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Quick Pulse

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QUESTIONS ABOUT THE SAFETY OF BISPHOSPHONATES

The FDA's Oncologic Drugs Advisory Committee (ODAC) met on March 4, 2005, in Gaithersburg MD, to discuss safety concerns – specifically osteonecrosis of the jaw (ONJ) – associated with two intravenous (IV) bisphosphonates from Novartis, Zometa (zoledronic acid) and Aredia (pamidronate disodium). Prior to 2001, only one or two cases a year of ONJ were reported by maxillofacial surgeons, but the number of cases has been increasing rapidly. The FDA acknowledged there have been reports of ONJ in osteoporosis patients on oral bisphosphonates, but the discussion at this panel meeting was limited to IV bisphosphonate use by cancer patients.

ONJ Spontaneous Reports to the FDA

Year	ONJ Reports
2001	1 (femoral head)
2002	9
2003	60
2004	69
Total to date	**654**
Aredia only	21% (163 patients)
Aredia followed by Zometa	28%
Zometa only	49%
Aredia, Zometa, or another bisphosphonate	2%

ONJ has been described as "exposed bone in the maxilla or mandible." It is due to disruption of the resorption-remodeling cycle of bone and inhibition of endothelial cell proliferation. ONJ tends to heal poorly, and secondary infections can lead to loss of teeth and segments of jaw bones.

Aredia was approved by the FDA in 1991, in connection with standard anti-neoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. It is also approved for the treatment of moderate or severe hypercalcemia associated with malignancy and for the treatment of patients with moderate-to-severe Paget's disease of the bone.

Zometa was approved in 2001 for the treatment of multiple myeloma and in patients with documented bone metastases from solid tumors, in connection with standard anti-neoplastic therapy. It is also approved for hypercalcemia of malignancy. The typical dose is 4 mg/month.

Both drugs had their label changed in 2003 to include information about ONJ in the adverse events section. Additional labeling changes about ONJ were made in the fall of 2004, and in September 2004, Novartis issued a Dear Doctor letter regarding ONJ.

The Zometa label already has precautions, including the following:

- ONJ has been reported in cancer patients receiving treatment regimens including bisphosphonates.
- Many patients were also receiving chemotherapy and corticosteroids.
- The majority of cases are associated with dental procedures.
- Many patients with ONJ had signs of local infection including osteomyelitis.
- ONJ has multiple well-documented risk factors, including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease).
- A baseline dental exam is recommended if a patient has risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).
- Although causality cannot be determined, it is prudent to avoid dental surgery or invasive dental procedures as recovery may be prolonged.
- There are no data as to whether discontinuing therapy reduces the risk of ONJ.

The FDA posed five questions to the panel for discussion, but there was no vote on any of these:

1. Discuss the information content communicated by the FDA and Novartis regarding ONJ in patients receiving Zometa and Aredia. Should any other information be communicated?
2. It is known that the potent IV bisphosphonates, Zometa and Aredia, bind to bone for many months after infusion. Discuss whether there are data or a strong rationale to support discontinuation of bisphosphonate therapy in patients having invasive dental procedures.
3. For patients who develop ONJ, are there data suggesting that temporary interruption or discontinuation of therapy is indicated?
4. Discuss the potential value of establishing a Registry of patients receiving bisphosphonates to obtain additional information regarding ONJ associated with bisphosphonate use.
5. Discuss additional approaches or studies that should be done to evaluate ONJ and its management.

An oral surgeon told the panel: "As of yesterday, the 105th patient was seen in my practice alone…I don't know why we are seeing so much…Clearly, there are more and more patients because of the publicity, but a lot of the patients are local people. There is truly a spectrum of disease, from tiny spots that are easy to diagnose to cases of large exposed bone …This is not something that requires rocket science to diagnose. I don't expect oncologists to look in a patient's mouth, but if awareness is made to the patient that this is a possible problem, then the diagnosis can be easily made…I have many patients who have lost their job over this complication, who did very poorly…We have no indices of who will do well or who will lose their job…We need to educate patients, oncologists, and the general dentists. I think the dentists are caught in the middle here…The patients often wind up in an oral surgeon's office…and oral surgeons are probably one of the most aware groups…Oncologists are a distant third…The main focus is to educate oncologists and the general dentists."

THE FDA PERSPECTIVE

Two FDA officials and an invited expert, Dr. Brian Durie of Cedars-Sinai Outpatient Cancer Center in Los Angeles CA, provided an overview of the ONJ problem.

The profile of a patient with ONJ is:

- Diagnosis of malignancy.
- No head and neck radiotherapy.
- Treatment regimen included IV bisphosphonates.
- High proportion had a recent invasive dental procedure.

Other points made by FDA officials and experts:

- Zometa and Aredia are effective drugs for the bone metastasis indication.
- The true *incidence* of ONJ is unknown. ONJ is a rare event. There is no ICD-9 code for ONJ.
- The FDA epidemiologist commented, "We believe these cases present a highly plausible safety signal. Most cases affect the jaw, lending plausibility to a common mechanism. A significant number of reports have been received."

Dr. Durie reported the results of an anonymous, web-based survey he conducted in summer 2004, in which 1,203 patients (904 with multiple myeloma and 299 with breast cancers) were interviewed. The survey ruled out thalidomide (Celgene's Thalomid), Millennium's Velcade (bortezomib), dexamethasone, Thal/Dex (thalidomide+dexamethasone), and prednisone as increasing the likelihood of ONJ. The survey found 75 cases of ONJ, and 67 cases of suspicious ONJ (SONJ).

- Multiple myeloma patients – 62 with ONJ, and 54 with SONJ.
- Breast cancer patients – 13 with ONJ, and 23 with SONJ.

Mean Time from Multiple Myeloma Diagnosis to Onset of ONJ or Suspicious ONJ

Drug	ONJ	Suspicious ONJ (SONJ) **
Zometa only	18 months *	19 months
Aredia+Zometa	70 months	11 months
Aredia only	72 months *	32 months
No Aredia / Zometa	41 months	10 months

* p<.002. ** No SONJ is p<.05

Dr. Durie pointed out that:

- ONJ and SONJ are both linked to bisphosphonate use.
- ONJ and SONJ are more frequent and occur earlier with Zometa vs. Aredia.
- The increased occurrence of ONJ and SONJ since 2001 correlates with the introduction of Aredia and Zometa. He said, "Why did we starting seeing ONJ in 2001? Six years is average time to onset with Aredia, and that is the time since Aredia came on the market. Eighteen months is the average time for ONJ onset with Zometa, and that is when Zometa came on the market…So, the incidence is related to when these products came on the market."
- Prior dental problems (such as dental extraction) are common precedents of ONJ and SONJ.
- Precautions related to dental care and bisphosphonate use "can make ONJ and SONJ a preventable problem."

The implications for patient care, according to Dr. Durie, are:

- Patients should receive thorough dental exams and complete any required procedures before beginning bisphosphonate therapy, if possible.
- Patients on bisphosphonates should be discouraged from performing elective oral surgery/procedures without special precautions.
- Patients with ONJ should be treated with antibiotics/chlorhexidine. Surgery is contraindicated.
- Prophylactic use of Aredia and Zometa should be limited to situations where there is no indication of bone disease or predisposition to bone disease.
- Consider use of Aredia rather than Zometa in patients with known dental problems.
- Consider decreased frequency of bisphosphonates for longer-term stable patients.
- Consider temporarily discontinuing bisphosphonates in patients with severe osteonecrosis and/or with a need for surgery.

THE NOVARTIS PERSPECTIVE

1.9 million Americans have been treated with Aredia since its launch, and 1 million Americans have been treated with Zometa since its launch. A Novartis official said, "We believe the increase in cases (of ONJ) is related to increased awareness of ONJ." She criticized the web survey's accuracy and suggested it was biased.

A Novartis official said that MD Anderson Cancer Center is doing a chart review of all 4,032 IV bisphosphonate users at that institution, as identified by their pharmacists. The data presented were on the first 25% of those charts, which were done in a non-randomized manner. That is, the charts of patients with the greatest number of infusions were reviewed first, and seven charts were reviewed out of sequence because of suspected ONJ.

MD Anderson Chart Review of ONJ Occurrences in IV Bisphosphonate Patients

Disease	Patients	ONJ
Breast cancer	631	11
Multiple myeloma	148	6
Medullary thyroid	N/A	1
Other	184	0
Total	**963**	**18**

MD Anderson Interim Data on 18 ONJ Cases

Drug	Cases of ONJ
Aredia only	4
Zometa only	3
Fosamax then Zometa	1
Aredia then Zometa	10
Median time to onset of ONJ	**30 months**

Novartis officials also stressed the value of Aredia and Zometa in metastatic bone disease. Other points they made include:

- ~1.9 million patients had been exposed to Aredia and 1 million to Zometa as of December 4, 2004.
- IV bisphosphonates have had a major impact in reducing skeletal-related events (SREs) in cancer patients with metastatic bone disease.

Bisphosphonate Impact on SREs

Cancer type	Placebo	Aredia + Zometa	% change
Prostate	1.5	0.7	Down 47%
Breast (source #1)	3.7	2.4	Down 35%
Breast (source #2)	1.42	0.7	Down 50%
Myeloma	2.0	1.0	Down 50%
Others	2.7	1.7	Down 37%

- Novartis received the first spontaneous report of ONJ in an IV bisphosphonate-treated cancer patient in December 2002.

- Risk factors specific to jaw bones may play a role – e.g., exposure to external environment through teeth, or risk of trauma from repeated dental procedures.
- There is no consensus on diagnostic criteria for ONJ.
- Osteoradionecrosis occurs in an estimated 8.2% of patients following head and neck radiation.

Incidence of ONJ in Aredia and Zometa Trials

Disease	Number of patients	Cases of ONJ	Tumor type
Total exposed patients			
Aredia	1.9 million	---	---
Zometa	1 million	---	---
Pivotal trials			
Aredia	1,334	2	Multiple myeloma
Zometa	2,730	4	3 multiple myeloma 1 head & neck
Placebo	1,347	0	---
Other completed trials			
Aredia	26 trials 1,214 patients	0	---
Zometa	23 trials 3,217 patients	0	---
Placebo	273	0	---
Ongoing trials			
Zometa	1,476	4	2 breast cancer 1 prostate cancer 1 multiple myeloma

Novartis is continuing to study the ONJ problem. A source indicated that Novartis is considering working with Kaiser Permanente on a larger study of the issue. The company also has taken steps to make patients and doctors aware of this problem, including:

- Patient outreach meetings with advocacy groups.
- New brochure that doctors can distribute to patients with information on ONJ, including definition, signs, and symptoms.
- Plans to develop – with the help of an expert panel – a case definition and severity scale.
- Obtaining follow-up data about ONJ on patients in pivotal trials.
- Implementing new studies that include prospective monitoring for ONJ, including:
  - Study 2352, a Phase III randomized trial in metastatic breast cancer and multiple myeloma to start in 4Q05.
  - SWOG-0307, a randomized Phase III trial in adjuvant breast cancer that is under discussions.
  - A prospective registry for ONJ or an ONJ natural history study to start in 2H05.
- A retrospective chart review for ONJ will be initiated in 2Q05 in multiple myeloma patients.

PUBLIC WITNESSES

Dr. Felice O'Ryan, an oral surgeon at Kaiser Permanente, which has 3.2 million members in northern California, showed the panel photos of patients she has seen with ONJ due to IV bisphosphonates. She said, "I don't consider these problems minor or insignificant, and neither do my patients. I feel the FDA and Novartis have done a poor job of informing people of this potential risk. I have informed our oncologists about this...but the oncologists are not particularly comfortable doing oral exams…so some of this has been missed…I have at least 30 unsolicited patients…Most of the cases I have are not associated with a dental extraction…When we have discontinued (bisphosphonate) treatment, I have only seen patients (continue to) progress. There is no healing, no cure."

Multiple myeloma organizations and patients stressed the value of IV bisphosphonates in that disease. Scott Santarella, from the Multiple Myeloma Research Foundation, said, "Bisphosphonates are essential therapy for this disease…The risks are minimal vs. the benefits they provide." Bruce Holmberg, a multiple myeloma patient, told the panel the risk is worth the benefit to him. Another patient said, "I am on Zometa with an active lifestyle…In January 2004, I was diagnosed with ONJ. With antibiotics, it cleared up within approximately six months, and I am still on Zometa and thankful to have the lifestyle I have."

PANEL DISCUSSION

Advisory committee member comments indicated there are still many unanswered questions, the panel would like more information, there is real concern that ONJ is a growing problem, and there are no easy answers. Comments included:

- "I don't regret voting for approval (of Zometa and Aredia) because I think there is benefit…but I worry if the promotion is as accurate as I would like…After Zometa's approval, it was a freight train making it close to medical malpractice for patients with metastatic disease not to get Zometa." A Novartis official responded, "Zometa is actively promoted. Aredia is no longer promoted. Aredia has been generically available since 2001…There is practically zero Aredia utilization. Any Aredia use has moved over to generic pamidronate."
- "I am worried that simply stopping the product for a month or two won't help…You want to advise patients (of the risk of ONJ) prior to ever starting these products. And you have to do it in a proactive way…We also need to know what is the proper duration of these drugs, and I don't think there are data on that yet."
- "My assumption is that you (Novartis) reached 25% or less of the patients (with the 50,000 patient safety booklets)."
- "I think Novartis's attitude is somewhat defensive."

- "How do you (Novartis) know that you are reaching anyone, especially the oral surgeon (with your message)? There should be an evaluation component, and the FDA may want to insist on that. The idea of a Registry is good. Ongoing clinical trials sound nice, but are they long enough and big enough to get a safety signal?"
- *Chair:* "As time goes on, there are more and more cases…and what was an appropriate stance 12-18 months ago may not be quite appropriate today…As a clinician, I am struggling with the clinical expression…Is it trivial, medium level, or a serious and incapacitating problem?… I have never had a habit of sending patients to a dentist prior to (now)...and I don't know that will solve the problem…but it is not an unreasonable thing to do."
- *Dr. Richard Pazdur,* Director of Oncology Drug Products at the FDA: "No one is saying this is a trivial situation …Many doctors are (not very aggressive about informing patients about this complication). Medical oncologists don't get into peoples' mouths very often...That isn't a focus of their investigation...They may not be paying attention…Many patients are started on chemotherapy without a visit to a dentist or a thorough exam."
- "A scoring system (for ONJ) would be useful."
- "I think it's great dentists are aware of this problem (ONJ), but are medical oncologists being made aware of this?

NO DECISIONS MADE

The FDA's Dr. Pazdur summed up the meeting this way: "Some of the questions we posed (about IV bisphosphonates and ONJ) don't have answers. We have to evolve that data. In my mind, listening to what was said, several major areas that Novartis, the FDA and investigators need to work on include:

1. Duration and how optimally to use this drug. The half-life (of Zometa) is very, very, very long in bone. Do people need the same dosing schedule over time?
2. Greater awareness by the treating community – oncologists, nursing personnel, oral surgeons, and dentists.
3. Is there a preferential bisphosphonate – Aredia vs. Zometa? There were some interesting data presented. We have to remember the basis for approval in multiple myeloma was non-inferiority for Zometa (vs. Aredia). So, is there a big advantage if you have a toxicity issue? We don't know this."

Dr. Pazdur added, "These are hypothesis-generating data. But these are major questions that need to be answered. Our reason for bringing this to the committee was to highlight the safety issues. This is one of the few times we get to have a public face to the FDA to highlight not only efficacy but also safety issues."

Thus, it appears that Zometa is likely to get another label change and will face more scrutiny, but the value in cancer outweighs the risks – at least for now. If the incidence of ONJ continues to increase, Zometa could face further regulatory action or even become a second-line therapy (behind Aredia or generic pamidronate). This is not likely in the near-term, and perhaps never, but it is something that warrants watching. An expert predicted, "I think it unlikely that these findings will have an important impact on the use of bisphosphonates in cancer. That treatment is very valuable as a way to minimize the progression of bone metastases and to limit other skeletal complications. If there is a lesson to be learned, it would be that tooth extraction should be done only under the most important circumstances in these patients…This will be an important clinical issue to pursue, and Novartis is being very aggressive (in a good way) of exploring these issues and attempting to understand both the nature of the clinical problem and its relationship to bisphosphonate therapy."

However, outside of cancer the regulatory hurdles for bisphosphonates (oral and IV) clearly have become higher. The two key areas most likely to be affected are:

- **Zometa for osteoporosis.** Novartis has been testing a 5 mg once-yearly IV Zometa to prevent osteoporosis. This is far less total annual milligrams than is used in cancer (which is 4 mg/month). The regulatory path for the annual dosing appears likely to be much more difficult, and it may not be approvable at all. In an interview before the panel meeting, an expert said, "The issue was first raised by a Florida dentist about a year ago. He described about 30 cases of ischemic necrosis of the jaw in patients with cancer being treated (mostly) with zoledronate and pamidronate. The doses used were very high (for zoledronate about 4 mg/month, compared to the 5 mg/year being evaluated for osteoporosis)."
- **Oral bisphosphonates.** There is no immediate concern about oral bisphosphonates causing ONJ, but the questions are: Do oral bisphosphonates also cause ONJ but just take longer to produce the effect? In the future will there be a spike in ONJ cases due to oral bisphosphonates? In a interview unrelated to the panel meeting, an expert said, "The reports of this happening in patients being treated with these bisphosphonates for osteoporosis are rare." A West Coast expert added, "There have been a handful of cases with osteonecrosis of the jaw described in patients receiving other types of bisphosphonates, including Fosamax (Merck, alendronate)…Most of the bone experts think that there is not a relationship between these jaw findings and the doses of therapy used for the treatment of osteoporosis. Recall that the doses of IV bisphosphonates used in the treatment of patients with cancers that have spread to bone are very much higher than the doses used to treat osteoporosis."

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