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Thomas Rj Moreau, Vincent Bondet, Juliette Ramos, Naïm Ouldali, Marie-Alexandra Alyanakian, et al.. IFN- β plasmatic levels are best predictors of muscle disease activity than IFN- α in a longitudinal cohort of patients with juvenile dermatomyositis. 2023. <pasteur-05120654>

HAL Id: pasteur-05120654

<https://pasteur.hal.science/pasteur-05120654v1>

Preprint submitted on 19 Jun 2025

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IFN- β plasmatic levels are best predictors of muscle disease activity than IFN- α in a longitudinal cohort of patients with juvenile dermatomyositis

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Research Article

Keywords: juvenile dermatomyositis, interferon, myositis-specific auto-antibodies, MDA5, muscle

Posted Date: November 14th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-3582695/v1>

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Abstract

This study was conducted to identify the contribution of myositis-specific antibodies (MSAs) on the correlation between type I interferon (IFN-I) plasma levels and disease activity in juvenile dermatomyositis (JDM) patients. We prospectively obtained 198 samples from 49 JDM patients. Autoantibody levels were determined for all patients. Muscle activity was scored using Childhood Myositis Assessment Scale (CMAS) and Manual Muscle Testing in 8 muscles (MMT-8) and skin involvement with a Disease Activity Score (DAS). Three homebrew digital ELISA measuring respectively the IFN- α 2 subtype, all 12 interferon alpha (IFN- α) subtype proteins (Pan- α), and interferon beta (IFN- β) were used to quantify IFN-I in patient's plasma. Correlations between IFN-I titers and clinical scores were evaluated using linear mixed-effect models. In our entire cohort, Pan- α and IFN- β were associated with all three clinical scores. Correlations between IFN- β plasma levels and muscle disease activity were stronger than those with IFN- α levels. After stratification on MSAs expression, we found a relatively equal distribution for the most frequent MSAs phenotypes (MDA5+:n=13, NXP2+:n=12, TIF1g+:n=11, No MSAs:n=13). We observed an association between CMAS and IFN- β in all 4 subgroups. In contrast, Pan- α levels were associated with clinical scores only in MDA5+ patients. In this subgroup, IFN- α 2 was also strongly associated with muscle scores. These findings underscore the potential role of IFN- β in blood as a reliable biomarker of muscle disease activity in JDM, irrespectively of MSAs positivity. The association of IFN- α subtypes plasma levels with clinical scores only in MDA5+ patients suggests a distinct pathophysiological mechanism in this subgroup.

Introduction

Juvenile Dermatomyositis (JDM) is a rare inflammatory autoimmune paediatric disease [1]. Main symptoms include heliotrope rash and symmetrical proximal muscle weakness [1]. JDM is known to be associated with a type I interferon (IFN-I) signature [2]. IFN-I in humans consists of a family of proteins composed of 12 IFN- α subtypes, IFN- β , IFN- ϵ , IFN- κ and IFN- ω . All IFN-I bind to the same IFNAR1/IFNAR2 receptor and promote the transcription of interferon stimulated genes (ISGs) in peripheral blood [3], muscle [4,5] and skin [6] of JDM patients. IFN-I gene scores have been previously associated with disease activity in JDM [7]. More recently, Childhood Myositis Assessment Scale (CMAS) has been correlated with plasmatic levels of the ISG chemokine CXCL10 [8] and muscle expression of ISG15 [4]. The relative contributions of IFN-I subtypes to this signature, and to the pathophysiology remain unclear. We previously demonstrated that JDM patients had significantly higher plasmatic levels of interferon alpha protein (IFN- α) as compared to healthy donors and that these levels were positively associated with ISG scores [9] and with disease activity status in JDM [10]. However, in another study elevated protein concentrations of interferon-beta (IFN- β) in blood of adult dermatomyositis have been detected [11]. Additionally, IFN- β but not IFN- α serum levels were correlated with Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [12].

Myositis-specific auto-antibodies (MSAs) are detected in approximately 75% of patients [13] and were proposed to define subgroups of JDM patients with distinctive clinical and histological manifestations

[1, 14, 15, 16]. Most frequent MSAs in JDM patients are directed against melanoma differentiation-associated gene 5-positive (MDA5), transcriptional intermediary factor 1 alpha/gamma subunits (TIF1g), or nuclear matrix protein 2 (NXP2). MDA5+ patients display notable skin lesions, with less frequent and less severe muscle weakness, and are prone to lung involvement [1, 17]. In contrast, JDM patients expressing anti-NXP2 antibodies have a disease that primarily affects muscles and limited skin damage [15, 17], whereas a subset of TIF1g+ patients exhibits severe and distinct cutaneous manifestations, which may require second- or third-line treatments [1, 16]. In this context, our objective was to address the contribution of IFN-I subtypes to the disease activity of JDM patients, depending on the expression of the main MSAs.

Materials And Methods

Patient recruitment and samples collection

We prospectively recruited diagnosed patients at each medical visit from 2017 to 2022 in three paediatric French referral centres for rare diseases (AP-HP Necker – Enfants Malades, AP-HP Robert Debré, and AP-HP Trousseau). JDM diagnosis was assessed according to the European Neuro Muscular Center (ENMC) classification criteria for adult and juvenile idiopathic inflammatory myopathies. All samples were collected after informed consent and approved by the Comité de Protection des Personnes (N° EudraCT: 2018-A01358-47 in France) in Lithium Heparin tubes within hours of sampling and centrifuged 5min at 450g to separate plasma which was frozen until further batched analysis. All samples were banked over the period 2017-2022 with an average of 4 samples per patient. Clinical scores (DAS, CMAS, MMT-8) were performed by clinicians whenever possible. DAS (from 0 being skin health to 10 being the most damage), CMAS, MMT-8 (respectively from 0 for muscle damage to 52 and 80 for muscle health) were respectively available for 160, 117 and 70 samples out of 198 samples quantified.

Simoa assay development

Simoa IFN-I arrays were developed using a Quanterix Homebrew Simoa assay according to the manufacturer's instructions and previously described in 2016 [9]. Pan- α and IFN- β titres were measured simultaneously on the same samples using a multiplexed method, whereas IFN- α 2 measures were assessed in another experiment. Thus, some samples in our JDM cohort have been quantified for Pan- α and IFN- β , some only for IFN- α 2 and some for all three IFN-I assays. All samples followed the same protocol. After thawing and centrifugation at 10,000g ; +4°C ; 10min to remove all possible debris, plasmas was diluted in *Sample diluent* (Quanterix) generally at 1:6 dilution depending on available plasma volumes and to obtain an optimal detection of proteins.

For the Pan- α assay, two autoantibodies specific for IFN- α subtypes were used as described in Rodero et al. 2017 [9]. For the calibrator we used recombinant Human IFN- α 17 (Alpha I) from PBL Assay Science. The top of the 95% confidence interval around the lower plateau of the sigmoid calibration curve

corresponds to the limit of detection (LOD). The LOD, including the dilution factor, was calculated at 1.08 fg/ml from the mean value of blanks plus two standard deviations.

The antibody capture clone (BMS216C, Invitrogen) and antibody detection clone (CUST0443, Invitrogen) for the IFN- α 2 assay were different from those for the Pan- α assay, but the methods was similar as described above [18]. Recombinant IFN α 2 (Invitrogen) was used as calibrator. The LOD was at 1 fg/ml.

For the IFN- β assay, capture antibody (710906-9 mouse clonal antibody, PBL Assay Science) and detector antibody (710323-9, PBL Assay Science) were used according to the same method described above, except with a biotin/antibody ratio of 40/1. The LOD was at 0.47 pg/ml.

Correlation analyses

All correlation analyses between IFN-I assays and clinical scores were performed using R v4.3.0. We used the *lme4* package to estimate linear mixed models and assess significant correlations between each different variable (IFN-I assays, three clinical scores).

Results

Description of our JDM cohort

Forty-nine patients were prospectively included. Sixteen were included at diagnosis with a mean age of 8 years old. **Table 1** summarizes their clinical and biological characteristics, and treatments.

Muscle scores are more strongly correlated with IFN- β than IFN- α in JDM patients.

First, we evaluate the association between Pan- α (all 12 IFN- α subtypes) and IFN- β plasmatic levels and the disease activity in our entire cohort of JDM patients. We found that IFN- β and Pan- α were associated with all three clinical scores (DAS, CMAS, MMT-8). Interestingly, muscle clinical scores CMAS and MMT-8 were more strongly correlated with IFN- β (CMAS $r = -0.4232$, $p = 0.0002$; MMT-8 $r = -0.4191$, $p = 0.0003$) plasma levels (**Fig.1A**) compared to Pan- α plasma levels (CMAS $r = -0.3152$, $p = 0.0067$; MMT-8 $r = -0.3625$, $p = 0.0022$) (**Fig.1B**).

Association between IFN- β plasmatic levels and CMAS in all subgroups of MSAs

Covert et al. recently showed that in a paediatric skeletal muscle model, IFN- β but not IFN- α was correlated with a decrease of contractile force. Interestingly, after administration of Janus kinase inhibitors (JAKi) *in vitro*, these effects were abolished [19]. This suggests that IFN- β may be more involved in muscle damage than IFN- α . In adult dermatomyositis, IFN- β blood levels but not IFN- α , were significantly associated with adult dermatomyositis compared to other inflammatory myopathies [11]. Furthermore, we observed a stronger correlation between IFN- β plasmatic levels and muscle clinical scores, outperforming the correlation with Pan- α levels. Thus, we stratified our cohort depending on MSAs

positivity to decipher whether autoantibodies affected the correlation between disease activity and IFN- β plasmatic levels. We found that IFN- β titres were correlated with CMAS score in all 4 groups, MDA5+ ($r = -0.6748$; $p = 0.0002$), NXP2+ ($r = -0.5836$; $p = 0.0363$), TIF1g+ ($r = -0.4978$; $p = 0.0133$), No MSAs ($r = -0.6132$; $p = 0.0259$) (**Fig.2**). Additionally, IFN- β and MMT-8 were strongly correlated in MDA5+ and NXP2+ patients while IFN- β and DAS were found to moderately correlate only in patients without MSAs. Overall, we showed that IFN- β plasmatic levels in JDM patients are associated with disease activity in the muscle, regardless of MSAs expression suggesting that IFN- β may not be the underlying cause of the clinical variability observed across MSAs status. However, IFN- β in blood may be a reliable marker of muscle disease activity in JDM.

IFN- α subtype plasmatic levels correlate with clinical scores only in MDA5+ patients

We next examined if IFN- α subtypes (Pan- α) were also associated with disease activity in our cohort of patients based on MSAs positivity. In MDA5+ patients, we observed a strong correlation between Pan- α titres and muscle clinical scores, CMAS ($r = -0.7477$; $p < 0.0001$) and MMT-8 ($r = -0.7404$; $p < 0.0001$). In contrast, DAS was moderately correlated with Pan- α ($r = 0.3015$; $p = 0.0495$) in those patients (**Fig.3**). These results are consistent with previous studies reporting the role of IFN- α subtypes in the pathophysiology of MDA5+ patients [20,21]. Furthermore, our findings suggest that IFN- α subtypes may have a significant influence in muscles of MDA5+ patients. Interestingly, we did not find any significant correlations between Pan- α titres and any of the three clinical scores in the remaining three MSAs subgroups. Indeed, IFN- α subtypes do not seem to be involved in the pathophysiology of JDM with other MSAs (TIF1g+, NXP2+) or without MSAs (None). Considering that the Pan- α assay detects all 12 subtypes of IFN- α , we investigated whether muscle clinical scores in MDA5+ patients were specifically associated with a particular subtype of IFN- α using a more specific assay for IFN- $\alpha 2$ [18]. We found very strong associations between IFN- $\alpha 2$ titres and muscle clinical scores (CMAS $r = -0.7553$, $p < 0.0001$; MMT-8 $r = -0.7659$, $p < 0.0001$) (**Fig.4**). In contrast, DAS skin score and IFN- $\alpha 2$ titers were poorly associated and not statistically significant (DAS $r = 0.2629$, $p = 0.1012$) (**Fig.4**).

Discussion

JDM is an autoimmune disease with complex and heterogeneous pathological outcomes. In JDM, ISGs correlate with disease activity both at transcriptomic and proteomic levels. Yet, the relative contribution of IFN-I subtypes to the pathophysiology remains unclear. In adult and juvenile dermatomyositis, several studies have revealed significant associations between disease activity and IFN- α [10,22] or IFN- β [12,19] plasmatic levels. In our study, we observed correlations between clinical scores (muscle and skin) and both IFN- α and IFN- β plasmatic levels in JDM patients. Intriguingly, Tabata et al. previously reported that in adult dermatomyositis, the IFN-I score was significantly correlated to active skin disease but not to muscle weakness [21]. One limitation of utilizing an IFN-I score is the inability to distinguish whether IFN- α or IFN- β is the driving force behind this score. Here, within our entire JDM cohort, we demonstrate that the correlation between IFN- β plasma levels and muscle disease activity is higher than the correlation between IFN- α levels and muscle disease activity. Muscle stem cells (MuSCs) from dermatomyositis

patients exhibited a significantly reduced proliferation *in vitro*, mainly attributed to high levels of IFN- β and resulting in impaired myotube formation. Interestingly, blocking IFN-I signalling with JAK inhibitors or anti-IFNAR antibody restored dermatomyositis MuSCs proliferation to healthy levels [23]. In addition, IFN- β contributed to mitochondrial dysfunction in human myotubes. This dysfunction led to muscle weakness in an autoimmune myositis mouse model [24]. While the exact reasons behind these observations remain to be elucidated, it indicates the complex interplay between IFN- β and affected muscles. Following a stratification of our cohort depending on MSAs expression, we found strong correlations between IFN- β and CMAS in all subgroups. These findings underscore the potential role of IFN- β in peripheral blood as a reliable biomarker of muscle damage in JDM, irrespectively of MSAs positivity. Considering previous studies in adult dermatomyositis [25], our results are in favor of a therapeutic approach specifically targeting IFN- β in juvenile dermatomyositis.

Using a Pan- α assay, we found that MDA5+ JDM is the only subgroup where IFN- α protein plasma levels correlate with clinical activity, both in the muscle and the skin (CMAS, MMT-8, DAS). Our observations are in line with previous studies reporting that the IFN-I pathway was significantly upregulated in MDA5 patients compared to other MSAs subgroups [17,21]. Thus, IFN- α subtypes may specifically contribute to the pathophysiology of MDA5+ patients. To gain a deeper insight into the contribution of IFN- α subtypes to these correlations in MDA5+ patients, we used an assay specific for IFN- α 2. With this assay, we lost the correlation with skin clinical score while correlations with muscle disease activity remained as high as for the Pan- α assay. This suggests that IFN- α 2 may be more related to muscle pathophysiology in MDA5+ JDM than the other IFN- α subtypes. However, it does not exclude the possibility that other IFN- α subtypes not tested here may also play a role.

There are several limitations to our study. First, samples collection was carried out in the context of patients' hospital visits, rather than at fixed time intervals. Secondly, our biocollection is heterogeneous in terms of treatment: out of 49 patients, 16 patients had at least one sample collection without any treatment while 14 patients received JAK inhibitors at different time points. Further recruitment is needed to ensure sufficient statistical power to allow stratification by treatment variable.

Recent studies focusing on MDA5+ patients have shed light on the overactivation of IFN-I signalling and its implication in lung, vascular, and skin complications [20,26,27]. Of particular interest, MDA5 autoantibodies are the only myositis-specific antibodies directly involved in the IFN-I signalling pathway. Understanding the interactions between MDA5 autoantibodies and IFN-I signalling would offer valuable insights into the mechanisms behind the severe clinical manifestations observed in these patients. Future studies will help to uncover novel therapeutic targets, opening the way for more personalised and effective therapies to improve outcomes. In a clinical context where molecules targeting interferon signaling such as JAK inhibitors, or anti IFN- β (PF-06823859) are evaluated in adult [25] and juvenile dermatomyositis, a better understanding of the specific pathophysiology of each patient will help to better define individual targeted strategies. Indeed, JAK inhibitors, which block IFNAR signalling, are

efficient in a subset of patients with refractory JDM [28]. Our results suggest that an anti IFN- β strategy might be also a useful targeted treatment regardless of MSAs expression in patients with JDM.

In conclusion, our study emphasizes the role of IFN- β in blood as a reliable biomarker of muscle disease activity in JDM, irrespectively of MSAs positivity. The association of circulating IFN- α subtypes plasma levels with disease activity scores only in MDA5+ JDM patients suggests a distinct pathophysiological mechanism in this subgroup compared to other JDM patients.

Declarations

Fundings

The authors acknowledge funding from the ANR (Agence Nationale de Recherche), grant number ANR-21-CE17-0025 JDMINF2 and from DMU MEFADO Département Médico-Universitaire Médecine de l'enfant et de l'adolescent Necker Hospital Enfants-Malades, AP-HP, Paris, France.

The authors would like to thank the Comité des fêtes of Kervardel and its generous donators for their financial supports. We also would like to thank Sabrina Guermah for her technical assistance.

Disclosure of Conflicts of Interest/Competing Interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

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

Authorship contributions

Data acquisition: TRJM, VB, JR, NO, JLC

Clinical recruitments: MAA, CB, GD, NBD, JLC, LAE, BF, MLF, AI, PQ, CV, AWM, CG, IM

Resources: MAA, JLC, JPH

Project conceptualization, administration and supervision: MPR, BBM, DD, IM, CG

Data analysis and interpretation: TRJM, MPR, BBM, DD, IM, CG

Writing-original draft: TRJM, MPR, BBM, DD, IM, CG

Writing-review and editing: TRJM, VB, JR, NO, MAA, CB, GD, CD, NBD, JLC, LAE, BF, MLF, JPH, AI, PQ, CV, AWM, CG, IM, DD, BBM, MPR

Ethics approval

All samples were collected after informed consent and approved by the Comité de Protection des Personnes (N° EudraCT: 2018-A01358-47 in France).

Consent to Participate

Informed consent was obtained from all patients and their parents enrolled in the study.

Consent for Publication

Not applicable

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Table 1

Table 1: Baseline demographic, clinical, biological, and treatment characteristics in 49 JDM patients

Juvenile dermatomyositis cohort (n = 49)

General features

Female / male ratio	2.5/1
Median age at diagnosis, years (IQR)	8 (2.6–15.2)
Cutaneous involvement (%)	49 (100)
CMAS [0-52], (IQR)	41 (6-50)

Myositis-specific antibodies status

MDA5+	13
NXP2+	12
TIF1g+	11
No MSAs	13

Treatments

Corticosteroids (n) (first line/second line)	49/0
Methotrexate (n) (first line/second line)	27/0
MMF (first line/second line)	0/8
Rituximab ((first line/second line)	0/6
Cyclophosphamide ((first line/second line)	0/1
IVIg (first line/second line)	11/13
Baricitinib (n) (first line/second line)	1/16

Values are median (IQR) or number of patients (%), CMAS: Childhood Myositis Assessment Scale, IVIG: intravenous immunoglobulins, MMF: mycophenolate MOfetyl, MSAs: Myositis-Specific Antibodies.

Figures

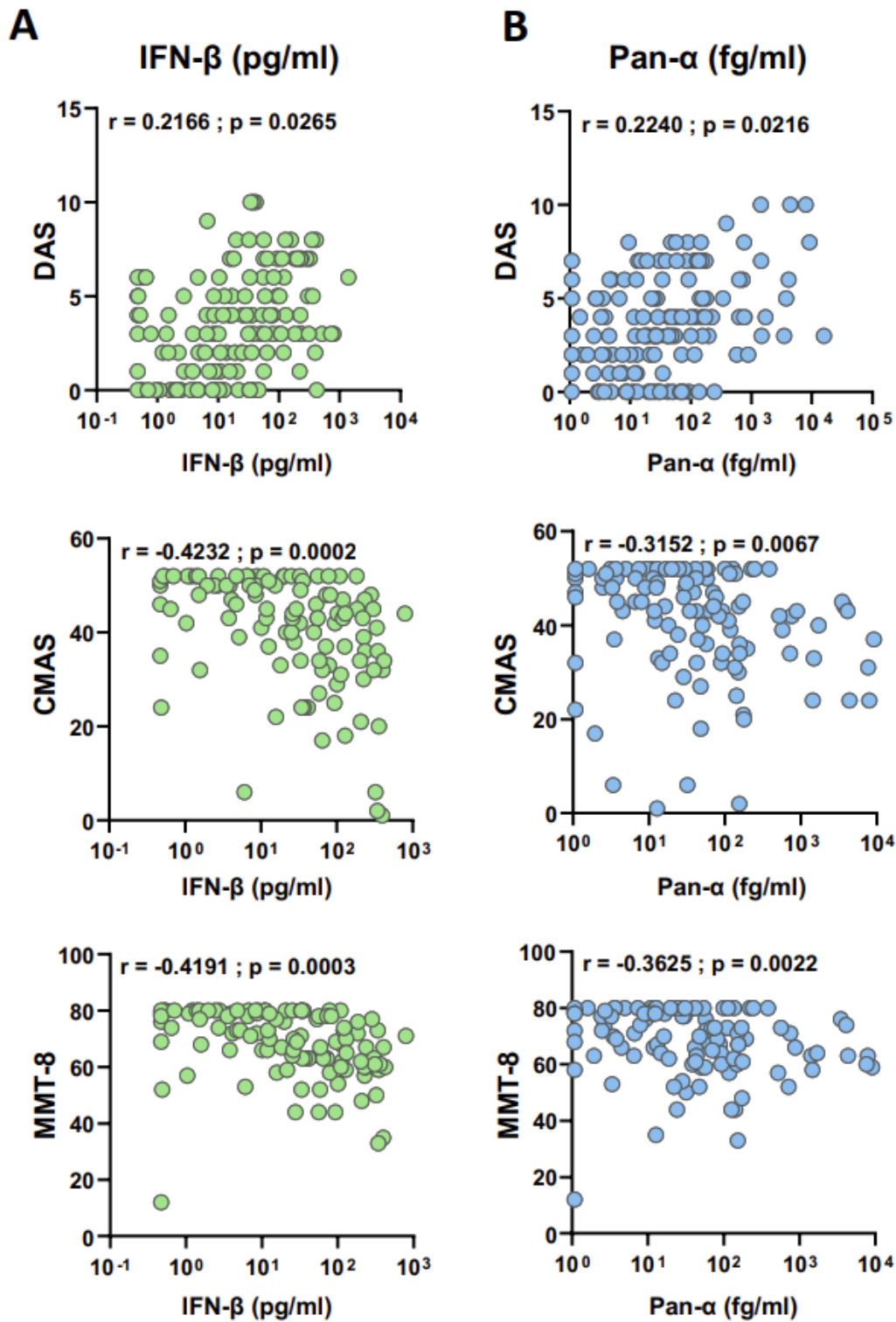


Figure 1

Association between clinical scores and IFN-I plasmatic level in our entire JDM cohort. Correlations between all clinical scores (CMAS, MMT-8, DAS) and plasmatic levels of IFN-β (A) and Pan-α (B) have been evaluated. Muscle clinical scores CMAS and MMT-8 were more strongly correlated with IFN-β plasma levels compared to Pan-α plasma levels. These results indicate that IFN-I play a role in the pathophysiology of JDM. IFN-β may be a best predictor of muscle disease activity than IFN-α.

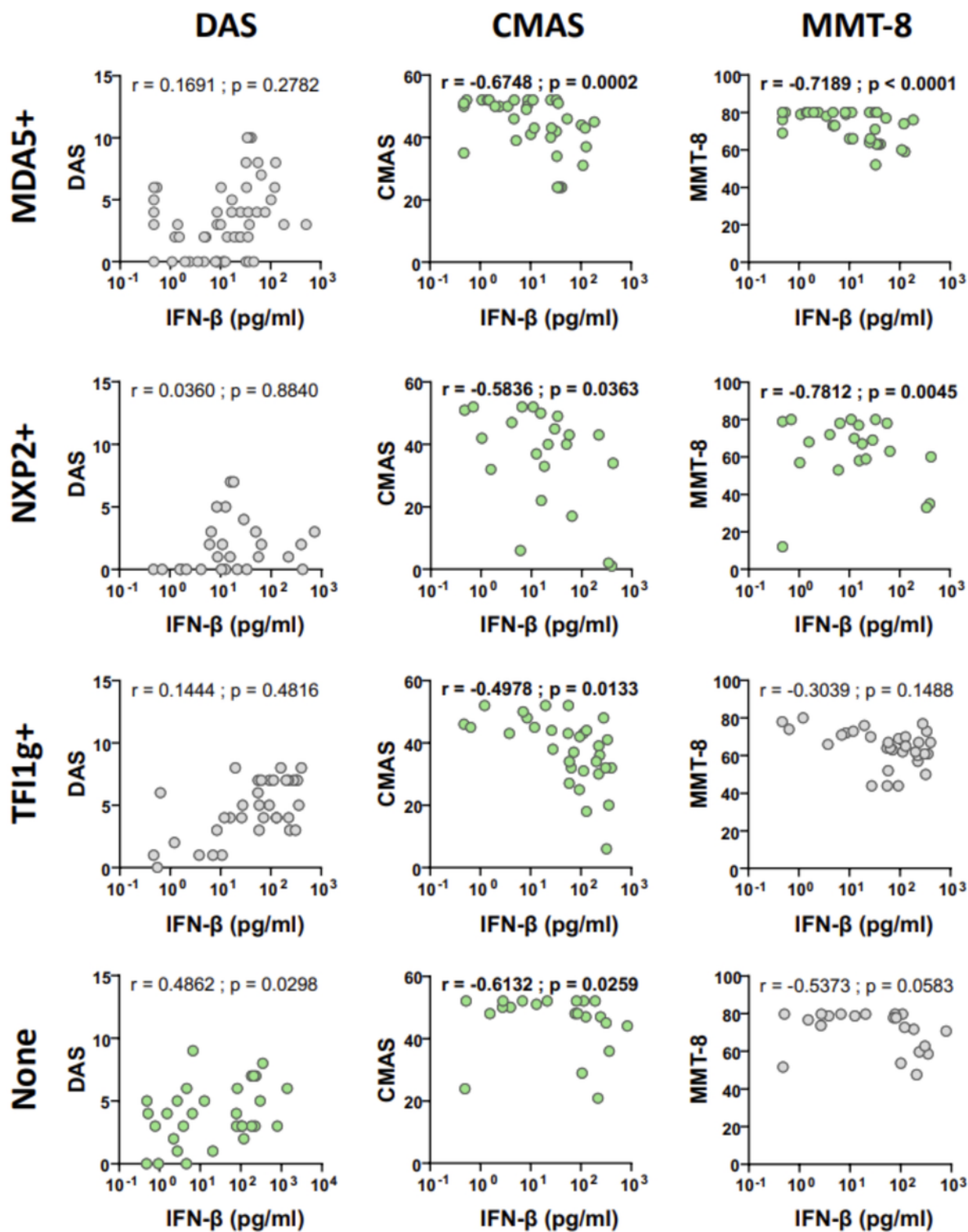


Figure 2

Association between clinical scores and plasmatic IFN- β levels in different subgroups of MSAs positive JDM patients. Significant correlations between CMAS and plasmatic levels of IFN- β were found in all 4 subgroups. Correlations between IFN- β and MMT-8 were found only in MDA5+ and NXP2+ patients while IFN- β was correlated with DAS in patients without MSAs (None). This is suggesting that in all subgroups of JDM, IFN- β may play a significant role in muscle activity and may not be the underlying cause of the

clinical variability observed across MSAs status. However, IFN- β in blood may be a reliable biomarker of muscle disease activity in JDM.

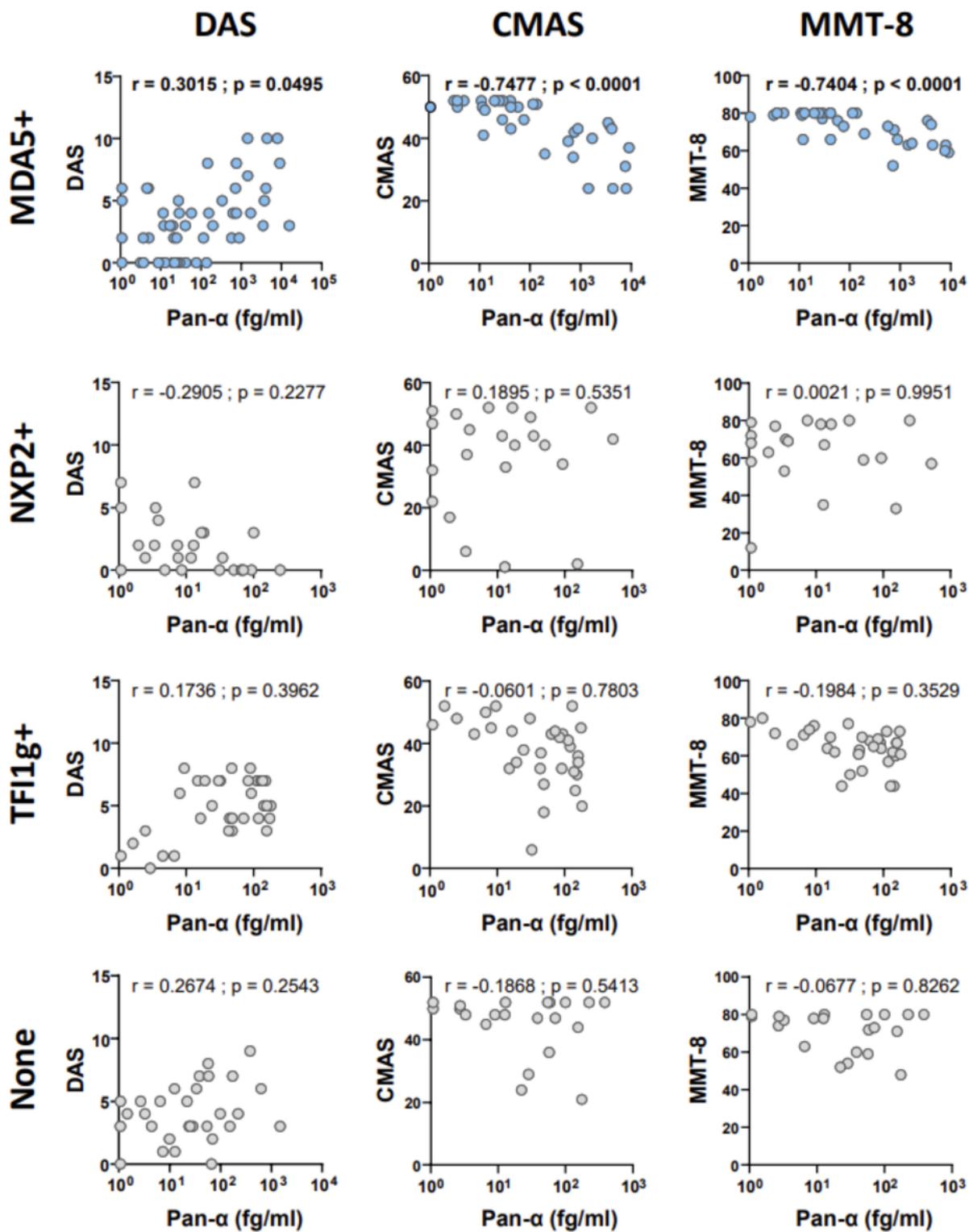


Figure 3

Association between clinical scores and plasmatic Pan- α level in different subgroups of MSAs positive JDM patients. Significant correlations between all clinical scores (CMAS, MMT-8, DAS) and plasmatic

levels of Pan- α were found only in MDA5+ patients. Very strong correlations are found between muscle tests scores and Pan- α titers while there was a moderate correlation between skin score and Pan- α levels. IFN- α subtypes may play a significant role in the disease activity of MDA5+ patients, particularly in relation to muscle involvement rather than skin manifestations.

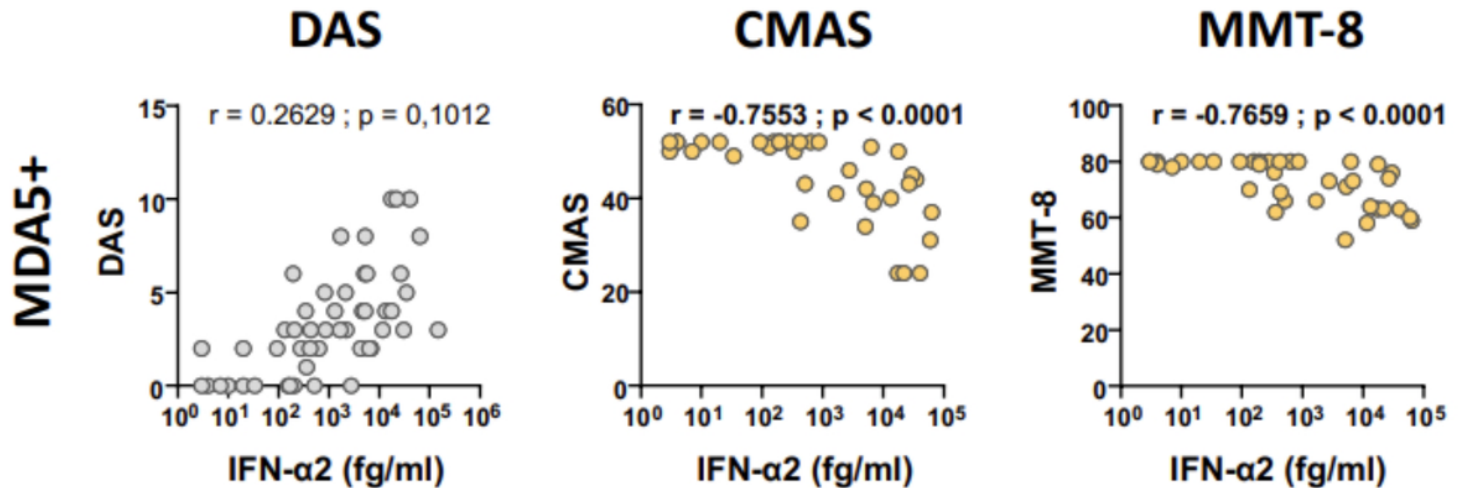


Figure 4

Association between clinical scores and plasmatic IFN- α 2 levels in different subgroups of MSAs positive JDM patients. Very strong correlations remained between muscle scores (CMAS and MMT-8) and plasmatic IFN- α 2 levels in MDA5+ patients. We have previously shown that muscle scores correlate with Pan- α (**Fig. 3**). This suggests that amongst IFN α subtypes, IFN- α 2 may be a subtype responsible for muscle activity in MDA5+ patients.