Comparative cardiovascular safety of strontium ranelate and bisphosphonates amongst patients with no contraindications: A multi-database study in 5 EU countries by the EU-ADR Alliance

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Background

Newly identified risk of cardiovascular safety associated with the use of strontium ranelate (SR) have led to new contraindications and restricted use in May 2013 by the EMA/PRAC. We present the final results of the Post-Authorization safety Study (PASS) that was requested by the EMA.

Objectives

To evaluate the risk of thromboembolic events and the new risk of cardiac events among new users of SR and oral bisphosphonates (BP) without contra-indications for SR.

Methods

We conducted three multinational, multi-database (Aarhus Denmark, HSD Italy, IPCI Netherlands, SIDIAP Spain, and THIN UK), nested case-control studies. Within a cohort of new users of SR or BP who started index therapy before June 2013 and with no contraindications for SR use, we matched cases of 1) Acute myocardial infarction, AMI, and 2) Venous Thromboembolism, VTE, and 3) cardiovascular death, CVD, up to 10 controls on gender, year of birth, index date, and country. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals (CIs) according to current vs past SR use, and current SR vs current BP use, adjusting for potential confounders, within each database. Data were pooled using (random effects) meta-analysis. VTE and CVD events were validated in all but Danish data.

Results

For VTE (5614 cases, 56 036 controls), an excess risk was found with current vs past SR use, with adjusted OR (aOR) of 1.30 [95%CI 1.04-1.62], and with current SR compared with current BP use: aOR 1.24 [0.96-1.61]. No excess risk of AMI (5477 cases, 54 674 controls) was found with neither current vs past SR (aOR 0.71 [0.56-0.91]) or current use of SR vs current BP: aOR 0.89 [0.70 to 1.12]). Finally, no increased risk of CVD (3019 cases, 29 871 controls) was seen with current vs past SR use (aOR 0.68 [0.48-0.96]), but risk was higher with current SR vs current BP use: aOR 1.35 [1.02-1.80].

Conclusions

This study found no evidence of an increased risk of AMI but a 25-30% excess risk of VTE in SR users without contra-indications. Despite no excess risk in the comparison of current vs past SR users, a 35% excess risk of CVD was observed when current SR and current BP users were compared. The latter disparity could be partially explained by cessation of such preventative therapies in end-of-life, or by residual confounding by indication.