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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 osteoporosis 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 are enormous.
• A study from 2002 estimated national health care expenditures due to osteoporotic fractures to be about $24 million annually, with about 75% of the costs going to direct medical care (Desa, Duncan, Sloan, 2003)

Figure 1: Global process of osteoporosis

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?

Literature Review

Incidence rates of MRONJ:
• General population:
  - 0.000606 to 0.001% (Syrigda et al., 2016) and (Dynamaed Plus, 2017)
  - BP:
    - Between 0% to 0.2% (Loyson et al., 2017)
  - 13.1 times greater in patients on BP therapy vs placebo group (Dodd, 2014)
  - Denosumab:
    - 0.04% to 10% (Loyson et al., 2017)
  - 15.5% after BP and then denosumab (Loyson et al., 2017)
• Global incidence:
  - Higher risk of early 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 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 (Dodd, 2014)
• Duration of treatment: incidence is higher with longer duration of treatment, particularly when therapy exceeds four years (Up to Date, 2017)
• Osteoporosis treatment: incidence is higher with treatment with denosumab compared to patients remaining on BPs

Table 1: Disease frequency of MRONJ reported by various studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Denosumab 1mg/yr</th>
<th>Denosumab 2mg/yr</th>
<th>Denosumab 12mg/yr</th>
<th>Denosumab 12mg/yr, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate (%)</td>
<td>0.11%</td>
<td>0.15%</td>
<td>0.2%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Figure 2: Molar values of BP and denosumab

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.

Abstract

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 calculated to be 14% (Brett, 2010).

There are many different treatment options for osteoporosis, among them BPs and denosumab, and there is not 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 into account to make a joint decision about osteoporosis treatment.

Acknowledgements

I would like to thank the UND faculty for their continued support and dedication to the education of their PA students. I would like to thank my advisor, Daryl Sieg, for his insight and direction throughout my PA education. I would also like to thank all of my preceptors who have helped guide my education and learning experiences. A sincere thank you to Emily Hunley, PA and Chul Spear for their assistance and input into this final project. Lastly, I cannot thank my family and fiancé enough for their love, support, and patience through this extensive yet rewarding journey.

References


Discussion

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

A wide variety of incidence 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 (Berenstein, Stupack, 2017). 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?

Combing can greatly increase a patient’s risk for MRONJ, but again the prevalence rates reported vary greatly from 1.1% to 55% higher than a patient in the control group. This may be due to the 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.

Corticosteroids can also increase a patient’s risk.

Bisphosphonates have 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 calculated to be 14% (Brett, 2010).
• There are many different treatment options for osteoporosis, among them BPs and denosumab, and there is not 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 into account to make a joint decision about osteoporosis treatment.