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EMA 2010 Priorities for Drug Safety Research

Long-term adverse skeletal effects of bisphosphonates

The bisphosphonates are a class of drugs which act on bone metabolism to decrease osteoclast activity. There are two subclasses of bisphosphonates: nitrogen-containing bisphosphonates inhibit a key enzyme in the mevalonate pathway leading to disruption of regulatory proteins and loss of osteoclast activity whereas non-nitrogen containing bisphosphonates inhibit ATP-dependent intracellular enzymes leading to osteoclast apoptosis. Decreased osteoclast activity leads to reduced bone turnover, increased bone mass and improved mineralisation. Different bisphosphonates have different therapeutic indications but in general bisphosphonates are authorised for use in oncology, for the treatment of post-menopausal osteoporosis and for the treatment of Paget's disease and osteogenesis imperfecta.

Osteonecrosis of the jaw is a rare event which has been seen in association with the use of all the bisphosphonates currently licensed in Europe. More recently, stress or insufficiency fractures of the femur, which present differently from fractures associated with osteoporosis, have been identified as a possible adverse drug reaction. These fractures occurred after minimal or no trauma, were often bilateral and were preceded by thigh pain weeks or months prior to complete fracture. Primarily associated with the use of alendronic acid, it is unclear whether this is an alendronic acid specific event or whether it is a class effect.

It is difficult to detect skeletal bone effects due to bisphosphonates because of confounding. Osteonecrosis of the jaw was identified because it has a very low background incidence and so a signal of several cases in association with bisphosphonate use caused more detailed examination. Similarly, an unusual fracture of the femur after minimal trauma again raised a suspicion of an adverse drug effect.

Areas of particular interest for research are:

- To generate methodologies to study the relationship between bisphosphonate use and long term adverse skeletal events in human populations.
- To measure the incidence of osteonecrosis of the jaw and incidence of stress/insufficiency fractures in association with high dose and long-term use of bisphosphonates. Specific research outputs will include the estimation of the above incidences by class, by compound, type of administration, dose, duration, indication etc. Possible methods might include meta-analyses, nested case control studies or other observational studies using existing databases and registries where possible.

Addendum October 2009:

In January 2009, Denmark requested the CHMP to review issues related to osteonecrosis of the jaw following the use of bisphosphonates. In its Opinion dated 24th September 2009 ([EMEA/CHMP/292474/2009](http://www.emea.europa.eu/CHMP/292474/2009)), the CHMP summarised the available information and made recommendations including areas where further research is needed. These should be taken into consideration when proposing research projects on this topic.