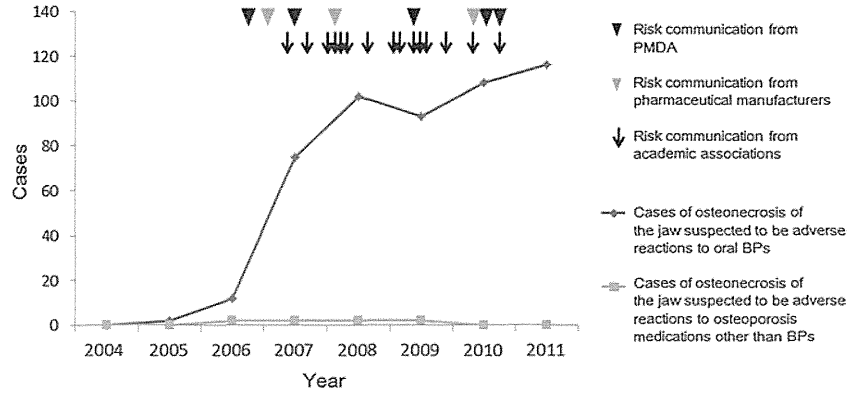

Figure 1. Trends in the number of ONJ cases per year reported to the Drug Adverse Reactions Reporting System of the PMDA and risk communication activities. Legend: The cases of ONJ that were suspected adverse reactions to oral bisphosphonates and those that were suspected adverse reactions to other agents for osteoporosis, reported to the Drug Adverse Reactions Reporting System of the PMDA, are shown as a dark gray line and a light gray line, respectively. Black arrowhead: risk communication from the PMDA; gray arrowhead: risk communication from pharmaceutical manufacturers; arrow: risk communication from academic associations

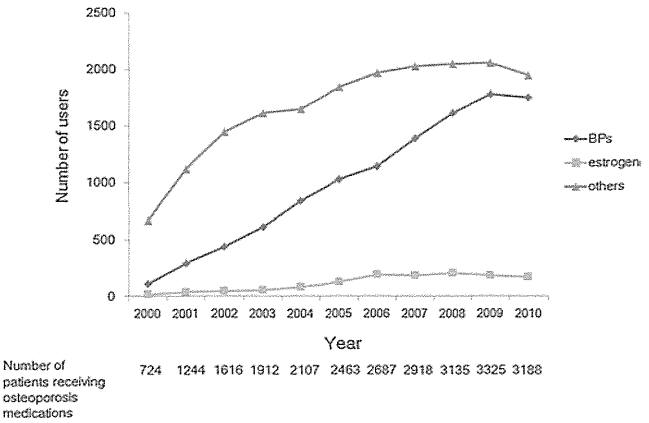

Figure 2. The number of patients prescribed each agent for osteoporosis in the cohort. Legend: The numbers of patients prescribed bisphosphonates, estrogen and a selective estrogen receptor modulator, as well as other agents for osteoporosis, each year in a cohort of 6293 osteoporosis patients are illustrated with a dark gray line of diamonds, a gray line of triangles and a light gray line of squares, respectively. The year 2000 contains 2 months, and the year 2010 contains 10 months. The numbers of patients receiving osteoporosis medications in each year are shown below the graph

increased before 2006 and since then has remained approximately constant.

The EMRs of a total of 1987 patients with records of ONJ or inflammatory conditions of the jaw that were possibly related to ONJ were manually reviewed, and 46 patients were confirmed to have ONJ.[18]

The incidence proportion of confirmed ONJ in the BP group increased approximately four-fold in 2009 and 2010, compared with the pre-2009 level. The incidence proportion of confirmed ONJ in the non-BP group remained low (Figure 3a). Both of the incidence proportion of confirmed ONJ cases and that of inflammatory conditions of the jaw increased after 2009; however, the increase in inflammatory conditions of the jaw was not as high as that of confirmed cases (Figure 3b). This measure was therefore not a good surrogate for confirmed ONJ in this study.

DISCUSSION

Risk communication efforts by pharmaceutical manufacturers and academic associations began within 1 year after the package insert was revised in October 2006, and ONJ was increasingly reported to the PMDA within 1 year. In our cohort, the incidence proportion of ONJ, diagnosed according to standardized criteria, increased in 2009 and in later years. During this period, BPs were frequently prescribed, and there were no increases in the use of alternative agents, such as selective estrogen receptor modulators.

Physicians' case reports regarding ONJ in 2003[4,5] in the USA led to revisions of package inserts in 2004 to 2005.[7,25,26] In Japan, the pharmaceutical manufacturers revised the package inserts for intravenous BPs in 2005 and for oral BPs in 2006 and 2007, but the revision was delayed for 2 years after the revision in the USA. The physicians' case reports regarding ONJ were first published in 2007, 4 years after their publication in the USA; thus, the physicians' reports in Japan did not contribute to the increased suspicion of ONJ related to BPs or to the revision of the package insert. Academic associations were rather active in risk communication in the later dissemination phase. Physicians and academic associations have been able to detect new safety concerns for marketed drugs and to conduct epidemiological studies effectively, and we should reconsider academic associations, as well as the regulatory authority

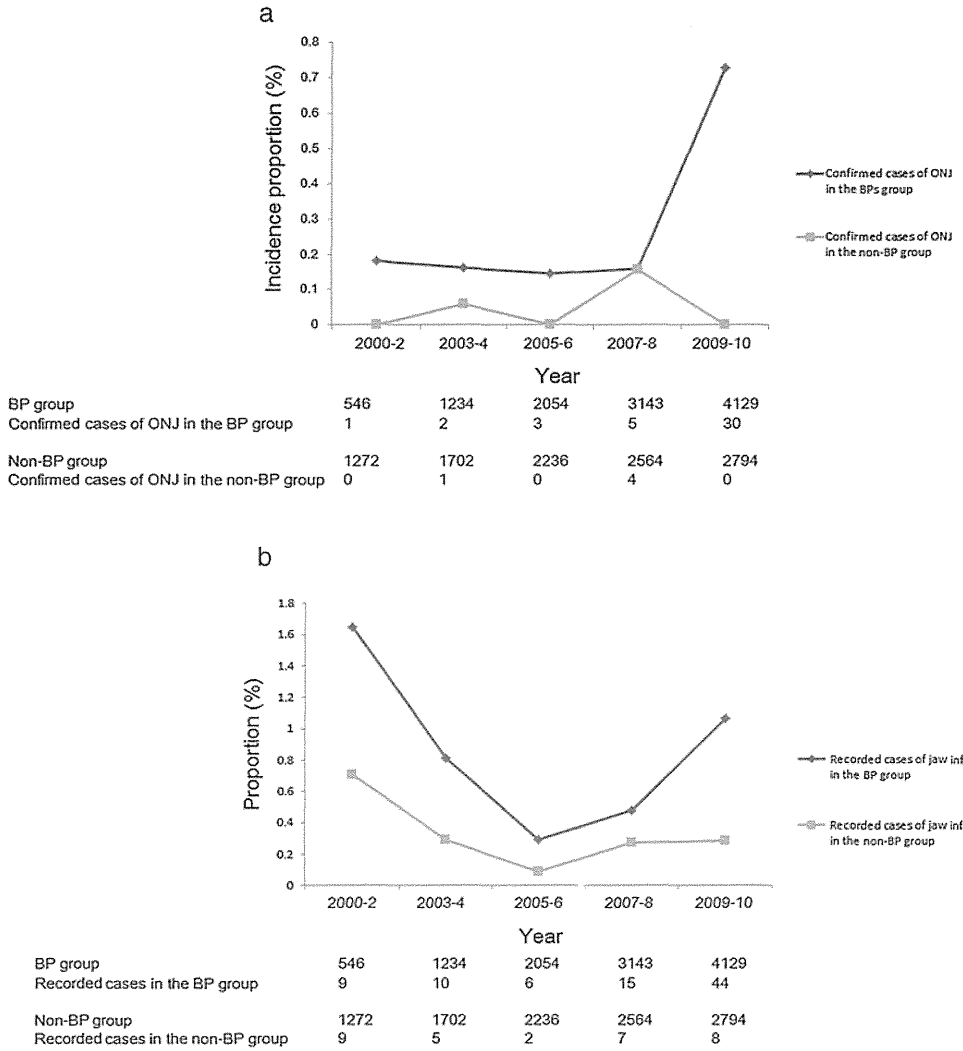

Figure 3. (a). The incidence proportion of confirmed cases of ONJ in the cohort. Legend: The incidence proportions of the confirmed ONJ cases in 100 BP-group patients in 2000–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010 are indicated by a dark gray line of diamonds. The incidence proportions of confirmed ONJ cases per 100 non-BP-group patients in each 2- to 3-year period are indicated by a light gray line of squares. The number of patients in the BP group, the number of confirmed ONJ cases in the BP group, the number of patients in the non-BP group and the number of confirmed ONJ cases in the non-BP group are shown below the graph. (b). The proportions of recorded ONJ cases in the cohort. Legend: The proportions of recorded cases of inflammatory conditions of the jaw in 100 BP-group patients in 2000–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010 are indicated by a dark gray line of diamonds. The proportions of recorded cases of inflammatory conditions of the jaw in 100 non-BP-group patients in each 2- to 3-year period are indicated by a light gray line of squares. The number of patients in the BP group, the number of recorded cases of inflammatory conditions of the jaw in the BP group, the number of patients in the non-BP group and the number of recorded cases of inflammatory conditions of the jaw in the non-BP group are shown below the graph

and pharmaceutical manufacturers, as resources for monitoring and minimization of the risks of medicines and for ensuring the accuracy of information.

We evaluated the impact of risk communications by analyzing the prescriptions of medications for osteoporosis and the incidence proportion of ONJ. The use of BPs increased steadily, but the prescriptions for BPs were not influenced by the risk communications in this study. BPs are among the most established drug types for the treatment of osteoporosis in postmenopausal women,[27] and the gradual increase in the use of BPs over the periods, before and after the dissemination of the safety information, was reasonable considering the risk–benefit balance. We could not determine whether the physicians prescribed BPs after considering the risk–benefit balance or simply did not receive the safety information. Many confounding factors can influence the prescription of BPs, such as the active participation of academic associations or the perceptions of physicians and patients toward adverse events. Physicians might hesitate to change prescribing habits because of known obstacles, such as the lack of time during outpatient care and the desire to maintain trust in the physician–patient relationship.[28]

The rapid increase in the cases of ONJ that were suspected adverse reactions to oral BPs reported to the regulatory authority after the risk communications efforts might indicate that the primary cause of the increase was awareness of the disease because the increase was quite sharp. The incidence proportion of ONJ in the BP group increased in our cohort, although the increase occurred 3 years after the risk communications began. There would have been few missed or misdiagnosed cases of ONJ in our cohort because the cases were diagnosed based on an extensive manual review of the EMRs, using well-established criteria. There might have been other causes for the increase in the incidence proportion of ONJ in our cohort in addition to risk communication; one possibility is the longer exposure to BPs[8,29] in the cohort. Longer exposure and risk communication occurred simultaneously; therefore, we could not distinguish the impact of risk communication from that of longer exposure. There was a time difference between the increase in the number of cases of ONJ reported in the Drug Adverse Reactions Reporting System and the increase in the incidence proportion of ONJ in the cohort. The cases of ONJ reported to the Drug Adverse Reactions Reporting System include past cases of ONJ: cases that occurred before 2006 might be reported as cases of ONJ after 2006. Moreover, the diagnosis of ONJ is not standardized and might include other inflammatory conditions of the jaw. However, the number of ONJ patients in the cohort reflects the number of active ONJ patients diagnosed in the hospital. The difference between the recording and the diagnosis of ONJ most likely resulted in the time difference.

Previous reviews have found it difficult to estimate the average effect of risk communication on clinical practice[16,17,30] because of heterogeneity in the study designs, analyses, outcome measurements, therapeutic areas and types of communication. ONJ can be reduced with preventive measures, including clinical oral examinations and good oral hygiene.[31,32] Unfortunately, we did not observe a decrease in the incidence proportion of ONJ in our cohort during this study period, which would have been the clinical outcome. Additional appropriately designed research is warranted to understand the effects of past communications strategies and to estimate the impact of future communication.

The limitations of our study are described below. First, factors other than safety information collected in our study, such as pharmaceutical use, could have simultaneously influenced the incidence proportion of ONJ. Second, we did not consider the scale, the duration or the content of the risk communication; it is therefore not possible to evaluate the impact of each risk communication material quantitatively. Third, the data on drug use and on the incidence proportion of ONJ in Kyoto University Hospital were limited to a single institution in Japan; thus, the generalizability of the results cannot be assured. The much higher incidence of ONJ in our study compared to the published literature might be explained by the inclusion of numerous steroid users, older patients and inpatients. Moreover, the cohort study was subject to a referral bias toward the selection of more severe cases, given that our department is the lead institution for oral and maxillofacial surgery in Kyoto City, as discussed in our previous report.[18] We could not account for BP exposure that occurred before consultation at Kyoto University Hospital, which might have affected the incidence proportion of ONJ. Finally, this study was retrospective, using a database derived from the EMRs, and the data were not as accurate and consistent as they would have been in a prospective study.

CONCLUSION

The use of oral BPs increased in osteoporosis patients, regardless of the safety notifications concerning ONJ related to BPs. ONJ was increasingly diagnosed after the dissemination of safety information about BP-related ONJ using repetitive and mixed communication methods; the impact of these communications materials was not clear. Our evaluation of the risk communication materials suggests that appropriate cooperation models involving the parties concerned with pharmacovigilance should be planned for the dissemination of safety information and for the delivery and evaluation of new safety concerns with marketed drugs.

CONFLICT OF INTEREST

Eriko Sumi collected information on when, how and what type of risk communications regarding osteonecrosis of the jaw were released from pharmaceutical companies.

KEY POINT

- The use of oral bisphosphonates (BPs) in osteoporosis patients has increased regardless of safety concerns about osteonecrosis related to BPs. Osteonecrosis of the jaw was increasingly diagnosed after risk communication; however, the impact of the risk communication was not clear. Safety notifications were disseminated diligently after the package insert was revised. However, there was no surveillance for osteonecrosis of the jaw before the revision.

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REFERENCES

1. Campisi G, Fedele S, Colella G, *et al.* Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. *J Rheumatol* 2009; **36**: 451–453; author reply 453. DOI: 10.3899/jrheum.080843
2. Ruggiero SL, Dodson TB, Assael LA, *et al.* American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws--2009 update. *J Oral Maxillofac Surg* 2009; **67**: 2–12. doi:10.1016/j.joms.2009.01.009.
3. Khosla S, Burr D, Cauley J, *et al.* Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007; **22**: 1479–1491. doi:10.1359/jbmr.0707onj.
4. Migliorati CA. Bisphosphanates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003; **21**: 4253–4254. doi:10.1200/JCO.2003.99.132.
5. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; **61**: 1115–1117.
6. U.S. Food and Drug Administration, Memorandum. 2003. http://www.fda.gov/OHRMS/DOCKETS/ac/05/briefing/2005-4095B2_03_03-FDA-TAB2.pdf (accessed 2013/3/5)
7. Edwards BJ, Gounder M, McKoy JM, *et al.* Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. *Lancet Oncol* 2008; **9**: 1166–1172. doi:10.1016/S1470-2045(08)70305-X.
8. Bamias A, Kastritis E, Bamia C, *et al.* Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005; **23**: 8580–8587. doi:10.1200/JCO.2005.02.8670.
9. Dimopoulos MA, Kastritis E, Anagnostopoulos A, *et al.* Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 2006; **91**: 968–971.
10. Badros A, Weikel D, Salama A, *et al.* Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 2006; **24**: 945–952. doi:10.1200/JCO.2005.04.2465.
11. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007; **65**: 369–376. doi:10.1016/j.joms.2006.11.003.
12. Ruggiero S, Gralow J, Marx RE, *et al.* Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract* 2006; **2**: 7–14.
13. Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations. *J Am Dent Assoc* 2006; **137**: 1144–1150.
14. Lo JC, O'Ryan F, Yang J, *et al.* Oral health considerations in older women receiving oral bisphosphonate therapy. *J Am Geriatr Soc* 2011; **59**: 916–922. doi:10.1111/j.1532-5415.2011.03371.x.
15. Hong JW, Nam W, Cha IH, *et al.* Oral bisphosphonate-related osteonecrosis of the jaw: the first report in Asia. *Osteoporos Int* 2010; **21**: 847–853. doi:10.1007/s00198-009-1024-9.
16. Dusetzina SB, Higashi AS, Dorsey ER, *et al.* Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care* 2012; **50**: 466–478. doi:10.1097/MLR.0b013e318245a160.
17. Piening S, Reber KC, Wieringa JE, *et al.* Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands. *Clin Pharmacol Ther* 2012; **91**: 838–845. doi:10.1038/clpt.2011.308.
18. Yamazaki T, Yamori M, Yamamoto K, *et al.* Risk of osteomyelitis of the jaw induced by oral bisphosphonates in patients taking medications for osteoporosis: a hospital-based cohort study in Japan. *Bone* 2012; **51**: 882–887. doi:10.1016/j.bone.2012.08.115.
19. Yamamoto K, Sumi E, Yamazaki T, *et al.* A pragmatic method for electronic medical record-based observational studies: developing an electronic medical records retrieval system for clinical research. *BMJ Open* 2012; **2**. doi:10.1136/bmjopen-2012-001622.
20. Junquera L, Gallego L. Nonexposed bisphosphonate-related osteonecrosis of the jaws: another clinical variant? *J Oral Maxillofac Surg* 2008; **66**: 1516–1517. doi:10.1016/j.joms.2008.02.012.
21. Mawardi H, Treister N, Richardson P, *et al.* Sinus tracts--an early sign of bisphosphonate-associated osteonecrosis of the jaws? *J Oral Maxillofac Surg* 2009; **67**: 593–601. doi:10.1016/j.joms.2008.09.031.
22. Hutchinson M, O'Ryan F, Chavez V, *et al.* Radiographic findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure. *J Oral Maxillofac Surg* 2010; **68**: 2232–2240. doi:10.1016/j.joms.2010.05.003.
23. Bertoldo F, Santini D, Lo Cascio V. Bisphosphonates and osteomyelitis of the jaw: a pathogenic puzzle. *Nat Clin Pract Oncol* 2007; **4**: 711–721. doi:10.1038/ncponc1000.
24. Pharmaceuticals and Medical Devices Agency Safety Information. September 2010. http://www1.mhlw.go.jp/kinkyu/iyaku_j/iyaku_j/anzenseijyouhou/272.pdf (accessed 1 February)
25. Lamb T. Did Merck Fail To Warn About Fosamax Side Effects? 2006. http://www.drug-injury.com/druginjurycom/2006/04/fosamax_drug_co.html (accessed 2013/6/30)
26. MERCK. Statement by Merck Regarding FOSAMAX® (alendronate sodium) and Rare Cases of Osteonecrosis of the Jaw 2010. http://www.mercknewsroom.com/news/statement-merck-regarding-fosamax-alendronate-sodium-and-rare-cases-osteonecrosis-jaw (accessed 2013/6/30)
27. Papaioannou A, Morin S, Cheung AM, *et al.* 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010; **182**: 1864–1873. doi:10.1503/cmaj.100771.
28. Bahri P. Public pharmacovigilance communication: a process calling for evidence-based, objective-driven strategies. *Drug Saf* 2010; **33**: 1065–1079. doi:10.2165/11539040-000000000-00000.
29. Marx RE, Cillo JE, Jr, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007; **65**: 2397–2410. doi:10.1016/j.joms.2007.08.003.
30. Piening S, Haaijer-Ruskamp FM, de Vries JT, *et al.* Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf* 2012; **35**: 373–385. doi:10.2165/11599100-000000000-00000.
31. Dimopoulos MA, Kastritis E, Bamia C, *et al.* Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann Oncol* 2009; **20**: 117–120. doi:10.1093/annonc/mdn554.
32. Bonacina R, Mariani U, Villa F, *et al.* Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients. *J Can Dent Assoc* 2011; **77**: b147.
33. Tanaka Noriaki KH, Takaoka K, Hashitani S, Sakurai K, Urade M. Two cases of bisphosphonate-associated osteonecrosis of the mandible. *Jpn J Oral Maxillofac Surg* 2007; **53**: 392–396.
34. Shimahara Masashi AY, Imai Y, Mizuki H, Shimada J, Furusawa K, Morita S, Ueyama Y. A survey of bisphosphonate-related osteomyelitis/osteonecrosis of the jaws. *Jpn J Oral Maxillofac Surg* 2007; **53**: 594–602.
35. PMDA. Bisphosphonate-Related Osteonecrosis of the Jaws. 2009. http://www.mhlw.go.jp/topics/2006/11/dl/tp1122-1l01.pdf (accessed 2013/6/3)
36. Urade Masahiro TN, Shimada J, Shibata T, Furusawa K, Kirita T, Yamamoto T, Ikebe T, Kitagawa Y, Kurashina K, Seto K, Fukuda J. A follow-up survey of 30 cases of bisphosphonate-related ostemyelitis/osteonecrosis of the jaws: present status after 2 years. *Jpn J Oral Maxillofac Surg* 2009; **55**: 553–561.
37. Yoneda T, Hagino H, Sugimoto T, *et al.* Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. *J Bone Miner Metab* 2010; **28**: 365–383. doi:10.1007/s00774-010-0162-7.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix 1. List of drugs studied in cases of OMJ reported to the regulatory authority

Appendix 2. List of International Classification of Diseases (ICD-10) code for osteoporosis studied in the cohort study

Appendix 3. List of drugs studied in the cohort study

Appendix 4. List of International Classification of Diseases (ICD-10) code for inflammatory conditions of the jaw studied in the cohort study