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Patient Health Protection

European Medicines Agency 2013 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 and are administered in different posologies but in general bisphosphonates are used in oncology, for the treatment of post-menopausal osteoporosis and for the treatment of Paget's disease and osteogenesis imperfecta.

Osteonecrosis of the jaw (ONJ) is a rare event which has been seen in association with the use of all the bisphosphonates currently licensed in Europe - see scientific opinion published in September 2009 by the European Medicines Agency's Committee for Human Medicinal Products (CHMP) (http://www.emea.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500051428.pdf). Genetic factors may be important in the development of bisphosphonate-related ONJ, with recent findings suggesting a possible role of the RBMS3 gene (Nicoletti et al The Oncologist 2012; 17: 279-287).

Atypical subtrochanteric and diaphyseal femoral fractures have also been reported rarely with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These atypical femoral fractures present differently from fractures associated with osteoporosis and are considered a class effect of all bisphosphonates currently licensed in Europe - see scientific opinion adopted in June 2011 by the CHMP (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Bisphosphonates_31/WC500117118.pdf)

It is difficult to detect adverse 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.

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The purpose of the project is two-fold:

- To generate methodologies to study the relationship between bisphosphonate use and long term adverse skeletal events in human populations, including the study of the optimal duration of bisphosphonate treatment for osteoporosis to attempt to minimise long-term risks.
- To measure the incidence of osteonecrosis of the jaw and other relevant sites, and incidence of atypical femoral fractures in association with high dose and long-term use of bisphosphonates, taking into account duration of treatment and different time windows at risk of developing the event, including long-term risks, and also other possible risk factors (including genetic factors). Data on the comparative safety of the different bisphosphonates would be important.

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.