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TNF-inhibitors or bisphosphonates in chronic nonbacterial osteomyelitis? - Results of an international retrospective multicenter study

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A B S T R A C T

Chronic nonbacterial osteomyelitis (CNO) can cause significant morbidity, including bone pain and damage. In the absence of clinical trials, treatments include non-steroidal anti-inflammatory drugs, corticosteroids, TNF-inhibitors (TNFi) and/or bisphosphonates. In a retrospective chart review in the United Kingdom and Germany, we investigated response to TNFi and/or pamidronate. Ninety-one patients were included, receiving pamidronate ($n = 47$), TNFi ($n = 22$) or both sequentially (n = 22). Patients with fatigue [$p = 0.003$] and/or arthritis [$p = 0.002$] were more frequently treated with TNFi than pamidronate. Both therapies were associated with clinical remission at 6 months, and reduction of bone lesions on MRI at 12 months. While not reaching statistical significance, pamidronate resulted in faster resolution of MRI lesions. Fewer flares were observed with TNFi. Failure to respond to pamidronate was associated with female sex [$p = 0.027$], more lesions on MRI [$p = 0.01$] and higher CRP levels [$p = 0.03$]. Randomized clinical trials are needed to confirm observations and generate evidence.

1. Introduction

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder of unclear etiology. Clinical manifestations of CNO are variable, spanning a spectrum from monophasic episodes with a unifocal bone lesion at one end, to chronically active or recurrent disease affecting multiple bone sites at the other. Multifocal disease is also referred to as chronic recurrent multifocal osteomyelitis (CRMO),

though CNO is the increasingly accepted terminology for this condition [1,2]. Especially at early disease stages, clinical presentations can be mild and non-specific. Symptoms include bone pain, local swelling and/ or warmth, and sometimes signs of systemic inflammation on laboratory tests, such as (usually mildly) elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Additional symptoms, such as fever, skin inflammation (acne, psoriasis, palmoplantar pustulosis, etc.), inflammatory bowel disease and arthritis can be present in some

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patients [1,2].

In the absence of widely agreed criteria, diagnosis can be challenging and relies on the exclusion of differentials, including infection and malignancy [1,2]. While three sets of criteria have been proposed and can aid in diagnosis, none have been independently validated [3–5].

Although CNO is considered a rare disease [6], incidence and prevalence are likely to be underestimated [7]. Though initial studies from Europe suggested a geographic and ethnic over-representation of Northern and Central Europe, all continents and ethnicities are affected [8].

The exact molecular pathophysiology of CNO is unknown and likely multifactorial [9–13]. The activation of innate immune cells resulting in an imbalance between pro- (IL-6, TNF-α) and anti-inflammatory (IL-10) signals play a role [14–19]. A hallmark of monocytes from CNO patients is enhanced NLRP3 inflammasome activation and subsequently increased IL-1β release [14,18]. The underlying molecular mechanisms of this appear to be multiple and may vary between individuals affected.

In the absence of published evidence from prospective, randomized trials, treatment of CNO is largely empiric, based on personal experience, case reports and retrospective analysis of patient cohorts [8,20–23]. The Childhood Arthritis & Rheumatology Research Alliance (CARRA) recently proposed consensus treatment plans to harmonize clinical care of patients and prospectively collect treatment response data [24]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used as first-line treatment in patients without vertebral involvement, and their efficacy has been suggested by the only available prospective study in CNO [25]. However, more than 50% of CNO patients treated with NSAIDs flare within the first 2 years [23]. Corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs; methotrexate, sulfasalazine), biopharmaceutical agents (usually TNF inhibitors; TNFi) and/or bisphosphonates (usually pamidronate) have been reported as second-line treatment options [11,17,26–30]. Though case collections reported efficacy of all aforementioned treatment options, patient numbers were small, and direct comparisons have been challenging.

This retrospective international multicenter study evaluated clinical and radiological treatment response to TNFi and the bisphosphonate pamidronate.

2. Methods

2.1. Study population

Response to treatment with pamidronate and/or TNFi was evaluated in children and adolescents (<18 years) with CNO. Data were retrospectively collected from patient medical records in tertiary centers with pediatric rheumatology departments, or district general hospitals supported by a tertiary pediatric rheumatology service (January 1st, 2002 to December 31st, 2020). The study was approved by the ethics committee of Technische Universität Dresden, Germany (EK 369102014), and the Alder Hey Internal Review Board, Liverpool, UK (National audit). A total of 126 patients were reviewed from the following referral centers: [1] Royal Hospital for Children, Glasgow, UK, [2] Royal Hospital for Children and Young People, Edinburgh, UK, [3] University Hospital Crosshouse, Kilmarnock, UK, [4] Ninewells Hospital, Dundee, UK, [5] Raigmore Hospital, Inverness, UK, [6] University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK, [7] Klinikum Stuttgart, Stuttgart, Germany, [8] Universitätsklinikum Carl Gustav Carus, Dresden, Germany.

2.2. Case definition

In the absence of evaluated diagnostic criteria, CNO was defined using a combination of the clinical score from Jansson et al. [4] and the "Bristol criteria" for CNO [5], and (in some cases) bone biopsies. Diagnosis was confirmed by expert consultant pediatric rheumatologists and radiologists.

2.3. Collection of demographics and clinical information

The following data were collected: i) demographic characteristics (sex, age at onset, age at diagnosis, delay in diagnosis, number of flares during follow-up, follow-up time,), ii) clinical findings (number of initial painful sites, local inflammatory signs, fever, weight loss, fatigue, lymphadenopathy, arthritis, inflammatory bowel disease, cutaneous manifestation including psoriasis, palmoplantar pustulosis, acne), and iii) diagnostic tools used (complete blood cell count (CBC), CRP, ESR, microbiological status and bone biopsy at diagnosis).

2.4. Assessment of clinical disease activity

No standardized and prospectively evaluated outcome measures are available for CNO. Thus, clinical disease activity was assessed on the basis of i) patient- or parent reported symptoms, including musculoskeletal pain, swelling, warmth, limited range of motion, ii) physician reported signs of inflammation including local swelling, heat, redness and limited range of movement, and iii) systemic inflammatory markers (CBC and cell differentiation, CRP, ESR). Clinical outcomes were assessed at 0, 3, 6, 12 and 24 months, and at last visit.

Partial clinical remission was defined as over-all patient and physician reported clinical improvement and normalization of inflammatory parameters. *Complete clinical remission* was defined as the absence of subjective and objective signs of inflammation. *Flare* was defined as new onset of clinical symptoms after temporary remission. *Inefficacy* was defined by the absence of improvement or disease progression resulting in treatment escalation.

2.5. Imaging and radiological disease activity assessment

At the time of diagnosis, the majority of patients (*n* = 76) received whole-body imaging (whole-body MRI; WB-MRI, or bone scintigraphy); the remainder underwent local MRI of the site of pain (*n* = 15). Radiologically active bone lesions were defined as abnormal by pathologically increased signal intensity in bone marrow on turbo inversion recovery magnitude (TIRM) of short tau inversion recovery (STIR) MRI sequences. *Partial radiological remission* was defined as overall reduction of bone lesions; *full radiological remission* was defined as the absence of CNO-associated bone lesions on whole-body imaging. *Flare* was defined as new bone lesion(s) on whole-body imaging after temporary remission. *Inefficacy* was defined as continuous evidence of bone lesions or mixed response on imaging resulting in treatment escalation.

Data on the total number of bone lesions on WB-MRI before, and 6 and 12 months after treatment initiation with pamidronate and/or TNF-inhibitors were only available from Alder Hey Children's NHS Foundation Trust (Liverpool), Klinikum Stuttgart (Stuttgart), and Universitätsklinikum Carl Gustav Carus (Dresden).

2.6. Statistical analysis

Statistical analysis was performed using Stata 12.0 software (StataCorp, Lakeway Dr. College Station, USA). Kolmogorov-Smirnov tests and graphical presentation with histograms were applied to test normal distribution of data. Categorical variables were reported as absolute numbers and proportions (percent); and continuous variables as means ± standard deviation (SD) or median with ranges, depending on the presence of normal distribution. Parametric Student's *t*-tests and the two-tailed, non-parametric Wilcoxon rank-sum (Mann-Whitney) tests were used to test for differences between two groups comparing continuous data. Categorical variables were tested for statistical significance, using two-tailed chi-square. For paired non-parametric data, Wilcoxon signed-rank tests were used to determine significant differences between the number of bone lesions on imaging studies before and after therapy. Kaplan-Meier survival curves indicate the probability of therapy failure and therapeutical switch between pamidronate and

TNFi. For all analyses, differences between groups were considered statistically significant by two-sided *p*-values of <0.05.

3. Results

3.1. Demographic and clinical characteristics

A total of 126 patients were identified, 35 of whom were excluded for the following reasons: no treatment with pamidronate and/or TNFi (*n* = 19); uncertain diagnosis (*n* = 6), insufficient data for treatment evaluation (n = 6); parallel treatment with pamidronate and TNFi (*n* = 4). A total of 91 patients fulfilled the study criteria and were included in the data analysis (Fig. 1). Of these, 47 received singular therapy with pamidronate, 22 received TNFi, and 22 patients were treated sequentially with both therapies: 19 patients were first treated with pamidronate and switched to TNFi, and 3 initially received TNFi followed by pamidronate (Fig. 1B).

The demographic and clinical characteristics of patients are summarized in Table 1. Previously, 16 patients of the cohort were included in an analysis of treatment response and long-term outcomes in CNO [23]. In the present study cohort, median age at disease onset was 9.7 ± 2.9 years with a mild female predominance (1.6:1). CNO patients were followed for a mean of 4.6 ± 3.8 years and developed 1.8 ± 1.6 flares during follow-up. Fifty-one percent (*n* = 46) showed local inflammatory signs, including swelling, warmth or redness; 11% (*n* = 10) exhibited fevers of >38.0 °C. A total of 91 patients in this cohort reported 188 painful sites (mean: 2.1 ± 1.5 locations per patient), most commonly affecting lower extremities (86/188; 46%), pelvis (40/188; 21%), spine (30/188; 16%) and clavicle (23/188; 12%). 50 patients presented CNO-related extra-osseous symptoms, including arthritis (28/91; 31%), inflammatory bowel disease (8/91; 9%), lymphadenopathy (4/91; 4%), and dermatological manifestations (20/91; 22%) including psoriasis (11/91; 12%), acne fulminans (3/91; 3%) and palmoplantar pustulosis (2/91; 2%). Thirty-one percent (*n* = 28) of the CNO patients developed arthritis, 6 of these distant from bone lesions (6/28, 21%) and 22 children adjacent to bone lesions (22/28, 79%). In most patients, arthritis affected the axial skeleton, namely sacroiliac joints (11/28, 39%), hips (5/28, 18%) and ankles (6/28, 21%). In nearly half of patients with arthritis (13/28; 46%) CNO was diagnosed first, and arthritis developed later during the disease course.

Demographic composition of treatment groups (*n* = 22 TNFi, *n* = 47 pamidronate) was comparable. Clinical characteristics, however, differed with fewer clinical signs of local inflammation in CNO patients treated with TNFi [10/22(45%) vs 29/47(62%), *p* = 0.049], but more comorbidities, including arthritis [11/22(50%) vs 7/47(17%), *p* = 0.002] and inflammatory bowel disease (IBD) [4/22(18%) vs 2/47(4%), *p* = 0.05] (Table 1).

3.2. Laboratory findings

At diagnosis, CBC and cell differentiation were available for 63 patients and delivered normal results in 65%. Mild thrombocytosis (482–615 GPt/l) was present in 11% (7/63), anemia (6.5–8.0 g/dl) in 8% (5/63), and monocytosis (0.85–1.98/mm^3) in 16% (10/63). Inflammatory markers were available for 87 patients, 57% (50/87) of whom presented with elevated CRP (mean: 25 ± 48 mg/l) and/or ESR (mean: 33 ± 31 mm/h). Of 13 patients with CRP levels >50 mg/l, 38% (5/13) experienced comorbidities, including psoriasis (5/13, 38%), arthritis (23%; 3/13), or Crohn's disease 8% (1/13). Clinical chemistry parameters collected included lactate dehydrogenase, liver enzymes, alkaline phosphatase, calcium, phosphate, IgG, IgA and IgM, which were not significantly altered across this CNO patient cohort.

HLA-B27 was determined in 40 patients, 8 (20%) of whom tested positive. Seven of the 8 (87.5%) HLA-B27 positive patients showed axial involvement. Involvement of the sacroiliac joint was significantly more frequently detected in the HLA-B27 positive patients than in the HLA-B27 negative tested children [6/8(75%) vs 8/32(25%), *p* = 0.008], while spinal lesions were more common in HLA-B27 negative patients, without reaching statistical significance [1/8(12%) vs 10/32(31%), *p* = 0.288]. Seven of the 8 HLA-B27 positive CNO patients were treated with TNFi (as initial second-line treatment following treatment with NSAIDs (*N* = 5) or after failure to respond to pamidronate (*N* = 2)). In those patients in whom HLA-B27 status was known, those treated with TNFi (*n* = 22 tested) were significantly more often HLA-B27 positive compared to the bisphosphonate group (*n* = 32 tested) [7/22(32%) vs 3/32(9%), *p* = 0.039].

Bone biopsies were performed in 60% of CNO patients in this cohort (55/91), predominantly showing lymphoplasmacytic infiltrates (45%; 25/55), fibrosis (27%; 15/55), and signs of bone remodeling (16%; 9/55).

3.3. Whole-body imaging

The majority of patients underwent whole-body imaging (76/91; 84%) at the time of diagnosis (WB-MRI: 60%, bone scintigraphy: 16%). At diagnosis, the mean number of radiologically active bone lesions was
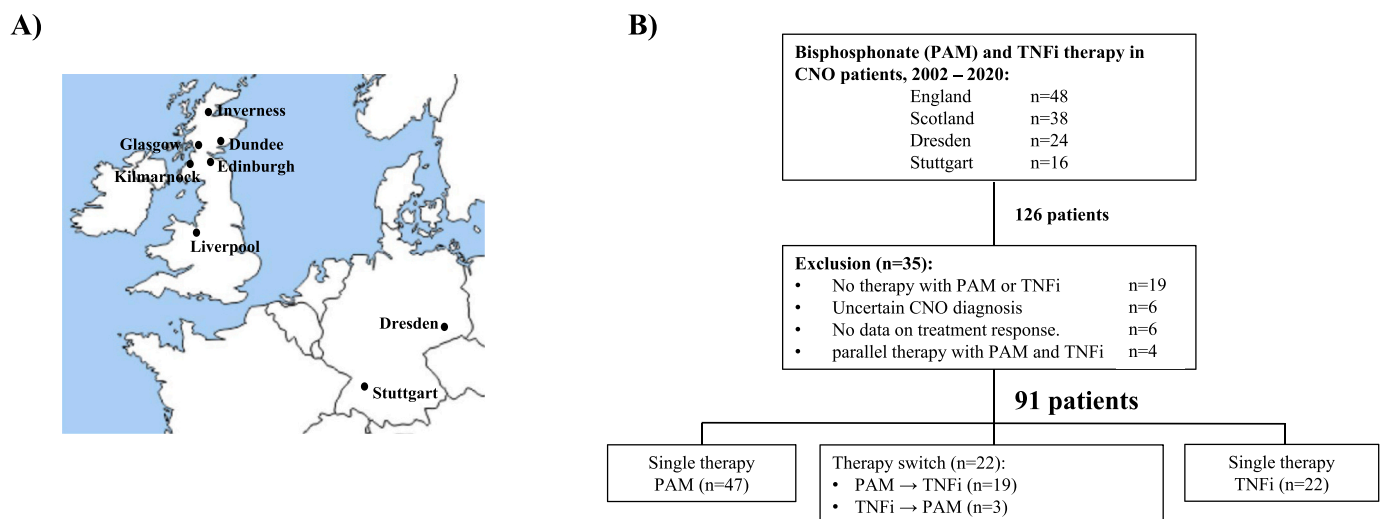
A)

B)

Fig. 1. Centers and patients recruited. A) Participating centers in the United Kingdom (86 patients) and Germany (40 patients). B) Flow chart showing all included children with chronic non-bacterial osteomyelitis under therapy with TNF-inhibitors or bisphosphonates. PAM: pamidronate, TNFi: TNF-inhibitor.

Table 1

Baseline characteristics. 91 children chronic non-bacterial osteomyelitis CNO were either treated with TNF-inhibitors (n = 22), Bisphosphonates (n = 47), or both (n = 22).

	All CNO patients (n = 91)	TNF-Inhibitors (n = 22)	Bisphosphanates (n = 47)	p-value
Demographic characteristics				
Number Males (%)	35 (38)	10 (45)	21 (45)	NS
Age at symptom onset, years (mean ± SD)	9.7 ± 2.9	9.9 ± 3.4	9.5 ± 2.9	NS
Age at diagnosis, years (mean ± SD)	10.8 ± 2.7	10.5 ± 3.1	10.8 ± 2.7	NS
Delay in diagnosis, months (mean ± SD)	14.4 ± 18.8	8.9 ± 13.5	17.1 ± 21.9	NS
No. of flares during follow up (mean ± SD)	1.8 ± 1.6	1.5 ± 1.1	1.6 ± 1.5	NS
Follow up, years (mean ± SD)	4.6 ± 3.8	3.2 ± 2.7	3.7 ± 3.0	NS
No. of initial painful sites (mean ± SD)	2.1 ± 1.55	2.5 ± 1.7	1.8 ± 1.1	NS
Clinical characteristics				
Local inflammatory signs[a] (%)	46 (51)	10 (45)	29 (62)	**0.049**
Fever[b] (%)	10 (11)	3 (14)	5 (11)	NS
Fatigue (%)	9 (10)	6 (27)	0 (0)	**0.003**
Lymphadenopathy (%)	4 (4)	1 (5)	2 (4)	NS
Arthritis (%)	28 (31)	11 (50)	7 (17)	**0.002**
Inflammatory bowel disease (%)	8 (9)	4 (18)	2 (4)	NS
Skin involvement[c] (%)	20 (22)	3 (14)	9 (19)	NS
Radiological characteristics in MRI				
No. of radiological lesions, initial (mean ± SD)	4.6 ± 4.3	7.2 ± 5.1	2.9 ± 2.5	**0.000**
No. of radiological lesions, total (mean ± SD)	7.2 ± 5.0	9.8 ± 5.9	4.8 ± 3.2	**0.000**
Unifocal manifestation, initial (%)	13 (14)	2 (1)	11 (23)	NS
Whole body imaging (%)	76 (84)	21 (95)	35 (75)	**0.038**
-WB-MRI	60 (66)	21 (95)	23 (49)	**0.000**
- scintigraphy	16 (18)	0 (0)	12 (26)	**0.009**
No. of patients with lesions in long bones	52 (57)	18 (73)	22 (51)	NS
Epiphysis plate involvement (%)	21 (23)	8 (36)	9 (19)	NS
Spinal involvement (%)	26 (29)	6 (27)	11 (23)	NS
Complication[d] (%)	22 (24)	3 (14)	14 (30)	NS
- vertebral body fracture	8 (9)	0 (0)	6 (13)	NS
- hyperostosis	11 (12)	2 (9)	8 (17)	NS
Laboratory markers				
Hemoglobin (9.5–16 g/dl)	11.9 ± 1.9	11.8 ± 2.1	11.9 ± 1.9	NS
Leukocytes (GPt/l)	8.4 ± 2.7	8.9 ± 2.7	8.2 ± 2.8	NS
Thrombocytes (GPt/l)	363 ± 90	394 ± 60	354 ± 107	NS
CRP (> 5 mg/l)	24.6 ± 48.3	17.8 ± 26.8	18.3 ± 33.9	NS
ESR (> 15 mm/1st h)	33 ± 31	42 ± 25	29 ± 29	NS
Biopsy				
Number of Bone biopsy (%)	55 (60)	3 (14)	24 (51)	**0.003**

CRP = C reactive protein; ESR = erythrocyte sedimentation rate; NS = not significant.

[a] Presence of swelling, redness and/or heat.

[b] Temperature > 38.0 °C/100.4 °F.

[c] Psoriasis, palmoplantar pustulosis, acne fulminans.

[d] Hyperostosis, vertebral fracture, gibbus, compression of blood vessels, or nerve affection.

4.6 ± 4.3 per patient, which increased to 6.5 ± 5.7 lesion per patient during follow-up across the entire CNO collective. A total of 513 bone lesions were detected. Patients treated with TNFi exhibited a higher number of lesions at treatment initiation when compared to the pamidronate treatment group [9.8 ± 5.9 vs 4.8 ± 3.2, $p < 0.001$], and more frequently received WB-MRI than bone scintigraphy [21/22(95%) vs 23/47(49%), p < 0.001].

A relative minority of 14% (13/91) experienced unifocal CNO, the remaining 86% were classified as multifocal CNO (CRMO). A total of 29% (26/91) exhibited bone lesions in the clavicle (bilateral in 6 patients), and 8% exhibited mandibular lesions (7/91). Most patients presented with bone lesions affecting lower extremities (65/91; 71%) with growth plate (epiphyseal) involvement in 23% (21/91). Metaphyses (54%) and epiphyses (32%) of long bones were affected in the majority of patients, while active bone lesions in diaphyses (14%) were less commonly seen. Twenty-nine patients (32%) had spinal involvement with a total of 61 active vertebral lesions, predominantly affecting the thoracic spine (66%; 40/61), followed by the lumbar spine (25%; 15/61). This translates to cervical involvement in 2/29 (7%) patients, thoracic in 20/29 (69%) and lumbar involvement in 11/29 patients (38%). In seven children (24%; 7/29) spinal lesions were clinically asymptomatic. Eight patients (8/29; 29%) developed vertebral body fractures, 6 of whom were treated with singular pamidronate, while 2 were sequentially treated with pamidronate followed by TNFi.

Additional disease-associated sequelae included hyperostosis (11/91; 12%) most commonly affecting the clavicle and mandible, followed by gibbus formation (2/91, 2%), pathological fracture of the tibia (1/91, 1%), and subclavian vein compression by para-osseous inflammation (1/91, 1%).

3.4. Treatment

At the time of diagnosis 30% (27/91) of patients received treatment with antimicrobial agents. Eighty-two patients initially received NSAIDs (90%), the remaining patients either had concomitant inflammatory bowel disease ($N = 8$) or intolerance to NSAIDs ($N = 1$). The mean treatment duration with NSAIDs was 24.5 ± 25.8 months.

During the disease course, DMARDs were prescribed in 31 patients (31/91, 34%; methotrexate: 23/31; 74%, sulfasalazine: 8/31; 26%), 9 of whom (29%) were treated concomitantly with TNFi due to comorbidities (n = 6 arthritis, n = 3 IBD).

Corticosteroid use varied between centers and - as used short term - was not included in the analysis.

A total of 44 CNO patients were treated with **TNFi** [$n = 26$ (59%) Germany; $n = 18$ (41%) UK], including etanercept ($n = 24$), adalimumab ($n = 17$) and infliximab ($n = 10$). TNFi were administered at standard doses commonly used in the treatment of Juvenile Idiopathic Arthritis [31,32]. Within the group of patients receiving TNFi, treatment choices varied slightly between countries. Of the 26 patients from Germany most patients received etanercept [$N = 22(85\%)$] or adalimumab [$N = 4(15\%)$], and no infliximab was used. Of the 18 patients treated with TNFi in the UK, most received adalimumab [$N = 9(50\%$], p = 0.01], followed by infliximab [$N = 7(39\%)$, p = 0.001] and etanercept [N = 2 (11%), $p < 0.001$].

A total of 22 patients received TNFi after or together with NSAIDs as first and singular second-line treatment without further escalation; 19 patients (28%) received TNFi after failure to respond to bisphosphonates (Fig. 2). Notably, 3 patients (7%) received pamidronate after inefficacy
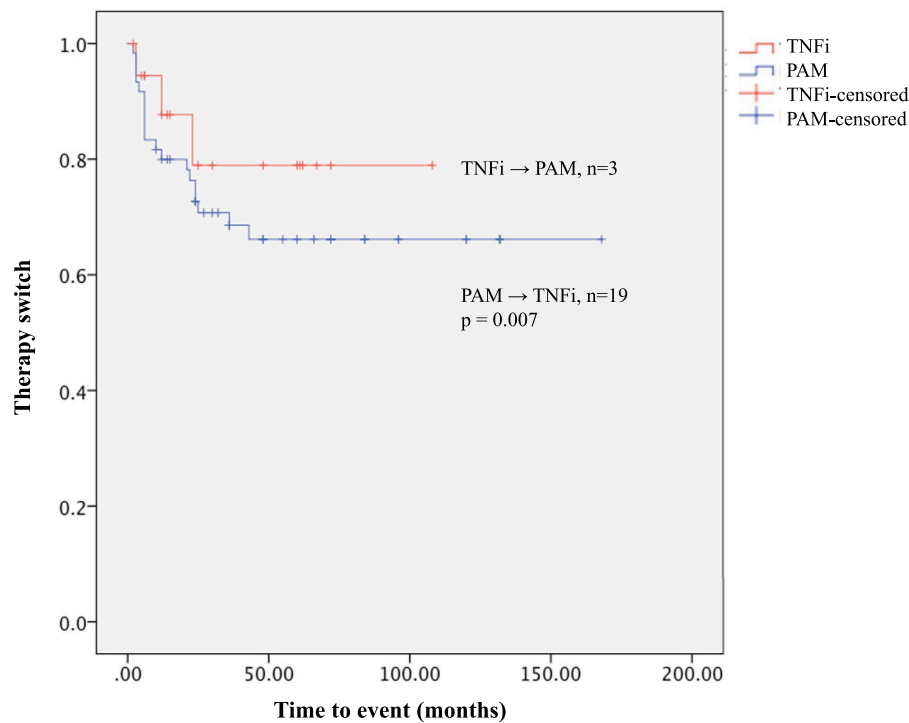
Fig. 2. Dynamics of treatment failure. Kaplan Meier analysis of CNO patients with therapy switch between pamidronate (PAM) and TNF-inhibitors (TNFi).

of TNFi. Thus, significantly more children with CNO experienced treatment failure with pamidronate when compared to TNFi during the observation period [$p = 0.007$] (Fig. 2). In 6/44 children (14%) receiving TNFi, a second biological DMARD ($n = 3$ adalimumab, $n = 2$ infliximab, $n = 1$ tocilizumab) was subsequently prescribed; one patient received a third TNFi.

Side-effects of TNFi were recorded in 4 patients. One girl experienced abdominal pain (etanercept), another developed leukocytoclastic vasculitis of the skin (adalimumab), and two patients developed psoriasis while on infliximab. Side-effects resulted in discontinuation of treatment in all cases.

Sixty-nine patients were treated with **bisphosphonates** (pamidronate in all cases), 47 of whom received it as singular second-line treatment. Three patients had previously failed TNFi treatment and were switched to pamidronate. Pamidronate was applied in patients from Liverpool, Stuttgart and Dresden (47 patients) with 1 mg/kg/day pamidronate on 3 consecutive days (first dose in the first cycle 0.5 mg/kg/day; max. 60 mg/day), which was repeated after 3 and 6 months. Few patients were treated with a 4th cycle, depending on disease activity. Patients from Scotland ($n = 22$) received pamidronate for 3 consecutive days (1 mg/kg/day, max. 90 mg/day) for induction treatment; relapses were treated ad hoc, with the vast majority of patients receiving pamidronate again for 3 consecutive days. However, there were some variations from this, such as single days, monthly doses, or repeat 3 consecutive days at 3-monthly intervals that affected a minority of cases. Sub-group comparisons were not performed because of the relatively small sample size and the retrospective nature of this study. Overall, pamidronate was tolerated, with only mild transient side-effects recorded, typically during the first treatment cycle. Side-effects included influenza-like symptoms, headaches and asymptomatic hypocalcemia that did not result in discontinuation of treatment. Notably, none of the patients treated with pamidronate developed osteonecrosis of the mandible.

3.5. Clinical and radiological characteristics and response to treatment

In CNO patients who received **TNFi**, active lesions on imaging (37/44, 84%), multifocality of bone lesions (43/44, 98%) and elevated inflammatory markers (24/44, 55%) were frequently documented before treatment initiation/escalation. CNO patients treated with TNFi overall showed good clinical response. Three months after therapy initiation, clinical response data were available for 43 of 44 patients. At 3 months, 70% showed partial (30/43), and 21% complete remission (9/43) (Fig. 3A, left). At 6 and 12 months, comparable rates of clinical remission were recorded (6 months: 35/39, 90%; 12 months: 31/34, 91%) with a higher proportion of patients reaching complete clinical remission (6 months: 20/39, 51%; 12 months: 22/34, 65%). During the first year of follow-up, TNFi therapy was ineffective in 14% (6/43) patients, and disease flares occurred in 12% (5/43). Three of these patients subsequently received treatment with pamidronate and were included in the bisphosphonate group (3/43; 6.9%).

Within the first year after treatment initiation, one or more follow-up MRIs were available for 91% (40/44) of patients treated with TNFi. After 6 months of TNFi treatment, 27 WB-MRIs were available, showing complete or partial remission in 85% (23/27) with a stable condition after 12 months (23/27, 85%) (Fig. 3A, right). New bone lesions were present in 22% (6/27) within the first year of treatment. The total number of active bone lesions per patient on WB-MRI reduced significantly after 12 months of TNFi respectively pamidronate treatment [*TNFi:* Median 7 [2–26] to 2 (0–8) bone lesions per patient, $p = 0.004$; Pamidronate: Median 5 (0–23) to 1 (0–12) bone lesions per patient, $p = 0.007$] (Fig. 4A).

When compared to patients receiving TNFi, CNO patients who received **bisphosphonates** (pamidronate), at initiation, more frequently exhibited local signs of inflammation [29(62%) vs 10(45%), $p = 0.049$] and vertebral fractures [6(13%) vs 0(0%), $p = 0.079$]. After 3 months, 21/65 (32%) individuals reached partial and 35/65 complete remission (54%). After 6 and 12 months, full clinical remission was achieved in 33/61 (54%) and 35/51 (69%). Notably, 24 CNO patients receiving pamidronate failed to reach clinical remission within the first year of treatment (24/65, 37%). Ineffectiveness was recorded in 11 (17%), disease flares or worsening were present in 13 (20%) patients (Fig. 3B, left).

Whole-body imaging throughout the first 12 months after treatment initiation was available in 46/69 (67%) patients. Improvement was seen
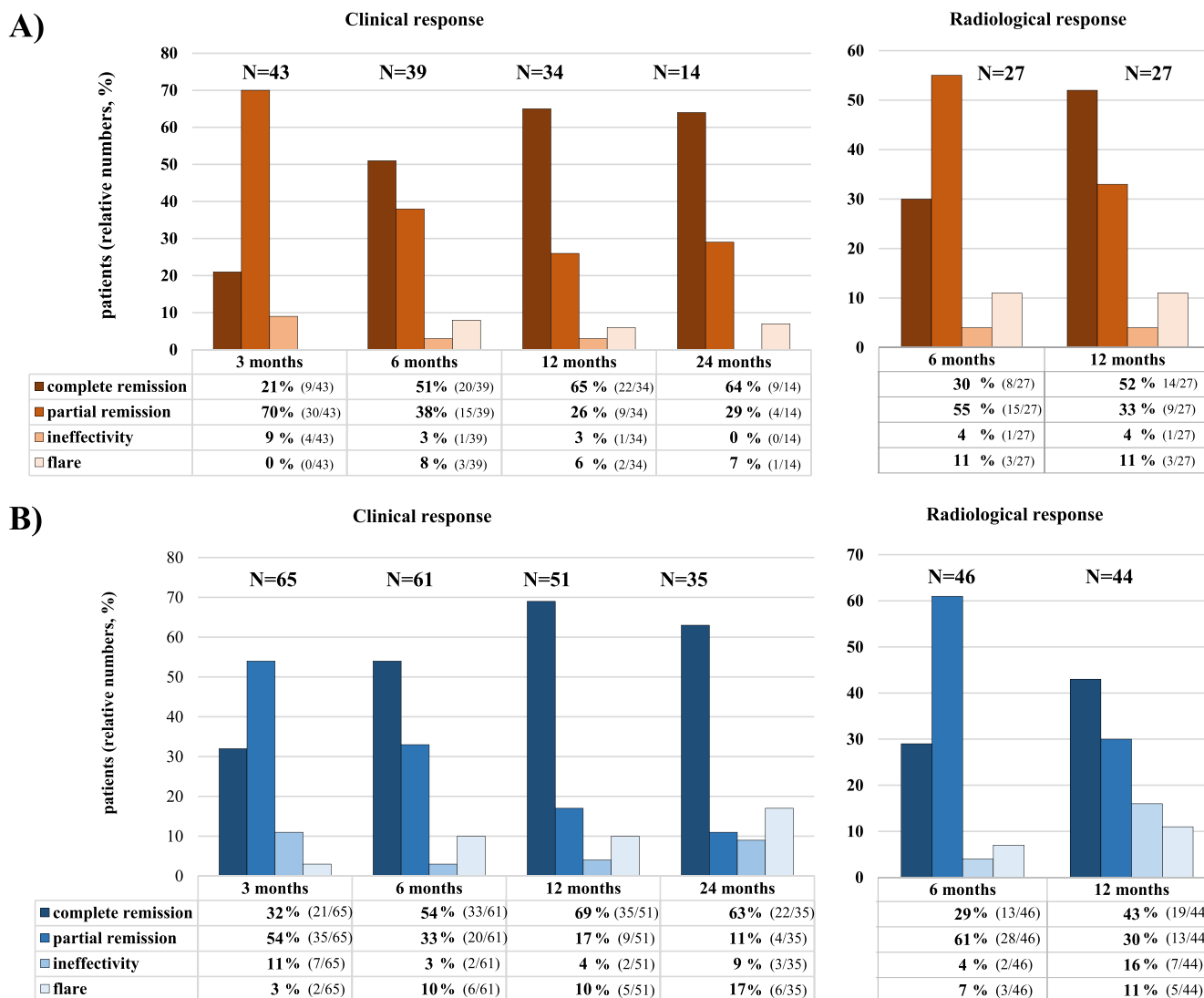
A)

Clinical response

	3 months (N=43)	6 months (N=39)	12 months (N=34)	24 months (N=14)
complete remission	21% (9/43)	51% (20/39)	65 % (22/34)	64 % (9/14)
partial remission	70% (30/43)	38% (15/39)	26 % (9/34)	29 % (4/14)
ineffectivity	9 % (4/43)	3 % (1/39)	3 % (1/34)	0 % (0/14)
flare	0 % (0/43)	8 % (3/39)	6 % (2/34)	7 % (1/14)

Radiological response

	6 months (N=27)	12 months (N=27)
complete remission	30 % (8/27)	52 % (14/27)
partial remission	55 % (15/27)	33 % (9/27)
ineffectivity	4 % (1/27)	4 % (1/27)
flare	11 % (3/27)	11 % (3/27)

B)

Clinical response

	3 months (N=65)	6 months (N=61)	12 months (N=51)	24 months (N=35)
complete remission	32% (21/65)	54% (33/61)	69 % (35/51)	63% (22/35)
partial remission	54% (35/65)	33% (20/61)	17 % (9/51)	11% (4/35)
ineffectivity	11% (7/65)	3 % (2/61)	4 % (2/51)	9 % (3/35)
flare	3 % (2/65)	10 % (6/61)	10 % (5/51)	17% (6/35)

Radiological response

	6 months (N=46)	12 months (N=44)
complete remission	29% (13/46)	43 % (19/44)
partial remission	61% (28/46)	30 % (13/44)
ineffectivity	4 % (2/46)	16 % (7/44)
flare	7 % (3/46)	11 % (5/44)

Fig. 3. Clinical and radiological response to treatment. A) TNF-inhibitors, B) bisphosphonates.

in 41/46 (89%) after 6 months and 32/44 (73%) after 12 months (Fig. 3B, right). Failure to respond or disease flares on imaging were observed in 17/46 (37%) patients during the first year. Another 7 patients relapsed after 24–43 months. Notably, the median number of bone lesions per patient on initial whole-body imaging before treatment initiation was higher in the TNFi group when compared to patients treated with pamidronate [5(0–23) vs 7(0–26)]. Considering reduction of the number of bone lesions on MRI, 12 months after treatment initiation, a higher percentage total improvement was achieved receiving TNFi [100% to 14%, $p = 0.001$] when compared to pamidronate [100% to 40%, $p = 0.011$] (Fig. 4B).

3.6. Time to treatment response

Considering time to improvement, patients treated with pamidronate achieved complete clinical [median: 3 [3–12] vs 6 [3–24] months, $p = 0.254$] and radiological remission [median 6 [6–12] vs 12 [6–12] months, $p = 0.160$] slightly earlier when compared to patients treated with TNFi. However, differences failed to reach statistical significance.

After 3 months, slightly more patients treated with pamidronate were free of pain and achieved complete clinical remission when compared to patients receiving TNFi [21/65 (32%) vs 9/43(21%), $p =$

0.196]. Differences, however, did not reach statistical significance. After 6 months, clinical treatment response was comparable with complete remission following pamidronate in 54% (33/61) and TNFi in 51% (20/39) (Fig. 3). Furthermore, median numbers of radiological bone lesions per patient decreased more rapidly in response to pamidronate therapy when compared to TNFi. At 6 months, a reduction from median of 5 to 1 (0–12) was seen in patients treated with pamidronate that compared to median 7 to 5 lesions in patients receiving TNFi (but did not reach significance). No differences were noted at 12 months [1(0–12) vs 2(0–8)] (Fig. 4A).

Considering the chronic nature of CNO, patients treated with TNFi experienced fewer flares when compared to individuals receiving pamidronate by 12 [2/34(6%) vs 5/51(10%), $p = 0.519$] and 24 months [1/14(7%) vs. 6/35(17%), $p = 0.366$] (Fig. 3, left).

3.7. Sub-analysis of treatment responder versus non-responder

As a result of ongoing inflammatory activity or flares, after a median of 10 months (2–43 months), 19 patients initially receiving pamidronate were prescribed TNFi. In 10 of these children (52%) clinical improvement was achieved with TNFi treatment after 6 months, persisting in 8 patients after 12 months (Fig. 4).
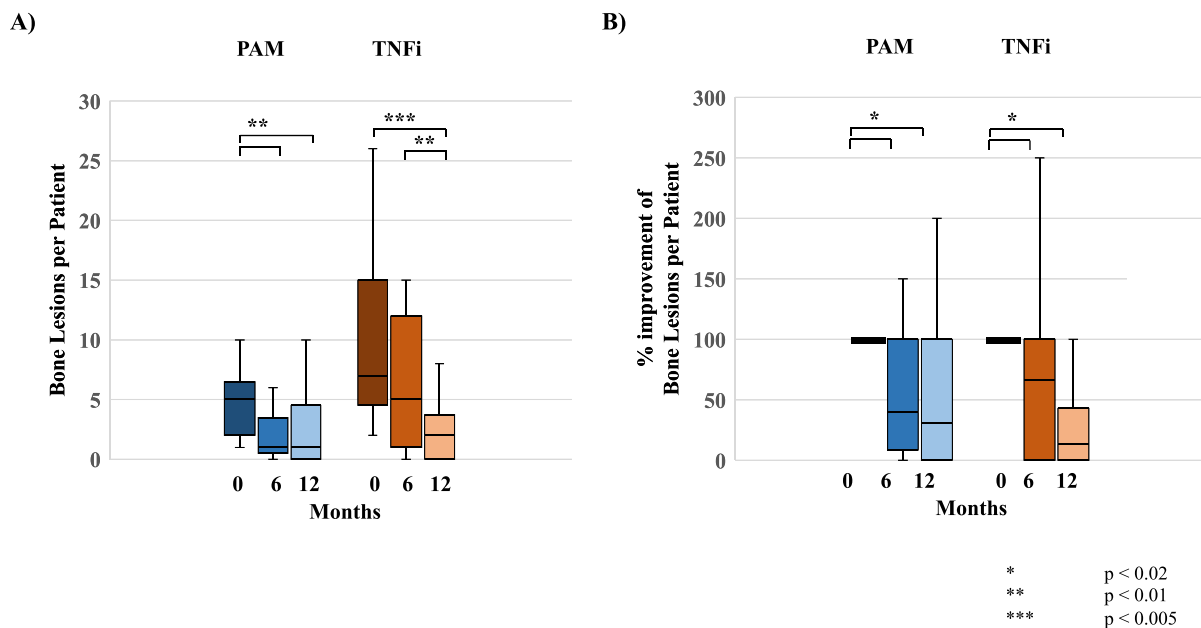
Fig. 4. Bone lesions on whole-body magnetic resonance imaging. A) absolute numbers, median and range, B) percent improvement on whole-body imaging at 6 and 12 months after therapy with pamidronate (PAM) or TNF-inhibitors (TNFi). At treatment initiation, bone lesions were defined as 100% to show the percentage decrease in the number of bone lesions per patient.

The 19 patients who did not respond to pamidronate differed significantly from 47 CNO patients who responded in sex, number of radiological lesions, and elevated blood inflammatory markers (Table 2). Patients who failed to respond to pamidronate were predominately female [16(84%) vs 26(55%), $p = 0.02$] showed increased numbers of radiological lesions [at diagnosis: 5.7 ± 5.6 vs 2.9 ± 2.5, p = 0.02, maximum: 8.8 ± 7.3 vs 4.8 ± 3.2, p = 0.01] on whole-body imaging, and exhibited higher CRP levels [51.0 ± 83.3 mg/l vs 18.3 ± 33.9 mg/l, $p = 0.03$].

Notably, five patients who did not respond to pamidronate did not receive third-line treatment during the observation period. A small group of 3 patients showed no clinical and radiological long-term therapy response on either bisphosphonates or TNF-inhibitors as second line therapy. All of these 3 patients were female with a mean age of 9.8 ± 2.3 years. Two patients were treated with pamidronate followed by etanercept, the third with pamidronate followed by infliximab. The last patient developed severe form of psoriasis after initiation of TNFi which resulted in discontinuation of treatment. The patients showed 7.3 ± 5.77 bone lesions in whole-body MRI with involvement of the lower extremity (femur, tibia, fibula and foot bones) in all cases, vertebral lesions in 2, and sternal lesion in 1 patient.

4. Discussion

In the absence of clinical trials, treatment of CNO varies between centers and is largely based on personal experience, expert opinion, case reports and small case series. To harmonize diagnostic and therapeutic approaches and collect treatment response data prospectively, consensus treatment plans (CTPs) have recently been proposed in an international effort lead by CARRA [24]. Treatment plans are based on the current "standard of care" and have been agreed in consensus meetings following nominal group techniques. However, in the absence of data comparing responses to treatment options, CNO patients can be assigned freely to alternative CTPs by clinicians.

Currently, based on clinical experience and the only available prospective observational treatment study, NSAIDs are considered first-line treatment in patients without vertebral involvement [25]. While NSAIDs provide timely improvement of pain and control bone inflammation in some CNO patients, more than 60% of patients develop flares within 5

years [23]. Furthermore, NSAIDs alone are considered not sufficiently effective in CNO with vertebral involvement [25]. In patients with failure to respond to NSAIDs or with primary vertebral involvement, several treatment options have been discussed, including methotrexate, sulfasalazine, biopharmaceutical drugs (namely TNFi), and bisphosphonates [1,2,8,24,33–37]. In Europe, TNFi and the bisphosphonate pamidronate are commonly chosen as second-line treatments in CNO. The present study aimed to assess efficacy of these two treatment options and, where possible, compare treatment responses including their dynamics in a retrospective multi-center approach including experienced centers in Germany and the UK.

The pro-inflammatory cytokine TNF-α is expressed at increased levels in monocytes and sera from CNO patients [17,18,38]. Because of these observations and clinical overlap with conditions usually treated with TNFi (including spondylarthritis, IBD, psoriasis, etc.), they have been introduced to the care of CNO patients and can be effective in patients refractory to other treatment options [23,39–42]. Bisphosphonates inhibit osteoclast activity and have successfully been used in CNO [11,34,43–47]. Notably, in addition to its effects on osteoclasts, pamidronate has inhibitory effects on pro-inflammatory cytokine expression [11].

To our knowledge, the present study is the largest published case series on clinical and radiological treatment response to second-line treatments in CNO. Thirty-nine of 43 patients (91%) treated with TNFi experienced clinical response after 3 months and maintained partial or complete remission after 12 months. High clinical response rates to TNFi are comparable to other published cohorts [41,48] 47,48. Considering reported side-effects of TNFi, it is worth mentioning that 2 CNO patients in this cohort developed psoriasis, both during ongoing infliximab therapy. Asking the question of whether this is a side-effect of TNFi that may occur especially frequently in CNO patients undergoing treatment with TNFi is intriguing. However, as psoriasis has been reported as an associated condition in CNO [8,51–53], and the sample size of this study is limited, this question cannot be reliably answered, and prospective studies in larger cohorts are needed.

However, the lack of defined outcome measures (including definitions of partial versus complete response), no consistent time points of evaluation across studies, and the retrospective design of published case series are a likely causes for the absence of formal comparisons between

Table 2

Characteristics of pamidronate responders (n = 47) and non-responders (n = 19).

	PAM-Responder (n = 47)	PAM-Non-Responder (TNFi switch) (n = 19)	p-value
Demographic characteristics			
Number Males (%)	21 (45)	3 (16)	**0.027**
Age at diagnosis, years (mean ± SD)	10.8 ± 2.7	11.0 ± 2.4	NS
Delay in diagnosis, months (mean ± SD)	17.1 ± 21.9	10.1 ± 9.2	NS
No. of flares during follow up (mean ± SD)	1.6 ± 1.5	2.7 ± 2.1	**0.035**
Follow up, years	3.7 ± 3.0	6.9 ± 5.2	NS
Comorbidities			
Arthritis (%)	7 (17)	6 (32)	NS
Inflammatory bowel disease (%)	2 (4)	1 (5)	NS
Skin involvement* (%)	9 (19)	8 (42)	**0.053**
Radiological characteristics in MRI			
No. of radiological lesions, initial (mean ± SD)	2.9 ± 2.5	5.7 ± 5.6	**0.024**
No. of radiological lesions, total (mean ± SD)	4.8 ± 3.2	8.8 ± 7.3	**0.011**
Unifocal manifestation, initial (%)	11 (23)	2 (11)	NS
Whole body imaging (%)	35 (75)	17 (89)	NS
-WB-MRI	23 (49)	14 (74)	NS
- scintigraphy	12 (26)	3 (16)	NS
No. of patients with lesions in long bones	22 (51)	14 (74)	**0.047**
Spinal involvement	11 (23)	6 (32)	NS
Complication	14 (30)	2 (10)	NS
- vertebral body fracture	6 (13)	1 (5)	NS
- hyperostosis	8 (17)	1 (5)	NS
Inflammatory markers			
CRP (> 5 mg/l)	18.3 ± 33.9	51.0 ± 83.3	**0.033**
ESR (> 15 mm/1st h)	29 ± 29	43 ± 40	NS

CRP = C reactive protein; ESR = erythrocyte sedimentation rate; NS = not significant.

TNFi and pamidronate in CNO/CRMO. Fifty-six of 65 patients (86%) receiving pamidronate reached clinical remission at 3 months. While proportions of combined full and partial remission were largely comparable between patients treated with TNFi and pamidronate at 3 months, slightly more patients treated with pamidronate experienced full clinical remission at this early time point.

Few studies have investigated radiological response to TNFi or bisphosphonate therapy, and widely agreed outcome measures do not exist. In the present study, follow-up WB-MRI was conducted in 91% of CNO patients treated with TNFi within the first year and showed significant reduction of radiologically active bone lesions. When compared to individuals receiving pamidronate, CNO patients treated with TNFi exhibited significantly more radiological lesions at treatment initiation, which correlated with overall increased inflammatory activity in these patients (CRP and ESR). Thus, it appears that most colleagues choose TNFi in particularly "active and inflammatory" CNO phenotypes if vertebrae are not involved.

In agreement with observations from the present study, a retrospective observational study observed reduction of active bone lesions (median 6 to 2 lesions per patient after 1 year) on follow-up MRI in response to pamidronate +/− TNFi [49]. Authors reported high rates of persistent disease activity despite pamidronate therapy [10/32 children (31%)], which were consecutively treated with TNFi. Also, these observations compare to this presented cohort in which patients 28% (19/69) of patients treated with pamidronate failed to sufficiently improve and were subsequently prescribed TNFi. This is of particular interest,

because fewer patients failed initial TNFi treatment [3/44 (7%)]. Overall, fewer treatment adjustments from TNFi to pamidronate, and fewer flares in the TNFi treatment sub-cohort suggest (slightly) higher efficacy as compared to pamidronate. Together with reducing cost of biological treatment and no need for hospital admissions for administration of adalimumab or etanercept argues for the use of TNFi in CNO refractory to NSAIDs. This strategy may be particularly promising in HLA-B27 positive CNO patients. Notably, 20% of the 40 tested CNO patients exhibited the HLA-B27 variant, which is above the 8–10% expected in healthy European populations [54–56]. While HLA-B27 positivity associated with axial involvement (sacroiliitis in 75% (6/8), coxarthritis in 12.5% (1/8), vertebral lesions in 12,5% (1/8) of HLA-B27 positive patients) and increased use of TNFi, vertebral lesions were more common in the HLA-B27 negative group of CNO patients. Notably, analysis of data from the HLA-B27 positive CNO sub-cohort is limited by few complete datasets available (40 patients tested, 8 positive) and the possibility of increased testing in individuals with enthesitis and/or axial involvement.

While aforementioned findings may primarily argue for the use of TNFi in a majority of CNO patients (particularly without vertebral involvement), clinical and radiological remission was reached slightly earlier in patients receiving pamidronate (without reaching statistical significance). This is supported by Gaal et al., who reported earlier remission in a small cohort of patients with mandibular CNO in response to pamidronate as compared to TNFi (median 2 vs. 17 months, $p = 0.01$) [50]. Kostik et al. reported higher response rates to pamidronate in patients with spinal CNO when compared to peripheral CNO. Furthermore, among 29 patients with spinal involvement response rates to bisphosphonates (90.9%) was higher as compared to TNFi (66.7%) [42].

Notably, several clinical and demographic features were associated with failure to respond to pamidronate and may therefore aid in stratifying patients towards optimal treatment. These include female gender, high number of active radiological bone lesions on MRI, and elevated CRP and ESR. As pamidronate use is viewed particularly critically due to long elimination time in young women of reproductive age, TNFi may be considered more favorable in these patients [57]. A common reason for the choice of pamidronate over TNFi is "cost". However, when comparing cost associated with outpatient TNFi use with 3–4 cycles of pamidronate that requires admission to hospital for treatment administration, differences are indeed negligible. This may change further as the recent introduction of biosimilars may reduce cost of TNFi treatment [58]. Concerns exist in relation to pamidronate and osteonecrosis of the jaw [59–61]. While most data confirm predisposition for this complication in older patients with underlying malignancy [59,60,62], no published evidence exists that may suggest occurrence of Bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the context of CNO or in children and adolescents with other bone disease like osteogenesis imperfecta [62–64]. While in the present and additional large cohorts no osteonecrosis of the jaw was seen during follow-up, awareness of possible long-term complications, including osteonecrosis, is necessary [43,65,66].

In this cohort, 3/91 (3.2%) patients exhibited a refractory disease course and neither responded to bisphosphonates nor TNFi. Based on the current pathophysiological understanding involving increased inflammasome assembly and IL-1β release, IL-1 blockade may be a promising alternative target [11,14,15,18]. Pardeo et al. recently reported mixed clinical response to recombinant IL-1 receptor antagonist (anakinra) treatment in a small cohort of 9 children with refractory CNO [67]. Further alternative treatment targets may include the down-stream pro-inflammatory cytokine IL-6 [68,69], and the effector Th17 cytokine IL-17 [70,71]. However, none of the above can currently be considered as part of routine practice or "standard of care" in CNO.

While delivering interesting observations in relation to induction and maintenance of remission with pamidronate or TNFi, the present study has limitations. Patient data were collected retrospectively with a lack of randomization, contributing to different cohort sizes and not perfectly

matched demographic characteristics. This may likely have contributed to higher inflammatory activity and more comorbidities in the sub-cohort of CNO patients treated with TNFi. We were unable to normalize for comedications used (including corticosteroids) and variable treatment protocols. Although the present study represents the largest study available investigating and comparing second-line treatment responses in CNO, because of the rarity of the condition and independent of international collaboration, sample size is still relatively small. Thus, results from this study require to be interpreted with caution. Lastly, while showing promise for the treatment of CNO patients, neither TNFi nor pamidronate are licensed for CNO and can therefore only be considered as "off label" options.

5. Conclusions

In children with CNO refractory to NSAID or with primary spinal involvement, both bisphosphonates and TNFi are effective therapies. A slightly more rapid clinical and radiological response to pamidronate (not statistically significant) was observed as compared to TNFi, which may argue for its use in patients with vertebral involvement to prevent further damage. Fewer flares and reduced use of third-line treatments suggests higher efficacy of TNFi. Based on preliminary findings from this study, demographic and clinical markers may aid in predicting failure to respond to pamidronate and stratifying patients to TNFi treatment. Though delivering detailed clinical and radiological response data from a large international cohort, data require to be confirmed in randomized clinical trials.

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