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ORIGINAL ARTICLE

Simulated effects of early menopausal bone mineral density preservation on long-term fracture risk: a feasibility study

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Abstract

Summary Prevention of early menopausal bone loss may reduce the future burden of osteoporosis. In this modelling exercise, an osteoporosis prevention strategy involving 5-year infusions of zoledronic acid, beginning early in menopause, reduced long-term fracture risk and the proportion of aging women with femoral neck densitometric osteoporosis. This strategy warrants further evaluation.

Introduction Preventing early menopausal bone loss may substantially reduce the future burden of osteoporosis. We modelled the effects of infrequent zoledronic acid infusions on long-term fracture risk.

Methods Data from the Canadian Multicentre Osteoporosis Study (CaMos) were used to determine the expected natural history of femoral neck areal bone mineral density (BMD) and fracture risk (using FRAX®) from ages 50–80 for women with no antiresorptive drug exposures. We modelled the effects of three infusions of zoledronic acid (at ages 50, 55, 60) on long-term fracture risk, assuming this intervention would preserve BMD until age 65 years, followed by losses mirroring early menopausal BMD loss.

Results At age 65, untreated women and zoledronic acid recipients had expected mean (SD) femoral neck T-scores of − 1.5(1.0) and − 0.8(1.0), 10-year major osteoporotic fracture (MOF) risks of 9.8%(5.0) and 8.0%(3.7) and hip fracture risks of 1.7%(2.4) and 0.8%(1.2), respectively. At age 80, untreated women and zoledronic acid recipients had expected femoral neck T-scores of − 1.9(0.9) and − 1.4(0.9), MOF risks of 17.9%(8.2) and 14.9%(6.4) and hip fracture risks of 6.3%(6.2) and 4.4%(4.5), respectively. The expected proportion of women with femoral neck T-score ≤ − 2.5 was 14.9% for untreated women and 3.8% for zoledronic acid recipients at age 65, increasing to 28.1% and 12.0%, respectively, at age 80. Numbers-needed-to-treat to prevent one case of densitometric osteoporosis were 9 at age 65 and 5 at age 80.

Conclusion Infrequent infusions of zoledronic acid, initiated early in menopause, are expected to reduce long-term fracture risk and result in a substantial reduction in the proportion of women with densitometric osteoporosis after age 65.

Keywords Bisphosphonate · Bone mineral density · Fracture risk · FRAX · Osteoporosis · Prevention

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Introduction

Under current osteoporosis management paradigms, pharmacologic treatments are targeted to individuals considered to be at the highest risk of fracture [1], on the basis of clinical risk factors and/or low bone mineral density (BMD) [2–4]. Ten-year risk of fracture can be estimated using the FRAX® tool [5]. However, most women do not meet recommended treatment thresholds until after age 65 [6–8], by which time they have already experienced substantial bone loss or a fragility fracture. Much of this loss occurs during the early menopausal years [9, 10] (beginning 1 year after the final menstruation) and cannot be reversed with first-line antiresorptive therapies [11]. This paradigm is reactive and may be unacceptable to many women who would prefer to take a proactive approach to preservation of bone mass even before attaining a high-risk status [12]. Exercise and supplementation with calcium and vitamin D offer only minimal to modest protection against bone loss in menopausal women and adherence is poor, even in clinical trials [13, 14]. Hormone therapy [15, 16] and oral bisphosphonate medications [17, 18] both effectively preserve bone mass for women early in menopause, but safety concerns with long-term (> 5 year) continuous administration have precluded their adoption as preventative therapies [19, 20].

Zoledronic acid (ZOL) is a long-acting intravenous bisphosphonate. When administered annually for 3 years to menopausal women (mean age 73 years) at high risk of fracture in a placebo-controlled trial, ZOL significantly reduced the incidence of clinical and morphometric vertebral and non-vertebral fractures [21]. In a second placebo-controlled trial of menopausal women (mean age 71 years) who were not at high risk of fracture (median 10-year MOF risk 12% and hip fracture risk 2.4%), in which ZOL was administered at 18-month intervals, this medication also reduced the incidence of vertebral and nonvertebral fractures [22]; the results of this trial also suggested cardiovascular and mortality benefits with ZOL [23]. Furthermore, a single infusion of ZOL has been shown to preserve bone mineral density (BMD) and reduce markers of osteoclastic bone resorption for 5 or more years in menopausal women (mean age 64 years) [24], with two infusions administered approximately 6 years apart resulting in preserved BMD over 11 years [25].

Although data regarding the effects of ZOL in early menopausal women are limited, one controlled trial demonstrated that a single infusion of ZOL improved BMD throughout 24 months of follow-up in the subgroup of participants who were within 5 years of menopause at baseline, an effect that was comparable with women who were more than 5 years postmenopausal [26]. This existing evidence suggests that very infrequent (i.e. every 5 years) administration of ZOL could be used to prevent early menopausal bone loss, which might be expected to result in substantial long-term reductions in morbidity, mortality and health care costs associated with osteoporosis and fragility fracture.

We hypothesised that a preventative strategy consisting of very infrequent infusions of ZOL, beginning early in menopause, would result in clinically meaningful long-term preservation of bone mass and reductions in fracture risk at the population level. To test this hypothesis, we modelled the effects of very infrequent treatment with ZOL, beginning at approximately age 50 (i.e. around the time of menopause) on estimated long-term BMD and fracture risk using data from a large population-based cohort.

Methods

Participants

This modelling exercise utilised data from all women who participated in the Canadian Multicentre osteoporosis study (CaMos) and were aged ≥ 50 years at the time of enrollment. Briefly, CaMos is a prospective, multicentre, population-based longitudinal cohort study involving 9423 randomly selected community-dwelling adults from nine clinical centres across the country (n = 6539 women) [27]. The post-hoc analysis was approved by the Health Research Ethics Board for the University of Manitoba (project ID H2004:017O [HS24265]).

Data collection

Construction of the CaM*os* cohort and data collection procedures have been previously described [27, 28]. In brief, relevant assessments at baseline included an extensive health questionnaire, administered by a trained interviewer and BMD measurement with cross-calibrated dual-energy x-ray absorptiometry (DXA) instruments [29]. Data obtained using Lunar machines were converted to equivalent Hologic values [29]. The following data were obtained from baseline records of eligible women: age, height, weight, body mass index, history of fracture, diagnosis of rheumatoid arthritis, smoking, alcohol intake, history of parental hip fracture and femoral neck BMD. Women were stratified into one of seven age categories (50, 55, 60, 65, 70, 75, 80 years) using the category closest to their age at the time of baseline CaMos assessment.

Model for natural history of bone loss and fracture risk

Data collected for women in the 50-year age stratum were used to determine the expected distribution of femoral neck BMD and fracture risk factors around the time of menopause, the entry-point for our model. Using the mean and SD from the 50-year age stratum, we first randomly generated the expected femoral neck BMD at age 50 years for all women. In order to model the expected natural history of femoral neck

BMD loss for untreated, menopausal women, we then estimated current age femoral neck BMD using previously published longitudinal data on femoral neck BMD loss from age 55 to 80 (in 5-year intervals) from women CaMos participants who had not been treated with hormone therapy or bisphosphonates [28]. Mean (SD) 10-year fracture risk estimates for each age stratum from 50 to 80 were then determined with FRAX (Canadian model, Version 3.8), using the simulated femoral neck BMD (based upon age-category at baseline) and each participant's actual clinical risk factors at the baseline assessment. The Canadian FRAX tool has been validated in the Canadian population and shows good calibration and predictive precision [30, 31].

Model for early intervention with bone-preserving therapy

We modelled the effects of receiving three infusions of ZOL, beginning at age 50 and spaced 5 years apart (i.e. infusions administered at ages 50, 55, 60) on expected femoral neck BMD and FRAX risk estimates from age 55 to 80. Our base model assumed the following: (1) each infusion of ZOL maintains femoral neck BMD for 5 years [24]; (2) bone loss resumes 5 years after the third and final ZOL infusion (i.e. at age 65); (3) bone loss begins at the same rate as expected at age 50 in the absence of ZOL treatment (i.e. early intervention with ZOL delays but does not prevent the rapid decline in BMD seen early in menopause); (4) ZOL recipients have the same distribution of FRAX clinical risk factors as untreated women and (5) no woman in the model receives any subsequent antifracture therapy. In other words, we modelled the effects of complete preservation of femoral neck BMD from ages 50 to 65, with a resumption in BMD decline at age 65 at a rate that mirrors the losses expected from age 50 onwards in untreated menopausal women. When calculating FRAX risk estimates for ZOL recipients, we used the same clinical risk factors as were used in the absence of treatment. Given the long skeletal half-life of ZOL, it is possible that the simulated intervention might prevent the rapid phase of early menopausal bone loss altogether. As a sensitivity analysis, we modelled a second scenario, in which the rate of bone loss experienced by ZOL recipients after age 65 mirrors the expected natural losses from age 65 onwards in untreated women (i.e. ZOL recipients have the same BMD trajectory as untreated women from age 65 onwards).

Number-needed-to-treat (NNT) to prevent one case of densitometric osteoporosis at the femoral neck or a 10-year fracture risk exceeding common treatment thresholds (MOF risk ≥ 20%, hip fracture risk ≥ 3%) [2, 4] were calculated for each age stratum using the following formula: NNT = 1/(expected proportion of untreated women with the outcome − expected proportion of ZOL recipients with the outcome).

Outcomes

The primary outcome was the difference in simulated mean FRAX 10-year MOF risk estimates at ages 55, 60, 65, 70, 75 and 80, between women who receive three infusions of ZOL at 5-year intervals beginning at age 50 and untreated women. Secondary outcomes were the difference in simulated mean FRAX 10-year hip fracture risk estimates between ZOL-treated and untreated women at ages 55, 60, 65, 70, 75 and 80, comparison of simulated mean BMD at the femoral neck among ZOL-treated and untreated women at each 5-year age increment and comparison of the proportion of the population expected to have a T-score ≤ − 2.5 (densitometric osteoporosis) at the femoral neck at each 5-year age increment, with or without ZOL treatment, NNTs to prevent densitometric osteoporosis, 10-year MOF risk ≥ 20% and 10-year hip fracture risk ≥ 3%).

All statistical analyses were performed using Statistica (Version 12.0, StatSoft, Inc., Tulsa, OK, USA).

Results

Of the 9423 CaMos participants, 4631 were women aged ≥ 50 years at the time of baseline assessment with valid BMD measurements. At baseline, women in the 50-year age stratum (n = 355) had mean (SD) age 51.1 (0.8) years, femoral neck BMD 0.765 (0.114) g/cm^2 (T-score: − 0.8), 10-year MOF risk 3.9% (1.4) and 10-year hip fracture risk 0.3% (0.3). Distribution of clinical fracture risk factors at baseline is shown for each age stratum in Table 1.

Figure 1 compares simulated change in femoral neck BMD and fracture risk from ages 50 to 80 in untreated women (i.e. natural history of bone loss) and in women treated with three infusions of ZOL at ages 50, 55 and 60. At age 65, for the untreated group, the expected mean (SD) femoral neck T-score was − 1.5 (1.0), corresponding to a mean (SD) FRAX 10-year MOF risk of 9.8% (5.0) and hip fracture risk of 1.7% (2.4). At age 80, the expected mean (SD) femoral neck T-score for the untreated group was − 1.9 (0.9), corresponding to a MOF risk of 17.9% (8.2) and hip fracture risk of 6.3% (6.2). At age 65, ZOL-treated women would be expected to have mean (SD) femoral neck T-score − 0.8 (1.0), 10-year MOF risk of 8.0% (3.7) and hip fracture risk of 0.8% (1.2). Assuming no further pharmacotherapy, at age 80, the expected mean (SD) femoral neck T-score for ZOL-treated women would be − 1.4 (0.9), corresponding to a 10-year MOF risk of 14.9% (6.4) and a hip fracture risk of 4.4% (4.5).

Figure 2 shows the proportion of women expected to have femoral neck T-scores in the osteoporosis range (i.e. ≤ − 2.5) within each age stratum, with or without preventative ZOL treatment. Among untreated women, densitometric osteoporosis at the femoral neck is expected in 14.9% at age 65 and

Table 1 Characteristics of women used to model changes in femoral neck areal bone mineral density and 10-year fracture risk over time

	Age stratum*						
	50 (n = 355)	55 (n = 635)	60 (n = 748)	65 (n = 1000)	70 (n = 901)	75 (n = 700)	80 (n = 292)
Age (year), mean (SD)	51.1 (0.8)	55.1 (1.4)	60.1 (1.5)	65.1 (1.4)	69.9 (1.4)	74.7 (1.4)	79.7 (1.4)
BMI (kg/m^2), mean (SD)	27.1 (5.4)	27.4 (4.9)	27.4 (5.1)	27.2 (4.9)	27.3 (5.2)	26.7 (4.4)	26.6 (4.8)
Prior fracture, n (%)	3 (0.8%)	19 (3.0%)	50 (6.7%)	95 (9.5%)	145 (16.1%)	138 (19.7%)	64 (21.9%)
Parental hip fracture, n (%)	33 (9.3%)	61 (9.6%)	70 (9.4%)	96 (9.6%)	75 (8.3%)	36 (5.1%)	15 (5.1%)
Current smoking, n (%)	73 (20.6%)	112 (17.6%)	114 (15.2%)	130 (13.0%)	121 (13.4%)	55 (7.9%)	21 (7.2%)
Glucocorticoids, n (%)	1 (0.3%)	3 (0.5%)	11 (1.5%)	10 (1.0%)	11 (1.2%)	22 (3.1%)	6 (2.0%)
Rheumatoid arthritis, n (%)	3 (0.8%)	6 (0.9%)	6 (0.8%)	7 (0.7%)	8 (0.9%)	10 (1.4%)	3 (1.0%)
Alcohol ≥ 3 units/day, n (%)	5 (1.4%)	5 (0.8%)	4 (0.5%)	10 (1.0%)	8 (0.9%)	11 (1.6%)	0 (0.0%)

*Women were stratified based on the age they were closest to at the time of data collection. *BMI* body mass index, *BMD* bone mineral density, *FN* femoral neck

28.1% at age 80. Among women who receive preventative ZOL, the proportion expected to have femoral neck T-score ≤ − 2.5 is 3.8% at age 65 and 12.0% at age 80. NNTs to prevent densitometric osteoporosis at the femoral neck, 10-year MOF risk ≥ 20% and 10-year hip fracture risk ≥ 3% are shown in Table 2.

Simulated differences in femoral neck BMD and fracture risk in ZOL recipients who resume rapid BMD loss beginning at age 65, and those who lose BMD at a slower rate from age 65 onwards, were small (data shown in Supplementary Materials), indicating that different rates of BMD loss after ZOL treatment are expected to have a similar effect on long-term fracture risk.

Discussion

Within current osteoporosis paradigms, treatment is generally not offered until substantial irreversible bone loss or a fragility fracture has already occurred. We modelled the effects of a preventative approach to women's bone health, in which three infusions of the long-acting intravenous bisphosphonate, ZOL, are administered at 5-year intervals, beginning at age 50 (i.e. taking that age as the onset of menopause). Assuming maintenance of BMD for 5 years following each ZOL infusion, this strategy would result in a fourfold reduction in the development of densitometric osteoporosis at the femoral neck by age 65 and would also significantly lower the long-term risk of fracture at the population level, by 15–20% for MOF and 30–50% for hip fracture.

Delaying the development of osteoporosis and lowering long-term fracture risk with ZOL is expected to have benefits at both the population and individual levels. Global population estimates indicate that there are approximately 140 million women aged 65 to 69 years. Our model indicates that the average 10-year risk of fracture for 65-year-old untreated women is 9.8% for MOF and 1.7% for hip fracture. Therefore, women aged 65 to 69 could be expected to have almost 14 million MOFs by the ages of 75 to 79, of which more than 2 million are hip fractures. An early preventative strategy with ZOL could potentially avoid 2 million of these MOFs (1 million hip fractures). Preventative ZOL administration also has the potential to reduce osteoporosis-related health care utilisation in other ways. By substantially reducing the proportion of menopausal women who meet BMD criteria for a diagnosis of osteoporosis, this strategy is expected to lower the demand for baseline and serial BMD scans from age 65 onwards, and, for many women, delay the requirement to undergo a 'traditional' course of pharmacotherapy to prevent fracture. There is ongoing uncertainty regarding optimal long-term management of women who require initiation of traditional anti-fracture therapy at an early age (e.g. < 70 years), as concerns about long-term side effects of first-line antiresorptive agents—atypical femur fractures in particular—preclude continuous use for more than 5–10 years [32]. A preventative ZOL strategy is not expected to increase the risk of atypical femoral fracture, given that exposure to the medication is low (i.e. three infusions over 10 years), and even in settings of continuous bisphosphonate treatment, risk of atypical femur fracture drops sharply in the year following discontinuation [32, 33]. Osteonecrosis of the jaw is another adverse event associated with bisphosphonate treatment. However, the risk of osteonecrosis of the jaw with the typical bisphosphonate treatment regimens for osteoporosis is exceedingly low (incidence of less than 0.01%) [34], and the risk is anticipated to be even lower with the extended dosing interval modelled in this study. At the individual level, preventative ZOL is expected to reduce the proportion of women who are identified as having osteoporosis later in life, a diagnostic label that has been shown to provoke concern, even if fracture risk is not high [35], and may result in the curtailing of behaviours such as exercise, that are not only beneficial for health but also

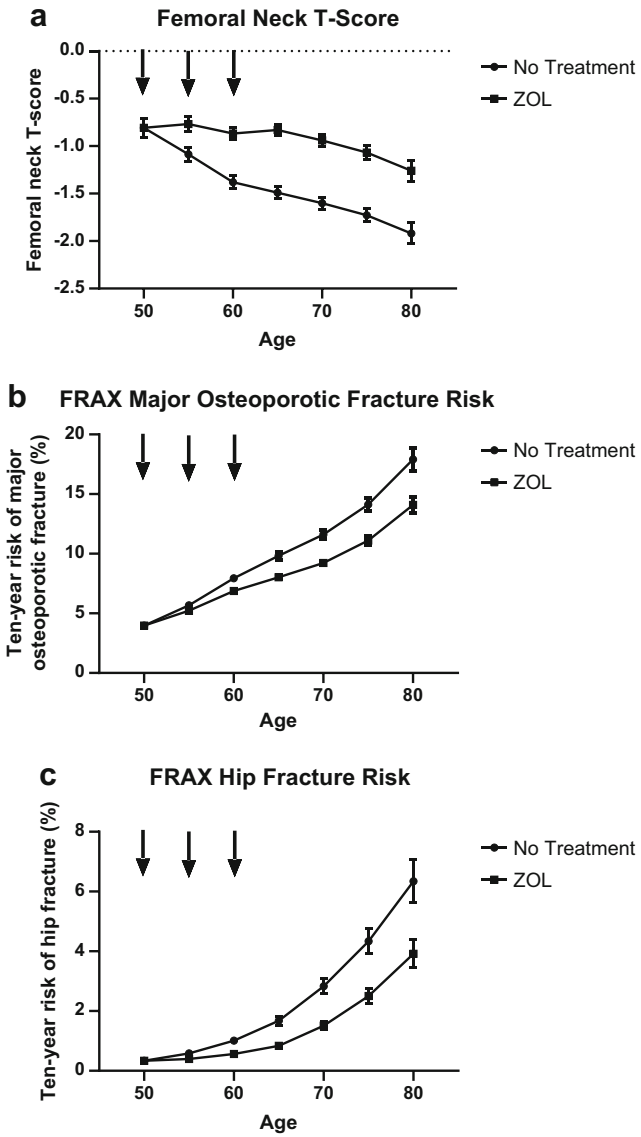

Fig. 1 Simulated femoral neck T-scores (panel **a**), expected 10-year major osteoporotic fracture risk (panel **b**) and expected 10-year hip fracture risk (panel **c**) from age 50 to 80 in untreated women (circles) and in women who received infusions of zoledronic acid (ZOL) at ages 50, 55 and 60 (squares). Data are means and 95% confidence intervals. Some confidence intervals cannot be shown as they are smaller than the corresponding data points. Down arrows signify the time of ZOL administration

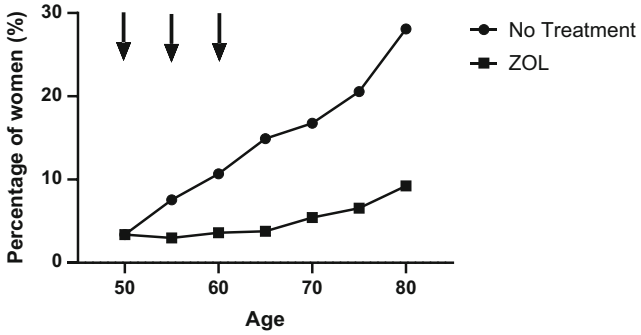

Fig. 2 Proportion of women aged 50–80 expected to have densitometric osteoporosis (simulated femoral neck T-score ≤ − 2.5) after receiving either: no treatment (circles), or treatment with zoledronic acid (ZOL) at ages 50, 55 and 60 (squares). Down arrows signify the time of ZOL administration

improve quality of life. Additionally, while it is not known whether the preventative ZOL strategy modelled in this study would have similar effects, some controlled trials of ZOL have suggested that treatment with this agent may confer a lower incidence of cancer, cardiovascular disease and mortality [36].

For the purpose of this modelling exercise, we assumed that each infusion of ZOL would preserve BMD for 5 years. At present, no clinical trials have evaluated the effects of very infrequent ZOL on very long-term changes in BMD for women early in menopause. However, existing evidence suggests that the demonstrated long-term effects of ZOL on BMD in older women might reasonably be extrapolated to those early in menopause. In a randomised trial that included a subgroup analysis of women within 5 years of menopause who received an infusion of ZOL at baseline and were followed for 2 years, improvements of 4.0% at lumbar spine, 2.0% at the femoral neck and 2.6% at the total hip were observed at the end of follow-up. Women from the same trial who were more than 5 years from menopause at baseline had similar improvements of 4.8% at the lumbar spine, 1.5% at the femoral neck and 2.1% at the total hip [26, 37]. Although the trial participants were only followed for 2 years, these results indicate that the BMD effects of ZOL are similar in early menopausal and older women, and suggest that the 5-year BMD preservation seen following a single infusion of ZOL in another trial of older women (mean age 64 years) [24] may also apply to the

Table 2 Estimated number of early menopausal women requiring treatment with three infusions of zoledronic acid (ZOL) at ages 50, 55 and 60 to prevent one case of densitometric osteoporosis or a 10-year fracture risk exceeding common treatment thresholds

Outcome	Age stratum					
	55 (n = 635)	60 (n = 748)	65 (n = 1000)	70 (n = 901)	75 (n = 700)	80 (n = 292)
Femoral neck T-score ≤ − 2.5	22	14	9	9	7	5
10-year MOF risk ≥ 20%	635	249	30	17	12	7
10-year hip fracture risk ≥ 3%	64	19	10	6	4	4

Data are numbers needed to treat (NNT) to prevent one case of the outcome

early menopausal population. The findings from our modelling exercise warrant further investigation with a proof-of-concept study to assess the duration for which a single infusion of ZOL can preserve BMD when administered in the early menopausal period.

The validity of our model is contingent on some additional assumptions, although we were deliberately conservative in order to avoid over-estimating the effects of a preventative ZOL approach on fracture risk. For example, we assumed mere BMD stability following ZOL administration, even though a single infusion of ZOL has been shown to increase BMD over 2 years of follow-up in a population early in menopause [26]. Our base model anticipated loss of bone mass following the third and final ZOL infusion at a rate comparable to early menopausal women. However, it is probable that BMD would decline more slowly in ZOL-treated individuals, reflecting the long half-life of ZOL in the skeleton and its potent antiresorptive activity. Of interest, a sensitivity analysis which modelled a slower rate of BMD loss following ZOL cessation showed a similar effect on simulated long-term fracture risk. It was also assumed that ZOL recipients would have a comparable distribution of FRAX clinical risk factors as an untreated control population at each 5-year age increment, although it is possible that ZOL-treated women may in fact sustain fewer fractures than untreated women between age 50 and 80, in which case our model would actually underestimate the effect of ZOL on 10-year fracture risk, as history of fracture is an input in the FRAX calculator. An additional assumption was that all women in the 50-year age stratum used to construct the model were either perimenopausal or recently menopausal, although, in fact, some women in this stratum would have been premenopausal and others > 5 years into menopause. However, given that the average age of menopause is 51 years [38, 39], it is reasonable to anticipate that discussions about preventative ZOL would begin around age 50 in the majority of cases. Our model was based only on femoral neck BMD, as this site is the reference standard for the densitometric diagnosis of osteoporosis [40], and accordingly, is the only the region of interest incorporated in FRAX. Inclusion of other sites (lumbar spine, total hip) in the model would not change long-term FRAX risk estimates, but would be expected to demonstrate even greater benefits in terms of the proportion of women with densitometric osteoporosis from ages 65 to 80.

It is important to recognise that this model considers the effects on BMD and fracture risk if all eligible women in the population received preventative ZOL. In reality, it is unknown what proportion of eligible women would embrace this approach, which uses a pharmacologic intervention at a time when they are asymptomatic and at low fracture risk. ZOL has been associated with osteonecrosis of the jaw, atrial fibrillation, acute kidney injury and uveitis [21, 41]. These side effects are rare, and it is presently unknown whether incidence in early menopausal woman would be comparable to what has been reported in older populations. Additionally, treatment with ZOL can also result in the development of an acute phase response after the first infusion in 20% or more individuals [42]; although this inflammatory response is generally mild and transient, it may pose a barrier to therapy for some women. However, we have observed that more than a quarter of women who are considered to be at low risk of fracture (i.e. FRAX 10-year MOF risk < 10%) wish to proactively initiate pharmacologic treatment to reduce their long-term fracture risk, while only half of women with FRAX 10-year MOF risk ≥ 20% express interest in starting antiresorptive therapy, even though treatment is much more likely to result in near-term fracture risk reduction in this population [12]. These data indicate that many patients place high value on preventing bone loss, although the enthusiasm for a preventative ZOL approach amongst the target population of women early in menopause requires formal assessment. Whether preventative ZOL is more effective in certain groups of early menopausal women (such as those with lower BMD than expected for age, alterations in bone microarchitecture, or fracture risk that is higher than the age-matched average) also requires further evaluation, with the view that such an intervention might ultimately be directed to the individuals most likely to benefit.

Conclusions

This modelling exercise, developed using data from a large, population-based cohort, suggests that early treatment with very infrequent ZOL has the potential to significantly reduce long-term fracture risk. Further investigation of a preventative ZOL strategy is warranted, beginning with an assessment of the acceptability of such an approach among women in the early menopausal period, and a proof-of-concept study evaluating the effect of infrequent ZOL on BMD in this population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-05826-5.

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Availability of data and material Access to data is provided at the discretion of the CaMos investigators and requires an application to the CaMos data access panel.

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Compliance with ethical standards

Conflicts of interest EOB has received honoraria from Amgen and Eli-Lilly outside the submitted work. JPB has received research support from Mereo BioPharma, Radius Health and Servier; has served as a consultant for Amgen and Servier; and has served on speakers' bureaus for Amgen. SNM has received an institutional research grant from Amgen outside the submitted work. TT has received honoraria as consulting fees from Abbvie, Sandoz, Novartis, Amgen, Janssen and Pfizer. WDL, JCP, CSK, SMK, BCL, TA and GAK have nothing to disclose.

Ethics approval Ethical approval for this post-hoc analysis of CaMos data was from the University of Manitoba Health Research Ethics Board (H2004:017O [HS24265], approval date August 5 2020). For the primary CaMos study, ethics approval was granted through McGill University and the appropriate research ethics board for each of the nine participating centers.

Consent to participate Signed informed consent was obtained from every study participant in accordance with the Helsinki Declaration.

Consent for publication Consent to use and publish CaMos data was provided by the CaMos investigators.

Code availability N/A

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