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British Journal of Oral and Maxillofacial Surgery 53 (2015) 13–17

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed

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Accepted 2 September 2014
Available online 2 October 2014

Abstract

Recent data suggest that the traditional definition of bisphosphonate-associated osteonecrosis of the jaw (ONJ) may exclude patients who present with the non-exposed variant of the condition. To test the hypothesis that a proportion of patients with ONJ remain undiagnosed because their symptoms do not conform to the traditional case definition, we did a secondary analysis of data from MISSION (Multicentre study on phenotype, definition and classification of osteonecrosis of the jaws associated with bisphosphonates), a cross-sectional study of a large population of patients with bisphosphonate-associated ONJ who were recruited in 13 European centres. Patients with exposed and non-exposed ONJ were included. The main aim was to quantify the proportion of those who, according to the traditional case definition, would not be diagnosed with ONJ because they had no exposed necrotic bone. Data analysis included descriptive statistics, median regression, and Fisher's exact test. A total of 886 consecutive patients were recruited and 799 were studied after data cleaning (removal or correction of inaccurate data). Of these, 607 (76%) were diagnosed according to the traditional definition. Diagnosis in the remaining 192 (24%) could not

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http://dx.doi.org/10.1016/j.bjoms.2014.09.001

be adjudicated, as they had several abnormal features relating to the jaws but no visible necrotic bone. The groups were similar for most of the phenotypic variables tested. To our knowledge this is the first study in a large population that shows that use of the traditional definition may result in one quarter of patients remaining undiagnosed. Those not considered to have ONJ had the non-exposed variant. These findings show the importance of adding this description to the traditional case definition.

Keywords: Osteonecrosis; Jawbones; Bisphosphonates

Introduction

Osteonecrosis of the jaws (ONJ) is a potentially severe and debilitating adverse reaction to bisphosphonates and other antiresorptive agents such as denosumab. It typically manifests as painful and often infected areas of necrotic bone, and can lead to severe chronic pain and facial disfigurement, which can adversely affect the ability to eat and speak, and lowers the quality of life.[1–3] Its aetiopathogenesis remains enigmatic, and hypotheses have focused on reduced bony turnover, infection, toxicity of the soft-tissue, and antiangiogenesis.[1] The epidemiology also remains unclear, and reported incidence varies widely. Overall, it is estimated that necrosis can develop in the jaw in about 8–10% of patients with malignancy who are given high-potency bisphosphonates (such as zoledronic acid) intravenously, and in 0.01–0.1% of those with osteoporosis who take low-potency bisphosphonates (such as alendronate) orally. However, reported rates vary between 0.004% and 51%.[2,3] Data relevant to denosumab given subcutaneously in patients with metastatic cancer and osteoporosis seem to replicate those when high-potency bisphosphonates are given intravenously, and low-potency bisphosphonates are taken orally.[4] The individual risk of developing ONJ is also affected by factors such as the cumulative dosage or duration of antiresorptive treatment, concomitant exposure to antiangiogenic agents, procedures that affect the jaws such as tooth extractions, and dental infections.[5,6] Management strategies are largely based on expert opinion rather than experimental data.[7] Depending on the extent of disease and severity of symptoms, infections and pain can be treated conservatively, or by minimally invasive surgical debridement or aggressive resection of necrotic bone, or both.[7] Outcomes, which typically vary and are unpredictable, are often poor when disease is extensive.[8]

Several authors have suggested that the burden of ONJ associated with antiresorptive agents, is largely underestimated, as the disease is often underdiagnosed and under-reported.[9] This however remains controversial, and to obtain robust incidence data, some authors of recent trials have adopted a rigorous process of adjudication to identify all those who could have the disease.[4,10] Recent data suggest that an incomplete case definition, introduced a decade ago and based only on clinical evidence of exposed necrotic bone, could have contributed to epidemiological estimates being inconsistent because it excluded cases with no obviously exposed bone.[9,11–18]

We did a multicentre study of the clinical phenotype of ONJ in a large group of patients to test the hypothesis that use of the traditional case definition by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[7] and the American Society for Bone and Mineral Research (ASBMR),[19] which has largely been adopted in previous studies, results in a proportion of patients remaining undiagnosed. Our main aim was to estimate the number of patients who would not be diagnosed with ONJ because of their phenotype, and more specifically, because of the absence of exposed necrotic bone.

Methods

Study design

We did a secondary analysis of a multicentre cross-sectional study known as MISSION (Multicentre study on phenotype, defInition, and claSSification of osteonecrosIs of the jaws associated with bisphosphONates),[20] which was reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations.[21]

Setting

Researchers at the Universities of Verona and Palermo (Italy), and University College, London (UK) designed the study and sent a collaboration proposal to Italian centres of oral medicine and oral or maxillofacial surgery with a special interest in the diagnosis and management of ONJ. Of the 13 sites that contributed to MISSION, 10 agreed to participate. Full details of MISSION have been reported elsewhere.[20] The ethics committees of the coordinating and participating centres approved the study and the patients' consent to participate was obtained where specifically required.

Inclusion criteria

Patients referred to the participating centres between January 2004 and December 2011 were eligible for MISSION if they had previously had, or were currently having treatment

with bisphosphonates and they had no history of radiotherapy to the jaws. Those with exposed ONJ (long-standing (8 weeks or more) transmucosal exposure of necrotic bone in the jaw),[7,19] or non-exposed ONJ (presence of otherwise unexplained pain in the jaws, fistula, swelling, mobile teeth, or mandibular fracture) were eligible.[11–13] Non-exposed ONJ was diagnosed after the exclusion of common diseases of the jaw such as odontogenic infections and bony disorders known to cause similar manifestations.[11–13] Other inclusion criteria of MISSION, which were not relevant to our objectives (such as the availability of computed tomography (CT) and no previous history of operations on the jaws), have been reported elsewhere.[20] Cases were assessed at each participating centre by multidisciplinary teams including specialists who prescribe bisphosphonates (oncologists, haematologists, and rheumatologists) and specialists in oral medicine or maxillofacial surgery, or both.

Data collection

We collected data between March and December 2012, and retrospectively reviewed hospital notes of consecutive patients diagnosed with ONJ between January 2004 and December 2011. Clinical data relating to ONJ were extracted by local researchers at one time point and entered into a purposely developed electronic case report form. A detailed description of all data collected by MISSION has previously been published.[20] For our secondary analysis, we collected data on age, sex, indication for use of bisphosphonate, and type and cumulative dose, concurrent use of steroids, site of ONJ, presence of pain, history of tooth extraction, and dental or periodontal infection. The medical statistician responsible for data analysis managed the database and data were cleaned according to standard procedures. Stata 13.1 (Stata Corp, College Station, USA) programs were written to ensure reproducibility of database management.

Study aim

The primary aim of MISSION was to investigate the agreement between the AAOMS staging system and CT imaging to assess the extent of ONJ disease.[20] The aim of our secondary analysis was to quantify the proportion of patients who would not be considered to have ONJ according to the case definition of the AAOMS and ASBMR. We also compared selected clinical characteristics of patients with exposed and unexposed ONJ.

Statistical analysis

Descriptive statistics are given as median (IQR) for continuous variables and as numbers or percentages for categorical variables. Categorical variables between groups were compared using Fisher's exact test, and continuous variables using median regression. The latter has been reported to detect the equality of medians better than non-parametric tests, as non-parametric tests can make implausible assumptions about the location and shape of the distributions to be compared.[22] Probabilities of less than 0.05 were considered significant. Statistical analysis was done using Stata 13.1 and programs were written to ensure the reproducibility of statistical analysis.

Results

Details of the study population

Overall, 886 consecutive patients were recruited at the 13 study centres. Those with missing or conflicting data were excluded from analysis ($n = 87$, 10%) so 799 patients were included.[20] All had been treated with bisphosphonates. A total of 607 had exposed, and 192 had non-exposed ONJ. The patients with exposed ONJ had a median age of 68 years and were mostly women (66%); 32% of them had breast cancer and 80% had had treatment with zoledronate. Those with non-exposed ONJ had a median age of 69 years and were also mostly women (73%); 33% of them had breast cancer and 71% had had treatment with zoledronate. Other clinical features of the 2 groups are shown in Tables 1 and 2.

Association between exposed bone, and the AAOMS and ASBMR case definition

The symptoms of the 607 (76%) patients who had exposed ONJ fitted the AAOMS and ASBMR criteria. In all, bone was exposed through the oral mucosa or facial skin. The remaining 192 (24%) could not be diagnosed using the

Table 1
Comparison of continuous measurements between patients with exposed and non-exposed osteonecrosis of the jaw (ONJ).

	Exposed ONJ			Non-exposed ONJ			*p* value
	No. of patients	Median	(IQR)	No. of patients	Median	(IQR)	
Age (years)	607	68	(61–75)	192	69	(63–76)	0.33
Zoledronate (mg)	484	76	(48–120)	137	72	(48–132)	0.52
Pamidronate (mg)	70	2160	(990–4320)	29	2610	(2160–4320)	0.39
Alendronate (mg)	81	13,440	(5880–21,280)	44	14,560	(6720–26,860)	0.75
Neridronate (mg)	2	724	(648–800)	0	–	–	–
Risedronate (mg)	8	3630	(3080–11,310)	4	7335	(5565–11,115)	0.31
Ibandronate (mg)	21	3600	(450–18,000)	9	2850	(1350–3950)	0.77

Table 2
Comparison of categorical measurements between patients with exposed and non-exposed osteonecrosis of the jaw (ONJ).

	Exposed ONJ ($n = 607$)		Non-exposed ONJ ($n = 192$)		p value
	No.	(%)	No.	(%)	
Male	206	(34)	51	(27)	0.06
Zoledronate	484	(80)	137	(71)	0.02
Pamidronate	70	(12)	29	(15)	0.21
Alendronate	81	(13)	44	(23)	0.002
Neridronate	2	(<1)	0	–	–
Risedronate	10	(2)	5	(3)	0.37
Ibandronate	21	(4)	9	(5)	0.51
Other bisphosphonates	250	(41)	93	(48)	0.08
Steroids	175	(29)	49	(26)	0.41
Mandible	383	(63)	135	(70)	0.07
Maxilla	224	(37)	57	(30)	0.07
Pain	489	(81)	134	(70)	0.003
Cancer (all)	345	(57)	99	(52)	0.21
Breast cancer	192	(32)	64	(33)	0.66
Myeloma	166	(27)	44	(23)	0.26
Osteoporosis	91	(15)	48	(25)	0.002
Tooth extraction	348	(57)	86	(45)	0.003
Dental infection	82	(14)	43	(22)	0.004

criteria, as they had no evidence of long-term exposure of bone. The main clinical features of both groups are shown in Tables 1 and 2. Characteristics between groups were mostly similar, but differences were significant for an underlying diagnosis of osteoporosis, treatment with alendronate or zoledronate, history of tooth extraction, dental infection, and presence of pain (Table 2).

Discussion

Our findings clearly show that use of the traditional AAOMS[7] and ASBMR[19] case definition results in nearly a quarter of patients with ONJ remaining undiagnosed. Those who were not adjudicated to have ONJ were diagnosed with the non-exposed variant, the clinical manifestations of which have been consistently and well described by different groups of investigators during the last few years.[11–13,23] Of note, although some patients' symptoms seemed to fit the AAOMS case description of stage 0 disease classification, they could not be diagnosed unless bone was exposed.

Development of an accurate case definition relies on meticulous phenotyping, and it is essential to understand the epidemiology of the disease and to design clinical trials. The most widely adopted case definition of bisphosphonate-associated ONJ (AAOMS[7] and ASBMR[19]) is based on criteria introduced 10 years ago and states that 3 features must be present: exposed bone in the maxillofacial region that persists for more than 8 weeks, previous or current treatment with bisphosphonates, and no history of radiation to the jaws. Cases included in clinical studies have therefore relied largely on clinical evidence of long-standing necrotic areas of bone exposed through the mucosa or facial skin. Since 2008, several independent studies have reported that ONJ does not always present with these features. The non-exposed variant, which is characterised by a number of other clinical features that develop in the absence of bony exposure, includes otherwise unexplained pain in the jaws, fistula, loose teeth, swelling, and in advanced cases, pathological fracture of the mandible.[11–18] The AAOMS eventually acknowledged the existence of these features and included the non-exposed variant in its classification as stage 0,[7] but they did not change their case definition and it continues to focus on clinical evidence of long-standing bony exposure, a paradox highlighted by other authors who called for it to be changed urgently.[16–18] As the definition, and not the revised staging system, tends to be used to decide whether cases are included in clinical trials and epidemiological studies, revising the staging system without changing the case definition will not have an impact on diagnosis.

We compared the main clinical features of diagnosed and non-diagnosed patients to test whether important characteristics differed. Many characteristics were similar but some clinical variables, which included underlying treatment with zoledronate, history of tooth extraction before the development of osteonecrosis, and pain, were more commonly seen in patients with exposed ONJ. We speculate that this association may reflect the typical features of patients referred to our centres during the years when ONJ was first recognised – for example, those who had been given bisphosphonates intravenously and had painful exposed bone after dental extraction. We also found that use of alendronate, presence of osteoporosis, and dental infection were more commonly seen in patients with the non-exposed variant. This again may reflect the fact that evidence of the development of ONJ in patients who take bisphosphonates orally for osteoporosis

has become more robust only in recent years, and dental recommendations regarding invasive operations and reports on the characteristics of the non-exposed variant have been published. Interestingly, our results confirm a recent observation from a smaller single-centre study of 102 patients with ONJ (non-exposed in 14), which suggested that both types belong to the same disease entity.[23]

Our paper has a number of strengths, which include the size of the study population, the multicentre design, and the accurate definition of outcomes. Recruitment of consecutive patients at the study centres, and accurate data collection and analysis to minimise the risk of selection bias are also strengths. Limitations include retrospective data collection and the limited geographical variability as all centres but one were located in Italy.

Conclusions

Our findings highlight the importance of including the non-exposed variant in the traditional case definition of ONJ, particularly in the context of adjudication of cases for clinical trials and epidemiological studies. They also suggest that some previous reports may have underestimated the true incidence of bony necrosis of the jaw.

Conflict of interest

We have no conflicts of interest.

Ethics statement

The Ethics Committee of the coordinating centre and of each participating centre approved the study and patients gave their written consent to participate, where required.

Acknowledgments

Part of this work was undertaken at University College London/University College London Hospital, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centre funding scheme.

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