ROCHE

Position Paper

Clinical Endpoints for Osteoporosis Therapy Trials

This paper presents ROCHE's opinion on the current position and use of clinical trial endpoints in the development of compounds for the treatment and prevention of postmenopausal osteoporosis. It aims at a line of argumentation for potential alternative use and definition of these endpoints in the future based on accumulated medical and scientific evidence since the last edition of the currently active guidelines. The argumentation in this paper deliberately restricts its focus to specific aspects and characteristics of bisphosphonates and does not attempt to generalize to other compounds that may be used in these indications.

Principal fracture efficacy evaluation – vertebral fractures

Historically, BMD changes induced by pharmacological treatment have not translated into fracture efficacy in 100% of clinical trials performed. The foremost example was treatment with fluoride, which induced large BMD gains at the lumbar spine without decreasing the incidence of osteoporotic fractures [1] . Therefore, the evaluation of fracture efficacy through an adequate and well-controlled clinical trial remains a requirement for a new molecular entity and the cornerstone for the characterization of the efficacy of a new compound. The present FDA guideline adequately meets this requirement. Two fracture endpoints are generally used to assess anti-fracture efficacy, the incidence of morphometric vertebral fractures and the incidence of clinical or symptomatic fractures. Clinical fractures are associated with clinical symptoms and are usually clearly identified by radiographs and thus are easier to document. A larger fraction of morphometric vertebral fractures do not come to clinical attention and are

diagnosed by pre-planned radiographs of the lumbar and thoracic vertebral spine independent of clinical symptoms of vertebral fracture. The assessment of vertebral fractures involves separate, independent and centralized radiograph readings for the verification of the fractures employing recognized and reproducible methodology. This central reading of pre-planned, scheduled radiographs allows the assessment of efficacy in preventing the occurrence of new vertebral fractures as well as the worsening of pre-existing vertebral fractures within a controlled and quantifiable diagnostic framework. ROCHE is supportive in maintaining the existing requirements for the demonstration of fracture efficacy using the incidence of new morphometric vertebral fractures as a primary endpoint and as a cornerstone for the demonstration of efficacy for new molecular entities in the treatment of osteoporosis.

Role of BMD as a surrogate for fracture efficacy

Low BMD is well established as a risk factor for osteoporotic fractures and patients with higher BMD have a lower risk of fractures (controlling for other variables). On the other hand, for agents not impairing bone quality, increased BMD predicts increased bone strength and lower fracture risk. This has been demonstrated in several animal species with a number of antiresorptive agents and has been confirmed in clinical trials with agents like alendronate, risedronate and raloxifene [2-6] .

Due to the differences in metabolism and distribution of cancellous and cortical bone at various sites of interest throughout the skeleton (i.e. lumbar spine, hip, distal forearm

etc.), a different magnitude of BMD increases is observed at these different sites. The range of BMD increases induced by the bisphosphonates expressed as a ratio of BMD increase at the hip over the BMD increase at the lumbar spine is very similar for the bisphosphonates currently approved or submitted for drug approval. Thus, for a given magnitude of BMD change at the lumbar spine, a corresponding consistent fraction of BMD increase at the hip (irrespective of the individual bisphosphonate) is achieved. The data generated to date for various bisphophosphonates do not provide evidence for different degrees of BMD increase at the hip that are independent of the magnitude of BMD change at the lumbar spine.

Relationship between BMD changes and vertebral fracture risk

The current scientific literature supports a clear relationship between BMD changes at the lumbar spine and hip induced by bisphosphonate treatment, and fracture efficacy, through several meta-analyses (including a large number of adequate and well-controlled clinical trials). Meta-analyses of randomized, controlled clinical trials are considered the highest level of evidence in evidence-based medicine [7] . These analyses demonstrate for a number of antiresorptive agents (approved or investigational) a significant association between the magnitude of increase in BMD at the lumbar spine and hip, and the reduction in new vertebral and nonvertebral fractures [8, 9] . The meta-analysis published by Wasnich and Miller used Poisson regression analysis to quantify the relationship between therapy-induced BMD changes and vertebral fracture risk reduction. The model was able to robustly predict the increasing reduction in vertebral fracture risk as a function of the change in BMD at both the lumbar spine and the hip. A small but still significant

reduction in fracture risk was observed for mere maintenance of the BMD status (a BMD increase of zero). This is in concordance with regression analysis data generated for ibandronate by ROCHE in the BONE trial [10] in which already the prevention of further bone loss at either the lumbar spine or the hip resulted in a reduction in vertebral fracture risk. The regression analysis performed by Wasnich and Miller showed a nearly linear relationship between the magnitude of BMD gains at either the lumbar spine or the hip, and the magnitude of vertebral fracture risk reduction. Additional data, which originally were not included in this analysis, arose through clinical trials with risedronate and ibandronate. The risedronate data were investigated using the model by the authors, and the risedronate data confirmed the results of their previous analysis. The retrospective application of the BONE study data demonstrates an equally good fit of the data to the model in terms of the predicted reduction in vertebral fracture risk for both the BMD changes at the lumbar spine and the total hip. The hypothesis is furthermore supported by a multiple variable regression analysis published by Hochberg et al, using the alendronate data of the FIT trial [11] . The results of this analysis corroborate a relationship between the magnitude of BMD increases induced by this bisphosphonate therapy at either the hip or the lumbar spine and the magnitude of risk reduction for new vertebral fractures.

Relationship between BMD changes and nonvertebral fracture risk

The investigation of the relationship between BMD changes and risk of fractures has very recently been extended by an even larger meta-analysis on a total of 18 clinical trials investigating antiresorptive agents including a total of more than 2400 patients [8] . This analysis explored the relationship between BMD changes after 1 year at the lumbar spine

and the hip as well as changes in markers of bone turnover and the risk of nonvertebral fractures. Using Poisson regression analysis, a significant association between the magnitude of BMD increases at both the lumbar spine and the hip and the magnitude of risk reduction for nonvertebral fractures could be shown after 1 year. Furthermore, a significant association between nonvertebral fracture risk reduction and the magnitude of suppression of biochemical markers of bone resorption and in particular bone formation was demonstrated. Despite the observed smaller BMD increase at the hip compared with the spine as mentioned above, the predicted net effect on nonvertebral fracture risk was the same for BMD changes at either the spine or the hip. While a small fraction of the effect on vertebral fractures in the aforementioned analyses [9] could not be explained by the changes in BMD at the lumbar spine or the hip (treatment effect independent from therapy-induced BMD changes), an independent effect of treatment was not observed in the case of nonvertebral fractures [8] . Thus, treatment–induced changes in BMD at either the lumbar spine or the hip appear to explain all of the risk reduction in nonvertebral fractures [8] . The models described above were recently validated using data from published head-to-head comparison trials of alendronate versus alfacalcidol and alendronate versus calcitonin. The predicted reductions in vertebral fracture risk based on the BMD changes determined in these head-to-head trials were very similar to the observed reductions in large clinical trials [12] .

In conclusion, there is strong evidence, resulting from a substantial number of adequate and well-controlled clinical trials, that BMD increases induced by bisphosphonate

treatment (and the magnitude of these increases) explain the risk reduction observed for vertebral, as well as nonvertebral fractures.

Extension of inference of established fracture efficacy to additional administration regimens through comparative BMD investigations

Based on the above stated body of evidence, it appears plausible to use BMD assessments as a a surrogate for fracture efficacy. However, it must be understood that this should only be pursued after the demonstration of fracture efficacy in an adequate and well-controlled clinical trial with a primary endpoint being the incidence of morphometric vertebral fractures for each new molecular entity under investigation. Based on this primary characterization of a molecule by demonstrating fracture risk reduction efficacy, along with corresponding changes in BMD and biochemical markers of bone turnover, it appears plausible that for further administration of the same molecule in different administration forms and regimens a comparable level of fracture efficacy can be assumed based on a comparison of the magnitude of BMD changes for the respective treatment. This, however, can only be applied to treatment regimens that do not leave the time frame of continuous dosing, i.e. any dosing interval that does not exceed the resorption period of the osteoclast. The demonstration of an equivalent magnitude of change in BMD should be performed by an adequate and well-controlled trial evaluating therapeutic equivalence by means of non-inferiority testing using an appropriate margin of non-inferiority. Such an approach has recently been used and approved for alendronate's and risedronate's weekly administration regimen.

Extension of inference of nonvertebral fracture efficacy through comparative BMD investigations

Clinical trials exploring the efficacy of bisphosphonates on vertebral fracture risk reduction have recruited study populations with quite different fracture risk levels despite very similar inclusion criteria. In the BONE trial for example [10] , the risk for vertebral as well as nonvertebral fractures was considerably lower than in trials investigating currently approved bisphosphonates despite similar inclusion criteria. Consequently, an effect on nonvertebral fracture risk reduction was not apparent in this study unless patients in higher risk-level strata were analyzed.

The above stated regression analyses exploring the relationship between BMD changes and risk reduction for vertebral and nonvertebral fractures suggest that this relationship exists within the class of bisphosphonates. ROCHE therefore proposes to compare the changes in BMD induced by the bisphosphonate under investigation with the BMD gains achieved by an already approved bisphosphonate with already demonstrated nonvertebral fracture efficacy. This approach should link and translate the demonstration of BMD gains to nonvertebral fracture efficacy. Based on the accumulated evidence about the efficacy of bisphosphonates it appears difficult to justify a continued requirement for the demonstration of nonvertebral fracture efficacy by placebo-controlled clinical trials.

ROCHE therefore proposes to base a claim for nonvertebral fracture efficacy on the demonstration of non-inferiority of the change in BMD of the molecule under investigation compared with the BMD gains being achieved by a reference standard established by an active comparator. Due to the high variability and overall smaller

magnitude of gains in BMD at the hip it is proposed to use lumbar spine BMD changes as the primary endpoint in such trials with hip BMD being a secondary endpoint. A clinically meaningful non-inferiority margin already used in the past could be 1.5% or 30% of the smallest BMD difference between active treatment and placebo derived from comparable data.

As a practical approach, ROCHE therefore proposes a trial combination for approval of a new molecular entity in the class of bisphosphonates, which should demonstrate fracture efficacy as a base characterization extended by a BMD bridging concept to already registered compounds in order to fully characterize efficacy of the compound under investigation. The combined information about these investigations as part of the compound label should thus be provided by:

1. A 3-year phase III fracture trial demonstrating significant fracture efficacy for morphometric vertebral fractures as the primary endpoint as its first part.
2. As the second component, an additional phase III trial with the primary endpoint being the change in BMD at the lumbar spine and the secondary endpoint being the change in BMD at the hip.

With this approach, a class-label for bisphosphonates with regards to vertebral and nonvertebral fracture efficacy based on the above stated requirements should be established.

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