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CASE REPORT
PRIKAZ SLUČAJA

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Effect of Denosumab Therapy on Pain Level in Diffuse Sclerosing Osteomyelitis of the Mandible: a Case Report

Primjena denosumaba na bol tijekom terapije difuznoga sklerozirajućeg osteomijelitisa mandibule: prikaz slučaja

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Abstract
This is the first case report where two patients were under uniform denosumab administration protocol in diffuse sclerosing osteomyelitis (DSO) treatment and were closely monitored for 18 months. **Objectives:** This study aimed to describe the beneficial effects of denosumab in DSO treatment as well as pain relief and the significant lack of long-term use due to poorer outcomes after repeated use. DSO of the jaw is a poorly understood rare chronic disease the treatment of which is still very challenging despite a rapid development of medicine. Different medical treatments have been proposed without any significant long-lasting success. Bisphosphonates have offered substantial clinical benefit in DSO therapy, but due to harmful pharmacodynamic properties, denosumab therapy has been used to replace bisphosphonate therapy. Patients had a reduction in pain intensity with each subsequent application of denosumab but with less success than the first administration of denosumab. This case report has shown that denosumab could be a promising conservative treatment option for pain treatment in patients suffering from DSO.

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Introduction

Diffuse sclerosing osteomyelitis (DSO) of the mandible is a poorly understood rare chronic disease characterized by recurrent cheek swelling, trismus, and severe mandibular pain with the absence of fistula formation or suppuration in clinical examination (1-3).

In addition to clinical finding, it has a striking radiological finding characterized by partial osteolytic and osteosclerotic processes at the initial stage of the disease. Over time, bone sclerosis becomes more prominent with noticeable sub-

Uvod

Difuzni sklerozirajući osteomijelitis (DSO) čeljusti rijetka je kronična bolest koju obilježavaju oteklina, trizmus i jaka bol u čeljusti uz izostanak stvaranja fistule ili gnojenja (1 – 3). Osim kliničkoga nalaza, u početnoj fazi bolesti i radiološki nalaz pokazuje osteolitičke i osteosklerotske promjene na kosti. Tijekom godina skleroza postaje izraženija s primjetnim subperiostalnim stvaranjem kosti, periostalnom reakcijom, širenjem lamine dure i gubitkom konture mandibularnog kanala (3, 4).

periosteal bone formation, periosteal reaction, lamina dura spreading, and mandibular canal boundary loss (3, 4).

Despite the development of medicine, treating this disease is still very challenging. Attempts have been made with long-term steroid, analgesic and antibiotics therapy, hyperbaric oxygen therapy and aggressive oral surgery procedures, all without significant long-lasting success (3, 5, 6).

Promising results have been reported concerning the treatment of DSO with bisphosphonates, mainly with intravenously administered ibandronate (7, 8).

By inhibiting the osteoclasts, the bisphosphonates inhibit bone resorption and remodeling. Although intravenous bisphosphonates show promising results in therapy DSO, their noticeable deficiency is a very long half-life in bone (approximately ten years) and the possibility of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Denosumab, a monoclonal antibody used in this case report, has some favorable characteristics compared to ibandronate. Denosumab inhibits the receptor activator of nuclear factor-kB ligand (RANKL) and potently inhibits osteoclast differentiation, function, and survival, thus decreasing bone resorption and remodeling. Furthermore, unlike bisphosphonates, denosumab does not accumulate in bone, and its effect on modelling is reversible and lasts for approximately six months (9-11).

We showed two cases where denosumab was used to treat mandibular pain in DSO since other conservative treatments were not successful and did not have long-lasting satisfactory effects.

Case reports

DSO was diagnosed after clinical and radiological examination, bone biopsy, and histological analysis with no bacterial colonization in microbiological testing. Both patients were conservatively treated with analgesics (diclofenac, ibuprofen), corticosteroids and antibiotics, and hyperbaric oxygen therapy, but without significant long-lasting success.

Written informed consent was obtained from the patient, and a routine blood testing (differential blood count, complete blood count, renal function test, a 25-hydroxy vitamin D test, and ionized calcium test) was performed on each patient before every denosumab application. All complications, symptoms related to the disease and mandibular pain levels on the VAS scale were recorded every day for 18 months. The level of pain was evaluated on a scale from 0 to 10 according to the visual analogue scale (VAS), where the endpoints were marked as zero, meaning “no pain”, and ten meaning “unbearable pain”. The pain level was measured the day after the denosumab application and for the following six months. The 25-hydroxy vitamin D test blood levels were within normal as patients were under supplementation during the treatment. Before each denosumab application, a detailed clinical examination, new multislice computed tomography (MSCT) and scintigraphic imaging were performed (Figure 1, Figure 3).

Unatoč razvoju medicine, liječenje te bolesti još uvijek je vrlo zahtjevno. Dugotrajna primjena kortikosteroida, analgetika i antibiotika, hiperbarična terapija kisikom i agresivni kirurški zahvati standardni su načini terapije, ali nisu pokazali znatan dugotrajni uspjeh (3, 5, 6).

Zabilježeni su dobri rezultati u liječenju DSO-a bisfosfonatima, uglavnom intravenski primijenjenim ibandronatom (7, 8).

Inhibiranjem osteoklasta, bisfosfonati smanjuju resorpciju i remodelaciju kosti. Iako intravenski primijenjeni pokazuju obećavajuće rezultate u liječenju DSO-a, njihov je nedostatak vrlo dug poluživot u kosti (oko deset godina) i mogućnost pojave osteonekroze čeljusti (BRONJ) prouzročene bisfosfonatima.

Denosumab, monoklonsko protutijelo korišteno u ovom slučaju, ima nekoliko povoljnih svojstava u usporedbi s ibandronatom. Inhibira receptor aktivatora nuklearnog faktora-kB (RANKL) liganda i snažno suprimira diferencijaciju, funkciju i preživljavanje osteoklasta, smanjujući resorpciju i remodelaciju kosti. Nadalje, za razliku od bisfosfonata, denosumab se dugoročno ne nakuplja u kostima. Učinak je reverzibilan i traje otprilike šest mjeseci (9 – 11).

Prikazujemo dva slučaja u kojima je denosumab korišten za liječenje boli kod pacijenata s DSO-om zato što su druge konzervativne metode bile neuspješne i nisu dale dugotrajne zadovoljavajuće rezultate.

Prikazi slučajeva

DSO je dijagnosticiran nakon kliničkoga i radiološkoga pregleda, biopsije kosti, histološke analize te mikrobiološkog testiranja. Obje pacijentice uglavnom su liječene analgeticima (diklofenak, ibuprofen), kortikosteroidima i antibioticima te hiperbaričnom terapijom kisikom, ali bez značajnog dugotrajnog uspjeha.

Obje su potpisale informirani pristanak, a rutinsko testiranje krvi (diferencijalna krvna slika, kompletna krvna slika, testovi bubrežne funkcije, 25-hidroksi vitamina D i ioniziranog kalcija) obavljeno je prije svake primjene denosumaba. Komplikacije, simptomi vezani uz bolest i intenzitet boli bilježeni su svaki dan tijekom 18 mjeseci. Razina boli procjenjivala se na ljestvici od 0 do 10 prema vizualnoj analognoj ljestvici (VAS) na kojoj je „nedostatak boli“ označen nulom, a „nepodnošljiva bol“ brojem deset. Tijekom liječenja ordinirani su suplementi vitamina D pa su njegove vrijednosti u krvi bile uredne. Prije svake aplikacije denosumaba obavljen je detaljan klinički pregled, nova višeslojna kompjutorizirana tomografija (MSCT) čeljusti i scintigrafija kostiju (slike 1. i 3.).

Clinical case 1

A 59-year-old woman visited the Department of Maxillofacial and Oral Surgery 90 days after the first right molar and the second premolar were extracted, and mandibular pain and swelling were still present. The patient stated that the post extraction wound took a long time to heal, while the intraoral examination showed a normal-looking mucosa without signs of acute odontogenic or other infections that could explain her present symptoms. A panoramic radiograph and an MSCT showed an expansion of the mandibular buccal and lingual cortical bone on the right side, pronounced bony sclerosis of the mandibular right side, which was more voluminous than the contralateral side of the mandible, Figures 1 and 2. DSO was identified considering clinical, radiological examination, microbiological testing, and biopsy with histology diagnosis. This DSO was treated with antibiotics, NSAID, corticosteroids, and HBO but without pain relief for three years. Then, the surgical and other conservative treatment modalities were explained, and denosumab therapy started after explaining the possible risks of developing MRONJ.

The patient was administered subcutaneously with the first injection of 60 mg of denosumab (Prolia® 60 mg) in August 2019. Intermittent mild mandibular pain occurred and lasted for ten days, hence taking analgesics was unnecessary. After that, there was a pain-free period for about four months, after which severe pain occurred. Six months after the first administration, the subcutaneous 60mg denosumab was repeated due to the re-onset of pain, after which, in the next thirty days, the pain was characterized as severe decrease in a pain-free period that lasted for the next three months. Again, after a pain-free period, severe pain occurred. Six months after the second, the third injection of 60 mg of denosumab was administered. The pain gradually decreased, and after six weeks, it completely disappeared, which lasted only two days. After that, the pain gradually increased, with short-term remissions, and at week 19 it became almost unbearable. The reduction or disappearance of mandibular swelling followed the reduction in pain. Each subsequent application of denosumab was less successful than the previous one, Figure 3. A one-way repeated measures ANOVA was performed to compare VAS scores on the first, second and third subcutaneous denosumab administration. The mean values of VAS were 2.935±3.938, 4.609±4.337 and 5.516±2.760 for the first, second and third denosumab administration, respectively. There was a significant effect in VAS scores among administrations, Wilks' Lambda=0.515, F (2, 182) =85.718, p< 0.001. In addition, the post-doc test with Bonferroni adjustment for multiple comparisons showed a statistically significant difference in VAS scores among pairs of three administrations (p<0.001).

Clinical case 2

A 66-year-old woman was referred to the Department of Maxillofacial and Oral Surgery because of jaw swelling, and the mandibular pain was classified as "cannot be worst". Between May 2018 and May 2019, she was treated with different analgesics (diclofenac, ibuprofen), steroids and antibiot-

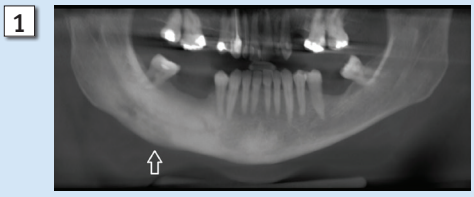
Klinički slučaj 1

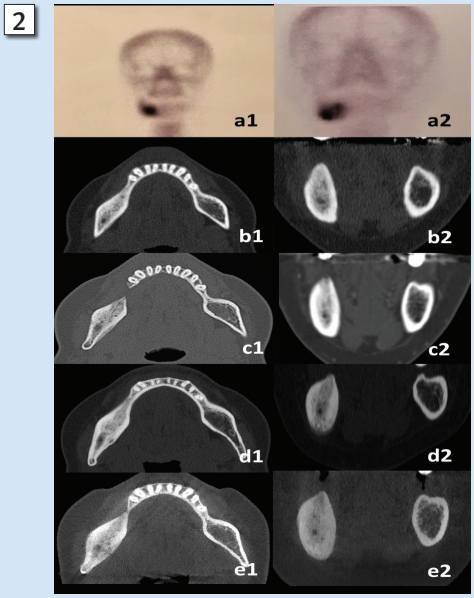
Na Odjel maksilofacijalne i oralne kirurgije javila se 59-godišnja pacijentica zbog bolova i otekline u donjoj čeljusti. Prije 90 dana ekstrahirala je prvi desni donji kutnjak i drugi desni donji pretkutnjak. Navodi da je postekstrakcijska rana dugo cijelila, no intraoralnim pregledom ustanovljena je normalna sluznica bez znakova akutnih odontogenih ili neodontogenih upala koje bi mogle objasniti njezine simptome. Na MSCT-u je uočena voluminoznija desna strana mandibule s ekspanzijom bukalne i lingvalne kortikalne kosti i izraženom koštanom sklerozom (slike 1. i 2.). Na temelju kliničkoga i radiološkoga pregleda, mikrobiološkog ispitivanja i biopsije s histološkom dijagnozom, postavljena je dijagnoza difuznoga sklerozirajućeg osteomijelitisa mandibule. Liječena je standardnom terapijom tri godine, ali bez smanjenja boli. Pokušalo se i s kirurškim i drugim konzervativnim načinima liječenja, a terapija denosumabom počela je poslije prihvaćanja rizika od pojave medikamentne osteonekroze čeljusti (MRONJ).

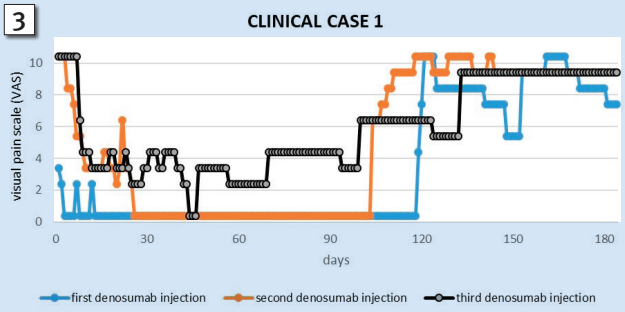
Pacijentici je supkutano ubrizgana prva injekcija denosumaba od 60 mg (Prolia® 60 mg) u kolovozu 2019. godine. Prvih desetak dana povremeno se pojavljivala blaga bol, ali nije imala potrebu za analgetikom. Potpuno bezbolno razdoblje trajalo je oko četiri mjeseca, nakon čega su se ponovno pojavili jaki bolovi. Šest mjeseci poslije prve primjene ponovljena je supkutana doza od 60 mg denosumaba, ali je tada bezbolno razdoblje trajalo tri mjeseca. Šest mjeseci poslije druge injekcije, primijenjena je treća od 60 mg denosumaba. Bolovi su postupno slabjeli, a poslije šest tjedana potpuno su nestali, što je trajalo samo dva dana. Zatim su se postupno intenzivirali, uz kratkotrajne remisije, da bi u 19. tjednu postali gotovo nepodnošljivi. Smanjenje ili odsutnost otekline čeljusti pratilo je smanjenje boli. Svaka sljedeća primjena denosumaba bila je manje uspješna od prijašnje (slika 3.). Provedena je jednosmjerna ANOVA ponovljenih mjerenja za usporedbu rezultata VAS-a pri prvoj, drugoj i trećoj supkutanoj primjeni denosumaba. Srednje vrijednosti VAS-a bile su 2,935 ± 3,938, 4,609 ± 4,337 i 5,516 ± 2,760 za prvu, drugu i treću primjenu denosumaba. Postojao je značajan učinak u rezultatima VAS-a među primjenama – Wilksova Lambda = 0,515, F (2, 182) = 85,718, p < 0,001. Osim toga, post-hoc test s Bonferronijevom prilagodbom za višestruke usporedbe pokazao je statistički značajnu razliku u rezultatima VAS-a među parovima od tri primjene (p < 0,001).

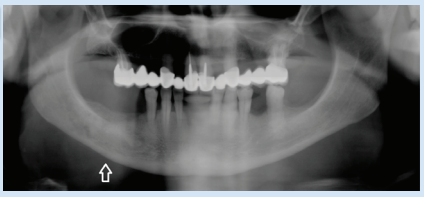
Klinički slučaj 2

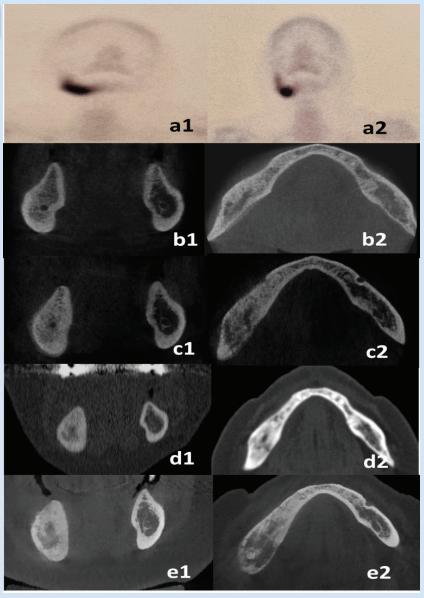
Na Odjel maksilofacijalne i oralne kirurgije zbog otekline i izrazite boli u donjoj čeljusti upućena je 66-godišnja pacijentica. Panoramskom radiografijom i MSCT-om ustanovljena je koštana skleroza desne strane mandibule (slike 4. i 5.) te je na temelju kliničkoga i radiološkoga pregleda postavljena











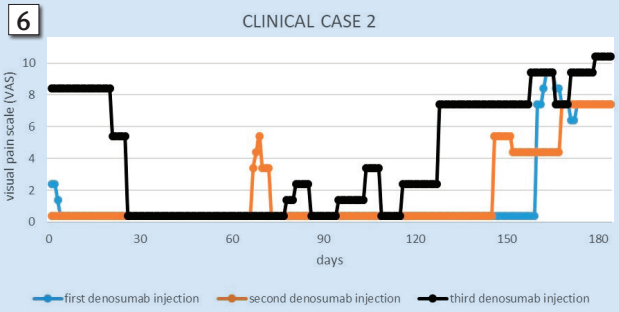


Figure 1 An orthopantomograph before the treatment with Prolia® 60 mg showed sclerosis of the right side of the mandible of a 59-year-old woman.

Slika 1. Ortopantomogram 59-godišnje pacijentice prije liječenja denosumabom (Prolia® 60 mg) – pokazuje sklerotično promijenjenu desnu stranu mandibule

Figure 2 Scintigraphy with increased metabolic activity in the right mandible before the first denosumab administration (a1). Unchanged metabolic activity after last denosumab therapy (a2). Coronal and axial radiological examinations (MSCT) of a 59-year-old woman with diffuse sclerosing osteomyelitis show a discretely increased bone sclerosis of the right corpus of the mandible with the noticeable subperiosteal bone formation during denosumab therapy, before denosumab therapy (b1, b2), before a second dose (c1, c2), before third dose (d1, d2) and six months after the third dose of denosumab therapy (e1, e2).

Slika 2. Scintigrafija kosti pokazuje pojačanu metaboličku aktivnost na desnoj strani mandibule prije prve aplikacije denosumaba (a1) – nakon posljednje terapije stanje je nepromijenjeno (a2); MSCT snimka 59-godišnje pacijentice u koronalnom i aksijalnom presjeku – diskretno je pojačana sklerozacija kosti desne strane korpusa mandibule sa subperiostalnom nakupinom kosti tijekom terapije denosumabom: prije terapije (b1, b2), prije druge doze (c1, c2), prije treće doze (d1, d2) te 6 mjeseci poslije posljednje doze

Figure 3 Comparison of pain level on VAS scale during six months after first, second and third denosumab administration in first clinical case

Slika 3. Usporedba stupnja boli na vizualno analognoj ljestvici (VAS) kod prve pacijentice poslije prve, druge i treće primjene denosumaba

Figure 4 An orthopantomograph before the treatment with Prolia® 60 mg showed sclerosis of the right side of the mandible of a 66-year-old woman.

Slika 4. Ortopantomogram 66-godišnje pacijentice prije liječenja denosumabom (Prolia® 60 mg) – vidljiva je pojačana sklerozacija kosti na desnoj strani mandibule

Figure 5 Scintigraphy with increased metabolic activity in the right mandible before first denosumab administration (a1) and (a2) unchanged metabolic activity after last denosumab therapy. Coronal and axial radiological examinations (MSCT) of a 66-year-old woman with diffuse sclerosing osteomyelitis show less pronounced bone sclerosis of the right mandible during the denosumab therapy period: before denosumab therapy (b1, b2), before a second dose (c1, c2), before third dose (d1,d2) and six months after the third dose of denosumab therapy (e1, e2).

Slika 5. Nalaz scintigrafije kosti koja pokazuje pojačanu metaboličku aktivnost na desnoj strani mandibule prije prve primjene denosumaba (a1) i nepromijenjeno stanje poslije posljednje aplikacije (a2); MSCT u koronalnom i aksijalnom presjeku 66-godišnje pacijentice – tijekom vremena vidljiva je manje izražena skleroza na desnoj strani mandibule: prije terapije denosumabom (b1, b2), prije druge doze (c1, c2), prije treće doze (d1, d2), šest mjeseci poslije posljednje doze (e1, e2)

Figure 6 Comparison of pain level on VAS scale during six months after first, second and third denosumab administration in second clinical case

Slika 6. Usporedba intenziteta boli na vizualno analognoj ljestvici (VAS) poslije prve, druge i treće primjene denosumaba kod druge pacijentice

ics, but without any significant long-lasting success. She was also treated with hyperbaric oxygen therapy, which did not show clinically significant improvement. Panoramic radiograph and MSCT revealed bone sclerosis of the right mandible with noticeable subperiosteal bone formation, Figures 4 and 5. Clinical and radiological examination excluded odontogenic and temporomandibular etiology, and DSO was diagnosed. The diagnosis was confirmed by bone biopsy, histological analysis and no bacterial colonization in microbiological testing.

She was offered surgical treatment for the DSO, which she refused, and after being informed about the risk of the development of MRONJ, she agreed to treatment with denosumab.

In October 2019, she received an injection of 60 mg of denosumab (Prolia® 60 mg) subcutaneously, and two days later, she was pain-free. With no analgesics, the pain-free period lasted over five months. At week 24, after the denosumab application, severe pain occurred with one episode of mild relief. The second injection of 60 mg of denosumab subcutaneously was given, and the pain decreased during the day of application; then, in the ninth week, moderate pain appeared, which disappeared after a few days, and reappeared in the 20th week. It was more pronounced to the point of severe pain and it did not decrease. A significant effect on pain reduction in the third application of 60 mg of denosumab was achieved at the end of the second week, while the pain completely disappeared at the end of the third week. The tolerable state lasted until the 18th week when the pain began to increase to unbearable at 25 week. The reduction or disappearance of jaw swelling also followed the reduction in mandibular pain. Each subsequent application of denosumab was less successful than the previous one (Figure 6). A one-way repeated measures ANOVA was performed to compare VAS scores on the first, second and third subcutaneous denosumab administration. The mean values of VAS were 1.016±2.517, 1.272±2.359 and 3.777±3.708 for the first, second and third denosumab administration, respectively. There was a significant effect in VAS scores among administrations, Wilks'Lambda = 0.557, F (2, 182) = 72.377, p<0.001. Post-Hoc test with Bonferroni adjustment for multiple comparisons showed a statistically significant difference in VAS scores between the first and third administrations and second and third administrations (p<0.001).

Discussion

Although it significantly affects the quality of life due to recurrent swelling, trismus, and severe mandibular pain, the pathophysiology remains largely unknown, and DSO treatment is still unsuccessful. Given the current methods of DSO treatment, it was necessary to explore another conservative, non-surgical treatment (3, 6-8). The first studies using bisphosphonates in the treatment of DSO have been conducted since 2001. They have shown a relatively successful treatment option but with inconsistent protocols, routes of administration, types, and doses of bisphosphonates (3, 7). To the best of our knowledge, only two scientific papers with

sumnja na DSO. Od svibnja 2018. do svibnja 2019. liječena je analgeticima, kortikosteroidima i antibioticima te hiperbaričnom terapijom kisikom, no klinički nije postignuto znatno poboljšanje. Dijagnoza je potvrđena biopsijom kosti, histološkom analizom i mikrobiološkom pretragom.

Ponuđeno joj je kirurško liječenje, što je odbila, a nakon što je obaviještena o riziku od nastanka MRONJ-a pristala je na liječenje denosumabom.

U listopadu 2019. primila je injekciju od 60 mg denosumaba (Prolia® 60 mg) supkutano i poslije dva dana bol je nestala, što je trajalo više od pet mjeseci. U 24. tjednu poslije primjene lijeka pojavila se jaka bol s jednom epizodom blagoga olakšanja. Aplicirana je druga injekcija od 60 mg denosumaba supkutano, bol se smanjila već u danu primjene, a zatim se u 9. tjednu pojavila umjerena bol koja je nestala za nekoliko dana, a u 20. tjednu ponovno se pojavila, bila je izraženija i nije se smanjivala. Značajan učinak na smanjenje boli pri trećoj primjeni jednake doze denosumaba postignut je na kraju drugog tjedna, a bol je potpuno nestala na kraju trećeg tjedna. Podnošljivo stanje trajalo je do 18 tjedana kada su se bolovi počeli pojačavati do nepodnošljivih u 25. tjednu. Smanjenje ili nestanak otekline čeljusti također je pratilo slabljenje boli u donjoj čeljusti. Svaka sljedeća primjena denosumaba bila je manje uspješna od prijašnje (slika 6.). Provedena je jednosmjerna analiza varijance za nezavisne uzorke (ANOVA) ponovljenih mjerenja za usporedbu rezultata VAS-a pri prvoj, drugoj i trećoj supkutanoj primjeni denosumaba. Srednje vrijednosti VAS-a bile su 1,016 ± 2,517, 1,272 ± 2,359 i 3,777 ± 3,708 za prvu, drugu i treću primjenu. Postojao je značajan učinak u rezultatima VAS-a među administracijama – Wilks'Lambda = 0,557, F(2, 182) = 72,377, p < 0,001. Post-hoc test s Bonferronijevom prilagodbom za višestruke usporedbe pokazao je statistički značajnu razliku u rezultatima VAS-a između prve i treće primjene te druge i treće primjene (p < 0,001).

Rasprava

Pacijentima s DSO-om znatno je narušena kvaliteta života zbog ponavljajućih oteklina, trizmusa i intenzivne boli, a time i česte uporabe analgetika i antibiotika. Patofiziologija same bolesti još uvijek je nepoznata te je potrebno istražiti nove načine liječenja (3, 6 – 8). Godine 2001. objavljene su prve studije u kojima su se autori za tu svrhu koristili terapijom bisfosfonatima. Iako su se pokazali razmjerno uspješnima, način primjene, vrsta i doza samoga lijeka nije standardizirana (3, 7). Koliko nam je poznato, samo su autori dvaju radova s ukupno trima slučajevima izvijestili o liječenju DSO-a denosumabom (1, 12), a ovo je prvi prikaz slu-

three cases reported the treatment of DSO with denosumab (1, 12), and this is the first case report that closely followed patients for 18 months with three denosumab administration. A dose of 60 mg denosumab was used because it is the most commonly used dose in osteoporosis and is safe and reliable (12).

Our findings have shown significant results of mandibular pain regression and reducing swelling in both patients after they had previously been on different conservative treatment methods: antibiotics, hyperbaric oxygen therapy, and steroids, which did not show significant long-lasting success.

Similarly, positive results have been established in a study by Otto et al. where 11 patients with DSO were successfully treated with bisphosphonate ibandronate. In contrast, after the recurrence of symptoms characteristic of DSO, one year after initial therapy with bisphosphonates, and one patient was treated with a subcutaneous administration of 60 mg denosumab, resulting in the disappearance of all symptoms and inflammatory activity (7). Hallmer et al. (1) obtained similar results when using denosumab subcutaneously, in contrast to Otto et al. (12), but without prior intravenous use of bisphosphonates, resulting in the complete disappearance of pain symptoms in both treated patients. Doses of denosumab in the first clinical case administered subcutaneously were significantly higher than in our cases. During the first three months, 120 mg were given every month and then two times 120 mg in the following eleven months. In the second clinical case, the denosumab administration protocol was similar to ours.

There were also some differences in our report on the success of therapy compared to Otto et al. (12) and Hallmer and al. (1). In our cases, patients were closely monitored for a more extended period, and the patients had a reduction in the intensity of pain with each subsequent application of denosumab following reducing of swelling, but with less success than the first administration of denosumab. After every next denosumab application, the average rated pain on the VAS scale was higher. After the first denosumab administration was VAS 2.934; after the second, VAS was 4.608; and after the third, VAS was 5.516. In the second clinical presentation, moderate pain on the VAS scale was rated after the first administration, VAS 1.016; after the second, VAS 1.571; and after the third, VAS 3.777.

The exact pathophysiological mechanism of action of antiresorptive drugs in the treatment of DSO and mandibular pain reduction is unclear. There are several theories about the aforementioned. Otto et al. consider that disrupting the RANK / RANKL / OPG system affects the osteoclastic and osteoblastic activity. The mechanism of that system is considered to impact the emergence of the DSO. Excessive activity of osteoclasts or inaccuracy in interaction and coupling between osteoclasts and osteoblasts will eventually cause an increase in osteoblast activity and, consequently, bone sclerosis.

Consequently, the inhibition of osteoclasts may reduce osteoclastic pain mediator excretion, pain levels and swelling (12,13). However, antiresorptive therapy, which is used in DSO therapy, has some limitations associated with developing MRONJ. Therefore, we decided on conservative de-

ja kada se 18 mjeseci pozorno pratilo pacijente s trima aplikacijama. Primijenili smo dozu od 60 mg supkutano jer je često korištena za pacijente s osteoporozom te je sigurna i pouzdana (12).

Otto i suradnici uspješno su 11 pacijenata s DSO-om liječili bisfosfonat ibandronatom. Nakon ponovne pojave simptoma, godinu dana poslije inicijalne terapije bisfosfonatima, jedan je pacijent liječen supkutanom primjenom 60 mg denosumaba, što je rezultiralo nestankom svih simptoma i regresijom upale (7). Hallmer i suradnici (1) dobili su slične rezultate pri supkutanoj primjeni denosumaba, ali za razliku od Otta i suradnika (12), prije toga bez intravenske primjene bisfosfonata, što je rezultiralo potpunim nestankom boli kod oba liječena pacijenta. Primijenjene doze denosumaba bile su znatno više nego u našim slučajevima. Tijekom prva tri mjeseca aplicirano je bilo 120 mg svaki mjesec, a zatim dva puta po 120 mg u sljedećih jedanaest mjeseci. U drugom kliničkom slučaju protokol primjene denosumaba bio je sličan našemu.

U usporedbi s Ottom i suradnicima (12) i Hallmerom i suradnicima (1), u našim slučajevima pacijentice su dulje pomno praćene, bol im se smanjivala poslije svake primjene denosumaba, ali s manje uspjeha nego tijekom prve uporabe. Prosječna ocjena boli poslije prve primjene VAS-om iznosila je 2,934, poslije druge 4,608, a poslije treće 5,516. U drugoj kliničkoj prezentaciji, umjerena bol na VAS ljestvici ocijenjena je poslije prve primjene, s VAS-om 1,016, poslije druge, s VAS-om 1,571; a poslije treće 3,777.

Točan patofiziološki mehanizam djelovanja antiresorptivnih lijekova u liječenju DSO-a i smanjenju mandibularne boli nije jasan. O navedenome postoji nekoliko teorija. Otto i suradnici smatraju da poremećaj RANK / RANKL / OPG sustava utječe na osteoklastičnu i osteoblastičnu aktivnost. Pretjerana aktivnost osteoklasta ili promjene u interakciji osteoklasta i osteoblasta na kraju će prouzročiti povećanu aktivnost osteoblasta i, posljedično, sklerozu kosti. Inhibicija osteoklasta također može smanjiti izlučivanje osteoklastičnog medijatora boli, razinu boli i otekline (12). No antiresorptivna terapija ima ograničenja povezana s razvojem BRONJ-a. Zato smo se u našim slučajevima odlučili za konzervativnu terapiju denosumabom jer, u usporedbi s bisfosfonatima, imaju kraći poluvijek (~26 dana) i ne nakupljaju se u kostima, tj. eliminiraju se šest mjeseci poslije primjene (9, 10).

nosumab therapy to treat our patients because compared to bisphosphonates, they have a shorter half-life (~26 days) and have no bone accumulation, i.e. they are eliminated six months after administration (9, 10).

Conclusions

In conclusion, these case reports show the benefits of denosumab in DSO pain with short-term intake. However, there is a significant reduction in success with each subsequent dose. Therefore, in our cases, a fourth denosumab administration was planned, with a dose twice as large as the previous or alternative surgical resection. Furthermore, it is unknown whether higher doses and more frequent administration of denosumab, different routes, and administration protocols would be more effective and lead to a longer duration of the complaint-free interval. However, further research is needed with control groups and longer follow-ups to confirm the aforementioned statements.

Zaključak

Ovi prikazi slučajeva pokazuju pozitivan učinak denosumaba na smanjenje boli kod pacijenata s DSO-om, ali i znatno manji uspjeh poslije svake sljedeće doze. Zato se u našim slučajevima planira četvrta primjena denosumaba s dvostruko većom dozom od prijašnjih ili, alternativno, kirurška resekcija. Nije poznato bi li veće doze i češća primjena denosumaba, te različiti načini i protokoli bili učinkovitiji i omogućili dulju remisiju pa su potrebna dodatna istraživanja s duljim praćenjem pacijenata.

Conflict of interest

The authors declare no conflict of interest

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Sažetak

Opisane su dvije pacijentice s difuznim sklerozirajućim osteomijelitisom (DSO) mandibule koje su liječene denosumabom prema jednakom protokolu i praćene su 18 mjeseci. Cilj je bio opisati korisne učinke denosumaba u liječenju DSO-a, ali i slabije djelovanje na ublažavanje boli poslije dugotrajne primjene. DSO čeljusti nedovoljno je istražena rijetka kronična bolest čije je liječenje, unatoč razvoju medicine, još uvijek vrlo izazovno. Predloženim metodama ne postiže se značajan i dugotrajan uspjeh. Bisfosfonati su se pokazali korisnima u liječenju DSO-a, no zbog štetnih farmakodinamičkih svojstava potrebna je alternativna terapija. Ovaj prikaz slučaja pokazuje da se dvjema pacijenticama bol smanjila poslije poslije aplikacije denosumaba čiji je najjači učinak uočen poslije prve primjene. Denosumab bi mogao biti opcija konzervativnog liječenja boli koja obećava kad je riječ o pacijentima s DSO-om.

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