New strategies for osteoporosis patients previously managed with strontium ranelate

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Abstract: The aim of this article is to describe potential alternatives to patients no longer eligible for management with strontium ranelate for osteoporosis according to the recommendations by the European Medicines Agency. A systematic search of Pubmed was done for papers on fracture efficacy of various treatments for osteoporosis, and potential harms especially in terms of cardiovascular events and stroke. The results showed that drugs more efficacious in terms of relative risk reduction of fractures than strontium ranelate were alendronate, risedronate, zoledronate, and denosumab. Raloxifene, as for strontium, may be associated with an increased risk of deep venous thromboembolism and fatal stroke. In terms of cardiovascular events special attention may be given to calcium supplements. Thus, patients at risk of stroke and ischemic cardiac events such as acute myocardial infarction should not use strontium ranelate. Ideally more efficacious drugs in terms of fracture reduction should be used such as alendronate, risedronate, zoledronate or denosumab. Raloxifene may pose a special problem as this too may be associated with an increased risk of fatal strokes. Other less-potent drugs in terms of fracture reduction should only be used if no alternatives are available (ibandronate, pamidronate, clodronate). Parathyroid hormone or analogs may be used for a limited time interval in specially selected patients and needs to be followed up with antiresorptive treatment to prevent loss of the bone gained. However, it should be remembered that no head-to-head comparison studies exist.

Keywords: alendronate, bisphosphonate, cardiovascular, denosumab, raloxifene, stroke, strontium ranelate, teriparatide

Introduction

Recent publications have cast doubt on how to best manage patients previously treated with strontium ranelate [EMA, 2014a, 2014b, 2014c; Cooper *et al.* 2014; Abrahamsen *et al.* 2014]. The European Medicines Agency (EMA) regarding strontium has recommended ‘further restricting the use of the medicine to patients who cannot be treated with other medicines approved for osteoporosis. In addition these patients should continue to be evaluated regularly by their doctor and treatment should be stopped if the patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina. As recommended in a previous review, patients who have a history of certain heart or circulatory problems, such as stroke and heart attack, must not use the medicine’.

Therefore osteoporosis patients with these cardiovascular and cerebrovascular conditions should be managed by other drugs against osteoporosis, and the use of strontium ranelate restricted to osteoporosis patients without these conditions not tolerating other drugs against osteoporosis.

In the choice of strontium ranelate one should be aware about the anti-osteoporosis efficacy of this drug compared with other drugs, i.e. strontium ranelate may be less efficacious in terms of relative reduction of fracture risk than alendronate, risedronate, zoledronate, and denosumab (see Table 1), but more efficacious than etidronate or raloxifene. However, it should be remembered, that no head-to-head comparison studies exist. In terms of efficacy both

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Table 1. Effects on various fracture outcomes of different drugs for osteoporosis (evidence from meta-analyses or RCT if no meta-analyses were available). Values are relative risk estimates and 95% confidence intervals. Statistically significant associations are highlighted in bold.

Drug	Spine fractures	Nonvertebral fractures	Hip fractures
Strontium ranelate	0.63 (0.56-0.71) [O'Donnell <i>et al.</i> 2006]	0.86 (0.75-0.89) [O'Donnell <i>et al.</i> 2006]	0.85 (0.61-1.19) [O'Donnell <i>et al.</i> 2006]
Alendronate	0.55 (0.45-0.67) [Wells <i>et al.</i> 2008a]	0.84 (0.74-0.94) [Wells <i>et al.</i> 2008a]	0.61 (0.40-0.92) [Wells <i>et al.</i> 2008a]
Risedronate	0.63 (0.51-0.77) [Wells <i>et al.</i> 2008b]	0.80 (0.72-0.90) [Wells <i>et al.</i> 2008b]	0.74 (0.59-0.94) [Wells <i>et al.</i> 2008b]
Zoledronate	0.30 (0.24-0.38) [Black <i>et al.</i> 2007]	0.75 (0.64-0.87) [Black <i>et al.</i> 2007]	0.59 (0.42-0.83) [Black <i>et al.</i> 2007]
Etidronate	0.59 (0.36-0.96) [Wells <i>et al.</i> 2008c]	0.98 (0.68-1.42) [Wells <i>et al.</i> 2008c]	1.20 (0.37-3.88) [Wells <i>et al.</i> 2008c]
Ibandronate	0.48 (0.32-0.72) [Chestnut <i>et al.</i> 2004]	1.09 (0.80-1.50) [Chestnut <i>et al.</i> 2004]	N/A [Chestnut <i>et al.</i> 2004]
Raloxifene	0.7 (0.5-0.8) [Ettinger <i>et al.</i> 1999]	0.9 (0.8-1.1) [Ettinger <i>et al.</i> 1999]	1.1 (0.6-1.9) [Ettinger <i>et al.</i> 1999]
Denosumab	0.31 (0.20-0.47) [Cummings <i>et al.</i> 2009]	0.80 (0.67-0.95) [Cummings <i>et al.</i> 2009]	0.60 (0.37-0.97) [Cummings <i>et al.</i> 2009]
Teriparatide	0.35 (0.22-0.55) [Neer <i>et al.</i> 2001]	0.62 (0.40-0.97) [Neer <i>et al.</i> 2001]	0.50 (0.09-2.66) [Neer <i>et al.</i> 2001]
Recombinant 1-84 PTH	0.42 (0.24-0.72) [Greenspan <i>et al.</i> 2007]	0.97 (0.69-1.35) [Greenspan <i>et al.</i> 2007]	0.97 (0.20-4.81) [Greenspan <i>et al.</i> 2007]

the fracture types that can be prevented or not prevented and the relative fracture reduction needs to be taken into account.

The first question may thus be: for whom may strontium ranelate be indicated? This may be formulated as follows:

- (1) patients not tolerating other osteoporosis therapies (say bisphosphonates), and not having the cardiovascular risks mentioned by the EMA;
- (2) patients already started on strontium ranelate, tolerating this and not having the cardiovascular risks mentioned by the EMA.

Before starting a patient not tolerating other drugs against osteoporosis, it should be taken into consideration that all potentially more efficacious drugs in terms of fracture prevention should have been tried first (see Table 1), i.e. a patient not tolerating alendronate should have tried risedronate, intravenous (IV) zoledronate, and denosumab, all of which potentially are more efficient than strontium ranelate.

The second question is to consider what patients need to shift from strontium ranelate. This would

be patients not tolerating strontium ranelate and/or having the cardiovascular risks mentioned by the EMA. Again patients shifting from strontium ranelate should not be rotated to less-efficacious anti-osteoporosis drugs or drugs carrying similar cardiovascular risk profiles.

In the following, the potential options will be discussed from the point of view of (a) effectiveness in terms of fracture prevention and (b) cardiovascular risks.

Fracture prevention alternatives to strontium ranelate

First it is necessary to consider the fracture preventive efficacy of strontium ranelate. It has been shown to prevent morphological and clinical vertebral fractures [Meunier *et al.* 2004] and non-vertebral fractures [Reginster *et al.* 2004]. It has not in the primary analyses been shown to be efficacious in preventing hip fractures [Reginster *et al.* 2004]. However, a subgroup analysis has pointed at a potential hip fracture preventive effect in high-risk patients (age >74 years and femoral neck bone mineral density (BMD) T score <−3, corresponding to −2.4 according to National Health and Nutrition Examination

Survey [NHANES] reference) [Reginster *et al.* 2004].

The fracture reducing potential of drug alternatives should thus be measured against this.

Bisphosphonates

For the bisphosphonates the following drugs are generally available (see Table 1).

Alendronate. This is efficacious against spine fractures, nonvertebral fractures, hip fractures, i.e. more efficacious in terms of fracture types prevented than strontium ranelate. This evidence stems from randomized controlled trials (RCT) and meta-analyses.

Risedronate. This is efficacious against spine fractures, nonvertebral fractures, hip fractures, i.e. more efficacious in terms of fracture types prevented than strontium ranelate. This evidence stems from RCTs and meta-analyses.

Etidronate. This has been shown only to be efficacious against vertebral fractures, i.e. not more efficacious in terms of fracture types prevented than strontium ranelate. This evidence stems from RCT and meta-analyses.

Ibandronate. This has been shown to be efficacious against vertebral fractures, i.e. not more efficacious in terms of fracture types prevented than strontium ranelate. A *post hoc* subgroup analysis found that oral ibandronate significantly reduced nonvertebral fractures compared with placebo in people at high risk of fractures (T score < -3). However, it found no significant difference between intermittent oral ibandronate and placebo [Chestnut *et al.* 2004]. This evidence stems from RCTs and a meta-analysis, the latter however limited by the fact that only one of the included RCTs contributed a control group.

Pamidronate. Only limited evidence from small RCT is available [Brumsen *et al.* 2002; Reid *et al.* 1994]. Pamidronate may potentially be efficacious against vertebral fractures (however, this was only backed by evidence from one of the studies [Brumsen *et al.* 2002]), i.e. it does not seem more efficacious in terms of fracture types prevented than strontium ranelate. It should be observed that pamidronate is not licensed for osteoporosis.

Clodronate. The evidence is mixed. One RCT pointed at a reduction in vertebral fracture risk [McCloskey *et al.* 2004], whereas this was not backed by another larger trial [McCloskey *et al.* 2007]. The second large RCT pointed at a reduction in nonvertebral fractures [McCloskey *et al.* 2007], a finding not supported by the first RCT [McCloskey *et al.* 2004]. Clodronate thus seems less efficacious in terms of fracture types prevented than strontium ranelate. It should be noted that clodronate is not licensed for osteoporosis.

Zoledronic acid. Zoledronic acid has been documented to be effective against spine fractures, nonvertebral fractures, and hip fractures in a large-scale RCT [Black *et al.* 2007], i.e. more efficacious in terms of fracture types prevented than strontium ranelate.

Selective estrogen receptor modulators

For the selective estrogen receptor modulators, raloxifene and bazedoxifene are available.

Raloxifene. Raloxifene is only effective against vertebral fractures [Seeman *et al.* 2006; Barrett-Connor *et al.* 2006; Ensrud *et al.* 2008; Nakamura *et al.* 2006], i.e. it is less efficacious in terms of fracture types prevented than strontium ranelate. This evidence stems from RCTs and meta-analyses.

Bazedoxifene. Bazedoxifene is also only effective against vertebral fractures [Silverman *et al.* 2008], i.e. it is less efficacious in terms of fracture types prevented than strontium ranelate. This evidence stems from one RCT.

Denosumab

Denosumab has been shown to be effective against spine fractures, nonvertebral fractures and hip fractures [Cummings *et al.* 2009] in a RCT, i.e. more efficacious in terms of fracture types prevented than strontium ranelate.

Parathyroid hormone or analogs

These drugs have bone anabolic properties, but may be restricted for special groups and only used for a limited time period of 1.5–2 years.

Teriparatide. Teriparatide has been shown to be effective against spine fractures and nonvertebral fractures but not hip fractures [Neer *et al.* 2001]

in a RCT, i.e. efficacious against the same fracture types as strontium ranelate.

Recombinant human 1-84 PTH. This is only effective against spine fractures [Greenspan *et al.* 2007] in a RCT, i.e. not more efficacious in terms of fracture types prevented than strontium ranelate.

Activated vitamin D such as alfacalcidol or calcitriol

These may be effective against vertebral fractures and perhaps against nonvertebral fractures, although the evidence is limited according to existing meta-analyses of RCTs [Avenell *et al.* 2009]. These drugs may not be more efficacious in terms of fracture types prevented than strontium ranelate.

Patients with treatment failure

Another group of patients which may merit shifts from or to strontium ranelate are patients with treatment failure. A recent paper [Diez-Perez *et al.* 2012] defined treatment failure on anti-osteoporosis drugs as: (1) two or more incident fragility fractures; (2) one incident fracture and elevated serum cross-linked C-terminal telopeptide of type I collagen (β CTX) or procollagen type I N-terminal propeptide (PINP) at baseline with no significant reduction during treatment, a significant decrease in BMD, or both; or (3) both no significant decrease in serum β CTX or PINP and a significant decrease in BMD. Such patients should be given more efficacious treatment (alendronate, risedronate, zoledronate, denosumab, teriparatide; cf. Table 1) than the treatment they are already on if at all possible.

No human evidence for an effect of strontium ranelate in glucocorticoid-induced osteoporosis (GIO) exists [Sun *et al.* 2013], i.e. it should not be used. This in contrast to alendronate [Yang *et al.* 2013, Adachi *et al.* 2001, Saag *et al.* 1998], risedronate [Reid *et al.* 2001], etidronate [Campbell *et al.* 2004], raloxifene [Mok *et al.* 2011], zoledronate [Sambrook *et al.* 2012], and parathyroid hormone [Saag *et al.* 2007], for which evidence for an effect on BMD and/or fractures exist from RCTs. These drugs should thus preferentially be used in GIO.

Cardiovascular risks of anti-osteoporosis drugs as alternatives to strontium ranelate

The EMA discourages the use of strontium ranelate in patients with prior stroke of

myocardial infarction and discontinuation if high blood pressure or angina pectoris develops. Special care should thus be taken to choose other drugs for osteoporosis, not only at least as efficacious in terms of fracture preventive effect and fracture types prevented, but also in terms of not having the same cardiovascular side effects or other serious side effects. In the following section of this article, we shall look systematically into the side effects (acute myocardial infarction [AMI], stroke, deep venous thromboembolism), but also into the individual drugs against osteoporosis.

Calcium

The basic treatment for almost all patients with osteoporosis are calcium plus vitamin D. However, calcium supplements have been associated with both AMI as well as stroke [Bolland *et al.* 2008, 2010, 2011] in meta-analyses. It should be noted that no dose-response relationship was seen [Reid *et al.* 2011], and no such relationship was seen for say the bisphosphonates in observational studies [Vestergaard, 2012; Vestergaard *et al.* 2011] except for an increase at low doses with a decrease with increasing doses.

When shifting from strontium ranelate one should then also consider the potential association of calcium with or without supplements of vitamin D with cardiovascular mortality. It should be noted that the data on calcium and cardiovascular mortality remain controversial.

Bisphosphonates

For alendronate an excess risk of AMI have been seen with low adherence [Vestergaard, 2012] in an observational study. However, among those adherent to alendronate actually a decrease in the risk of AMI was seen in an observational study [Vestergaard, 2012]. For etidronate no excess or decrease in the risk of AMI was seen in this observational study. For alendronate the AMI pattern with dose may be related to the fact that subjects with AMI may be likely to discontinue the drug and thus a 'healthy survivor bias' among those adherent to the drug [The Coronary Drug Project Research Group, 1980].

For strokes an increased risk was seen with low adherence to alendronate, but no decrease with higher doses in an observational study [Vestergaard *et al.* 2011]. For etidronate no clear pattern was

present [Vestergaard *et al.* 2011] in this observational study.

Thus no contraindications for shifting to bisphosphonates in terms of stroke or AMI seem present.

The usual contraindications such as risk of ulcerations in the upper gastrointestinal tract [Vestergaard *et al.* 2010c] should of course be observed along with the more rare risk of osteonecrosis of the jaw [Khosla *et al.* 2007; Cartsos *et al.* 2008; Vestergaard, 2012]. Thus, the potential side effects of the alternative drug also need to be taken into consideration.

An increased risk of deep venous thromboembolism has been reported with strontium ranelate in a meta-analysis [O'Donnell *et al.* 2006]. An increased risk has also been seen in those treated with bisphosphonate, but the risk was present already before start of the drugs in an observational study, and the risk may be related to say immobilization stemming from the underlying disease (osteoporosis) being treated [Vestergaard *et al.* 2010b]. This may thus also be the case for strontium.

A further challenge may be the risk of serious atrial fibrillation described with bisphosphonates in a meta-analysis [Mak *et al.* 2009]. However, one observational study indicated that the excess risk could be related to chronic obstructive pulmonary disease (COPD) being treated with glucocorticoids and thus being associated with osteoporosis, but the COPD also being associated with increased pulmonary arterial pressure and thus potentially atrial fibrillation [Vestergaard *et al.* 2010a]. Also the overall risk of atrial fibrillation may not be increased [Mak *et al.* 2009].

Little evidence is present for pamidronate and clodronate, but these also appear less potent than strontium ranelate in bone terms.

Raloxifene

Raloxifene may be more problematic as an alternative to strontium ranelate as it seems less efficacious in terms of fracture prevention as it does not seem to prevent nonvertebral fractures (Table 1). Furthermore, raloxifene has been associated with an increased risk of fatal stroke in older women with an increased cardiovascular risk in a RCT [Barrett-Connor *et al.* 2006].

Overall no increased risk of cardiovascular events and stroke have been observed with raloxifene in the largest RCT [Barrett-Connor *et al.* 2002], the results for overall stroke risk being backed by epidemiological data [Vestergaard *et al.* 2011].

Raloxifene has also been associated with an increased risk of deep venous thromboembolism in a RCT [Adomaityte *et al.* 2008] probably due to its estrogenic properties.

Denosumab

For denosumab no increased risk of stroke, cardiovascular events, peripheral vascular disease, or atrial fibrillation was present in a large RCT [Cummings *et al.* 2009].

Parathyroid hormone and analogs

For recombinant 1-84 PTH no increase in the risk of vascular disorders (no specific data for stroke or myocardial infarctions given except for one case of fatal myocardial infarction in both the treated and placebo group) was seen in the largest RCT [Greenspan *et al.* 2007].

For teriparatide no specific data on stroke or myocardial infarction were present in the available RCT [Neer *et al.* 2001].

Activated vitamin D

Little evidence is present for these drugs. However, if the calcium-phosphorous product is increased ectopic calcifications may appear, which may lead to cardiovascular events. Calcium and phosphorous levels thus should be monitored. Furthermore, there is evidence for a fracture reducing potential less than for strontium ranelate.

Overall considerations

Study design and inclusion criteria may affect outcomes. Less weight may be placed in observational studies than RCTs. Strontium ranelate has mainly been studied in older subjects, whereas the age limits for inclusion have meant that few subjects were available in the oldest age groups for several of the other drugs. A number of *post hoc* subgroup analyses have been performed. However, less emphasis may be placed on these as they are performed *post hoc* and in some cases relies on few subjects in the older age groups. Also

no head-to-head comparisons of drugs against osteoporosis are present in the older age groups.

Fracture risk increases with age on top of the increase with decreasing BMD. However, the decrease in BMD with age may far from explain the increase in fracture risk. The main aim of drugs against osteoporosis is to increase BMD, i.e. they may not address other risk factors for fracture such as increased risk of falls. The mechanisms behind falls may be complex and include say reduced eyesight with age, decreased muscle function, comedications, etc. Other measures besides drugs against osteoporosis may thus be indicated in some elderly patients.

Also cardiovascular risk increases with age. The fracture preventive effect of strontium ranelate has primarily been shown in elderly subjects, i.e. subjects *a priori* at high risk of cardiovascular events. The documentation for its effect among younger subjects is thus less prominent. This also needs to be taken into account when considering patients for drugs against osteoporosis.

In subjects on bisphosphonates concerns about low bone turnover, atypical femur fractures, and osteonecrosis of the jaw have been raised. Patients on long-term (>5 years) bisphosphonates may stop the bisphosphonates provided that their BMD has responded adequately and no further risk factors are present [Black *et al.* 2006]. What to do in patients not responding adequately to bisphosphonates is not finally determined. However, no definite data that shift to strontium ranelate may be superior exist in terms of atypical femur fractures [Lampropoulou-Adamidou *et al.* 2013]. Also in terms of osteonecrosis of the jaw no evidence exists for noninferiority or superiority of strontium ranelate compared with other drugs against osteoporosis [Vestergaard, 2012].

In terms of severe osteoporosis, this may be defined in several ways, one could be the presence of a fracture (the World Health Organization definition). Another definition was used in a subgroup analysis in one of the strontium trials as high-risk patients, i.e. age >74 years and femoral neck BMD *T* score <−3, corresponding to −2.4 according to NHANES reference. The latter was based both on low BMD and advanced age as an independent risk factor for fractures. The first definition is based on a clinical endpoint of sustaining a fracture. Other definitions may be based on more pronounced decreases in BMD (say

T-score <−4). These definitions may affect how treatment outcome may be.

Some studies have indicated a potential effect of strontium ranelate on osteoarthritis and pain [Reginster *et al.* 2013]. However, any such effect should not be prominent in deciding which drug to use for osteoporosis, as the main focus is fracture prevention and avoidance of the potentially fatal cardiovascular events.

Conclusions

Patients at risk of stroke and ischemic cardiac events such as AMI should not use strontium ranelate. Ideally more efficacious drugs in terms of fracture reduction should be used such as alendronate, risedronate, zoledronate, or denosumab. Raloxifene may pose a special problem as this too may be associated with an increased risk of fatal strokes. Other less-efficacious drugs in terms of fracture reduction should only be used if no alternatives are available (ibandronate, pamidronate, clodronate). Parathyroid hormone or analogs may be used for a limited time interval in specially selected patients and needs to be followed up with antiresorptive treatment to prevent loss of the bone gained.

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Conflict of interest statement

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