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Comparison of different treatment approaches of pediatric chronic non-bacterial osteomyelitis

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Abstract

Chronic non-bacterial osteomyelitis (CNO) is a chronic inflammatory bone disease which usually manifests in children and adolescents. There are a few data about pathogenesis and treatment. The aim of the study to compare the efficacy of different treatment approaches in pediatric CNO cohort patient. Fifty two children (25 boys and 27 girls) with CNO with average age at the onset of the disease 8.4 years (5.4; 11.0), number of foci − 3.0 (2.0; 6.0, incl. multifocal cases in 80.8%). Non-steroid anti-inflammatory drugs (NSAID) was the first-line treatment for non-vertebral cases, as well as pamidronate (PAM) for vertebral involvement. Second-line treatment includes sulfasalazine (SSZ), methotrexate (MTX), PAM and tumor necrosis factor-α inhibitors (TNFα-inh). We evaluated the dynamics of pain, patient's and physician's (MDVAS) assessment with visual-analog scale (VAS) and ability to each medication to achieve remission of CNO activity. According to the NSAID, MTX, SSZ, PAM and TNFα-inh groups the following data were registered: patient's VAS: − 14.2% ($p = 0.05$), − 50.0% ($p = 0.04$), − 23.1 ($p = 0.89$), − 83.3% ($p = 0.0001$), − 73.6% ($p = 0.0007$); painVAS: − 21.9% ($p = 0.01$), − 18.6% ($p = 0.13$), + 36.4 ($p = 0.89$), − 79.7% ($p = 0.00016$), − 74.1%, ($p = 0.0015$); MDVAS: − 13.8% ($p = 0.13$); − 56.4% ($p = 0.09$), + 30.8% ($p = 0.89$), − 74.7%, ($p = 0.0001$), − 82.1 ($p = 0.0015$) respectively. The ability of each treatment strategy to achieve the CNO remission was 52.6%, 44.4%, 57,1%, 88.8% and 73.3%, respectively (log-rank test, $p = 0.001$). The efficacy of treatment approaches for CNO depended on the severity of the disease. NSAID, methotrexate, and sulfasalazine were effective in forms without spine involvement, but pamidronate and TNF-a inhibitors were useful in vertebral forms of CNO. Pamidronate and TNF-a inhibitors more extensively suppressed CNO activity. The randomized controlled trials for assessment of the efficacy and safety of these medications is mandatory to confirm these results.

Keywords Chronic non-bacterial osteomyelitis · Pamidronate · TNFα-inhibitors

Introduction

Chronic nonbacterial osteomyelitis (CNO) is a chronic inflammatory bone disease which usually manifests in children and adolescents [1]. Chronic nonbacterial osteomyelitis is also known as chronic non-bacterial osteitis and chronic recurrent multifocal osteomyelitis. CNO is a disease with a heterogeneous chronic persistent or relapsed course with a possibility of spontaneous healing without any treatment [2, 3]. Adult patients have a very similar disease, known as SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis). CNO pathogenesis is not studied comprehensively. Association of CNO with different inflammatory diseases, especially rheumatic, dermatological and inflammatory bowel diseases (IBD) is well known [4–6]. Cytokine disbalance is the crucial point of CNO pathogenesis. Patients with CNO have decreased the production of anti-inflammatory

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cytokine—interleukin-10 and hyperproduction of proinflammatory cytokines—tumor necrosis factor-α (TNFα) and interleukin-1 [7–9]. Due to spontaneous hyperproduction of proinflammatory cytokines without features of autoimmunity, CNO refers to a group of autoinflammatory diseases [1, 10]. Anti-inflammatory effect of anti-cytokine biologics in CNO confirms the autoinflammatory mechanisms underlying CNO pathogenesis [11–13]. Several autoinflammatory diseases and syndromes related to mutations in genes, which control IL-1β-mediated signal pathway include a CNO as a part of the clinical picture, e.g., DIRA-syndrome, Majeed syndrome, where the high efficacy of using IL-1 blockers was demonstrated [14–16].

There are no approved treatments for CNO. The efficacies of non-steroid anti-inflammatory drugs (NSAID), methotrexate (MTX), sulfasalazine (SSZ), pamidronate (PAM), anti-IL1 and TNFα-inhibitors (TNFα-inh) are shown in several previous research [6, 17].

The study aimed to compare the efficacy of non-randomized different treatment approaches in the pediatric patient with CNO cohort.

Patients and methods

Fifty two children (25 males and 27 females) with CNO with an average age at the disease onset 8.4 years (5.4; 11.0) were included in the non-randomized observation study. The mean disease duration was − 4.0 (2.4; 5.7) years. The diagnosis of CNO was determined by the criteria created by Jansson et al. [3, 18], with exclusion of other reasons of bone diseases. Imaging modalities included X-ray, computed tomography, MRI and bone scintigraphy.

Outcomes assessment

According to the current recommendations for treatment of CNO, we used a step-up treatment strategy. Treatment depended on the presence of severity, the presence of spine destruction and efficacy of previous treatment. The first-line therapy includes NSAID in cases with any peripheral bone involvement with pain (mandatory) and other signs of inflammation or spine involvement without signs of spine destruction [19]. Duration of NSAID usually lasted 6–12 months in cases of appropriate response. Patients treated with NSAIDs were only referred to the NSAID group. If NSAIDs failed, then, methotrexate and sulfasalazine were added. In case of severe bone destruction, intense bone pain, NSAID and methotrexate/sulfasalazine fail, the next step was applying bisphosphonates [20]. TNF-a inhibitors were used in the cases with intensive bone inflammation and undesirable effects of previous treatment lines [6]. In each step, NSAID tolerated as a concomitant treatment. Also, MTX or SSZ could be tolerated in patients, treated with TNF-α inhibitors as a concomitant therapy, especially when CNO was associated with other conditions, e.g., IBD or juvenile idiopathic arthritis (JIA).

In the cases of spine involvement with bone destruction, NSAID was used only at the diagnostic step, then bisphosphonates were used to prevent bone destruction and complications [20]. In the cases of severe spine involvement, if bisphosphonates fell or the patient had signs of inflammation similar to ankylosing spondylitis, the TNF-a inhibitors were prescribed. Also, TNFa-inhibitors could be used, if bisphosphonates had an insufficient effect (Fig. 1). The term "inefficacy" means unchanged pain and radiologic appearance, leading to treatment escalation; "partial response" means a decrease in pain, inflammatory parameters at least on 50%, and radiographic improvement, demonstrated in decreasing of (1) surface of foci, (2) foci counts, (3) bone marrow edema intensity on MRI, but presence of at least clinical active focus; and "inactive disease" (complete remission) means the resolution of pain, normalization of inflammatory parameters (ESR < 20 mm/h, CRP < 5 mg/l), and radiographic healing. Patients with inactive disease was tolerated with the presence of 1–2 clinically inactive foci (bone marrow edema on MRI). As a rule, the decision about "efficacy or inefficacy" or changing the treatment line was made by the most experienced CNO physician, if the previous treatment arm failed. Usually, we waited for at least 3 months for evaluation of the efficacy of the treatment line, except urgent situation (e.g., rapid spine destruction).

The efficacy of treatment evaluated through dynamics of pain visual analog scale (pain VAS), patient's VAS and physician's (MDVAS) assessment and ability to each medication to achieve remission of CNO activity. The CNO remission was diagnosed if patient had no fever, pain, clinically active

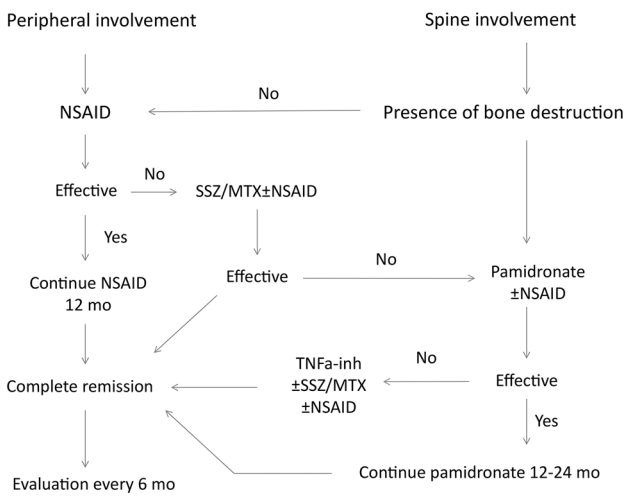

Fig. 1 The schematic treatment algorithm for patients with CNO

foci, concomitant arthritis and evidence of laboratory activity: normal white blood cells (WBC), hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets and absence of disease activity according to the data of pain VAS, patient's VAS and MDVAS. We have evaluated the time before inactive disease (ID) status was achieved. If the patient had several following treatment arms, each treatment arm was evaluated separately: 52 patients had 85 treatment episodes so that some patients could be evaluated several times. In the cases, when next step-line medication added to previous one, the first treatment arm was defined as "ineffective" and the second medication was evaluated as separate treatment arm so that some patients could be included in the subgroup analysis several times (2–4 times).

We have not compared and evaluated the combination of different treatment arms (e.g., bisphosphonates and TNFα-inh). The mean follow-up period was 3.0 (2.2–4.7) years. All patients were evaluated approximately every 6 months after the start of NSAID. Written consent was obtained according to the declaration of Helsinki. Approval of the protocol of this trial was approved by the local Ethics Committee of Saint-Petersburg State Pediatric Medical University (protocol number 10/8 from 23.10.2017).

Statistics

Descriptive statistics are reported in terms of medians and interquartile ranges (IQRs) for continuous variables and in terms of absolute frequencies and percentages for categorical variables. We used a non-parametric statistic because all variables had no normal distribution. To check whether the distribution was normal or not we used the Kolmogorov–Smirnov test. Wilcoxon's matched paired test was used for comparing two dependent variables. Survival analysis with achievement ID status and flare as the events of interest was conducted by means of the Kaplan–Meier method. The log-rank test compared survival curves. $p < 0.05$ was considered statistically significant. The software Statistica (release 9.0, StatSoft Corporation, Tulsa, OK, USA) was used for data analysis. p values < 0.05 were considered to indicate a significant difference.

Results

The demographic characteristics are in Table 1. All inflammatory measures are related to the time of diagnosis before first-line treatment. The patients had predominantly multifocal type of CNO, one-third of patients had spine involvement, and 6 of them had spine surgery. Concomitant immune-mediated diseases, mainly arthritis (enthesitis-related arthritis, psoriatic arthritis, ankylosing spondyloarthritis, undifferentiated arthritis) observed in 67.3% patients of our group, MRI signs of sacroiliac involvement detected in 10/12 (83.3%) of cases with pelvic bones involvement.

Treatment assessment

The mean treatment duration was − 1.6 (1.2–2.9) years. The ability of each treatment arms to achieve the remission for NSAID is 52.6%, for sulfasalazine − 57.1%, for methotrexate − 44.4%, for pamidronate 88.8%, for TNFα-inhibitors − 73.3%. The most useful kinds of treatment were TNFα-inhibitors and pamidronate. Table 2 shows the dynamics of clinical activity indicators (patient's VAS, PainVAS, and MDVAS). In all patients, who achieved remission on NSAID, pamidronate, and sulfasalazine the treatment discontinued. Only in 33.3% of patients treated with methotrexate, it was discontinued. Several patients required repeated courses of NSAIDs. We did not see any significant relapses during the treatment. The Survival analysis with the achievement of inactive disease (ID) status and flare as the events of interest was conducted by means of the Kaplan–Meier method and presented in Fig. 2.

The main side effects included several cases of elevated liver enzymes and nausea in patients, treated with NSAID, sulfasalazine, and methotrexate. "Flu-like syndrome" was observed in all patients during the first course of pamidronate, required used of antipyretics and corticosteroids. Further treatment with bisphosphonates did not associate with side effects.

Discussion

CNO is a disease with relatively favorable outcomes and the possibility of spontaneous flares and remission. Due to peculiarities and heterogeneity of CNO courses, it is challenging to organize randomized clinical trials. Data about treatment modalities based on the data of retrospective studies, case and case series reports and expert opinions. Despite the known disadvantages of retrospective studies, there are no other alternative ways to evaluate the efficacy of treatment modalities in CNO. The positive sides of our study related with single center experience with the same diagnostic tests and therapeutic approaches with a mean follow-up period of 3.0 years, required for more proper evaluation of treatment outcomes. Also, we suppose that splitting patients and different treatment protocols depending on the presence of spine involvement has made the results of our study more precise. The limitations of the study refer to the retrospective type of study, absence of randomization and control group and a possibility of CNO patients to spontaneous flares and remission, which can influence the actual efficacy

Table 1 The basic demography of studied population with CNO

Parameters	Results ($n=52$)
Gender, females, *n* (%)	27 (51.9)
Onset age, years	8.4 (5.4; 11.0)
Family history on rheumatic diseases, *n* (%)	4 (7.7)
Concomitant rheumatic disease, *n* (%)	35 (67.3)
Monofocal forms, *n* (%)	10 (19.2)
Skeletal involvement	
Spine, *n* (%)	18 (34.6)
Femur, *n* (%)	18 (34.6)
Tibia, *n* (%)	23 (44.2)
Fibula, *n* (%)	9 (17.3)
Foot bones, *n* (%)	22 (42.3)
Pelvis, *n* (%)	12 (23.1)
Clavicula, *n* (%)	6 (11.5)
Sternum, *n* (%)	5 (9.6)
Humerus, *n* (%)	6 (11.5)
Ribs, *n* (%)	4 (7.7)
Radius, *n* (%)	3 (5.8)
Ulna, n (%)	2 (3.8)
Hand bones, *n* (%)	3 (5.8)
Maxilla, *n* (%)	1 (1.9)
Scapula, *n* (%)	1 (1.9)
Fever, *n* (%)	20 (38.5)
Number of clinical foci/patient	3.0 (2.0; 6.0)
Hemoglobin, g/dl	12.0 (10.9; 12.8)
White blood cells, $\times 10^9$/l	7.8 (6.7; 9.2)
Platelets, $\times 10^9$/l	331.0 (262.0; 399.0)
Erythrocyte sedimentation rate, mm/h (n.v. < 20 mm/h)	26.0 (11.0; 41.0)
C-reactive protein, mg/l (n.v. < 5.0 mg/l)	8.2 (4.3; 34.0)
Clinical assessment of CNO activity	
Patient's VAS, mm	45.5 (35.5; 67.0)
Pain VAS, mm	44.5 (29.0; 76.5)
MD VAS, mm	47.0 (34.5; 70.5)
Diagnostic delay, months	6.3 (2.0; 17.8)

MDVAS physician's visual analog scale, *VAS* visual analog scale, *n.v.* normal value

of the medication. The spontaneous remission in CNO was an obstacle for proper evaluation of the treatment response. Also, the lack of whole-body imaging in all patients is an essential limitation of the study since CNO could present with asymptomatic lesions and we had difficulties in the lesion count.

Our group has some features, which differ from several previously reported studies: high rate of spine involvement (34.6%) with pathological vertebral fractures in 14/52 (26.9), high rate of concomitant rheumatic diseases (67.3%) and low positivity of family history on rheumatic diseases (7.7%). In previous studies, the lower rate of spine involvement was 15–25%, and pathological fractures in 11% was detected [21, 22], the rate of concomitant rheumatic/immunopathological diseases ranged from 15 to 50% and higher rate (till 49%) of positive family history on rheumatic/immunopathological diseases [17, 21, 22]. The rate of arthritis in previous studies ranged from 15 to 39% [17, 21, 22] and in our study, it is the highest – 29/52 (55.8%). According to previous data, we can suppose that our group is more severe than the one found in previously published research, which had a significant influence over the treatment efficacy. Often patients with CNO have arthritis nearest to bone foci, but also some patients have arthritis not anatomically related to bone foci. Two patients had started as a typical CNO and further developed typical enthesitis-related arthritis. It was unclear about the pathogenesis of joint involvement in CNO patients. In some patients, arthritis is an evident immune-mediated disease with similar pathogenesis as CNO, which is especially evident for psoriatic arthritis, HLA B27 associated arthritis. On

Table 2 The dynamics of VAS parameters of CNO activity before and after the treatment depends on the treatment approach

Treatment	Before	After	Change, %	*p*
Patient's VAS				
NSAID	43.0 (31.5; 61.5)	31.0 (11.5; 45.0)	−14.2 (−74.0; 7.5)	0.055
Sulfasalazine	31.0 (26.0; 32.0)	27.0 (5.0; 32.0)	−23.1 (−29.0; 23.1)	0.89
Methotrexate	40.0 (30.0; 43.0)	19.2 (10.0; 38.0)	−50.0 (−70.5; −14.9)	0.038
Pamidronate	63.0 (35.0; 78.0)	10.0 (3.0; 27.0)	−83.3 (−94.6; −53.9)	0.0001
TNFα-inh	45.0 (34.0; 57.0)	12.2 (4.0; 23.0)	−73.6 (−88.5; −41.1)	0.0007
Pain VAS				
NSAID	38.5 (24.5; 60.0)	22.0 (8.0; 46.0)	−21.9(−80.0; 10.1)	0.01
Sulfasalazine	22.0 (22.0; 32.0)	24.0 (7.0; 30.0)	36.4 (−66.7; 36.4)	0.89
Methotrexate	32.0 (31.0; 37.0)	30.0 (0.0; 36.0)	−18.6 (−100.0; −11.8)	0.13
Pamidronate	52.0 (30.0; 89.0)	10.0 (0.0; 18.0)	−79.7 (−100.0; −53.8)	0.00016
TNFα-inh	42.0 (27.0; 66.0)	12.0 (3.0; 24.0)	−74.1 (−96.0; −36.3)	0.0015
MDVAS				
NSAID	41.0 (29.5; 63.0)	30.5 (11.0; 54.5)	−13.8 (−64.5; 14.1)	0.13
Sulfasalazine	26.0 (26.0; 35.0)	28.5 (8.0; 34.0)	30.8 (−34.2; 30.8)	0.89
Methotrexate	40.0 (27.0; 52.0)	24.0 (4.0; 42.0)	−56.4 (−85.1; −12.2)	0.09
Pamidronate	71.0 (34.0; 85.0)	14.0 (5.0; 27.0)	−74.7 (−91.2; −47.5)	0.0001
TNFα-inh	43.0 (35.0; 72.0)	10.0 (5.0; 31.0)	−82.1 (−93.1; −37.1)	0.0015

MDVAS physician's visual analog scale, *VAS* visual analog scale, *NSAID* non-steroid anti-inflammatory drugs, *TNFα-inh* tumor necrosis factor-α inhibitors. Data presented in the median and interquartile range

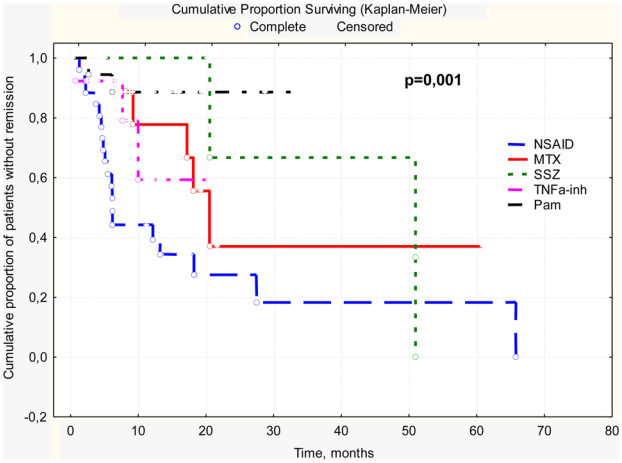

Fig. 2 Comparison of the ability of different treatment arms to achieve the remission in 52 children with CNO

the other side, in some patients with subchondral localization of bone inflammation sites, arthritis possibly may have a concomitant character, as a reaction of a close-located synovial membrane.

Non-steroid anti-inflammatory drugs are the first-line treatment in our study with improvement in 52.6% that is very similar to earlier published data [23]. Data of German CNO registry showed that 1-year naproxen monotherapy (15 mg/kg/day) leads to a decrease in the number of clinical and radiological foci up to 2.5–4 times and the markers of CNO activity [19]. In the USA multicentre study, 13% of patients achieved complete remission [6]. Indometacin used in doses 1.5–2.5 mg/kg/day was also active and may recommend for CNO treatment due to its ability to decrease osteosclerosis formation through the prostaglandins inhibition [24]. Complete remission on NSAID was noted in 50% and partial remission 52–77% in the two most recent studies [17, 21]. It is necessary to note that NSAIDs usually show higher efficacy in mild or moderate diseases; our rate of complete remission is relatively high because of applying discriminative approach and avoiding using prolonged NSAID treatment in the patients with spine destruction.

The peculiarity of our study is the absence of corticosteroids in the treatment of CNO. We usually avoid the usage of corticosteroids, because if any misdiagnosis occurred the corticosteroids can mask the proper disease. According to the literature, corticosteroids can rapidly decrease the bone inflammation, pain, and fever. The expected efficacy according to the study conducted by Borzutzky [6] was 95%. Complete remission in the Eurofever study was observed in 37% and partial remission in 54% of patients on corticosteroids [17].

Methotrexate is a drug approved for different pediatric rheumatic diseases and could be used in the cases when CNO associated with other rheumatic diseases, especially arthritis, psoriasis. As a rule, part of patients treated with MTX is not high and ranged from 12% in the Eurofever study to 30/70 (42.8%) in the USA and 17.3% in our trial [6, 17]. Complete remission achieved in 20% in the USA study,

22% in the Eurofever study and 44.4% in our study [6, 17]. In our cohort, the response to MTX is higher, but a better response to MTX had patients with concomitant arthritis.

Sulfasalazine is another DMARD, usually used in the combination of CNO with inflammatory bowel diseases, enthesitis-related arthritis, but rarely than other medication: only 9.6% in the Eurofever registry, 31.4% in the USA study and 13.5% in our study [6, 17]. The rate of complete remission ranged from 18% in the USA study to 38% in the Eurofever registry and 57.1% in our study [6, 17]. The highest rate of complete remission in our study could be explained by the small sample size of group patients, treated with sulfasalazine, selection of patients (association with other immunopathological diseases) or possible self-healing of the patients.

In our study, the most potent effect was observed in the pamidronate, despite the use of pamidronate in the most severe subgroup patients with spine involvement. Bisphosphonates (BP) were predominantly used for the treatment of different forms of osteoporosis and other bone metabolic diseases and prevention of bone destruction in the cases of metastatic bone involvement. The central mechanism is the inhibition of osteoclastic-mediated bone resorption [25]. It is also known as the anti-inflammatory effect of BP, but the precise mechanism is not precise. The efficacy of BP in the treatment of ankylosing spondylitis and CNO was earlier shown [20, 26, 27]. The treatment with PAM reduced pain, signs of inflammation and encouraged bone healing [24, 28]. In the Eurofever registry, pamidronate provided complete remission in 51%, in the recent study of Schnabel 2017; the rate of complete remission is 83%, similar to our results − 88.8% [17, 21]. It is noteworthy to state that, that single center studies provided more similar results, as compared to the multicenter ones. In our study, we used PAM predominantly in the cases with vertebral involvement to stop vertebral fractures and prevent spine deformity, and other orthopedic complications, and rarely in non-vertebral forms when NSAIDs, MTX and SSZ fail. This approach is similar to recent recommendations to use pamidronate or zoledronate in spine involvement [29].

Despite several benefits of bisphosphonates treatment, there are still some concerns, which do not allow its extensive use in children. First, bisphosphonates do not approve in childhood; second, bisphosphonates may accumulate in bones (sometimes more than 10 years) and may have a negative impact on bone metabolism and strength, especially when applied in high doses [30]. Also, some concerns refer to secondary hypocalcemia, secondary fragility, and a possibility to affect the fetal skeleton, if pregnancy occurs in young women who previously received bisphosphonates (long-term bone persistence, releasing from bone to circulation and transport through the placenta from mother to the fetus). The negative impact of bisphosphonates on bone development in the animal fetus were shown in several studies [31–33]. Two meta-analyses limit the data about people. The first one included 51 cases in 1950–2008 years, and the second one included 65 cases of applying bisphosphonates during the pregnancy in 1945–2014 years [34, 35]. Fortunately, in both papers, no cases of fetal skeletal involvement were documented, but it is necessary to use bisphosphonates in children with special care. Also, when using bisphosphonates followed by transient hypocalcemia and it can be required to check the blood calcium level after infusion and to make the correction. Chronic treatment with bisphosphonates required adequate calcium and vitamin D supplementation to prevent osteomalacia [36]. Another often side-effect of bisphosphonates is developing "flu-like" syndrome. In our study, all patients developed "flu-like" syndrome in the first 3-day cycle of pamidronate and usually required applying antipyretics and corticosteroid premedication. All further cycles of pamidronate did not accompany with "flu-like" syndrome and did not require use of any premedication.

The data about hyperproduction of TNF-α and association of CNO with some TNF-α-related diseases lay in the base for successful blockade of this cytokine with TNFα-inhibitors [36]. In previous studies, treatment with TNFα-inh the highest rate of remission was reported and ranged from 46% in the study of Borzutzky [6] to 67% in Schnabel [21]; in Eurofever registry 38/486 (7.8%) patients received different kinds of biologics, and approximate efficacy is near 50% [17]. Despite known information about efficacy and side effects of biologics in juvenile idiopathic arthritis, the experience of biologics in CNO is limited. According to the data from recent studies, the efficacy of TNFα-inhibitors is a little less than bisphosphonates. In our study, the efficacy of pamidronate and TNFα-inhibitors is quite similar. In the recent consensus treatment plans for CNO refractory to NSAIDs and with active spinal lesions, the plan B recommends using TNFα-inhibitors with or without methotrexate [29]. TNFα-inh was used as the last step of the CNO treatment, but now it may be a second treatment option equal with DMARDs and bisphosphonates [29]. TNFα-inh may combine with other medication such as NSAID, MTX, and SSZ that often used in real pediatric rheumatology practice in the management of patients with juvenile idiopathic arthritis (JIA). TNFα-inhibitors have a reliable and fast anti-inflammatory effect, ability to decrease the pain and they do not impact bone metabolism and do not persist in bone as bisphosphonates. TNFα-inhs officially approved in several rheumatic conditions such as juvenile idiopathic arthritis, psoriasis, psoriatic arthritis and IBD, which may associate with CNO, so one kind of treatment required to treat both conditions in CNO associated with someone. Some concerns with applying biologics are related to increased risk of infections, especially tuberculosis, risks of malignancy, which required further randomized trials.

Conclusion

The efficacy of treatment approaches for CNO depended on the severity of the disease. NSAID, methotrexate, and sulfasalazine were effective in forms without spine involvement, but pamidronate and TNF-a inhibitors were useful in vertebral forms of CNO. Pamidronate and TNFa inhibitors more extensively suppressed CNO activity. The randomized controlled trials for assessment of the efficacy and safety of these medications is mandatory to confirm these results.

Author contributions All authors were involved in drafting the article or revising it critically. All authors approved the final version to be submitted for publication. Dr. Kostik, Dr. Kopchak, and Dr. Mushkin had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: Kostik, Kopchak, Mushkin. Acquisition of data: Kostik, Kopchak, Chikova, Isupova. Analysis and interpretation of data: Kostik, Kopchak, Mushkin.

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Compliance with ethical standards

Informed consent Informed consent obtained from all parents/guardians of minors participating in the study according to the declaration of Helsinki.

Ethical approval The study was approved by the local Ethics Committee of St.-Petersburg State Pediatric University (protocol number 10/8 from 23.10.2017).

Conflict of interest The authors declare that they have no conflict of interests.

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