ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Bone mineral density in children with juvenile idiopathic arthritis after one year of treatment with etanercept

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SUMMARY

Introduction/Objective Juvenile idiopathic arthritis (JIA) is the most frequent chronic inflammatory, rheumatic disease of childhood, associated with disturbance of bone mineral metabolism, which develops gradually and progressively, and if untreated eventually leads to osteoporosis in adulthood.
The aim of our study was to evaluate bone mineral density (BMD) in patients with JIA treated with etanercept over a period of one year.

Methods The prospective cohort study included 94 JIA patients (66 female, 28 male), their median age being 14.77 years. BMD was measured by dual-energy X-ray absorptiometry on the lumbar spine. Disease activity was assessed using the American College of Rheumatology Pedi 50 criteria.

Results After one year of treatment with etanercept, we found a statistically significant increment in all osteodensitometry variables (p < 0.001). Annual enhancement for the whole group was as follows: bone mineral content 15.8%, BMD 7.2%, BMD_{vol} 4.2%. Z-score improved from -0.86 to -0.58 SD at the last visit, but decreased in rheumatoid factor-positive polyarthritis patients. Patients with systemic JIA had the lowest Z-score. Z-score correlated with functional disability level. BMD was lower in the group treated with glucocorticoids.

Conclusion Our results showed significant improvement of bone mineral density in children with JIA after one year of treatment with etanercept. Rheumatoid factor-positive and systemic JIA subtypes and treatment with glucocorticoids are the risk factors for impairing bone mineral metabolism.

Keywords: juvenile idiopathic arthritis; bone mineral density; anti-TNF

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most frequent autoimmune, rheumatic disease in childhood. Inflammatory process affects primarily the synovial joints and cartilage, leading to excessive production of proinflammatory cytokines. Longstanding inflammation beginning in childhood, when the development of the skeletal system and growth are not yet completed, may cause many complications such as growth retardation, disturbance of bone metabolism leading to osteopenia and osteoporosis, which become apparent when fractures occur [1, 2, 3].

Disturbance of bone metabolism in JIA develops gradually and progressively and it is the result of interaction of many factors. The most important is disease activity and severity, genetic predisposition, duration of the disease, number of affected joints, poor nutrition, medications, especially glucocorticoids (GC), delayed puberty, reduced physical activity, lack of exposure to the sun, and others [4].

There is evidence that JIA is associated with low bone mineral density (BMD), as a result of impairment of bone mineral acquisition during adolescent growth spurt and the inability of achieving optimal peak bone mass. Forty-one percent of adolescents with early-onset JIA had low bone mass > 11 years after disease onset. The development of low total-body bone mineral content (BMC) correlated with the duration of active disease, disease severity, measures of bone resorption, weight, and height [5]. It is a reasonable approach in improving bone health and preventing fractures to suppress disease activity using more efficient therapeutic options. Etanercept (ETN), as a tumor necrosis factor (TNF) blocker, has shown its effectiveness inducing prompt and sustained suppression of disease activity [6, 7]. In addition, there is growing evidence that ETN could have a protective role in preventing structural bone damage by increasing osteoblastic and decreasing osteoclastic activity [8].

There are several modalities of assessing pediatric skeleton, but dual-energy X-ray absorptiometry (DXA) remains the preferred method because of its high precision, accuracy, reproducibility, speed, and especially low radiation exposure and availability of reference data [9].

The aim of our study was to examine bone mineral status in patients with JIA after one year of treatment with ETN.

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METHODS

We undertook a prospective study that included 94 consecutive children with established diagnosis of JIA, referred to the Institute of Rheumatology, the main tertiary care referral hospital in the country, between January 2010 and December 2016. The main inclusion criterion was that those failed to achieve inactive disease according to Wallace et al. [10] criteria despite previously treatment with GC and/or methotrexate (MTX), or had intolerance to MTX have been started on ETN 0.4 mg/kg of body weight twice weekly. The biologic therapy was commenced according to the local criteria for reimbursement covered by health insurance.

According to the International League of Associations for Rheumatology classification, 10 (10.6%) patients had systemic onset (sJIA), 28 (29.8%) patients had polyarthritis rheumatoid factor (pJIA RF) negative, 15 (16%) had polyarthritis RF positive, 20 (21.3%) patients had extended oligoarthritis, 19 (20.2%) had enthesitis and arthritis, and two patients (2.1%) had psoriatic arthritis, who were included in the polyarticular seronegative JIA group for futher analysis, because their clinical presentation was arthritis of peripheral joints [11].

Physical examination, laboratory investigation, and functional ability assessment were done at baseline and 12 months after introducing ETN.

The impact of arthritis on physical ability was estimated using the Serbian version of the Childhood Health Assessment Questionnaire (CHAQ) [12]. This questionnaire, which contains 69 questions regarding usual daily living activities, was completed by a parent or a child if he/she was older than 12 years, and refers to physical ability during the week prior to the clinic visit. CHAQ disability index (CHAQ DI) ranges from 0 (best) to 3 (worst). CHAQ DI represents the average sum of the entire eight areas covered by CHAQ and is divided into four categories: 0 = no disability, 0.1–0.5 = mild, 0.6–1.5 = moderate, and > 1.5 = severe disability [13].

Disease activity was assessed according to the criteria by Giannini et al. [13], which include physician's global assessment of disease activity (PGA) on a 100-mm visual analogue scale (VAS), parent's or patient's assessment of overall well-being on VAS (ranging from 0 mm, being the best, to 100 mm, being the worst), functional ability (CHAQ), number of joints with active arthritis and number of joints with limited range of motion (LOM) as clinical variables, erythrocyte sedimentation rate (ESR) as a laboratory sign of inflammation. Active joint was defined if joint swelling or any two of the following signs were present: LOM, joint pain/tenderness, or joint warmth. The patients were divided into two groups according to the American College of Rheumatology Pediatric 50 definition of improvement [10]. If the patients demonstrated at least 50% improvement from the baseline in at least three of any six core set variables with no more than one indicator worsening by more than 30%, they were considered as responders.

The treatment was analyzed recording the number of patients receiving GC, MTX administered at a dose of 10–15 mg/m² of body surface area per week.

Written informed consent form was obtained from parents or from patients if they were older than 18 years. The study was approved by the Ethics Committee of the Institute of Rheumatology of Belgrade, Serbia.

Osteodensitometry examination was performed using LUNAR DPX-L pediatric software DXA absorptiometry device. Measurements of BMD were performed on the lumbar spine (anterior–posterior scan), and the value from the L2–L4 segment was taken for analysis at the beginning of treatment with ETN and 12 months later. During the examination, the patients were in the supine position with flexed hips and knees at 90°, in order to correct the physiological lordosis of the lumbar spine.

BMD area expressed in g/cm², bone mineral content (BMC) in g/cm, and Z-score expressed in standard deviation (SD) were taken for analysis. Z-score signifies a patient's BMD mean – BMD from an age- and sex-matched reference group, divided by SD for the reference group; the manufacture's database of Italian population of children was used. According to the Z-score, the patients were divided into two groups: group I with Z-score < -1 SD, and group II with Z-score ≥ -1 SD.

In order to eliminate the effect of the length of the bone on BMD, we used the formula $BMD_{vol} = BMD \times [4 / \pi \times L2–L4$ region width in cm], representing volumetric bone mineral density (BMD_{vol}) expressed in g/cm³ [14].

Statistical analysis

Data were evaluated by descriptive statistics and analytical models using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). To describe the groups, descriptive statistical methods were used: the grouping and graphical representation; calculating measures of central tendency (arithmetic mean – $\bar{x}$, the median – Med.); calculating measures of variability (standard deviation – SD, standard score variations – SSD), and calculating the relative numbers.

From analytical statistical methods, Student's t-test and analysis of variance were used to test for differences between groups of respondents for parametric data, and Mann–Whitney U-test and χ² test were used for nonparametric data. To test the normality of distribution of data, Kolmogorov–Smirnov test was used. To assess correlation, the data were applied to a single linear correlation and Spearman's rank correlation.

RESULTS

The median baseline age of 94 patients with JIA was 14.77 years (range of 5–20 years), the median disease duration was 4.42 years (0.72–19). Almost three quarters of patients were female. Demographic and clinical characteristics of the patients are shown in Table 1.

At the entry of study, 12 patients (12.8%) were of preschool age, 20 (21.3%) were 7–12 years old, and 62 (66%) were teenagers. The patients were nine years old (median) at the time the first symptoms of JIA appeared, and 33

Table 1. Baseline demographic and clinical characteristics of the patients

Characteristics	Value (n = 94)
Female/male ratio	66/28 (70.2/29.8)
Age, median (min.–max.), years	14.77 (5.0–20.0)
Age at the onset of the disease, median (min.–max.), years	9.0 (1.08–16.0)
Disease duration, median (min.–max.), years	4.42 (0.72–19)
JIA subtypes	
Systemic	10 (10.6)
Polyarticular, RF negative	28 (29.8)
Polyarticular, RF positive	15 (16.0)
Oligoarticular, extended	20 (21.3)
Enthesitis-related arthritis	19 (20.2)
Psoriatic arthritis	2 (2.1)
No patients on methotrexate	79 (84.0)
No patients on glucocorticoids	22 (23.4)

Table 2. Disease activity core set variables at baseline and after 12 months

Variables	Baseline	After 12 months	% of improvement	p
PGA (mm)	46.4	9.2	81.8	< 0.001
Parent/patient assessment of well-being (mm)	37.5	12.4	47.9	< 0.01
Number of joints with LOM	10.1	4.7	69.9	< 0.001
Number of active joints	9.7	0.2	81.1	< 0.001
CHAQ	0.7	0	66.8	< 0.001
ESR (mm/h)	34	17	39.8	< 0.001

All values are median;
LOM – limited range of motion; PGA – physician global assessment; CHAQ – childhood health assessment questionnaire; ESR – erythrocyte sedimentation rate

Table 3. Osteodensitometry evaluation of the patients at baseline and after 12 months

Variables	Baseline (mean ± SD)	After 12 months (mean ± SD)	p
BMD	0.90 ± 0.25	0.95 ± 0.240	< 0.001
BMC	32.75 ± 16.65	36.19 ± 16.18	< 0.001
Z-score	-0.86 ± 1.23	-0.58 ± 1.21	< 0.001
BMD_{vol}	0.31 ± 0.05	0.32 ± 0.55	< 0.001

BMD – bone mineral density; BMC – bone mineral content; BMD_{vol} – bone mineral density volumetric

Table 4. Z-score according to the arthritis subtype

Arthritis subtype	Baseline*	After 12 months**	p
Systemic	-2.14	-1.87	0.085
Polyarticular, RF negative	-0.66	-0.36	0.005
Polyarticular, RF positive	-0.63	-0.69	0.377
Oligoarticular, extended	-0.85	-0.66	0.041
Enthesitis-related arthritis	-0.76	-0.31	0.010

Intergroup (Kruskal–Wallis)
*p = 0.052
**p = 0.033

(35.1%) were of preschool age. More than half of the patients (57.4%) had disease duration of less than two years, and 11 patients (11.7%) suffered from arthritis more than 10 years.

All the patients had polyarthritis, were non-responsive or had adverse reactions to previous MTX treatment. It was the first condition for prescribing biologic therapy covered by health insurance system in our country. The most frequent was polyarticular seronegative arthritis group, comprising one third of the patients.

At baseline, 79 patients (84%) were treated with MTX, and 22 patients (23.4%) received oral GC.

Disease activity core set criteria according to Giannini et al. [13] at baseline and at the last visit after 12 months are presented in Table 2.

We found significant improvement in all six core set variables representing disease activity, a year after introducing ETN (p < 0.001); the most pronounced improvement was observed in PGA and clinical manifestations of the disease (81%). At baseline, 56 (59.5%) patients had moderate and severe functional disability (DI 0.5–1.5 and above 1.5, respectively), but at the end of the follow-up period, 77 (81.9%) patients had no limitations or had mild limitations in performing everyday activities (p < 0.001).

At the last visit, 82 (87.2%) patients met the American College of Rheumatology Pedi 50 criteria and were assigned to the group of responders, while 12 (12.8%) patients did not show satisfied therapeutic effect and were assigned to the group of non-responders. Among non-responders, there were three patients with sJIA, five with pJIA RF negative, and three patients with RF positive polyarthritis. Non-responders, with the exception of one female patient, were slightly older and were younger at the onset of the disease; however, this was not statistically significant except in relation to GC treatment and disease duration, which was longer in non-responders. In the non-responder group at baseline, 50% of the patients continued GC treatment, and 33.3% of patients were continuing the treatment at the last visit. In the responder group, only two patients used GC at the end.

At baseline, the two groups did not differ with regard to osteodensitometry variables (BMD, BMC, Z-score, and BMD_{vol}). Bone mineral status of patients at baseline and at the last evaluation is presented in Table 3.

After one year of treatment with ETN, statistically significant increment in all osteodensitometry variables was present (p < 0.001). Mean annual enhancement for BMC was 15.8%, 7.2% for BMD, and 4.2% for BMD_{vol} for the entire group of patients. The Z-score also improved from -0.86 to -0.58 SD after one year of treatment.

According to the type of arthritis, there was an intergroup difference in the Z-score at baseline (p = 0.052) and after one year (p = 0.033). Patients with sJIA had the lowest Z-score (-2.14 SD, -1.87 SD, respectively); all were on GC.

Analyzing the groups separately according to the arthritis subtype, after 12 months of treatment, all osteodensitometry values significantly improved for the seronegative polyarticular onset (p < 0.001), and enthesitis-related arthritis patients (for BMD and BMD_{vol}, p < 0.001, for Z-score and BMC p < 0.01). In contrast, in pJIA RF-positive patients, Z-score decreased from -0.63 SD to -0.69 SD. In this group, the only statistically significant improvement was found with regard to BMC (p = 0.041).

The results are presented in Table 4.

At the first osteodensitometry measurement, 44 patients (46.8%) had a Z-score below -1 SD; one year after, 11 out of 44 patients improved their Z-score (p < 0.01). During the study period, we observed significant height and weight increase in the patients (data not shown).

Disability index calculated from the CHAQ negatively correlated with the Z-score at baseline, as well one year after (p = 0.017 vs. p = 0.002). One third of the patients with moderate and severe functional limitations had a Z-score below -1 SD from the reference value. Seventy percent of patients with very low BMD (< -2 SD) had moderate or severe disability at baseline, and 50% at the last examination. The values are presented in Figure 1.
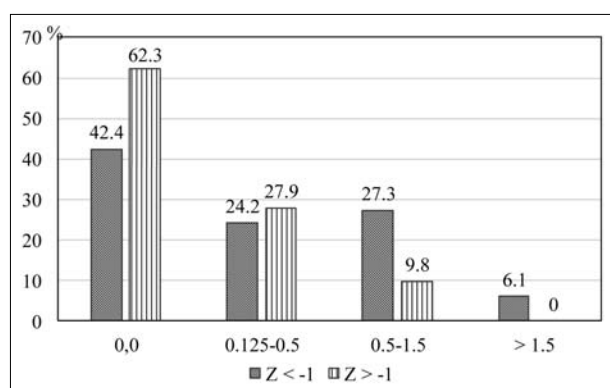
p = 0.021

Figure 1. Correlation of Z-score with disability level on the last evaluation

BMD, BMC, and BMD_{vol} were lower in the GC group (p < 0.01). At the end of the study, GC were stopped in 12/22 patients (54.4%); the dosage of GC was decreased in 6/22 patients (27.3%), and the dosage of GC was not changed in four patients (18.3%); all were nonresponders.

DISCUSSION

Over the last 15 years, the outcome of children with JIA dramatically improved with introducing biologic therapy as a regular treatment option. ETN has been the first anti TNF-blocker licensed for use in JIA. Remarkably, rapid and sustained efficacy of ETN in controlling inflammation, inhibiting progression of joint destruction, and acceptable safety profile was confirmed [6, 7].

We performed a prospective study to investigate bone mineral status in patients with JIA treated with ETN over a period of one year. Our results confirmed excellent ETN efficacy in suppressing disease activity, which reflected on PGA (the improvement was as much as 82%), on parents' or patients' assessment from the clinical point of view (number of joints with active arthritis decreased from 9.7 to 0.2), as well on laboratory signs of inflammation. Rapid decrement of C-reactive protein and thrombocytes and enhancement of hemoglobin were also recorded, but the data are not shown.

There are many risk factors that contribute to bone fragility: high disease activity, poor nutrition, reduced physical activity, growth impairment, puberty delay and inability to reach adequate peak bone mineral accretion, treatment with GC especially, and others. According to Markula-Patjas et al. [15], compressive fractures, mainly thoracic, were associated with a high level of disease activity, high body mass index, and exposure to a high dose of GC, but not with disease duration, nor with BMD.

Assessment of pediatric skeletons can be performed by many methods: X-ray, quantitative computed tomography, quantitative ultrasonography, magnetic resonance imaging, but DXA remains a preferred method for clinical measurement of bone mineral density in children because of many advantages previously mentioned. Paediatric Position Development Conference of the International Society of Clinical Densitometry put JIA on the list of secondary diseases that may affect the skeleton and gave recommendations for interpretation of DXA results in pediatric population. The terms "osteopenia" and "osteoporosis" should be avoided at pediatric age. BMC and BMD Z-score of ≥ 2 SD below what is expected should be labelled "low for age." Diagnosis of osteoporosis in children can be made when both low bone mass and bone fracture history are present [16].

In our previous study, we confirmed decreased BMD in JIA patients, compared with healthy peers (Z-score -1.02 vs. -0.09 SD, p < 0.001). Systemic onset, polyarthritis, longer treatment, and higher cumulative GC dosage, higher damage (functional status and radiologic stage) were risk factors for low BMD. Some of these patients participated in this study but were subsequently not treated with biologics [17]. This study did not include a control group, but the patients were prospectively followed during one year and results at baseline served for further statistical analysis.

Lien et al. [18] explored predictors of bone mass in children with early arthritis (mean disease duration 19.3 months) compared with healthy children. A value between -1 SD and -2 SD was defined as low BMD and BMC, and very low if it was less than -2 SD of the reference value of the healthy population. During a two-year follow-up period, it was found that 24% of patients and 12% of controls had low and very low total BMC. Bone formation and resorption were reduced in the patient group. The results of that study point out that bone metabolism disturbance begins in the early stages of the disease. Patients with polyarthritis had significantly lower BMC compared to the children with oligoarthritis.

In our study, 28.7% of the patients had low BMD, and 18.1% had very low BMD at baseline. This group comprised 17 patients, their median disease duration being 6.3 years, mean number of active joints 12, with moderate functional disability (CHAQ DI 0.88). After one year of treatment, number of patients with low BMD decreased to 19.2%, and 15.9% of the patients had a Z-score below -2 SD. Only one girl with sJIA had a compressive vertebral fracure. Her Z-score at baseline was -3.9, which decreased by the end of study to -4.4 SD; she was a non-responder with a seven-year-long GC treatment.

French et al. [5] found that the average age of 40% of patients with JIA is 35years, that their disease duration is

27 years, and that they had osteopenia at the spine and femoral neck. Risk factors for developing osteopenia were functional class II and higher during adolescence, inadequate participation in organized sports and other forms of physical activity during adolescence, smoking, insufficient dietary calcium intake during adolescence. According to the results, the majority of adult patients reached normal peak of bone mass, but it was significantly lower compared to the healthy population.

Unquestionably, the role of bone remodeling belongs to proinflammatory cytokines such as the TNF, interleukin-1, interleukin-6, interleukin-17, as well as matrix metalloproteinases produced in synovial membrane, which cause the destruction of joint bone and cartilage. Their presence in affected joints can cause excessive osteoclastogenesis, bone resorption, and suppression of osteoclastogenesis [19].

The first study addressing bone mineral status on JIA patients treated with ETN published by Simonini et al. [20] included 20 patients. The patients were younger and disease duration was shorter, and functional disability was higher than in our study. Bone status was determined by broadband ultrasound attenuation at the calcaneus; however, they agreed that DXA remains the gold standard for measuring BMD. After one year of ETN treatment, responders showed higher broadband ultrasound attenuation and Z-score than non-responders.

In the responder group, we found important improvements in all densitometry variables compared to the baseline; in the nonresponder group, statistically significant improvement was only for BMC, which could be explain by the increased linear growth, which was observed, but the data are not presented.

Patients with sJIA on both evaluations had the lowest Z-score and there was no increasing during treatment with anti-TNF blocker. Stagi et al. [21] presented similar results from a large cohort group of 245 patients, with a wider range of age (9–28 years) than that in our study. Patients with sJIA had significant reduction in cortical and trabecular BMD as well, compared to the control group. In our group of patients, the Z-score decreased in RF pJIA patients during one year. The patients were all female, 6/15 were treated with GC, CHAQ 0.725 corresponded to moderate functional disability. In sJIA patients, the Z-score did not significantly increase, confirming that both JIA subtypes have unfavorable outcome, resulting in joint destruction and higher disability in adulthood.

Deleterious effect of GC on inhibition of bone formation caused by a decrease in the number of osteoblasts is well known. It eventually leads to decreasing bone remodeling and increases the tendency towards fractures. Patients treated with GC had lower BMD compared to non-GC patients in our study. At the last observation, BMD_{vol} and Z-score did not improve significantly. We did not analyze in more details the GC group (duration, cumulative dosage, etc.). Thornton et al. [22] examined bone health in adults with a history of JIA; oral GC was associated with lower BMD at both the spine and the hip. Similar results were revealed in a study by Tang et al. [23] – main predictors of low spine BMD were the JIA subtype, disease activity, BMD, and GC exposure.

Doubtlessly, reduced bone mass and density in JIA develop as a result not only of impairment of bone turnover, but also due to lower muscle strength, poorer physical health, and high level of functional disability.

We are aware of some limitation of our study. We had no control group of healthy children and did not include biochemical markers of bone turnover. One year of follow-up period is too short for understanding all aspects of influence of anti-TNF blockers on bone mineral metabolism.

CONCLUSION

Our results confirmed a significant improvement in BMD during one year of treatment with ETN, as well as its efficacy on disease activity. Longitudinal studies and larger cohorts could give better understanding of the long-term outcome and safety of anti-TNF blockers.

In the meantime, our task as physicians is to carefully monitor our patients, apply the best therapeutic options for better control of disease activity, and advise them to make some lifestyle changes, such as reducing or discontinuing smoking and excessive alcohol intake, participation in weight-bearing exercises and sports activities, consumption of dietary calcium and vitamin D supplementation in order to prevent long-term consequences.

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Густина кости код деце са јувенилним идиопатским артритисом после годину дана лечења етанерцептом

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САЖЕТАК

Увод/Циљ Јувенилни идиопатски артритис (ЈИА) јесте најчешће хронично, запаљенско реуматско обољење у детињству, удружено са поремећајем минералног костног метаболизма, који се развија постепено и прогресивно и доводи до остеопорозе у одраслом добу.
Циљ наше студије је био да се испита костни минерални статус код болесника са ЈИА после годину дана лечења етанерцептом.

Метод Проспективна кохортна студија је укључила 94 болесника са ЈИА (66 девојчица, 28 дечака) просечног узраста 14,77 година. Минерална густина кости (МГК) мерена је двоструком апсорпциометријом *X* зрака на лумбалној кичми. Степен активности болести је процењиван *ACR*50 критеријумима.

Резултати После годину дана лечења етанерцептом установили смо статистички значајно побољшање у свим ос-теодензитометријским показатељима (*p* < 0,001). Годишње повећање за целу групу било је: укупно минерала у костима 5,8%, МГК 7,2%, МГК$_{вол}$ 4,2%. 3-скор се поправио са -0,86 до -0,58 СД на крају истраживања, али је у групи болесника са РФ позитивним полиартритисом дошло до смањења 3-ско-ра. Најнижи 3-скор су имали болесници са системским ЈИА. 3-скор је корелисао са степеном функцијске неспособности. Болесници лечени гликокортикоидима имали су значајно нижу минералну густину.

Закључак Наши резултати су показали значајно побољ-шање минералне густине кости код деце са ЈИА после годи-ну дана лечења етанерцептом. Болесници са РФ позитивним полиартритисом и системским артритисом, као и они који примењују гликокортикоиде, имају већи ризик за поремећај костног метаболизма.

Кључне речи: јувенилни идиопатски артритис; минерална густина кости; анти-ТНФ