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COMMENTARIES

Risedronate or Alendronate for the Prevention of Osteoporotic Fractures: Is There a REAL Difference?

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Commentary on: Silverman SL, Watts NB, Delmas PD, Lange JL, Lindsay R. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporos Int*. 2007 Jan;18(1):25-34.

Alendronate and risedronate are the two most commonly prescribed drugs for fracture prevention in osteoporosis. Placebo-controlled, randomized controlled trials (RCTs) suggest that these two amino-containing bisphosphonates have comparable *efficacy* to reduce the incidence of new vertebral, non-vertebral and hip fractures. Yet questions of mostly commercial interest remain concerning the *effectiveness* of these two drugs in "real life". A recent observational study (REAL) in patients from two major health plan providers' databases in the US concludes to a significantly lower incidence of non-vertebral and hip fractures after 6 months and one year in patients receiving risedronate compared to alendronate (1). This new observation leads us to wonder whether there are real differences between the two drugs.

Meta-analysis of RCTs indicates that the risk reduction of new morphometric vertebral fractures appears to be of similar magnitude with alendronate and risedronate (-40% to -50%) (2-4). However, their efficacy in reducing the risk of non-vertebral fractures has been more variable (-15% to -30%) and difficult to compare, due to differences in the definition of non-vertebral fractures and of baseline patient characteristics, and marked differences in the dropout rate in those studies (2-4). Systematic reviews and meta-analyses, although considered to provide the highest level of evidence, sometimes concluded to the superiority of alendronate versus risedronate in reducing non-vertebral fractures, sometimes to the opposite, partly because of different statistical approaches (intention-to-treat or per-protocol) (5-7). The efficacy of both drugs on hip fractures (-20 to -60%), however, appears to be comparable despite differences in the patients' profile included in the RCTs and/or in the methodology of the analyses that were performed (8;9).

Head-to-head studies overcome the biases that exist when comparing drug efficacy from different trials with different outcome definitions and different patient characteristics. A RCT (Fosamax-Actonel Comparison Trial, FACT) actually demonstrated a significantly higher suppression of bone turnover markers and gain of BMD, two well-accepted surrogate markers for anti-fracture efficacy, with alendronate than risedronate in postmenopausal women (10). Had FACT been a bridging study, or a study comparing the efficacy of a drug in men and women, it would be considered sufficient evidence for greater efficacy of one agent over the other. Yet because of some differences in the baseline rate of bone turnover between the alendronate and risedronate groups in this study, and because FACT did not bring direct evidence for anti-fracture *efficacy*, it has been heavily criticized, based on the relatively poor relationship we know between fracture risk reduction and an increase in BMD.

Instead, we now have a REAL head-to-head comparison of the *effectiveness* of risedronate and alendronate on the incidence of fractures. REAL being an observational study, it ranks lower than any RCT or meta-analysis in the hierarchy of evidence-based medicine. Nevertheless, the number of patients observed in this study, namely more than 21,000 for alendronate

and more than 12,000 for risedronate, was impressive, together with a rigorous methodological approach to exclude in particular traumatic fractures, existing fractures and re-fractures at the same site, as well as patients with less than 6 months of enrollment in the health care system before the beginning of the observation period or less than 3 months of enrollment after it began (1). Moreover, baseline characteristics indicated a slightly greater risk of fractures in the risedronate group, because of inclusion of a greater proportion of patients using glucocorticoids, diagnosed with osteoporosis or osteopenia, or suffering from rheumatoid arthritis. On the contrary, patients receiving risedronate were 40% more likely to have previously received calcitonin or raloxifene. After 6 and 12 months of observation, the relative risk of non-vertebral fractures was 19% (p=0.05) and 18% (p=0.03) lower, whereas the relative risk of hip fracture was 46% (p=0.02) and 43% (p=0.01) lower, respectively, on risedronate than on alendronate. Such a marked difference in *effectiveness* between the two drugs may appear surprising considering the similarities in *efficacy* summarized above. The 43% relative risk reduction with risedronate represents 10 to 15 less hip fractures per 12,000 patients intended to be treated, which is a 0.1% absolute risk reduction (by ITT). Two non-mutually exclusive hypotheses have been raised to explain these results. First is the possibility that risedronate reduces fracture risk more rapidly, i.e., after 6 months, which would provide an advantage over a short period of observation as in REAL. Second, risedronate, having a somewhat lower affinity for the bone matrix than risedronate, could be released and captured by osteoclasts more readily; also, its molecular binding characteristics to the osteoclast farnesyl pyrophosphate synthase (FPPS) could provide more stable inhibition of the enzyme than alendronate (11). However these characteristics did not appear to provide greater efficacy to risedronate in the pivotal and head-to-head trials.

The REAL study has some clear limitations: 33% and 37% of patients prescribed alendronate and risedronate, respectively, were censored before 12 months because of the end of available data, and 41% in each group were censored because of the end of therapy adherence, leaving 5300 (24%) and 2450 (20%) patients in the alendronate and risedronate groups, respectively, after 12 months. Thus, more patients have left before one year in the risedronate group (4/5 patients) than the alendronate group (3/4 patients), and the number of patients at risk thereby increased over time in the alendronate relative to the risedronate group. Moreover, by intention-to-treat analysis, the rate ratio of non-vertebral fractures had a confidence interval including 1, i.e., absence of a significant difference between drugs. The same was true when the authors performed sensitivity analyses adding patients with less than 6 months medical records in the database before the observation period, and also when all fractures were considered without exclusions (see above).

In summary, this observational study by design cannot demonstrate whether there are “real” differences in *efficacy* between the two drugs. However it might suggest that to reproduce drug efficacy, as demonstrated in RCTs, in real life, full adherence to treatment is required.

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