Interferon Chemokine Score and Other Cytokine Measures Track With Changes in Disease Activity in Patients With Juvenile and Adult Dermatomyositis

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Objective. Our aim was to identify cytokines and chemokines in patients with adult dermatomyositis (DM) and juvenile dermatomyositis (JDM) that predict changes in disease activity.

Methods. Multiplexed immunoassays (Meso Scale Discovery) enabled simultaneous measurement of interferon (IFN)-regulated chemokines and other pro- and anti-inflammatory cytokines specific to differentiation of specific T-cell and innate pathways. Cytokine scores were computed for IFNCK (IP-10, MCP-1), Th1 (IFNγ, TNFa, and IL2), Th2 (IL4, IL10, IL12, and IL 13), Th17 (IL6, IL17, IL1β), macrophage (MIP-1α, MIP-1β, IL8), and regulatory (IL10, TNFa) factors. Spearman correlation and mixed models were used to examine whether cytokines at a previous visit predict change in disease activity at the next visit.

Results. The study included 36 patients (16 DM and 20 JDM) with at least two visits (87 patient intervals between two visits). Mean age (SD) at inclusion was 56.9 (18.4) years for DM and 10.8 (6.6) years in JDM, 67% of patients were female, 89% Caucasian. The mean (SD) physician global, muscle and extra-muscular disease activity Visual Analog Scale scores at inclusion were 41 (26), 36 (30), and 34 (21) mm, respectively. The change in IFN score from one visit to the next was associated with the change in physician global (P = 0.010) and extramuscular (P < 0.001) disease activity scores. Preliminary results revealed significant correlations of previous IFNCK score and IL-6 with subsequent disease activity measures, but after adjustment for multiple visits per patient, these associations did not reach statistical significance.

Conclusion. There is a potential relationship between IFNCK and other cytokine scores seen in adult and juvenile DM with future disease states.

INTRODUCTION

Serum cytokines play an important role in the pathogenesis of myositis by initiating and perpetuating various cellular and humoral autoimmune processes. The aim of this study was to measure interferon-inducible chemokines (IFNCK), Th1, Th2, Th17, macrophage, and regulatory cytokines in patients with adult dermatomyositis (DM) and juvenile dermatomyositis (JDM) at multiple visits to identify biomarkers correlated with and predictive of changes in disease activity, as well as to determine whether these biomarkers differ between DM and JDM patients.

METHODS

Subjects. Blood samples and clinical data were obtained prospectively from children and adults with new-onset disease (less than 6 months of clinical symptoms) that fulfill the Bohan and Peter criteria (1,2) for the diagnosis of DM at baseline. All subjects had a definitive diagnosis of DM and were seen at the Division of Mayo Clinic College of Medicine, Rochester, Minnesota; 3Timothy B. Niewold, MD, Theresa L. Wampler Muskardin, MD: New York University Medical Center; 4Jeffrey Dvergsten, MD, Ann M. Reed, MD: Duke University, Durham, North Carolina; 5Erik Peterson, MD, Emily C. Baechler, PhD: University of Minnesota, Minneapolis.

The authors disclose that they have no relevant conflicts of interest to disclose.

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Rheumatology at Mayo Clinic, Rochester, Minnesota. This study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from each participant. Disease activity measures included the extramuscular disease activity, which includes lung, skin, and joint disease; physician global activity; muscle visual analogue scale; and the manual muscle testing of eight muscle groups (3). Flare and improvement were defined as a 20 mm or more increase or decrease, respectively, in global disease activity between visits based on previous expert consensus (4). Data on autoantibodies (ie, anti–Jo-1, anti–double-stranded DNA, anti-Smith, anti-ribonucleoprotein, anti–Sjögren’s syndrome-related antigen A, anti–Sjögren’s syndrome-related antigen B, immunoglobulins G and M, anti-cardiolipin, and others) and muscle enzymes (ie, aldolase, lactate dehydrogenase, aspartate aminotransferase [AST], alanine aminotransferase [ALT]) were obtained from medical record review. Patients provided blood samples at their initial visit and at subsequent clinical visits.

**Measurement of serum cytokines and chemokines.** Serum was isolated from blood drawn and, multiplexed sandwich immunoassays (Meso Scale Discovery, Rockville, MD) were used to quantitate the serum levels of interferon (IFN)-regulated chemokines, IFN-α and IFN-γ, and the serum levels of inflammatory cytokines. A composite IFN-regulated score was generated based on serum levels of two IFN-regulated chemokines (IFN-γ–induced protein 10 [IP-10] and monocyte chemoattractant protein-1 [MCP-1]) as previously described (5). Similar scores were generated for Th1 (IFN-γ, tumor necrosis factor alpha [TNF-α], interleukin [IL]-2, Th2 (IL-4, IL-10, IL-12p70, IL-13), Th17 (IL-6, IL-17, IL-18), macrophage related (macrophage inflammatory protein [MIP]-1α, MIP-1β, and IL-8), and regulatory cytokines (IL-10 and TNF-α). Samples were run in duplicate, and calibrated recombinant proteins were used to generate standard curves.

Normalized cytokine scores were computed by first calculating the 95th percentile of serum concentration levels for each chemokine and then setting concentration levels 95th percentile or greater to the 95th percentile value to reduce extreme outliers as previously described (6). For each chemokine, the data were rescaled to a maximum value of 1.0. For each subject, the rescaled values were summed up, and the sum was adjusted to a 100-point scale. Our chosen cytokine scoring systems included individually validated markers by a number of reports in the literature (7–10). IP-10 was included within the composite IFN-regulated chemokine score as a marker of the effects of IFN and not to suggest it was specifically upregulated only because of IFN, since many cytokines and chemokines including IP-10 are a matrix of overlapping responses.

**Statistical methods.** Descriptive statistics (means, percentages, etc) were used to summarize the data. Consecutive visits within 6 months of each other were included in the analysis with the first visit of each pair referred to as “previous” and the second visit referred to as “current.” Cytokine scores were used in the primary analyses to reduce dimensionality of the data. Secondary analysis involved analyses of the individual cytokines to ensure important findings were not obfuscated by the use of the cytokine scores. Preliminary analyses were performed using Spearman correlation methods, which did not account for multiple visits in the same patient. Mixed models with random effects to account for multiple visits in the same patient were used to examine whether changes in cytokine scores were associated with changes in disease activity measures and whether cytokine scores at the previous visit predicted disease activity measures at the next visit. All models were adjusted for disease activity at the previous visit. Other potential adjustors were not included because of the limited sample size. Interactions between cytokine effects and DM/JDM were examined to determine whether the cytokine/chemokines had different effects in DM compared to JDM. P values less than 0.05 were considered to be statistically significant. Adjustment for multiple comparisons was not performed because the use of cytokine scores reduced the number of comparisons for each specific hypothesis to just six. However, the Bonferroni correction would consider P values less than 0.008 to be significant. Analyses were performed using SAS version 9.4 (SAS Institute) and R 3.2.0 (R Foundation for Statistical Computing).

**RESULTS**

The study included 36 patients (16 DM and 20 JDM) with at least two visits (123 visits total; 87 patient visit intervals between 2 visits). Mean age (SD) at inclusion was 56.9 (18.4) years in DM and 10.8 (6.6) years in JDM, 67% female, and 89% Caucasian (Table 1). Most patients were included at their time of diagnosis. The mean (SD) physician global, muscle, and extramuscular disease activity Visual Analog Scale scores at inclusion were 41 (26), 36(30), and 34(21) mm, respectively. In addition to the myositis associated and specific autoantibodies reported in Table 1, there was one patient with anti-Scl70 and anti–Jo-1 and one patient with anti-polymyositis/scleroderma No differences were seen between the DM and JDM groups (Table 1).

In DM and JDM combined, the change in IFN score from one visit to the next was associated with the change in physician global (P = 0.010) and extramuscular (P < 0.001) disease activity scores after adjusting for the disease activity scores at the previous visit (Figure 1, left panels). The association between change in IFN score and muscle disease activity was weaker and did not reach statistical significance (P = 0.15). The change in macrophage score was also significantly associated with the change in muscle disease activity (P = 0.01), but not with physician global (P = 0.11) or extramuscular disease activity (P = 0.76). However, there was some evidence that the associa-
tions between changes in macrophage score and changes in disease activity measures differed for JDM compared with DM (P for interaction between change in macrophage score and JDM/DM: P < 0.001 for physician global, P = 0.040 for muscle, and P < 0.001 for extramuscular disease activity; Figure 1, right panels).

Preliminary analyses of correlations between previous cytokine scores and subsequent disease activity measures

| Table 1. Baseline characteristics of 36 patients with juvenile and adult dermatomyositis |
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| Characteristics | DM (N = 16) | JDM (N = 20) | Total (N = 36) | P value |
| Age at diagnosis, years, mean (SD) | 56.0 (18.0) | 8.1 (4.2) | 29.4 (27.1) | <0.001 |
| Sex, female | 13 (81%) | 11 (55%) | 24 (67%) | 0.09 |
| Race | | | | 0.31 |
| American Indian/Alaskan Native | 0 (0%) | 1 (5%) | 1 (3%) | |
| Black or African American | 0 (0%) | 2 (10%) | 2 (6%) | |
| White | 16 (100%) | 16 (80%) | 32 (67%) | |
| Other | 0 (0%) | 1 (5%) | 1 (3%) | |
| Anti-Jo-1 antibodies | 0/16 (0%) | 1/19 (6%) | 1/35 (3%) | 0.35 |
| Anti–double-stranded DNA antibodies | 0/10 (0%) | 0/18 (0%) | 0/28 (0%) | ... |
| Anti-Smith antibodies | 0/14 (0%) | 1/18 (6%) | 1/32 (3%) | 0.37 |
| Anti-RNP antibodies | 0/14 (0%) | 2/18 (11%) | 2/32 (6%) | 0.20 |
| Anti-SSA antibodies | 4/15 (27%) | 2/18 (11%) | 6/33 (18%) | 0.33 |
| Anti-SSB antibodies | 0/15 (0%) | 1/18 (6%) | 1/33 (3%) | 0.35 |
| IgG anti-cardiolipin antibodies | 0/3 (0%) | 0/16 (0%) | 0/19 (0%) | ... |
| IgM anti-cardiolipin antibodies | 0/3 (0%) | 0/15 (0%) | 0/18 (0%) | ... |
| Physician global disease activity (0-100), mean (SD) | 39.1 (26.3) | 43.2 (25.9) | 41.4 (25.8) | 0.86 |
| Muscle disease activity (0-100), mean (SD) | 34.1 (28.4) | 38.4 (32.2) | 36.5 (30.2) | 0.59 |
| Global extraskeletal muscle disease activity (0-100), mean (SD) | 31.4 (21.4) | 35.5 (21.1) | 33.7 (21.0) | 0.60 |
| MMT8a | 69.0 (13.5) | 69.4 (10.2) | 69.2 (11.6) | 0.97 |
| Creatinine kinase | 1190 (3843) | 1271 (2942) | 1234 (3326) | 0.30 |
| Aldolase | 32.2 (64.2) | 20.8 (25.9) | 25.3 (44.6) | 0.09 |
| LDH | 225.2 (30.7) | 474.5 (362.2) | 386.5 (312.1) | 0.16 |
| AST | 38.2 (21.2) | 82.4 (102.7) | 62.6 (79.7) | 0.36 |
| ALT | 43.5 (27.8) | 80.6 (96.7) | 64.3 (75.8) | 0.76 |
| Any glucocorticoid use | 11 (69%) | 8 (40%) | 19 (53%) | 0.09 |
| Any DMARD use | 10 (63%) | 5 (25%) | 15 (42%) | 0.023 |

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, adult dermatomyositis; DMARD, disease-modifying anti-rheumatic drug; JDM, juvenile dermatomyositis; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; MMT8, manual muscle test of eight muscle groups; RNP, ribonucleoprotein; SSA, Sjögren’s syndrome–related antigen A; SSB, Sjögren’s syndrome–related antigen B; a Values are n (%) unless otherwise specified.
among the combined JDM/DM cohort using Spearman correlation methods revealed significant positive and negative correlations between previous IFN cytokine scores and subsequent global ($r = 0.24; P = 0.027$) and muscle ($r = 0.22; P = 0.046$) disease activity measures, with a weak correlation between IFN cytokine score and extramuscular disease activity ($r = 0.19; P = 0.076$). Similar correlations were noted for previous IL-6 measures and subsequent global ($r = 0.27; P = 0.011$), muscle ($r = 0.20; P = 0.059$), and extramuscular ($r = 0.18; P = 0.090$).

Furthermore, when mixed models were used to account for multiple visits per subject when examining previous cytokine scores as potential predictors either of subsequent disease activity measures or of changes in disease activity measures in the combined JDM/DM cohort, no significant associations were found ($P > 0.05$ for all comparisons). Specifically, there was no apparent association between previous IFN score and subsequent physician global ($P = 0.82$), muscle ($P = 0.87$), or extramuscular ($P = 0.59$) disease activity. There was also little evidence that the predictive ability of the cytokine values differed between JDM and DM. The left panels of Figure 2 depict the previous IFN cytokine scores plotted against the subsequent disease activity measures. The slope for adult DM patients is flat, and the steeper

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**Figure 1.** Changes in interferon (IFN) and macrophage cytokine/chemokine scores plotted against changes in physician global, muscle and extramuscular disease activity (DA) scores among patients with adult (open circles and dashed lines) and juvenile (triangles and solid lines) dermatomyositis.
The slope for JDM patients is driven by just a few values. The only significant interactions between previous cytokine scores and JDM/DM status were for Th2 score (interaction $P = 0.025$ for physician global and $P = 0.014$ for muscle disease activity), which indicated no predictive ability of Th2 scores among adult DM and a weak association among JDM (Figure 2, right panels).

Because examination of continuous disease activity measures can obfuscate nonlinear associations, we also examined potential predictors of flare and improvement. A total of 6 visits met the definition for flare, and 24 visits met the definition for improvement. The previous Th17 score was significantly associated with flare, even after adjustment for previous global disease activity score (odds ratio: 2.17 per 10 unit increase; 95% confidence interval: 1.10-4.27; $P = 0.026$; Figure 3). No other significant associations between flares and cytokines, autoantibodies, or muscle enzymes were found. The previous macrophage cytokine score was positively significantly associated with improvement ($P = 0.037$), but this association did not persist after adjusting for previous global disease activity ($P = 0.87$). Similarly, the previous IL-8 value was also associated with improvement ($P = 0.011$), but not after adjustment for previous global disease activity ($P = 0.46$). Previous elevated AST and ALT were also significantly associated with improvement, and the other muscle enzyme measures were weakly ($P = 0.06-0.15$) associated with improvement, but these
DISCUSSION

In this study, we are exploring the use of serum biomarkers as predictors of disease improvement or flare in both DM and JDM. We see trends, as seen in previously published papers (6,11,12), that demonstrate that INF-related chemokines are associated with disease activity and suggest that INF-related chemokines in DM and JDM most closely relate to improvements in disease activity as measured by a physician global score and extramuscular scores. Changes in muscle disease was trending with disease activity but was not statistically significant. However, a correlation of change in the macrophage score was associated with change in muscle disease.

Our ability to predict future trends showed that prior increased IFN cytokine scores were related to subsequent global and muscle disease activity measures, whereas the extramuscular disease activity was weakly associated. IL-6, a cytokine strongly associated with disease activity in JDM (6) showed a correlation with the next visit disease activity that was primarily associated with subsequent global measures and, to a lesser extent, muscle and extramuscular.

When mixed models were used to examine prior cytokine scores as potential predictors of subsequent disease activity measures or of changes in disease activity measures in the combined JDM/DM cohort, no significant associations were found ($P > 0.05$ for all comparisons). Specifically, there was no apparent association between a previous IFN score itself and subsequent physician global ($P = 0.82$), muscle ($P = 0.87$), or extramuscular ($P = 0.59$) disease activity. There was also little evidence that the predictive ability of the cytokine values differed between JDM and DM.

We also wanted to look at the potential use of the biomarkers to predict future flare. The prior Th17 score was significantly associated with flare even after adjustment for prior global disease activity score. No other significant associations between flares, cytokines, autoantibodies, or muscle enzymes were found. The prior macrophage cytokine score and IL-8 value were significantly associated with improvement, but this association did not persist after adjusting for prior global disease activity scores. However, perhaps the change in scores at a visit might be more predictive of future flare than the actual values at a visit (eg, the difference between visit 1 and 2 predicting flare at visit 3). Unfortunately, we did not have enough disease flares to assess this.

We recognize that this manuscript is limited by the number of cases for both adult and juvenile dermatomyositis subjects, and the trends we are reporting may be clarified with a larger cohort of subjects. It is also possible that the disease severity scores may not accurately capture changes in disease activity. Further limitations are that INF-inducible T-cell α chemoattractant, which is typically a component of the IFN score, was not measured because of a manufacturer change in the configuration of the multiplex assays.

Prediction models to date have included use of clinical measures (skin rash, degree of weakness, gastrointestinal symptoms, dysphagia, dysphonia, and ulcerations), age, race, and duration of symptoms prior to diagnosis to predict outcomes of disease without identifying any predictors of time to remission (13,14). However, presence of nailfold abnormalities and Gottron’s papules did suggest a more persistent disease course. More recently, myositis-specific autoantibodies and autoantibodies, plus muscle biopsies in JDM, are seen more often in disease subsets and with clinical features and are capable of predicting outcomes (15,16). Reports of cytokines and chemokines (11,12) related to disease activity include biomarkers related to Type- I INF, IL-6, IL-17, MCP-1, Galectin 9, and Eotaxin have been published, yet markers to predict disease outcome continue to be lacking (6,11,17,18). However, we believe that unique cytokine and chemokine patterns relate to disease phenotype or subtype and that these differing patterns may help us understand the differences in outcome and treatment needs (11,19). Our data support this hypothesis in that high levels of Type-1 INF and IL-6 relate to a high degree of disease activity based on muscle and physician assessment, and these individuals appear to be more likely to improve with our present treatment recommendations (20,21).

In conclusion, there appears to be a potential relationship between cytokine and chemokines seen in DM and JDM with future disease states. Further modeling of varying biological fac-

Figure 3. Previous Th17 cytokine/chemokine scores plotted for visits with and without flares among patients with adult (open circles) and juvenile (triangles) dermatomyositis, where reference lines depict group medians
tors reported to be associated with disease subsets and outcome is needed to refine our ability to predict disease outcome, flare, and remission in DM and JDM.

**AUTHOR CONTRIBUTIONS**

Criterion 1:

a) Substantial contributions to study conception and design: Crowson, Hein, Pendegraft, Strausbauch, Reed

b) Substantial contributions to acquisition of data: Hein, Strausbauch, Ernste, Amin, Wampler Muskardin, Reed

c) Substantial contributions to analysis and interpretation of data: Crowson, Pendegraft, Reed

Criterion 2: Drafting the article or revising it critically for important intellectual content: Crowson, Hein, Pendegraft, Strausbauch, Niewold, Ernste, Dvergsten, Amin, Wampler Muskardin, Peterson, Baechler, Reed

Criterion 3: Final approval of the version of the article to be published: Crowson, Hein, Pendegraft, Strausbauch, Niewold, Ernste, Dvergsten, Amin, Wampler Muskardin, Peterson, Baechler, Reed

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