Relationship of fracture risk to change in bone resorption with risedronate in the HIP study: Is there a plateau response? A. Blumsohn1, J. L. Hutton2

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Abstract

Understanding the determinants of bone remodeling-induced change in fracture risk is a prerequisite to rational prescribing and therapeutic monitoring. A previous abstract (Blumsohn, Barton, Chines, Eastell. JBMR, 2003; 18:S258), and draft publication failed to shed light on the true relationship between change in bone resorption (\(\Delta NTX\)) and fracture risk in the Hip Study. The study included 1,992 women (FN 1,075), aged 74 SD 3, who received Ca and either 5mg risedronate or 2mg or placebo for 3 years. Randomisation and event codes were supplied to authors in 2006. Data did not provide evidence to support previous conclusions.

Previous reports on disease data suggested risk of incident vertebral fracture (\(\Delta NTX\)) decreases beyond -50% \((\Delta NTX < -50\%)\), and the relationship was “non linear” with “little further improvement in fracture benefit below a decrease of 30 to 35%”. It further suggested that another marker \((\Delta PINP)\) was superior to \(\Delta NTX\). We used several statistical models as well as visual inspection to evaluate a possible plateau-based threshold -30% or -40%.

Visual inspection showed no evidence of a plateau near the putative threshold. With 5mg risedronate incidence of V# occurred with change in NTX beyond -40% \((\Delta NTX < -40\%)\) and Aligned/NTX. The response was allowed to take different values and below the threshold, for both linear and quadratic functions. Conclusion: Essentially were the same for all models, with or without inclusion of linear terms of the untransformed (5mg) dose.

Results: Simpson inspection of data not used with a plateau relationship between \(\% NTX\) and fracture risk with threshold near -30% in patients on risedronate. Disclosure: Study funded by Procter & Gamble Pharmaceuticals

Background

This abstract focuses on the relationship between data and representation of that data in ASBMR abstract and associated draft publication prepared by the sponsor in 2006.

Similar concerns raised about representation of data in the larger HIP-VERT population (2.5) and the VERT population alone (3). Randomisation and event codes revealed to authors in 2006.

Statistical analysis

A large number of statistical models (see abstract, full statistical report available from authors) as well as visual inspection were used to evaluate a potential “plateau” at putative -30% or -40% threshold.

Results: Visual inspection of data not used with a plateau relationship between \(\% NTX\) and fracture risk with threshold near -30% in patients on risedronate.

Results: Figure 1. Various displays of the distribution of change in NTX at 5mg or at both doses. a) Distribution of \(\% NTX\). The solid vertical line indicates the putative plateau threshold at -30%. b) Distribution of fracture risk for 5mg risedronate. c) Distribution of fracture risk for 5mg risedronate.

Conclusions: This study provides no evidence to support a plateau relationship between \% NTX and fracture risk with threshold near -30% in patients on risedronate.

References