Aromatase Inhibitor Induced Bone Loss in Postmenopausal Women with Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials and Critical Appraisal of Guidelines.

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Review question

Randomized controlled trials:
-What is the effect of anti-resorptive therapy (bisphosphonates and denosumab) on bone mineral density (BMD) in postmenopausal women with non-metastatic breast cancer on aromatase inhibitors?
-What is the effect of anti-resorptive therapy (bisphosphonates and denosumab) on fragility fracture incidence in postmenopausal women with non-metastatic breast cancer on aromatase inhibitors?

-What is the effect of anti-resorptive therapy (bisphosphonates and denosumab) on bone turnover markers in postmenopausal women with non-metastatic breast cancer on aromatase inhibitors?

Guidelines:

-What screening tools are recommended in present day guidelines to detect aromatase inhibitors induced bone loss in postmenopausal women with non-metastatic breast cancer?

-What are the recommendations on diet, exercise and pharmacologic interventions to prevent aromatase inhibitors induced bone loss in postmenopausal women with non-metastatic breast cancer?

-What population of postmenopausal women on aromatase inhibitors are candidates for pharmacological intervention for the management of aromatase inhibitors induced bone loss?

-What are the treatment options for aromatase inhibitors induced bone loss in postmenopausal women with non-metastatic breast cancer?

-What is the quality of available guidelines and the strength of recommendations provided by guidelines on the assessment, prevention and management of aromatase inhibitors induced bone loss?

Searches

We searched MEDLINE, PubMed, Embase databases, and the Cochrane Library, using MeSH terms and keywords relevant to aromatase inhibitors, bone loss, anti-resorptive agents (bisphosphonates and denosumab), osteoporotic fractures and breast cancer without language or time restrictions from Jan 1, 2005 for randomized controlled trials (RCTs) and Jan 1, 2009 for guidelines, both until December 6, 2019.

Types of study to be included

Inclusion:
1- Randomized controlled trials:

-Duration of at least one year

-Since most major trials were concluded after 2005, we only include trials published after 2005

2- Guidelines, position statements, expert panel opinions

-Since most guidelines were developed or updated after 2009, we only include guidelines published after 2009

Exclusion:

1- Reviews, observational studies, cohorts, systematic reviews

2- Previous versions of a guideline on the topic by the same organization (for example: inclusion of NCCN 2013 guideline and exclusion of NCCN 2009 guideline)

Condition or domain being studied

Breast cancer is the most common cancer in women with substantial morbidity and mortality (Hadji 2017). The majority of breast cancers are hormone responsive, resulting in the use of adjuvant endocrine therapy, such as gonadotropin releasing hormone agonists, aromatase inhibitors and anti-androgens, as part of estrogen suppressive therapy (Hadji 2017). Aromatase inhibitors increase bone turnover and osteoclast activity, leading to a 2 to 4 folds greater bone loss, compared to post-menopausal women not on aromatase inhibitors (Hadji 2017), therefore incurring an increased fracture risk. Similarly, in the Arimidex, Tamoxifen Alone or in Combination (ATAC) study, which compared anastrozole, tamoxifen, and the combination of both, found that patients on anastrozole alone had a 33% higher fracture rate compared to tamoxifen, after 5 years of treatment (Cuzick 2010). Furthermore, the Breast International Group (BIG) 1-98 trial showed that the incidence of bone fractures was significantly higher in patients treated with letrozole (9.3%) compared to those on tamoxifen (6.5%) (Rabaglio 2009).

Participants/population

Inclusion criteria:
- Postmenopausal women (natural, chemical or surgical menopause)

- Non-metastatic breast cancer (Ductal Carcinoma in Situ or invasive)

- Treated with aromatase inhibitor therapy

Exclusion Criteria:

- Patients at high risk of developing breast cancer

Intervention(s), exposure(s)

Oral bisphosphonate (alendronate, clodronate, ibandronate, or risedronate), intravenous bisphosphonate (pamidronate or zoledronic acid) or denosumab

Comparator(s)/control

Placebo, or control or another anti-resorptive drug, or delayed treatment (after occurrence of either a fracture or significant BMD loss following treatment with aromatase inhibitors)

Main outcome(s)

Randomized Controlled trials:

-Effect of anti-resorptive therapy (bisphosphonates and denosumab) on BMD at the Lumbar Spine and Hip, at 12 months in postmenopausal women with non-metastatic breast cancer on aromatase inhibitors. (Mean percentage change in BMD)

Our analysis of the above-mentioned outcomes will be conducted for 3 comparisons: oral bisphosphonates vs. control or placebo, IV bisphosphonates vs. control or placebo and denosumab vs. control or placebo.

Guidelines:

- Quality of available guidelines through Appraisal of Guidelines for Research and Evaluation II (AGREE II instrument) scores for each guideline and strength of recommendations and level of evidence provided by guidelines on the assessment, prevention and management of aromatase inhibitors induced bone loss

* Measures of effect

For continuous data (change in BMD), we will report the weighted mean differences with their corresponding 95% confidence intervals.

Additional outcome(s)

Randomized Controlled trials:
-Effect of anti-resorptive therapy (bisphosphonates and denosumab) on BMD at the Lumbar Spine and Hip, at 24, 36 and 60 months in postmenopausal women with non-metastatic breast cancer on aromatase inhibitors. (Mean percentage change in BMD)

-Effect of anti-resorptive therapy (bisphosphonates or denosumab) on fracture incidence. Fractures will be captured at yearly intervals throughout trial duration, whether described as atraumatic or traumatic, and identified as:

1. Reported clinical fractures at any site (excluding phalanges of hands or feet, carpal or metacarpal bones, tarsal or metatarsal bones and skull, nasal or facial, clavicle, tibial, fibular or patellar fractures)

2. Reported clinical (history or confirmed by X-ray) or morphometric vertebral fractures

3. Reported major osteoporotic fractures (MOF): vertebral, or hip or forearm or humeral fractures

-Effect of anti-resorptive therapy (bisphosphonates and denosumab) on bone turnover markers at 12, 24, 36 and 60 months (Mean percentage change in bone markers)

Our analysis of the above-mentioned outcomes will be conducted for 3 comparisons: oral bisphosphonates vs. control or placebo, IV bisphosphonates vs. control or placebo and denosumab vs. control or placebo.

Guidelines:

- Screening methods for aromatase inhibitors induced bone loss in postmenopausal with non-metastatic breast cancer patients on aromatase inhibitors treatment (DXA scan measurement, serial height measurements, serum levels of bone markers, assessment of risk factors etc…)

- Prevention of aromatase inhibitors induced bone loss through diet, exercise and pharmacological measures in postmenopausal with non-metastatic breast cancer patients on aromatase inhibitors treatment

-Candidates for pharmacological intervention to treat aromatase inhibitors induced bone loss in postmenopausal women with non-metastatic breast cancer

- Treatment options for aromatase inhibitor induced bone loss in postmenopausal women with non-metastatic breast cancer (oral bisphosphonates, intravenous bisphosphonates and denosumab)

* Measures of effect

For continuous data (change in serum bone markers), we will report the weighted mean differences with their corresponding 95% confidence intervals. For dichotomous data (fracture incidence), we will report the risk ratio and its 95% confidence interval.

Data extraction (selection and coding)

We will review the retrieved titles and abstracts in duplicate and independently (AB and ABK), using a screening form prepared a priori, based on our PICO question. We will retrieve the full text of all citations included by at least one reviewer. We will conduct full text screening in duplicate and independently, using a standardized form. At every step, we will conduct a calibration exercise on a sample of title and abstracts or full texts, to standardize the screening process between the two reviewers. We will solve disagreement at the level of full text screening by discussion with a third author (MC, GEHF, AA or CVP). We will develop two data collection tables a priori, one for randomized controlled trials and one for guidelines. Data extraction will be done in duplicate and independently.
We will abstract data for the following variables:

1-Randomized controlled trials:

-Author name, journal, year of publication, and name of trial

-Population characteristics (country of origin, number of participant, age, BMI, comorbidities, medications, onset and type of menopause, baseline BMD, T-score, previous fractures, stage of cancer eligible for study entry, duration on AIs, chemotherapy use, tamoxifen use, prior hormonal replacement therapy use, quality of life, BMD machine and bone markers assays).

-Characteristics of the intervention (dose, frequency, duration, loss to follow up)

-Outcomes including: mean or percent change in BMD, proportion of fractures in each treatment arm along with their type, sites, level of trauma and whether they have been adjudicated, and bone markers at different time points

2-Guidelines:

-Source, journal and year of publication

-Development group method, guideline’s question(s)

-Recommendations on screening patients

-Recommendations on prevention methods (calcium, vitamin D and exercise)

-Indications to treat and treatment options (T score for treatment, Risk Factors, FRAX use, drop in BMD, special considerations, anti-resoptive use, anti-resorptive dose)

-Strength of recommendations

-Items related to the quality of guidelines

Risk of bias (quality) assessment

Two reviewers (a senior researcher (AA, GEHF or MC), and a junior researcher (AB and ABK) will use Version 1 of the Cochrane risk-of-bias tool for randomized trials to assess the risk of bias for each outcome independently (Higgins 2011). We will assess the following domains: bias due to sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting (Higgins 2011). The reviewers will judge each study as either low risk of bias, high risk of bias, or unclear. If any disagreement occurs between the two reviewers, it will be resolved through discussion or with the help of a third reviewer/expert in the field (MC/GEHF/AA) as needed.

Guidelines appraisal

We will perform guidelines appraisal based on AGREE II instrument independently and in duplicate. This tool will assess the quality of guideline using 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability and editorial independence (Brouwers 2010).

Strategy for data synthesis

For each outcome and each comparison, a separate meta-analysis will be performed if at least two trials were identified. Our primary analysis will consist of 3 comparisons: (1) oral bisphosphonates vs. control or placebo, (2) IV bisphosphonates vs. control or placebo and (3) denosumab vs. control or placebo. We will use RevMan 5.3 to combine, calculate and report the findings. We will test for statistical heterogeneity using the I^2 statistic. We will perform heterogeneity tests to assess for any variability between combined studies. In case of high levels of heterogeneity between the trials (I^2 >=50%), we will perform sensitivity and subgroup analyses to identify and explain the source of heterogeneity. We will include subjects who took anti-resorptive drugs prior to being randomized to treatment to prevent aromatase inhibitors induced bone loss. We will however note duration of such treatment and offset time period prior to randomization, as specified in each trial, and conduct sensitivity analyses excluding such trials for the meta-analysis.
In order to assess reporting bias, we will look for published protocols of the included studies. If protocols were not published, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization for ongoing trials or trials that have been completed but not published. We will then evaluate if selective outcome reporting was present. All outcomes should be reported or an explanation of not reporting them should be available in the publication. In case of small sample bias, we will use the random effect estimate rather than the fixed effect estimate. We will explore the possibility of publication bias using a funnel plot if at least 10 studies are available in the final meta-analysis. If the funnel plot shows asymmetry, we will consider publication bias.

Analysis of subgroups or subsets

-We will perform subgroup analyses by study duration and age since menopause. In addition, we will perform subgroup analyses by menopause type (natural, chemical, surgical) for change in BMD.
-As sensitivity analysis we will combine both IV bisphosphonate and denosumab into parenteral vs. control or placebo.

-In case of any missing data, we will contact the authors of the individual studies to obtain the relevant information. We will perform sensitivity analyses to assess the impact of including trials with missing data, high attrition rates, trials that do not perform an intention to treat analysis or trials with high risk of bias on the overall treatment effects.

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Meta-analysis, Systematic review

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English

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Lebanon

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Review Ongoing

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Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

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03 August 2020

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03 July 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
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