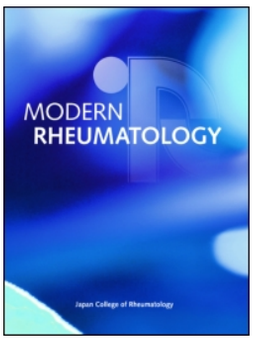

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90K immunostimulatory glycoprotein in children with juvenile idiopathic arthritis

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ABSTRACT

Objectives: To assess whether circulating levels of 90K glycoprotein are increased in children with juvenile idiopathic arthritis (JIA) at different stages of the disease, compared to healthy controls and to evaluate potential over time changes in its concentrations following treatment with the antitumor-necrosis factor (TNF) drug etanercept.

Methods: 90K glycoprotein, C-reactive protein, erythrocyte sedimentation rate, TNF, antinuclear antibodies, rheumatoid factor and the Juvenile Arthritis Disease Activity Score were assessed in 71 children: 23 with newly diagnosed JIA, 23 with established and active JIA and 25 healthy controls. Patients, eligible for anti-TNF treatment, underwent a similar clinical/laboratory assessment after 6- and 12-month etanercept therapy.

Results: At baseline, significant differences were found in 90K levels between the three study groups: JIA at onset (157.7 [131.4–241.5] μg/ml), JIA on treatment (90.0 [68.8–120.2] μg/ml) and control group (58.0 [44.5–79.0] μg/ml), (p for trend $<.001$), with the JIA at onset group showing the highest values. In the JIA on treatment group, following one-year etanercept treatment, a significant reduction in 90K was detected already at 6 months (74.3 [56.0–104.1] μg/ml $p = .001$) and a further decline was observed at 12 months (49.3 [46.0–67.6] μg/ml $p < .001$).

Conclusion: Our study showed that 90K glycoprotein levels are increased in JIA children compared to healthy controls, suggesting a potential pathogenetic role in the JIA. Besides, 12 months of therapy with etanercept can reduce 90K levels.

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90K/Mac-2 BP; juvenile idiopathic arthritis; children; etanercept; biomarkers

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease during childhood, and it is associated with potential short- and long-term disability [1,2].

JIA pathogenesis is incompletely understood, although several studies have highlighted a dysregulation in the innate and adaptive immune system as a potential mechanism implicated in the disease [3,4]. Systemic JIA is an autoinflammatory disease with abnormalities in the innate immune system. Aberrant activation of phagocytes leads to the release of pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6, IL-18, and pro-inflammatory S100-proteins, which contribute to the multisystem inflammation of systemic JIA. In contrast, the oligo/polyarticular subtype of JIA is mainly an antigen-driven lymphocyte-mediated autoimmune disease characterized by abnormalities in the adaptive immune system. T-cell activation leads to the production of the pro-inflammatory cytokines Interferon (IFN)γ and IL-17, which in turn can drive the activation of innate immune system [5].

In recent years, an important area of research in JIA has been the identification of disease biomarkers that are more sensitive and reliable than the traditional acute-phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Several biomarkers have been investigated; however, their incorporation into clinical care still requires validation and standardization [6].

Serum 90K/Mac-2 BP glycoprotein is a heavily glycosylated protein, originally identified in the supernatant of human breast cancer cells [7] and then found to be expressed and secreted by most normal and tumor cells [8]. This protein belongs to the scavenger receptor cysteine-rich protein superfamily, which includes CD5, CD6, M130, complement factor 1 and several other proteins implicated in the regulation of the immune system [9].

High concentrations of 90K glycoprotein can induce the production of cytotoxic effector cells (natural killer/NK and lymphokine-activated killer cell activity/LAK), whereas at low concentrations, it has a stimulatory effect on monocytes [8]. In addition, 90K may enhance the activation of accessory cells [10] and the expression of MHC class-I antigens [11]. 90K may also increase lymphocyte proliferative response to T-cell receptor agonists (such as superantigens and allogenic cells) and down-regulate the proliferative response to anti-CD3 MoAb [12].

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Circulating levels of 90K are frequently increased in patients with neoplastic, infective and immune diseases [13–18].

However, up to now, there are no data on the potential role of 90K in the context of JIA or other rheumatic diseases, where 90K glycoprotein might be deranged due to the inflammatory environment and the immune system changes [8] and might represent a potential new biomarker for the disease.

The aim of the present study was to assess whether circulating levels of 90K glycoprotein are increased in children with JIA at different stages of the disease, compared to healthy controls. A second aim of the study was to assess potential over time changes in serum 90K glycoprotein levels in children with JIA following treatment with the anti Tumor-necrosis Factor (TNF) drug etanercept.

Materials and methods

Study population

The study population included three groups: 23 newly diagnosed JIA children and adolescents, 23 children and adolescents with established and active JIA and 25 healthy controls.

Group 1 (newly diagnosed JIA patients)

Twenty-three newly diagnosed JIA children, classified according to International League of Asssociations for Rheumatology (ILAR) criteria [19], who had been referred to the Rheumatologic Unit (Department of Pediatrics, University of Chieti) were recruited to the study. The group included 14 males and nine females, with a mean age of 6.7 ± 4.3 years. Eighteen of them (78.3%) were affected by oligoarthritis and five subjects (21.7%) had polyarthritis. Ten (43.5%) were antinuclear antibodies (ANA) positive. None had been previously subjected to any kind of therapy.

Group 2 [patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs)+methotrexate (MTX)]

Twenty-three children (14M/9F), followed at the Rheumatologic Unit (Department of Pediatrics, University of Chieti), with JIA diagnosed from a mean of 2.9 ± 2.5 (median[range]: 2.0 years [1.2–4.5]), already on treatment and eligible for the treatment with etanercept represented group 2. They had a mean age of 9.7 ± 4.4 years and they had been diagnosed with JIA at a mean age of 6.7 ± 4.2 years. All patients of this group showed active disease. Nine (39.1%) had polyarticular disease, nine (39.1%) had extended oligoarticular disease, two (8.7%) had psoriatic arthritis and three (13.1%) had enthesitis-related arthritis. Two patients (8.7%) were rheumatoid-factor (RF)-positive and seven (30.4%) were ANA positive. All patients had previously undergone second-line therapy with MTX (mean treatment duration of 1.3 ± 2.0 years). Due to active phase of the disease, all patients required concomitant administration of NSAIDs, namely ibuprofen and naproxen. None had previously received biologic therapy. A Mantoux or QuantiFERON-TB test was done in all patients before starting the biologic drug.

Etanercept was administered by subcutaneous injection once weekly at the dose of 0.8 mg/kg or twice weekly at the dose of 0.4 mg/kg, according to current recommendations. Patients and their parents were previously trained by dedicated staff on the correct administration of the drug and were monitored for compliance with weekly telephone calls.

Group 3 (control group)

Twenty-five healthy controls (14M/11F; mean age 10.9 ± 4.6 years), admitted to the local Pediatric ward for minor diseases (trauma, fractures) were recruited as control group.

They were examined for the study only after complete recovery from the disease they had been admitted for, after 4-6 weeks. None of the study participants were taking any medication.

All participating patients or their parents/guardian gave informed consent. The study was approved by the Ethical Committee of the University of Chieti, Italy.

Methods

Assessments

At the beginning of the study, a complete physical examination, including anthropometric measurements (height, weight), was performed in all study participants.

Fasting blood samples were collected to measure 90K/glycoprotein, CRP, ESR), pro-inflammatory cytokines TNF, ANA and RF.

In group 1 and 2, disease activity score was also assessed. Group 2 underwent a similar clinical/laboratory assessment after 6 and 12 months of etanercept therapy.

Disease activity score

JIA disease activity was assessed by the Juvenile Arthritis Disease Activity Score (JADAS), a validated score adopting four criteria: [1] number of active joints; [2] physician global assessment of disease activity measured on a 10 cm visual analog scale (VAS), where 0 means no activity and 10 means maximum activity; [3] parent/patient global assessment of well-being measured on a 10 cm VAS, where 0 means very well and 10 means very poor; and [4] ESR. We used the 27-joint reduced count (JADAS-27) that was found to be a good surrogate for the whole joint count in JIA. The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (first to third), proximal interphalangeal joints (first to fifth), hips, knees and ankles. ESR value was normalized to a 0–10 scale according to the following formula: (ESR (mm/h) – 20)/10. Before making the calculation, ESR values <20 mm/h were converted to 0 and values >120 mm/h were converted to 120. The JADAS is calculated as the simple linear sum of the scores of its components, which yields a global score of 0–57 for JADAS-27, 0 corresponding to total remission and 57 to maximum disease activity [20].

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Laboratory procedures

Serum 90K/Mac-2 BP was determined by immunosorbent ELISA using a commercial kit (DS, Siena Italy).

CRP was measured with a particle-enhanced immunonephelometric assay with a lower detection limit of 0.32 mg/dl. ESR was calculated using the Westergren technique. The normal range values were 0–15 mm/h in males and 0–20 mm/h in females. ANA were tested by an indirect immunofluorescence method using HEp-2 cells as substrate. Patients were defined as ANA-positive if they had at least two positive results on indirect immunofluorescence at a titer ≥1:160 and ANA-negative if they had negative results in all determinations made during the entire follow-up period.

Quantitative measurement of serum TNF was performed with an immunofluorescence flow cytometry in multiplex sandwich ELISA (BD Cytometric Bead Array: CBA), Human Inflammatory Cytokines Kit (BD Bioscience, San Jose, CA). The kit assay provides a method of capturing soluble TNF with distinct fluorescence intensity beads using flow cytometry. With this methodology, however, only free TNF can be measured; indeed, in patients who are treated with anti-TNF biologic drugs, the ELISA test does not recognize the TNF molecules linked to the drug.

Statistical analysis

Variables were expressed as mean ± SD or median [interquartile range (IQR)] unless otherwise stated. Non-normally distributed variables were logarithmically transformed before analyses.

One-way ANOVA was used to assess differences in continuous variables at baseline between the three study groups, followed by Bonferroni *post hoc* analysis to assess differences between each pair of groups (JIA at onset vs. JIA on treatment; JIA at onset vs. controls; JIA on treatment vs. controls). Differences in categorical variables were assessed by chi-square or Fisher's exact text.

Repeated-measures ANOVA was used to assess changes over time in the study variables, with Bonferroni posthoc analysis to test for differences between the three study time points in the JIA on treatment group.

Spearman correlation analysis was used to assess associations between variables of interest. The statistical significance level was $p < .05$.

All calculations were made with the computer program SPSS (Statistical Package for the Social Sciences), version 22 for Windows (SPSS Inc, Chicago, IL).

Results

Baseline characteristics

The demographic, clinical and biochemical characteristics of the study population are reported in Table 1. Group 1 and 2 included 23 children with a similar distribution of boys and girls ($p = .73$). The mean age of the study population was 9.1 ± 4.7 years. Children from group 2 and 3 had a similar mean age, whereas children from group 1 were younger.

At baseline, significant differences were found in 90K levels between the three study groups with the JIA group at onset showing the highest 90K levels (Table 1). Levels of 90K were significant different between the JIA onset group and the control group as well as between the JIA on treatment group and controls and between JIA onset and JIA on treatment groups. These differences persisted even after adjusting for age and sex.

At baseline, significant differences between the three groups were also found in CRP and ESR and in the JADAS score (Table 1).

Clinical and laboratory data during the study period: baseline versus 6- and 12-month treatment

In the JIA on treatment group (group 2), following 12 months etanercept treatment, there was a significant reduction in 90K levels. A significant decline was detected already at 6 months (from 90.0 [68.8–120.2] to 74.3 [56.0–104.1] μg/ml $p < .001$) and a further decline was observed at 12 months (49.3 [46.0–67.6] μg/ml $p < .001$).

Treatment with etanercept was also associated with a significant decline in CRP, ESR and TNF levels (Table 2).

JADAS-27 score significantly improved during the treatment period and the number of involved joints decreased.

A significant association was found between changes in 90K levels between baseline and 12 months post-treatment (delta 90K) and changes in TNF levels during the same time period (delta TNF): regression coefficient $\beta = 0.48$; $p = .020$ (Figure 1). In contrast, there were no significant associations

Table 1. Demographic, clinical and biochemical characteristics of the study population.

Characteristics	JIA at onset	JIA treated with NSAIDs + MTX	Controls	*p*
n.	23	23	25	
Sex (F/M)	9/14	9/14	11/14	.73
Age (years)	6.7 ± 4.3	9.7 ± 4.4	10.9 ± 4.6	.005[a,b]
Disease duration (years)	–	2.0 [1.2–4.5]	–	
JIA subtypes				
Oligoarthritis	18 (78.3%)	9 (39.1%)	–	
Polyarthritis	5 (21.7%)	9 (39.1%)	–	
Psoriatic arthritis	–	2 (8.7%)	–	
Enthesitis-related arthritis	–	3 (13.1%)	–	
90K (μg/ml)	157.7 [131.4–241.5]	90.0 [68.8–120.2]	58.0 [44.5–79.0]	<.001[a,b,c]
ESR (mm/h)	22.0 [11.0–34.0]	29.0 [16.5–52.0]	7.0 [3.0–8.5]	.001[b,c]
CPR (mg/dl)	0.79 [0.32–3.83]	1.0 [0.39–2.40]	0.32 [0.32–0.32]	.027[b,c]
ANA +	10 (43.5%)	7 (30.4%)	–	
RF+		2 (8.7%)	–	

Data are mean ± SD, median [IQR] or *n* (%). *p* values for Bonferroni *post hoc* analysis: a (1 vs. 2), b (1 vs. 3) c (2 vs. 3).

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Table 2. Clinical and laboratory data at baseline and after 6 and 12 months of etanercept treatment.

	Baseline	6 months	12 months	*p*
90K (μg/ml)	90.0 [68.8–120.2]	74.3 [56.0–104.1][a]	49.3 [46.0–67.6][a,*]	<.001
JADAS-27	23.9 ± 8.6	10.3 ± 5.9[a]	6.5 ± 4.6[a,*]	<.001
N active joints	7.0 [6.0–14.5]	3.0 [1.0–5.0][a]	0 [0.0–3.0][a,*]	<.001
ESR (mm/h)	29.0 [16.5–52.0]	10.0 [5.0–23.0][a]	9.0 [4.5–15.0][a]	<.001
CRP (mg/dl)	1.0 [0.39–2.40]	0.32 [0.32–0.65][a]	0.32 [0.30–0.41][a]	<.001
TNF (pg/ml)	9.50 [3.90–30.50]	5.90 [1.50–12.30][a]	2.30 [1.00–12.00][a]	<.001

p values are for repeated measures ANOVA.
[a]*Post hoc* analysis: $p < .05$ versus baseline.
**Post hoc* analysis: $p < .05$ for difference between T6 and T12.

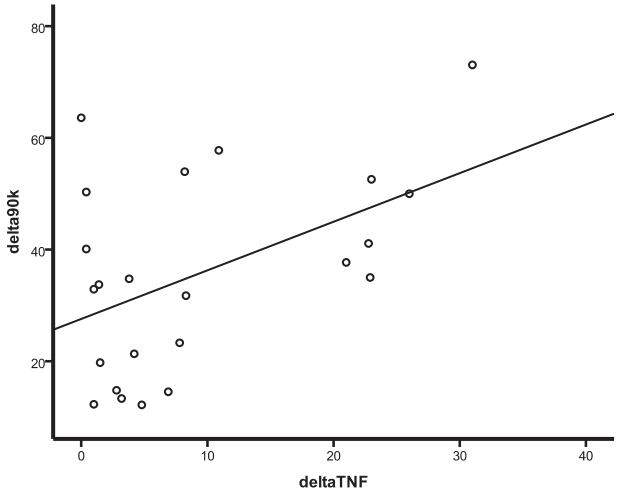

Figure 1. Association between changes in 90K and TNF between baseline and 12-month post-treatment with etanercept.

between changes in 90K and variations (delta) in disease activity score (β = 0.08; *p* value .72), or other markers (delta CRP: β = 0.03; *p* = .89; delta ESR: β = 0.130; *p* = .57).

90K levels at 12 months in the treated group were not statistically significant different from those in the control group at baseline (*p* = .3).

Discussion

The main finding of the present study was that 90K levels were significantly increased in children with JIA compared to controls, particularly at the onset of the disease. Of interest, treatment with etanercept was associated with a significant decrease of 90K levels over a 12-month period.

90K is synthesized and secreted by different cell types, including hematopoietic cells and glandular or mucosal epithelia and is present in the serum and other biologic fluids of normal subjects in the μg/ml range [21]. Increased levels of the protein have been observed in tissues and serum of patients with different types of cancer or infected by viruses [22].

The biological function of 90K is not well defined yet, although a general role within the immune defence system is supported by the finding that 90K binds the Mac-2 lectin, which is expressed by activated macrophages and appears to play a role in the mediation of a cellular immune response, possibly by stabilizing the adhesion of T cells to accessory cells [8].

As JIA recognizes an autoimmune pathogenesis, with several immune system abnormalities detected in the sera and synovial fluid of patients affected by this condition, it is of great interest to understand whether 90K might have a role in the complex immune dysregulation pattern of JIA.

To the best of our knowledge, this is the first study investigating circulating 90K levels in children with JIA, whereas few previous studies evaluated the role of this protein in other autoimmune pediatric diseases [13,23]. Pelliccia et al. found higher levels of both 90K protein and the soluble intercellular adhesion molecule 1 (sICAM1) in Henoch–Schoenlein purpura children compared to healthy controls and there was a significant association between these two molecules. In addition, higher levels of 90K were associated with severe gastrointestinal symptoms [13]. Tumini et al. reported an independent association between age at onset of type-1 diabetes and serum 90K levels, while no correlation between 90K and clinical or biochemical data (i.e. patient's age, duration of disease, glycemic control, insulin requirement) were observed [23]. The authors speculated that 90K may play a role in modulating autoimmune β-cellular destruction in type-1 diabetes. All these data suggest a role for 90K in natural immunity and confirm that it behaves as a potent immunostimulatory protein with positive effects on cell-mediated immune response and cytokine production.

Previous *in vitro* studies demonstrated that 90K/Mac-2 BP is involved in the cytokine loops: its expression seems to be induced by IFNα, IFNγ and TNF [14,24], whereas 90K may stimulate the secretion of IL-1, IL-6, GM-colony-stimulating factor and TNF [25].

In JIA patients, T cell activation of adaptive immune system, including the production of pro-inflammatory cytokines IFN-γ and IL-17, also drives the activation of innate immune system, which involves neutrophils, macrophages and synoviocytes, and induces the production of many other inflammatory cytokines, chemokines and mediators such as IL-1, IL-6 and TNF [5].

One can hypothesize that 90K glycoprotein might be linked to the cytokine production involved in the pathogenesis of JIA.

Our study showed that 90K/MAC-2BP glycoprotein serum levels were significantly higher in JIA children compared to healthy controls, both in JIA at onset and in the methotrexate plus NSAIDs group. In addition, significantly higher levels of 90K were observed in children with JIA at onset compared to children with established JIA already treated with NSAIDs and MTX. Besides, all patients already on treatment showed a progressive decrease of 90K levels after 12 months of additional therapy with etanercept. In our study, the reduction of serum 90K glycoprotein levels in JIA children correlated with the reduction of the pro-inflammatory cytokine TNF.

Based on these observations, it can be hypothesized that the 90K glycoprotein and the TNF cytokine are molecules jointly involved in JIA inflammation. This hypothesis is supported by the finding that treatment with etanercept, an anti-TNF drug, led to a clear improvement not only in

disease activity but also in inflammatory status and a reduction of 90k and TNF serum levels.

Some study limitations need to be acknowledged. In particular, the small sample size and the lack of assessment of 90K over time in newly diagnosed JIA groups. Besides, a potential study limitation was lack of re-assessment of the control group at the end of the study. Nevertheless, the study results suggest a potential role of 90K glycoprotein in the immune dysregulation involved in the development of JIA, and a potential beneficial effect of etanercept in modulating its levels. Further studies, in larger sample sizes are required to confirm the present findings in order to be able to draw firm conclusions on the potential role of 90K in JIA pathogenesis and its potential clinical utility. Moreover, studies involving other autoinflammatory/autoimmune diseases may add new information about the role of 90K protein in these pathologies.

Conflict of interest

None.

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