THE BIPHOSPHONATES DELUSION

The first publications about **biphosphonates**, which were initially named diphosphonates, were available in 1969, now more than 40 years ago. Biphosphonates are internalized by osteoclasts where they interfere with specific biochemical pathways (Russell, 2011). They enhance osteoclasts apoptosis and they inhibit osteoclasts attachment to the bone matrix (Dominguez et al., 2011). They are therefore used for the treatment of fragility fractures due to post-menopausal and male osteoporosis, plus also in the case of glucocorticoid side effects, Paget's bone disease and bone metastasis (Dominguez et al., 2011). They can be classified between nitrogen-containing (such as alendronate or risedronate) and non-nitrogen-containing (such as etidronate or clodronate).

Bisophosphonates have become the most popular treatment for post-menopausal osteoporosis and their use has risen continuously since their introduction in the 1990s (Hollick and Reid, 2011). Adverse inflammatory side effects are common, especially esophageal irritation and gastro-intestinal reactions, but also cutaneous reactions, ocular side effects, and acute phase reactions in the case of intravenous administration (Hollick and Reid, 2011). More recently, reports of serious side effects have prompted concerns about the long-term use of biphosphonates.

Risedronate and even more notably alendronate use is linked to what are called atypical subtrochanteric fractures and femoral shaft fractures, both linked to bone insufficiency (Angthong and Angthong, 2011). More worrying is the fact that a longer duration of the biphosphonate treatment increases the odds of insufficiency fractures (Meier et al., 2012), which certainly raises concerns about how long the patients should be taking these drugs.

Other side effects confirm that bone solidity does not necessarily reflect bone density. "*Dental practitioners should be aware of the increased risk of implant failure associated with oral biphosphonate use in the population*" (Yip et al., 2012). Practically speaking, it is well known that many dentists specializing in dental implants do not accept patients following these biphosphonate treatments due to the excessive risk of implant failure. Another concern lies in the association between biphosphonate use and jaw osteonecrosis (Arrain and Masud, 2011).

Besides, it appears that patients in need of operative fixation of biphosphonate-associated femur fractures have higher complication rates than their usual femur fractures counterparts (Prasarn et al., 2012). Interestingly, among 43 retrospectively reviewed patients compared with 20 controls, "the biphosphonate cohort had a higher rate of intraoperative fractures (21% versus 0%) and postoperative plate fractures (30% versus 0%) (Prasarn et al., 2012). It is worth mentioning that biphosphonates use cannot be recommended for chronic kidney disease patients suffering from osteopenia/osteoporosis due to the risk of adynamic bone disease (Amerling et al., 2010).

More classic and the object of several published reports are inflammatory ocular side effects such as uveitis and scleritis. Odds ratio approximate 1.5 for both conditions (Etminan et al., 2012). Common symptoms seen in this type of orbital inflammation include pain, diplopia, and blurry vision (Peterson and Bedrossian, 2012).

Other severe side effects of long-term biphosphonate use are subject to some controversy but they have been discussed in useful reviews. Esophageal irritation represents a frequent complication of such treatments, with increasing concerns about a potential link with esophageal cancer, even if strict casualty is indeed difficult to demonstrate (Haber and McNatty, 2012). Once again, the length of biphosphonate administration could be the issue, as with another controversial severe side effect consisting in atrial fibrillation (Sewerynek & Stuss, 2011).

In conclusion, we should mention a recent review of the most relevant articles reporting serious adverse effects of biphosphonates. "*Biphosphonates reduce vertebral fractures in short-term use while in long-term can cause osteonecrosis [of the] jaw, esophageal cancer, atrial fibrillation, and increase the risk of atypical fractures and probably adynamic bone disease*" (Salari and Abdollahi, 2012). We can only share the conclusion of these authors, i.e. that prescribers should "*consider full assessment of risk-benefit and the duration of treatment*".

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