Efficacy of intravenous neridronate in transient osteoporosis of the hip

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Abstract

Objective

To evaluate the efficacy and safety of intravenous (iv) neridronate in patients affected by transient osteoporosis of the hip (TOH).

Methods

We retrospectively evaluated the clinical records of patients affected by TOH treated with iv neridronate in our department. We treated patients with a value of visual analogue scale (VAS)-pain ≥ 80/100 mm at diagnosis, limited range of movement and magnetic resonance images (MRI) findings suggestive of TOH. The regimen used was: one iv infusion at day 0, 3, 6, 9 (100 mg for each infusion: total of 400 mg). This protocol was repeated in refractory cases. Recovery was defined as VAS-pain level ≤20/100. Concomitant use of analgesics was allowed. Paired Student t-test was used to assess VAS-pain change.

Results

Five patients were male, 3 were female. Mean age was 54.5±2.12 years old. Mean body mass index was 26.57±2.22. Mean time to diagnosis, since the onset of the symptoms, was 75±21.21 days. Mean number of neridronate infusions was 7.5±2.56. Mean time of recovery was 57±45.96 days. Mean VAS-pain at baseline was 84±2,24. Mean VAS-pain after treatment was significantly reduced ($p<0.001$) with a value of 12.12±6.46. None of the patients needed analgesics after treatment. No adverse event was reported. In 5 cases, post-treatment MRI showed complete bone marrow oedema resolution.

Conclusion

Intravenous neridronate is effective and safe in the treatment of TOH and its use may lead to a faster resolution of the disease.

Key words

neridronate, bone marrow oedema, hip, transient osteoporosis, pain

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Introduction

Transient osteoporosis of the hip (TOH) is a rare and usually self-limiting condition of unknown origin presenting with pain and limited function of the hip, characterised by bone marrow oedema (BME) on magnetic resonance images (MRI) (1). BME is characterised by an alteration of bone marrow signal intensity on MRI with high signal on fluid-sensitive sequences T2/proton density with fat suppression and short tau inversion recovery (STIR) (2, 3) (Fig. 1). THO should be differentiated from other BME causes such as inflammatory, degenerative, neoplastic, or vascular conditions and diagnosis relies on anamnestic, clinical, and imaging findings (4, 5). Despite its self-limiting nature, physician's attention must focus on the eventual evolution to avascular necrosis (AVN) and there is still debate as to whether TOH should be considered a reversible form of AVN, or a form of non-traumatic complex regional pain syndrome (CRPS) (6). TOH is characterised at MRI by femoral head BME often sparing its medial part and less frequently extending to the femoral neck, and rarely to the trochanter and associated in half of the cases to subchondral fractures (7) (Fig. 2). On the opposite, AVN differs from TOH for the distribution of BME with "band-like" lesion with low signal intensity on T1 weighted images and the high intensity signal called "double-line" sign on T2 weighted images at MRI (8). Relatively to the treatment, only few case series and not controlled case studies are available in literature and in general, use of bisphosphonates may lead to a faster resolution of TOH with a good safety profile (1, 9-13). Neridronate is an amino bisphosphonate which has been shown to be effective and then registered for the treatment of Paget's disease of bone and osteogenesis imperfecta and more recently for CRPS (14). The aim of this case series is to evaluate the efficacy and safety of intravenous (iv) neridronate in patients affected by TOH.

Case series and methods

We retrospectively evaluated the clinical records of patients affected by TOH treated with iv neridronate in our department, from June 2014 to December 2020. All patients gave their written informed consent for the treatment. The diagnosis of TOH was made after excluding infections, cancers, seronegative spondylarthritis or rheumatoid arthritis and connective tissue disease and was based on history, clinical and MRI findings. The following information were evaluated: sex, age, Body Mass Index (BMI), history of trauma, comorbidities, diagnostic delay, time to recovery, number of neridronate infusions, visual analogue scale (VAS)-pain value, serum creatinine, calcium and 25-OH-Vitamin-D. Hip MRI was performed at baseline and evaluated by an expert radiologist and then discussed with a rheumatologist. Only in 5 cases MRI was performed after treatment. At diagnosis, all patients complained of hip pain and limited range of movement, with a value of VAS-pain ≥80/100 mm (range 0–100). Recovery was defined as a VAS-pain level ≤20/100 after treatment. The therapeutic regimen used was: one iv neridronate infusion (100 mg) at day 0, 3, 6, 9 (total of 400 mg in 10 days). This therapeutic regime was repeated 30 days after the first cycle, if a VAS-pain value ≤20/100 was not reached, within one month. An eventual third cycle was allowed. All patients received oral Vitamin-D supplementation. Concomitant use of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) together with use of canes or wheelchair was allowed, and prevention from weight bearing was suggested. Concomitant magnetotherapy and physical rehabilitation was allowed. A telephonic follow-up was performed, after recovery, to assess the onset of clinical symptoms related to AVN or adverse events.

Statistical analysis

Data are reported as mean ± standard deviation (SD) and range for continuous variables, whereas categorical and dichotomous variables are reported as frequencies and percentage. The non-parametric Spearman rank test was applied to correlate variables. Paired Student t-test was used to assess change of VAS-pain. Statistical significance was

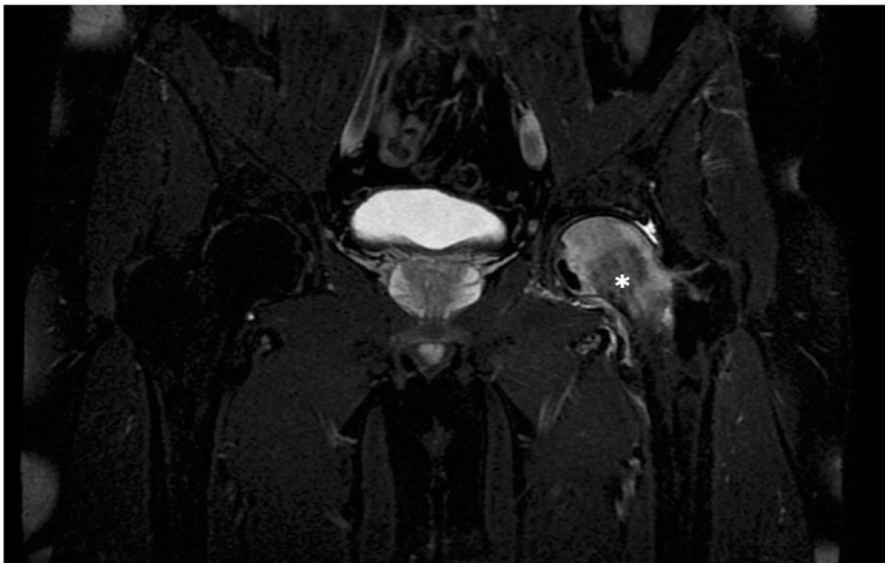

Fig. 1. Coronal magnetic resonance image (STIR-sequence) showing transient osteoporosis of the left hip, tipically caracterised by bone marrow oedema of femoral head and neck (marked with a star).

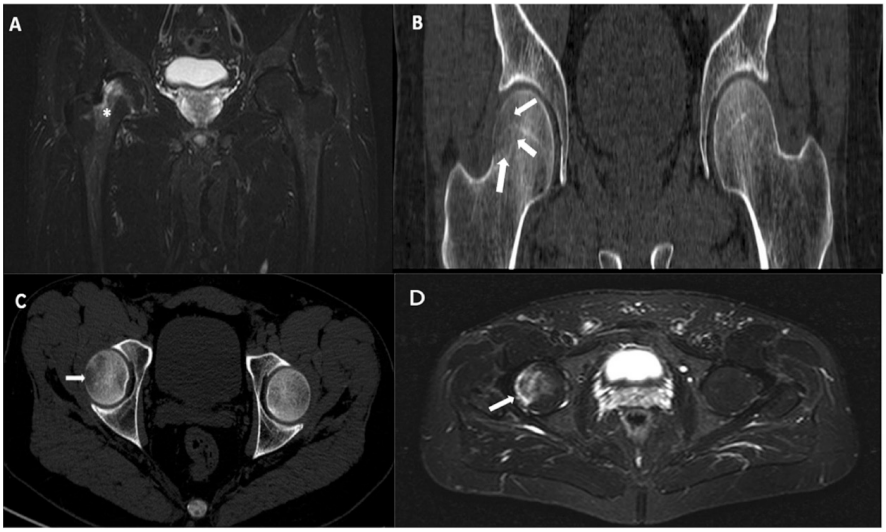

Fig. 2. A: Coronal image of magnetic resonance (MRI) (STIR-sequence), showing transient osteoporosis of the right hip, tipically caracterised by bone marrow oedema (BME) of the femoral head, spreading to the femoral neck (marked with a star), sparing the medial parts.
B: Coronal reconstraction image of pelvis computered tomography (CT) scan of the same patient, showing osteopenia (white arrows) in the lateral part of the right femoral head and neck, in the same area involved by BME.
C: Axial image of pelvic CT scan of the same patient, showing an osteopenic area corrisponding to BME (white arrow).
D: Axial MRI (STIR-sequence) showing right femoral head BME (white arrow), of the same patient.

set at a *p*-level of 0.05. The statistical analyses were performed using Jamovi ® v. 1.6.16 statistical package.

Results

A total of 8 patients were treated. Five patients were male, 3 were female. None of the women was pregnant. Mean age was 54.5±2.12 years old. Mean body mass index (BMI) was 26.57±2.22. Four patients had unremarkable medical history, 1 patient was affected by autoimmune thyroiditis, 1 patient was affected by prostatic hypertrophy, and 2 patients were affected by arterial hypertension. Four patients had a previous history of minor trauma of the affected hip, preceding the onset of TOH. One patient underwent magnetotherapy, 1 rehabilitation. The diagnostic delay before the treatment was 75±21.21 days (range 30–120). All patients were treated with at least 1 cycle of iv neridronate. Mean number of neridronate infusions was 7.5±2.56 (range 4–12). Mean time of recovery was 57±45.96 days (range 15–150). Only in 5 cases was MRI performed after treatment, showing a complete resolution of BME (Fig. 3). Mean VAS-pain before treatment was 84±2.24. Mean VAS-pain after treatment decreased significantly (paired Student t-test $p<0.001$) with a value of 12.12±6.46. After treatment, use of analgesics, NSAIDs or orthopaedic aids were no more needed. Serum levels of calcium and creatinine were in range and levels of 25-OH-Vitamin-D were sufficient before treatment. Only 2 patients experienced mild fever and self-limiting diffuse arthro-myalgia. No long-time adverse event was reported. None of the patients experienced AVN symptoms at the telephonic long-term follow up. Spearman analysis showed a direct significant correlation between disease duration and recovery time (rho = 0.8; $p=0.017$) and between number of infusions and disease duration (rho=0.728; $p=0.041$) and recovery time (rho=0.877; $p=0.004$). Results are reported in Table I.

Discussion

We reported the clinical and radiological efficacy of iv neridronate in the treatment of TOH in a cohort of 8 patients. A positive correlation between diagnostic delay and recovery time was assessed. Consequently, a greater number of neridronate infusions are needed to fasten recovery, with a good safety profile. Neridronate led to TOH resolution in an about 2 months' period, with a dramatic decrease in VAS-pain level. Our result differs from the only evidence in literature of neridronate in TOH where its intramuscular use had led to clinical resolution in 8 months (9). In our case series, use of iv neridronate seemed to fasten TOH resolution compared to other bisphosphonates or conservative treatment (1, 9, 11, 15, 16). Although the use of neridronate is considered off-label in TOH, we treated our patients with the regimen proposed for CRPS and in refractory cases, patients were treated with two or more cycles of neridronate (14). Efficacy and safety of

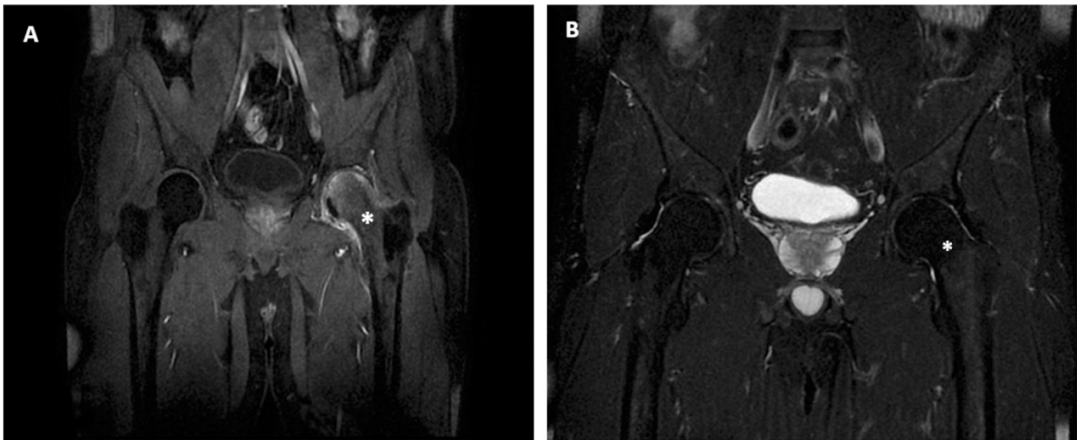

Fig. 3. Coronal magnetic resonance images (STIR-sequence) showing the favourable evolution of bone marrow oedema of the left femoral head (marked with a star) in a patient before (**A**) and after (**B**) treatment with neridronate.

Table I. Features of our patients affected by transient osteoporosis of the hip.

Total patients: 8	
Mean age (years)	54.5 ± 2.12
Sex	5M/3F
Mean BMI (kg/m^2)	26.575 ± 2.22
History of trauma	4/8
Diagnostic delay (days) since first symptoms	75 ± 21.21 (range 30–120)
Mean number of neridronate infusions	7.5 ± 2.56 (range 4–12)
Mean time for recovery (days)	57 ± 45.96 (range 15–150)
Mean VAS-pain before treatment	84 ± 2.24
Mean VAS-pain after treatment	12.12 ± 6.46*
Need of analgesics before treatment (Acetaminophen/NSAIDs)	8/8 (100%)
Need of analgesic after treatment (acetaminophen/NSAIDs)	None
Other treatments	- Magnetotherapy: 1/8 - Physical Rehabilitation: 1/8

VAS: visual analogical scale. NSAIDs: non-steroidal anti-inflammatory drugs. Continuous variables are reported as mean ± standard deviation (SD) and range (in parenthesis).
*VAS-pain after treatment, showing a significative decrease (paired Student t-test $p<0.001$).

bisphosphonates in BME is well established with many reports both for CRPS and other bone marrow lesions such as osteoarthritis (17-21). Among BME causes, THO has been less highlighted than others with a raising attention since the early 2000s when Varenna *et al*. successfully treated 16 patients affected by TOH with iv pamidronate with an imaging outcome reached in four months (11). Later, Emad *et al*. reported the use of oral alendronate in TOH, with BME resolution in a range varying from 3 to 6 months (13, 22). Both oral and iv bisphosphonates seem to be effective in TOH with a recovery time varying from few weeks to nine months (1, 10, 23, 24). This wide variability in recovery time could be explained by the diagnostic delay. Indeed, in our cohort, those who received an earlier diagnosis, reached an earlier healing. Vice versa patients whose diagnosis was delayed, were more refractory to treatment. In 4 cases of our cohort, TOH occurred after a physical stress or minor trauma. One of these patients was a surgeon, and it is possible to hypothesise that the prolonged standing position he assumed could have triggered TOH. Indeed, in a recent report Bashaireh *et al*. curiously underlined as being a physician could be a risk factor to develop this condition, and in general physical stimulation as well as alcohol consumption, steroid usage, smoking, hypothyroidism, and low vitamin D levels could be a risk factor for TOH development (25). One of our patients concurrently underwent rehabilitation. Literature lacks evidence about conservative treatment and few papers describe TOH resolution only by using forearm crutches (15). None of our patients underwent hyperbaric oxygen therapy which seemed to show efficacy in achieving resolution of pain, reduction of BME on MRI in patients suffering from TOH that failed to respond to other conservative methods (16). On the opposite, one of our patients underwent several cycles of magnetotherapy with no effect on disease evolution. Indeed, magnetotherapy could be more appropriate for patients in early stages of AVN and electromagnetic field stimulation may be able to either preserve the hip or delay the time until surgery (26). None of our patients progressed to AVN, which could be a dangerous complication of TOH (6). In 5 cases the non-progression to AVN was demonstrated by a post treatment MRI, while a long-term telephonic follow-up was performed for all patients with none of them referring symptoms related to AVN. Histopathology of TOH is very similar to the early stages of AVN presenting with areas of interstitial and intrasinusoidal fluid in the marrow cavities, fat cell destruction and fibrovascular regeneration together with osteoblast and irregular woven bone aiming to increase bone formation activity (27). This active bone formation is supposed to be the key for the reversible course of TOH (28). Moreover, the efficacy of bisphosphonate in TOH could be explained by the reactive bone formation in the marrow spaces and above all by the osteoclastic bone resorption present in many cases, demonstrated on biopsy specimens (29). It is possible to speculate that neridronate could inhibit the osteoclastic activity halting BME evolution. Among the limits of our study there is the absence of post treatment MRI control in 3 cases. The reason is connected to the fast brilliant clinical response on pain and hip function soon after the first neridronate cycle in these

cases. The eventual MRI re-evaluation could have strengthened our results. However, we believe the presence of AVN with no clinical manifestation would be a very unusual event and in 3 cases we felt that a control MRI could not be mandatory. Finally, the positive prognosis was confirmed by the absence of symptoms related to AVN in a long-time telephonic follow-up in those 3 patients not requiring health cares for hip problems. Another limit of our study relies on the retrospective analysis of clinical records together with the few numbers of treated patients. Finally, it must be kept in consideration the availability of neridronate exclusively in Italy and its iv-use limited to public hospitals. This last point should be considered by physicians in view of containing access to health facilities, in this pandemic historical period (30). From this perspective, a more convenient alternative could be represented by intramuscular neridronate as recently proposed at least for CRPS (31).

Conclusion

In conclusion, intravenous neridronate is effective and safe in the treatment of TOH and its use may lead to a faster resolution of this disease. A greater number of neridronate infusions is necessary to treat patients with diagnostic delay. To our knowledge this is the first evidence of efficacy of intravenous neridronate in TOH. However larger prospective studies are needed to show the possible efficacy of neridronate in this situation.

References

1. ASADIPOOYA K, GRAVES L, GREENE LW: Transient osteoporosis of the hip: review of the literature. *Osteoporos Int* 2017; 28: 1805-16.
2. STARR AM, WESSELY MA, ALBASTAKI U, PIERRE-JEROME C, KETTNER NW: Bone marrow edema: pathophysiology, differential diagnosis, and imaging. *Acta Radiologica* 2008; 49: 771-86.
3. ZANETTI M, BRUDER E, ROMERO J, HODLER J: Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology* 2000; 215: 835-40.
4. MANARA M, VARENNA M: A clinical overview of bone marrow edema. *Reumatismo* 2014; 66: 184-96.
5. RAGAB Y, EMAD Y, ABOU-ZEID A: Bone marrow edema syndromes of the hip: MRI features in different hip disorders. *Clin Rheumatol* 2008; 27: 475-82.
6. RADKE S, KENN W, EULERT J: Transient bone marrow edema syndrome progressing to avascular necrosis of the hip: a case report and review of the literature. *Clin Rheumatol* 2004; 23: 83-8.
7. KLONTZAS ME, VASSALOU EE, ZIBIS AH, BINTOUDI AS, KARANTANAS AH: MR imaging of transient osteoporosis of the hip: an update on 155 hip joints. *Eur J Radiol* 2015; 84: 431-4.
8. MALIZOS KN, KARANTANAS AH, VARITIMIDIS SE, DAILIANA ZH, BARGIOTAS K, MARIS T: Osteonecrosis of the femoral head: etiology, imaging, and treatment. *Eur J Radiol* 2007; 63: 16-28.
9. LA MONTAGNA G, MALESCI D, TIRRI R *et al*.: Successful neridronate therapy in transient osteoporosis of the hip. *Clin Rheumatol* 2005; 24: 67-9.
10. EVANGELATOS G, FRAGOULIS GE, ILIOPOULOS A: Zoledronic acid in nine patients with transient osteoporosis of the hip. *Clin Rheumatol* 2020; 39: 291-3.
11. VARENNA M, ZUCCHI F, BINELLI L, FAILONI S, GALLAZZI M, SINIGAGLIA L: Intravenous pamidronate in the treatment of transient osteoporosis of the hip. *Bone* 2002; 31: 96-101.
12. VERVERIDIS AN, PARASKEVOPOULOS K, KESKINIS A, PETKIDIS GI, TILKERIDIS K: The efficacy and safety of bisphosphonates in patients with bone marrow edema syndrome/transient osteoporosis: A systematic literature review. *J Orthop* 2020; 22: 592-7.
13. EMAD Y, RAGAB Y, SAAD MA, RASKER JJ: Transient regional osteoporosis of the hip with extensive bone marrow edema (BME): Dramatic improvement after three months of Alendronate therapy. *Radiol Case Rep* 2021; 16: 2487-90.
14. VARENNA M, ADAMI S, ROSSINI M *et al*.: Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study. *Rheumatology* (Oxford) 2013; 52: 534-42.
15. GULER O, OZYUREK S, CAKMAK S, ISYAR M, MUTLU S, MAHIROGULLARI M: Evaluation of results of conservative therapy in patients with transient osteoporosis of hip. *Acta Orthop Belg* 2015; 81: 420-6.
16. VERVERIDIS AN, PARASKEVOPOULOS K, KESKINIS A *et al*.: Bone marrow edema syndrome/transient osteoporosis of the hip joint and management with the utilization of hyperbaric oxygen therapy. *J Orthop* 2020; 22: 29-32.
17. FREDIANI B, GIUSTI A, BIANCHI G *et al*.: Clodronate in the management of different musculoskeletal conditions. *Minerva Med* 2018; 109: 300-325.
18. ROLVIEN T, SCHMIDT T, BUTSCHEIDT S, AMLING M, BARVENCIK F: Denosumab is effective in the treatment of bone marrow oedema syndrome. *Injury* 2017; 48 :874-879.
19. VARENNA M, ZUCCHI F, FAILONI S, BECCIOLINI A, BERRUTO M: Intravenous neridronate in the treatment of acute painful knee osteoarthritis: a randomized controlled study. *Rheumatology* (Oxford) 2015; 54:1826-32.
20. FLORES-ROBLES BJ, SANZ-SANZ J, SANABRIA-SANCHINEL AA *et al*.: Zoledronic acid treatment in primary bone marrow edema syndrome. *J Pain Palliat Care Pharmacother* 2017; 31:52-56.
21. GALLUCCIO F, ALLAM AES, PERDISA F, CHANG KV: Short-term teriparatide for bone marrow edema secondary to complex regional pain syndrome: case reports on efficacy after two years of follow-up. *Cureus* 2020; 12: e8119.
22. EMAD Y, RAGAB Y, EL-SHAARAWY N *et al*.: Transient osteoporosis of the hip, complete resolution after treatment with alendronate as observed by MRI description of eight cases and review of the literature. *Clin Rheumatol* 2021; 31: 1641-7.
23. KIBBI L, TOUMA Z, KHOURY N, ARAYSSI T: Oral bisphosphonates in treatment of transient osteoporosis. *Clin Rheumatol* 2008; 27: 529-32.
24. LAMARCA M, HERNANDEZ M, CAMPILLOS JM, LAPRESTA M, TOBAJAS JJ: Subcapital fracture of the hip in transient osteoporosis of pregnancy. *Taiwan J Obstet Gynecol* 2009; 48: 423-4.
25. BASHAIREH KM, ALDARWISH FM, AL-OMARI AA *et al*.: Transient osteoporosis of the hip: risk and therapy. *Open Access Rheumatol* 2020; 12:1-8.
26. MASSARI L, FINI M, CADOSSI R, SETTI S, TRAINA GC: Biophysical stimulation with pulsed electromagnetic fields in osteonecrosis of the femoral head. *J Bone Joint Surg Am* 2006; Suppl 3: 56-60.
27. NAIDES SJ, RESNICK D, ZVAIFLER NJ: Idiopathic regional osteoporosis: a clinical spectrum. *J Rheumatol* 1985; 12: 763-8.
28. PLENK H JR, HOFMANN S, ESCHBERGER J *et al*.: Histomorphology and bone morphometry of the bone marrow edema syndrome of the hip. *Clin Orthop Relat Res* 1997; 334: 73-84.
29. MCCARTHY EF: The pathology of transient regional osteoporosis. *Iowa Orthop J* 1998; 18: 35-42.
30. GEBRU AA, BIRHANU T, WENDIMU E *et al*.: Global burden of COVID-19: Situational analyis and review. *Hum Antibodies* 2021; 29: 139-48.
31. VARENNA M, BRAGA V, GATTI D *et al*.: Intramuscular neridronate for the treatment of complex regional pain syndrome type 1: a randomized, double-blind, placebo-controlled study. *Ther Adv Musculoskelet Dis* 2021; 13:17.