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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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Abstract

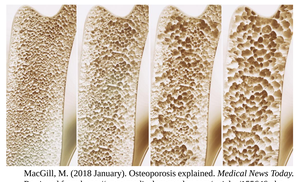
As the baby boomer generation continues to age, the diagnosis of osteoporosis and its side effects will continue to increase. Denosumab and bisphosphonates (BPs) are some of the most common medication classes used to treat osteopenia and osteoporosis, but it is believed that both medications have the 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 a wide range of reported incidence rates among different studies. My research found that denosumab carries a slightly higher risk of MRONJ versus bisphosphonates, but the difference was found to be statistically insignificant. Uncovered 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: 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).
- This will have a significant impact on age-related health care; a loss of bone mineralization and mass in the forms of osteopenia and osteoporosis being a major issue.
- Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every three seconds (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.
- A study from 2002 estimated national health care expenditures due to osteoporosis fractures to be about $12 billion annually, with about 75% of the costs going to direct medical care (Desai, Duncan, Sloan, 2003).

Figure 1: Gradual process of osteoporosis



MacGill, M. (2018 January). Osteoporosis explained. *Medical News Today*. Retrieved from https://www.medicalnewstoday.com/articles/155646.php

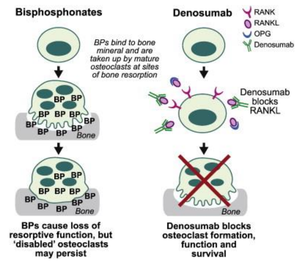
Statement of the Problem

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.

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?

Figure 2: Mode of action of BPs and denosumab



Barton, R., Ferrari, S., Russell., G. (2010 November). Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone* 48(4), 677-692. https://doi.org/10.1016/j.bone.2010.11.020.

Literature Review

- Incidence rates of MRONJ:
  - General population:
    - 0.000006% to 0.001% (Syejda et al., 2016) and (DynaMed Plus, 2017)
  - BP:
    - Between 0% to 0.2%; up to 6.7% (Loyson, et al., 2017)
    - 13.1 times greater in patients on BP therapy vs placebo group (Dodson, 2014)
  - Denosumab:
    - 0.04% to 10% (Loyson et al., 2017)
  - 15.5% after BP and then denosumab (Loyson et al, 2017).
    - Slightly higher risk of MRONJ early after switching from BPs to denosumab compared to patients remaining on BPs
    - Based on global incidence rates, the switch from BPs to denosumab can be considered as safe as initially starting denosumab therapy (Loyson et al., 2017).
- Contributing factors:
  - Cancer treatment: The risk in cancer patients is about 50-100 times greater than in patients exposed to placebo (Dodson, 2014).
  - Duration of treatment: incidence is higher with longer duration of treatment, particularly when therapy exceeds four years (Up to Date, 2017).
  - Operative treatment: dental procedures that invade bone increase risk (De Paula, Black, & Rosen, 2016).
  - 52 to 61% of MRONJ patients reported tooth extraction as the precipitating event (Ruggiero et al., 2014).
- Demographic, systemic, other factors:
  - Age and gender are variably reported as risk factors.
  - Tobacco use has been inconsistently reported as a risk factor.
  - Corticosteroids are associated with an increased risk as they can further weaken bones (Ruggiero et al., 2014).
  - Patients with a single nucleotide polymorphism (SNP) in a specific gene associated with bone density and collagen formation were 5.8 times more likely to develop MRONJ (Ruggiero et al., 2014).
    - Studies suggest a likely genetic link between MRONJ and BP therapy.

Discussion

Table 1: Disease frequency of MRONJ reported by various studies

	Medication				
Indications for treatment	Placebo	IV BP	Oral BP	Denosumab	Study design
Malignancy					
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
Sugimoto et al., 2014				0.1% (775)	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

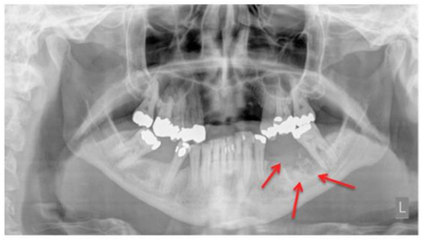
Note. Sample size in parenthesis
Adapted from "Medication-Related Osteonecrosis of the Jaw" by S. Ruggiero, T. Dodson, J. Fantasia, R. Goodday, T. Aghallo, B. Mehrota, and F. O'Ryan, 2014, *Journal of Oral and Maxillofacial Surgery*, 72, p 1938-1956. Copyright 2014 by American Association of Oral and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

- **Is the incidence rate of MRONJ greater in those patients treated with denosumab or bisphosphonates?**
  - A wide variety of incidences rates were reported with both medications.
    - Several studies have reported a slightly higher rate with denosumab compared to BPs, but the differences are not statistically significant (Berenson, Stopeck 2017). See Table 1
    - Moreover, the risk of MRONJ in osteoporotic patients continues to be very low regardless of drug type or dosing schedule (Ruggiero et al., 2014).
    - Many studies used different doses, administration schedules, sample sizes, and patients with varying comorbidities, making it difficult to compare the results with full confidence.
    - In general practice, it can also be difficult to identify the medication to blame, because of the common practice of how and when these medications are prescribed.
- **Are there any precipitating factors or conditions that increases incidence rates of MRONJ with treatment of denosumab or bisphosphonates?**
  - 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 may be due to the higher dosages used for cancer treatment versus dose used for osteoporosis.
  - There are many different comorbidities that greatly increase the MRONJ risk.
    - One of the greatest risk factors is dental procedures and current oral disease.
    - Other risk factors include increasing patient age and gender and family history.
    - Corticosteroid use can also increase a patient's risk.
    - Tobacco has been inconsistently reported as a risk factor.
- In summary, my research is mostly inconclusive.
  - 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.

Applicability to Clinical Practice

- As potential future providers, a large proportion of our patients will most likely be elderly, so it is imperative to be aware of common conditions that could affect this population, like osteoporosis.
- Both conditions can be debilitating and cause significant physical impairment and fractures if left untreated, a major concern being hip fractures.
- Hip fractures in particular 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).
- There are many different treatment options for osteoporosis, among them BPs and denosumab, and there is not a one-size-fits-all solution.
- 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 osteoporosis treatment.

Figure 3: MRI of patient demonstrating osteonecrosis of the jaw



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