Review Article

Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG

Peyman Hadji,⁎,1,2,4 Matti S. Aapro,7 Jean-Jacques Body,1,2 Michael Gnant,4, Maria Luisa Brandi,1,2,4,5 Jean Yves Reginster,5, M. Carola Zilliken,8,3 Claus-C. Glüer,1,3, Tobie de Villiers,1,6, Rod Baber,6 G. David Roodman,1,2, Cyrus Cooper,1,1 Bente Langdahl,3, Santiago Palacios,1,6, John Kanis,1,3, Nasser Al-Daghri,5, Xavier Nogues,1,5, Erik Fink Eriksen,3, Andreas Kurth,1,4, Rene Rizzoli,1,1,5, Robert E. Coleman,1,2,4

⁎Correspondence to: Prof. Dr. med. P. Hadji, Philipps-University of Marburg Krankenhaus Nordwest Dept. of Bone Oncology, Endocrinology and Reproductive Medicine, Steinbacher Hohl Frankfurt, Germany.

1 IOF: International Osteoporosis Foundation
2 CABS: Cancer and Bone Society.
3 ECTS: European Calcified Tissue Society.
4 IEG: International Expert Group for AIBL.
5 ESCEO: European Society for Clinical and Economics Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases.
6 IMS: International Menopause Society.
7 SIOG: International Society for Geriatric Oncology.

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ABSTRACT

Background: Several guidelines have been reported for bone-directed treatment in women with early breast cancer (EBC) for averting fractures, particularly during aromatase inhibitor (AI) therapy. Recently, a number of studies on additional fracture related risk factors, new treatment options as well as real world studies demonstrating a much higher fracture rate than suggested by randomized clinical controlled trials (RCTs). Therefore, this updated algorithm was developed to better assess fracture risk and direct treatment as a position...
Bisphosphonate
Denosumab

1. Introduction

Breast cancer is the most frequent cancer in women leading to a significant morbidity and mortality [1]. Early diagnosis and improved treatment regimens have significantly increased survival leading to a greater potential for experiencing long term side effects from cancer treatments including bone loss and fractures. Skeletal homeostasis is achieved through coupled and balanced bone resorption and bone formation. Several local and systemic factors regulate these processes, including estrogen, a key regulator of bone resorption. Physiologic decreases in estrogen levels after menopause lead to an increased risk for osteoporosis (low bone mineral density [BMD]) and fractures, and this risk can be exacerbated by breast cancer and its therapies [2]. Systemic therapies for breast cancer can additionally interfere with bone turnover, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization into estrogen [2-4]. In addition, some therapies for breast cancer might directly affect bone formation [5]. Regardless of the underlying mechanism, patients with breast cancer are at risk for cancer treatment-induced bone loss (CTIBL).

The majority of breast malignancies are hormone responsive, and adjuvant endocrine therapy is used routinely to prevent breast cancer recurrence and death [6,7]. Tamoxifen was the past treatment of choice for endocrine-responsive postmenopausal breast cancer and was found to preserve BMD in postmenopausal (but not premenopausal) women [8], and fracture risks remained similar in postmenopausal tamoxifen users and non-users [9]. However, aromatase inhibitors (AI) have now replaced tamoxifen as the treatment of choice for hormone-responsive breast cancer in most postmenopausal women because of both better efficacy and fewer serious side effects such as induction of uterine cancers and thromboembolic events [6,7,10,11]. However, because AIs prevent peripheral estrogen production, they suppress estrogen levels beyond that attained from a natural menopause, thereby leading to accelerated bone loss and an increased fracture risk [12-15].

Besides a reduction in quality of life, increased morbidity and treatment induced fractures lead to an increase in the health economic burden. A recent study reported that compared to the general population, breast cancer patients had fracture incidence rate ratios of 1.25 (95% CI: 1.23–1.28) and 1.18 (95% CI: 1.14–1.22) for hospitalization due to any bone fracture and hip fracture, respectively. These ratios remained significantly increased for 10 years. Women taking aromatase inhibitors were at an increased risk of fracture as compared with women taking tamoxifen (HR 1.48; 95% CI: 0.98–2.22). Additionally, breast cancer patients hospitalized for a bone fracture showed a higher risk of death (HR 1.83; 95% CI: 1.50–2.22) compared with those without bone fracture [16].

1.1. What is the size of the problem?

AI-associated bone loss (AIBL) leads to a marked increase of bone resorption, with a 2–4 fold increased bone loss compared to physiologic postmenopausal BMD loss. As a result, women receiving adjuvant AI therapy for breast cancer are at increased risk for fractures [25–28], which leads to increased morbidity and mortality [29]. Randomized controlled trials (RCTs) including an AI for 5 years suggested an increased absolute fracture risk of around 10% indicating that one out of ten women will eventually fracture [25–28]. However, these studies had stringent inclusion and exclusion criteria that may not reflect fracture risk in the unscreened population seen in routine clinical practice. The real-world fracture risk has been investigated in a number of case-control studies, prescription based analysis as well as single center studies and even in a recent RCT. In the latter, the fracture incidence in women with BC on an AI was reported to be around 18–20% after 5 years follow-up indicating that in clinical practice, about one in five women will sustain an AI related fracture [30–38]. After termination of AI treatment, bone turnover normalizes, BMD and fracture risk can partially recover [25–28]. Recently, conflicting evidence on the increased duration of AI treatment for up to 10 years has been reported [39–42]. For those advocating an increased duration of AI treatment for up to 10 years, a further increased fracture risk, adding to the 2–3% per annum has to be taken into account.

1.2. How to assess osteoporosis related fracture risk

In 1993, the first operational definition of osteoporosis was based on a decreased in BMD eg. a T-score at the femur neck of < −2.5 [43,44]. In the past years, we have accumulated an expanded understanding of fracture risk factors other than BMD [5,45], resulting in several national and international bone health guidelines being updated to provide more comprehensive insights into fracture risk assessment and clinical decision making regarding antiresorptive therapy (Table 1) [5,6,11,46–53]. A key advance in this field has been the development of the FRAX algorithm developed by the former WHO Collaborating Center at Sheffield, UK (http://www.sheffield.ac.uk/FRAX/), an easy-to-use online tool for assessing fracture risk in postmenopausal women with or without BMD data. The FRAX algorithm is based on data from large-scale, population-based cohorts from different parts of the world, and uses factors such as age, body mass index (BMI), smoking history,
Table 1
Summary of guidelines for antiresorptive use in women with breast cancer.\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Source</th>
<th>Whom to treat</th>
<th>Antiresorptive</th>
<th>Dose</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO [5]</td>
<td>All women receiving AI therapy with ( \geq 1 ) of the following T-score ( \leq -2.0 ). Any 2 of the following risk factors T-score ( &lt; -1.5 ), age ( &gt; 65 ) yr, low BMI (&lt; 20 kg/m(^2)), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use ( &gt; 6 ) mo, and smoking</td>
<td>Zoledronate</td>
<td>4 mg IV q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td>SIOG [5]</td>
<td></td>
<td>Denosumab</td>
<td>60 mg SC q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td>ASCO [48]</td>
<td>Women with T-score ( \leq -2.5 )</td>
<td>Aledronate</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>St. Gallen [6]</td>
<td>Women with T-score between ( -1.0 ) and ( -2.5 ) should receive individualized therapy</td>
<td>Risedronate</td>
<td>70 mg/wk</td>
<td>Follow-up at 2 yr to re-assess</td>
</tr>
<tr>
<td>UK Expert Group [49]</td>
<td>Al therapy and T-score ( &lt; -1.0 )</td>
<td>Denosumab</td>
<td>35 mg/wk</td>
<td>Follow-up at 2 yr to re-assess</td>
</tr>
<tr>
<td></td>
<td>T-score ( &lt; -2.0 )</td>
<td></td>
<td>150 mg PO/mo or</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3 mg IV q 3 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual bone loss &gt; 4% at LS or TH</td>
<td>Zoledronate</td>
<td>4 mg IV q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Follow-up at 2 yr to re-assess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal women receiving AI therapy with ( \geq 1 ) of the following T-score ( &lt; -2.0 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual bone loss &gt; 4% at LS or TH</td>
<td>Zoledronate Other BPs may be considered</td>
<td>4 mg IV q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td>Belgian Bone Club [47]</td>
<td>Women with T-score ( &lt; -2.5 ) or history of fragility fracture</td>
<td>Zoledronate</td>
<td>4 mg IV q6mo</td>
<td>At least 2 yr, possibly as long as AI therapy</td>
</tr>
<tr>
<td>International Expert Group (Hadjii et al.) [51]</td>
<td>Women with T-score between (-1.0) and (-2.5) plus other risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low BMI (&lt; 20 kg/m(^2)), family history of hip fracture, personal history of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fragility fracture after age 50, oral corticosteroid use &gt; 6 mo, and smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Expert Panel (Aapro et al.) [46]</td>
<td>Women with ( \geq 2 ) of the following risk factors: AI use, T-score ( &lt; -1.5 ), age ( &gt; 65 ) yr, corticosteroid use ( &gt; 6 ) mo, family history of hip fracture, personal history of fragility fracture after age 50, T-score ( \leq -2.0 )</td>
<td>Zoledronate</td>
<td>4 mg IV q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Denosumab</td>
<td>60 mg SC q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td>ESCEO position paper (Rizzoli et al.) [50]</td>
<td>All women receiving AI therapy with (T-score hip/spine ( &lt; -2.5 ) or ( \geq 1 ) prevalent fragility fracture), to women aged ( \geq 75 ) irrespective of BMD, and to patients with T-score ( &lt; -1.5 ) \geq 2 clinical risk factors or FRAX-determined 10-year hip fracture probability ( \geq 3% )</td>
<td>Denosumab s.c., or possibly oral BP</td>
<td>4 mg IV q6mo</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; GnRH, gonadotropin-releasing hormone; IV, intravenous; LS, lumbar spine; mo, month; NCCN, National Comprehensive Cancer Network; PO, oral; q, every; TH, total hip; UK, United Kingdom; wk, week; yr, year.

\( a \) Limited evidence for the use of other agents was available when these guidelines were written.

\( b \) Calcium and vitamin D supplements are to be used in conjunction with BPs, and exercise when appropriate is recommended by most panels.

Personal and family history of fracture, smoking, glucocorticoid use, and secondary causes of osteoporosis, to assess long-term fracture effect. However, FRAX is not designed to assess fracture risk in women with breast cancer, and indeed may substantially underestimate the effect of AI therapy—the "secondary osteoporosis" option in the FRAX tool has a much smaller effect on fracture risk than would be expected for AI therapy. Moreover, as clinical trials comparing AIs with tamoxifen mature, it is evident that AIs have a large effect on acute fracture risk during active treatment \[26,27\], which might be underestimated by FRAX, an algorithm designed to provide long-term (10-year) fracture risk. As it appears that the independent fracture risk in AIBL is equivalent to that seen in RA, it has recently been suggested to use the bypass of rheumatoid arthritis in FRAX as it has been proposed in type 2 diabetes \[54\].

With regard to AIBL, a retrospective, case-controlled study in 402 postmenopausal women with newly diagnosed breast cancer demonstrated that using a combination of BMD and clinical risk factors identified more than 28% of these women as candidates for bone-directed therapy, compared with less than 10% identified by BMD criteria alone \[55\]. Additionally, Neuner et al. \[56\] reported that age and BMI were particularly associated with an increased hip fracture risk in women with breast cancer.

1.3. Additional anticancer benefits of adjuvant bisphosphonates

In past years, a large number of clinical trials investigating the use of antiresorptive agents, such as bisphosphonates and denosumab (a monoclonal antibody against the receptor activator of nuclear factor kappa B ligand [RANKL]), for the prevention and/or treatment of AIBL have been reported.

Population-based case-control studies suggest that oral bisphosphonate treatment for postmenopausal osteoporosis may reduce the incidence of invasive breast cancers \[57–59\]. Moreover, phase II studies have demonstrated direct anticancer effects of zoledronate on disseminated tumor cells in the bone marrow of patients with early breast cancer \[60–63\], and subset analyses from ongoing trials show that the addition of zoledronate to neo-adjuvant chemotherapy can reduce residual tumor size and improve pathologic response rates compared with chemotherapy alone \[64\].

Early trials of adjuvant bisphosphonates for the prevention of bone metastases in early breast cancer were promising but inconclusive \[65–68\]. This was due to the broad inclusion criteria for many of the trials; it is now clear that adjuvant bisphosphonates have no effects on breast cancer recurrence or mortality in premenopausal women with all the benefits restricted to women who are either postmenopausal or have had a menopause induced postoperatively with goserelin \[69,70\].

Recently, Coleman et al. confirmed the anticancer effect of bisphosphonates in a meta-analysis conducted by the Early Breast Cancer Clinical Trials Group (EBCTCG), decreasing the incidence of bone recurrence by 34% and breast cancer specific mortality by 17% \[71\]. Additionally, an expert panel of oncologists and bone experts has published a consensus statement for the use of adjuvant bisphospho-
nates in women with BC [72]. In light of these developments, we have updated our recommendations for the prevention and treatment of AIBL in postmenopausal women with early breast cancer [5].

2. Methods

2.1. Systematic literature review

With regard to clinical prognostic risk factors for fracture in breast cancer patients, we used a recent systematic review [5]. For prevention and treatment of AIBL, we undertook PubMed® searches of MEDLINE® (National Library of Medicine, Bethesda, MD) and other databases were performed to identify clinical trials of antiresorptive agents used for the prevention and treatment of AIBL from Jul 2010 through April 2016. In addition, the Cochrane Register of Controlled Trials and databases of ongoing and unpublished trials http://www.clinicaltrials.gov were searched. Additional information was obtained from abstracts presented at international meetings including the St. Gallen Breast Cancer Conference, European Breast Cancer Conference (EBCC), San Antonio Breast Cancer Symposium (SABCS), and ASCO annual meetings and breast cancer symposia (Table 2).

An evidence-based medicine approach was used to determine when to initiate antiresorptive therapy for AIBL, to determine the appropriate antiresorptive therapy, and to define follow-up/monitoring procedures. All reports were reviewed and the available data assessed for the level of evidence used to guide treatment recommendations (Table 3).

3. Identification of fracture risk in women with breast cancer

Several additional clinical risk factors have been validated in large, prospective, population-based studies in postmenopausal women and were previously characterized according to their impact on overall fracture risk independently of both age and BMD (Evidence level IA) [5]. Risk factors found to increase fracture risk in women with breast cancer in addition to AI therapy included, T-score < −1.5, age > 65 years, low BMI (< 20 kg/m²), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use > 6 months, rheumatoid arthritis, and smoking [73–79] (Evidence level IA). Additionally, a recent study suggests that cancer associated muscle weakness leads to increased immobility with an increased risk for osteoporosis and fracture [80]. Recent data suggest that BMD measurement alone should not be the sole criterion for determining fracture risk, and that an overall fracture risk assessment that combines risk factors provides a more accurate evaluation. It is also important to note that the use of corticosteroids at a dose of > 2.5 mg prednisolone (or equivalent) daily for more than 3 months is an established risk factor based on data from non-malignant disease settings. When combined with chemotherapy regimens, the doses of oral corticosteroids are typically higher, and might negatively impact bone health over a shorter period of time. Finally, in order to identify and manage secondary causes of osteoporosis, complete baseline laboratory assessments should include serum levels of calcium, phosphate, 25-OH vitamin D, C-reactive protein, alkaline phosphatase, thyroid-stimulating hormone, and gamma-glutamyl transpeptidase; complete blood count; creatinine clearance; and protein electrophoresis (serum and/or urine).

4. Selecting a treatment to prevent AIBL

Available data from randomized clinical trials in more than 6000 patients suggest that denosumab, intravenous and oral bisphosphonates can effectively prevent AIBL in patients with breast cancer (Table 2)

<table>
<thead>
<tr>
<th>Antiresorptive agent (Trial)</th>
<th>N</th>
<th>BMD data, n¹</th>
<th>Dose</th>
<th>Treatment duration</th>
<th>Follow-up, months</th>
<th>Mean BMD increase from baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronate (ZO-FAST) [69]</td>
<td>1,065</td>
<td>1,065</td>
<td>4 mg q6mo</td>
<td>5 yr</td>
<td>36b</td>
<td>4.39</td>
</tr>
<tr>
<td>Zoledronate (Z-Fast) [81]</td>
<td>602</td>
<td>602</td>
<td>4 mg q6mo</td>
<td>5 yr</td>
<td>61</td>
<td>6.19</td>
</tr>
<tr>
<td>Zoledronate (N03CC) [82]</td>
<td>558</td>
<td>395</td>
<td>4 mg q6mo</td>
<td>5 yr</td>
<td>24</td>
<td>4.94</td>
</tr>
<tr>
<td>Zoledronate (E-ZO-Fast) [83]</td>
<td>527</td>
<td>527</td>
<td>4 mg q6mo</td>
<td>5 yr</td>
<td>36</td>
<td>5.98</td>
</tr>
<tr>
<td>Denosumab (IBIS II) [88]</td>
<td>252</td>
<td>252</td>
<td>60 mg q6mo</td>
<td>2 yr</td>
<td>24</td>
<td>6.2c</td>
</tr>
<tr>
<td>Denosumab (ABCSG-18) [92,93]</td>
<td>3420</td>
<td>3420</td>
<td>60 mg q6mo</td>
<td>3 yr</td>
<td>36</td>
<td>10.2</td>
</tr>
<tr>
<td>Risedronate (SABRE) [85]</td>
<td>154</td>
<td>111</td>
<td>35 mg/wk</td>
<td>2 yr</td>
<td>24</td>
<td>2.2c</td>
</tr>
<tr>
<td>Risedronate [86]</td>
<td>87</td>
<td>87</td>
<td>35 mg/wk</td>
<td>2 yr</td>
<td>24</td>
<td>0.4c</td>
</tr>
<tr>
<td>Clodronate [87]</td>
<td>61</td>
<td>61</td>
<td>1,600 mg/day</td>
<td>3 yr</td>
<td>60</td>
<td>-1.0c</td>
</tr>
<tr>
<td>Risedronate (IBIS II-Stratum II) [88]</td>
<td>260</td>
<td>150</td>
<td>35 mg/wk</td>
<td>3 yr</td>
<td>36</td>
<td>1.1c</td>
</tr>
<tr>
<td>Risedronate (IBS II) [106]</td>
<td>213</td>
<td>132</td>
<td>35 mg/wk</td>
<td>2 yr</td>
<td>24</td>
<td>1.1%c</td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; AIBL, aromatase inhibitor-associated bone loss; BMD, bone mineral density; LS, lumbar spine; mo, months; NR, not reported; TH, total hip; yr, years.

¹ Number of patients randomized to bisphosphonate vs placebo and evaluable for BMD at the reported timepoint;
² BMD data available for 36 months’ follow-up; disease recurrence outcomes available for 48 months’ follow-up.
³ Estimates based on published graph.
The data supporting IV bisphosphonate therapy to prevent AIBL in postmenopausal women with early breast cancer comes predominantly from 4 independent studies with a total of more than 2700 postmenopausal women with early breast cancer (Table 2) [69,81–83]. The 3 companion Zometa®-Femara® Adjuvant Synergy Trials (Z-FAST, N=602; ZO-FAST, N=1065; E-ZO-FAST, N=527) compare the efficacy of zoledronate (4 mg IV q6mo) given in conjunction with AI therapy (immediate group), or after a BMD decrease to a T-score < −2.0 at any side or a non-traumatic fracture (delayed group) [81,83]. The final 61-month update from Z-FAST showed that delaying zoledronate resulted in losses in BMD at lumbar spine (LS) and total hip (TH) (−2.42% and −4.12%, respectively; P≤0.0003 for both vs. baseline) [101]. However, patients who immediately initiated zoledronate continued to gain BMD at the lumbar spine (LS) and total hip (TH) (6.19% and 2.57%, respectively; P≤0.0003 for both vs. baseline). Similar results for the 60-month analyses of the ZO-FAST studies confirmed that immediate zoledronate not only prevented bone loss, but patients continued to gain BMD during the 5 years of therapy (Table 2) [69,83,102]. Women receiving immediate zoledronate gained BMD at LS and TH (4.39% and 1.6%, respectively; P < 0.0001 vs. delayed group for both), versus BMD losses at both sites in the delayed zoledronate group (−5.4% and −4.2%, respectively; P < 0.0001 vs. baseline for both). Similar BMD gains and losses were observed in E-ZO-FAST at 36 months’ follow-up [83].

Another trial examined the efficacy of zoledronate (4 mg IV q6mo) for preventing AIBL in postmenopausal women with endocrine-responsive breast cancer who started adjuvant letrozole after completing ≤6 years of tamoxifen treatment [82]. Similar to the BMD increases seen in the Z-FAST, ZO-FAST, and E-ZO-FAST studies, women in the N03CC (ALLIANCE) trial who received immediate zoledronate had significantly increased mean BMD at LS (3.66% at 12 months and 4.94% at 24 months) and TH (1.02% at 12 months and 1.22% at 24 months) compared with baseline (P < 0.001 for all comparisons) [82]. At the 12- and 24-month post-baseline assessments, women in the delayed zoledronate group lost BMD at the LS (−1.66% and −2.28%, respectively) and TH (−1.41% and −3.34%, respectively).

None of these studies (Z-FAST, ZO-FAST, and E-ZO-FAST and N03CC Study) were designed to show a significant difference in fracture incidence between the treatment arms [103]. Despite the absence of fracture data, the BMD data from these 4 well-designed RCTs demonstrates that zoledronate (4 mg q6mo) at initiation of AI therapy can effectively prevent AIBL in postmenopausal women.

Zoledronate given on a 6 monthly schedule appears to be very well tolerated. The most common adverse events are transient infusion-site reactions and mild flu-like symptoms with rare renal adverse events and exceptionally osteonecrosis of the jaw (ONJ). [69,81–83].

### 4.3. Oral bisphosphonates

#### 4.3.1. Level of evidence: II–III

Several randomized clinical trials have investigated the efficacy of oral bisphosphonates for preventing AIBL. (Table 2) [85–90,104,105].
Because of the complex trial designs of some of these studies, the numbers of patients randomized to AI therapy alone versus AI therapy plus bisphosphonate is much smaller than the overall number of patients enrolled. Therefore, the evidence for oral bisphosphonates is less robust compared to IV zoledronate.

The Study of Anastrozole with the Bisphosphonate Risedronate (SABRE) compared the efficacy of risedronate (35 mg/wk oral) versus placebo for 2 years in postmenopausal women with hormone receptor-positive early breast cancer receiving adjuvant anastrozole who also had a moderate risk of fragility fracture \((n=154)\) [85]. At 24 months, oral risedronate significantly increased LS BMD by 2.2% and TH BMD by 1.8% versus baseline \((P < 0.0001\) for each vs. placebo). A similar trial in postmenopausal women with breast cancer receiving AI therapy demonstrated that oral risedronate (35 mg/wk) initially improved BMD versus baseline, but only modestly increased LS BMD (0.4%) and TH BMD (0.9%) at 24 months [86]. Among women enrolled in the International Breast Cancer Intervention Study (IBIS-II) bone substudy \((n=613)\), women with osteopenia \((n =59)\) receiving anastrozole plus risedronate (35 mg/wk) had better LS (0.32%) and TH (0.67%) BMD compared with women receiving anastrozole alone after 36 months of follow up [88]. The 3-year results showed that risedronate could prevent bone loss over the three years at the spine although the treatment was less effective at the hip [106]. These observations are consistent with the outcome of the Arimidex Bone Mass Index Oral Bisphosphonate (ARBI) trial in which 35 mg oral risedronate weekly was added to anastrozole in osteopenic patients which led to a significant increase of lumbar spine BMD over 2 yrs of 6.6% \((n =93)\) [106]. The most recent RCT including risedronate vs. placebo was reported by Greenspan in which, after 24 months of follow up, BMD increased more in the active treatment group compared to placebo with an adjusted difference at 24 months of 3.9% at the spine and 3.2% at the hip \((both \ p < 0.05)\). Additionally, the adjusted differences in bone turnover markers between the active treatment and placebo groups were 0.09 ± 0.04 nmol/LBCE for CTX and 23.3 ± 4.8 μg/mL for P1NP \((both \ p < 0.05)\). Women with greater 12-month decreases in CTX and P1NP in the active treatment group had a greater 24-month increase in spinal BMD \((p < 0.05)\) [107].

In the 60-month analysis of the Arimidex®-Bondronat® (ARIBON) study, monthly oral ibandronate (150 mg) prevented bone loss in osteopenic women \((n =25)\) compared with placebo \((n =25)\) and in a small number of patients with pre-existing osteoporosis \((n =13)\) Oral ibandronate increased LS BMD by 5.01% and TH BMD by 1.19% [89,108].

In the BATMAN study, all 303 postmenopausal women with early breast cancer (EBC) received anastrozole (1 mg daily), calcium and vitamin D weekly [109]. All osteoporotic patients received weekly alendronate (70 mg) while osteopenic patients received alendronate or placebo in accordance to a given algorithm. At three years, lumbar spine mean BMD increased \((15.6\%, \ p < 0.01)\) in the osteoporotic group. BMD in the osteoporotic group with early intervention increased at three years \((6.3\%, \ p =0.02)\). No significant change was seen in the late intervention group. No change was observed in those with osteopenia without alendronate. There was a significant drop in lumbar spine \((-5.4\%)\) and hip \((-4.5\%)\) mean BMD, in the normal BMD group, none of whom received alendronate [110]. A second short term RCT randomly assigned patients to 5 mg of alendronate and 0.5 μg of calcitriol or placebo. After 24-week of treatment, between group differences is lumbar spine BMD was 3.0% \((p < 0.005)\). The increase in C-telopeptide after 24 weeks was significantly less in the treatment group compared with that in the placebo group \((35.2 ± 17.5\% vs. 109.8 ± 28.6\%, \ p < 0.05)\) [109]. In all of the studies of oral bisphosphonates, patients who did not receive a bisphosphonate experienced substantial BMD loss during AI therapy [111].

Oral bisphosphonates were generally well tolerated in these trials. However, the rigid dosing requirements for oral bisphosphonates (fasting before and after dosing, the need to remain upright after dosing, etc) have been associated with some inconvenience for patients (Table 4). Moreover, patients’ compliance and persistence with oral therapies is suboptimal, even with potentially life-saving interventions such as adjuvant endocrine therapy [112,113]. In the case of supportive treatments such as antiresorptives, insights from the osteoporosis setting show very low long-term adherence to treatment [114]. In one study, less than 20% of patients receiving daily bisphosphonate achieved clinically relevant persistence levels over 1 year, compared with approximately 30% of patients receiving weekly bisphosphonate [115]. In this setting, non-persistence has been associated with increased fracture rates (ie, poor clinical outcomes) [116,117]. Trends toward better compliance with less-frequent dose schedules have been reported in multiple studies in women with postmenopausal osteoporosis [118–120]. Because of the strong association between compliance and clinical outcome [119], strategies to improve patients’ compliance and persistence with oral bisphosphonate therapy are necessary to ensure benefit from these agents in the AIBL setting.

### Table 4
Comparison of antiresorptive agents.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Long-term safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bisphosphonates</td>
<td>Oral (self) administration</td>
<td>Limited efficacy data available</td>
<td>Established in the osteoporosis setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need to follow strict dosing guidelines</td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor compliance and persistence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No data for risedronate or alendronate to assess effects on underlying breast cancer</td>
<td></td>
</tr>
<tr>
<td>IV bisphosphonates (Zoledronate)</td>
<td>Efficacy data from large trials with long follow-up</td>
<td>IV administration by healthcare provider</td>
<td>Established in the osteoporosis and AIBL settings</td>
</tr>
<tr>
<td></td>
<td>Can be administered during routine twice-yearly oncologist visits</td>
<td></td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td></td>
<td>Compliance can be ensured</td>
<td></td>
<td>Adverse events are generally mild and manageable</td>
</tr>
<tr>
<td></td>
<td>Can be administered during routine twice-yearly oncologist visits or administration by healthcare provider</td>
<td></td>
<td>Established in the osteoporosis and AIBL settings with anti-fracture efficacy in both</td>
</tr>
<tr>
<td></td>
<td>Compliance can be ensured</td>
<td></td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse events are generally mild and manageable</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Limited efficacy data available</td>
<td>Rebound effect after treatment termination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Costs</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AIBL, aromatase inhibitor-associated bone loss; IV, intravenous; sc, subcutaneous.
5. Treatment and follow-up recommendations for patients receiving aromatase inhibitors

5.1. Fracture prevention

5.1.1. Level of evidence: I

5.1.1.1. Grade of recommendation: A. Our guidance for antiresorptive therapy to treat or prevent AIBL in women with early breast cancer is derived from well-designed randomized controlled studies, and is based on validated risk factors with or without BMD measurements (Evidence level 1A) (Fig. 1). All patients beginning AI therapy should be advised to exercise moderately (resistance and weight-bearing exercise). Whereas weight-bearing exercise has beneficial effects on BMD [121] (Evidence level 1A), fracture risk reduction has not been demonstrated [122,123] (Evidence level 1A). With regard to calcium and vitamin D, the International Osteoporosis Foundation recommends a daily intake of 1200 mg calcium and 800–1000 IU vitamin D for postmenopausal women (guidelines available at www.iofbonehealth.org). Elderly women, or those with reduced physical activity and sunlight exposure, may need higher levels of these nutrients. For these high-risk for fracture individuals, the measurement of 25-OH Vitamin D levels is recommended and high dose vitamin D supplementation given if deficient [124]. For other postmenopausal women receiving AI therapy, a dose of at least 800 (and up to 2000) IU of vitamin D every day is recommended to maintain replete levels. It is important to note, that a recent meta-analysis has underlined that the use of Vitamin D+/-calcium supplementation alone has been shown to be ineffective for fracture risk prevention in women with breast cancer (Evidence level 1 A) [125].

For patients initiating an AI treatment not receiving bisphosphate for recurrence prevention, a BMD measurement is advised. Patients with a T-score ≥ −2.0 and no other fracture risk factor, BMD and risk status should be reassessed after 12 months. If no adjuvant antiresorptive therapy is initiated an annual BMD decrease of ≥5–10% should trigger investigation for secondary causes of bone loss such as vitamin D deficiency etc. and an antiresorptive treatment for fracture prevention initiated. All patients initiating or receiving AI therapy with any 2 of the following risk factors should receive antiresorptive therapy: T-score < −1.5, age ≥ 65 years, low BMI (< 20 kg/m²), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use of > 6 months, and current or history of smoking. Any patient initiating or receiving AI therapy with a T-score < −2.0 should receive antiresorptive therapy irrespective of the presence of other risk factors. Based on current evidence, subcutaneous denosumab (60 mg twice yearly) and intravenous zoledronate (4 mg q6mo) are the preferred agents for prevention and treatment of AIBL. The advantages and limitations of the different antiresorptive therapies investigated in the AIBL setting are summarized in Table 4.

For oral bisphosphonates, 35 mg risedronate/week is the bisphosphonate with the strongest evidence for prevention of AIBL. In all patients receiving oral bisphosphonate therapy, BMD should be monitored and compliance assessed every 1–2 years. Periodic assessment of bone resorption markers may offer a convenient, noninvasive measure of compliance with therapy [5,126]. In case of poor compliance or unsatisfactory BMD changes after 1–2 years, a switch to denosumab or intravenous bisphosphonate is recommended. For patients receiving denosumab, intravenous bisphosphonates or other agents, BMD monitoring during therapy should be performed on an individualized basis and in accordance to local guidelines.

Patients receiving AIs are at elevated risk for fracture for at least the duration of AI treatment [26]. As a result, we recommend continuing antiresorptive therapy for as long as the patient is receiving an AI (up to 5–10 years). Currently, denosumab and zoledronate are the only antiresorptive agent with proven efficacy and safety in large prospective RCTs over a long duration [81,101]. Consequently, side-effect profiles and management should be taken into account when selecting an antiresorptive agent to prevent or treat AIBL.

5.2. Disease recurrence prevention – adjuvant bisphosphonate

5.2.1. Level of evidence: I

5.2.1.1. Grade of recommendation: A. Important evidence was provided by the recent Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of data of > 18,000 patients from postmenopausal breast cancer patients showing that adjuvant bisphosphonates (i.e. zoledronate, oral clodronate and oral ibandronate) reduce recurrences in bone and prolong survival in postmenopausal women [71]. Overall, despite a reduction in bone metastases, BPs had no significant effect on breast cancer recurrence (rate ratio 0.94) and the effect on breast cancer mortality, though significant, was small (RR = 0.91). However, in postmenopausal women or those receiving ovarian suppression with goserelin, clinically

![Fig. 1. Recommended algorithm for managing bone health in women receiving aromatase inhibitor (AI) therapy for breast cancer.](image-url)
Important benefits were seen with improvements in overall breast cancer recurrence (RR = 0.86), distant recurrence at any site (RR = 0.82), bone recurrence (RR = 0.72) and breast cancer-specific mortality (RR = 0.82) (Fig. 2) (Evidence level 1A) [71]. In spite of the outstanding evidence and its magnitude it must be noted that bisphosphonates do not currently have regulatory approval for the prevention of breast cancer recurrence which currently limits the ability to prescribe these agents unless the patient fulfills the AIBL criteria for intervention.

Recently, an international expert panel of oncologists and bone experts has published a consensus statement recommending the routine use of adjuvant bisphosphonates in women with BC at intermediate or significant risk for disease recurrence due to adverse clinical or biological characteristics such as node positive disease, a T2 or above, grade II/III breast tumor or disease found to be ER negative or HER-2 positive (Fig. 3) [72]. This include where available, that women with breast cancer may be recommended to receive bisphosphonates irrespective of fracture risk. In this setting, BMD monitoring may not be necessary.

5.3. Disease recurrence prevention – denosumab

5.3.1. Level of evidence: III

5.3.1.1. Grade of recommendation: C. Early disease free survival (DFS) results from the ABCSG-18 study suggest a benefit on disease recurrence with an absolute decrease in events of 2.1% at five years compared to placebo. Hereby, disease free survival was significantly reduced in patients on denosumab vs. placebo HR 0.87 (CI 0.66–0.99; p < 0.041) in the sensitivity analysis but not in the ITT (HR 0.816, CI 0.66–1.00; p < 0.051) analysis [72]. The follow-up was too short to see effects on mortality. Further reports as of the s-CARE study results are anticipated in the next 12–18 months and will help to define the role of denosumab as a disease modifying agent.
6. Conclusions and future directions

It is evident that, in addition to BMD, clinical risk factors can greatly influence fracture risk. In addition to morbidity and mortality, fractures are associated with high healthcare costs and increased healthcare utilization for several months after fracture incidence [127–129]. In the European Union the economic burden of incident and prior fragility fractures was estimated at €37 billion in 2010. Acute hip fracture costs in Europe were €13,800 but varied widely from approximately £2000 in Bulgaria to about £25,000 in Denmark [130]. Additionally, vertebral and especially hip fractures are likely to result in prolonged disability and loss of independence, thereby leading to increased indirect costs. Improvements in assessing fracture risk can help identify patients who need pharmacologic intervention to improve bone health, thereby reducing fracture incidence. We have presented an evidence-based algorithm for assessing bone health in women with breast cancer and initiating antiresorptive therapy in postmenopausal women initiating AI therapy for early stage breast cancer as well as in other postmenopausal women not being considered for an AI treatment and in those receiving ovarian suppression therapies. Based on current evidence, six-monthly denosumab or zoledronate for the duration of AI therapy is recommended for the prevention of AIBL in postmenopausal women receiving adjuvant AI therapy with zoledronate recommended when effects on disease recurrence are the priority and denosumab when fracture risk is the dominant concern. Long-term efficacy and safety data for other agents continue to mature, and should be taken into consideration as they become available.

In addition to the established risk factors used in our bone health algorithm, other potential fracture risk factors in women with breast cancer include chemotherapy, radiotherapy, low weight, and family history of hip fractures. Further studies examining the role of these factors are warranted. Furthermore, periodic (annual) assessment of breast cancer patients with these potential risk factors may be prudent.

Overall, data from the AIBL setting as well as long-term use in the treatment of postmenopausal osteoporosis indicate that denosumab and bisphosphonates are safe and effective agents for preserving bone health during adjuvant endocrine therapy for breast cancer. In addition, emerging anticancer benefits from bisphosphonates provide additional reasons to proactively use these agents during adjuvant AI treatment. Ongoing trials and the recent Oxford-meta analysis underlined the potential of oral and intravenous bisphosphonates and perhaps of denosumab to prevent breast cancer bone recurrence and to increase breast cancer survival. Therefore, the role of antiresorptive agents in early breast cancer has significantly been extended.

Conflicts of interest

Dr. Hadji has received honoraria, unrestricted educational grants, and research funding from the following companies: Amgen, AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer and Roche.

Dr. Aapro has conducted studies and is a consultant on bone-modifying agents for Amgen, Bayer-Schering, Novartis, and Roche.

Dr. Body has received consultancy and speaker fees from Amgen.

Dr. Grant has received institutional research support from AstraZeneca, Roche, Novartis, and Pfizer, and has received lecture fees and honoraria for participation on advisory boards from Roche, AstraZeneca, Celgene, Novartis, OBI-Pharma, and Amgen. He has served as a consultant for Accelerons, and an immediate family member is employed by Sandoz.

Dr. Brandi served as consultant and has received grants recipient from Alexion, Abiogen, Amgen, Eli Lilly and Shire.

Dr. Reginster received consulting fees or paid advisory boards: SERVIER, IBSA-GENEVRIER, UCB, ASAHI, RADIUS HEALTH, MEDA, PIERRE FABRE. Lecture fees when speaking at the invitation of sponsor: MERCK SHARP AND DOHME, IBSA-GENEVRIER, SERVIER, DANONE, PHARMEVO, CNIEL, MEDA, DAIRY RESEARCH COUNCIL (DRC). Grant Support from Industry (All through Institution): MERCK SHARP & DOHME, AMGEN, LILLY, SERVIER, PFIZER, DANONE, MEDA, CNIEL, IBSA-GENEVRIER.

Dr. De Villiers has received honoraria, unrestricted educational grants or served as a speaker for: Adcock Ingram, Abbott, Amgen, Aspen, Bayer, MSD, Novartis and Pfizer.

Dr. Nasser AI-Daghibi has no conflict of interest.

Dr. Baber has received honoraria and consultancy fees from Pfizer, Abbott and Besins.

Dr. Kanis reports grants from Amgen, grants from Lilly, non-financial support from Medimaps, grants from Unigene, non-financial support from Asahi, grants from Radius Health, other from AgNovos, outside the submitted work; and Dr. Kanis is the architect of FRAX but has no financial interest.

Dr. Zillikens has received fees for lectures and participation in advisory boards from Amgen, Eli Lilly and MSD.

Dr. Glier on the speaker bureau for Amgen and received honoraria for lectures.

Dr. Langdahl has received fees for lectures and participation in advisory boards from Amgen, Merck, UCB, and Eli Lilly and research funding to her institution from Eli Lilly, Novo Nordisk and Amgen.

Dr. Roodman has received research funding to his institution from Novartis and Amgen.

Dr Eriksen has received fees for speaker engagement and consultancy from Eli Lilly, Novartis, Merck, Amgen, IDS and EffRx.

Dr. Nogues has received consultancy fees and speaker fees from Lilly, and Amgen.

Dr. Palacios has received honoraria or consultation fees: Pfizer, Servier, Amgen, MSD, Preglem, Gynea, Sandoz, Procare Health, Bayer, MSD, Serelys and Shionogi and participated in company sponsored speaker’s bureau of Servier, Pfizer, GSK, Abbott, Ferrer, Bioiberica, Shionogi, Amgen, Novo Nordisk, Teva, Bayer Healthcare, Serelys and Gedeon Richter.

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All other authors have no conflict of interest to declare.

References


