Differences in the Profiles of Circulating Levels of Soluble Tumor Necrosis Factor Receptors and Interleukin 1 Receptor Antagonist Reflect the Heterogeneity of the Subgroups of Juvenile Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether levels of soluble tumor necrosis factor receptor 55 (sTNFR55), sTNFR75, and interleukin 1 receptor antagonist (IL-1Ra) can differentiate different subtypes of juvenile rheumatoid arthritis (JRA), and to determine if the levels of these proteins correlate with disease activity.

Methods. Serum sTNFR (55 and 75) and IL-1Ra levels were measured by ELISA in 34 patients with JRA and these values were correlated with disease subtype and activity.

Results. Serum sTNFR55 levels were significantly elevated in patients with systemic onset JRA (SoJRA) (mean ± 2 SD, 2.9 ± 1.8 ng/ml) ($p \leq 0.05$) compared to rheumatoid factor positive (RF+) polyarticular JRA (2.1 ± 0.6), RF– polyarticular JRA (1.5 ± 0.6), and pauciarticular JRA (1.4 ± 0.4). There was a trend for elevation of sTNFR75 levels in patients with SoJRA compared to other subtypes ($p = 0.08$). More patients had elevated levels of sTNFR75 than sTNFR55 (15 vs 7). This was true for all subsets (SoJRA 7 vs 5; polyarticular JRA 4 vs 2; and pauciarticular JRA 4 vs 0). In contrast to sTNFR, IL-1Ra levels were significantly elevated in RF+ polyarticular JRA compared to the other subgroups ($p \leq 0.001$). We found statistically significant Pearson correlations between (1) sTNFR75 and hemoglobin concentration; and (2) IL-1Ra and number of active joints and number of joints with effusions.

Conclusion. The increased serum level of sTNF receptors in SoJRA suggests that TNF is likely more important than IL-1 in systemic inflammation and in particular in SoJRA. Conversely, IL-1 is likely more important in the inflammatory arthritis of JRA and in particular in the pathogenesis of RF+ polyarticular JRA. Our results suggest that cytokines have differing roles in JRA subtypes and likely reflect JRA subtype heterogeneity. (J Rheumatol 2002;29:1071–8)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS INFLAMMATION TUMOR NECROSIS FACTOR SOLUBLE RECEPTORS CYTOKINES INTERLEUKIN 1 RECEPTOR ANTAGONIST

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Juvenile rheumatoid arthritis (JRA), the most common form of inflammatory arthritis in children, can be divided into 3 major subtypes: systemic onset (SoJRA), polyarticular, and pauciarticular JRA[1-5]. The 3 subtypes share the common feature of chronic arthritis beginning in childhood or adolescence. Despite extensive study, the cause and pathogenesis of JRA remain unclear. Studies have provided evidence that there are immunoregulatory abnormalities, including abnormal cytokine production, with activation of the immune system. The immune abnormalities may differ in different subtypes of JRA[6,7]. Tumor necrosis factor (TNF), interleukin 1 (IL-1), and IL-6 have been shown to be important in JRA, while studies in other diseases suggest that elevated circulating cytokine levels may lead to systemic inflammation and cartilage and bone destruction[8-20].

Direct measurement of circulating serum cytokine levels is complicated. The presence of inhibitors can interfere with the accuracy of measurement of cytokine levels and cytokines are unstable *ex vivo*. Despite rigorous attention to the details of proper sample collection, accurate measurements may be difficult[7,21-24]. Circulating soluble receptors, including soluble tumor necrosis factor receptor (sTNFR), and biological circulatory inhibitors, such as IL-1 receptor antagonist (IL-1Ra), regulate the function of TNF and IL-1, respectively. Detection of these regulatory molecules may be used as an accurate, indirect method of assessing cytokine activity[8,22,25-33].

We report on the levels of soluble TNF receptors and IL-1Ra in the sera of children with JRA as an indirect measurement of cytokine activity. Our aim in examining the cytokine profile of patients with JRA was to better understand the biologic differences that may explain the clinically distinct JRA subtypes. The sample size was small so that any statistically significant differences would be clinically relevant. A secondary aim was to determine whether measurement of these cytokine inhibitors would accurately reflect disease activity.

MATERIALS AND METHODS

The study group consisted of 34 patients (22 girls, 12 boys), aged 2–16 years (mean 8.8 yrs), with a duration of disease ranging from 6 months to 10 years (mean 2.9 yrs). All patients met the American College of Rheumatology criteria for the diagnosis of JRA[1] and were seen over a 2 year period at the Hospital for Sick Children arthritis clinic (a tertiary referral hospital). Patients were selected on the availability of an accurate clinic assessment and a serum sample from the same visit.

Active disease was defined clinically and was adapted from our previous description[34]: (1) Patients with systemic onset JRA (SoJRA): active arthritis of one or more joints or systemic features excluding uveitis; (2) patients with polyarticular JRA: active arthritis in one or more joints; (3) patients with pauciarticular JRA: active arthritis in one or more joints. As can be seen the definition of active disease varied by disease subtype.

Inactive disease was defined clinically as the absence of pain, swelling, or joint tenderness and the absence of any extraarticular disease.

Clinical data. Clinical information was obtained by review of medical records. All patients had been assessed by a pediatric rheumatologist for disease activity and inflamed joints at the time of blood sampling independent of the laboratory measurement.

Eleven patients had systemic onset JRA, 10 had rheumatoid factor negative (RF–) polyarticular JRA, 3 had RF+ polyarticular JRA, and 10 had pauciarticular JRA. Patient characteristics are shown in Table 1.

Medication. Twenty-eight patients were taking antirheumatic medication, while 6 patients were taking no medication. Seventeen patients were taking only a single nonsteroidal antiinflammatory drug (NSAID), while the other 11 were taking multiple drugs. Patients' medication(s) are shown in Table 2.

Laboratory studies. Serum samples from all patients were frozen at –70°C until assayed. IL-1Ra levels were measured by a commercial ELISA according to the manufacturer's instructions (IL-1Ra Quantikine, R&D Systems, Minneapolis, MN, USA). It has been shown that rheumatoid factors do not interfere with the IL-1Ra assay when $F(ab')_2$ fragments are used[35]. Normal values are 489 ± 171 pg/ml (mean ± standard deviation). sTNFR55 and sTNFR75 concentrations were measured using specific ELISA binding assays[32]. Normal values are 1.7 ± 0.8 ng/ml and 3.2 ± 1.1 ng/ml for sTNFR55 and sTNFR75, respectively. All normal values were derived from age matched children.

Statistical analysis. Comparisons between groups were made using the Mann-Whitney test. Correlation between sTNFR, IL-1Ra, and disease activity variables were determined initially by Spearman's rank test and then using Pearson's correlation. All statistics were performed on a Macintosh computer using Data Desk or Statview software.

RESULTS

sTNFR55. Elevated circulating sTNFR55 levels were found in 7 patients: 5 had SoJRA, and 2 had polyarticular onset JRA (one with RF+ and one with RF–). No patient with pauciarticular JRA had elevated circulating sTNFR55 level (Figure 1). The mean sTNFR55 level in patients with SoJRA (2.9 ± 1.8 ng/ml) was significantly increased compared to the mean level from patients with RF+ polyarticular JRA (2.1 ± 0.6 ng/ml), RF– polyarticular JRA (1.5 ± 0.6 ng/ml), and pauciarticular JRA (1.4 ± 0.38 ng/ml) ($p < 0.05$).

sTNFR75. Fifteen patients had elevated circulating sTNFR75 levels: 7 patients had SoJRA, 4 had polyarticular JRA (2 RF+ and 2 RF–), and 4 had pauciarticular JRA (Figure 2). There was a statistically significant difference in the mean sTNFR75 levels in patients with SoJRA (5.5 ± 3.46 ng/ml) compared to the mean sTNFR75 level from patients with the other subtypes of JRA (3.2 ± 2.3 ng/ml) ($p < 0.04$).

IL-1Ra. Six patients had elevated circulating IL-1Ra levels. Markedly elevated levels of IL-1Ra were found in all 3 patients with RF+ polyarticular JRA, and in only one of the patients with RF– polyarticular JRA. Two patients with SoJRA also had increased levels of IL-1Ra, while no patient with pauciarticular JRA showed an increased IL-1Ra level (Figure 3). The levels of IL-1Ra in the 3 patients with RF+ polyarticular JRA were significantly elevated (26 ± 16.3 ng/ml) compared with the patients with RF– polyarticular JRA (0.25 ± 0.38 ng/ml), SoJRA (0.5 ± 0.8 ng/ml), and pauciarticular JRA (0.03 ± 0.1 ng/ml) ($p < 0.001$). The difference in IL-1Ra levels between patients with RF+ and RF– polyarticular JRA was seen despite the fact that all patients with polyarticular JRA in both groups had active arthritis.

Correlation with disease activity. We next examined whether sTNFR and IL-1Ra levels correlated with disease activity. Twenty-five of 34 patients had active disease (8/11 patients with SoJRA, all 13 with polyarticular JRA, and 4/10 with pauciarticular JRA). Conversely, 9 patients had inactive disease (3 with SoJRA and 6 with pauciarticular JRA). Eight of the 9 patients with inactive disease had a normal erythrocyte sedimentation rate (ESR) (< 20 mm/h), a white blood cell (WBC) count < 10.0×10^9/l, a normal serum albumin (> 35 g/l), normal hemoglobin for age, a normal platelet count (< 450,000/l), and normal serum IgG level (< 10.0 g/l). One patient classified as inactive with systemic onset JRA had an elevated ESR, 92 mm/h, elevated WBC at 28,000/l, and elevated platelet count at 898,000/l,

Table 1. Patient characteristics.

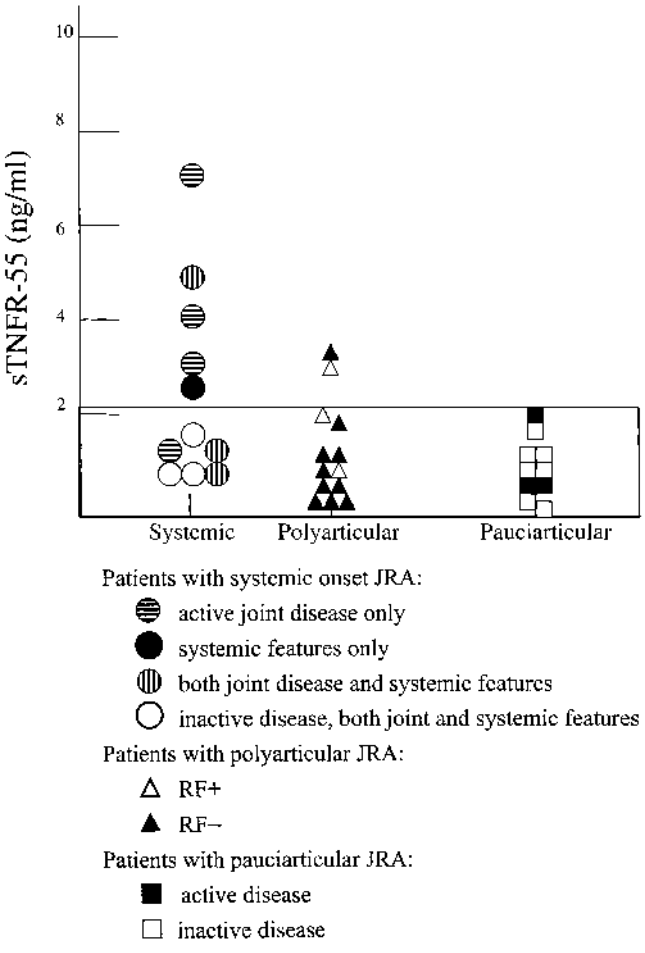
Type of JRA	Sex Distribution	Disease Duration	Mean Age at Disease Onset, yrs	Disease Activity
Systemic onset	5 F, 6 M	5 mo to 8 yrs	7.9	8 active, 3 nonactive*
Polyarticular RF–	8 F, 2 M	3 mo to 10 yrs	8.8	All 10 active
Polyarticular RF+	3 F, 0M	2 to 15 mo	9.9	All 3 active
Pauciarticular	6 F, 4M	5 mo to 9.5 yrs	7.8	4 active, 6 nonactive

* One patient had active systemic features without active arthritis, 4 patients had both active systemic features and active arthritis, and 3 patients had active arthritis without active systemic features.

Table 2. Medication at the time of sera samples. All patients taking methotrexate (MTX), sulfasalazine, prednisone, and gold were also receiving NSAID

Type of JRA	Medication						
	NSAID Only	MTX	Prednisone	Sulfasalazine	Gold	Hydroxychloroquine	No Medication
Systemic onset	8	2*	1	0	0	0	2
Polyarticular RF–	3	2	0	2	1	0	1
Polyarticular RF+	1	0	2	0	0	0	0
Pauciarticular	6	0	0	0	0	1	3
Total	18	4	3	2	1	1	6

* One patient received monthly intravenous immunoglobin in addition to weekly MTX and daily NSAID and one patient received prednisone in addition to weekly MTX and daily NSAID.



but a normal hemoglobin level, and had discontinued all medication with no active arthritis and no evidence of active systemic features by history or physical examination.

sTNFR55 levels were elevated in 7 of 25 patients with active disease and in none of the 9 patients with inactive disease. There was a trend for differences in the levels of serum sTNFR55 between patients with active disease (2.2 ± 1.4 ng/ml) compared to patients with inactive disease (1.4 ± 0.3 ng/ml) ($p < 0.06$). Five of the 8 patients with active SoJRA (one active arthritis only, one active systemic features only, and 3 with both active arthritis and active systemic features) and only 2 of the 13 patients with polyarticular JRA (one RF+ and one RF–) had elevated sTNFR55 levels (all 13 patients with polyarticular JRA had active disease). Four of 5 patients with active systemic features of SoJRA had elevated sTNFR55 levels, while the one of 3 patients with active polyarthritis but not active systemic symptoms had elevated levels. None of the 3 patients without active arthritis and without active systemic features had elevated levels. Therefore 13 of 16 patients with active polyarthritis but without fever had normal

Figure 1. Concentrations of sTNFR55 in patients with JRA by subtype. Patients with systemic-onset JRA are shown as circles, those with polyarticular JRA as triangles, and those with pauciarticular JRA as squares. Patients with systemic-onset JRA were divided into those with active joint disease only; systemic features only; both joint disease and systemic features; and inactive disease, both joint and systemic features. All patients with polyarticular JRA were active. Patients with pauciarticular JRA were divided into those with active and those with inactive disease. The area within the box represents mean + 2 SD of the mean (mean level was 1.6 ng/ml). All values > 2.2 ng/ml are considered abnormal.

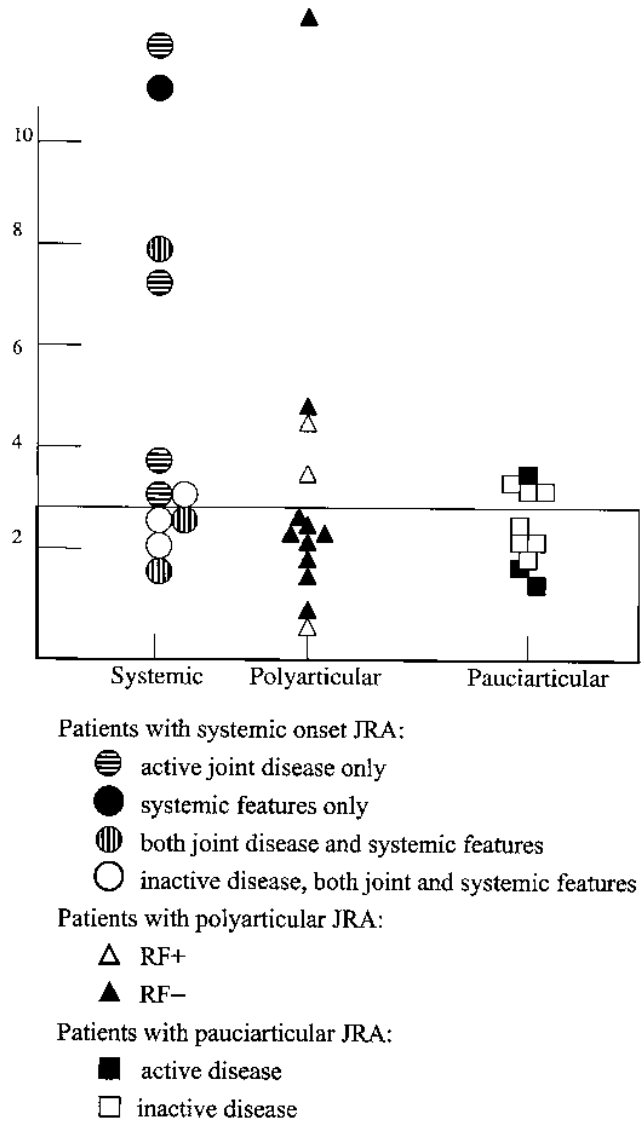


Figure 2. Concentrations of sTNFR75 in patients with JRA by subtype. Patients with systemic-onset JRA are shown as circles, those with polyarticular JRA as triangles, and those with pauciarticular JRA as squares. Patients with systemic-onset JRA were divided into those with active joint disease only; systemic features only; both joint disease and systemic features; and inactive disease, both joint and systemic features. All patients with polyarticular JRA were active. Patients with pauciarticular JRA were divided into those with active and those with inactive disease. The area within the box represents mean + 2 SD of the mean (mean level was 2.1). All values > 3.1 ng/ml are considered abnormal.

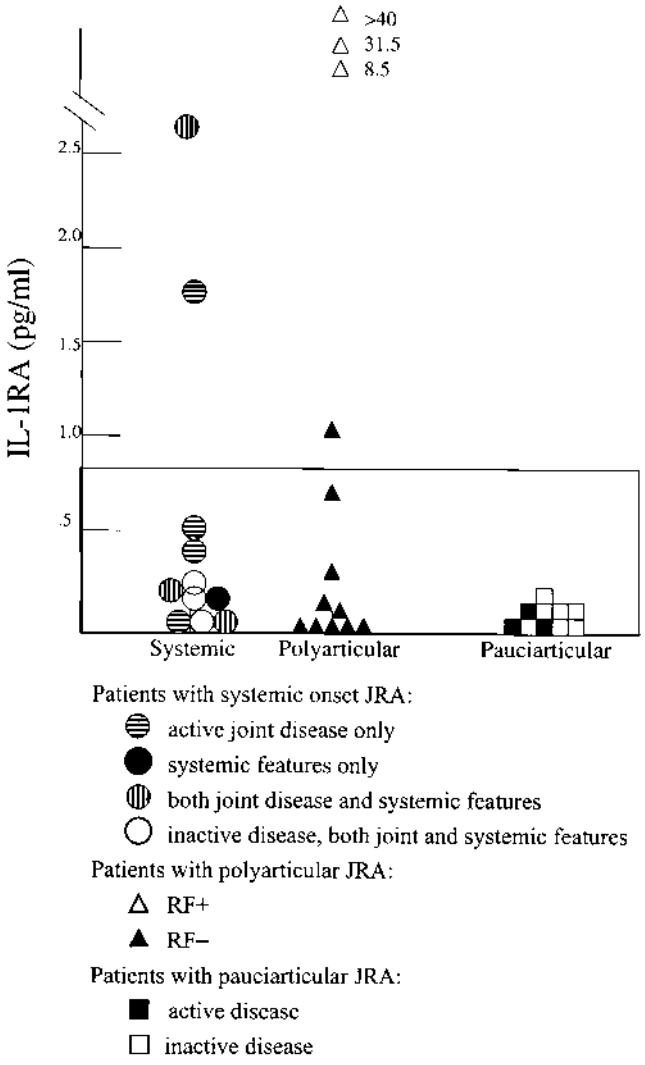


Figure 3. Concentrations of sTNFR75 in patients with JRA by subtype. Patients with systemic-onset JRA are shown as circles, those with polyarticular JRA as triangles, and those with pauciarticular JRA as squares. Patients with systemic-onset JRA were divided into those with active joint disease only; systemic features only; both joint disease and systemic features; and inactive disease, both joint and systemic features. All patients with polyarticular JRA were active. Patients with pauciarticular JRA were divided into those with active and those with inactive disease. The area within the box represents mean + 2 SD of the mean (mean level was 0.392). All values > 0.830 ng/ml are considered abnormal.

sTNFR55 levels. When we compared patients with systemic JRA and active systemic disease to patients with systemic JRA and inactive systemic disease (they could have active arthritis), there was a trend for elevated levels in patients with active disease despite the small numbers of patients (3.6 ± 0.74 vs 2.1 ± 0.62 ng/ml; p = 0.147). All patients with pauciarticular JRA, whether with active or inactive disease, had normal levels of sTNFR55. Using Pearson correlations we did not find any statistically significant correlation between sTNFR55 and any clinical and laboratory features of disease (Table 3).

Elevated levels of sTNFR75 were found in 11 of the 25 (44%) patients with active disease and 4 of the 9 (44%) with inactive disease. The mean serum sTNFR75 level did not significantly differ between the patients with active disease (4.3 ± 3.4 ng/ml) compared to patients with inactive disease (2.9 ± 0.5 ng/ml) (NS). The patients with elevated sTNFR75 levels consisted of 7 patients with SoJRA (6 with active disease, one with clinically inactive disease), 4 patients with active polyarticular JRA (2 RF+ and 2 RF–), and 4 patients

Table 3. Clinical and laboratory measures.

Type of JRA	TNF BP75, ng/ml	TNF BP55, ng/ml	IL-1Ra, ng/ml	No. of Active Joints	No. of Joint Effusions	Hemoglobin, g/l	WBC $\times 10^9$/ml	Platelet $\times 10^9$/ml	ESR, mm/h	IgG, g/L	Total Protein, g/l	Albumin, g/l
Pauci	2.9	1.5	< 0.16	1	1	133	4.7	234	1	9.5	72	43
Pauci	3.3	1.9	0.32	0	0	126	6.4	367	18	9.4	NA	NA
Pauci	3.4	0.8	< 0.16	0	0	135	5.6	386	1	NA	NA	NA
Pauci	3.4	1.5	< 0.16	0	0	131	9.2	332	10	11.7	74	42
Pauci	2.4	1.0	< 0.16	0	0	116	7.8	340	13	8.0	69	41
Pauci	2.1	1.4	< 0.16	0	0	142	5.0	226	1	10.2	76	43
Pauci	2.4	1.4	< 0.16	0	0	118	9.3	427	13	10.8	NA	NA
Pauci	3.5	2.1	< 0.16	5	5	108	8.4	445	82	18.6	NA	NA
Pauci	2.0	1.2	< 0.16	2	2	130	11.5	439	23	6.1	75	44
Pauci	1.9	1.2	< 0.16	1	1	120	5.0	269	2	18.4	74	41
Poly	2.8	1.5	< 0.16	7	7	123	6.9	332	17	16.7	79	40
Poly	12.8	2.9	0.01	9	5	119	9.1	337	8	12.7	77	39
Poly	2.6	1.3	0.2	18	7	104	7.6	302	9	11.2	80	41
Poly	2.2	1.6	< 0.16	2	2	130	7.7	250	1	NA	NA	NA
Poly	5.3	2.1	0.34	1	1	111	9.4	258	20	10.6	69	39
Poly	2.3	1.4	< 0.16	11	3	116	6.8	368	11	12.5	77	41
Poly	1.4	1.1	1.1	12	10	106	8.7	428	38	13.4	75	41
Poly	2.3	1.3	< 0.16	11	9	139	8.0	303	1	11.5	78	44
Poly	1.8	1.2	0.76	7	0	122	5.8	219	3	14.5	70	40
Poly	2.8	1.2	< 0.16	9	7	116	10.1	388	14	9.4	72	40
Poly*	1.0	1.4	> 40.0	39	39	108	12.1	622	NA	22.7	77	39
Poly*	3.8	2.2	31.5	11	1	123	10.0	435	21	13.3	79	41
Poly*	5.0	2.6	8.5	7	1	97	5.4	446	NA	6.4	61	29
Systemic**	8.0	4.3	0.56	10	8	77	19.1	944	56	52.1	97	34
Systemic**	12.2	6.7	1.6	14	14	99	18.6	637	45	8.1	69	33
Systemic**	3.5	2.6	< 0.16	14	12	93	10.9	656	37	17.7	67	35
Systemic**	3.8	1.7	0.54	8	8	105	8.8	444	16	9.5	70	38
Systemic	2.7	1.6	0.12	0	0	138	7.4	325	1	NA	NA	NA
Systemic	3.5	1.4	< 0.16	0	0	115	28.6	868	92	10.7	73	42
Systemic	3.0	1.4	0.24	0	0	115	6.7	333	16	10.8	71	39
Systemic	1.3	1.5	0.23	11	1	123	7.2	246	9	14.8	76	41
Systemic	7.7	5.2	2.8	4	2	114	8.8	417	11	10.5	73	42
Systemic	3.0	1.5	< 0.16	9	6	108	10.6	576	30	12.9	75	36
Systemic**	11.2	2.4	0.1	0	0	106	8.1	266	38	11.1	75	40

* RF+.
** Patients with systemic onset JRA who had active systemic features.
NA: Not available.

with pauciarticular JRA (one active and 3 inactive). Of the 6 patients with active SoJRA one had active systemic features without active arthritis, 4 had both active arthritis and active systemic features, and one had active arthritis without active systemic features. Unlike the results for sTNFR55, when we compared patients with active systemic features and systemic JRA to patients with inactive systemic features and systemic JRA (they may have only active joints), although the numbers were small there was a statistically significant difference in the mean sTNFR75 levels between the 2 groups of patients with systemic JRA (7.6 ± 1.5 vs 3.5 ± 0.9 ng/ml; $p < 0.05$). Using Pearson correlations, we found a statistically significant correlation between sTNFR75 and hemoglobin level ($p = 0.0118$) (Table 3). However, the correlation was no longer statistically significant when corrected for multiple correlations.

Serum IL-1Ra levels were elevated in 6 of 25 patients with active disease and none of the patients with inactive disease. Although there was a trend for differences in mean serum IL-1Ra levels, the mean serum IL-1Ra level was not statistically significantly different between the patients with active disease (3.6 ± 9.9 ng/ml) and those with inactive disease (0.18 ± 0.06 ng/ml) ($p = 0.16$). There was a wide range in the values for patients with active JRA. In SoJRA, only 2/8 patients with active disease had elevated levels while the levels were normal in all 3 patients with inactive disease. A high IL-1Ra level was found in only one of the 5 patients with SoJRA who had fever, although the sera sample for IL-1Ra measurement was not taken during the time of the fever but during a flare of the systemic disease associated with fever (fever within 24–48 h of the sample). All 3 patients with RF+ and only one patient with RF–

polyarticular JRA had elevated IL-1Ra levels. Therefore 5 of 6 patients with elevated IL-1Ra levels were afebrile. Serum IL-1Ra levels were normal in all 10 patients with pauciarticular JRA, regardless of disease activity. Using Pearson correlations, we found a statistically significant correlation between IL-1Ra levels and number of active joints ($p < 0.001$) and number of effusions ($p = 0.001$) (Table 3). Both these correlations remained statistically significant when corrected for multiple correlations.

DISCUSSION

Cytokines are important mediators of inflammation and are likely important in the inflammation of JRA. However, direct accurate measurement of these cytokines in the sera or synovial fluid of patients is difficult and the levels measured may not reflect their biological significance. In contrast, soluble receptors or receptor antagonists generally have longer half-lives and circulate freely, and their secretion is generally regulated by production of their respective cytokines. In JRA the candidate cytokines associated with joint damage and systemic features are IL-1, IL-6, and TNF. As previous reports described a role for IL-6 in JRA[13–16,18,36,37], this work focused on the role of TNF and IL-1.

There are 2 recognized soluble TNF receptors, sTNFR55 and sTNFR75, that have been found to circulate freely, and abnormal levels have been associated with multiple disease states[31]. After stimulation, the sTNFR75 receptor is more rapidly shed and in larger amounts than the sTNFR55 receptor. We found elevated sTNFR75 levels in the sera of patients with all 3 subtypes of JRA. However, the highest levels, and the greatest number of patients with elevated levels, were seen in patients with active SoJRA and in particular if fever and/or rash were present at the time of measurement, and only a minority of patients with polyarticular and pauciarticular JRA had elevated levels. The highest mean levels of sTNFR55, the largest number of patients with elevated levels, and the highest levels were found in patients with SoJRA and active systemic features. Most patients with polyarticular JRA and all patients with pauciarticular JRA had normal levels of sTNFR55. De Benedetti, *et al* demonstrated that sTNFR75 and sTNFR55 levels, but not serum TNF levels, were associated with persistent and severe systemic SoJRA and were associated with coagulation abnormalities and macrophage activation syndrome[38]. Taken together, our results and others' strongly suggest that abnormal TNF production is important in systemic JRA. This does not contradict findings of a role for IL-6, as the production of TNF may lead to IL-6 production and IL-6 levels have been shown to correlate with sTNFR levels in JRA[8,14,15,30,39,40].

Our results suggest that elevated sTNFR55 levels do not simply reflect activation of the immune system nor the degree of inflammation, as there was no direct correlation with sTNFR levels and joint count or other inflammatory measures. However, there was a trend for correlation of hemoglobin levels and sTNFR75 levels. A recent report examining *in vitro* sTNFR production corroborates our findings, as sTNFR production was not related to joint count, ESR or CRP (measures of inflammation)[41]. The importance of TNF in JRA is further emphasized by the description of elevated levels of TNF-α, TNF-ß, and sTNFR55 and sTNFR75 receptors in the synovial tissues of patients with JRA[8,42,43]. Taken together, the results of the studies in patients with JRA confirm that TNF is likely an important proinflammatory cytokine in JRA and in particular in SoJRA.

Studies in adult RA, JRA, and IL-1 knockout mice revealed the importance of IL-1 in arthritis[14,15,21,26,27,44-49]. In particular, studies in IL-1 knockout mice suggest that IL-1 may be particularly important in the cartilage damage and joint destruction[47]. In RA, IL-1Ra levels were significantly correlated with both measures of disease activity and more importantly with joint destruction in patients with RF+ RA[27]. Elevated IL-1Ra levels in all patients tested with RF+ polyarticular JRA, a disease with poor joint outcome, and the observation of a statistically significant correlation of IL-1Ra levels and number of active joints and number of joints with effusions support a role for IL-1 in joint damage. It is likely that RF+ polyarticular JRA represents the very early onset form of severe, erosive adult RA. The only other patients with elevated IL-1Ra levels were 2 patients with SoJRA and one with RF– polyarticular JRA. Both of these subtypes of JRA are associated with joint destruction, although destructive arthritis is seen in a smaller percentage of patients with SoJRA and RF– polyarticular JRA than the percentage of patients with RF+ polyarticular JRA with joint destruction. However, these 3 patients had radiographic evidence of destructive arthritis.

We found elevated IL-1Ra levels in some patients with SoJRA and active arthritis but without fever or other systemic disease. Conversely, 4 patients with SoJRA who had fever showed normal IL-1Ra levels. The normal IL1-Ra levels seen in our patients with SoJRA differs from a previous study that demonstrated that an inhibitor of IL-1 was present in the urine of children with fever. This observation was demonstrated in the face of low or undetectable IL-1 levels[11,50,51]. Consistent with our observations, it has been shown that the production of IL-1Ra was no different in patients with SoJRA and controls and that the IL-1Ra production was not related to disease activity[45]. Increases of IL-1 can result in a persistent elevation of IL-1Ra levels for many days despite the inability to detect IL-1 itself[52], and IL-6, an important cytokine in JRA, may also induce the production of IL-1Ra[16,53]. Therefore the fever in SoJRA may be the result of the action of multiple cytokines. Elevated IL-1Ra levels indicate the previous presence of these molecules and elevated IL-1Ra levels may reflect the presence of active arthritis in these patients.

These results suggest that IL-1 is likely important in the pathogenesis of the arthritis in JRA and in particular in RF+ polyarticular JRA, while TNF and/or IL-6 (work by De Benedetti, *et al*[16,40]) may be more important than IL-1 in the overall inflammation seen in SoJRA. However, a combination of IL-1 with TNF and/or IL-6 may be important in the fever of SoJRA. In pauciarticular JRA low levels of circulating cytokine receptor likely reflect the relatively low systemic cytokine production or relatively low total cytokine production by these patients. We suggest that TNF and IL-1 (see below) may be important locally in the joint, but this low "cytokine load" may be reflected in the good preservation of joint function seen in this disease. Interestingly, RF– polyarticular JRA is generally a more benign form than RF+ polyarticular JRA (although it may be severe in individual cases). Therefore the differences in IL-1Ra levels, and by inference IL-1 production, in patients with RF+ and RF– may reflect the more benign course of disease in the latter group and a biological difference between these 2 subtypes of polyarticular JRA. However, similar to the observations with TNF, the presence of normal circulating IL-1Ra levels does not negate a role for IL-1 in local tissue inflammation, but rather the association of normal levels of IL-1Ra with good joint outcome is of clinical interest. Therefore TNF, IL-1, and IL-6 likely have important, but distinct, roles in the different JRA subtypes. The differences in the production of these cytokines in the different JRA subsets may explain the marked clinical heterogeneity of JRA.

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