JOMI CURRENT ISSUES FORUM

The development of osteonecrotic lesions of the jaws has been described as being associated with the use of bisphosphonates. Although most clinical reports described the association between necrotic lesions and the use of this group of medications for the management of osseous lesions associated with malignancies such as multiple myeloma, metastatic breast cancer, or prostate cancer, there are reports of osteonecrosis in the jaws of patients who are using oral bisphosphonates to treat osteoporosis.

Given the number of patients taking this medication for the management of osteoporosis, it is obvious that the risks and benefits of the medication need to be clearly defined. Could you comment on the risks of oral bisphosphonate use toward the development of osteonecrotic lesions of the jaws? In addition, could you postulate on studies that may better define this risk?

Editor's Note: *Current Issues Forum* provides the opportunity for invited individuals with expertise and experience to express their opinions on selected current topics of interest in the field of oral and maxillofacial implants. The comments expressed herein represent personal opinion, factual material, or experience-based information provided by the contributors and do not represent positions of Quintessence Publishing Company or the *JOMI* editorial staff. Suggested topics for consideration, as well as responses to the participants' contributions, are solicited from our readers.

Nicholas M. Dello Russo, DMD, MScD, *attended Tufts School of Dental Medicine and graduated in 1970. He was awarded the Alumni Award in Periodontology at Tufts. His specialty training was completed at Boston University School of Graduate Dentistry, where he studied under Drs Henry Goldman, Gerald Kramer, and Myron Nevins. He received an MScD at Boston University and did research involving scanning electron microscopy of the various periodontal tissues. He is an attending periodontist, Department of Oral Surgery, at the Massachusetts General Hospital and an instructor at Harvard School of Dental Medicine.*

Bisphosphonates are an extremely useful class of drugs that are employed to reverse, delay, or prevent bone resorption in patients with life-threatening diseases.[1,2] While their exact mechanism of action is still being studied, they appear to have both an antiangiogenic effect and a potential inhibitory effect on osteoclasts. Bisphosphonates have a great affinity for bone and concentrate within the skeletal system, where they suppress osteoblastic activity by preventing pluripotential cells from differentiating into osteoclasts and/or interfering with osteoclast metabolism, thereby increasing cell apoptosis. It is this reduction in bone resorption that accounts for the increased bone density seen in patients taking bisphosphonates. Patients who are candidates for bisphosphonate therapy include those with bone resorptive disorders such as multiple myeloma and Paget disease as well as patients with cancer that has metastasized in the long bones and spine. It is unclear whether bisphosphonates actually prolong the lives of these patients, but there is no doubt that they greatly improve patients' quality of life by mitigating skeletal fractures, spinal collapse, and the severe pain often associated with bone metastases. For these conditions bisphosphonates are generally given intravenously and for extended periods of time. Patients with moderate to advanced osteoporosis, who are at high risk for hip fractures, are also candidates for bisphosphonate therapy, and in these patients the drugs are often given orally.

As with all medications, side effects do develop. Some appear quickly, but others manifest themselves only after long periods of exposure to the drug. The side effect that is of most concern to us as dental clinicians is avascular jaw necrosis.[3] This rather dramatic event has received a great deal of publicity over the past year, and a debate is ongoing within the medical and dental communities as to what the actual and relative risks are and how patients receiving bisphosphonates should be treated. Since there are no prospective, randomized, placebo-controlled studies available, we, as clinicians, have to look at several case reports and retrospective studies that have been published. Some centers question whether bisphosphonate-induced jaw necrosis actually exists as a separate entity.[4] The drug manufacturers are in a defensive mode, trying to limit any potential litigation. Where does that leave us as clinicians? How do we sort through the fog surrounding this issue and develop reasonable therapeutic strategies?

These are 2 points I would like to put forth.

First, almost all the case reports I reviewed for this forum strongly suggest a causal relationship between bisphosphonates and jaw necrosis. This relationship is stronger for the intravenous forms of the drug. Some centers report incidences as high as 10%[5] for patients on intravenous bisphosphonates. These patients may not be candidates for elective oral surgery. Patients who take bisphosphonates orally and at lower doses present a special problem. Some researchers have taken the position that there is virtually no risk in treating these patients.[6] I am less sanguine about this and believe that caution is advised. Bisphosphonates have a strong affinity for bone and, because their half life is so long (>10 years), they become concentrated within the skeletal matrix. This means that a patient taking bisphosphonates orally for several years may be at as high a risk for jaw necrosis as one receiving the drug intravenously for a shorter period of time. The prudent course is to follow the recommendations of the American Dental Association and various specialty organizations when treating these patients.

Secondly, there is an important lesson to be learned by the way bisphosphonates have been marketed to patients. Because bisphosphonates have proven to be so effective in treating patients who were at risk for life-threatening bone resorption, their use has been extended to include patients with less severe conditions, such as mild osteoporosis, osteopenia, and even periodontal disease.[7] This was done with little or no research as to the effectiveness or long-term consequences. A similar situation occurred with rofecoxib (Vioxx; Merck, Whitehouse Station, NJ), which was the first nonsteroidal anti-inflammatory drug that was an effective analgesic without severe gastrointestinal side effects. The drug was such a success that Merck sponsored several long-term multicenter studies to see if the drug could be used in other situations. Two of these studies, VIGOR and APPROVe,[8] found a significant increase in the number of cardiac events in patients who took rofecoxib for extended periods of time, and the drug was withdrawn from the market in 2004. Because Merck sponsored these studies, it controlled their design and the manner in which results were disseminated to the medical profession. By the time the drug was withdrawn, hundreds of patients may have suffered heart attacks or died.

The sad fact is that we live at a time when clinical research is being sponsored by drug companies,[9] and many speakers at our scientific conferences are being paid, directly or indirectly, by manufacturers to promote their products. We trust the editors of our journals to vet articles and inform us of any possible conflicts of interest, but some authors are less than forthcoming about their relationships with the drug manufacturers. In final analysis, it is up to us to read the literature with a critical eye and make our clinical judgments based on sound reasoning and not the exaggerated claims made by drug companies or their representatives.

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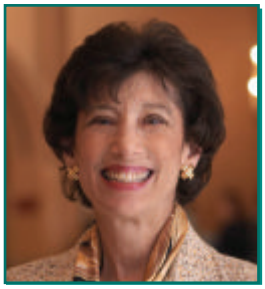

Marjorie K. Jeffcoat, DMD, *is the Morton Amsterdam Dean and Professor of Periodontics at the University of Pennsylvania School of Dental Medicine. Prior to her appointment in July 2003, Dr Jeffcoat served as Assistant Dean of Research and Professor and Chair of the Department of Periodontics at the University of Alabama at Birmingham School of Dentistry. A 1976 graduate of the Harvard School of Dental Medicine, Dr Jeffcoat also taught periodontology at Harvard for 10 years. Dr Jeffcoat was elected to the Institute of Medicine in October 2005. Among her national committee posts, Dr Jeffcoat is currently a member of the National Institutes of Health-NIDCR Advisory Committee for Research on Women's Health, the National Institutes for Dental Research National Advisory Committee, the American Academy of Periodontology Clinical Trials Committee, the Academy of Osseointegration Board of Directors, and the International Association for Dental Research Board of Directors. She is a past president of the Academy of Osseointegration, the American Association for Dental Research, and the International Association for Dental Research. Dr Jeffcoat also serves on the editorial boards of the* Journal of Periodontology, Current Opinion in Dentistry, *and* Journal of Periodontal Research, *and from 2001 to 2004 was editor of the* Journal of the American Dental Association.

Bisphosphonates have been used for more than 30 years for a range of purposes, including:

- Intravenous (IV) formulations for diagnostic imaging of osseous disease
- Low-dose oral formulations for mitigation of bone loss due to osteoporosis
- High-dose oral formulations for treatment of metabolic bone disease such as Paget disease
- High-dose IV formulations for metabolic bone disease
- High-dose IV formulations, usually used in conjunction with high-dose steroids and cytotoxic drugs, for the treatment of bone cancers such as multiple myeloma

Why the Concern?

In recent years, individual case reports and case series have reported a new entity termed "osteonecrosis of the jaws". Osteonecrosis of the jaws is manifested by necrosis (ie, death) of the jaw, which can be diagnosed when the jaw refuses to heal after 6 weeks. By definition, osteonecrosis of the jaws is not mere inflammation or slow healing around sutures. It is a distinct, serious, and potentially disfiguring condition.

Why Are Bisphosphonates Important?

The majority of marketed drugs in the bisphosphonate class are taken for osteoporosis in low dose-oral formulation for the prevention and treatment of osteoporosis. Osteoporosis is a serious and sometimes fatal disease affecting both men and women. Of those patients who break a hip, more than 20% die within a year of sequelae of the fracture. As one of the few effective modalities for treatment and prevention of osteoporosis, bisphosphonates figure in the medical history of a growing percentage of dental patients.

Prevalence of Osteonecrosis of the Jaws with Low-Dose Oral Bisphosphonates

Although millions of patients have taken low-dose bisphosphonates, the prevalence of osteonecrosis of the jaws is too small to calculate at present. Controlled studies in hundreds of patients have shown a prevalence of 0%—ie, zero instances of osteonecrosis of the jaws. On the contrary, patients taking bisphosphonates were found to gain bone around the teeth and lose 43% fewer teeth than control patients. There were no adverse events in the patients who required tooth extraction in the bisphosphonate-treated groups.

The effect of bisphosphonates on the success of dental implants was assessed in a controlled study of 130 patients. Each subject in the test group had been receiving bisphosphonates for 3 years prior to implant placement. The patients remained on the drug for the subsequent 5-year period, for a total bisphosphonate treatment period of 8 years. The bisphosphonate-treated group showed no evidence of osteonecrosis of the jaws, infection, bone loss, implant loss, or implant mobility.

Based on the evidence so far, I do not consider therapy with current low-dose bisphosphonates to be a prima facie bar to dental treatment via customary protocols. Taking a "drug holiday" for several weeks clearly does not make sense, due to the long half-life (years) of the drug in the bones. But all bisphosphonates are not alike. Keep abreast of the latest findings for specific drugs.

The Prevalence of Osteonecrosis of the Jaws with IV Bisphosphonates

It seems clear that most cases of bisphosphanate-related osteonecrosis of the jaws have occurred in patients receiving the drug intravenously. Almost

without exception, such patients are seriously ill and have been receiving a cocktail of cytotoxic drugs and steroids which have documented adverse effects on bone. The situation here is utterly different from a low-dose antiosteoporosis regimen.

In treating these patients, careful collaboration with the oncologist is critical. The dentist's first responsibility is not to interfere with ongoing life-saving treatment, and if that means that an implant must be delayed, or a less-than-ideal alternative must be substituted, then so be it. I spend extra time with these patients, explaining the special risks they face and assuring them that we can proceed with the implant after their most pressing needs are addressed.

Can Patients Not on Bisphosphonates Present with ONJ or ONJ-like Bone?

While hard data are lacking here, my personal experience is yes. For example, osteoradionecrosis is a well-documented condition with a clear initiating factor. I have also treated occasional cases of osteonecrosis associated with autoimmune diseases such as pemphigus. In each of these cases, the patient was receiving cytotoxic drugs and high-dose steroids.

In summary, millions of patients are taking bisphosphonates in the oral low-dose form for prevention and treatment of osteoporosis. The safety profile has been excellent; to date, the prevalence of osteonecrosis of the jaws is too low to calculate. On the other hand, high-dose bisphosphonates, prescribed in conjunction with other drugs for serious bone disease, have had documented adverse osseous effects. Case series suggest osteonecrosis of the jaws in this population, but the lack of controlled studies makes it difficult to determine prevalence. The 2 treatment regimes (high and low dose) are fundamentally different and should have completely distinct impact on the dentist's treatment plan.

Remember, osteoporosis is potentially fatal and can destroy the patient's quality of life. In the absence of any evidence to the contrary, it seems irresponsible to suspend or discontinue antiosteoporosis therapy in favor of implant therapy on the basis of a vague fear.

However, this story is a rapidly emerging one. In the best interests of your patients, watch for new data, protocols, and drugs. Remember, our values should include preserving life, quality of life (including independence and mobility), and esthetics.

Robert E. Marx, DDS, *professor of surgery and chief of the Division of Oral and Maxillofacial Surgery, Miller School of Medicine, University of Miami, is a highly respected surgeon, researcher, and educator who has pioneered new concepts and treatments for pathologies of the oral and maxillofacial area as well as new techniques in major reconstructive surgery. He has made valuable contributions in the use of hyperbaric oxygen following radiation therapy; in the development of platelet-rich plasma; and in elucidating the relationship between smoking and carcinogenesis. For the past 30 years, he has trained scores of residents and fellows, many of whom have themselves established distinguished careers. He has published an impressive number of book chapters and journal articles as well as a textbook (with Diane Stern),* Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment *(Quintessence, 2003), which received the 2003 Award for Best Medical Book from the American Medical Writers Association. Among his most recent publications is his book* Oral & Intravenous Bisphosphonate–Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment. *He has received many other prestigious awards, including the Harry S. Archer Award, the William J. Gies Award, the Paul Bert Award, and the Donald B. Osbon Award.*

Oral bisphosphonate-induced osteonecrosis of the jaws is both similar to and different from intravenous bisphosphonate–induced necrosis. The similarities are that both are caused by aminobisphosphonates (ie, nitrogen-containing side chains on the R2 position of the bisphosphonate molecule) and produce exposed bone beginning in the alveolar area that fails to heal. The differences are that oral bisphosphonate–induced osteonecrosis, as compared to intravenous bisphosphonate–induced osteonecrosis, is less frequent (0.007% to 0.01% incidence versus 0.8% to 12% incidence), less severe, predictable by a simple blood test, responsive to discontinuation of the drug, and curable with surgical debridements.[1]

Five oral bisphosphonates are in use in the United States: etidronate (Didronel; Procter & Gamble, Cincinnati, OH), which is used to reduce heterotopic bone in orthopedic conditions and to treat Paget disease; tiludronate (Skelid; Sanofi Pharmaceuticals, New York, NY), which is used to treat Paget disease; and alendronate (Fosamax; Merck, Whitehouse Station, NJ), residronate (Actonel; Procter & Gamble), and ibandronate (Boniva; Hoffmann-La Roche, Nutley, NJ), which are all used to treat osteopenia/osteoporosis.

Only Fosamax, Actonel, and Boniva are nitrogen-containing oral bisphosphonates and therefore may cause bisphosphonate-induced osteonecrosis of the jaw. I have treated 34 cases of oral bisphosphonate-

induced osteonecrosis of the jaw, 32 due to Fosamax and 2 due to Actonel. Since Boniva was first introduced into the US marketplace in April 2006, patients have not yet had sufficient exposure to the drug to assess its risk.

Mechanisms Responsible for Bisphosphonate–Induced Osteonecrosis of the Jaw

All bisphosphonates inhibit the enzyme farnesyl synthetase and thereby interrupt the mevalonate branch pathway critical to osteoclast survival. The osteoclast first becomes dysfunctional and then succumbs as bisphosphonate accumulates in the bone. Since the osteoclast is the pivotal cell responsible for bone remodeling, severely affected bone becomes old, dies, and eventually becomes exposed. Although all bisphosphonates are rapidly absorbed and accumulate in all bones, clinical disease is most frequently observed in the alveolar bone of the jaw because the turnover rate is 10 times more rapid in this bone than in other adult bones.[2]

Data from a study by my research team of 184 patients who underwent oral surgical procedures while taking an oral bisphosphonate and from my 34 oral bisphosphonate–induced osteonecrosis of the jaw cases indicate that the risk for developing exposed bone is neglible with oral bisphosphonate exposure of less than 3 years and that the risk of osteonecrosis increases proportionately with each year of exposure beyond 3 years. This is due to the long half-life of oral bisphosphonates in bone (10 years or more) and its reduced absorption via the oral route, which results in a bioavailability of only 0.64%. The accumulation of bisphosphonate in bone occurs very gradually when the drug is taken orally. Therefore, the bone marrow osteoclast precursor population is able to replenish and keep pace with the loss of mature osteoclasts. In addition, despite the long half-life of oral bisphosphonates, there remains a sufficient population of osteoclast precursors that will replenish the osteoclast population even after 3 years if the drug is discontinued. In contrast, intravenous bisphosphonates accumulate in bone more rapidly, exhausting the bone marrow population of osteoclast precursors and resulting in more rapid development of exposed bone (9 to 14 months) and irreversible bone toxicity. Once continuous oral bisphosphonate intake exceeds 3 years, the osteoclast precursor population begins to decrease and is less capable of keeping pace with the demands of bone remodeling. This increases the risk of osteonecrosis.

Comorbidities

Any disease process or procedure that increases the requirement for bone turnover can be considered a local factor of significance (eg, ongoing periodontal inflammation, periapical inflammation, tooth removal, implant placement, periodontal surgery, apicoectomy). Orthodontic tooth movement, which relies on osteoclast-mediated bone remodeling, may also pose a risk.

The systemic factor of greatest significance is prednisone use. Prednisone, which is often used to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis, causes a "steroid-induced osteoporosis" for which many patients are treated with an oral bisphosphonate. The combination of bisphosphonate and prednisone use causes osteonecrosis to appear sooner and to be more severe and less responsive to drug discontinuation or treatment. However, prednisone use alone does not cause osteonecrosis in the jaws.

Prevention

The breakthrough in prevention as well as management was the identification that the C-terminal telopeptide level in blood was correlated with osteoclastic activity and with clinical healing or response to surgical debridement.[1] The serum test, C-terminal cross-linking telopeptide (CTX), is a morning fasting blood test requiring only 1 mL of blood. It measures an octapeptide fragment of type I bone collagen that is released into circulation upon osteoclastic bone resorption. Currently the test is accomplished only at the Quest East Nichols laboratory in San Juan Capistrano, California. It has been demonstrated that a CTX value of 100 pg/mL or less represents a high risk for oral bisphosphonate–induced osteonecrosis, a CTX value between 100 pg/mL and 150 pg/mL a moderate risk, and a CTX value of greater than 150 pg/mL a minimal risk. Based on the CTX levels in my own patients (34 with bisphosphonate-induced osteonecrosis of the jaw and more than 100 patients who were on oral bisphosphonates when a surgical procedure was indicated), I offer the following recommendations:

- **Prevention in patients about to start on an oral bisphosphonate or those who have taken one for less than 3 years:** The accumulation of an oral bisphosphonate in bone is slowed by its minimal gastrointestinal absorption. Thus, during the first 3 years of bisphosphonate consumption, dental practitioners should strive to achieve optimum dental health. Inflammatory conditions should be

eliminated during this period so that the need for oral surgical procedures after 3 years of drug exposure can be reduced or eliminated. This translates into the initial removal of unsalvageable teeth followed by periodontal therapy and comprehensive restorative and prosthodontic dentistry. Dental implants may be placed in this time period. However, informed consent about an increased risk of implant failure after 3 years of drug exposure should be provided.

- **Prevention in patients who have received an oral bisphosphonate for 3 years or more and require an oral surgical procedure:** For these patients it is advisable to obtain a reference CTX value. If the CTX value is below 150 pg/mL, use of the drug should be discontinued temporarily. Such a suspension, also known as a "drug holiday," is usually acceptable to the prescribing physician due to studies that have documented the continued control of osteoporosis and prevention of fractures with long-term discontinuation of Fosamax.[3,4] If the prescribing physician is concerned about progression of the osteoporosis without ongoing drug therapy, nonbisphosphonate alternatives can be suggested. These include raloxifene (Evista; Eli Lilly, Indianapolis, IN), teriparatide (Forteo; Eli Lilly), or calcitonin-salmon (Miacalcin; Novartis, Basel, Switzerland). After a 4- to 6-month drug holiday another CTX test is advised. If the CTX value remains below 150 pg/mL, then the drug holiday should be extended for another 4 months. The CTX serum test should then be repeated. The rate of osteoclast recovery as measured by the CTX has been 25 pg/mL per month. In all cases observed, the level of CTX in the blood has recovered to a value in excess of 150 pg/mL in 6 to 9 months.

Treatment of Oral Bisphosphonate–Induced Osteonecrosis of the Jaw

In 50% of the oral bisphosphonate–induced osteonecrosis of the jaw cases I have treated, the exposed bone was spontaneously sequestered or resorbed 4 to 9 months after discontinuation of the drug. Spontaneous recovery was correlated with the CTX value exceeding 150 pg/mL. The remaining cases were resolved with an office-based debridement surgery 4 to 9 months after discontinuation of the drug (again, once the patient's CTX value exceeded 150 pg/mL).

It is recommended that exposed bone due to an oral bisphosphonate be initially managed with 0.12% chlorhexidine if it is nonpainful and there are no signs of infection. If pain or signs of infection are present, penicillin VK 500 mg 4 times daily is recommended in addition to chlorhexidine. For the penicillin-allergic patient, Levaquin 500 mg once daily is the best alternative.

At the initial visit a CTX test should be accomplished and a drug holiday suggested to the prescribing physician. The CTX should be repeated 4 months later and at 4-month intervals thereafter. Once the CTX value exceeds 150 pg/mL, office-based debridement can be considered. If the exposed bone shows radiographic signs of sequestration and the involucrum or exposed bone becomes mobile, the drug holiday may be extended in anticipation of a spontaneous sequesterectomy.

In summary, with common dental procedures, knowledge of bone turnover, and CTX blood testing, bisphosphonate-induced osteonecrosis of the jaw can be prevented in most cases, and in those cases in which osteonecrosis is already present, it can be resolved in a straightforward manner.

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Paul Fugazzotto, DDS, *received his DDS from New York University in 1979 and a certificate in advanced graduate studies in periodontology from Boston University in 1981. Since that time Dr Fugazzotto has maintained a private practice limited to periodontics and implant therapy in Milton, Massachusetts. Dr Fugazzotto has authored or coauthored more than 80 articles in refereed scientific journals. He is also the author of a monograph titled "Guided Tissue Regeneration: Maximizing Clinical Results" and a textbook titled* Preparation of the Periodontium for Restorative Dentistry. *Dr Fugazzotto is the senior editor of* Implant Realities. *He is also a fellow of the International Team of Implantology.*

Although the majority of reported cases of bisphosphonate-induced osteonecrosis have occurred in patients who have been treated with intravenous bisphosphonate therapy, Marx and coworkers and Ruggiero and coworkers have reported bisphosphonate-induced osteonecrosis of the jaw in patients with no history of malignancies who took oral bisphosphonates to treat osteoporosis. As of early 2006, approximately 200 cases of osteonecrosis in patients taking oral bisphosphonates had been reported.

While it is tempting to dismiss this problem as inconsequential considering the vast number of patients who utilize oral bisphosphonates due to osteoporotic concerns, and the incidence level (0.7 cases per 100,000 patient years of exposure based on reported cases), such dismissal would be a disservice to patients and our profession. It is imperative that we explore our current understanding of the problem, formulate reasonable treatment guidelines based on this understanding, better define the scope of the problem through research, and modify and update suggested treatment protocols as further facts come to light.

I recommend that full-time clinicians like myself approach the problem of bisphosphonate-induced osteonecrosis of the jaw as follows:

1. **Review the available literature.** It is important for us to define the precise scope of the problem in terms of our current knowledge. Although Drs Marx, Ruggiero, and their colleagues have reported significant numbers of patients presenting with bisphosphonate-induced osteonecrosis of the jaw following oral bisphosphonate use, most of their bisphosphonate-induced osteonecrosis of the jaw patients were referrals. Thus, the true prevalence is unknown. Secondly, in the studies reported thus far, the details of the therapy peformed are also unknown, including whether the surgical technique used was gentle, the teeth were extracted atraumatically, the sockets were thoroughly debrided, and primary soft tissue closure was obtained and maintained. Finally, it is important to know whether any dental comorbidities (poor oral hygiene, periodontitis, caries lesions, periapical lesions) or anatomic comorbidities (the presence of large mandibular tori, which render the covering soft tissues more friable, labile, and likely to slough postoperatively) may have affected the development of bisphosphonate–induced osteonecrosis of the jaw. Dr Jeffcoat recently published a single-blind controlled study of 25 patients with a history of oral bisphosphonate use. No postoperative sequellae occurred, and no implants had been lost 3 years after implant placement.
2. **Develop appropriate preoperative protocol for patients with a history of oral bisphosphonate use.** All dental comorbidities should be managed preoperatively. These include appropriate oral hygiene instruction, gentle supragingival and intrasulcular debridement as needed throughout the mouth, caries control, and endodontic therapy as needed. All active disease should be eliminated in the patient's mouth prior to the initiation of surgical therapy.

Trauma to the bone should be minimized in patients taking oral bisphosphonates. If a tooth is to be extracted, the bone should not be resected with a high-speed rotary instrument. Single-rooted teeth should be removed either by gentle luxation, if feasible, or using an extraction system, which requires placing a post in the canal of the tooth and utilizing impression material, a tray, and a "pulley"-type arrangement to lift the tooth out of the socket. If a multirooted tooth must be removed, the tooth should first be hemisected or trisected, and each root should be extracted as previously described. This technique avoids undue trauma to the bone through excessive manipulation upon resection.

If implant therapy is anticipated, the implant should be placed at the time of tooth removal so as to minimize the number of surgical insults to the patient. If no implant is needed, the defect should be thoroughly debrided, and a resorbable surgical sponge should be placed in the socket to help with clot stabilization.

Care should be taken through various flap designs to attain passive primary soft tissue closure, thus protecting the underlying bone and extraction socket during healing. Flap suturing should be kept to a minimum, and only interrupted resorbable sutures

should be utilized to minimize soft tissue ischemia due to suture tension.

A paper recently submitted by myself and Drs Jaffin, Lightfoot, and Kumar documents 159 implants placed in 2005 in 61 patients actively taking oral bisphosphonates. Thirty-nine implants were placed at the time of tooth removal. Bisphosphonate use ranged from 35 to 70 mg per week for 1 to 5 years. One patient who demonstrated an extensive torus at the time of removal of a mandibular first molar and immediate implant insertion with concomitant grafting developed a 2 × 3-mm area of exposed bone 1 week postoperatively. The area was gently debrided and was closed with covering soft tissues at the 4-week postoperative examination. The implants were followed for 12 to 23 months postinsertion. All implants were functioning successfully (Albrektsson criteria).

In my clinical practice, prior to initiating therapy, I am often asked:

1. What other treatment options are available? Endodontic therapy could be performed on the teeth in question, and they could be cut down to the gingival margin and left in situ. In incidences of root fracture or severe periodontal disease, such an option is not feasible. Even when such treatment can be carried out, what type of service has been performed for this patient? The patient is now for all intents and purposes missing a tooth and must undergo other types of prosthetic restoration to replace it to ensure intact, functional occlusion.
2. What would you do in your mother's mouth? Considering our current knowledge, and the options available to us, I would (and did) proceed with the indicated dental therapy, which included extraction of a single-rooted premolar and placement of an implant at the time of tooth removal.

While we must be aware of the potential for the development of bisphosphonate-induced osteonecrosis of the jaw, I believe that the steps I have outlined help render the risk reasonable in all patients except those who present with significant medical comorbidities.

Extensive work still needs to be done to answer a number of questions, including:

- What influence does the length of time of oral bisphosphonate use have on the potential development of bisphosphonate-induced osteonecrosis of the jaw?
- What influence does the dose of oral bisphosphonate taken have on the potential development of bisphosphonate-induced osteonecrosis of the jaw? What is the combined effect of time of use and dosage?
- What is the precise influence of various comorbidities on the potential for development of bisphosphonate–induced osteonecrosis of the jaw?
- Are there any diagnostic tools that could help us identify oral bisphosphonate users who are at greater risk of development of bisphosphonate–induced osteonecrosis of the jaw (eg, bone density readings, blood tests, etc)?

Larger controlled studies such as those of Dr Jeffcoat must be carried out in different settings. However, such studies do not represent our only avenue of exploration. Clinicians must compile and honestly assess data from their private practices. Pooling of data from a number of practices will generate very valuable information. Reports must include the techniques employed so as to determine the safest routes to root removal. These papers should document treatment results following extraction, implant placement, and extraction and simultaneous implant placement. Multisite papers documenting treatment of large numbers of oral bisphosphonate patients and the clinical outcomes of therapy could then be published.

I am currently contacting authors to compile their data. I will serve as the office site and take on the onus of drafting the paper, which will naturally be passed around and shared by all authors before publication. I would call upon the leaders in our field to come forward both as coordinators of other such sites and as contributing authors for these very important and necessary papers.