traitements biologiques, hors AMM, occupent une place de plus en plus importantes dans la stratégie thérapeutique. Une méta-analyse récente montre que les traitements biologiques bloquant l'IL-1 et l'IL-6 sont les plus efficaces dans la MSA, et ont de surcroît un effet d'épargne cortisonée.

Point d'importance majeure, la dichotomie ne serait pas seulement clinique et cytokinique mais peut-être également thérapeutique en ce qui concerne les traitements biologiques comme le suggèrent certains auteurs. La forme systémique de la MSA répondrait préférentiellement au blocage du récepteur de l'IL-1 (actuellement principalement représenté par l'anakinra) alors que la forme articulaire répondrait mieux au blocage du récepteur de l'IL-6 (actuellement principalement représenté par le tocilizumab).

Entériner la place prépondérante des ces deux biothérapies dans le traitement de la MSA a donc un intérêt majeur afin d'éviter la survenue de complications vitales fonctionnelles ou iatrogènes.

Enfin, arriver à prédire dès le diagnostic le traitement biologique auquel le patient est le plus susceptible de répondre est séduisant car cela permettrait potentiellement de gagner du temps dans la prise en charge avec les conséquences pronostiques que cela implique, et d'éviter de potentielles déboires thérapeutiques à nos patients.

L'objectif principal de cette étude était donc d'identifier au diagnostic des facteurs prédictifs cliniques et biologiques de bonne réponse préférentielle à l'anakinra ou au tocilizumab. Les objectifs secondaires étaient d'étudier si le choix de biothérapie (anakinra ou tocilizumab) et son délai d'initiation influençaient les chances de sevrage cortisonique dans la MSA, et de décrire les caractéristiques cliniques et biologiques des patients atteints de MSA en Aquitaine.

Article scientifique

Est présenté ici le manuscrit de l'article soumis pour publication à la revue *Arthritis Research and Therapy*.

Adult-Onset Still's Disease Biological Treatment Strategy Depends on the Phenotypic Dichotomy

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Key messages:

- What is already known about this subject?
 - The phenotype of adult-onset Still's disease can be dichotomized into systemic or chronic articular forms.
 - Biological treatments are dominated by IL-1 or IL-6 receptor inhibitors.
- What are the new lines of research suggested by this study?
 - The presence of arthritis and a chronic articular phenotype may be associated with a preferential response to tocilizumab, whereas the systemic form may be associated with a preferential response to anakinra.
 - Tocilizumab increases the likelihood of corticosteroid withdrawal regardless of delays in its initiation or when it is initiated relative to other treatment in the overall therapeutic strategy
- How might this impact clinical practice?
 - These results should help us better codify the treatment strategy for adult-onset Still's disease.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder. Its annual incidence is estimated to be between 0.16 and 0.62 per 100 000 persons globally(1), and its prevalence approximately 1-24 per million(2).

AOSD is an autoinflammatory disease resulting from multifactorial causes such as genetic factors and immunological imbalances involving macrophage, neutrophil and inflammasome hyperactivation or dysfunction(3).

Recent studies have concluded that there is a dichotomy between two major phenotypes of AOSD: a systemic pattern that presents with an acute onset associating high fever, skin rash, hematopoietic signs and sometimes visceral damage; and a chronic articular profile in which polyarthritis prevails(4,5). This phenotypic dichotomy is highlighted by recent studies showing that there are different cytokine imbalances in these two phenotypes. Although results may vary, this imbalance would sometimes favour interleukin (IL)-1 β , IL-18 and interferon (IFN)-gamma production in the systemic form; whereas in the chronic articular form, IL-6, IL-8, tumor necrosis factor (TNF)-alpha and IL-17 production would predominate(6–12).

The prognosis of AOSD is unpredictable as it can manifest with polyarticular erosive disease or life-threatening manifestations such as reactive hemophagocytic lymphohistiocytosis (rHLH). The disease course is also very polymorphic, ranging from a monophasic flare to polycyclic or chronic forms. This clinical and prognostic polymorphism presents a major challenge and makes it difficult to predict the outcome at the time of diagnosis and to determine appropriate management.

Therapy is therefore usually empirical, and beside methotrexate, biologics have played an increasing role in the chronic or refractory forms. A recent meta-analysis suggested that IL-1 and IL-6 receptor inhibitors are the most effective biotherapies for AOSD(13) and have a strong steroid-sparing effect. The systemic phenotype has been suggested to respond preferentially to IL-1 receptor inhibitors, such as anakinra, while the chronic articular form shows better responses to IL-6 receptor inhibitors, such as tocilizumab(6,7,14–17).

This exploratory study therefore aimed to identify initial clinical and/or biological factors that were predictive of a preferential response to anakinra or tocilizumab. Secondary objectives were to investigate whether the choice of biotherapy (anakinra or tocilizumab) and their delay in initiation influenced the likelihood of steroid discontinuation, and to describe the clinical and biological phenotypes of patients with AOSD.

Methods

Study design and data collection

A multicenter exploratory retrospective study of all patients diagnosed with AOSD at Bordeaux teaching hospital and Pau and Dax peripheral hospitals until 2018 was conducted. Patients included had to be 16 years old or older, to be diagnosed with AOSD, to meet the Yamaguchi and/or Fautrel criteria, to have a chronic or refractory disease course, and to receive or have received a biological disease-modifying antirheumatic drugs (bDMARD).

Exclusion criteria were: age younger than 16 years old, a diagnosis of systemic-onset juvenile idiopathic arthritis (SoJIA), an exclusion of AOSD diagnosis during disease course, Yamaguchi and Fautrel criteria not met, lack of data, absence of bDMARD during disease course.

Patients with AOSD were identified via ICD-10 code, via a diagnostic grid that automatically references autoimmune and inflammatory diseases at Bordeaux University hospital, via the bioinformatics services of each hospital, and via direct contact with the specialists treating the patients. Data regarding clinical and biological characteristics at diagnosis and treatment details were collected using a standard data extraction form. All the information was double-checked for any discrepancies.

The following demographic and clinical AOSD-related characteristics were collected: sex, date of birth, age at diagnosis, year of diagnosis, duration of disease, duration of disease at first bDMARD initiation, smoking habits, personal or familial history of rheumatic autoimmune inflammatory or neoplastic disease, type of Still's disease-related rash if present, arthralgia, arthritis, hands affected or not, early morning stiffness, myalgia, fever

characteristics, general deterioration and weight loss >4 kg, lymphadenopathy, pharyngitis, angina and visceral involvement (pleuritis, pericarditis, pulmonary hypertension).

The following biological characteristics were recorded: leukocytosis >10 000/mm³, neutrophilia >8000/mm³, eosinophilia >500/mm³, anemia with haemoglobin <12 g/dl, thrombocytosis >400 000/mm³, increased C-reactive protein (CRP) levels, maximum CRP at diagnosis, decreased albumin, increased liver enzymes, increased creatine kinase, increased lactate dehydrogenase (LDH), increased ferritin, decreased glycosylated ferritin, autoimmunity markers (antinuclear antibodies, antideoxyribonucleic acid, anti-extractable nuclear antigen, rheumatoid factor, antiβ2GP1, lupus anticoagulant, anticardiolipin), disseminated intravascular coagulation markers and rHLH markers (cytopenia, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in bone marrow).

Patients were classified as having two distinct disease patterns: the systemic form or the chronic articular form. In the absence of consensual criteria in this regard, this classification was based on expert opinions that was often spelled out in the medical reports, and was confronted to disease course outcome which was available due to the retrospective nature of this study.

Outcome measurements

A modified Pouchot score (range, 0-12), which considers 12 disease-related manifestations (18) (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels >3000 mg/L, lymphadenopathy, white blood cell count >15 000/mm, sore throat, myalgia,

and arthritis), was applied to assess disease activity. Patients had to have a modified Pouchot score of 0 to be considered in remission.

When data were insufficient to determine this score, the effectiveness of treatment was defined as follows: effective treatment was considered when all initial symptoms and biological anomalies had resolved; partially effective treatment was considered when all but one initial symptom or biological anomaly had resolved; and ineffective treatment was considered when two or more initial symptoms or biological anomaly persisted. The attending doctors assessed disease flares and relapses.

Treatment lines were assessed as follows: nonsteroidal anti-inflammatory (NSAIDs) were not considered a treatment modality for chronic and refractory AOSD; but corticosteroids, csDMARD and especially methotrexate (both galenic forms taken together) and cyclosporine, and bDMARD (anakinra, tocilizumab, canakinumab, infliximab, and etanercept) were considered treatment lines.

Statistical analysis

Quantitative variables are presented as mean with standard deviation or as median with interquartile range, and qualitative variables are presented as percentages. Analysis was performed on the following variables: all the clinical and biological manifestations included in the Yamaguchi or Fautrel criteria, common demographic characteristics, and all the symptoms or biological abnormalities usually observed during AOSD according to the literature and our personal experience. The nonparametric Mann-Whitney test was used to perform a univariate analysis of quantitative variables, and the Fisher exact test was used for qualitative variables. Calculations were

performed with STATA 13.1 SE software. P-values less than 0.05 were considered significant.

Results

Patients' characteristics

Twenty-seven patients were included in this study: 21 from Bordeaux teaching hospital, 4 from Dax hospital, and 2 from Pau hospital. Patient characteristics at diagnosis are described in **Table 1**.

All patients fulfilled both the Yamaguchi and Fautrel criteria. No patients had any personal or familial history of rheumatic, autoimmune, inflammatory or neoplastic disease. All patients presented with a fever above 38°C, mainly intermittent and vesperal fevers. The next most prevalent symptoms were arthralgia (96%), arthritis (52%), skin rash (81%), general deterioration (72%), and ear-nose-throat (ENT) symptoms (69%).

Eleven (40.7%) patients were classified as systemic form of disease, and 16 (59.3%) as chronic articular form.

All patients presented with elevated CRP levels. The next most commonly observed anomalies were neutrophilia (96%), low albumin (75%) and increased ferritin (73%). No patients presented with increased creatine kinase (CK), positive extractable nuclear antigen (ENA), positive antineutrophil cytoplasmic antibody (ANCA), positive anticitrullinated protein antibody (ACPA) or positive anticardiolipin. Nine patients were either ANA-positive (five), anti-DNA positive (one), or rheumatoid factor (RF)-positive (three) at diagnosis, but these results were always controlled to be negative.

The median duration of disease was 5 years (IQR 2-7) and 6.5 years (IQR 5-9) for the systemic and chronic articular forms respectively.

All patients presented a chronic refractory form of the disease, which required the off-label use of bDMARD because of failures of corticosteroids and synthetic disease-modifying antirheumatic drug (sDMARD) or necessity to reduce or stop corticosteroids.

Biological treatment efficacy

Table 2 presents the detailed responses to anakinra and tocilizumab among the patients included in the study. Twenty-six of 27 patients (96.3%) achieved remission with either anakinra or tocilizumab. The median delay in the introduction of the first biotherapy was 5 months (interquartile range (IQR), 1-21 months): this delay was median 1 month (IQR, 0-6) in the systemic form, and median 17 months (IQR, 4-38) in the chronic articular form.

A total of 15 patients received anakinra; 5 as a first-line treatment, 4 as a second-line treatment, 5 as a third-line treatment, and 1 as a fourth-line treatment. The median delay between diagnosis and the introduction of anakinra was 1.5 months (IQR, 0-14). Thirteen (86.7%) patients were responders, among which 3 (23.1%) also received methotrexate when remission was achieved. The 2 anakinra non-responders received anakinra as a third-line treatment: one had previously failed to respond to tocilizumab, the other later responded to tocilizumab and even managed to stop it.

A total of 17 patients received tocilizumab, 2 as a first-line treatment, 6 as a second-line treatment, 5 as a third-line treatment and 4 as a fourth-line treatment. The median delay between diagnosis and the introduction of tocilizumab was 17 months (IQR, 4-39 months). Fourteen patients (82.4%) were responders. Among the 3 tocilizumab nonresponders, one presented

with a systemic form and received tocilizumab as a first-line treatment but later responded to anakinra, one presented with a systemic form and received tocilizumab as a fourth-line treatment after responding to anakinra but was switched because of a suspicion of anakinra-induced toxidermia, one presented with a chronic articular form and received tocilizumab as a fourth-line treatment after failure of anakinra.

The difference of median duration of disease at the introduction of the first bDMARD in the anakinra-treated patients group and in the tocilizumab-treated patients group was statistically significant ($p=0.04457$): median 2 months (IQR, 0.25-12 months) in the anakinra-treated patients, and median 14.5 (IQR, 3.25-38.25 months) in the tocilizumab-treated patients.

Eight patients (29.6%) managed to stop their biological treatment without relapse at the last known visit which ranged from 6 to more than 24 months after biological treatment discontinuation: 3 of 13 (23%) anakinra responders and 5 of 14 (35.7%) tocilizumab responders. The difference in delays in initiation of anakinra or tocilizumab was not statistically significant between those who managed to stop their biotherapy without relapse versus those who could not stop their biotherapy or those who relapsed, with a median delay of 3 months (IQR, 1.25-13.75) versus 8.5 months (IQR, 1-23.25), respectively ($p=0.61$).

Five patients received both biotherapies. Two of these patients presented with a systemic form and were tocilizumab nonresponders but anakinra responders, one presented with a chronic articular form and was anakinra nonresponder but tocilizumab responder, one presented with a chronic articular form and did not respond to either biotherapy, and one

patient presented with a systemic form and responded to both biotherapies; this patient first responded to anakinra but corticosteroids couldn't be tapered so he was switched to tocilizumab in order to successfully stop corticosteroids.

One patient received canakinumab and failed to respond but was anakinra responder. Three patients received antitumor necrosis factor (TNF) agents but these treatments were not efficacious (2 etanercept, 1 infliximab): two of them presented a chronic articular form and one a systemic form.

One of 27 (3.7%) patients did not respond to either biotherapy (anakinra then tocilizumab) and died of a probably infectious-induced AOSD flare.

Predictive factors for preferential responses to anakinra or tocilizumab

Patients who responded to either biotherapies or no biotherapy were excluded from this analysis (n=2). **Table 3** describes the univariate analysis for potential predictive factors of a good therapeutic response to anakinra or tocilizumab.

A chronic articular phenotype and the presence of arthritis were associated with a preferential response to tocilizumab (n=12/14 vs. n=3/13, p=0.0009; n=10/14 vs. n=3/13, p=0.017), whereas a systemic form and the absence of arthritis were associated with a preferential response to anakinra (n=1/14 vs. n=9/13, p=0.0009; n=3/14 vs. n=9/13, p=0.017).

No difference in biological variables was statistically predictive of treatment response, although the presence of thrombocytosis seemed to be

preferentially associated with a better response to tocilizumab than to anakinra (n=8/14 vs. n=3/13, p=0.123).

Likelihood of steroid withdrawal depending on the specific biotherapy and delays in initiation of biotherapy

All patients received corticosteroids at diagnosis. Among the 26 patients in remission, 14 (53.8%) achieved corticosteroid withdrawal within a mean delay of 27 months: 10 (71.4%) were on tocilizumab, and 4 (28.6%) were on anakinra (**Table 2**).

Table 4 presents the likelihood of corticosteroid withdrawal depending on treatment with anakinra and tocilizumab: tocilizumab was associated with an increased likelihood of corticosteroid withdrawal (p=0.029), whereas anakinra did not seem to increase the likelihood of corticosteroid withdrawal (p=1.000).

A shorter delay before the initiation of anakinra or tocilizumab was not associated with a greater likelihood of corticosteroid withdrawal among biotherapy responders. Among anakinra responders, the difference in the median delay from diagnosis to anakinra initiation between those who achieved steroid withdrawal (n=4) and those who did not (n=10) was not statistically significant (p=0.5767): the median delay was 2.5 months (IQR, 0-8 months) among those who did not stop corticosteroids versus 2 months (IQR, 2-14 months) among those who stopped corticosteroids. Among tocilizumab responders, the difference in the median delay from diagnosis to tocilizumab initiation between those who achieved steroid withdrawal (n=11) and those who did not (n=5) was not statistically significant (p=0.9548): the median

delay was 17 months (IQR, 9-21 months) among the tocilizumab responders who did not stop corticosteroids versus 17 months (IQR, 4-38 months) among those who stopped corticosteroids. Initiating tocilizumab as the first-line treatment rather than as a second-line or later treatment did not improve the likelihood of corticosteroid withdrawal (n=1/2 vs. n=11/15, p=1.000). In addition, initiating tocilizumab as a first- or second-line treatment rather than as a third-line or later treatment also did not improve the likelihood of steroid withdrawal (n=6/8 vs. n=5/9, p=0.619); similarly, initiating tocilizumab as a first-, second- or third-line treatment did not improve the likelihood of steroid withdrawal compared to that from tocilizumab used as a fourth-line treatment (n=9/13 vs. n=2/4, p=0.584).

Discussion

This retrospective study was conducted to evaluate bDMARDs strategies in the management of AOSD, with a special attention to predictive factors of their efficacy and their effect on corticosteroid sparing. All but one patient achieved remission with either anakinra or tocilizumab. Our results support the dichotomy of AOSD in two phenotypes: treatment responses to bDMARD depended on disease phenotype, the presence of arthritis and a chronic articular phenotype were associated with a preferential response to tocilizumab, whereas the systemic form was associated with a preferential response to anakinra. In our cohort, anakinra did not increase the likelihood of corticosteroid withdrawal but tocilizumab did, regardless of delays in initiation, or when it was initiated relative to other treatment in the overall therapeutic strategy.

The clinical and biological characteristics of the patients included in this study seem similar to those of AOSD patients reported in the literature(19), with the exception of life-threatening conditions, which have been estimated to affect as many as 15-20% of AOSD patients, while only 8% were affected in this study.

Multivariate analysis was not performed because of the sample size, a limitation inherent to rare diseases such as AOSD. Rather than aiming to look for significant differences, the goal of this study was to establish a reference for future large-scale studies and compile data from registries to confirm the results.

The distinction between systemic and chronic articular forms is not always straightforward and no consensual criteria exist to distinguish these

two phenotypes. For example a systemic form progressing for several years, who received corticosteroids for a long time and who benefited from bDMARD late in disease course, might be confused for a chronic articular form.

These results highlight the excellent efficacy of anakinra and tocilizumab in AOSD, regardless of the phenotype, but show some differences between them. However, the retrospective nature of the study is a major limitation to compare these two drugs. The choice of biotherapy may have been different depending on their availability on the year of diagnosis: anakinra was launched on the market several years before tocilizumab and the effects of anakinra and tocilizumab on AOSD were not simultaneously described.

One could argue that clinicians may have influenced the choice of biotherapy by preferentially prescribing tocilizumab to patients presenting with arthritis or a chronic articular form, analogous to rheumatoid arthritis, and therefore distorted the results. Comparing these two bDMARDs is impossible outside a randomized controlled trial (RCT) and none ever demonstrated that tocilizumab should be preferentially prescribed to AOSD patients with arthritis(5,20,21).

Yet the following results reinforce our findings. All but three of the patients included in this study were diagnosed in 2009 or later and these three received anakinra or tocilizumab after both their efficacy were described in AOSD.

A major result of our study is that anakinra responders more commonly did not have arthritis, as the absence of arthritis was statistically associated with a better response to anakinra ($p=0.017$). Tocilizumab also showed less

efficiency on the systemic form. This result supports the notion that even if clinicians' choices may have been influenced by analogy to rheumatoid arthritis, their insights seem to be founded. Whether anakinra is effective for AOSD patients with joint involvement is indeed a subject of debate as the data seem to be inconsistent(4,22–25). In our study, 5 patients presenting with a chronic articular form received anakinra: 3 responded to anakinra and never received tocilizumab, one was an anakinra non-responder but responded to tocilizumab, and one responded to anakinra but had to be switched to tocilizumab in order to stop the corticosteroid.

The absence of demonstrated steroid-sparing with anakinra in this study is questionable as it demonstrated a steroid-sparing effect in several other studies(22,24,26). A channelling bias exists: the acute onset of the systemic phenotype and its potential life-threatening complications might cause the clinicians to be more cautious while tapering corticosteroids, and the tocilizumab-induced fall in CRP might reassure them. Furthermore, anakinra was made available before tocilizumab: the progressively known dramatic efficacy of anakinra may have reassured the clinicians and entice them into a faster corticosteroids tapering when tocilizumab was made available. In addition, three patients presenting a systemic form in our study were able to taper corticosteroids down to 5mg daily but the clinicians opted to maintain this dosage as a long-term therapy. Both the management and the place of corticosteroids in AOSD treatment strategy should maybe differ based on the differences between the two phenotypes.

No patients in this study responded to anti-TNF blockers, whatever the phenotype. The efficacy of these medications in AOSD is controversial, but

some studies suggest that they have a place in the treatment of the chronic articular form(27–29), while others have showed rather disappointing results(20,21,30). The excellent efficacy and clear steroid-sparing effect of tocilizumab determined in our study, concurring with the findings of a recent meta-analysis showing that AOSD patients treated with tocilizumab had a pooled remission rate of approximately 85% regardless of the phenotype(31), should make clinicians prioritize tocilizumab to anti-TNF blockers for patients with a chronic articular form of AOSD. Canakinumab is currently being investigated for this indication (NCT02204293). No patient in this study received abatacept or rituximab; the data are very limited but some authors reported efficacy in patients who fail to respond to TNF, IL-1 or IL-6 inhibition(32–37).

Physiopathological data may highlight the efficacy of IL-17 or IL-18 blockade in AOSD. A recent study investigated whether IL-18 inhibition, using the recombinant human IL-18 binding protein tadekinig alpha, is a therapeutic option in patients with AOSD in a phase 2 open-label trial(38). Half of the patients achieved remission at week 3, suggesting early therapeutic efficacy of IL-18 blockade in AOSD. IL-17(39) and INF- γ (40) blockade have not been studied yet but should be in the near future. Janus kinase (JAK) inhibitors may also be of interest, particularly in the chronic articular form of AOSD via their blockage of IL-6 and INF- γ pathways.

The two main goals when initiating a bDMARD in AOSD should be a complete remission and corticosteroids withdrawal or significant tapering.

This study does not reveal definitive answers regarding whether an early introduction of biologics improves the general prognosis of AOSD. We

believe that the early use of biologics in AOSD patients is worth considering. It is our impression that the earlier biologics are used, the shorter and smoother the disease course is. Similarly, other authors have suggested that biotherapies should be initiated earlier in the course of AOSD (13,19), arguing that earlier initiation may improve the prognosis mainly via a steroid-sparing effect. Notably, the results of this study suggest that the steroid-sparing effect of biologics is not influenced by delays in initiation of biological therapy.

One-quarter to one-third (29.6%) of our patients managed to stop biologics despite chronic or refractory forms of AOSD, raising the question of how and when to stop biologics in these patients. A channelling bias exists, as no predefined corticosteroids tapering strategy could be set due to the retrospective nature of this study but patients who managed to stop anakinra had all achieved remission for at least 6 to 12 months, had initially stopped corticosteroids, and then all underwent progressive reduction in their biological treatments before definitive discontinuation. Among patients who managed to stop tocilizumab, corticosteroids had always previously been stopped, and tocilizumab dosage was progressively decreased when it had been administered by perfusion or tapered when it had been administered by injections. The high percentage of patients who successfully discontinued biological treatments in our study should encourage clinicians to consider tapering biologics among patients without visceral involvement who are in clinical and biological remission for 6 to 12 months.

The first evidence-based clinical practice guidelines for the management of AOSD(41) emphasized the use of IL-6 inhibitors in the treatment of AOSD but IL-1 inhibitors were judged to be “weakly

recommended as a therapeutic agent against refractory AOSD” although one RCT and several case reports suggest otherwise. A proposal may be to treat a first flare of AOSD with corticosteroids and to introduce biologics in cases of steroid-refractory flares or as early as the second flare of AOSD. In that case, anakinra should be preferred when faced with the systemic form of AOSD, and tocilizumab in patients with the articular form. The well-known idea of a “window of opportunity” in rheumatoid arthritis may also be valid in AOSD, with the objective being to prevent the development of a self-perpetuating “cytokine storm”. Monitoring our patients’ cytokine profiles may lead to personalized tailor-made biological treatment strategies in the future, but the use of these tools in daily clinical practice remains unrealistic for now.

We need large-scale studies, prospective cohort studies, RCTs and international collaborative registries regarding this multifaceted disease. As emphasized in a recent editorial, these studies will have to be more precise about evaluating the patients’ disease course and particularly their phenotypes in order to concentrate research on the subgroup of patients with a chronic or refractory form of the disease(42). A national French cohort, the French Adult and Childhood Onset Still Disease Cohort (RaDiCo-ACOSTILL), was recently opened for inclusion and will surely help to shed light on these issues in the near future.

Conclusion

This study supports the dichotomy of AOSD in two phenotypes and introduces the idea that treatment responses to bDMARD depend on disease phenotype. The presence of arthritis and a chronic articular phenotype seem to be associated with a preferential response to tocilizumab, whereas the systemic form seem to be associated with a preferential response to anakinra. Although further research is needed, this exploratory study highlights the therapeutic implications of the phenotypic dichotomy of AOSD. These results should help us better codify treatment strategies for AOSD.

Declarations

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Availability of data and material and consent for publication

The authors state that they had full access to all the data in the study and they take responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit them for publication.

Authors' contributions

Study conception and design: François Vercruysse, Marie-Elise Truchetet

Acquisition of data: François Vercruysse

Analysis and interpretation of data: François Vercruysse, Thomas Barnetche, Marie-Elise Truchetet

Drafting of manuscript: François Vercruysse, Marie-Elise Truchetet, Thomas Barnetche

Critical revision: François Vercruysse, Marie-Elise Truchetet, Alexandre Balageas, Xavier Delbrel, François Lifermann, Emilie Shipley, Estibaliz Lazaro, Bruno Fautrel, Christophe Richez, Thierry Schaefferbeke

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Tables

Table 1

Table 1. Characteristics of the patients included in the study

n/N* (%)	Systemic form 11 (40.7)	Chronic articular form 16 (59.3)	Total 27
Demographic and clinical			
Sex : female	8 (73)	10 (63)	18 (67)
Age at first symptoms	33 (IQR 23-48)	29 (IQR 21-58.5)	30 (IQR 21-48)
Duration of disease (years)	5 (IQR 2-7)	6.5 (IQR 5-9)	6 (IQR 4-9)
Ever smoked	4 (36)	2/9 (22)	6/20 (30)
Still's disease-related rash	10 (91)	12 (75)	22 (81)
Evanescient erythema	4 (36)	8 (50)	12 (44)
Maculopapular rash	7 (64)	7 (44)	14 (52)
Urticaria rash	3 (27)	2 (13)	5 (18.5)
Arthralgia	10 (91)	16 (100)	26 (96)
Arthritis	3 (27)	11 (69)	14 (52)
Hands affected (arthralgia or arthritis)	9 (82)	14 (88)	23 (85)
EMS	7/8 (88)	13/14 (93)	20/22 (90)
Mylagia	9 (82)	8 (50)	17 (63)
Fever>38°C	11 (100)	16 (100)	27 (100)
Fever>39°C for longer than 7 days	4 (36)	4/15 (27)	8/26 (31)
Intermittent fever	9 (82)	10/15 (67)	19/26 (73)
Vesperal fever	8 (73)	9/15 (60)	17/23 (74)
Deterioration of the general state or weight loss>4kg	8 (73)	10/15 (67)	18/25 (72)
Lymphadenopathy	8 (73)	6/15 (40)	14/26 (54)
Pharyngitis	8 (73)	10/15 (67)	18/26 (69)
Angina	4 (36)	1/15 (7)	5/26 (19)
Visceral involvement	2 (18)	0 (0)	2 (8)
Pleuritis	1 (9)	1 (0)	1 (4)
Pericarditis	1 (9)	2 (0)	1 (4)
Pulmonary hypertension	1 (9)	3 (0)	1 (4)
Biological			
Neutrophilia>8000/mm3	11 (100)	14/15 (93)	25/26 (96)
Eosinophilia>500/mm3	1/10 (10)	0 (0)	1/25 (4)
Anemia<12 g/dl	6/10 (60)	9 (56)	15/26 (58)
Thrombocytosis>400 000/mm3	3/10 (30)	10 (63)	13/26 (50)
Increased C-reactive protein (CRP) levels	11 (100)	16 (100)	27 (100)
Maximum CRP at diagnosis	200 (IQR 160-300)	200 (IQR 67.5-254.5)	200 (IQR 104.5-267.5)
Low albumin	9/10 (90)	9/14 (64)	18/24 (75)
Increased AST or ALT	8 (73)	5/15 (33)	13/26 (50)
Increased ferritin	10 (91)	9/15 (60)	19/26 (73)
Ferritin 1000-5000	4 (36)	6/15 (40)	10/26 (38.5)
Ferritin 5000-10000	2 (18)	1/15 (7)	3/26 (11.5)
Ferritin>10 000	4 (36)	2/15 (13)	6/26 (23)
Glycosylated ferritin<20%	8 (73)	10 (63)	18 (66.7)
Glycosylated ferritin 20-40%	2 (18)	6 (38)	8 (29.6)
Glycosylated ferritin>40%	1 (9)	0 (0)	1 (3.7)
ANA-positivity	2 (18)	3 (19)	5 (18.5)
anti-DNA positivity	0 (0)	1 (6)	1 (3.7)
RF positivity	0 (0)	3 (19)	3 (11)
β2GP1 positivity	1/5 (20)	0 (0)	1/5 (20)
Lupus anticoagulant positivity	1/5 (20)	0 (0)	1/5 (20)
Disseminated intravascular coagulation	0 (0)	0 (0)	0 (0)
rHLH**	3 (27)	0 (0)	3 (11)
Increased triglycerids	5/7 (71)	1/10 (10)	6/17 (35)
Hemophagocytosis	3 (27)	0/5 (0)	3/8 (37.5)

*N is indicated when data was not available for all 27 patients

** reactive haemophagocytic lymphohistiocytosis

Table 2

Table 2. Delay in corticosteroids withdrawal and detailed responses to anakinra and tocilizumab among the patients included in the study

STILL	Phenotype	Corticosteroids				Anakinra-treated patients				Tocilizumab-treated patients			
		Stopped	Delay between diagnosis and steroid withdrawal (months)	Delay between diagnosis and initiation of first bDMARD (months)	Delay between diagnosis and initiation of anakinra (months)	Anakinra responders	Managed to stop anakinra	Line of treatment	Delay between diagnosis and initiation of tocilizumab (months)	Tocilizumab responders	Managed to stop tocilizumab	Line of treatment	
STILL 1	Chronic articular	Yes	12	39	0	-	-	-	39	Yes	No	No	Third
STILL 2	Systemic	No	-	0	0	Yes	Yes	*	9	No	-	-	Fourth
STILL 3	Systemic	No	-	1	1	Yes	No	First	-	-	-	-	-
STILL 4	Chronic articular	Yes	60	38	-	-	-	-	38	Yes	No	No	Second
STILL 5	Chronic articular	Yes	17	7	-	-	-	-	7	Yes	No	No	Second
STILL 6	Chronic articular	Yes	71	69	-	-	-	-	69	Yes	No	No	Second
STILL 7	Systemic	Yes	12	2	2	Yes	No	Second	20	Yes	Yes	Yes	Third
STILL 8	Systemic	Yes	20	12	-	-	-	-	12	Yes	No	No	Third
STILL 9	Chronic articular	No	-	21	-	-	-	-	21	Yes	No	No	Third
STILL 10	Chronic articular	No	-	4	4	No	-	Third and fifth	17	No	-	-	Fourth
STILL 11	Systemic	Yes	12	0	0	Yes	Yes	First and third	-	-	-	-	-
STILL 12	Chronic articular	No	-	**	-	-	-	-	**	Yes	No	No	Third
STILL 13	Chronic articular	Yes	45	24	24	No	-	Third	36	Yes	Yes	Yes	Fourth
STILL 14	Chronic articular	Yes	18	4	-	-	-	-	4	Yes	Yes	Yes	Second
STILL 15	Chronic articular	Yes	8	1	-	-	-	-	1	Yes	Yes	Yes	Second
STILL 16	Chronic articular	No	-	14	14	Yes	No	Fourth	-	-	-	-	-
STILL 17	Chronic articular	Yes	29	17	-	-	-	-	17	Yes	Yes	Yes	Fourth
STILL 18	Systemic	No	-	6	6	Yes	-	Third	-	-	-	-	-
STILL 19	Chronic articular	Yes	15	0	0	-	-	-	0	Yes	Yes	No	First
STILL 20	Systemic	No	-	0	0	Yes	Yes	First	-	-	-	-	-
STILL 21	Chronic articular	No	-	252	-	-	-	-	252	Yes	No	No	Second
STILL 22	Systemic	No	-	0	0	Yes	No	First	-	-	-	-	-
STILL 23	Systemic	No	-	0	8	Yes	No	Second	0	No	-	-	First
STILL 24	Chronic articular	No	-	1	1	Yes	No	Second	-	-	-	-	-
STILL 25	Chronic articular	No	-	24	24	Yes	No	Third	-	-	-	-	-
STILL 26	Systemic	Yes	6	14	14	Yes	No	Third	-	-	-	-	-
STILL 27	Systemic	Yes	53	2	2	Yes	No	Second	-	-	-	-	-

* First, third, fifth and seventh

** Unknown

Table 3

Table 3. Univariate analysis of predictive factors for a good therapeutic response to anakinra or tocilizumab (n=25)

	Anakinra responders (n=12)	Tocilizumab responders (n=13)	p value
Clinical variables			
Sex, F	8	10	0.673
Age at first symptoms	42.5 (IQR 22.5-54)	25 (IQR 21-36)	0.276
Ever smoked	4	2	1.000
Never smoked	4	5	0.170
Still's disease-related rash			
Evanescient erythema	6	6	1.000
Maculopapular rash	6	7	1.000
Urticaria	4	1	0.160
Arthralgia	11	13	0.480
Arthritis	3	10	0.017
Absence of arthritis	9	3	0.017
Hands affected (arthralgia or arthritis)	10	11	1.000
Early morning stiffness	8	11	1.000
Myalgia	9	7	0.411
Fever>39°C for longer than 7 days	5	3	0.667
Intermittent fever	9	9	1.000
Vesperal fever	7	8	0.635
Deterioration of the general state and/or weight loss>4 kg	7	9	0.371
Adenopathy	6	6	1.000
Pharyngitis	9	8	1.000
Angina	4	1	0.317
Phenotypic variables			
Systemic form	9	1	0.0009
Chronic articular form	3	12	0.0009
Biological variables			
Anemia<12g/dl	6	8	1.000
Thrombocytosis>400 000/mm ³	3	8	0.123
Thrombopénia<150 000/mm ³	1	0	0.458
Low albumin	8	8	0.646
Ferritin			
5000-10 000 (µg/L)	1	2	1.000
>10 000	3	2	0.645
Glycosylated ferritin<20%	6	10	0.226
ANA positivity	1	4	0.593
Hemophagocytosis	3	0	1.000

Table 4

Table 4. Likelihood of corticosteroid withdrawal stratified by biotherapy

Anakinra responders	Corticosteroids stopped			p value
	No	Yes	Total	
No	1	1	2	1.000
Yes	9	4	13	
<i>Total</i>	10	5	15	
Tocilizumab responders				
Tocilizumab responders	Corticosteroids stopped			p value
	No	Yes	Total	
No	3	0	3	0.029
Yes	3	11	14	
<i>Total</i>	6	11	17	

Serment d'Hippocrate



Au moment d'être admis 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 dans l'intimité des personnes, je tairai les secrets qui me seront confiés.

Reçu 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 et méprisé si j'y manque.



La stratégie de traitement par biothérapie de la maladie de Still de l'adulte dépend de la dichotomie phénotypique

Introduction: Le phénotype de la maladie de Still de l'adulte (MSA) peut être dichotomisé en une forme systémique et une forme articulaire chronique. A l'ère où les biothérapies et notamment le blocage des interleukines (IL)-1 et 6 jouent un rôle prépondérant dans son traitement, leurs place dans la stratégie thérapeutique reste à préciser. Cette étude avait pour objectif d'identifier des facteurs prédictifs cliniques ou biologiques de réponse préférentielle à l'anakinra ou au tocilizumab, et d'identifier si le choix de biothérapie et son délai d'initiation influençaient les chances de sevrage cortisonique.

Méthodes: Une étude exploratoire multicentrique rétrospective a inclus tous les patients atteints de MSA et ayant reçu une biothérapie dans trois hôpitaux régionaux jusqu'à 2018. Leur caractéristiques cliniques et biologiques au diagnostic et les données relatives aux traitements ont été recueillies. Une analyse univariée a été effectuée en utilisant le test statistique non-paramétrique de Mann-Whitney pour les variables quantitatives et le test exact de Fisher pour les variables qualitatives.

Résultats: Vingt-sept patients ont été inclus. Tous les patients sauf un ont atteint la rémission soit sous anakinra soit sous tocilizumab. La réponse au traitement dépendait du phénotype clinique : la présence d'arthrite et un phénotype articulaire chronique étaient associés à une réponse thérapeutique préférentielle pour le tocilizumab ($p=0.017$ et $p=0.0009$ respectivement), alors qu'une forme systémique et l'absence d'arthrite étaient associées à une réponse thérapeutique préférentielle à l'anakinra ($p=0.017$ et $p=0.0009$ respectivement). Le tocilizumab était associé à de meilleures chances de sevrage cortisonique ($p=0.029$) quel que soit son délai d'initiation ou sa place en terme de ligne thérapeutique.

Conclusion: Cette étude souligne l'importance de la dichotomisation phénotypique de la MSA et ses implications thérapeutiques. Ces résultats devraient nous permettre de mieux catégoriser les patients atteints de MSA et nous aider à codifier leur traitement.

Mots-clés: Maladie de Still de l'Adulte, Traitements Biologiques, Corticoïdes, Maladies auto-inflammatoires

Adult-Onset Still's Disease Biological Treatment Strategy Depends on the Phenotypic Dichotomy

Objectives: Adult-onset Still's disease (AOSD) phenotype can be dichotomized in systemic or chronic articular forms. As biologicals and particularly interleukin (IL)-1 and IL-6 blockers play a more and more prominent role in the treatment, their place requires clarification. This study aimed to identify factors predictive of treatment response to anakinra or tocilizumab, and investigate whether the choice of biotherapy and delays in the initiation of biotherapy influenced the likelihood of steroid discontinuation.

Methods: A multicenter exploratory retrospective study included all patients diagnosed with AOSD and receiving biological treatments in three regional hospitals until 2018. Clinical and biological characteristics at diagnosis and treatment related data were collected. The non-parametric Mann-Whitney test was used to perform univariate analysis for quantitative variables, and Fisher's exact test was used for qualitative variables.

Results: Twenty-seven patients were included. All but one patient achieved remission with either anakinra or tocilizumab. Treatment responses depended on disease phenotype: the presence of arthritis and a chronic articular phenotype were associated with a preferential response to tocilizumab with $p=0.0009$ and $p=0.017$ respectively, whereas the systemic form and the absence of arthritis were associated with a preferential response to anakinra with $p=0.0009$ and $p=0.017$ respectively. Tocilizumab increased the likelihood of corticosteroid withdrawal ($p=0.029$) regardless of delays in initiation or when it was initiated relative to other treatment in the overall therapeutic strategy.

Conclusion: This study highlights the therapeutic implications of the phenotypic dichotomy of AOSD and should help us better codify AOSD treatment.

Keywords: Adult-Onset Still's disease, Biologicals, Corticosteroids, Miscellaneous Rheumatic and Inflammatory Diseases