Etanercept Improves Lipid Profile and Oxidative Stress Measures in Patients with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To investigate the effect of 1-year treatment with the anti-tumor necrosis factor-α (TNF-α) drug etanercept on lipid profile and oxidative stress in children and adolescents with juvenile idiopathic arthritis (JIA).

Methods. Thirty children with JIA (22 females; mean age 12.3 ± SD 5.7 yrs), all eligible for anti-TNF-α treatment, were assessed at baseline and after 6- and 12-month treatment with etanercept. Disease activity was determined using the Juvenile Arthritis Disease Activity Score (JADAS). Blood samples were drawn to measure the acute-phase reactants C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), lipids, and the proinflammatory cytokines TNF-α, interleukin-1β (IL-1β), IL-6 and interferon-γ. To measure the oxidative stress marker 8-iso-prostaglandin $F_{2\alpha}$, 24-h urine samples were collected.

Results. Inflammatory indicators (CRP and ESR) and JADAS scores improved significantly after 1 year of etanercept treatment (all $p < 0.001$). Proinflammatory cytokines showed significant reduction during the study period (all $p < 0.001$). Similar reductions were detected in total cholesterol ($p < 0.001$), low-density lipoprotein cholesterol ($p = 0.04$), and triglycerides ($p < 0.001$), whereas no significant change was found in high-density lipoprotein cholesterol. No side effects were observed during the treatment period.

Conclusion. This study shows for the first time that anti-TNF-α therapy for JIA is associated not only with a beneficial effect on clinical disease activity and inflammatory indexes, but also with improved lipid profile and oxidative stress. These findings suggest that TNF-α blockers might reduce atherosclerotic risk in children with JIA. (J Rheumatol First Release April 1 2013; doi:10.3899/ jrheum.121281)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS CHILDREN ATHEROSCLEROSIS
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A large body of evidence suggests that patients with chronic inflammatory disorders, such as rheumatoid arthritis (RA), have an increased cardiovascular risk[1,2,3]. Atherosclerosis is a multifactorial process because of the interplay of several factors, one of the main ones being dyslipidemia[4]. In addition, chronic inflammation has been shown to be an independent risk factor for accelerated atherosclerosis[5]. Systemic inflammation induces structural changes in lipoproteins and an unfavorable lipid profile, leading to the so-called "atherogenic lipoprotein phenotype," characterized by decreased high-density lipoproteins (HDL), raised triglycerides (TG), and increased levels of small dense low-density lipoproteins (LDL)[6,7].

Oxidative stress is also implicated in the pathogenesis of cardiovascular disease (CVD)[8]. Several lines of evidence indicate that patients with inflammatory rheumatic diseases have abnormal lipid profiles[9] as well as increased oxidative stress markers[10], and these 2 factors contribute to the pathogenesis of atherosclerosis[10,11]. Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and IL-6 also play a part in the development of atherosclerosis and CVD in patients with inflammatory arthritis[12]. These cytokines, produced in the synovial tissue, can impair the function of several organs and tissues including adipose tissue, skeletal muscle, liver, and vascular endothelium, leading to a spectrum of proatherogenic changes including endothelial dysfunction, insulin resistance, dyslipidemia, and prothrombotic and prooxidative actions[13].

Based on this evidence, the potential role of anti-TNF-α agents in preventing CVD in patients with inflammatory

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rheumatic diseases has been assessed in several studies. In adults with RA, TNF-α inhibitors have been found to reduce carotid intima-media thickness (cIMT) and levels of inflammatory markers [C-reactive protein (CRP), proinflammatory cytokines] and to induce some potential beneficial changes in lipid levels, although with variable results across different studies[14,15,16,17,18]. Data from a recent systematic review and metaanalysis of studies investigating the modification of lipid levels with anti-TNF-α agents in RA suggest that TNF-α inhibitors induce a significant increase in HDL cholesterol, total cholesterol (TC), and TG levels. The increase in HDL cholesterol could have a cardioprotective effect, but no significant change was found in LDL cholesterol, which is a key agent in CVD[19].

In the pediatric population, patients with juvenile systemic lupus erythematosus have been shown to be particularly at risk of developing atherosclerosis, owing to their lifelong exposure to the effect of inflammation[20]. To date there are only scant data on CVD risk and no specific data on the potential beneficial effects of anti-TNF-α agents on CVD markers in children with JIA. Recently, in a small pilot study, we found that prepubertal children with JIA show early signs of subclinical atherosclerosis, such as increased cIMT, associated with chronic inflammation, suggesting that this population is at high risk for CVD[21]. In that study cIMT improved after therapy, particularly in children treated with anti-TNF-α agents.

To extend these preliminary findings, we designed the present study, where we evaluated the effect of 1-year treatment with etanercept on lipid profiles and markers of oxidative stress in children with JIA.

MATERIALS AND METHODS

Study population. From January 2008 through December 2011, 30 children with JIA referred to the Rheumatology Unit of the Department of Pediatrics, University of Chieti, were enrolled consecutively. The study population included 22 females (73%) and 8 males (27%) with diagnosis of JIA established according to the criteria of the International League of Associations for Rheumatology[16] and eligible for treatment with etanercept based on the presence of polyarticular joint involvement. All children were naive for biologic therapy.

At recruitment, all patients were receiving nonsteroidal antiinflammatory drugs (NSAID) and/or methotrexate, but they were not taking any other medication. Patients with classic atherosclerotic risk factors (obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, diabetes) and children treated with steroids were excluded. Among the exclusion criteria, there was also a family history of hypercholesterolemia, hypertension, hypertriglyceridemia, diabetes, and premature coronary heart disease in first-degree relatives.

The trial was approved by the Ethics Committee of the University of Chieti. Written informed consent was obtained from parents and oral assent from the children.

Study methods. All study participants were treated with etanercept for 12 months. 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. The drug was administered only in the 3 recommended injection sites, which include the front of the middle thighs, the abdomen (except for the 5-cm area right around the navel), and the outer area of the upper arm. Patients and their parents were previously trained by dedicated staff on correct administration of the drug and were monitored for compliance with weekly telephone calls.

All patients were assessed at baseline and after 6- and 12-month treatment with etanercept. At each study visit a complete physical examination, including anthropometric measurements (height, weight) was performed, and office blood pressure was measured.

Fasting and fresh blood samples were collected at baseline and after 6- and 12-month treatments with etanercept to measure acute-phase reactants (CRP and ESR), lipid profile (TC, HDL cholesterol, LDL cholesterol, and TG), proinflammatory cytokines [TNF-α, IL-6, IL-1β, interferon-γ (IFN-γ)]. An overnight urine collection was also obtained from all subjects to measure a marker of oxidative stress, 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$).

Calculations. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Patients were considered obese if BMI was ≥ 97th percentile for age and sex based on the Italian growth chart[22]. Abnormal blood pressure values were defined as systolic and diastolic blood pressures > 90th percentile for age and sex[23].

Height, weight, and BMI SD scores (SDS) were calculated based on the age and sex reference values for Italian children[22].

JIA disease activity was assessed by the Juvenile Arthritis Disease Activity Score (JADAS), a validated score adopting 4 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[17]. 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.

Laboratory methods. 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. Serum TC, HDL cholesterol, and TG levels were determined by the calorimetric enzymatic method (Vitros Chemistry Products). Coefficients of variation were 2.0% for TC, 3.3% for HDL, and 3.2% for TG. LDL cholesterol was calculated according to the Friedewald formula (LDL cholesterol = TC – HDL cholesterol – TG/5). Non-HDL cholesterol was calculated as TC minus HDL. In addition, we calculated the ratio between TC and HDL cholesterol at each study visit. Urinary 8-iso-$PGF_{2\alpha}$ was measured with an enzyme immunoassay kit (Direct 8-iso-Prostaglandin $F_{2\alpha}$; Assay Design Inc.). Quantitative measurement of proinflammatory cytokines in serum was performed with a multiplex sandwich ELISA (SearchLight Human Inflammatory Cytokine Array; Aushon BioSystems Inc.). Antinuclear antibodies (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 2 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 followup period.

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.

Repeated-measures ANOVA was used to assess changes over time in the study variables, with Bonferroni posthoc analysis to test for differences between the 3 study timepoints. Pearson correlation analysis was used to

assess associations between variables of interest. The statistical significance level was $p < 0.05$. Statistical analyses were performed with SPSS, version 19.0 for Windows (SPSS Inc.).

RESULTS

Baseline characteristics. Baseline demographic and clinical characteristics of the study population are reported in Table 1. The study population consisted of 30 children (22 girls), with a mean age at the beginning of the study of 12.3 ± 5.7 years and a median disease duration of 2.50 years (IQR 1.17–5.29). The mean age at disease onset was 7.26 ± 4.66 years. Out of 30 patients, 15 (50%) had polyarticular disease, 7 (23.3%) had extended oligoarticular disease, 3 (10%) had psoriatic arthritis, 2 (6.6%) had systemic-onset JIA with polyarticular progression, and 3 (10%) had enthesitis-related arthritis. Two patients (6.6%) were rheumatoid factor-positive (both were in the polyarticular subgroup) and 7 (23.3%) were ANA-positive.

All patients showed active disease at the beginning of the study and were assigned a disease score of 25.76 ± 8.70 for the JADAS-27.

All patients had previously undergone second-line therapy with methotrexate for a median duration of 1 year (IQR 0.48–2.65).

Because of the active phase of the disease, all patients required concomitant administration of NSAID, namely ibuprofen in 18 patients (60%) and naproxen in 12 (40%).

Clinical and laboratory data during the study period: baseline vs 6- and 12-month treatment. The results of laboratory and JADAS-27 assessments at baseline and after 6- and 12-month treatment are reported in Table 2.

Following etanercept treatment, there was a significant reduction in the JADAS-27 score and in the number of involved joints (both p for trend < 0.001). These reductions were already evident after 6-month treatment ($p < 0.001$) and were even more pronounced after 12-month treatment ($p < 0.001$).

Levels of inflammatory markers (ESR and CRP) decreased significantly after 6-month (ESR, $p < 0.001$; CRP, $p = 0.002$) and 12-month treatment compared to baseline (ESR, $p < 0.001$; CRP, $p = 0.001$).

Lipid profile also improved during the study period: TC and TG levels decreased significantly after 6 months (TC, $p = 0.016$; TG, $p < 0.001$) and 12 months [TC, percentage change from baseline (%Δ) = 13%, $p = 0.001$; TG, %Δ = 35%, $p < 0.001$] of treatment, whereas changes in LDL cholesterol became significant only after 12-month treatment (%Δ = 11%, $p = 0.038$). No significant changes were detected in HDL cholesterol (%Δ = 8%, $p = 0.59$). A significant decrease was found in non-HDL cholesterol ($p = 0.003$), whereas the TC/HDL ratio did not change significantly over time ($p = 0.3$).

Levels of the oxidative stress marker 8-iso-$PGF_{2\alpha}$ decreased significantly after 6 months ($p = 0.019$) and 12 months of treatment ($p < 0.001$).

The proinflammatory cytokines IL-1β, TNF-α, and IFN-γ showed significant reductions after 6 and 12 months of treatment (all $p < 0.001$), whereas changes in IL-6 reached statistical significance only after 12 months' treatment ($p < 0.001$).

No significant change in BMI occurred during the study period (Time 0: 16.87 ± 2.25 vs Time 12 mo = 17.20 ± 2.22 kg/m^2).

Considering changes in study measures between the end of the study and baseline, there was a significant association between ΔJADAS-27 and ΔIL-1β ($r = 0.42$, $p = 0.036$) and ΔIL-6 ($r = 0.47$, $p = 0.015$), whereas there was no significant association between ΔJADAS-27 and changes in lipid levels (ΔTC: $r = 0.11$, $p = 0.6$; ΔTG: $r = 0.13$, $p = 0.5$; ΔLDL: $r = –0.16$, $p = 0.4$), or between ΔJADAS-27 and Δ8-iso-$PGF_{2\alpha}$ ($r = –0.33$, $p = 0.1$). ΔESR was significantly associated with ΔTC ($r = 0.41$, $p = 0.04$) and ΔTG ($r = 0.39$, $p = 0.05$), whereas ΔCRP was associated only with ΔTG ($r = 0.41$, $p = 0.04$). In addition, ΔTNF-α was significantly associated with ΔIL-1β ($r = 0.70$, $p < 0.001$) and ΔIFN-γ ($r = 0.53$, $p = 0.01$). A significant association was also found between ΔIFN-γ and ΔIL-1β ($r = 0.48$, $p = 0.023$). No significant associations were found between Δ8-iso-$PGF_{2\alpha}$ and changes in lipid levels (ΔTC: $r = 0.03$, $p = 0.9$; ΔTG: $r = 0.16$, $p = 0.4$; ΔLDL: $r = 0.24$, $p = 0.2$).

Table 1. Baseline characteristics of the study population with juvenile idiopathic arthritis (JIA). Data represent number of subjects (n) or mean ± SD or median (interquartile range).

Characteristic	
No.	30
Sex, M/F	8/22
Age at onset of JIA, yrs	7.26 ± 4.66
Disease duration, yrs (IQR)	2.50 (1.17–5.29)
Methotrexate treatment duration, yrs (IQR)	1.00 (0.48–2.65)
JIA subsets	
Polyarticular	15
Oligoarticular extended	7
Systemic onset with polyarticular course	2
Psoriatic	3
Enthesitis-related arthritis	3

IQR: interquartile range.

DISCUSSION

To our knowledge, this is the first longitudinal study showing a beneficial effect of 1-year treatment with etanercept on lipid profile and oxidative markers, together with improvement in clinical activity and inflammatory markers, in children with JIA. Overall, these data suggest a potential beneficial effect of this drug on the cardiovascular profile of young patients with JIA.

Epidemiological and autopsy studies have shown that the atherosclerotic process begins early in childhood, although clinical disease manifestations do not become apparent until

Table 2. Clinical and laboratory data at baseline and after 6 and 12 months of etanercept treatment. Data represent means ± SD or median (interquartile range).

Measure	Baseline	6 Months	12 Months	p*
JADAS-27	26.63 ± 9.13	12.84 ± 6.91†	8.04 ± 6.51†	< 0.001
No. active joints	8.0 (6.0–18.2)	3.0 (2.0–7.5)†	1.5 (0.0–5.0)†	< 0.001
ESR, mm/h	35.00 ± 20.86	16.70 ± 12.09†	12.25 ± 7.97†	< 0.001
CRP, mg/dl	0.93 (0.33–2.17)	0.33 (0.32–0.83)†	0.32 (0.32–0.42)†	< 0.001
Total cholesterol, mg/dl	173.88 ± 34.21	157.20 ± 27.18†	151.68 ± 23.08†	< 0.001
LDL cholesterol, mg/dl	111.20 ± 23.23	102.16 ± 23.69	98.60 ± 22.39†	0.04
HDL cholesterol, mg/dl	45.89 ± 28.70	42.50 ± 17.13	42.10 ± 12.10	0.59
Triglycerides, mg/dl	83.96 ± 28.74	62.72 ± 18.15†	54.88 ± 11.12†	< 0.001
Non-HDL cholesterol, mg/dl	127.99 ± 24.40	114.70 ± 25.35	109.58 ± 23.44†	0.003
TC/HDL ratio	4.49 ± 1.76	4.18 ± 1.47	3.91 ± 1.6	0.3
8-isoPGF$_{2\alpha}$, ng/ml	22.39 (15.32–57.68)	12.39 (9.57–31.19)†	8.81 (4.75–15.39)†	< 0.001
IL-1ß, pg/ml	2.55 (1.40–4.93)	1.20 (0.63–2.79)†	0.50 (0.30–1.33)†	< 0.001
IL-6, pg/ml	25.80 (13.28–56.65)	18.40 (9.85–37.48)	12.25 (4.20–16.40)†	< 0.001
Tumor necrosis factor-α, pg/ml	8.90 (4.17–10.75)	2.95 (2.00–6.55)†	1.10 (0.80–2.35)†	< 0.001
Interferon-γ, pg/ml	8.20 (2.60–19.50)	2.60 (0.80–4.60)†	1.05 (0.52–4.47)†	< 0.001

* Repeated measures ANOVA. † Posthoc analysis: $p < 0.05$ versus baseline. JADAS-27: Juvenile Arthritis Disease Activity Score, 27-joint reduced count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TC: total cholesterol; IL: interleukin; PGF: prostaglandin F.

adulthood[24,25,26,27]. An increased risk of developing atherosclerosis is associated with several conditions, including autoimmune and chronic inflammatory diseases[2,12].

The pathogenesis of accelerated cardiovascular damage in patients with chronic inflammatory and autoimmune disorders appears complex and is not fully understood. Atherosclerosis is considered to be a dynamic inflammatory process that begins with activation of the vascular endothelium, with migration of leukocytes into the vascular wall, followed by lipid oxidation within the vessel wall, up to the development of typical atherosclerotic plaques[28]. A crucial role in the pathogenesis of atherosclerosis is played by lipids, dyslipidemia being one of the strongest predictors of CVD[29]. Evidence suggests that LDL particles infiltrate vessel walls, where they are retained in the intima by matrix components and undergo several modifications, including oxidation[30]. Inflammation can promote changes of LDL and reduce levels of the protective HDL, thus contributing to the pathogenesis of atherosclerosis[31,32].

TNF-α, one of the most important cytokines involved in JIA and RA, also promotes dyslipidemia and enhances oxidative modification of LDL[33]. In addition, TNF-α upregulates adhesion molecules on endothelial cells, contributing to fatty streak formation and progression of plaque formation[34].

The most important finding of our study was the significant improvement in lipid profile after 12 months' treatment with the TNF-α blocker etanercept in a group of children with JIA. TC, LDL cholesterol, and TG were significantly and progressively reduced after 6 and 12 months of therapy. This means that in our patients, etanercept changed the lipid profile toward an anti-atherogenic pattern. The finding that the observed changes in lipid profile were time-dependent was notable, in that a longer duration of treatment was associated with more marked changes in lipoprotein levels.

Our results are in agreement with previous studies in adults with RA, where the risk of developing CVD was decreased in patients treated with TNF-α blockers[35,36,37]. However, most previous studies were based on a short treatment period, up to 12–16 weeks[38,39,40], and the study populations did not include patients younger than 18 years. In addition, most adult studies mainly showed increased HDL, decreased TC and TG levels, or isolated changes in apolipoproteins, whereas no changes in LDL cholesterol or TG were reported[9,41,42].

Those results differ from ours: we mainly found an improvement in TC, LDL cholesterol, and TG levels, whereas HDL cholesterol did not change significantly over time. One potential explanation for these discordant findings might be the effect of age-related differences in the response of lipid levels to TNF-α blockers, an effect that includes already-lower levels before treatment, and a lack of other potential age-related modifiers of lipid levels.

The beneficial effect of anti-TNF-α treatment on lipid profile supports the role of TNF-α in the regulation of metabolism. This may be through a direct effect on mechanisms regulating synthesis and catabolism of lipid variables or through changes in other cytokines, such as IL-6 and IL-1, whose variations in our study were associated with similar changes in TNF-α.

Interestingly, in all previous studies a significant associ-

ation was found between decreased lipid levels and improvements in markers of disease activity[9,41,42].

In accord with other studies, we also observed a beneficial effect of etanercept on disease activity, demonstrated by a significant reduction of JADAS-27 scores after 6 and 12 months of treatment.

However, in our study, changes in TC and TG were only weakly associated with changes in inflammatory markers, but not with the JADAS score. This could be related to the small sample size of our study.

We were also able to show a beneficial effect of etanercept treatment on 8-iso-$PGF_{2\alpha}$, a well-known marker of oxidative stress and lipid peroxidation[43]. In our study population, 8-iso-$PGF_{2\alpha}$ levels were significantly reduced after 1 year of treatment. This finding suggests that oxidative stress markers might be another target of the action of etanercept, contributing to the beneficial effect in preventing atherosclerosis.

Our findings suggest not only that etanercept reduces disease activity, but it might also play an important role in preventing CVD in a population at increased risk, such as young people with JIA. Although the changes in lipid measures such as LDL cholesterol were modest, they are of value, particularly when dealing with a pediatric population, as small positive improvements in CVD risk factors could have a relevant effect if maintained over time[44].

However, some limitations of the study need to be acknowledged. In particular, these include the small sample size, which was partly justifiable with the involvement of a single center in the study, and the lack of a control group of healthy children, which could have been important to better assess the CVD profile of children with JIA at baseline and after treatment. These 2 factors limit the possibility of drawing robust general conclusions and imply that further larger studies are required in this field. Another potential limitation is the lack of direct assessments of endothelial damage or early vascular signs of atherosclerosis.

Our results confirm the efficacy of etanercept in improving clinical disease activity and reducing inflammation in children with JIA, and more importantly prove that this drug can improve lipid profile and oxidative stress markers. These results support the hypothesis that the vascular atherosclerotic changes associated with JIA might be prevented early in life. Therefore, all children with JIA should receive early and appropriate treatments to reduce not only the chronic inflammation but also the CVD risk associated with JIA. Further longitudinal studies are needed to confirm these results.

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