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Comparing Prevalence of Medication-Related Osteonecrosis of the Jaw (MRONJ) due to Denosumab and Bisphosphonates as a Side Effect of Osteoporosis Treatment

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Comparing Prevalence of Medication-related Osteonecrosis of the Jaw (MRONJ) due to
Denosumab and Bisphosphonates as a Side Effect of Osteoporosis Treatment

By

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ABSTRACT

As the baby boomer generation continues to age, the diagnosis of osteoporosis and its side effects will continue to increase. Denosumab and bisphosphonates (BPs) are some of the most common medication classes used to treat osteopenia and osteoporosis, but it is believed that both medications have the possible side effect of medication-related osteonecrosis of the jaw (MRONJ). The purpose of this paper is to uncover if MRONJ is a side effect of osteoporosis treatment and which medication carries the highest incidence rate. Through a review of several electronic databases and several peer reviewed research articles, a wide range of reported incidence rates of MRONJ for both medications were uncovered, along with many compounding possible risk factors. There is the wide range of reported incidence rates among different studies. Through the research, it is found that denosumab carries a slightly higher risk of MRONJ versus bisphosphonates, but the difference was found to be statistically insignificant. Founded risk factors include increasing age, gender, recent dental procedures, history of oral disease, and corticosteroid use. My research is impactful in the fact that as providers, we can be better informed about the differences between denosumab and bisphosphonates and the possible risk factors of MRONJ. We can use the information, along with possible other risk factors and our patient's history, to make joint decisions about what osteoporosis medication is right for our patients.

Keywords: osteonecrosis, jaw, medication-related, bisphosphonates side effects, denosumab side effects, abnormal fracture, osteoporosis

INTRODUCTION

The world's population is ageing: virtually every country in the world is experiencing growth in the number and proportion of older persons in their population, and the United States is no exception. Two factors—longer life spans and aging baby boomers—will combine to double the population of Americans aged 65 years and older during the next 25 years to about 72 million (CDC, 2013). By 2030, older adults will account for roughly 20% of the U.S. population, up from almost 14 percent in 2012 (CDC, 2013). This will have a significant impact on health care the age-related medical issues of aging; a loss of bone mineralization and bone mass in the forms of osteopenia and osteoporosis being a major issue. By definition from the World Health Organization (WHO), osteopenia is defined as a T-score of -1 to -2.5 measured by bone densitometry, while a score of less than -2.5 is diagnosed as osteoporosis. In other words, osteopenia is caused by a loss of bone density, with osteoporosis being a more severe condition. The United States Preventive Services Task Force (USPSTF) has a B grade recommendation for screening of osteopenia and osteoporosis via bone densitometry scan in women 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year old woman who have no additional risk factors (USPSTF, 2016). A grade B recommendation equates that the USPSTF recommends the service and that there is a high certainty that the net benefit is moderate compared to the risks. There is insufficient evidence to assess the balance of benefits and harms of screening in men (USPSTF, 2016).

Postmenopausal women are at greatest risk of developing osteoporosis due to accelerated loss in bone mass associated with the first several years of menopause (International Osteoporosis Foundation, 2017). 200 million women are affected worldwide, with incidence rates increasing with age (International Osteoporosis Foundation, 2017). According to the

International Osteoporosis foundation, worldwide osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every three seconds (International Osteoporosis Foundation, 2017). 24.5% of women and 5.1% of men aged 65 years and over with osteoporosis will experience a fracture of the femur or lumbar spine, according to the CDC (CDC, 2013). As the average life expectancy continues to increase, the frequency of developing fractures and costs associated with the disease are expected to more than double by 2026 (International Osteoporosis Foundation, 2017).

In addition to the personal burden and impact on quality of life, the costs associated with fracture treatment and rehabilitation are enormous. In Europe, the disability due to osteoporosis is greater than the causes by cancers, with the exception of lung cancer, and the lifetime cost is comparable or greater than many chronic diseases, such as asthma or high blood pressure (International Osteoporosis Foundation, 2017). A study from 2002 estimated national health care expenditures attributed to osteoporosis fractures for people aged 45 years and older to be about \$12 billion annually, with approximately 75% of the costs attributed for direct medical care associated with inpatient services, nursing home care, and outpatient services (Desai, Duncan, Sloan, 2003).

There are many different pharmacologic and non-pharmacologic treatment approaches to osteoporosis. Denosumab and BPs are two of the most common pharmacologic treatments prescribed for osteoporosis. However, both are not without their various side effects. Both medications have a possible side effect of osteonecrosis of the jaw, but in family practice, this is believed to be very rare. Through a literature review, I seek to answer the question of which medication class has the lowest incidence rate of osteonecrosis of the jaw as a side effect of the treatment for osteoporosis.

Statement of the Problem

There are many different approaches to treating osteoporosis. Denosumab and bisphosphonates are two of the most common pharmacologic treatments prescribed. However, both are not without their various side effects. Both medications are believed to have the possible side effect of osteonecrosis of the jaw, but this is believed to be very rare.

Statement of the Research Questions

Is the incidence rate of MRONJ greater in those patients treated with denosumab or bisphosphonates? Are there any precipitating factors or conditions that increases incidence rates of MRONJ with treatment of denosumab or bisphosphonates?

REVIEW OF LITERATURE

A comprehensive search was performed using several electronic databases, including CINAHL, PubMed, Clinical Key, and DynaMed Plus. Specific search keywords included: osteonecrosis, jaw, medication-related, bisphosphonates side effects, denosumab side effects, abnormal fracture, osteoporosis. A review of the literature yielded several high-quality reviews of randomized controlled trials, prospective cohort studies, and case control studies with clinical ascertainment of MRONJ. Studies were limited to those with the highest levels of evidence, those published after 2008, and to those with the highest level of evidence. Some articles were used to provide background information on pathophysiology of osteonecrosis of the jaw (ONJ). Several studies were excluded as they compared MRONJ in patients given the medications solely for cancer treatment, not for treatment of osteoporosis.

The drawback to many of the studies is the inconsistencies of the different study conditions, including length of treatment, age of patients, and varied sample sizes. Many studies

reported incidence rates, but did not state any other conditions of the studies. As the authors reported in the Journal of Oral and Maxillofacial Surgeons in 2014, the studies compared had sample sizes varying from 233 participants to 90,000 (see figure three).

Background information of bone physiology:

Osteopenia and osteoporosis are gradual processes, with many compounding contributing factors. The basic pathophysiology of bone loss is due to normal age-related changes in bone remodeling, as well as extrinsic and intrinsic factors that exaggerate this process. After age 30 to 45, the resorption and formation processes become imbalanced, and bone resorption exceeds formation (Lindsay & Cosman, 2014). This imbalance may begin at different ages and varies at different skeletal sites. Excessive bone loss can be due to an increase in osteoclastic activity and/or a decrease in osteoblastic activity. Increased number of bone remodeling site produces a reduction in bone tissue, and can result in permanent loss of tissue and disordered skeletal architecture. In cortical bone, increased remodeling creates more porous bone with decreased overall strength.

The imbalance between bone resorption and remodeling becomes more exaggerated in women after menopause. Estrogen deficiency is believed to cause bone loss by activation of new bone remodeling sites that exaggerates the imbalance between bone formation and resorption. The belief of the importance of estrogen for bone formation and strength is consistent with the most osteoporosis cases occurring in post-menopausal women, when a naturally steady decline in the amount of estrogen occurs (Lindsay & Cosman, 2014).

Many factors can increase the process of bone loss. Inadequate calcium during growth may impair peak bone mass. During adulthood, insufficient calcium intake contributes to relative secondary hyperparathyroidism and increases the rate of bone resorption to maintain normal

serum calcium levels. Vitamin D deficiency can also lead to compensatory secondary hyperparathyroidism and is an important risk factor for osteoporosis, leading to increased bone resorption inactivity can also result in significant bone loss. A large number of medications are potentially detrimental to bone strength, with the most common cause being glucocorticoids. The use of cigarettes over a significant period can also affect bone mass, both directly by its toxic effects or indirectly by modifying estrogen metabolism (Lindsay & Cosman, 2014).

MRONJ definition:

In 2003, Marx reported the first cases of what now become known as MRONJ (Coropiuc et al., 2017). Initially, osteonecrosis was reported only after treatment with bisphosphonates and was referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ). As other antiresorptive classes, like denosumab, seemed to lead to the same outcome, the term was soon altered to antiresorptive-related osteonecrosis of the jaw (ARONJ). Since 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has recommended the use of the term “medication-related osteonecrosis of the jaw” (MRONJ). This change is to better accommodate the growing number of cases of osteonecrosis that are associated with other anti-resorptives in patients who have not used bisphosphonates previously (Coropiuc et al., 2017).

To distinguish MRONJ from other delayed healing conditions and address evolving clinical observations and concerns about under-reporting of disease, the working definition of MRONJ has been modified from the 2009 AAOMS position paper (Ruggiero et al., 2014).

Patients are considered to have MRONJ if all the following characteristics are present:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks

- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

ONJ has three intensity stages, determined by the patient's symptoms and defects of the oral mucosa with bone exposure. But different agencies have different concepts on each stage criteria (see table one below)

Table 1: Different ONJ staging systems

Stage	Marx 2007 ^[55]	AAOMS 2009 ^[5]	SICMF-SIPMO 2012 ^[50]
At risk category		No evidence of exposed or necrotic bone in patients who have been treated with bisphosphonates	
Stage 0	Subclinical damage, microscopically represented by beginner hypocellularity osteoclast apoptosis and decrease of endosteal osteoblast	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone	
Stage 1	A: Painless exposed bone <1 cm B: Painless exposed bone >1 cm	Exposed/necrotic bone in patients who are asymptomatic and who have no evidence of infection	Focal BRONJ Clinical signs and symptoms: Bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity; and/or hypoesthesia/paraesthesia of the lips CT finding: Increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: Markedly thickened and sclerotic lamina dura; persisting alveolar socket; and/or cortical disruption 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)
Stage 2	A: Painful and infected single exposed bone <2 cm B: Painful and infected single exposed bone >2 cm	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Diffuse BRONJ Clinical signs and symptoms: The same as Stage 1 CT findings: Increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: Prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oroantral fistula 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)
Stage 3	A: Multiple exposed bone areas without clinical findings of osteolysis, orocutaneous fistula, or pathological fractures B: Exposed bone >3 cm or with clinical findings of osteolysis, or orocutaneous fistula, or pathological fractures	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: Pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor	Complicated BRONJ The same as Stage 2, with one or more of the following Clinical signs and symptoms: Extraoral fistula; displaced mandibular stumps; nasal leakage of fluids CT findings: Osteosclerosis of adjacent bones (zygoma, hard palate); pathologic mandibular fracture; and/or osteolysis extending to the sinus floor

Note. Adapted from “Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases,” by R. Coropciuc, K. Grisar, T. Aerden, M. Schol, J. Schoenaers, and C. Politis, 2017, *British Journal of Oral and Maxillofacial Surgery*, 55, p. 787-792. Copyright British Association of Oral and Maxillofacial Surgeons

Mode of action of denosumab and bisphosphonates:

There are two main pharmacological approaches to osteoporosis: anabolic therapy, which stimulates new bone formation; and anticatabolic or antiresorptive therapy, which decreases bone resorption and/or inhibits bone turnover. Of the antiresorptive therapies, BPs are the most widely used for patients with osteoporosis. All BPs directly suppress resorption by inhibiting osteoclast attachment and enhancing programmed cell death. Those osteoclasts that do survive have reduced resorptive activity. The three most common first-line BPs are alendronate, risedronate, and zoledronic acid. All treatments are nitrogen-containing, which target a specific metabolic enzyme, farnesyl pyrophosphate synthase (FPPS), which prevents the normal development proteins required for osteoclast function and survival (Hanley, Adachi, Bell & Brown, 2012).

Denosumab is one of the newest antiresorptive agents. It was the first FDA-approved biologic for the treatment of osteoporosis in both men and women (De Paula, Black, & Rosen 2016). Denosumab is a fully human monoclonal antibody to an osteoclast-differentiating receptor activator of nuclear factor-kappa B (RANK). The antibody binds directly to RANK ligand, which results in activation of hematopoietic cells of the osteoclast lineage, beginning the process of bone resorption (De Paula et al., 2016). By blocking this activation, denosumab inhibits osteoclast recruitment and maturation, slowing bone resorption. (Hanley et al., 2012). As a result, the medication increases bone mass density, and hence reduces the risk of fracture. Unlike BPs, denosumab does not persist in the skeleton long-term and needs to be administered once every six months to maintain efficacy. In fact, discontinuation of denosumab can lead to a rebound increase in bone resorption (De Paula et al., 2016).

One major difference between the two medication classes is the length of time the medication is taken. It is suggested that patients taking BPs for approximately five years

discontinue therapy as there appears to be residual bone density and fracture benefit, and there is no evidence that continuing therapy further increases bone density (Rosen, 2017). Denosumab on the other hand can be considered a life-sentence, because once a patient begins treatment, the patient's bone density can rapidly decrease once a dose is missed, so the medication is recommended to be continued chronically.

Other differences between the two medications include indication and cost. The indication for denosumab is having a diagnosis of osteoporosis at any location in the body via bone density scan. The medication is not to be taken for osteopenia without an osteoporosis diagnosis of at least one location in the body. BPs can be taken with for a diagnosis of either osteopenia or osteoporosis. Cost could also affect which medication is available to patients. Although both medications are usually well covered by insurance, one dose of a common BP averages about \$200, while one dose of denosumab can cost up to \$1,100 (Desai et al., 2003).

Incidence rate of ONJ with denosumab and bisphosphonates:

My research had uncovered a wide variety of reported incidence rates of MRONJ.

In the osteoporosis patient population, the incidence of MRONJ is estimated to be about 0.001-0.1%, marginally higher than the incidence rate in the general population at less than 0.001% (Svejda et al., 2016).

In patients with osteoporosis exposed to placebo agents, the risk of ONJ ranges from 0% to 0.2% (Dodson, 2014). For those patients taking zoledronate, a BP, the risk for MRONJ is 0.02% and approximates to the risk for MRONJ in patients exposed to placebo. For patients treated with denosumab, the risk for MRONJ ranges from 0.04% to 0.2% (Dodson, 2014). In 2008, 5.1 million patients older than 55 years received a prescription for BPs. A recent federal study

estimates that the prevalence of BP exposure was seven for every 100 persons in the United States who received a prescription for a BP in the outpatient setting (Dodson, 2014).

In a cross-sectional survey study of more than 13,000 patients, the prevalence of MRONJ in those receiving long-term oral BP therapy was reported at 0.1%. Felsenberg and Hoffmeister (2014) reported a prevalence of MRONJ among patients treated with BPs for osteoporosis of 0.0004%, which equates to less than one case per 100,000 patients exposed, based on reports to the German Central Registry of Necrosis of the Jaw. In a more recent report, Malden and Lopes (2012) derived an incidence report that 0.004% of patients exposed to a BP from 11 cases of MRONJ reported in a population of 90,000 people living in southeast Scotland. The advantage of these studies is the high population studied. But the other conditions of the studies, including demographics of the patients and time frame of the study is unknown. Based on a case-control study, the risk of MRONJ was 13.1 times greater among patients exposed to oral BPs than in patients without exposure (Dodson, 2014).

According to DynaMed Plus, the estimated incidence of MRONJ is 0.001%-0.01% in patients treated with either oral or IV BP therapy. This is only slightly higher than the approximate 0.001% incidence in the general population (DynaMed Plus, 2017). These values are hard to access because of no conditions of the studies are listed.

A systematic review of 92 publications evaluating BP MRONJ found an incidence of up to 12% after 36 months of exposure in cancer patients (Khanet et al., 2009). But in patients with osteoporosis, the incidence rate was found to be less than one case per 100,000 person-years of exposure (Khanet et al., 2009).

In one of the most recent meta-analysis of five randomized trials of denosumab versus bisphosphonates, the studies reviewed used different doses and schedules of administration for

denosumab and neither of which prospectively evaluated ONJ as an endpoint. The rate of ONJ was again higher with denosumab, but the difference was not statistically significant (1.7 versus 1.1 percent) (Berenson, Stopeck 2017).

Authors De Paula, et al., (2016) claim the prevalence of MRONJ is very low when bisphosphonates are used in the doses used to treat osteoporosis. When much higher doses are used to prevent the skeletal complications of cancer, MRONJ is a substantial concern. However, in osteoporosis patients, the prevalence is estimated to be less than one in every 100,000 patients exposed to oral or intravenous BPs who are otherwise healthy.

In another study published in July of 2017, the authors aimed to investigate if switching to denosumab from a BP is associated with a higher prevalence rate of MRONJ (Loyson et al., 2017). 110 patients were sequentially treated with BPs followed by denosumab. The median BP treatment time was 16 months and the median denosumab treatment was 13 months. 240 patients were in the BPs control group, while 240 patients were included in denosumab control group. About 6.7% of the patients developed ONJ during BP therapy, and 10% of patients developed ONJ during denosumab therapy. In the sequential group, 15.5% of patients developed ONJ after therapy of a BP and then denosumab. The incidence of MRONJ was 1.8%, 6.3%, 4.9%, 5.6%, and 3.4%, respectively in the first, second, third, fourth, and fifth year of treatment, an MRONJ incidence similar to that of the denosumab control group (Loyson et al., 2017). The authors concluded that patients treated for osteoporosis seem to have a slightly higher risk of MRONJ early after switching from BPs to denosumab compared to patients remaining on BPs. However, based on the global MRONJ incidence rates, the switch from BPs to denosumab can be considered as safe as initially starting denosumab therapy (Loyson et al., 2017). This study gave the some of the best details found regarding the conditions of the study. The drawback of this

study is the smaller sample size used as well as the congruency of the medications given after each other, making it difficult to assess which medication, or a combination of both, were responsible for the MRONJ.

In 2007, a literature review was performed to clarify the relationship between BP use and development of MRONJ for the treatment of osteoporosis. 11 publications from 1966 to 2006 reporting 26 cases of ONJ in patients being treated with BPs were included. (Pazianas, Miller, Blumental, Bernal, & Kothawala, 2007). This was one of the lengthiest literature reviews found that was included information of over nearly 40 years. The incidence rate was not reported by the authors. However, they did conclude that considering that millions of patients are prescribed BPs, the relative prevalence of MRONJ in these patients was low (Pazianas et al., 2007). It was not possible for the authors to draw any further conclusions about the associated between BP use and MRONJ in these identified studies because of incomplete reporting and the presence of compounding factors (Pazianas et al., 2007). Without any other statistics reported, it is also difficult for me to access the quality of this study.

In 2016, several authors conducted a longitudinal study of cases of MRONJ associated with denosumab and BPs. The incidence of MRONJ in subjects with osteoporosis was estimated at 0.001-0.01%. MRONJ was more common when BPs were taken intravenously than when they were taken orally, with between 2% and 9% of patients showing MRONJ with IV BP and 0.00001% patients with oral BP (Bagan et al., 2016).

During my research, I also consulted with Emily Huntley, Physician Assistant of rheumatology (EH PA-C) at Rapid City Medical Center. She has more than 13 years of clinical experience and has contact with osteoporosis patients on a daily basis. She is also very familiar with denosumab and BPs prescribed to treat osteoporosis. In her opinion, she believes the

rheumatology community is still “skeptical” regarding the reported side effect MRONJ of BPs and denosumab. She states that the medications are often “blamed” as the reason behind this side effect, but there are so many other variables and factors that compound the problem, and the medications are often “over-attributed” to the development MRONJ. She herself has not seen a case of MRONJ. EH PA-C has done research on the medications and has attended conferences by the International Endocrinology Society. It is understood that BPs slightly increase a patient’s chance of MRONJ, but not denosumab. This is somewhat contradictory to what my research has uncovered. EH PA-C believes that because denosumab is a newer class of medication, it has not been as studied in long term studies compared to BPs that have been around for years. It is understood by the professional endocrinology community that without any treatment, 0.6/100,000 people will develop ONJ, while on BP therapy, 1/100,000 patients will (personal communication, November 29, 2017). So, the risk is very slightly increased by 0.0000094%. Other stats are also difficult to interpret because many patients have been on BPs for about three to five years as recommended, prior to switching denosumab therapy. So, if a patient develops MRONJ, it is hard to determine what medication is specifically to blame.

Table 2: Osteonecrosis of the jaw risk (cases per 10,000 patients)

Therapy	Osteoporotic patients	Therapy	Cancer patients
Placebo ^[21,22]	0-2×10,000	Placebo ^[24-26]	0-1,9×10,000
Oral bisphosphonates <4 years ^[23]	10×10,000	Zoledronate ^[19,20,24-26]	33-110×10,000
Oral bisphosphonates >4 years ^[23]	21×10,000	Bevacizumab ^[27]	20×10,000
Zoledronate for 3 years ^[21]	1,7×10,000	Zoledronate + Bevacizumab ^[27]	90×10,000
Denosumab ^[22]	4×10,000	Denosumab ^[19,25]	70-190×10,000

Note. Adapted from “Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases,” by R. Coropciuc, K. Grisar, T. Aerden, M. Schol, J. Schoenaers, and C. Politis, 2017, *British Journal of Oral and Maxillofacial Surgery*, 55, p. 787-792. Copyright British Association of Oral and Maxillofacial Surgeons

Table 3: Disease frequency of MRONJ among various studies

Indications for treatment	Medications						Study design
	Placebo	Zolendronate	Oral BP	Denosumab	Bevacizumab	Bevacizumab and Zolendronate	
Malignancy							
Guarneri et al (2010)					0.2% (1076)	0.9% (233)	Systemic review
Qi et al (2013)	0% (1450)	1.1% (2928)		1.9% (4585)			Systemic review
Scagliotti et al (2012)		0.8% (400)		0.7% (411)			RCT
Coleman et al (2001)	0% (1675)	0.7% (1665)					RCT
Vahtsevanos et al (2009)		6.7% (1163)					Prospective cohort study
Mauri et al (2009)	0.019% (5382)	0.33% (3987)					Systemic review
Osteoporosis							
Papapoulos et al (2012)	0% (3383)			0.04% (4549)			RCT
Grbic et al (2010)	0.020% (4945)	0.017% (5864)					Systemic review
Malden and Lopes (2012)			0.004% (90000)				Prospective cohort study
Lo et al (2010)			0.1% (8572)				Cross-sectional

Note. Sample size in parenthesis

Adapted from “Medication-Related Osteonecrosis of the Jaw” by S. Ruggiero, T. Dodson, J. Fantasia, R. Goodday, T. Aghallo, B. Mehrota, and F. O’Ryan, 2014, *Journal of Oral and Maxillofacial Surgery*, 72, p 1938-1956. Copyright 2014 by American Association of Oral and Maxillofacial Surgeons.

Table 4: Risk of MRONJ among various studies

Authors, Year	Placebo	Zolendronate	Oral BP	Denosumab	Study design
Sugimoto et al., 2014				0.1% (775)	RCT
Bone et al., 2013					RCT
Long-term exposure group (6yr)				0.2% (2342)	--
Short-term exposure group (2yr)				0.1% (2207)	--
Papapoulos et al., 2012	0% (3383)			0.04% (4549)	RCT
Grbic et al., 2010	0.02% (4945)	0.02% (5864)			Systematic review
Malden and Lopes, 2012			0.004% (90000)		Prospective cohort study
Lo et al., 2010			0.1% (8572)		Cross-sectional

Note. Adapted from “The frequency of medication-related osteonecrosis of the jaw and its associated risk factors,” by T. Dodson, 2014, *Oral Maxillofacial Surgical Clinics of North America*, 27 pg 509-516. Copyright 2015 by American Association of Oral and Maxillofacial Surgeons

In summary, several studies have reported a slightly higher rate of MRONJ with denosumab compared to BPs, but the differences have been reported as not statistically significant (Berenson, Stopeck 2017). However, EH PA-C states that bisphosphonates carry the higher risk (personal communication, November 29, 2017). This contradiction is not surprising as the reported rates vary greatly from study to study, so it is difficult to come to a definitive conclusion between the two medication classes. Moreover, the risk of MRONJ in osteoporotic patients receiving antiresorptive therapy continues to be very low regardless of drug type (BPs, denosumab) or dosing schedule (Ruggiero et al., 2014).

Contributing factors of MRONJ:

Cancer treatment: According to Bagan et al., the incidence of MRONJ is greater in patients with cancer due to the higher doses of medications. Corresponding to a wide variety of reported incidence rates of MRONJ caused by BPs or denosumab for the treatment of osteoporosis, the incidence rates of MRONJ in cancer patients also varies greatly.

The risk of MRONJ in patients with cancer is about 50 times higher than the risk in patients with cancer exposed to placebo (Dodson, 2014), while another source reports the risk could be up to 100 times higher (Ruggiero, 2014). According to Dodson (2014), when compared with osteoporosis patients receiving antiresorptive therapy, the risk of MRONJ in patients with cancer managed with oral BPs or denosumab is about ten times greater.

Authors Svejda et al., (2016) state the incidence of MRONJ is highest in the oncology patient population and report a wide range of cases at 1-15% of patients. Among patients with cancer exposed to intravenous BPs, MRONJ risk ranged from 0% to 6.7% in one study (Dodson, 2014), while another source cited a range of 0.7% to 1.9% (Bagan et al., 2016). Another study reports the risk of ONJ among patients with cancer exposed to an oral BP to be 0.7% in a sample

of 704 patients (Dodson, 2014). This study is the only one with a listed sample size, so the validity of the all of the data is uncertain.

The majority of studies suggest that the best estimate of MRONJ among patients with cancer exposed to IV BPs is in the low single digit percentages ranging from 1-3%. But again, most of the study conditions are unknown, which is a significant drawback.

In a review study conducted in 2016, the authors aimed to perform a systematic review of the relation between treatment with denosumab and the incidence of MRONJ among cancer patients. A total of 8963 patients with a variety of solid tumors were included. The overall incidence of MRONJ receiving denosumab was 1.7%. The use of denosumab was associated with a significantly increased risk of MRONJ in comparison with the placebo control group. The authors concluded that denosumab combined with other risk factors including cancer treatment, favor the development of MRONJ (Boquete-Castro, Gomez-Moreno, Calvo, Aquilar, & Delgado, 2016). The strength of study is significant because of more complete reporting of the study conditions and large sample size.

Form given: MRONJ was more common when BPs were taken intravenously than when they were taken orally, with between 2% and 9% of patients showing MRONJ with IV BP and 1/100,000 patient with oral BP (Bagan et al., 2016).

Duration of medication therapy as a risk factor: Regardless of indications for therapy, the duration of BP or antiresorptive therapy is a significant risk factor for developing MRONJ. According to Berenson & Stopeck in Up to Date (2017), the incidence is higher with longer duration of treatment, particularly when the duration of therapy exceeds four years. The onset of MRONJ may be shortened by the presence of other comorbidities. In a retrospective series of 3994 patients who received IV bisphosphonates, the median duration of pamidronate, a BP, was

longer in those who developed ONJ compared with those who did not: 1.68 versus 0.59 years in breast cancer and 1.55 versus 0.3 years in multiple myeloma (Berenson & Stopeck, 2017). The same findings were noted among patients receiving zoledronic acid, a BP: 2.04 versus 0.73 years in breast cancer, and 1.85 versus 0.67 years in myeloma. In another study, the cumulative hazard of developing MRONJ increased according to the duration of IV bisphosphonate therapy: 0 percent at one year to 11 percent at four years. (Berenson & Stopeck, 2017). In patients with cancer exposed to zoledronate or denosumab, the incidence of developing ONJ was 0.6% or 0.5% after one year of taking the medication, 0.9% or 1.1% after two years, and 1.3% or 1.1% after three years, respectively (Ruggiero et al., 2014). The same statistics are quoted by Dodson, 2015. The risk for developing MONJ in patients taking denosumab plateaued around two or three years (Ruggiero et al., 2014). This data is very valid due to complete reporting and direct comparison of the different treatments. The data is strengthened more by the same statistics reported by two different sources.

In a study by Saad et al., (2014) the investigators combined three blinded phase trials and found similar results, including a plateau of incidence rate after two years for patients exposed to denosumab. In patients with cancer exposed to zoledronate or denosumab (n = 5,723), the incidence of developing ONJ was 0.5% or 0.8% after one year, 1.0% or 1.8% at two years, and 1.3% or 1.8% at three years, respectively. For patients receiving oral BP therapy to manage osteoporosis, the prevalence of MONJ increases over time, from nearly 0% at baseline to 0.21% after at least four years of BP exposure (Ruggiero et al., 2014).

Authors Fleisher et al., published a review in 2013 of a retrospective cohort study of patients to identify the onset of ONJ based on the exposure to BP therapy and associated triggers based on the route of BP administration. The records of 114 patients with a history of ONJ were

reviewed and divided into cohorts by the route of BP administration, with 76 patients having a history of IV BP therapy and 38 patients using oral BP treatment. The overall onset of MRONJ was earlier in the IV BP group, with a median onset of three years. The median onset in the oral BP group was five years. The authors concluded the median onset of ONJ for patients undergoing IV BP therapy occurs earlier than the median onset for patients undergoing oral BP therapy (Fleisher et al., 2013). However, the small sample size is a limiting factor to this study.

Another found that in patients receiving oral BP therapy to manage osteoporosis, the prevalence of ONJ increases over time from year zero at baseline to 0.2% after four or more years of BP treatment. After two years of treatment with denosumab, the incidence of MRONJ in patients was 0.09% and then nearly doubled to 0.2% after six years (Dodson, 2015).

Local factors:

Operative treatment: Patients who undergo dental procedures that invade bone, such as tooth implantation and tooth extraction, are at increased risk of MRONJ (De Paula, Black, & Rosen, 2016). Several studies have reported that in patients with MRONJ, tooth extraction is a common predisposing event, with 52 to 61% of patients reporting tooth extraction as the precipitating event (Ruggiero et al., 2014). In a case-control study of cancer patients exposed to zoledronate, tooth extraction was associated with a 16-fold increased risk of MRONJ when compared with counterparts without MRONJ (OR: 16.4, CI: 95%). The best estimate for the risk of developing MRONJ after tooth extraction or other dentalveolar procedures in patients exposed to oral BPs is 0.5% (Ruggiero et al., 2014). This was the one of the only studies found that reported a confidence interval. But a drawback of this study is that it was done in cancer patients not in osteoporosis patients, so the patient population varies from the intended population group, which could highly influence the significance of the results.

However, in a study by Fleisher et al., (2013), there was no difference found in rate of MRONJ occurring spontaneously or after dental extraction. The lack of evidence suggesting greater onset after dental extraction may provide clinical support for dentalveolar surgery that is indicated for patients with a history of BP therapy (Fleisher et al., 2013). This study has more validity to my research as the study observed osteoporosis patient instead of those undergoing cancer treatment.

Concomitant oral disease: Pre-existing inflammatory dental disease, such as periodontal disease, is a well-recognized risk factor for developing MRONJ (Ruggiero et al., 2014). Given that a common treatment of inflammatory dental disease is tooth extraction, pre-existing dental disease may compound the correlation between tooth extraction and the risk for MRONJ.

According to EH PA-C, it can be a tricky attempting to treat osteoporosis in patients with oral disease of any kind. In this situation, we as providers have to be able to weigh the benefits of treating versus the possible risks of treating.

Demographic, systemic, and other medication factors: Age and gender are variably reported as risk factors for MRONJ. The higher prevalence in the female population is likely a reflection of the underlying disease for which the agents are being prescribed, i.e., osteoporosis (Ruggiero et al., 2014). There is very limited data describing the occurrence of MRONJ in the pediatric population, as denosumab or BPs are very rarely prescribed to pediatric patients.

Corticosteroids are associated with an increased risk of MRONJ as they can further weaken bones (Ruggiero et al., 2014). Bone loss occurs soon after corticosteroid therapy is initiated and results from a complex mechanism involving osteoblastic suppression and increased bone resorption. When high doses of prednisolone greater than 20 mg/day or equivalent are used, the annual rate of loss of spinal bone density is 5-15% (Romas, 2008). The rate of bone loss is

most marked in the first six months after starting corticosteroids and can be as high as 27% (Romas, 2008). In contrast to premenopausal women, people over 50 years of age and postmenopausal women are more susceptible to osteoporosis, even with lower corticosteroid doses (Romas, 2008). Any condition that further decreases a person's bone density increases their chance of MRONJ, especially in this subset of patients that are already at risk of osteoporosis.

Tobacco use has been inconsistently reported as a risk factor for MRONJ. In a case-control study in 2012, tobacco use approached statistical significance as a risk factor for ONJ in patients with cancer (OR = 3.0; 95% CI, 0.8-10.4) (Ruggiero et al., 2014). In a more recent case-controlled studies, the authors were unable to find an association between tobacco use and MRONJ (Ruggiero et al., 2014).

Genetic factors: There have been several reports describing single nucleotide polymorphisms (SNPs) that have been associated with developing MRONJ. Most of these SNPs are located within regions of the gene associated with bone turnover, collagen formation, or certain metabolic bone diseases. In one study, an ONJ event rate of 57% was reported when SNPs were present in five candidate genes that were responsible for bone turnover. In a genome wide study, it was reported that patients with an SNP in a specific gene associated with bone density and collagen formation, were 5.8 times more likely to develop MRONJ. In a study that analyzed polymorphisms related to farnesyl diphosphate synthase, an enzyme specifically inhibited by BPs, a positive correlation was established with the carrier status and MRONJ (Ruggiero et al., 2014). Collectively, these studies suggest a likely genetic link between MRONJ and BP therapy.

According to EH PA-C, if patient has a family history of ONJ, she would potentially not recommend osteoporosis treatment in the form of BPs or denosumab. In our conversation, we discussed a hypothetical situation in which if a mother developed MRONJ, would she as a provider reconsider not initiating osteoporosis treatment in the form of a BP or denosumab for the daughter. She would potentially not start therapy in this situation, as the patient may have an increased risk of developing MRONJ. She would however, have an educational conversation with the daughter as a patient and highly recommended good dental hygiene and regular dental exams if the patient would choose to start therapy. A family history would not stop EH PA-C from starting osteoporosis therapy, but she would make sure the patient was well-informed and educated about the possible increased risk of complications. (personal communication, November 29, 2017).

DISCUSSION

The pathophysiology of MRONJ is complex and multifactorial. This paper sought to answer the questions: is the incidence rate of MRONJ greater in those patients treated with denosumab or bisphosphonates? And are there any precipitating factors or conditions that increases incidence rates of MRONJ with treatment of denosumab or bisphosphonates? Upon review of multiple studies, there are numerous statistical ranges and prevalence rates reported by numerous associations in different settings and demographics.

Is the incidence rate of MRONJ greater in those patients treated with denosumab or bisphosphonates?

Among the different studies, the prevalence rate of MRONJ with BP therapy ranged greatly between 0.0004-9%, and the rate with denosumab varied as well from 0.04-0.2%. One study reported a slightly higher risk after switching from a BP to a denosumab, from 6.7% to 10% (Loyson et al., 2017). One study found that the rate of MRONJ was also higher with denosumab, but authors concluded the difference was not statistically significant, as the difference was 1.7% versus 1.1% (Berenson & Stopeck, 2017). However, these studies used different doses and schedules of administration, so the varying conditions make it difficult to compare the results with full confidence. Many studies were unable to draw conclusions based on the minor differences in statistics, and it is common theme for them to conclude that the relative prevalence of MRONJ among patients is low.

According to EH PA-C, BPs cause MRONJ while denosumab does not (personal communication, November 29, 2017). This is somewhat contradictory to some research I have found, but reiterates the idea that it is very difficult to make a forgone conclusion between the

two medications. It is reasonable to think that because denosumab is a newer medication, it is not studied as well as BPs, which have been around for numerous years, and it may be possible for the known risk of MRONJ with denosumab to increase as the studies increase.

During my research, it was found to be rather difficult to find studies that solely compared BP with denosumab under the same conditions. Many studies used small and varying sample sizes, not all studies used control groups, and the lengths of the studies varied or were not reported. Also, many of the studies compared the rates of MRONJ after treatment of one medication and then the other. In this situation, it can be near impossible to say with complete confidence which medication is responsible for the MRONJ, or whether there is a compound effect of the two medications when used consecutively.

In the general population, it can also be difficult to identify the medication to blame, because of the common practice of how and when these medications are prescribed. In most cases, the osteoporotic patient is prescribed BP therapy for about five years until the therapeutic effect is maximized, and then often the patient is switched to denosumab or another class of medication to be used chronically. This transitioning to different medications can make it difficult to pinpoint the specific medication to blame if MRONJ develops. This is consistent with the information that I received during my interview with EH PA-C as well.

Also, during my search, I found many cases that compared the prevalence rate of MRONJ in patients with varying comorbidities. This variance makes it not possible to draw further conclusions about the potential associated between bisphosphonates use and MRONJ in identified studies because of incomplete reporting and the presence of confounding factors.

Are there any precipitating factors or conditions that increases incidence rates of MRONJ with treatment of denosumab or bisphosphonates?

Denosumab and BPs are often used as treatment for some cancers that can cause bone damage. The medications are used in higher doses compared to those used for osteoporosis. Cancer can greatly increase a patient's risk for MRONJ, but again the prevalence rates reported vary greatly from 1-15% and up to 50-100 times higher than a patient in the control group. This is logical, as a patient would have a greater chance of jaw bone necrosis if there is previously compromised bone strength due to cancer.

There are many different comorbidities that greatly increase the patient's chance of MRONJ. One of the greatest risk factors is dental procedures. One study found that in patients with MRONJ, 52-61% reported a history of tooth extraction (Ruggiero et al., 2014). However, a different study found no difference in MRONJ onset after tooth extraction (Fleisher et al., 2013).

Age and gender are variably reported as risk factors. A higher prevalence rate is consistent with the population of patients treated for osteoporosis, which is normally aging females. Corticosteroid use is also associated with increasing risk, as they can further weaken bones (Ruggiero et al., 2014). Studies including tobacco use shows inconclusive MRONJ association.

There could also possibly be a genetic link to developing MRONJ. One study reported an MRONJ rate of 57% with SNPs present on genes responsible for bone turnover (Ruggiero et al., 2014). Another study found that patients were 5.8 times more likely to develop MRONJ with an SNP in a specific gene that is associated with bone density and collagen formation (Ruggiero et al., 2014).

Although there are several risk factors to developing MRONJ, EH PA-C stated that not all risks are treated equally, and not all risk factors should prevent us as providers from halting therapy (personal communication, November 29, 2017). We as providers need to weigh the benefits versus risks for all the risk factor and base our decisions to treat with each individual patient in mind.

In summary, my research is mostly inconclusive. While a few source states a higher incidence rate of denosumab, most have inconclusive results or are unable to draw a conclusion. The wide ranges of reported prevalence rates of MRONJ in different studies under different conditions makes it extremely difficult to determine what class of medications, BPs or denosumab, causes the higher prevalence rate of MRONJ. I am unable to draw my own conclusion about what medication class causes the greatest risk of MRONJ; however, I was able to uncover numerous comorbidities and risk factors that would increase the chance of MRONJ. Although I was not successful in answering one of my research questions, I believe my research was successful as it allows for the acquisition of knowledge and application to future practice. I agree with several statements my research uncovered that the risk of MRONJ in osteoporotic patients receiving antiresorptive therapy continues to be very low regardless of drug type (BPs, denosumab) or dosing schedule (Ruggiero et al., 2014).

APPLICABILITY TO CLINICAL PRACTICE

My research was to determine which medication class has the highest prevalence rate of MRONJ and to uncover possible the risk factors. So how does this research apply to clinical practice? The baby boomer generation in the United States continues to age, and the population of Americans aged 65 years or older during the next 25 years is expected to double to about 72 million (CDC, 2013). In fact, by 2030, older adults are expected to account for roughly 20% of the U.S. population (CDC, 2013). During my clinical experiences, I have cared for many elderly patients. As potential future family practice providers, a large proportion of our patients will lie in this age range, so it is imperative to be aware of common conditions that could affect this population. Because of the USPSTF recommendation of bone density scans, many patients will have the diagnosis of osteopenia and/or osteoporosis. Both conditions can be debilitating and cause significant physical impairment if left untreated, with hip fracture being one of major significance.

Hip fracture in older adults is a leading public health concern. Hip fractures are associated with significant increased risk of mortality, loss of independence, and financial burden. In one study, the reported one-year mortality after sustaining a hip fracture was estimated to be 14% to 58% (Schnellet et al., 2010). A recent meta-analysis revealed that women sustaining a hip fracture had a five-fold increase and men almost an eight-fold increase in relative likelihood of death within the first three months following the injury as compared with age and sex-matched controls (Schnellet et al., 2010). Loss of function and independence among survivors is profound, with 40% of patients unable to walk independently and 60% requiring assistance one-year post-fracture. (International Osteoporosis Foundation, 2017). Because of

these losses, 33% of patients are completely dependent or in a skilled nursing facility in the year following a hip fracture (International Osteoporosis Foundation, 2017).

Because osteoporosis is becoming more and more prevalent as the baby boomers age, it is imperative to make every attempt to prevent hip and other fractures. This can be accomplished by following the recommended guidelines for bone density scans and by treating osteopenia and osteoporosis appropriately.

There are many different treatment options for osteoporosis, among them BPs and denosumab. Both treatments have their associated side effects, and it's crucial that we are aware of the different side effects for each. However, because there are many different classes of medications, there is not a one-size-fits-all solution for osteoporosis treatment. In any situation, we as providers have to be able to weigh the benefits of treating versus the possible risks of treating. We will need to take each patient's preference and personal medical history in to account to make a joint decision about what treatment is right for them.

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