DENTISTRY

Openventio PUBLISHERS

ISSN 2377-1623 Open Journal http://dx.doi.org/10.17140/DOJ-1-105

Case Report

*Corresponding author
Irene García-Ávila, DMD, PhD
Assistant Professor
University Dentistry Clinic-Alfonso X El Sabio
University of Madrid
Madrid, Spain
E-mail: Ireneiga@hotmail.com

Volume 1 : Issue 1
Article Ref. #: 1000DOJ1105

Article History
Received: November 6th, 2014
Accepted: December 12th, 2014
Published: December 16th, 2014

Citation
García-Ávila I, Hernández-Montero S, de la Cruz-Perez J, et al. Osteonecrosis of the jaw related to oral bisphosphonate treatment: a clinical case. *Dent Open J.* 2014; 1(1): 19-24. doi: 10.17140/DOJ-1-105

Osteonecrosis of the Jaw Related to Oral Bisphosphonate Treatment: A Clinical Case

Irene García-Ávila[1*], Sofía Hernández-Montero[2], Javier de la Cruz-Perez[3], Raul Casado-Estebaranz[4], Pilar Velasco-Bohórquez[5] and Juan M. Lorrio-Castro[6]

[1]Assistant Professor, University Dentistry Clinic-Alfonso X El Sabio, University of Madrid, Spain

[2]Maxillofacial Surgery, Department of Dentistry and Stomatology, Medical Association of Chartered Zaragoza, Madrid, Spain

[3]Head of Studies of Dentistry, University Alfonso X El Sabio, Madrid, Spain

[4]Department of Dentistry and Stomatology, Madrid, Spain

[5]Department of Dentistry and Stomatology (Oral Periodoncia Surgery), Madrid, Spain

[6]Departament of Dentistry and Stomatology, Oral Implants Surgery, University Alfonso X el Sabio, Madrid, Spain

ABBREVIATIONS: ONJ: Osteonecrosis of the Jaw; AAOMS: American Association of Oral and Maxillofacial Surgeons.

INTRODUCTION

Bisphosphonates are inhibitors of osteoclastic activity and hence cause inhibition of bone resorption.[1-3] These drugs, which are synthetic analogy of natural pyrophosphate, have proven their effectiveness in the treatment of diverse metabolic bone diseases related to quantitative alterations, as is the case of osteoporosis,[4-6] or qualitative ones, as in Paget's disease.[7] The most common way for their administration is orally.[5] These anti-resorptive drugs cause an increase of bone mineral density and a quick decrease of fracture risk.[8-13] They are also effective in oncology patients (breast cancer, prostate cancer, lung cancer, and multiple myeloma, among others).[14-19] Additionally, these medicines reduce the symptoms of bone pathology (bone pain, delay of the first new bone event, reduction in fracture appearance).[4,17-19] They are normally administered intravenously. Bisphosphonates have anti-cancer effect alone or in combination with other chemotherapy treatments, as they maximize antineoplastic effects.[20] In pediatrics, they are used in the treatment of diseases related to abnormal calcinosis or ectopic bone formation, as is the case of osteogenesis imperfect.[21-23]

Based on a total of 36 cases, Marx, et al. reported an adverse effect of the use of these drugs, which is called Osteonecrosis of the Jaw (ONJ).[24] Ruggiero, et al. further reported that of a total of 63 cases of patients with ONJ, 11.1% suffered originally from osteoporosis.[2]

Since then, numerous medical entities, scientific associations and expert committees have researched this adverse effect.[25-28] It is known that it can appear spontaneously,[16] with an estimated prevalence of 50% in the case of intravenously administered bisphosphonates and 30% in the case of oral administration.[29] On the other hand, it is usually associated with a trigger that invades the integrity of the bone tissue (e.g. tooth extractions, implants, periapical surgery[30-36] or mucous tissue (e.g. rubbing of poorly adapted prosthesis, or taking dental impressions).[37,38] There are factors inherent to the drug that can increase the risk of ONJ, such as bisphosphonate type, potency, or length of treatment. Usage of corticoids can also augment the risk of suffering from this complication. Additionally, there are factors inherent to the patient, such as

ISSN 2377-1623 Open Journal http://dx.doi.org/10.17140/DOJ-1-105

certain sucsystemic pathologies, presence of dental inflammatory pathologies, or ageing.[1,28-35,36, 37-40]

Certain measures and attitudes exist that can decrease the incidence of this pathology. Referral to a dentist for an oral-dental check and elimination of focuses that can put the patients at risk is advised when they are about to receive this therapy, since this oral and maxillofacial complication decreases the patients' quality of life and involves an important health cost, as well as monetary expenditure for the patient.[41-46]

A traumatic interventions are important in order to minimize the incidence of this dreaded effect in patients already undergoing treatment with bisphosphonates.[37,46-48]

Once the injury is set, some experts think that the clinical expressions or symptoms of ONJ can improve by temporarily or permanently discontinuing the bisphosphonates medication. They advise conservative or minimally aggressive treatments combined with long-lasting antibiotic therapy.[45,49-51]

It is desirable for specialists involved in administration of these therapies to count on studies designed with consensual, globally unified protocols that provide them with useful, validated information.

In this study, we present a case of ONJ in a patient undergoing oral bisphosphonates treatment.

CLINICAL CASE

A sixty-two-year-old woman undergoing oral bisphosphonate (Boniva®) treatment for osteoporosis for over 3 years. The patient attended a private clinic for right top canine extraction due to mobility. Six weeks later, she reported pain. During exploration, a gingival fistula with discharge (Figure 1) was observed, and therefore an intraoral radiography was performed (Figure 2).

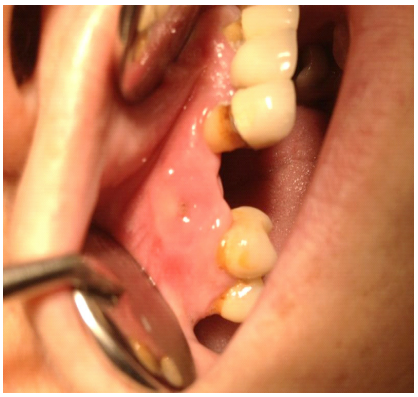

Figure 1: Image of intraoral injury. Gingival fistula can be observed.

Analgesic (Paracetamol 650 mg) and antibiotic (Amoxicilin/Clavulanic acid 1000 mg/125 mg, 2 pills every 12 hours) treatment was established for 15 days, combined with home mouthwash using chlorhexidine 0.12%.[37,52-53] An appointment was set for clinical assessment.

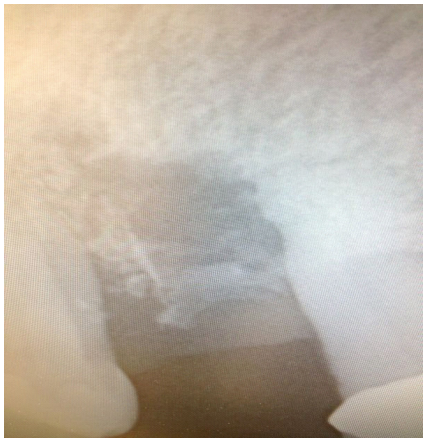

Figure 2: Radiologic image of the number 13 post-extraction socket. Osteolytic lesion can be observed.

After 8 weeks of persistent symptoms, a case of post-extraction ONJ was confirmed, American Association of Oral and Maxillofacial Surgeons (AAOMS) 2006.[15,28,54-56] The same conservative treatment was maintained for 15 more days, her prescription doctor was advised to withdraw the bisphosphonate medication and another appointment was made for a new control check.[37] Finally, it was decided to remove the falling necrotic tissue by surgical sequestrectomy,[1,53] performed with the use of local anaesthesia. The underlying bone was not operated on except for a slight curettage (Figure 3).

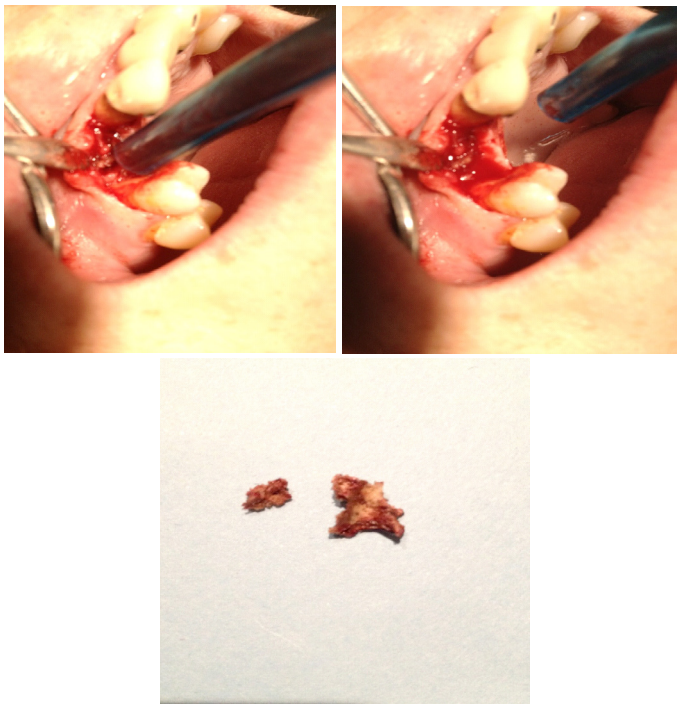

Figure 3: Surgical treatment: Sequestrectomy. Removal of necrotic bone.

It was a case of ONJ at clinical stage II, according the American Association of Oral and Maxillofacial Surgeons (AAOMS) classification.[2,57] The case evolved favourably, and with complete resolution.

ISSN 2377-1623 Open Journal http://dx.doi.org/10.17140/DOJ-1-105

DISCUSSION

Patients attending dental consultations with previous records of undergoing or having undergone oral bisphosphonates treatment (for postmenopausal, glucocorticoid, or male osteoporosis) are becoming more frequent.[3,8,9,58,59,60, 61]

The incidence of ONJ derived from oral bisphosphonates is lower than in the case of intravenous administering. Additionally, existing literature describes the extent and severity of these injuries to be less significant in the case of orally administered bisphosphonates, having a more favourable evolution and frequently ending in healing, in contrast to the more arduous evolution of lesions associated with intravenous therapy.[1,3,29,37,62,63]

Marx et al recommend suspending bisphosphonates treatment for at least two months previous to an intervention. This attempts to normalize the rate of bone turnover, owing to the inhibitory effect of the osteoclasts and a vascular necrosis (anti-angiogenic effect).[24,43,45] However some authors[44] disagree since the bisphosphonate remains embedded in the bone tissue for long periods of time (up to 12 years), and others consider that a critical concentration is necessary for this oral-jaw complication to occur.[64]

ONJ is a clinical entity related to: an alteration of the blood supply, an inhibition of the osteoblastogenesis, and the apoptosis of osteocytes. All the above result in a vascular necrosis of the bone tissue and frequently in super infection and bacterial colonization as well.[37,64,65] Strains of the genus Actinomyces have been found (specifically *A. naeslundii*, *A. israelii*).[66]

Overall, in order to stabilize the symptoms some authors propose a conservative treatment of the lesions, continued long-lasting antibiotic therapy, and discontinuation of bisphosphonates when possible.[49,51-52] Other authors propose the application of plasma rich in growth factors as an alternative therapy in order to stimulate the angiogenesis and repair of the local bone tissue.[67-69]

Decisions should be made by a complete multidisciplinary team (oral and maxillofacial surgeon, oncologist, and rheumatologist) on the basis of the current clinical stage according to the AAOMS.[51,70]

CONCLUSIONS

Informing the pharmacovigilance service is important in these clinical cases in order to know the real incidence of these lesions.

It is imperative to refer to the dentist all patients that are going to be treated with bisphosphonates, whether orally or intravenously, in order to eliminate possible risk factors to subsequently suffer ONJ.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

ACKNOWLEDGEMENTS

The authors thank all the contributors who made possible the execution of this clinical case.

REFERENCES

1. Vicente Rodríguez JC, Junquera Gutiérrez LM. Osteoquimionecrosis of the jaws induced by bisphosphonates. In: Machin Muñiz JA, ed. *How to identify, prevents, and treat complications in implant dentistry*. SA, Madrid, USA: Editorial Ripano; 2012: 385-397.

2. Ruggiero SL, Mehrotra B, RosenbergTj, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. 2004; 62: 527-534. doi: 10.1016/j.joms.2004.02.004

3. Bocanegra-Pérez S, Limiñana-Cañal JM, Vicente-Barrero M, et al. Bisphosphonates in primary care. Epidemiological study of management and impact of bisphosphonates in patients attending dental offices of the Canary Islands Health Service. *Advances in dentistry*. 2010; 26(3). 143-151.

4. Department of Pharmacy and Health Products. Recommendations for the assessment and treatment of primary osteoporosis in women of the Community of Madrid. Madrid, USA: 2008.

5. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med*. 2003; 19: 395-414.

6. Baron R. Anatomy and Biology of Bone Matrix and Cellular Elements General Principles of Bone Biology. Primer on the metabolic bone diseases and disorders of mineral research. Washington, DC, USA: 2003.

7. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacohter*. 2005; 39: 668-677. doi: 10.1345/aph.1E357

8. Cranney A, Welch V, Adachi JD, et al. Etidronate for treating and preventing postmenopausal osteoporosis (Cochrane review): In Cochrane Library. Chichesster, UK: John Wiley & sons, Ltd. 2004; 2. doi: 10.1002/14651858.CD003376.pub2

9. Cranney A, Guyatt G, Krolicki N, et al. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int*. 2001; 12: 140-151.

10. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*. 1995; 333: 1437-1443. doi: 10.1056/NEJM199511303332201

11. Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research-Group. *Lancet*. 1996: 1535-1541. doi: http://dx.doi.org/10.1016/S0140-6736(96)07088-2

12. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with post menopauesel osteoporosis: A randomised controlled trial. *JAMA*. 1999; 282(14): 1344-1352. doi: 10.1001/jama.282.14.1344

13. Reginster JY, Minnie HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int*. 2000; 11: 83-91.

14. Lunch A, Pérez Fidalgo JA, Chirivella I. Indications of bisphosphonates. In: Bagan JV, ed. *Osteonecrosis of the jaw by bisphosphonates*. USA: Valencia Oral Medicine SL; 2008: 1-110.

15. Sosa Henriquez M, Gómez de Tejeda de Romero MJ, Bagán Sebastián JV, et al. Osteonecrosis of the Jaws: Consensus document. Rev Osteoporos. *Metab Miner*. 2009; 1(1): 41-51.

16. Bagán JV, Diz Dios P, Gallego L, et al. Recommendations for prevention of osteonecrosis of the jaw (ONJ) in cancer patients treated with intravenous bisphosphonates. *Oral Med Oral Pathol Oral Cir*. 2008; 13(3): 161-167.

17. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of biphosponates in solid tumours: recommendations of an International expert panel. *Ann Oncol*. 2008; 19(3): 420-432. doi: 10.1093/annonc/mdm442

18. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med*. 1996; 334: 488-493. doi: 10.1056/NEJM199602223340802

19. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer*. 2001; 91: 1191-1200. doi: 10.1002/1097-0142(20010401)91:7<1191::AID-CNCR1119>3.0.CO;2-0

20. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007; 25(7): 829-836. doi: 10.1200/JCO.2005.05.3744

21. Yeste D, Carrascosa A, Audi L. Pathophysiology of calcium-phosphorus metabolism. In: Argente J, Carrascosa A, Gracia R, Rodriguez F. eds. *In the Treaty of Pediatric Endocrinology and Adolescencia*. Madrid, USA: Edimsa; 1995: 551-565.

22. Reeder J, MS, PA-C, Orwoll E, MD. Adults with OI. *N Engl J Med*. 2006; 355.

23. Glorieux FH. Cyclic administration of pamidronate therapy in children with severe osteogenesis imperfecta. *N Engl J Med*. 1998; 339: 947-952. doi: 10.1056/NEJM199810013391402

24. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg*. 2003; 61: 1115-1117. doi: 10.1016/S0278-2391(03)00720-1

25. Sosa Henriquez M, Gómez de Tejeda de Romero MJ, Bagán Sebastián JV, et al. Osteonecrosis de los Maxilares: Documento de consenso. *Rev Osteoporos Metab Miner*. 2009; 1: 41-51.

26. Spanish Agency for Medicines and Health Products. Information Note (ref 2005/17). Parenteral bisphosphonates and osteonecrosis of the jaw. Disponible en: http://www.agemed.es/actividad/alertas/docs/NI_2005-17.pdf

27. Spanish Agency for Medicines and Health Products. Information Note (ref 2005/17). Parenteral bisphosphonates and osteonecrosis of the jaw. Recomendaciones para la prevención de la osteonecrosis maxilar asociada al tratamiento con bisfosfonatos. Available at: http://www.agemed.es/actividad/alertas/usoHumano/seguridad/NI_2009-10_bisfosfonatos.htm 2005; Accessed 2014.

28. American Association of Oral and Maxillofacial Surgeons. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2007; 65: 369-376.

29. Junquera LM. Diagnosis, prevention and treatment of osteonecrosis of the jaw by bisphosphonates. Recommendations of the Spanish Society of Oral and Maxillofacial Surgery (SECOM). *Cient Dent*. 2008; 5(3): 229-237.

30. Marx RE, Cillo JE, Ulloa JJ. Oral Bisphosphonate induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg*. 2007; 65: 2397-2410. doi: 10.1016/j.joms.2007.08.003

31. Reid IR. Osteonecrosis of the jaw: Who gets it, and why? *Bone*. 2009; 44: 4-10. doi: 10.1016/j.bone.2008.09.012

32. Reid I. Patogénesis of osteonecrosis of the jaw. *IBMS Bonekey*. 2008; 2: 69-77.

33. Reid IR, Cundy T. Osteonecrosis of the jaw. *Skeletal Radiol*. 2009; 38: 107.

34. Cartsos VM, Zarvas AI. Bisphosphonate use and the risk of adverse jaw outcomes: A medical claims study of 714,217 people. *J Am Dent Assoc*. 2008; 139: 23-30. doi: 10.14219/jada.archive.2008.0016

35. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/ osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *J Oral MaxillofacSurg.* 2005; 63: 1567-1575. doi: 10.1016/j.joms.2005.07.010

36. Marx RE, Sawatari Y, Fortin M, Broumand V. Risk factors, recognition, prevention, treatment of Bisphosphonate-induced osteonecrosis of the jaws. *J Oral Maxillofac Surg.* 2006; 64: 96.

37. Bagán JV. La osteonecrosis de los maxilares por bifosfonatos. Valencia. *Medicina oral SL*. 2008; 1-110.

38. Reid IR, Grey AB. Is Bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone*. 2007; 41: 318-320. doi: 10.1016/j.bone.2007.04.196

39. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associeted osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007; 22: 1479-1491. doi: 10.1359/jbmr.0707onj

40. Bisphosphonates: Osteonecrosis of the jaw. *Drug Safety Update*. 2009; 3(4): 2-3.

41. Acero J, Burgueño M, de Vicente JC, et al. Diagnóstico, Prevención y tratamiento de la osteonecrosis de los maxilares por bifosfonatos. Recomendaciones de la Sociedad Española de Cirugía Oral y Maxilofacial (SECOM). Comisión Artículo extraido de la Revista Española de Cirugía Oral y Maxilofacial. Madrid, mayo-junio de. 2008; 30(3): 145-156.

42. Jiménez Soriano Y, Roda P. Prevention of Osteonecrosis of the jaw by bisphosphonates. In: Bagan JV, ed. *Osteonecrosis of the jaw by bisphosphonates*. Valencia, Spain: Medicina oral SL; 2008: 1-110.

43. Ruggiero S, Fantasia J, Carlson E. Bisphosphonate- related osteonecrosis of the jaw: Background and guidelines for diagnosis skating and Management. *Oral Surg Oral Med Oral Pathol.* 2006. 102(4): 433-441. doi: 10.1016/j.tripleo.2006.06.004

44. Gallego L, Junquera L. Consequence of therapy discontinuation in bisphosphonate-associated osteonecrosis of the jaws. *Br J Oral Maxillofac Surg.* 2009; 47: 67-68. doi: 10.1016/j.bjoms.2008.05.011

45. Magopoulos C, Karakinaris G, Telioudis Z, Vahtsevanos K, Dimitrakopoulos I, Antoniadis K. Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. *Am J Otolaryngol*. 2007; 28: 158-163. doi: 10.1016/j.amjoto.2006.08.004

46. Barker K, Rogers S. Bisphosphonate-associated Osteonecrosis of the jaw: A guide for the general dental practitioner. *Dent Update.* 2006; 33(5): 270-272.

47. Barrientos FJ, Peral B, de la Peña G, et al. Osteonecrosis of the jaws induced by bisphosphonates: Prevention and therapeutic attitude. *Rev Esp Cir Oral y Maxillofac*. 2007; 29(5): 295-308. doi: http://dx.doi.org/10.4321/S1130-05582007000500002

48. Edwards BJ, Hellstein JW, Jacobsen PL, Katlman S, Mariotti A, Migliorati CA, Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisory statement from the American Dental Asociation Council on Scientific Affairs. *J Am Dent Assoc.* 2008; 139: 1674-1647. doi: 10.14219/jada.archive.2008.0110

49. Hasegawa T, Shinshou Ri, Umeda M, et al. Cols. The observational study of delayed wound healing after tooth extraction in patients receiving oral bisphosphonate therapy. *J Craniomaxillofac Surg*. 2013; 41: 558-563. doi: 10.1016/j.jcms.2012.11.023

50. Mozzati M, Arata V, Gallesio G. Tooth extraction in patients on zoledronic acid therapy. *Oral Oncology*. 2012; 48: 817-821. doi: 10.1016/j.oraloncology.2012.03.009

51. Lerman MA, Xie W, Treister NS, Richardson PG, Weller EA,Woo SB. Conservative management of bisphosphonates-related osteonecrosis of the jaws: Staging and treatment outcomes. *Oral Oncology.* 2013; 49: 977-983. doi: 10.1016/j.oraloncology.2013.05.012

52. Marín Fernández AB, Arjona Giménez C, de Dios Navarrete J. Osteonecrosis de los maxilares asociada al uso de bifosfonatos: A propósito de cinco casos. *Rev Osteoporos Metab Miner.* 2012; 4(1): 37-41.

53. Carbonell Pastor E, Díaz Fernández JM, Murillo Cortés J. Treatment of osteonecrosis of the jaw by bisphosphonates. In: Bagan JV, ed. *Osteonecrosis of the jaw by bisphosphonates*. Valencia, Spain: Oral Medicine SL; 2008: 71-90.

54. American Dental Association Council on Scientific Affairs. Expert panel recommendations: Dental management of patients receiving oral bisphosphonate therapy. *J Am Dental Assoc.* 2006; 137: 1144-1150.

55. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw. 2009.

56. AAOMS position paper on BRONJ. JOMS. 2007; 65: 369-376. 2009 Update. *JOMS.* 2009; 67(1): 2-12.

57. Ruggiero SL, Fantasía J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: Background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006; 102(4): 433-441.

58. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: A crossectional study. *BMJ.* 1996; 313: 344-346. doi: 10.1136/bmj.313.7053.344

59. Recommendations for the assessment and treatment of primary osteoporosis in women of the Community of Madrid. Department of Pharmacy and Health Products. *Madrid.* 2008.

60. Carbonell C. Papel of bisphosphonates in preventing and treating osteoporosis. It butlletí dínformació therapeutic. *Barcelona.* 2004; 16(5): 19-24.

61. Clinical practice guidelines in postmenopausal osteoporosis, glucocorticoid and male. Committee of Experts SEIOMM. Special / Rev.OsteoporosisMetab documents. *Miner*. 2009; 1(1): 53-60.

62. Fresco ER, Ponte FR, Aguirre UM. Bisphosphonates and Oral Pathology II. Osteonecrosis of the jaws: Review of the literature up to 2005. *Med Oral Patol Oral Cir Bucal*. 2006; 11: 265-270.

63. Del Castillo Pardo de Vera JL, García de Marcos JA, Arroyo Rodríguez S, Galdeano Arenas M, Calderón Polanco J. Osteonecrosis of the jaws associated with the use of bisphosphonates. *Rev Esp Cir Oral y Maxilofac.* 2007; 29(5): 295-308.

64. Escobar López EA, López López J, Marques Soares MS, ChimenosKüstner E. Osteonecrosis of the jaw associated with bisphosphonates: a systematic review. 2007; 23(2): 91-101.

65. Naik NH, Russo TA. Bisphosphonates-related osteonecrosis of the jaw: The role of Actinomyces. *Clin Infect Dis.* 2009; 49: 1729-1732. doi: 10.1086/648075

66. Cristian P, Ruiz-Bravo E, Regojo R, Tarín V, Alonso S, Pérez-Míes B. Osteonecrosis of the jaws associated with Actinomyces infection and treatment with bisphosphonates. *Rev Esp Patol.* 2013; 46(3):153-157.

67. Mozzati M, Gallesio G, Arata V, Pol R, Scoletta M. Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: A report of 32 cases. *Oral Oncology.* 2012; 48: 469-474. doi: 10.1016/j.oraloncology.2011.12.004

68. Soydan SS, UcKan S. Management of bisphosphonate- related osteonecrosis of the jaw with a platelet-rich fibrin membrane: Technical Report. *J Oral Maxillofac Surg.* 2013; 1-5.

69. Longo F, Guida A, Aversa C, et al. Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: personal experience and review of the literatura. *Int J Dent.* 2014; 2014: 7. doi: 10.1155/2014/298945

70. Hernández Vigueras S, Jané-Salas E, Pérez Tomás R, López-López J. Osteonecrosis of the jaws associated with use of bisphosphonates: A review of 491 cases. *Av. Odontoestomatol.* 2012; 28(4): 199-209. doi: 10.4321/S0213-12852012000400005