

ORIGINAL ARTICLE

## Bisphosphonate-related osteonecrosis of the jaw in four Nordic countries and an indication of under-reporting

TORMOD B. KRÜGER<sup>1</sup>, MOHAMMAD N. SHARIKABAD<sup>2</sup> & BENTE BROKSTAD HERLOFSON<sup>1,3</sup>

<sup>1</sup>Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Norway, <sup>2</sup>Vitus Apotek Bekkestua, Former Senior Adviser, Norwegian Medicines Agency, Oslo, Norway, and <sup>3</sup>Department of Maxillofacial Surgery and Hospital Odontology, Radium Hospital, Oslo University Hospital, Norway

### Abstract

**Objective.** To assess reported cases of bisphosphonate-related osteonecrosis of the jaw (BONJ) to Medicines Agencies (MAs) in four Nordic countries and to compare the Norwegian MA data with BONJ cases retrieved through an e-mail survey to Oral and Maxillofacial Surgeons (OMS) in Norway. **Material and methods.** BONJ cases reported to the national MAs in each country from January 1st 2003 to September 30th 2010 were collected. An e-mail survey was sent to all active members of the Norwegian Association of Oral and Maxillofacial Surgeons ( $n = 54$ ) included questions on total BONJ cases seen in practice and route of drug administration during January 1st 2003 to December 31st 2009. **Results.** In total, 253 BONJ cases were reported to the MAs; 39 in Denmark, 44 in Finland, 51 in Norway and 119 in Sweden. These figures result in cumulative incidences (multiplied by 100,000) of 0.7, 0.8, 1.1 and 1.3, respectively. Intravenous administration was reported in 169 of the cases. The e-mail survey resulted in 35 responses reporting 214 BONJ cases, 4-times more cases than reported to the MA. **Conclusions.** Cumulative incidence of cases reported in this study differs to some degree in the four Nordic countries (Denmark < Finland < Norway < Sweden). In Norway, almost the same number of BONJ cases were reported through the questionnaire by OMS as in all four countries together (214 by OMSs vs 254 to MAs) and included a high number after per oral administration. The present results indicate a notable under-reporting in Norway and most likely in other Nordic countries.

**Key Words:** *adverse drug reaction, antiresorptive drugs, pharmacovigilance, osteonecrosis of the jaw, oral health*

### Introduction

Bisphosphonates are potent drugs that are widely in use to reduce risk of fractures in postmenopausal osteoporosis [1]. They are also utilized with a curative or palliative intent in Paget's disease, bone metastasis, multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta and similar conditions that might cause bone fragility.

Bisphosphonate-related osteonecrosis of the jaw (BONJ) is a serious and therapy resistant condition which reduces quality-of-life and complicates other treatment [2]. BONJ is defined as exposed bone that has persisted for more than 8 weeks in the maxillofacial region in an individual who has been or is under treatment with a bisphosphonate and who has not been exposed to radiation to the jaws [3]. BONJ was

first detected in 2003. Drug potency, intravenous administration and cumulative dosage are considered to be important risk factors [4–6]. Other drugs causing osteonecrosis of the jaw are bevacizumab, sunitinib and the new anti-bone resorptive drug denosumab. Predisposing factors include dental and periodontal disease, dental extractions, jaw bone surgery, glucocorticoid treatment, malignant disease, radiation and genetic factors [7].

The risk of BONJ development among patients taking bisphosphonates is unknown. Cross-sectional studies have estimated a prevalence of 0.8–12% by intravenous and less than 0.10% by per oral use [8,9].

According to the World Health Organization [10], pharmacovigilance is defined as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any

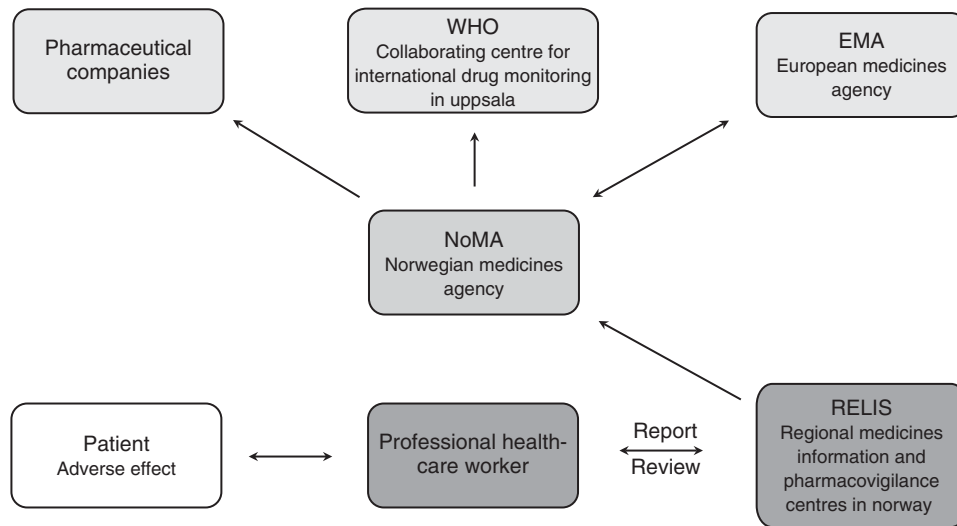


Figure 1. Report strategy of adverse drug reactions (ADR) for professional healthcare workers in Norway, which also represents the basic principles for ADR reporting in the other Nordic countries included in the study.

other possible drug-related problems'. Reporting of new and serious ADRs is mandatory by law for healthcare professionals in EU [11]. Medication-related osteonecrosis of the jaw has been on the watch-list of the Medicines Agencies (MAs) in the Nordic countries.

The main objective of the present study was to assess the number of BONJ cases reported to the medicine authorities in Norway, Sweden, Denmark and Finland during the period of 2003–2010. The second aim was to investigate if this reporting reflected the number of BONJ cases seen in clinical practice. All active members of the Norwegian Association of Oral and Maxillofacial Surgeons were asked to fill out a questionnaire about the number of BONJ cases they observed (2003–2009) and the route of administration in these patients, i.e. intravenous or per oral.

## Material and methods

The present study design was descriptive, retrospective and partly questionnaire-based and assessed BONJ cases reported to MAs in Norway (NOMA and RELIS), Sweden (MPA and Swedis), Finland (FIMEA) and Denmark (DHMA). In addition, all Norwegian oral and maxillofacial surgeons (OMS) were contacted through an e-mail survey. Data on BONJ cases reported by healthcare professionals from January 1st 2003 to September 2010 were obtained from the national drug monitoring agencies in the four Nordic countries. Data requested were total number of BONJ cases during the study time period, number of new cases each year, suspected drug and route of drug administration. The MAs in each country approved publication of the data provided.

Active members of the Norwegian Association of Oral and Maxillofacial Surgeons ( $n = 54$ ) were

invited to participate by responding to a questionnaire sent by e-mail. Data requested were number of BONJ cases observed in their clinical practice from January 1st 2003 to December 31st 2009, together with route of bisphosphonate administration; intravenous or per oral.

The cumulative incidence of BONJ was calculated by dividing the total number of MA or (for Norway only) OMS-retrieved cases by the population for each country. The population sizes used were; Denmark 5.5 million, Finland 5.4 million, Norway, 4.8 million and Sweden 9.3 million citizens (year 2010, according to Nordic Council of Ministers). Numbers were then multiplied by 100,000. Continuity corrected score interval model [12] was used and results were presented as cumulative incidence with their respective 95% confidence interval.

## Results

### Systems of reporting

The four included countries have similar ADR reporting systems; healthcare professionals file pre-made forms to a national MA. In each country, except for Finland, the reports are forwarded to regional offices which are the primary reporting contact for professional healthcare workers (Figure 1). Following evaluation and registration, the data is forwarded from these offices to the respective national centers (NOMA, MPA, DHMA) which organize data and report to the WHO's Collaborating Centre for International Drug Monitoring in Uppsala (UMC), Sweden and to the European Medicines Agency (EMA) in London, UK. Finland does not have regional offices and ADRs are reported directly to the national agency, FIMEA. The co-ordination of global international pharmacovigilance is done at the

Table I. Reported BONJ cases (*n*) in the Nordic countries from January 1<sup>st</sup> 2003 to September 30<sup>th</sup> 2010, based on data from the National Medicines Agencies. Some patients were registered as having received both intravenous and per oral bisphosphonate medication, which explains the discrepancy in the figures.

Country	Route of administration			Total ( <i>n</i> )	Cumulative incidence multiplied by 100,000 (95% CI)
	Peroral	Intravenous	Unknown		
Denmark	8	18	15	39	0.7 (0.5–1.0)
Finland	3	41	0	44	0.8 (0.6–1.1)
Norway	17	22	14	51	1.1 (0.8–1.4)
Sweden	57	88	0	119	1.3 (1.1–1.5)
Total	85	169	29	253	

UMC, including reports from more than 133 member countries [13].

In addition to the report systems above, there are reporting systems in Denmark, Norway and Sweden where patients can report ADRs without going through their physician, dentist or pharmacist. This study does not include patient reported data.

### **BONJ cases reported to MAs in four Nordic countries**

A total of 253 cases of BONJ were reported and recognized by the MAs in the four countries during the 7.75 years study period; 39 in Denmark, 44 in Finland, 51 in Norway and 119 in Sweden (Table I). The figures resulted in a cumulative incidence of 0.7, 0.8, 1.1 and 1.3 per100,000, respectively. The values of Sweden and Denmark were statistically different (0.7, CI = 0.5–1 vs 1.3, CI = 1.1–1.5,  $p < 0.05$ ).

The MAs in Denmark, Sweden and Norway also provided data on the suspected drugs related to the BONJ cases. Denmark reported zoledronic acid as the suspected drug in 82% of the BONJ cases. In the remaining 18%, the suspected drug was alendronate, ibandronate, pandronate and/or combinations of these drugs. In Sweden zoledronic acid was

suspected in 46% of the cases, alendronate in 35% and combinations and/or different types of bisphosphonate medications (bondronate, optinate, pamidronate) in 19%. The suspected drugs in Norway were zoledronic acid in 55% of the cases, alendronate in 31% and combinations and/or different other medications (pamidronate, ibandronate) in 14%. Although intravenous route of administration was most frequently reported in each country, per oral administration with alendronate was the suspected drug in more than one third of the BONJ cases in Sweden and Norway. In 30 of the total 253 cases, both intravenous and per oral bisphosphonate medication had been reported which explains the discrepancy between the figures in Table I. The yearly variations of BONJ cases for each of the four Nordic countries are shown in Figure 2.

### **BONJ cases reported by Norwegian OMS through an e-mail survey**

The e-mail questionnaire which was sent to 54 active Norwegian OMS resulted in 35 (65%) responses. The surgeons reported a total of 214 BONJ cases during the 7-year period; 103 after intravenous and 111 after per oral administration (Table II). This resulted in a 4-times higher cumulative incidence of BONJ compared to the incidence calculated on data retrieved from the Norwegian MA. Intravenously administered bisphosphonates were registered in 48% of the OMS cases compared to 43% though the national MA.

### **Discussion**

Since the first reports of BONJ in 2003, there has, to the authors' knowledge, not been any published data concerning under-reporting of this ADR. The few publications with a focus on ADR under-reporting state this as an important public health problem which needs to be addressed on a much larger scale [14,15].

The present study reviews the total number of ADR reported BONJ cases in 2003–2010 within four countries with similar national MAs. Except for Finland they all have regional offices as primary reporting

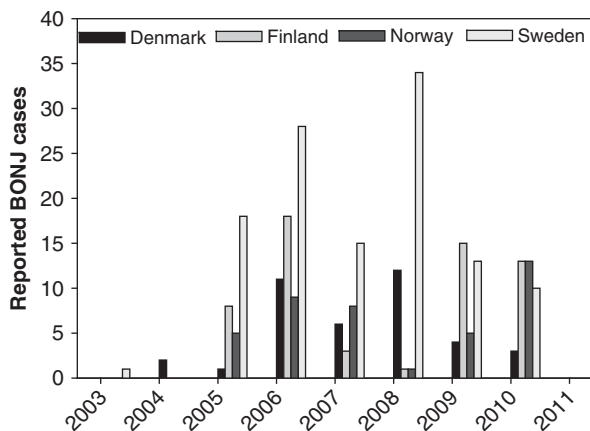


Figure 2. Reported cases of BONJ per year in four Nordic countries from January 1<sup>st</sup> 2003 to September 30<sup>th</sup> 2010, based on data from the National Medicines Agencies.

Table II. BONJ cases (*n*) reported to the Norwegian Medicines Agency (NOMA) during January 1<sup>st</sup> 2003 to September 30<sup>th</sup> 2010 in comparison to cases retrospectively gathered by active members of the Norwegian Association of Oral and Maxillofacial Surgeons (NOMS) during January 1<sup>st</sup> 2003 to December 31<sup>st</sup> 2009 reported through an e-mail survey.

	Intravenous	Peroral	Unknown	Total ( <i>n</i> )	Cumulative incidence multiplied by 100,000 (95% CI)
Cases reported to NOMA	22	17	14	51	1.1 (0.8–1.4)
Cases gathered from NOMS	103	111	0	214	4.5 (3.9–5.1)

contacts which forward their data to a national MA. The study shows that the cumulative incidence of reported BONJ cases to the MAs is quite similar in the included countries, except for a significant difference between Denmark and Sweden. This may be a coincidence due to the low numbers of reported BONJ cases. It is important to emphasize that the cumulative incidences reported in this study do not reflect the true incidence of BONJ in the included countries, which makes direct comparisons problematic.

The cumulative incidence of BONJ reported by the Norwegian OMS, in almost the same time period, was 4-times that of the NOMA cases. This strongly suggests a significant under-reporting. This interpretation may be biased by the fact that the data was retrospectively gathered by the OMS in the e-mail survey compared to the cases most probably reported consecutively to the MA. To overcome this uncertainty of under-reporting and to ensure more reliable statistics, a prospective approach is needed concomitant to interest and dedication from healthcare professionals in the four countries to report all their BONJ cases.

Sharikabad [16] reported that, as of November 16<sup>th</sup> 2010, 1954 cases of BONJ were found in the WHO's ADR database (MedDRA terminology search was osteonecrosis of jaw and bisphosphonates and bisphosphonate combinations). Of these cases, 1145 were related to zoledronic acid, 281 to alendronate, 280 to pamidronate, 123 to ibandronate and the rest to risedronate and 58 other bisphosphonates. Using the MedDRA terminology, 'bisphosphonates and osteonecrosis and bisphosphonate combinations' resulted in a much higher (8824) number of cases for the same period of time. Some of these cases, reported as osteonecrosis, might actually be BONJs. (WHO declares that this information is not saying anything about the origin, the causality or responsible pharmaceutical product for the side-effect and that this information does not represent the opinion of WHO.)

There is no specific ICD-10 diagnostic code designated to BON. The codes that are used most frequently are K10.2 inflammatory conditions of the jaw and the more unknown code M87.1; drug induced osteonecrosis. Unless specific codes are established, these two may be utilized in future prospective studies.

Although most cases of BONJ are seen by OMS, some patients may instead be treated within other

clinical specialities and be missing in our survey. Feedback from the OMS participating in this study indicates that lack of time and lack of knowledge about how and why to report were primary reasons for under-reporting. This is consistent with findings in the literature which suggest that, in general, only ~ 10% of all ADR are reported by healthcare workers [17].

Today, the senior citizens constitute a bigger part of the world's population than ever before [18], which in turn increases the risk of polypharmacy and drug interactions in general. As an increasing number of patients get treated for cancer and osteoporosis, a large number of patients are in need of medication regulating bone metabolism [19]. The importance of reliable reporting of ADRs is obvious and the consequences more severe if it stays under par. BONJ reporting is in all four countries mandatory by law, but this does not seem to have any impact on the frequency of reporting. If there are no active measures to control that the reporting is being done, the law itself does not serve its function.

To make clinicians increase their level of reporting and, thus, to obtain reliable data, a stronger presence of the MAs is needed. In addition, monitoring and informing healthcare workers about the importance of pharmacovigilance should be in focus. This will increase the awareness and the level of responsibility among healthcare professionals attitudes to pharmacovigilance, which in the end will be of benefit to our patients.

## Conclusions

Cumulative incidence of BONJs reported in this study differs to some degree in Nordic countries (Denmark < Finland < Norway < Sweden). In Norway alone almost the same number of BONJ cases were reported by OMSs as in all four countries (214 by OMSs vs 254 to MAs). The present results indicate a notable under-reporting in Norway and most likely in other Nordic countries. To better understand the scope of this ADR, there is a need to increase the level of reporting among healthcare professionals of BONJ and other drug-induced osteonecrosis cases related to new drugs on the market.

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