Chronic non-bacterial osteomyelitis (CNO) and chronic recurrent multifocal osteomyelitis (CRMO) with a focus on pamidronate therapy

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Chronic recurrent multifocal osteomyelitis (CRMO), also called chronic nonbacterial osteomyelitis (CNO) or nonbacterial osteomyelitis (NBO), is a rare autoinflammatory bone disease of unknown etiology. However, the number of patients properly diagnosed would increase with better knowledge of the disease. In this regard, whole-body magnetic resonance imaging (WB MRI) has been found to be a better predictor of active lesions than clinical examination. Importantly, the RINBO index (radiologic index for NBO) quantifies the involvement based on the WB MRI. Further, a chronic nonbacterial osteomyelitis MRI scoring (CROMRIS) has been developed as an online tool for assessing WB MRI. The therapy consists of non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates (pamidronate, zoledronate, etc.) and other drugs, including biologics. Pamidronate is an appropriate and safe therapy. The first pilot prospective randomised controlled trial (RCT) on pamidronate vs. placebo was carried out in adults. No RCT has been done in children yet. Besides RCTs, there are a number of issues to be explored in future, i.e. predictors of therapy effect, optimal therapy duration, predictors of therapy discontinuation and evaluation of optimal therapy protocol. Recently, the CNO clinical disease activity score (CDAS) was constructed and validated but the classification criteria are still being developed. As collaboration on this rare disease is essential, a prospective Chronic Nonbacterial Osteomyelitis International Registry (CHOIR) was established to generate future comparative effectiveness research data.

Key words: chronic recurrent multifocal osteomyelitis (CRMO), chronic nonbacterial osteomyelitis (CNO), nonbacterial osteomyelitis (NBO), SAPHO syndrome, diagnosis, therapy, pamidronate

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INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) was first described by Giedion in 1972 in a series of four children. Five years later, Probst, Bjorksten and Gustavson used the term CRMO to refer to the tendency of the disease to be recurrent. The term CRMO is still used for a clinical entity, however it is neither multifocal nor recurrent[1-3]. Many other terms are used in the literature for this condition: CNO (chronic nonbacterial osteomyelitis), chronic sclerosing osteitis, pustulotic arthrosteitis, etc. Further, also described is the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome) which is usually diagnosed in adulthood.

Over time there has been an evolution in both diagnostic methods and criteria, as well as treatment. Here we review diagnostic criteria and methods, including the recently published radiologic index for nonbacterial osteomyelitis (RINBO index), which quantifies the description of findings on whole-body MRI, which is the crucial imaging technology[4]; chronic nonbacterial osteomyelitis MRI scoring (CROMRIS) tool, an available online tool for assessing CNO/CRMO (ref.[5]), and the radiological activity index (RAI-CROMRIS) for quantification of the overall bone involvement in individual patients[6]. Further, there are treatment modalities described, including pharmacotherapy: NSAIDs (non-steroidal anti-inflammatory drugs) and DMARDs (disease-modifying drugs), both classical and biological. We focus on the role bisphosphonate pamidronate in the treatment of this rare autoinflammatory disease. That said, there is no validated predictor of response to therapy in current clinical practice. Many unanswered questions, both from clinical and molecular-biological research points of view, remain. International collaborative attempts/initiatives for better diagnostics and therapy of patients with CNO/CRMO have been started. First, retrospective and prospective projects led by Zhao et al. have been developing classification criteria and building a patient registry (Chronic Nonbacterial Osteomyelitis International Registry, CHOIR) (ref.[7]). Secondly, the preparation of prospective randomised clinical trials (RCTs) to study treatment for this rare disease is essential. For example, Ramanan et al. published a consensus opinion to develop RCTs to analyse adalimumab versus pamidronate in children with CNO/CRMO using a Bayesian design[8]. Last, but not the least, validation of a clinical disease activity score for CNO is necessary for future RCTs (ref.[9]).

Etiology

CNO/CRMO is classified as a bone autoinflammatory disorder based on the absence of high titer autoantibodies and/or autoreactive lymphocytes and "seemingly unprovoked" episodes of inflammation. The precise etiology

is still unknown. Cultivations are usually negative. Some authors have postulated that CNO/CRMO is triggered by exposure to a microbial agent. There are a few reports of bone cultures growing organisms (*Propionibacterium acnes*, *Mycoplasma*, and various *Staphylococcus* species), however contamination of specimens could not be excluded in these studies. Tissue damage by trauma might be another possible trigger, although this has not been found in most series[3]. The genetic background is being examined and *FBLIM1* homozygote mutation of the filamin-binding domain of the gene was detected in a CRMO child of consanguine parents[10]. There are also data showing the role of 18q21.3-22 locus in the development of CRMO (ref.[11]). However, the precise immunological basis of CNO/CRMO remains unknown. One German cohort revealed patients with ANA positivity which was not found in other cohorts. Data on HLA B27 is inconclusive. Nevertheless, CNO/CRMO or SAPHO syndrome patients can evolve into a picture consistent with spondyloarthropathy over time. There is a connection between CNO/CRMO and inflammatory bowel disease (Crohn disease and ulcerative colitis), supporting the idea that CNO/CRMO is part of the spondyloarthropathy spectrum of diseases. Cytokine and chemokine dysregulations in innate immune cells contribute to the pathophysiology of CNO/CRMO. While immune-regulatory cytokines IL-10 and its homologue IL-19 fail to be expressed from peripheral blood monocytes, increased monocyte expression of proinflammatory cytokines (IL-1ß, IL-6, TNF-α) and chemokines (IL-8, IP-10, MCP-1, MIP-1a, MIP-1b) has been described in CNO/CRMO. Reduced expression of IL-10 and IL-19 are caused by impaired activation of the mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase (ERK) pathway. Further, increased expression of proinflammatory cytokines in CNO/CRMO has been linked to uncontrolled activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. These imbalances can lead to osteoclast activation and osteolytic lesions[3,12-14].

Animal/mouse models of CRMO with *PSTPIP2* (proline-serin-threonine phosphatase) mutation have been developed to study the disease. CRMO mice show tail (segmental swelling), extremities (swelling and deformities of hindfoot and digits, nail discoloration), and skin (increased erythema of ear) involvement/affection. It has been confirmed that adaptive immunity is not necessary for the development of CRMO in mouse models[3]. Microbiome studies have provided interesting data on the role of particular pathogenes, such as *Kingella Kingae* and *Prevotella*[15]. Nonetheless, preventive modalities, including diet modifications, have yet to be published.

Epidemiology

CNO/CRMO is a rare disease, predominantly found in children and young adolescents. The peak onset of the disease is between 7 and 12 years. Onset before the age of 2 years is unusual and should prompt evaluation for a syndromic form of CNO/CRMO, including Deficiency of Interleukin-1 Receptor Antagonist (DIRA); pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA); and Majeed syndrome, as well as other differential diagnoses (malignancy, infection, etc.) (ref.[3]).

Females are affected at a rate of 2 to 4 times more often than males. However, there is a paper published with only females detected[16]. Currently there are hundreds of cases described in the literature, but the actual

Table 1. Different diagnostic CRMO criteria.

	King	Jansson	Bristol
Reference	23, 24	25	26
Number of criteria	4	4 major (M), 7 minor (m)	4
Should have	4 out of 4	2M or 1M+3m	3= A and B and either C1 or C2
Criteria list	≥2 typical bony lesions	M1. Multifocal bone lesions	A) The presence of typical clinical findings
		M2. Sterile bone biopsy with signs of inflammation and/or fibrosis or sclerosis	B) The presence of typical radiological findings (plain x-ray or preferably STIR MRI)
	duration ≥6 months		
	typical histologic features on bone biopsy	M3. Palmoplantar pustulosis or psoriasis	C1) more than one bone (or clavicle alone) without significantly raised CRP (CRP <30 g/L)
		M4. Radiologically proven osteolytic/sclerotic bone lesions	
	age <18 years at diagnosis	m1. Normal blood count	C2) if unifocal disease (other than clavicle), or CRP >30 g/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy.
		m2. Good general state of health	
		m3. Mild to moderately elevated CRP and ESR	
		m4. Observation interval longer than 6 months	
		m5. Hyperostosis	
		m6. Association with other autoimmune diseases	
		m7. The first or second degree relative with autoimmune disease or syndrome	

CRMO, chronic recurrent multifocal osteomyelitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; STIR, short tau inversion recovery.

incidence remains unknown. Estimated incidences in Germany range from 2 to 80 per 100,000 children. Early descriptions come from Scandinavia, however published data show worldwide spread affecting different ethnicities and races[3]. The data provided by Girschick et al. showed 486 patients (of whom 455 were children) with CRMO included in the Eurofever registry[17]. CRMO was probably at least as frequent as infectious osteomyelitides[18]. We described our series from one Czech pediatric rheumatology centre, including 20 patients[19]. New patients have been diagnosed since this period, including one female with CRMO and polyarticular juvenile idiopathic arthritis treated by pamidronate, methotrexate and biologic therapy[20]. Further, 37 and 16 CRMO patients from two other Czech pediatric rheumatology centres have been published[21-22].

Clinical course

CNO/CRMO is a disease with a chronic or frequently undulent course. The active disease and remissions may appear over time. Main clinical findings encompass localised bone pain and swelling of surrounding soft tissue. Systemic symptoms, such as fever, may also be present. Any bone can be involved. Metaphyses of long bones, clavicles, vertebral bodies and pelvis are the most frequently affected. The number of osteomyelitis lesions is described as varying between one and 18 (ref.[3]), but the use of WB MRI has increased the number of detectable lesions, i.e. Roderick et al. describe a female with 23 lesions detected by WB MRI (ref.[16]). Symmetric bone affections are found in 25% to 45% of patients. Moreover, the extraosseal presentation can be found, with skin lesions being the most frequent[3]. Recently, two phenotypes of CNO/CRMO differing in clinical presentation and laboratory findings were published by Cebecauerova et al.[21].

Diagnostic criteria

Currently, several diagnostic criteria are used in CNO/CRMO. These evolved mainly as a result of improving imaging technology reviewed in Table 1. While King´s criteria published in 1987 included histopathology[23-24], it is now possible to establish the diagnosis of CRMO in particular conditions without performing a biopsy. This approach is used in Jansson´s criteria published in 2007 (major and minor criteria combination) (ref.[25]) and the Bristol criteria[26]. Using the Bristol criteria, a biopsy could be avoided in case of multiple bone lesions or isolated clavicle involvement and CRP below 30 g/L (Table 1).

Classification criteria

Classification criteria are indispensable in future prospective RCTs, and are considered to be a priority in CNO/CRMO research by both specialists (clinicians and clinical academics), patients and family members[27]. There are ongoing initiatives aiming at classification criteria (ACR/EULAR) and outcome measures (OMERACT) that will enable the generation of evidence through clinical trials[9,28].

Diagnostic methods

A plain radiograph targeted to a clinically involved area is the first step in the radiological diagnostics of CNO/CRMO. Next, WB MRI with short tau inversion recovery (STIR) sequentions is recommended to locate asymptomatic lesions. Plain radiographs of these clinically silent lesions are performed afterwards or localised MRI is used to describe their extent. The major advantage of WB MRI is detection of these clinically silent/occult lesions which is particularly important in asymptomatic vertebral lesions[3,29-30]. Moreover, WB MRI is more sensitive than bone scans (scintigraphy) for detecting clinically and radiologically occult lesions. Another advantage of WB MRI is the ability to detect extraosseous lesions, such as myositis and synovitis. Eliminating radiation is an important benefit to WB MRI, which is why this technology has replaced bone scans (scintigraphy) in many institutions. Asymptomatic lesions can be screened using a Tc scintigraphy scan, but now the role of erstwhile more frequently used scintigraphy is to exclude tumor disease[3,30]. The use of computer tomography (CT) in the diagnostics of CNO/CRMO is rare due to radiation. WB MRI is usually performed using a 1.5 Tesla device[16]. The use of 3 Tesla devices has been published but their limitations are diminished fat suppression and increased tendency to artefacts compared to 1.5 Tesla devices[31]. The plain radiogram may be normal in the very early phase of CNO/CRMO or only show osteopenia. One of the most common radiographic findings is mixed osteolytic and sclerotic lesions with a predilection for metaphyses of the long bones. Periostal reaction may be present. Involvement of the small tubular bones is more likely associated with significant periostal reaction than it is seen in the long bones. Cortical thickening and progressive sclerosis of the lesions occur during the later phase/course of the disease and are followed by gradual normalisation of radiography findings over several years. Epiphyseal involvement is rare but may be present and could lead to premature epiphyseal fusion. Diaphyseal lesions are unusual, too. They are typically adjacent to involved metaphyses. Claviclar lesions are typically found in the medial part and may be of lytic destructive appearance with periosteal new bone formation when the disease is active. During healing, the sclerosis is increased. Repeated periods of remission and activity, frequently lead to progressive sclerosis and hyperostosis. Vertebral lesions typically show erosions of vertebral plates, sometimes associated with the reduction of intervertebral spaces which can even mimic infectious spondylodiscitis. A destructive lytic lesion involving the vertebral body may occur before its collapse. Vertebra plana may be revealed. Involvement of the pelvis may be detected on the surface of joints and synchondroses and are frequently of sclerotic appearance. Sacroiliitis may also be present as a part of pelvis involvement[3].

Active lesions on WB MRI typically show high signal intensity on T2-weighted and STIR images in combination with low signal intensity on T1-weighted images. The MRI picture changes during the development of lesions: Early MRI findings include bone marrow edema and periosseal

Table 2. The RINBO index.

Parameter of interest	Description	Criterion	Value
Number of radiologic active lesions (RAL)	unifocal	1	1
	paucifocal	2–4	2
	multifocal	≥5	3
Maximum size of patient' RAL	minor	<10 mm	1
	average	≤100 mm	2
	major	>100 mm	3
Extramedullary affection	acute	periosteal reaction and/or adjacent soft tissue edema	1
	chronic	hyperostosis	1
Spine involvement	acute	radiologically active spine lesion	1
	chronic	NBO related vertebral body deformation	1
Maximum index points			10

NBO, nonbacterial osteomyelitis; RAL, radiologic active lesion; RINBO, radiologic index for nonbacterial osteomyelitis.

edema. Thickened corticalis and progressive sclerosis are found later, followed by increasing sclerosis and hyperostosis in the phase of healing[3]. CNO/CRMO could be assessed using the RINBO index[4]. This quantifies parameters based on the WB MRI (Table 2). The maximal index value is 10. Recently, the modified RINBO (mRINBO) index assessing CNO/CRMO patients treated with pamidronate was published by Andreasen et al., showing its clinical utility[32].

The duration of the lesion influences the histopathological findings. In the early phase of the disease, the predominance of neutrophils is typical. In contrast, mixed inflammatory infiltrates with the predominance of lymphocytes and plasmocytes and different levels of sclerosis and fibrosis are typically detected in the late phase. Early in the course of the disease, abscesses and increased osteoclast activity with increased bone resorption are also present. Multinucleated giant cells, necrotic bone, areas of new bone formation, and the above-mentioned fibrosis can also be seen in later lesions. Histopathological pictures may even be heterogeneous during one phase, so it is necessary to assess several sections from each bioptic sample[3].

Inflammatory markers: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), full blood count and the differential count may be elevated but could also be normal. Most of the patients have slightly elevated ESR and CRP. The white blood count is typically normal or only slightly elevated. There are low titers of autoantibodies present. No strong association with HLA B27 is described. Higher levels of TNF-α and IL-6 are present in patient serum which shows their role in the pathogenesis of the disease[3].

Potential biomarkers have been widely sought for and reviewed[33-36]. Hofmann et al. described nine serum inflammation markers that enable us to distinguish CNO/CRMO patients from those with Crohn disease and healthy controls (Eotaxin, IL-12, IL-1RA, sIL-2R, IL-6, MCP-1, MIG, MIP-1b and RANTES). These proteins may be useful in future diagnostics, however, it is necessary to test them on larger multiethnic patient cohorts and in patients with coincident inflammatory diseases[37]. Interestingly, a combination of IL-6 and CCL11/Eotaxin was reported as a possible diagnostic marker of CNO/CRMO (ref.[38]). Validation of these markers is necessary.

Association with other diseases

In CNO/CRMO patients, other autoinflammatory diseases are present such as psoriasis (P), palmoplantar pustulosis (PPP), generalised pustular psoriasis (GP), inflammatory bowel diseases (IBD): Crohn disease (CD), ankylosing spondylitis and severe acne. Three published series described a high incidence of CD in relatives of CNO/CRMO patients, in particular 13% of patients had first or second-degree relatives suffering from CD, supporting an association between IBD and autoinflammatory bone diseases[3]. CD represents a rare disease coincidence described in the literature in a minority of patients (children or adults) with CRMO (refs.[39-40]). A recent publication describes 8 out of 37 CRMO children patients suffering from IBD (ref.[21]). In our series, one patient developed IBD (ref.[19]). CRMO and SAPHO syndrome may be the same disorder in different age groups (SAPHO is diagnosed mainly in adulthood) or distinct disorders in the same disease spectrum[3,15]. The foregoing remains a topic of discussion.

Methods for disease activity evaluation

Validated methods for the evaluation of disease activity are needed[41-42]. Monitoring clinical status and performing control WB MRI are essential. However, the appropriate time interval for WB MRI during follow-up is an unresponded question. Arnoldi et al. published a RINBO index as a new tool for CRMO evaluation[4]. Other tools are the chronic nonbacterial osteomyelitis MRI scoring (CROMRIS) for assessing CNO/CRMO and the radiological activity index (RAI-CROMRIS) for quantifying overall bone involvement in individual patients[5-6]. A recent publication by Andreasen et al. reported that pamidronate therapy decreased mRINBO from baseline to year one. Thus, mRINBO might be a potential scoring method to quantify changes in radiological disease activity. However, testing of the feasibility and validity of mRINBO is needed[32]. Recently, Reiser et al. suggested that a combination of improvement in physician global disease activity (PGDA), patient-reported overall well-being and

imaging-defined disease activity measures might document the inactivity of CNO disease[43]. Finally, the CNO clinical disease activity score (CDAS) was constructed and validated for disease monitoring and assessment of treatment efficacy[9].

Treatment

NSAIDs are the first therapy choice, and their effect is described in approx. 1/3 patients. The effect appears to be better in children with limited disease[15]. After NSAID failure, there are other drugs in the second line. Glucocorticosteroids, sulfasalazine, methotrexate (MTX), azithromycin, colchicine, hyperbaric oxygen, interferon-α,

Table 3. Summary of studies on CNO/CRMO therapy using pamidronate.

Study	Ref.	Therapy or follow-up	N	PAM	Criteria
Fraleigh et al. 2023	48	2021	1	1	NM
Reiser et al. 2023	43	2015–2021	400	34	NM
Stojkic et al. 2023	49	NM	1	1	NM
Andreasen et al. 2022	32	2007–2015	18	18	Bristol
Cebecauerova et al. 2022	21	2010–2020	37	8*	Bristol
Juszczak et al. 2022	50	2010–2019	42	42	NM
Bustamante et al. 2021	51	NM	25	15	NM
Giovannelli et al. 2021	52	2016–2018	3	3	NM
Karunaratne et al. 2021	53	NM	3	2	NM
Panwar et al. 2021	54	May 2010 – Jun 2017	32	32	Bristol
Ferrara et al. 2020	55	Jan 2012 – Dec 2017	3	1	NM
Gaal et al. 2020	56	2003–2017	12	6	own criteria
Kaneko et al. 2020	57	NM	1	1	NM
Andreasen et al. 2019	58	2007–2015	51	32	Bristol
Bouchalova et al. 2019	19	Jan 2011 – May 2016	20	14	NM
Kostik et al. 2019	47	NM	52	18*	Jansson
Sag et al. 2019	59	Jan 2008 – Jan 2017	15	1	NM
Sulko et al. 2019	60	2012–2018	76	41	Jansson
Ariza Jiménez et al. 2018	61	2010–2015	12	4	Jansson
Metz et al. 2018	62	NM	1	1	NM
Tronconi et al. 2018	63	NM	4	3	NM
Bouchalova et al 2017	20	2017	1	1	NM
Hirano et al. 2017	64	NM	1	1	NM
Schnabel et al. 2017	18	2004–2015	56	8	NM
Barral et al. 2016	65	2008–2015	7	5	NM
Pastore et al. 2016	66	2004–2014	47	15	Jansson
Roderick et al. 2016	26	Jan 2005 – Dec 2012	41	22	Bristol
Audu et al. 2015	40	2005–2014 CNO and IBD	3	1	NM
Kaiser et al. 2015	67	1995–2010	41	3	NM
Wipff et al. 2015	68	1995–2014	178	NM	NM
Ferraria et al. 2014	69	2005–2010	4	2	NM
Roderick et al. 2014	16	NM	11	11	Bristol
Handly et al. 2013	70	NM	1	1	NM
Schuller et al. 2013	71	2011–2013	4	4	NM
Ziobrowska-Bech et al. 2013	72	2001–2011	31	3	NM
Al Hajry et al. 2012	73	1990–2010	10	6	NM
Kuijpers et al. 2011	74	Mar 2005 – Dec 2008	7 (1 child)	7 (1 child)	NM
Hospach et al. 2010	45	Jan 2002 – Dec 2008	102	7	NM
Gleeson et al. 2009	44	2000–2006	7	7	NM
Miettunen et al. 2009	24	2003–2008	17	9	King
Catalano-Pons et al. 2008	75	NM to Jan 2008	40	NM	NM
Simm et al. 2008	76	NM	5	5	NM
Teruzzi et al. 2008	77	NM	4	4	NM
Compeyrot et al. 2007	78	NM	2	2	NM
Yamazaki et al. 2007	79	Jun 2000	1	1	NM
Kerrison et al. 2004	80	1996–2003 SAPHO	7	7	NM

*personal communication; N, number of patients; NM, not mentioned; PAM, pamidronate.

interferon-γ, calcitonin, bisphosphonates and biologic DMARDs (anti-TNF) treatment have all been used to treat CNO/CRMO. Recently bisphosphonates have been shown to be effective in the treatment of children with CNO/CRMO, predominantly in children with vertebral involvement in the form of vertebral fractures[15,44-47]. Different bisphosphonates were used: pamidronate, neridronate, alendronate, risedronate, or zolendronate. Pamidronate is used most frequently, and approximately 300 CNO/CRMO children are described (see Table 3). Some articles describe patients treated with bisphosphonates, but it is unclear how many of them were treated with pamidronate[67-68]. Pamidronate is also highly effective in patients resistant to other drugs[15]. A comparison of different drugs has recently been published by Kostik et al. The authors compared therapeutic regimens in 52 CNO/CRMO pediatric patients[47].

Nevertheless, the results of RCTs still need to be improved due to the rarity of the disease. There is only one randomised pilot clinical trial on CNO/CRMO comparing pamidronate and placebo in adults. The first data on 12 patients, showing the effect of pamidronate compared to placebo, has been published[81]. The authors found a decrease in the radiological score of active bone inflammation between baseline and week 36 in a group treated with pamidronate which remained unchanged in the placebo group. Active bone inflammation was assessed by WB MRI and CT (ref.[81]).

The prompt effect of pamidronate on the improvement of clinical findings could be seen even after the first dose of the drug, while the impact on radiological findings should be assessed in a prospective clinical study. A dose of 1 mg/kg/day for three consecutive days is usually recommended. The maximal dose is 60 mg/day. The first dose of the first series could be half, i.e. 0.5 mg/kg, with a maximum of 30 mg. The most frequent scheme is every 3 months, however, other intervals are reported in the literature[15,41]. An excellent response to therapy has been described in our series[19]. Similar results were reported, for example, by Roderick et al., describing the effect in 9 out of 11 patients (81.8%) and Kostik et al. with an effect in 88.8% of patients treated with pamidronate[16,47]. Excellent clinical effects of pamidronate are found in some patients even after the first dose[24,45]. Our clinical experience is similar[19]. There are even patients benefiting from a single dose.

Mineral dysbalances (calcium, phosphorus) may develop as side effects of pamidronate. These could be prevented by oral substitution before pamidronate therapy. Monitoring of serum mineral levels and substitution is important during and after the administration of pamidronate. A flu-like syndrome associated with pamidronate is known and can be prevented by antipyretics. A further risk is venous thrombosis at the site of the infusion cannula. Everyday use of new cannulae in patients with a history of this issue might be a secondary prevention. Zolendronate is also recommended in consensus treatment plans (CTPs) by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) (ref.[41,82]). There is also experience with biologic DMARDs (bDMARDs) with different outcomes. TNF-α inhibitors (adalimumab, etanercept, infliximab, and other TNF inhibitors) could be used according to CTPs for the treatment of CNO/CRMO (ref.[3,41]). Two patients in our series were treated with a TNF-α inhibitor with good effect[19]. Biologic anti-TNFalfa therapy targets defective cytokine regulation and restores the balance between highly proinflammatory cytokines and immunomodulatory cytokines IL-10 and IL-19 (ref.[15]). There is also data in the literature on using anti-IL-1 (ref.[3,83]). The use of bDMARDs is included in CTPs published by CARRA (Childhood Arthritis and Rheumatology Research Alliance) (ref.[41]). That said, uniform evidence-based recommendations for bDMARD indications are lacking.

Treatment response evaluation

Criteria for evaluation of treatment effectiveness have recently been validated for CNO (CDAS, clinical disease activity score) (ref.[9]). However, data on predictors of treatment response to bisphosphonates are lacking. Data from case series describe the effect of bisphosphonate/pamidronate, particularly in patients with involvement of the axial skeleton[44,45]. Given the unclear mechanisms of pamidronate effects in CNO/CRMO, it might be difficult to choose an appropriate predictor candidate. Also, in the case of other diseases which are successfully treated with pamidronate, such as osteoporosis, fibrous dysplasia and osteogenesis imperfecta, there are no treatment response predictors available[84].

Predictors of pamidronate therapy discontinuation

Activity on the WB MRI is frequently sustained even when clinical activity is absent. Roderick et al. assessed the response to pamidronate using the WB MRI. This enables a more precious assessment of response than isolated clinical examination, and it is an objective measurement of the effect of therapy[16]. A question for further research is, whether the level of activity on WB MRI could play a predictive role in pamidronate therapy discontinuation.

Tasks for the future

From a clinical and research (molecular-biology) viewpoint, many questions remain to be answered: How early should pamidronate be started in CNO/CRMO with no vertebral lesions? Which patients with CNO/CRMO are suitable for therapy with biologics? How are some patients benefiting from a combination of pamidronate and biologics? How early to start biologics? How long should the treatment with pamidronate be?

The diagnostics and therapy of CNO/CRMO could be improved by education and treatment with a focus on specialists (rheumatologists, orthopedic surgeons, general practitioners for children and adolescents, traumatologists, infectologists). Further, diagnostics, therapy and follow-up by experienced specialists in the field of rheumatology with expertise in this rare autoinflammatory disease will improve the care of CRMO/CNO patients.

International collaboration is vital for meeting the above-mentioned tasks[8,9,85].

CONCLUSION

CNO/CRMO is a rare autoinflammatory disease with an increasing number of described patients. WB MRI plays an essential role in the diagnostics. The therapy consists of NSAIDs, bisphosphonate pamidronate, and other drugs, including biologics. Bisphosphonate pamidronate is an appropriate and safe therapy. However, there are a number of unanswered questions i.e. predictors of therapy effect, predictors of therapy discontinuation and therapy protocol optimisation. The therapeutics effect of pamidronate should be studied in prospective RCTs. Finally, international collaboration is necessary to improve patient care.

Search strategy and selection criteria

We conducted a search of the existing literature using the scientific database PubMed, utilizing key terms such as "chronic recurrent multifocal osteomyelitis", "chronic nonbacterial osteomyelitis", "nonbacterial osteomyelitis" or "SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome". The search encompassed publications without any restrictions on the publication date. Several book chapters, conference abstracts and internet resources were also included.

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