

**THE INCIDENCE OF BISPHOSPHONATE RELATED OSTEONECROSIS OF THE
JAW FOLLOWING A SINGLE DOSE OF 5MG ZOLEDRONIC ACID FOR THE
TREATMENT OF OSTEOPOROSIS IN FRAIL, ELDERLY, INSTITUTIONALIZED
WOMEN**

by

Daniel Bair

BA, Syracuse University, 2007

DMD, University of Pittsburgh School of Dental Medicine, 2011

Submitted to the Graduate Faculty of
University of Pittsburgh School of Dental Medicine in partial fulfillment
of the requirements for the degree of
Masters of Dental Science.

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH
SCHOOL OF DENTAL MEDICINE

This thesis was presented

by

Daniel Bair

It was defended on

May 28, 2014

and approved by

Ali Seyedain, DMD, MDS, Assistant Professor, Director of Undergraduate Periodontics,

Department of Periodontics and Preventative Dentistry

Steven Levine, DMD, Assistant Professor, Department of Diagnostic Sciences

Thesis Director: Poursan Famili, DMD, MDS, MPH, PHD, Professor, Chair, Director of

Residency Program, Department of Periodontics and Preventative Dentistry

Copyright © by Daniel Bair

2014

THE INCIDENCE OF BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW FOLLOWING A SINGLE DOSE OF 5MG ZOLEDRONIC ACID FOR THE TREATMENT OF OSTEOPOROSIS IN FRAIL, ELDERLY, INSTITUTIONALIZED WOMEN

Daniel Bair, DMD, MS
University of Pittsburgh, 2014

Purpose: To evaluate the incidence of bisphosphonate related osteonecrosis of the jaw following a single dose of zoledronic acid for the treatment of osteoporosis in frail, elderly, institutionalized females.

Materials and Methods: Utilizing a longitudinal prospective study design, data was collected from one hundred eighty subjects who were randomly assigned to receive a single intravenous infusion of either zoledronic acid (5mg) or placebo. Dental evaluations were completed at baseline (Day 0) and at months 12 and 24. All patients received daily supplemental calcium and vitamin D throughout the course of the trial. Patients completed a questionnaire to provide information regarding their oral hygiene practices to ascertain information that may be helpful in detecting risk factors for development of BRONJ.

Results: Zero cases of osteonecrosis were detected at any time point in the 180 subjects who completed the 24-month follow up period. Subject's race, age, smoking status, oral hygiene practices, frequency of dental visits and use of a removable dental prosthesis did not contribute to the development of BRONJ.

Conclusion: The administration of a single dose of 5mg of zoledronic acid for the treatment of osteoporosis in frail, elderly, institutionalized women does not cause bisphosphonate related osteonecrosis of the jaw.

TABLE OF CONTENTS

1.0	INTRODUCTION	1
2.0	REVIEW OF LITERATURE	3
2.1.	DEFINITION AND PREVALENCE OF OSTEOPOROSIS	3
2.2.	CONSEQUENCE OF UNTREATED OSTEOPOROSIS	4
2.3.	MANAGEMENT OF OSTEOPOROSIS	5
2.4.	BISPHOSPHONATES	5
2.5.	COMPLIANCE OF ORAL BISPHOSOPHANTE THERAPY	6
2.6.	ZOLEDRONIC ACID	7
2.7.	DEFINITION AND CHARACTERISTICS OF BRONJ	7
2.8.	RISK FACTORS ASSOCIATED WITH BRONJ	8
2.9.	INCIDENCE AND PREVALENCE OF BRONJ	10
3.0	METHODOLOGY	11
4.0	RESULTS	13
4.1.	STATISTICAL ANALYSIS	14
5.0	DISCUSSION	18
6.0	CONCLUSION	20
	BIBLIOGRAPHY	21

LIST OF TABLES

Table 1. Population Age, Race, and Smoking Status	14
Table 2. Population Frequency of Dental Visits/Year, Subject Dental Health Assessment	15
Table 3. Population Hygiene Practices – Times Brush/Day, Floss/Day, Rinse/Day	16
Table 4. Population Use of a Removable Prosthesis	17

1.0 INTRODUCTION

According to the 2010 U.S. Census Report, persons 65 years of age or older currently account for 12.9% of the total population within the United States. By the year 2030, that percentage is expected to climb to 19%, representing a total of 72 million Americans, more than double the number reported in the 2000 Census. This rapid shift in the age of the population will present major challenges to our healthcare system as the number of individuals who suffer age-related illnesses increases (Aging, 2013).

Osteoporosis is an example of a disease that disproportionately affects older members of society. If untreated, osteoporosis is associated with high rates of morbidity, can significantly affect the quality of life and dramatically increases the risk of secondary life-threatening complications (WHO, 2004). Treatment for osteoporosis varies widely depending on the level of bone mass deficiency. Pharmacological intervention is often employed to treat advanced cases of the disease. The class of drugs that are typically utilized for osteoporosis therapy are known as bisphosphonates. Bisphosphonates interfere with osteoclast function and effectively reduce bone turnover. Bisphosphonates are prescribed in an oral form or through intravenous infusion. The oral form of the drug requires a strict daily or weekly drug regimen that must be preceded by a period of fasting and requires patients to ingest the tablet with a full glass of water to avoid esophageal irritation and remain upright for 30-60 minutes to maximize absorption (Rakel et al., 2011). Intravenous bisphosphonate therapy for the treatment of osteoporosis requires only yearly infusions making it a more practical and effective alternative for some elderly patients who may have difficulty complying with the dosing protocol required with the oral form. Unfortunately, the long-term use of intravenous bisphosphonates has been associated with the

undesirable side effect known as bisphosphonate related osteonecrosis of the jaw (BRONJ). The purpose of this study was to evaluate the incidence of BRONJ following a single dose of 5mg of zoledronic acid administered to elderly, institutionalized, post-menopausal women who suffer from osteoporosis. The results of this study could possibly contribute to the creation of a universal protocol for the treatment of osteoporosis in women who are admitted to nursing homes or assisted living communities.

2.0 REVIEW OF LITERATURE

2.1 DEFINITION AND PREVALENCE OF OSTEOPOROSIS

Osteoporosis is a bone disease characterized by a decrease in bone mass and increased risk of bone fracture. In 1997, the World Health Organization developed a working definition of osteoporosis based on the qualitative assessment of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA). The WHO concluded that a BMD that lies 2.5 standard deviations or more below the average value for young healthy women is considered diagnostic for the disease (Kanis et al., 2008). Projections based on this definition have concluded that as many as 12 million Americans over the age of 50 are living with osteoporosis and another 40 million are at risk with low bone mass. By 2020, those figures are estimated to jump to 14 million cases of active osteoporosis and 47 million cases of low bone mass (National, 2002). This dramatic increase in prevalence is the direct result of a shift in population demographic toward an aging senior population and an overall increase in the average life expectancy (Becker et al., 2010). As the number of new cases of osteoporosis and the corresponding increase in the number of disease-related morbidities continues to rise, management of osteoporosis will become a major challenge within the healthcare community.

2.2 CONSEQUENCES OF UNTREATED OSTEOPOROSIS

Individuals diagnosed with osteoporosis are at a heightened risk of suffering a debilitating bone fracture due to the deterioration of bone structure. Women, who are disproportionately affected compared to men, represent 80% of cases and have a 40-50% lifetime risk of experiencing an osteoporosis-related fracture (Department 2004, Johnell et al. 2005). The short and long-term consequences of a bone disease-related fracture can be devastating to a patient's health and can ultimately lead to permanent morbidity and even fatality. In 1990, the number of deaths worldwide that were associated with hip fractures was 740,000 (Johnell et al., 2004). In 1993, a Department of Commerce Report found that 300,000 hip fractures occurred in the United States every year and that an average of 24% (72,000) of individuals 50 years or older who experienced a hip fracture, died within one year (US, 1993). Those patients who do survive may continue to suffer from permanent disabilities, with as many as 7% of patients having 'some degree' of permanent disability and 8% requiring 'long-term institutional care' (Harvey et al., 2010, Leibson et al., 2002). Studies evaluating patients following an osteoporosis-related fracture have also reported a reduced 'health-related quality of life' (Boonen et al., 2008).

In 2004, the Surgeon General's report titled "Bone Health and Osteoporosis" described the serious impact the increased prevalence of osteoporosis could have on the overall health of the American population, as well as the financial burden it could exact on our entire health care system (Department, 2004). With an estimated 1.5 million fractures occurring each year as the result of osteoporosis, the direct cost of treating bone disease-related fractures is upwards of \$17 billion annually and is expected to reach \$25 billion by 2025 (Riggs et al., 1995, Burge et al., 2007).

2.3 MANAGEMENT OF OSTEOPOROSIS

If detected early, osteoporosis can often be managed effectively by simple modification of a patient's daily intake of calcium and vitamin D, as well as, by increasing an individual's level of physical activity. For patients who present with advanced stages of bone deterioration, more aggressive therapies involving administration of antiresorptive pharmaceuticals are often utilized (Department, 2004). Drug therapy for treatment of osteoporosis most commonly involves administration of a class of drugs known as bisphosphonates to help improve bone mineral density by decreasing bone turnover. Bisphosphonates are complex antiresorptive agents that act on specific biochemical and cellular pathways and inhibit osteoclast-mediated bone resorption without interfering with bone formation (Deal, 2009).

2.4 BISPHOSOPHNATES

The chemical structure of bisphosphonates is based on a derivative of inorganic pyrophosphate, a natural ring compound made up of two phosphate rings linked by an ester bond. Newer bisphosphonates incorporate a nitrogen or amino group that amplifies the potency of the drug's antiresorptive properties by 10-10,000 compared to the earlier non-nitrogen containing bisphosphonates (Drake et al., 2008). These newer aminobisphosphonates act by inhibiting farnesyl diphosphonate synthase, a critical component of cholesterol synthesis. Interference of this pathway results in disruption of the cell's ability to carry out intracellular transport, organize an intracellular scaffold and undergo cellular proliferation, ultimately disabling normal osteoclast function (Woo et al., 2006).

2.5 COMPLIANCE OF ORAL BISPHOSPHONATES

Bisphosphonates available for the treatment of osteoporosis can be administered in two main forms: a tablet or oral solution, which is absorbed following enteral drug administration, or a fluid solution, administered through an intravenous infusion. With over 190 million prescriptions dispensed worldwide, the oral form of bisphosphonates has been the most commonly employed treatment strategy for patients suffering from osteoporosis; however, the strict intake requirements, which involve a daily or weekly drug regimen and close supervision by a nurse for 30-60 minutes following ingestion, make it difficult for elderly patients to adhere to the rigorous dosing protocol (Advisory, 2007, Watts et al., 2010). An investigation examining the compliance of oral bisphosphonate therapy in post-menopausal women found that in patients over the age of 65, as few as 28% of individuals taking a daily oral bisphosphonate and 35% taking a weekly oral bisphosphonate continued treatment at the end of one year. Lack of stringent compliance to the oral therapy has significant influence on the effectiveness of treatment and has been shown to increase the risk of osteoporosis related fracture by up to 16% (Cramer et al., 2005). In an effort to avoid complications resulting from poor compliance with use of oral bisphosphonates, therapies utilizing once yearly intravenous bisphosphonate administration have been employed to treat cases of advanced osteoporosis.

2.6 ZOLEDRONIC ACID

In August 2007, the United States Food and Drug Administration approved the administration of zoledronic acid (Reclast[®]) once per year for the treatment of patients diagnosed with osteoporosis (Reclast, 2013). Unlike oral bisphosphonates that have a relative low bioavailability of less than 5%, greater than 60% of intravenously administered bisphosphonates is available for deposition within the bone matrix, thereby reducing the need for frequent administration (Gutta et al., 2007, Hamdy et al., 2010). The increased potency and long duration of activity, up to 12 months, has led to concern regarding the safety profile of IV bisphosphonates, particularly findings that have shown a positive correlation of long term IV bisphosphonate use with the development of osteonecrosis of the jaw (Reid et al., 2002, Dodson et al., 2009).

2.7 DEFINITION AND CHARACTERISTICS OF BRONJ

In 2007, the American Association of Oral and Maxillofacial Surgeons released a position paper that defined bisphosphonate-related osteonecrosis of the jaw as an exposed area of bone in the maxillofacial region that persists for greater than eight weeks, in a patient without any history of radiation therapy to the head or neck (Advisory, 2007). While the exact etiology behind BRONJ remains unclear, one of the predominate theories is that a decrease in osteoclast activity leads to a dramatic reduction in bone turnover, making the bone more susceptible to structural microdamage. In cases where bone becomes exposed through trauma or surgical therapy, the cumulative effects of bone microdamage, combined with the introduction of high quantities of

bacteria from within the oral environment, can result in a delay of healing and an inability of the tissues to initiate normal reparative processes (Siddiqi et. al., 2009).

The clinical presentation of BRONJ is characterized by localized bone sequestration and is associated with high levels of pain, soft tissue swelling, infection, and in some cases, loosening of teeth or draining fistula (Ficarra et al., 2007). During the early stages of development, signs of BRONJ may not be evident upon radiographic analysis. As the condition develops, areas of affected bone may appear mottled in nature and have a radiographic presentation similar to classic periapical pathology or inflammatory conditions such as osteomyelitis (Ficarra et al., 2007). Microscopic evaluation of histologic samples collected from areas of bone necrosis in patients suffering from BRONJ consistently show non-viable bone trabeculae with empty lacunae and chronic inflammatory cell infiltrate composed primarily of neutrophils, histiocytes, eosinophils and plasma cells. Although a wide variety of pathogenic bacterial species are routinely collected from sites of BRONJ, samples frequently show disproportionally high levels of infiltrating actinomyces species (Almazrooa et al., 2009, Dannemann et al., 2007, Ficarra et al., 2007).

2.8 RISK FACTORS ASSOCIATED WITH BRONJ

The central focus of a number of recent studies has been to outline the risk factors associated with the development of BRONJ. Differences in the cumulative dosage of the bisphosphonate administered, the duration of therapy, and the route of administration can significantly alter a patient's overall risk for osteonecrosis. Bisphosphonate therapy employed for the treatment of malignant diseases such as multiple myeloma or breast cancer typically places patients at an

increased risk of developing BRONJ because treatment requires a higher dosage, more frequent administration, and the use of the more potent intravenous forms of the drug (Statz et al., 2007).

The uneven distribution of cases of osteonecrosis among the various bisphosphonates has also been well documented. The IV bisphosphonates pamidronic acid (Aredia[®]) and zoledronic acid (Reclast[®]), two of the newer aminobisphosphonates, have been shown to increase the risk of BRONJ, compared to oral forms of the drug such as alendronic acid (Alendronate[®]) and risedronic acid (Actonel[®]) (Mavrokokki 2007 et al., Abu-Id et al., 2008). A hospital-based case-control study completed by Wessel et al. in 2008, evaluated the association between osteonecrosis and potential risk factors. The authors found a 30-fold increase in risk of osteonecrosis in patients treated with zoledronic acid and a statistically significant association between smoking and BRONJ.

Other factors such as patient's anatomic features, social behavior (i.e. smoking), population demographic, and certain systemic or genetic factors, have also been found to contribute to the development of BRONJ (Walter et al., 2008, Otto et al., 2011, Hess et al., 2008, Advisory, 2007, Katz et al., 2011, Dodson et al., 2009, Carstos et al., 2010, Abu-Id et al., 2008). A history of substandard dental health may also place a patient at an increased risk for BRONJ. Underlying dental health conditions or the completion of surgical dental procedures such as dental extractions, placement of dental implants, active periodontal disease, improperly fitting dentures, and areas of bony exostosis, can precipitate the onset of osteonecrosis. (Hoff et al., 2008). In a 2008 literature review, Rizzoli et al. found that the majority of cases of BRONJ occurred following tooth extraction and that the development of BRONJ was more concentrated in patients being treated for additional diseases (Rizzoli et al., 2008).

2.9 INCIDENCE OF BRONJ

The cumulative risk of developing BRONJ is estimated to range from 0.8 to 12% in patient populations who have a history of IV bisphosphonate use (Advisory, 2009). Reports estimating the incidence of BRONJ associated with oral bisphosphonates have found the range closer to 1 in 10,000 and <1 in 100,000 patient-treatment years. A 2008 comprehensive literature review analyzing the risk of BRONJ in patients with osteoporosis estimated an incidence rate of 1 event per 20,000-110,000 patient-years (Rizzoli et al., 2008). Similarly, the results of a large multi-center study evaluating the risk of osteonecrosis among patients being treated for osteopenia with yearly infusions of 5mg of zoledronic acid revealed only a single case of BRONJ among 5,903 patients treated over the course of 36 months (Grbic et al., 2010).

While studies specifically designed to evaluate the incidence of BRONJ in patients being treated for osteoporosis have found a lower incidence of BRONJ compared to populations being treated with IV bisphosphonates for malignant disease, the risk of developing BRONJ is still significantly higher than patients being treated with oral bisphosphonates. A 2010 medical claims study that evaluated the risk of adverse jaw outcomes in patients with a history of bisphosphonate use found that patients who were treated with IV bisphosphonates for osteoporosis had a fourfold increase risk of having a claim for ONJ compared to patients who had received the oral form (Cartsos et al., 2010).

3.0 METHODOLOGY

This study was a randomized, double blind, placebo-controlled clinical trial examining the incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in institutionalized, frail, elderly women suffering from osteoporosis. In order to meet eligibility requirements, participants were required to be 65 years or older, post-menopausal women, residing in an assisted living or nursing home facility, and having a DXA score (T-score -2.5 at the total hip, femoral neck or spine) or low bone mass (T-score < -2.0 at the total hip, femoral neck or spine) that met the WHO established criteria for osteoporosis. Exclusion criteria for this study were children, men, any patients with signs of subacute illness, patients with allergies or contraindications to bisphosphonate therapy, patients with creatinine clearance of less than $<30\text{ml/mm}$, and patients unable to bear weight or assist with transfer to the chair. The screening process was based on a detailed medical history, physical exam, dental exam, chart review, and baseline laboratory analyses, including BUN/creatinine, liver function tests, TSH, calcium, PTH, 25-hydroxyvitamin D, and alkaline phosphatase level. The only restriction for concomitant or previous medication use was a history of bisphosphonate use for greater than one year in the previous two years prior to enrollment.

Utilizing a longitudinal prospective study design, data was collected from one hundred eighty subjects ($n=180$) randomly assigned to receive a single intravenous infusion of either zoledronic acid (5mg) or placebo at baseline (Day 0). Subjects were monitored with institutional evaluations at screening, randomization, Day 1, Day 2, Month 6, Month 12, and Month 24, to assess clinical parameters related to the status of the subjects' bone mineral density and overall systemic condition. All participants received daily supplemental calcium and vitamin D throughout the course of the trial. During the screening process and at months 12 and 24,

dental assessments were conducted to evaluate the intra-oral quality of health of the teeth and soft tissues and to assess the status of the subject's dental hygiene. During these dental assessments, subjects were carefully evaluated for the presence of any acute infections, evidence of pathology, or signs suggestive of bisphosphonate-related osteonecrosis of the jaw. A questionnaire was also administered to each patient during evaluations to collect data on oral hygiene practices and ascertain information helpful in detecting risk factors for development of BRONJ. All screening and evaluation visits were conducted at the subjects' care facility.

Participants who met eligibility requirements were randomized in a 1:1 ratio to either 5 mg intravenous zoledronic acid or placebo given in a single dose. The placebo or study drug was prepared by the UPMC Investigational Drug Service (IDS) and was administered by means of an intravenous catheter.

A comprehensive description outlining the potential risks and benefits was provided to the participants and was reviewed prior to matriculation into the study. Those individuals who agreed to participate in the study signed a detailed informed consent agreement reviewing the purpose, nature of the study and the potential risks and benefits of the treatment.

The primary endpoints of the study were the development of BRONJ based on the 2007 definition provided by the American Association of Oral and Maxillofacial Surgeons, or the completion of the 24-month evaluation period without any development of bisphosphonate related osteonecrosis of the jaw.

Simple descriptive statistics were employed to compute participant demographic data and information collected from the dental surveys to help formulate relevant trends within the study population and assess the total number of cases of BRONJ.

4.0 RESULTS

The results of the trial are based upon all the data collected from the 180 randomized subjects at baseline, as well as the 12 and 24 month dental evaluations. Data collection began in December 2007 and was completed in February 2014. Patient information was collected from eleven institutions located within a 30-mile radius of the City of Pittsburgh, Pennsylvania. All subjects resided in a nursing home or assisted or independent living community.

Zero cases of BRONJ were detected in the study population, including subjects receiving bisphosphonates and placebo, at any time point within the study. Variations in participants' oral hygiene practices, social behaviors, population demographics and systemic health status had no influence on the development of adverse oral disease outcomes. During the clinical trial, dental screenings were completed at baseline on 59 subjects who chose not to enter the study, did not meet eligibility criteria, or were lost to follow up. Data presented within the results reflects only the information collected from the 180 subjects who completed the 24 month follow-up period.

4.1 STATISTICAL ANALYSIS

Analysis of the data collected revealed that 176 (97.8%) of the participants were greater than 75 years old, with the remaining 4 (2.2%) subjects ranging in age from 65-75 years (Table 1). The majority of subjects described themselves as Caucasian (97.8%), with 6 (3.3%) participants identifying their race as African American (Table 1). Among the 180 participants, 48 (25.7%) reported a previous history of tobacco use, while 6 (3.3%) subjects reported current tobacco use and 126 reporting no history of tobacco use (70%) (Table 1).

TABLE 1

Population Age, Race and Smoking Status

Age	55-65	65-75	>75
# Subjects	0/180	4/180	176/180
Percentage	0%	2.2%	97.8%
Race	Black	White	Other
# Subjects	6/180	174/180	0/180
Percentage	3.3%	96.7%	0%
Smoking Status	Current	Former	No History
# Subjects	6/180	48/180	126/180
Percentage	3.3%	26.7%	70.0%

The structure of the study was purposefully designed to allow a realistic assessment of the oral hygiene behavior and professional dental practices within an elderly patient population. Eighty-nine subjects (49.4%) reported only seeking dental care in the case of an emergency, while 31 (17.2%) subjects reported visiting their dentist once per year, and 60 (33.3%) subjects reported routine care at six month intervals (Table 2). All participants in the study were asked to describe the condition of their dental health as good, fair, or poor. One-hundred subjects (55.6%) reported their dental health as good, while 67 (37.2%) described their dental health as fair, and 13 subjects (7.2%) reported the condition of their dental health as poor (Table 2).

TABLE 2

Population Frequency of Dental Visits Per Year, Subject Dental Hygiene Assessment

Dental Visits/Year	Emergency Only	1/Year	2/Year
# Subjects	89/180	31/180	60/180
Percentage	49.4%	17.2%	33.3%
Dental Health Assessment	Poor	Fair	Good
# Subjects	13/180	67/180	100/180
Percentage	7.2%	37.2%	55.6%

An important component of the study was to evaluate the oral hygiene practices of individual subjects to assess the dental health of the study population and investigate trends that may be helpful in predicting cases of BRONJ. Each subject was asked to indicate the number of times per day they brushed their teeth, flossed their teeth, and used any mouth-rinsing agent (Table 3). Participant responses range from zero times per day to three times per day for each question. Analysis of the data revealed that most subjects within the study routinely brush their teeth twice per day and do not use mouth rinse or floss their teeth.

TABLE 3

Population Hygiene Practices – Times Brush/Day, Times Floss/Day, Times Rinse/Day

Times Brush/Day	0/Day	1/Day	2/Day	3/Day
# Subjects	4/180	47/180	61/180	16/180
Percentage	2.2%	26.1%	33.9%	8.9%
Times Floss/Day	0/Day	1/Day	2/Day	3/Day
# Subjects	91/180	25/180	7/180	5/180
Percentage	50.1%	13.9%	3.9%	2.8%
Times Mouthrinse/Day	0/Day	1/Day	2/Day	3/Day
# Subjects	107/180	61/180	11/180	1/180
Percentage	59.4%	33.9%	6.1%	0.1%

Of the 180 participants, seventy-three subjects reported routinely wearing a removable prosthesis: 50 (27.8%) subjects presented with a complete maxillary and mandibular denture and the remaining 23 (12.8%) subjects wore a single arch complete denture or a removable partial denture (Table 4).

TABLE 4
Population Use of a Removable Prosthesis

Removable Prosthesis	Complete Dentures	Removable Prosthesis (Single Arch CD, RPD(s))
# Subjects	50/180	23/180
Percentage	27.8%	12.8%

5.0 DISCUSSION

The majority of cases of BRONJ occur in patient populations that require frequent administration of intravenous bisphosphonates for the treatment of malignant disease. The purpose of this study was to evaluate the incidence of BRONJ following a single infusion of zoledronic acid. Irrespective of subjects' hygiene practices, age, race, history of tobacco use, or utilization of a removable dental prosthesis, no subjects within the study presented with any symptoms suggestive of BRONJ through the 24-month follow-up period. These results indicate that a single dose of 5mg zoledronic acid administered intravenously for the treatment of osteoporosis does not appear to be associated with the development of bisphosphonate-related osteonecrosis of the jaw in postmenopausal women.

In 2007, a large multi-center study titled 'The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial' investigated the clinical benefit of utilizing intravenous bisphosphonate therapy to treat cases of advanced osteoporosis. A total of 7,765 patients were recruited for the study and 3,876 subjects received 1-3 doses of 5mg zoledronic acid over the course of 36 months. The authors concluded that a "once-yearly infusion of zoledronic acid significantly reduced the risk of vertebral, hip and other fractures" (Black et al., 2007). Similar findings were reported in a comprehensive literature review published by Woodis in 2008 in *The Annals of Pharmacology*. The review analyzed the results of five randomized controlled studies and concluded that yearly zoledronic acid administration decreased bone turnover markers, reduced the vertebral fracture rate by approximately 70%, and significantly increased bone mineral density in the hip, femur, and spine (Woodis et al., 2008).

In 2008, Rizzoli et al. completed a literature review analyzing the risk of developing BRONJ in patients being treated for osteoporosis. The review included studies utilizing oral as well as intravenous forms of bisphosphonates. The authors concluded that the risk of osteonecrosis is low and estimated an incidence rate of 1 event per 20,000-110,000 patient-years (Rizzoli et al., 2008). These findings were reinforced by a study published in 2010 by Grbic et al., which evaluated the incidence of osteonecrosis among 5,903 patients enrolled within the HORIZON Study. The results indicated that among the 5,903 patients who received zoledronic acid, only a single case of osteonecrosis was documented. The authors concluded that the incidence of BRONJ was less than one in 14,200 patient treatment-years and that the risk of osteonecrosis is rare among patients being treated for osteopenia with yearly infusions of 5mg of zoledronic acid (Grbic et al., 2010). The results obtained within our clinical trial correlate closely with the findings of previously completed studies. The overall risk of developing BRONJ in a population being treated for osteoporosis appears to be very low.

6.0 CONCLUSION

We conclude from our study of 180 frail, elderly, institutionalized women, that a single dose of 5mg zoledronic acid for the treatment of osteoporosis does not cause bisphosphonate related osteonecrosis of the jaw. Recommendations for future clinical trials include incorporating a larger sample size and extending the follow-up period.

BIBLIOGRAPHY

- Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, et al: "Bis-phosphy jaws" e high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 36: 95e103, 2008
- "Aging Statistics." Department of Health and Human Services. N.p., n.d. Web. 05 September 2013.
- Almazrooa, SA., Woo, SB. Bisphosphonate and Nonbisphosphonate-Associated Osteonecrosis of the Jaw: A Review. *JADA* 2009;140;864-875.
- Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg.* 2007;65:369–376.
- Becker, DJ, Kilgore, ML, Morrisey, MA. The Societal Burden of Osteoporosis. *Current Rheumatology Report.* 2010 Jun; 12 (3): 186-91.
- Black DM, Delmas PD, Eastell R, for the HORIZON Pivotal Fracture Trial Group. Once-yearly zoledronic acid 5 mg for treatment of post- menopausal osteoporosis. *N Engl J Med.* 2007;356:1809-1822.
- Boonen, S, Singer, AJ. Osteoporosis Management: Impact of Fracture Type on Cost and Quality of Life in Patients At Risk for Fracture I. *Current Medical Research and Opinion.* 2008 Jun;24(6):1781-8.
- Burge R, Dawson-Hughes B, Solomon DH, et al.: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007, 22:465–475.
- Cartosos VM, Zhu S, Zavras AI: Bisphosphonate use and the risk of adverse jaw outcomes: A medical claims study of 714,217 people. *J Am Dent Assoc* 139:23, 2008
- Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005;21: 1453-60.
- Dannemann C, Gratz KW, Riener MO, Zwahlen RA. Jaw osteonecro- sis related to bisphosphonate therapy: a severe secondary disorder. *Bone.* 2007;40(4):828-834.
- Deal, C. Potential new drug targets for osteoporosis. *Nat Clin Pract Rheumatol.* 2009;5:20–27.

- Department of Health and Human Services. Bone health and osteoporosis: a report of the Surgeon General. Rockville, MD: Department of Health and Human Services, Office of the Surgeon General, 2004.
- Dodson, TB. Intravenous bisphosphonate therapy and bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2009 May;67(5 Suppl):44-52.
- Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action in clinical practise. *Mayo Clin Proc* 2008;83(9):1032–45.
- Ficarra, G, Beninati, F. Bisphosphonate-related Osteonecrosis of the Jaws: An Update on Clinical, Pathological and Management Aspects. *Head and Neck Path*. 2007 1:132-140.
- Grbic JT, Landesberg R, Lin S-Q, et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. *JADA* 2008;139(1):32-40.
- Gutta R, Louis PJ. Bisphosphonates and osteonecrosis of the jaws: science and rationale. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104: 186–93.
- Hamdy, RC. Zoledronic acid: clinical utility and patient considerations in osteoporosis and low bone mass. *Drug Des Devel Ther*. 2010 Nov 18;4:321-35.
- Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. *Nat Rev Rheumatol*. 2010;6(2):99–105.
- Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med* 2008;121:475-83, e3.
- Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, et al: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 23: 826e836, 2008.
- Johnell O, Kanis J. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897-902.
- Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int* 2005;16(Suppl 2):S3-7.
- Kanis JA, on behalf of the World Health Organization Scientific Group 2007. Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK, 2008.
- Katz, J, Gong, Y, Salmasinia, D, Hou, W, Burkley, B, Ferreira, P, Casanova, O, Y, T, Langaee, J, Moreb, S. Genetic polymorphisms and other risk factors associated with

- bisphosphonate induced osteonecrosis of the jaw. *Int. J. Maxillofac. Surg.* 2011; 40: 605-611.
- Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: A population-based study. *J Am Geriatr Soc.* 2002 Oct; 50(10): 1644-50.
- Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in australia. *J Oral Maxillofac Surg* 2007; 65:415-423 .
- National Osteoporosis Foundation. America's bone health: the state of osteoporosis and low bone mass in our nation. Washington (DC): National Osteoporosis Foundation; 2002.
- Otto S, et al., Bisphosphonate-related osteonecrosis of the jaws: Characteristics, risk factors, clinical features, localization and impact on oncological treatment, *Journal of Cranio-Maxillo-Facial Surgery* (2011), doi:10.1016/j.jcms.2011.05.003
- Rakel, A, Boucher, A, Ste-Marie, L. Role of Zoledronic Acid in the Prevention and Treatment of Osteoporosis. *Clinical Interventions in Aging.* 2011; 6 89-99.
- "Reclast (Zoledronic Acid) Approval Package." U.S. Food and Drug Administration. N.p., n.d. Web. 12 September 2014.
- Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, Widmer A, Devogelaer JP, Kaufman JM, Jaeger P, Body JJ, Brandi ML, Broell J, Di Micco R, Genazzani AR, Felsenberg D, Happ J, Hooper MJ, Ittner J, Leb G, Mallmin H, Murray T, Ortolani S, Rubinacci A, Saaf M, Samsioe G, Verbruggen L, Meunier PJ. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *NEJM.* 2002;346(9):653-61.
- Riggs BL, Melton LJ 3rd. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995 Nov;17(5 Suppl):505S-11S.
- Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papa-poulos S, Sezer O, Sprafka M, Reginster JY. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 2008; 42: 841- 847.
- Siddiqi, A, Payne, AG, Zafar, S. Bisphosphonate-induced osteonecrosis of the jaw: a medical enigma? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2009 Sep;108(3):e1-8.
- Statz TA, Guthmiller JM, Humbert LA, Johnson GK. Intravenous bisphosphonate-associated osteonecrosis of the jaw. *J Periodontol.* 2007;78:2203-8.
- Strampel W, Emkey R, Civitelli R. Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Saf.* 2007;30(9):755-763.

- US Department of Commerce. Hip fracture outcomes in people aged fifty and over: mortality, service use, expenditures, and long-term functional impairment (Office of Technology Assessment, Congress of the United States, Washington, DC, 1993).
- Walter C, Al-Nawas B, Grotz KA, et al: Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. *Eur Urol* 54:1066, 2008
- Watts NB, Diab, DL. Long-Term Use of Bisphosphonates in Osteoporosis. *J Clin Endocrinol Metab* 2010; 95: 1555-65.
- “WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level: Summary Meeting Report.” World Health Organization. 2004.
- Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.
- Woodis, C.B. Once-Yearly Administred Intravenous Zoledronic Acid for Postmenopausal Osteoporosis. *The Annals of Pharmacotherapy* 2008; 42: 1085-89.