Treating Osteoporosis: Do Bisphosphonates Really Increase the Risk of Osteonecrosis of the Jaw?

Osteoporosis is a major public health problem. Osteoporotic fractures result in significant morbidity, increased mortality and have a significant economic impact on healthcare systems. This is particularly true for hip fractures. Data from a study of hip fractures among Irish postmenopausal women showed a 23.6% mortality at 2 years compared to 10.1% among controls[1]. Hip fracture can lead to a reduction in independent mobility and living. The cost per hip fracture admission in Ireland has been estimated at 14,339[2], which is in line with estimates from other European countries[3] These figures do not include additional indirect costs such as long-term residential care from loss of independence.

Bisphosphonates have been available in oral form for the prevention and treatment of osteoporosis and Pagetâ s disease for over a decade. They are among the most commonly prescribed medications in the world. In 2006, the total number of US prescriptions for alendronate (Fosamaxfi) was 16,720,000 and for risedronate (Actonel´fi) was 9,265,000 making them the 14th and 41st most commonly prescribed brands in the US market[4]. In Ireland in 2007, according to industry figures, there were over 60,000 people on oral alendronate, risedronate and ibandronate. Currently only oestradiol, strontium ranelate, alendronate, risedronate and zoledronate have been shown to reduce the risk of hip fracture.

Concerns have been raised in the medical literature, and more recently in the public media, relating to the association of bisphosphonates with osteonecrosis of the jaw (BONJ)[5-7]. Osteonecrosis of the jaw (ONJ) itself is not a new phenomenon, having been reported in the mid 19th century associated with match makers using phosphorous[8] and in more recent times associated with chemotherapy[9] and radiotherapy[10]. A rare condition, the background incidence in the general population is unknown.

However until recently there has been no widely accepted definition of ONJ or BONJ, leading to diagnostic ambiguity and concern regarding the accuracy of cases reported in the literature. A working definition for BONJ has recently proposed by the American Society for Bone and Mineral Research (ASBMR) as- â an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.â The differential diagnoses includes several disorders of the jaw and oral cavities which have a similar clinical presentation including alveolar osteitis, osteomyelitis, gingivitis, periodontitis and periapical pathology[11].

Since 2003 several hundred cases of BONJ have been reported in the medical literature, more than 95%[12] of which involve patients treated with bisphosphonates for metastatic bone disease and hypercalcaemia of malignancy. Such patients are treated with much higher doses of bisphosphonates than persons with osteoporosis, which may have greater potency and are administered intravenously. These persons reportedly often have multiple co morbid and confounding risk factors for ONJ i.e. cancer, use of chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, anaemia, coagulopathy, infection.

ONJ lesions have a spectrum of clinical manifestations from asymptomatic areas of exposed bone to painful osseous cavities with purulent drainage; the mandible is more often affected than the maxilla. Histology[13] confirms the presence of infection and necrosis and it can be indistinguishable from osteonecrosis complicated by infection or osteomyelitis with secondary osteonecrosis.

There are more than 60,000[14] patient-years of exposure to oral bisphosphonates in controlled clinical trials for the treatment of osteoporosis. To date no cases of BONJ has been reported. (with follow up as long as 10 years on some of these patients.[15]) There are less than 60 reported cases of ONJ[11] associated with oral bisphosphonate therapy for osteoporosis in the literature. The recently published HORIZON[16] trial probably best illustrates the discrepancy between the case reports and results of controlled clinical studies. This clinical trial, involving nearly 7000 women over 3 years, was designed to primarily evaluate the safety and efficacy of intravenous zoledronic acid as therapy for osteoporosis. It should be noted that most of the cases of BONJ in the medical literature have been attributed to this agent to date[12]. Despite this, a blinded independent judiciary panel of experts found only a single case in both the active treatment and placebo groups, both of whom appear to have had osteomyelitis[17]. This again underscores the lack of knowledge of its incidence of ONJ in the general population, and the lack of evidence to support a causative mechanism between these agents and ONJ. Despite the lack of good scientific information, an estimated risk for ONJ in patients taking a bisphosphonate for osteoporosis is between 1/10,000 to 0.7 per 100,000 patient treatment years[11,18].

As stated above, the majority of publications relating to this condition are anecdotal case reports and small series of cases. Such reports, while not irrelevant, are considered the weakest form of evidence in establishing a â cause and effectâ relationship. The weight of evidence from randomized controlled trials, and large observational studies with appropriate control groups does not support an increased risk of ONJ in persons treated with bisphosphonates for osteoporosis. This implies that there is either no increased risk, or, if there is, it is likely very small.

So what should we tell our patients and what advice should be given to dental and medical professionals concerned about this entity?

1. Although ONJ has been added to the precautions section of the prescribing information of all agents, at this time this is not supported by data from clinical trials and the best available evidence today does not support a cause and effect relationship.

2. There is no evidence to support a routine dental examination before the start of oral bisphosphonate[11], (in contrast to what the American Dental Association guidelines recommend) nor for stopping the agent for anyone undergoing dental work.

3. Reassurance by explaining that if there is a risk, which is not clear at this time, it is likely very small. As with everything we do, risk should be put in perspective: the risk of developing this condition would seem to be much less than oneâ s lifetime risk of dying in a plane (1:5000), less than the risk of a DVT while taking the oral contraceptive pill[19] (3-6 fold increased risk) and far less than the life-time risk of fracture (40% for a 50 year old white woman, 13% for a 50 year old white man), or death following a hip fracture.

As medical professionals our primary concern is our patientsâ wellbeing, and thus we are constantly urged to take care in prescribing. It is incumbent upon societies and regulatory authorities to likewise take care when issuing warnings on prescribing information. In clinical practice, patients have started stopping bisphosphonate therapy or are worried about continuing therapy. There is a burden of uncertainty among patients and health care professionals about an entire class of drugs which are of clear proven benefit for a major public health condition.

However, the evidence that such treatment leads to or causes ONJ is tenuous. Further study is needed to better understand this entity in order to make evidence based decisions on management and prevention of ONJ.

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