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ORIGINAL RESEARCH

Criteria Associated with Treatment Decisions in Juvenile Idiopathic Arthritis with a Focus on Ultrasonography: Results from the JIRECHO Cohort

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ABSTRACT

Background: The treatment of children with juvenile idiopathic arthritis (JIA) to prevent disability is a major challenge in paediatric rheumatology. The presence of synovitis, which is difficult to detect in children, is associated with structural damage. Musculoskeletal ultrasonography (MSUS) can be used in patients with JIA to reveal subclinical synovitis.

Objective: The primary aim was to determine whether the use of MSUS was associated with therapeutic modification in patients with JIA. The secondary aim was to identify other factors associated with therapeutic decisions.

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Methods: We conducted an observational study based on the JIRECHO multi-centre cohort, which was developed to provide a systematic MSUS follow-up for patients with JIA. Follow-up occurred every 6 months and included clinical and MSUS examinations. We included children who underwent MSUS of the elbows, wrists, second metacarpophalangeal joints, knees and ankles, which was performed by expert sonographers. Clinical and biological data, disease activity scores and information on therapeutics were collected.

Results: A total of 185 visits concerning 112 patients were recorded. Three groups were defined according to the therapeutic decision: escalation (22%, $n = 40$), de-escalation (14%, $n = 26$) or stable (64%, $n = 119$). In the "therapeutic escalation" group: the presence of ultrasonographic synovitis in B-mode and the presence of grade 2 or 3 synovitis in B-mode were not significantly more frequent than in the "stable therapeutic or de-escalation" group (80% versus 65%, $p = 0.06$; 33% versus 19%, $p = 0.06$), and the patient's and physician's visual analogue scale (VAS) scores, the clinical JADAS and the C-reactive protein level were significantly higher, but only physician's VAS score remained in the model of logistic regression. In the "therapeutic de-escalation" group: there was no difference in the presence of US synovitis compared with the "stable therapeutic or escalation" group (62% versus 69%, $p = 0.48$).

Conclusion: Even though US synovitis tended to be more frequent in patients with therapeutic escalation, the study did not show that the presence of synovitis in MSUS was statistically associated with therapeutic modifications in patients with JIA. Treatment remained stable despite the presence of US synovitis.

Keywords: Juvenile idiopathic arthritis; Ultrasonography; Synovitis; Therapeutic decision; Treatment

Summary points

During follow up of patients with juvenile idiopathic arthritis, a therapeutic modification was observed in 36% of the visits

Therapeutic modifications were not influenced by musculoskeletal ultrasonography of ten joints

Therapeutic remained stable despite the presence of synovitis on MSUS

INTRODUCTION

Juvenile idiopathic arthritis (JIA) belongs to a heterogeneous group of rare chronic inflammatory diseases that can cause short- and long-term disability [1, 2]. The International League of Associations for Rheumatology (ILAR) has defined several subtypes of JIA depending on the number of arthritic joints, the presence of enthesitis, immunological characteristics and systemic signs [3].

The treatment of JIA to prevent structural damage causing pain and disability is an important challenge in paediatric rheumatology. Methotrexate (MTX), the most commonly prescribed conventional disease-modifying antirheumatic drug, biologics and, more recently, JAK inhibitor drugs, are the treatment options currently available based on national and international guidelines [4, 5]. Treatment modifications made by the physician are based on therapeutic efficacy, side effects and patient-reported outcome. Therapeutic efficacy is assessed by the Juvenile Disease Activity Score (JADAS) and the presence of synovitis, biological inflammation or structural damage [6–9]. The severity and duration of synovitis have been correlated with the risk of joint destruction [10]. However, synovitis is difficult to detect in children; musculoskeletal ultrasonography (MSUS) in B-mode and power Doppler (PD) mode can be used in patients with JIA to

reveal subclinical synovitis [11, 12]. For adults with rheumatoid arthritis (RA), MSUS is more sensitive in detecting synovitis and inflammatory activity when paired with PD US [13–15] than clinical examination and is commonly utilized owing to its easy adaptability; however, it is still under evaluation in controlled trials or in cohorts [16, 17]. In JIA, the use of MSUS to adapt the treatment has not yet been established.

The Juvenile Idiopathic Rheumatisms (JIR) cohort is an international European database that aims to collect retrospective and prospective information for children with inflammatory and rheumatic diseases. It was created by a group of paediatric rheumatologists from Belgium, France and Switzerland in 2013 [18]. More recently, the JIRECHO cohort was developed to provide a systematic MSUS follow-up for patients with JIA. This systematic MSUS follow-up is based on the scoring system of synovitis according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) paediatric MSUS group [19, 20]. The reliability among a large group of sonographers was good, suggesting the applicability of this scoring system in clinical practice and multi-centre studies [21].

The primary aim was to determine whether the presence of synovitis identified by ultrasonography (US) in B-mode and power Doppler was associated with therapeutic modifications in JIA. The secondary aim was to identify other factors that could be associated with treatment modification in JIA.

METHODS

Study Design and Patients

We conducted an observational study from January 2019 to March 2021 based on a multicentric cohort of patients diagnosed with JIA who were included in the JIRECHO cohort [18]. Ethical approval for this study was obtained from the French Ethics Committee (CCTIRS) and the National Commission for Data Protection and Liberties (CNIL). A non-opposition form was obtained for each patient/parent(s) after appropriate information about the study was provided. Anonymous data were collected for each patient with JIA seen in an expert centre. The subtype of JIA was defined according to the ILAR-defined JIA categories as determined by the reporting physician [3].

Patients were included in the JIRECHO cohort at diagnosis, on disease flare-up or during follow-up upon request from the physician. Patients were followed up every 6 months with both clinical and US examinations. We included children who underwent standardized MSUS of the elbows, wrists, second metacarpophalangeal (MCP) joints, knees and ankles, which was performed by either an independent sonographer or by the physician according to the OMERACT paediatric US scoring system [19, 20]. Synovitis on US was defined by the presence of joint effusion and/or synovial hypertrophy in B-mode ($\geq$ grade 1) associated or not with Doppler signals ($\geq$ grade 1). US was performed within 7 days around the clinical outpatient visit, by expert sonographers with good experience in the field of JIA (at least 2 years practical experience in paediatric US) who previously participated in the study of the reliability of the OMERACT paediatric ultrasound synovitis definitions and scoring system in JIA [21]. Sonographers included rheumatologists, radiologists and paediatricians.

For all included patients, clinical examination results, patient and physician visual analogue scale (VAS) scores for pain and global disease, and biological results were recorded. We used the clinical JADAS10 (cJADAS) to assess global disease activity. The cJADAS contains three measures: the patient's and physician's VAS scores and the number of any active joints up to a maximum of ten joints [6, 22]. Low disease activity was defined by a cJADAS $\leq$ 1.5 and $\leq$ 2.5 for the oligoarticular and polyarticular forms, respectively. We collected data on the following inflammatory biological markers: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Concerning the treatment, the type of therapy with the dose and the frequency of administration were documented (i.e. for corticosteroids, methotrexate, etanercept, etc.). Patient assessment regarding the effectiveness and occurrence of adverse

events (AEs) was performed at baseline and the follow-up every 6 months.

Each visit for which data were complete was recorded. We excluded the visits where clinical, MSUS or therapeutic data were missing, or when US was performed more than 7 days around the clinical outpatient visit.

Therapeutic modifications were decided by the physician after the MSUS examination and the outpatient visit. Treatments included non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, methotrexate, biologics or glucocorticoid injections. Three groups of patients were defined according to therapeutic decision made by the expert: the escalation group, in whom treatment was increased (treatment implementation of NSAIDs, corticosteroids, methotrexate or biologics, use of glucocorticoid injections, switch or dose increase); the de-escalation group (discontinuation of treatment or dose decrease); and the stable therapeutic group. These groups were evaluated to determine whether the use of MSUS was associated with an increase or decrease in the treatment of patients with JIA.

Statistical Analyses

For baseline characteristics of patients, data are presented as mean ± standard deviation (SD) or number (%). For the primary objective, the sample we used for statistical analyses was the total number of visits. We performed a univariate analysis by the Mann–Whitney *U* test (for continuous variables) and Pearson or Fisher's χ^2 test (as appropriate for binary variables) to compare the characteristics of patients at each medical visit. Receiver operating characteristic (ROC) curves were generated using items statistically associated with treatment escalation. Statistical significance was defined as $p < 0.05$. Univariate statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 25.0; SPSS Inc., Chicago, IL, USA) and logistic regression using R++ (The Next Step, 2022, France).

RESULTS

Baseline Characteristics

The JIRECHO database identified 189 patients with a total number of 301 visits (Fig. 1). Patients who were included were selected from six centres. In total, we enrolled 112 patients, mainly females (72%), with a mean age of 9 ± 4 years (range, 1–17 years) at inclusion. According to JIA subgroups, the studied patients included 46% with oligoarticular JIA, 22% with polyarticular JIA, 16% with undifferentiated arthritis, 7% with psoriatic arthritis, 5% with enthesitis-related arthritis and 4% with systemic JIA. Detailed demographic characteristics and laboratory tests at inclusion are indicated in Table 1.

Factors Associated with Therapeutic Modification

The total number of visits that we were able to analyse according to the recommended clinical and US examinations and the quality of the data entered, including baseline visits and follow-ups, was 185. Of these, 58% were initial visits and 42% were follow-up visits. Therapeutic escalation and de-escalation were observed at 40 (22%), and 26 (14%) visits, respectively (Fig. 1).

Therapeutic escalation: We first evaluated the factors associated with an increase in treatment in the escalation group. We compared the group of patients for whom treatment was increased with patients for whom treatment was decreased or stable (Table 2).

The presence of at least one joint with synovitis in B-mode US was higher in patients with therapeutic escalation than in other patients (80% versus 65%, $p = 0.06$) and the presence of grade 2 or 3 synovitis in B-mode was also numerically superior (33% versus 19%, $p = 0.06$). There was no significant difference for the presence of at least one joint with synovitis in PD US, which were present in 12/40, 30% versus 34/145, 23%; $p = 0.4$. The results were similar for the presence of grade 2 or 3 synovitis in PD US (7.5% versus 4%, $p = 0.4$).

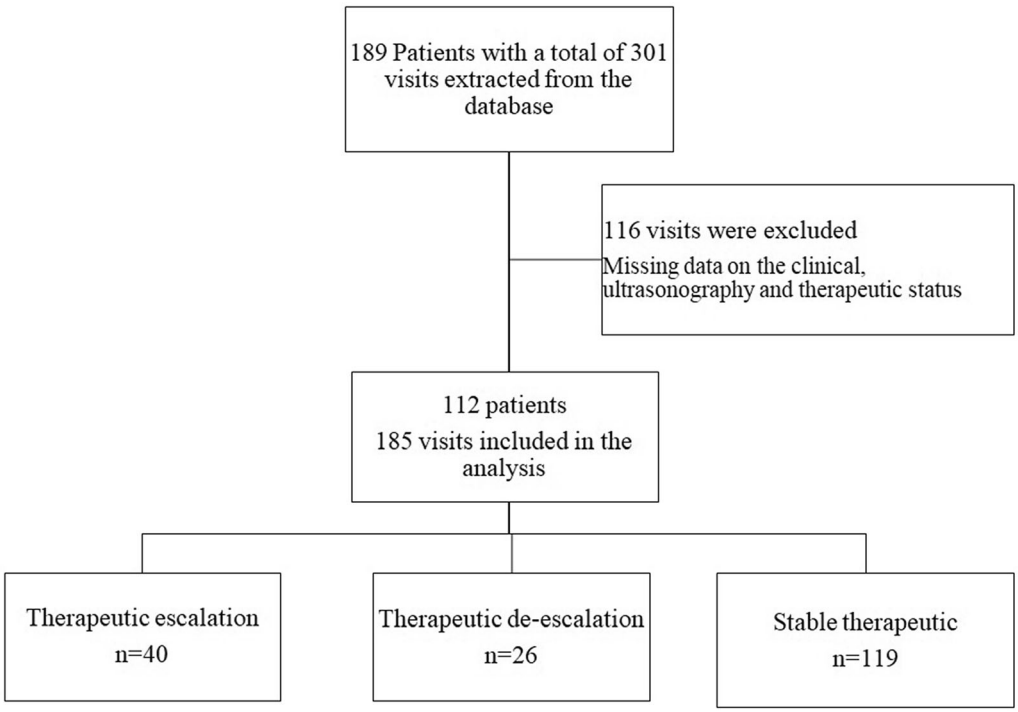

Fig. 1 Flow chart. A total of 189 patients with 301 visits were extracted from the database. Visits with missing data on the clinical and musculoskeletal US examination or the therapeutic status were excluded. A total of 185 visits were included in the analysis for the primary outcome

No differences were observed in tenderness or swelling of the ten analysed joints between the two groups except for second MCP joint pain. Patients with treatment escalation had less second MCP joint tenderness than other patients (0% versus 11%, $p = 0.02$).

Patient-reported outcome (patient's VAS) was statistically associated with therapeutic escalation ($p < 0.01$). Patients with therapeutic escalation also had higher physician's VAS scores ($p < 0.0001$), cJADAS scores ($p = 0.02$) and ESR and CRP levels ($p = 0.001$ and $p = 0.01$, respectively). Only physician's VAS scores remained in the model of logistic regression.

Therapeutic de-escalation: we compared the group of patients for whom therapy was decreased with patients for whom treatment was increased or stable (Table 3). No significant difference was observed for the presence of at least one joint with synovitis in B-mode (62% versus 69%, $p = 0.48$). There was a trend to have fewer joints with grade 2 or 3 B-mode synovitis than other patients but the difference was not significant (8% versus 24%, $p = 0.06$). There was no significant difference for the presence of at least one joint with synovitis in PD US (15% versus 26%, $p = 0.23$) or the presence of grade 2 or 3 synovitis in PD US (0% versus 6%, $p = 0.36$). The level of CRP was statistically associated with therapeutic de-escalation ($p = 0.008$). Only CRP remained in the model of logistic regression.

ROC Curve Analyses

We generated ROC curves for US factors and other factors that were statistically significant (Fig. 2) in the therapeutic escalation group to determine their weight. ROC curves were not generated in the de-escalation group as the number of events was low ($n = 26$) and only one variable was statistically associated with de-escalation. Regarding synovitis on US, the presence of at least one joint with synovitis in B-mode US showed high sensitivity (Se) (92%) but low specificity (Sp) (24%) [area under the

Table 1 Patients' characteristics

Characteristics	Total, n = 112
Age, years	9 (4.1)
JIA duration, years	3 (3.5)
Sex, women (women/total)	81 (72)
JIA subtype	
Systemic onset	4 (4)
Persistent or extended oligoarthritis	51 (46)
Polyarthritis RF negative	19 (17)
Polyarthritis RF positive	6 (5)
Psoriatic arthritis	8 (7)
Enthesitis-related arthritis	6 (5)
Undifferentiated arthritis	18 (16)
Ultrasound performed at diagnosis	30 (27)
Laboratory features	
Rheumatoid factor positivity	6 (5)
Anti-nuclear antibody positivity	54 (48)
HLA-B27 positivity	11 (10)

Values are mean (± SD) or n (%)
JIA, juvenile idiopathic arthritis; HLA-B27, human leucocyte antigen B 27

curve (AUC) 0.58, 95% CI 0.4–0.75]. Concerning other factors, a physician's VAS score ≥ 2.25 showed moderate Se (67%) and Sp (74%) (AUC 0.68, 95% CI 0.5 to 0.85). The Se and Sp for cJADAS ≥ 1.5 and cJADAS ≥ 2.5 were 67%/40% and 67%/47% (AUC 0.66, 95% CI 0.48–0.85), respectively. The Se and Sp for CRP levels ≥ 4 mg/l and ESR (≥ 6.5 mm/h) were 58%/66% (AUC 0.64, 95% CI 0.45–0.82) and 83%/50% (AUC 0.72, 95% CI 0.55–0.88), respectively.

We tried to stratify the analysis on the visits of patients (at diagnosis and during follow-up) but only two patients in the subgroups "follow up" had a treatment escalation, leading to non-relevant ROC curves.

Therapeutic modification

At baseline, 76 patients were treated with NSAIDs, 7 patients were treated with corticosteroids, 59 patients were treated with MTX and 10 patients with biologics.

Treatment initiation occurred in 26 visits: NSAIDs, corticosteroids, MTX and biologics were initiated in 10, 6, 9 and 2 visits respectively. In addition, 17 patients received glucocorticoid injections. Biotherapies were switched in two patients. Regarding NSAIDs and MTX, the dosage was increased in four visits. Treatment was discontinued in 22 visits: NSAIDs, corticosteroids, MTX and biotherapies were withdrawn in 8, 5, 7 and 4 visits, respectively. Finally, the dosages of MTX and NSAIDs were decreased in four visits. It should be noted that some patients could have had simultaneous treatments such as initiation of corticosteroids and methotrexate for example or discontinuation of more than one treatment during the same visit.

DISCUSSION

In this study, we investigated the factors associated with therapeutic modifications in patients with JIA, focusing on ultrasonography. The factors were evaluated in a cohort of patients with JIA who benefited from MSUS in expert centres [21].

The data of 185 visits were analysed. As the cohort was recent, we used the number of visits for our sample instead of the number of patients, which allowed us to have a larger sample. Moreover, when checking the data, we noticed that some important data were missing from the medical visits as the presence of clinical and US synovitis and we excluded them. This explains why not all patients in our study had a follow-up visit.

First, the presence of synovitis in B-mode US was not statistically associated with therapeutic escalation, although the number of joints with synovitis was higher for patients whose treatments were intensified. Moreover, the presence of synovitis in PD-mode US was not significantly higher in the "therapeutic escalation"

Table 2 Comparison between the group of patients with JIA with therapeutic escalation and with stable treatment or de-escalation

Characteristics	Therapeutic escalation°, *n* = 40	Stable therapeutic or de-escalation, n = 145	*p* value
Sex, women, *n* (%)§	29 (73)	107 (74)	0.87
JIA subtype, *n* (%)§			0.3
Systemic onset	0 (0)	5 (4)	
Persistent or extended oligoarthritis	20 (50)	63 (43)	
Polyarthritis RF negative	8 (20)	29 (20)	
Polyarthritis RF positive	3 (7.5)	5 (4)	
Psoriatic arthritis	0 (0)	15 (10)	
Enthesitis-related arthritis	3 (7.5)	10 (7)	
Undifferentiated arthritis	6 (15)	18 (12)	
Tender joint count, *n* (%)			
Knee§	14 (35)	48 (33)	0.82
Elbow§	6 (15)	25 (17)	0.74
Wrist¶	7 (18)	25 (17)	1
Second MCP joint¶	0 (0)	16 (11)	0.02
Ankle§	11 (28)	36 (25)	0.73
Swollen joint count, *n* (%)			
Knee¶	4 (10)	16 (11)	1
Elbow¶	3 (7.5)	2 (1)	0.07
Wrist¶	3 (7.5)	12 (8)	1
Second MCP joint¶	0 (0)	10 (7)	0.12
Ankle¶	3 (7.5)	9 (64)	0.72
Laboratory tests, *n* (%)			
RF positivity¶	3 (7.5)	5 (3)	0.39
ANA positivity§	19 (48)	76 (50)	0.48
HLA-B27 positivity§	6 (15)	17 (11.7)	0.41
Ultrasonography, *n* (%)			
Synovitis in B-mode§*	32 (80)	93 (65)	0.06
Grade 2 or 3 synovitis in B-mode§	13 (33)	27 (19)	0.06
Synovitis in PD§*	12 (30)	34 (23)	0.4
Grade 2 or 3 synovitis in PD¶	3 (7.5)	6 (4)	0.4
Patient's VAS score (median, QI–Q3)	3 (0–6)	0 (0–3)	0.003

Table 2 continued

Characteristics	Therapeutic escalation°,*n* = 40	Stable therapeutic or de-escalation,n = 145	*p* value
Physician's VAS score (median, QI–Q3)	3 (1–6)	1 (0–2.5)	< 0.0001
Clinical JADAS (median, QI–Q3)	7 (1–11)	2.5 (0–7)	0.02
ESR (mm/h)** (median, QI–Q3)	36 (12–53)	6.5 (2–20)	0.001
CRP (mg/l)*** (median, QI–Q3)	9 (1–41)	3 (0.7–5)	0.01

Values are *n* (%) or mean (± SD)

JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; RF, rheumatoid factor; ANA, anti-nuclear antibodies; HLA-B27, human leucocyte antigen B27; PD, power Doppler; VAS, visual analogue scale; JADAS, juvenile arthritis disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

°Treatment implementation of nonsteroidal anti-inflammatory drugs, corticosteroids, methotrexate or biologics, use of glucocorticoid injections, switch or dose increase

§Pearson χ^2 test was used

¶Fisher's exact test was used

*Presence of at least one joint with grade 1, 2 or 3 synovitis

**Data on ESR level were available for 20 patients in therapeutic escalation group and 44 patients in the stable therapeutic or de-escalation group

***Data on CRP level were available for 22 patients in therapeutic escalation group and 65 patients in the stable therapeutic or de-escalation group

group. Additionally, the presence of grade 2 or 3 synovitis in B-mode was higher in patients with "therapeutic escalation" compared with patients with "stable therapeutic or de-escalation", but not statistically significant.

Others factors associated with treatment modification were analysed, and the presence of arthritis on clinical examination of the ten most commonly affected joints in JIA (elbows, wrists, second MCP joints, knees, ankles) was not associated with the intensification of therapy. The major factors associated with therapeutic decisions, especially treatment escalation, were based on patient outcome, disease activity scores and biological activity markers. Indeed, the physician's and patient's VAS scores were both significantly higher in patients with therapeutic escalation, as well as the cJADAS and CRP and ESR levels. Secondly, second MCP tenderness was more elevated in patients with stable treatment than in patients with therapeutic intensification. This elevation could suggest that joint tenderness is sometimes considered more as a chronic pain than a sign of disease activity. Overall, the ROC curve analyses showed that the physician's VAS score, the cJADAS, the inflammatory biological markers and the presence of at least one joint with synovitis in B-mode US had moderate Se and Sp.

Regarding treatment de-escalation, we did not find any association between MSUS, clinical or biological items and treatment decisions except for CRP lower levels. Thus, in our study, we were unable to determine how the physician decided on decreasing treatments. Once again, the presence of synovitis on US was not significantly different in patients with therapeutic de-escalation compared with patients with stable treatment. However, for patients with therapeutic de-escalation, there were fewer joints with grade 2 or 3 synovitis in B-mode US. We hypothesize that there was no significant difference because of the small number of patients in this group.

The role of MSUS in patients with JIA is under investigation [23]. Ultrasound-detected synovitis have been shown to be common in patients with JIA in clinical remission. Rebollo-Polo et al. [24] also demonstrated that patients with JIA who met the criteria for clinical

Table 3 Comparison between the group of patients with JIA with therapeutic de-escalation and with stable treatment or escalation

Characteristics	Therapeutic de-escalation°, *n* = 26	Stable therapeutic or escalation, *n* = 159	*p* value
Sex, women, *n* (%)§	20 (77)	116 (73)	0.67
JIA subtype, *n* (%)§			0.16
Systemic onset	2 (8)	3 (2)	
Persistent or extended oligoarthritis	13 (50)	70 (44)	
Polyarthritis RF negative	7 (26)	30 (19)	
Polyarthritis RF positive	2 (8)	6 (4)	
Psoriatic arthritis	1 (4)	14 (9)	
Enthesitis-related arthritis	0 (0)	13 (8)	
Undifferentiated arthritis	1 (4)	23 (15)	
Tender joint count, *n* (%)			
Knee§	8 (31)	54 (34)	0.75
Elbow¶	4 (15)	27 (17)	1
Wrist¶	3 (12)	29 (18)	0.58
Second MCP joint¶	3 (12)	13 (8)	0.48
Ankle§	5 (19)	42 (26)	0.44
Swollen joint count, *n* (%)			
Knee¶	2 (8)	18 (11)	0.74
Elbow¶	1 (4)	4 (3)	0.54
Wrist¶	1 (4)	14 (9)	0.7
Second MCP joint¶	3 (12)	7 (5)	0.15
Ankle¶	1 (4)	11 (7)	1
Laboratory tests, *n* (%)			
RF positivity¶	2 (8)	6 (4)	0.32
ANA positivity§	11 (42)	84 (53)	0.51
HLA-B27 positivity¶	1 (4)	22 (14)	1
Ultrasonography, *n* (%)			
Synovitis in B-mode§*	16 (62)	109 (69)	0.48
Grade 2 or 3 synovitis in B-mode§	2 (8)	38 (24)	0.06
Synovitis in PD§*	4 (15)	42 (26)	0.23
Grade 2 or 3 synovitis in PD¶	0 (0)	9 (6)	0.36
Patient's VAS score (median, QI–Q3)	1.5 (0–2.75)	1 (0–3)	0.63

Table 3 continued

Characteristics	Therapeutic de-escalation°, $n = 26$	Stable therapeutic or escalation, $n = 159$	p value
Physician's VAS score (median, QI–Q3)	1 (0–3.5)	0.5 (0–3.25)	0.74
Clinical JADAS (median, QI–Q3)	5 (0–6)	3 (0.5–8)	0.9
ESR (mm/h)** (median, QI–Q3)	6 (2–15)	11 (2–26)	0.14
CRP (mg/l)*** (median, QI–Q3)	1 (0.9–11)	5 (0.95–9)	0.008

Values are n (%) or mean (± SD)

JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; RF, rheumatoid factor; ANA, anti-nuclear antibodies; HLA-B27, human leucocyte antigen B27; PD, power Doppler; VAS, visual analogue scale; JADAS, juvenile arthritis disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

°Discontinuation of nonsteroidal anti-inflammatory drugs, corticosteroids, methotrexate, biologics or dose decrease

§Pearson χ^2 test was used

¶Fisher's exact test was used

*Presence of at least one joint with grade 1, 2 or 3 synovitis

**Data on ESR level were available for 12 patients in therapeutic de-escalation group and 72 patients in the stable therapeutic or escalation group

***Data on CRP level were available for 11 patients in therapeutic de-escalation group and 76 patients in the stable therapeutic or escalation group

remission showed pathologic findings in B-mode or PD MSUS. However, Nieto-González et al. [25] reported that subclinical synovitis detected by MSUS was not a predictor of flares following TNF inhibitor therapy tapering in a JIA population. Thus, persistent inflammation could be detected by MSUS, but its significance has not yet been elucidated. Therefore, the relevance of these findings in therapeutic decisions is uncertain.

In adults, the role of MSUS is clearer [26]. In patients with RA, it has been demonstrated that MSUS found more synovitis than clinical joint examination, especially in B-mode and for the shoulders, wrists and metatarsophalangeal joints [27]. Naredo et al. [28] showed that, in RA, synovitis on US was better correlated with CRP and ESR than physical examination findings. This study indicates that therapeutic decisions in RA could depend on MSUS complementary to clinical assessment. In a literature review on the evaluation of structural damage related to RA, MSUS appeared to be sensitive in detecting synovitis and erosions [29]. Studies have shown that patients with RA in clinical remission could have subclinical synovitis that could cause structural damage [30, 31]. Thus, MSUS could help therapeutic decisions to achieve remission.

Our study had some limitations. First, the SARS-CoV-2 pandemic led to a delay in patients' follow-up, which could also explain why the number of visits was lower than expected. Second, the study was not blinded. The clinician was aware of all the patients' characteristics, and this could have lessened the impact of US in comparison to clinical characteristics. Third, we selected patients who underwent MSUS of the ten most commonly affected joints in JIA: the second MCP joints, wrists, elbows, knees and ankles. Collado et al. [32] have previously shown the pertinence and feasibility of a reduced US ten-joint evaluation. Moreover, it appears difficult to analyse all the joints via US in children. However, in daily practice, this score should be suitable to the JIA subtype, clinical examination and stage of disease. Although we analyses the same joints for clinical tenderness and swelling, it seems difficult for physicians not to consider the other joints

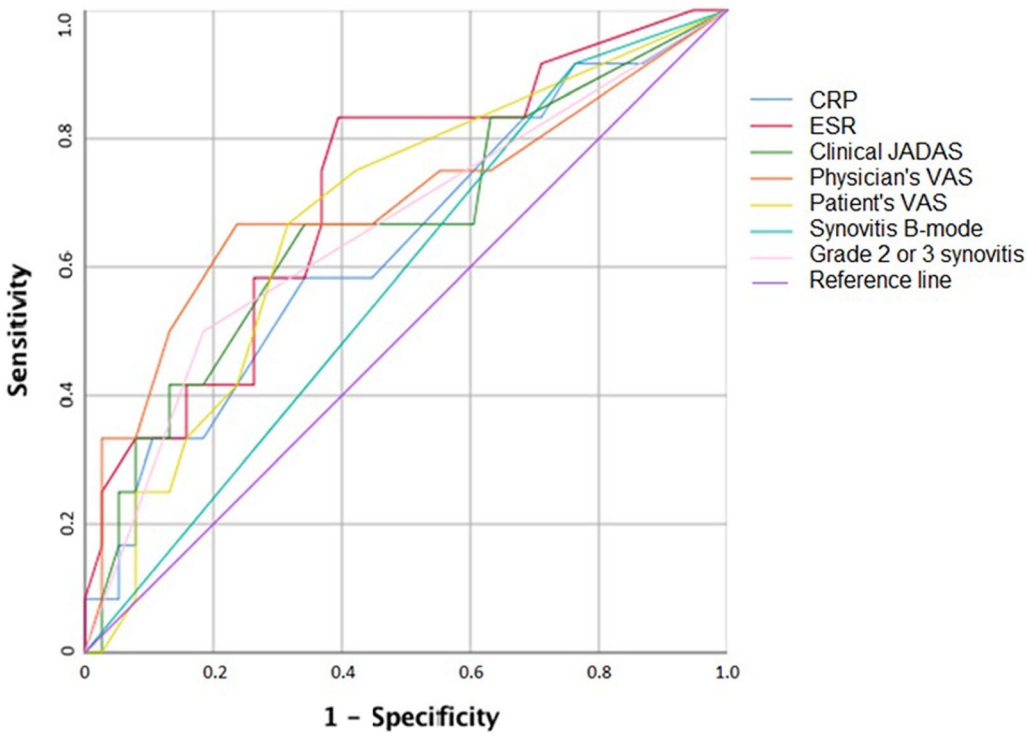

Fig. 2 Receiver operating characteristic (ROC) curves for treatment escalation in patients with JIA according to clinical and biological characteristics and the presence of synovitis on US. Sensitivity/specificity: CRP levels (≥ 4 mg/l as cut-off value) 58.3%/65.8% (AUC 0.64, 95% CI 0.45–0.82), ESR (≥ 6.5 mm/hour as cut-off value) 83%/50% (AUC 0.72, 95% CI 0.55–0.88), Clinical JADAS (≥ 1.5 as cut-off value) 66.7%/39.5% (AUC 0.66, 95% CI 0.48–0.85), physician's VAS score (≥ 2.25 as cut-off value) 66.7%/73.7% (AUC 0.7, 95% CI 0.5–0.85), patient's VAS score (2.5 ≥ 1 as cut-off value) 41.7%/76.3% (AUC 0.68, 95% CI 0.5–0.85), synovitis in B-mode US (≥ 1 as cut-off value) 91.7%/23% (AUC 0.58, 95% CI 0.4–0.75), grade 2 or 3 synovitis in B-mode US (≥ 1 as cut-off value) 50%/98.6% (AUC 0.66, 95% CI 0.47–0.85)

when examining patients, which might lower the impact of US. Moreover, with a reduced protocol, we may have missed subclinical synovitis, especially for patients with persistent and extended oligoarthritis, representing most of our patients. Fourth, patients were included during their routine follow-up and not at a specific point such as disease diagnosis or flare-up. This explains the low number patients with therapeutic modification, which might have reduced the impact of MSUS and the absence of a significant difference between groups, although the number of joints with synovitis on US differed.

Our study showed several strengths. This study is the first to evaluate the impact of MSUS examinations on therapeutic modifications in patients with JIA in a cohort. Furthermore, the reliability of the sonographers at the different centres, which was evaluated prior to this study, was found to be good [21]. Finally, our study was a real-life study that represents routine practice, which is naturally associated with some limitations.

CONCLUSION

The presence of synovitis in B-mode and PD US was not associated with therapeutic modifications in patients with JIA, even though the Se and Sp were similar to the physician's VAS score and the global disease activity score (cJADAS).

Consequently, as consensual training in paediatric MSUS is growing, the use of this tool according to the paediatric OMERACT rules will allow us to further develop randomized, blinded and prospective studies with a larger number of patients to evaluate the impact of MSUS on treatment decisions in patients with JIA and long-term outcomes.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Ethical approval for this study was obtained from the French Ethics Committee (CCTIRS) and the National Commission for Data Protection and Liberties (CNIL).

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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