minimal important change in the SF-36 PF is considered ~20 points [7].

In the future, case reports of BMES will probably continue to be published, and analyses based on aggregated data from individual patients have the potential to provide information about the natural course and generate hypotheses regarding the effect of interventions. To investigate the effects of baseline characteristics and to facilitate adjustments in multivariate analyses, we propose the following variables be included in future reports: age (years), sex, smoking status, pregnancy (trimester), symptom duration (weeks), previous number of BMES episodes and affected anatomical area. If available, bone mineral density, as measured by the T score of the total hip, would be useful. Preferably outcomes should be reported at intervals of no longer than 4 weeks until symptom resolution.

To date, most articles on BMES have focused on interventions, not on the natural course of the disease. While awaiting placebo-controlled studies, we particularly wish to encourage authors to provide data from untreated patients. Guidelines for preparing case reports have recently been developed [8].

**Rheumatology key message**

- Outcome measures for pain and physical functioning were proposed for primary bone marrow oedema syndrome.

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**References**


The search identified 48 reports of AFFs and 60 of ONJ. Exclusion of reports involving multiple bisphosphonates left 41 cases of AFFs and 56 cases of ONJ. Diagnostic accuracy [4, 5] was confirmed for all patients where medical records and radiographs were available (21 patients with AFFs and 19 with ONJ).

The risk of reported AFFs and ONJ during the study period was <0.05% for all bisphosphonate users. As expected, most reports were associated with alendronate (Table 1). Four risedronate users had reported AFFs and seven users reported ONJ. None were identified for ibandronate, etidronate or clodronate. Compared with other oral bisphosphonates, the age- and sex-adjusted RR for alendronate was 2.33 (95% CI 0.83, 6.67) for AFF and 1.72 (95% CI 0.78, 3.85) for ONJ. The corresponding RR for AFF or ONJ was 1.96 (95% CI 1.04, 3.70).

Irrespective of the type of oral bisphosphonate, both AFFs and ONJ are rare ADRs. Nevertheless, our results indicate that treatment with alendronate confers a doubled risk of these reported events compared with other oral bisphosphonates. To our knowledge, no such direct risk comparison has previously been reported.

The pathogenesis of AFFs and ONJ is not well established. Microscopic cracks normally occur in bone with an estimated frequency of 0.2 microcracks/mm² in the lower limb [6]. Usually this damage is healed by bone remodelling. If bone resorption is inhibited by bisphosphonates, this physiological process may be impaired and the natural repair of crack lesions cannot take place, eventually leading to fatigue fractures. Moreover, anti-angiogenesis and soft tissue toxicity might be bisphosphonate properties of especial importance for the development of ONJ; differences in mineral binding affinities among bisphosphonates influence their differential distribution within bone, their biological potency and their duration of action and inhibitory effects on osteoclasts [3]. Interestingly, alendronate has greater bone affinity, a greater effect on bone turnover and greater anti-angiogenic effects compared with other oral bisphosphonates [3, 7].

Strengths of our study include the nationwide collection of data and validation of the reported outcomes. However, our study is limited by its observational design and we cannot rule out the possibility of differential reporting of adverse events for different bisphosphonates. Only a minority of all atypical fractures of the femur are reported as adverse events [8], even though the number of reports tended to increase during our observation period. Nevertheless, based on case series results, a higher risk of ONJ and AFFs with alendronate use compared with other bisphosphonates has been suggested. This hypothesis is strengthened by our results, but before a causal interpretation can be established, the findings need confirmation in studies using other designs and within other settings.

**Rheumatology key message**

- Compared with other oral bisphosphonates, alendronate use confers a doubled risk of major adverse skeletal events.

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